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Preface

The term "somatosensory system" covers the wide array of specialized receptors, peripheral nerves, and central processing stages underlying the transduction and processing of somatosensory signals. Collectively, these are engaged in sensing, perceiving, and acting—upon stimulation of the body surface or during muscle activity. Cutaneous (skin) sensations are essentially multimodal and are classically described as the senses of touch, temperature, itch, and pain. Afferent types belonging to the class of small-diameter, unmyelinated C fibers have been implicated in each of these functions. Yet so far, the functional neurophysiology and contribution of non-nociceptive mechanoreceptive C afferents to somatosensory signaling have not been researched comprehensively. This volume, therefore, represents an effort to encompass the breadth and depth of our current knowledge of the physiology and function of C-tactile (CT) afferents (or C low-threshold mechanoreceptors, CLTMs). The focus of the chapters ranges from the skin to the brain and from behavior to psychology. The chapters also identify the issues that need to be resolved and point the way toward the future of research in this relatively young, but growing, field of inquiry. This book thus offers the bulk of currently available evidence, knowledge, and insight on CT afferent physiology.

The first eight chapters deal with *Peripheral Low-Threshold Mechanoreceptors and Psychophysical Observations* and provide the essential backdrop for CT neurophysiology: the afferent receptors and nerves in the skin and their sensory and perceptual impact. In their chapter, Åke Vallbo et al. outline the history of the discovery of C-mechanosensitive afferents, which began with Yngve Zotterman's observations in cats in the 1930s. These experiments were the first to identify C low-threshold mechanoreceptors (CLTMs). Vallbo et al. highlight the importance of the microneurography technique in the development of single-unit afferent recordings in healthy humans, which ultimately led to the discovery of CTs in the late 1980s and early 1990s. Until then, CLTMs had been characterized in experimental mammals without much overriding concern about how to interpret their general function. As Vallbo's chapter points out, Zotterman's original speculation that CTs may be involved in tickle sensations is generally regarded as an insufficient proposition for CT function, not well-supported by subsequent evidence. However, more recent

evidence has raised this possibility again (Fukuoka et al. 2013). While the discovery in humans might have surprised some who considered CLTMs to be a phylogenetically older afferent type, which was also expected to be absent in humans, it also prompted the need to build a stronger interpretive framework for the growing body of observations, allowing more directed experimentation. As Vallbo describes, the currently prevailing framework puts CTs at the center of a "second system" of tactile transduction which ultimately plays roles in emotionally and socially relevant touch interactions between individuals.

The chapters by Pitcher et al., Seal and Lumpkin, Donadio, and Vrontou summarize evidence, primarily from animal research, characterizing the functional properties of CLTMs from a neurophysiological and molecular neurobiological basis. The translational power of this approach is yet to be realized with respect to CTs (the human equivalent of CLTMs), and it seems likely that there are at least two groups of CLTMs that differ in membrane properties such as receptor expression. There may also be subgroups of CT afferents waiting to be discovered, as has proved to be the case with C-nociceptors. The chapter by Ackerley et al. provides background on the theoretical issues raised by the central idea of a "second system" for tactile information processing, in particular the contrast between CT's proposed role in "affective touch" as opposed to "discriminative touch." Norrsell's chapter rounds off the peripheral physiology perspective with a historical overview that encompasses the neuroscience and psychophysics approaches that have been brought to bear on CT research. This section closes with Guest and Essick bringing us up to date with more current psychophysical approaches to understanding the complexity of human touch and in particular the separate function of active touch with the hands compared with affective touch from the body.

Chapters 9–13 deal with *Central Processing of Low-Threshold Mechanoreceptor Input* and follow the CT afferent from the skin to the spinal cord and onward to the cortex of the brain. Andrew and Craig's chapter summarizes evidence that CLTM afferents project to the dorsal horn of the spinal cord in mammals in anatomical association with other classes of thinly myelinated and unmyelinated afferents, reinforcing their function within an interoceptive network. This anatomical, and thereby functional, separation of CTs from A-LTMs is further underscored by human patient evidence, summarized in the chapter by Cole et al., where patients with a complete loss of A-LTMs, but survival of CTs, provide further evidence for an affective touch system in human skin. The chapters by Björnsdotter and Morrison present evidence of cortical projections to insular cortex and wider cortical networks that process CT input. It is here we begin to see how CTs may be well positioned to play a fundamental role in social behavior. Finally, the chapter by Rolls provides further supporting evidence for reward-associated and top-down properties of CT function with respect to representations in the orbitofrontal cortex, relevant to both observed and received touch.

The "social touch" hypothesis described by Vallbo and others comes into its own in chaps. 14–19, *Low-Threshold Mechanoreceptor Signaling in Social and Sexual Behavior.* Gallace and Spence's chapter discusses evidence from cognitive psychology and social psychology, supporting the view that touch plays a central role in

human social interactions, with a specific link to affective touch and well-being. This theme is picked up in McGlone et al.'s chapter which focuses on a more neuroethological approach to grooming behaviors. Here, a case is made for CTs providing the necessary reward valence to promote grooming and nurturing touch, which in human primates sees its expression in sustaining a global cosmetic industry. The chapter by Löseth and Leknes explores the neurochemistry of social touch, in particular how the brain's mu-opioid signaling is mediated by touch to give rise to specific behaviors in social situations. Schirmer et al.'s chapter takes the so-called "Midas touch" effect—the contribution of touch to positive feelings and prosocial behaviors—as its starting point. They explore the consequences and potential mechanisms underlying casual forms of touch, such as those occurring in many social situations, where they can induce a positive effect on the recipients of such touches. Giorgiadis and Kringelbach's chapter looks at the influences of pleasant touch from a sexual intercourse perspective, making a case for genital touch to act as a "proximal master" in the perception of pleasurable sexual touch. The section ends with Fulkerson offering a critical philosophical examination of recent discourse on affective touch, in which a note of caution is sounded about the types of inferences we can draw about CT function, as well as to what extent, and how, affective touch can be regarded as a natural kind of touch distinct from other kinds.

Chapters 20–24, *Clinical Implications of Low-Threshold Mechanoreceptor Signaling*, presents several chapters that focus on patient populations and therapeutic approaches involving CT afferents and affective touch. In one way or another, the chapters in this section all explore the wider clinical implications of the "social touch" framework—as well as circumstances under which CT-mediated touch may interact with nociceptive signaling. CT-mediated touch may be relevant in specific disorders, such as chronic pain, psychiatric disorders, and developmental disorders such as autism spectrum disorders (ASD). Thompson's chapter makes a case for a more concerted effort in recognizing the potential for affective touch to be deployed in clinical contexts by building an argument with the recent advances in our understanding of the functional properties of CTs. Gentsch et al., also focusing on interpersonal touch, make a case for how affective touch shapes our sense of self and impacts fundamental aspects of body awareness, such as embodiment. Field's chapter reviews the multiple effects of massage therapies that specifically use gentle touch, describing evidence of how such touch affects weight gain in preterm infants; meanwhile, gentle touch may also have positive effects on depression in adults. Cascio's chapter provides an overview of the role of touch in ASD and other closely related disorders, such as obsessive-compulsive disorder, for which there is a growing body of evidence that such conditions may have their genesis in a developmental failure of the CT system—peripherally and/or centrally. The final chapter by Liljencrantz et al. explores the possible mechanisms of CT-mediated effects on pain in human experimental models of tactile allodynia. This provides an important departure from the emphasis on CTs as pleasure related and raises critical questions about the potential role of CTs in modulatory interactions with other afferent types.

The various discourses on CLTM/CT affective touch nerves and their central projections described in this book serve to demonstrate that the sensory modality we

call “touch” is far richer than a solely mechanical detection sense. It has been long recognized by somatosensory researchers that discrimination is a fundamental property of tactile sensing. However, a sensory system for affective touch is an often-overlooked submodality that we need to include when talking about the skin senses. We now need to incorporate and recognize the central role of affective touch in human emotion. Affective touch is typically associated with slowly moving, low-force mechanical stimulation of the skin and often gives rise to pleasant sensations. As evidenced in this book, cutaneous unmyelinated low-threshold (C-tactile, CT) afferents seem to be particularly important for affective touch behavior and perception. Operating alongside the fast myelinated detection system, there is the slow CLTM/CT system that predominately projects not to primary somatosensory cortices but instead to the posterior insular cortex—part of the limbic system and a first step in the processing of “feelings” in orbitofrontal cortical areas. Gentle touch reduces stress and lowers blood pressure; it elevates pain thresholds, increases tips if you are a waiter (Crusco 1984), can communicate up to eight emotions (Hertenstein et al. 2009), is of fundamental importance in sexual and nurturing behavior, and shapes the destiny of the social brain. Although there are still enormous gaps in our knowledge of the mechanisms by which the rewarding nature of affective touch is encoded and processed, we hope this collection of papers will provide an overview of the current understanding of this novel class of cutaneous low-threshold C-mechanoreceptive afferents.

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Chapter 1
Sensual Touch: A Slow Touch System Revealed with Microneurography

Åke Vallbo, Line Löken, and Johan Wessberg

Abstract Unmyelinated afferents responding to light touch were first described in furry animals in 1939. In humans, a similar type of afferents was identified about 50 years later (CT, C tactile) using the microneurography technique. CT afferents are present in hairy but not in the glabrous skin. Receptive fields are small (maximal 35 mm^2) and patchy.

Thresholds of CT and Aβ tactile afferents fall in the same range, whereas response properties differ in most other respects. CT afferents exhibit a pronounced and long-lasting fatigue. Maximal impulse rate is about ten times higher in Aβ as CT rate does not exceed 100 impulses s^{-1}.

CT afferents exhibit intermediate adaptation.

A key difference emerges when the dynamic range is explored using light touch stimuli moving over the skin surface. In Aβ afferents, the impulse rate increases monotonously with speed of movement, whereas in CT afferents maximal rate occurs at a fairly low speed (about 1–3 cm s^{-1}) which corresponds fairly well to human caressing movements. The CT response to a moving touch stimulus is dependent on the temperature of the moving object with the optimal response at a neutral temperature. A similar effect is not present in Aβ afferents.

Psychoneural analyses indicate that subjects' estimate of pleasantness during slowly moving skin touch matches the impulse rate of CT when the speed of movement or temperature of the moving object is varied. Aβ afferents do not exhibit a similar correspondence.

Functional properties of CT afferents as well as psychoneural correlations are consistent with the interpretation that the CT system has a key role in physical contact with an amiable conspecific, that is, your parents, lover, kin, or friends. It seems

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that the social touch hypothesis is a reasonable interpretation of the survival value of a seemingly superfluous tactile system. On the other hand, the exact role of the CT system remains to be clarified.

Keywords Human • Hairy skin • C tactile afferent • Microneurography • Psychoneural correlation • Social touch

It is now well established that the human touch system is not as uniform as earlier thought. Innocuous mechanical events are mediated not only by fast-conducting myelinated afferents (Aβ) but, in addition, by slowly conducting unmyelinated afferents (C). Thus, the human tactile system is dual at the level of primary afferents, consisting of a fast and a slow system, differing in conduction velocity by a factor of about 50. Similar dual systems are also present in furry animals. However, different terms and acronyms are currently used for the slowly conducting tactile afferents, that is, CT (C tactile) in human studies and CLTMR (C low threshold mechanosensitive receptors) in studies of furry animals. Still other terms and acronyms may be found in earlier papers. In the present chapter, the term "tactile afferents" is preferred rather than "mechanoreceptive" or "mechanosensitive" afferents as these terms would include units with lower sensitivity which are commonly assumed to have nociceptive functions. To complete the list, it may be noticed that there is yet another set of tactile afferents in furry animals in addition to the fast-conducting Aβ and the unmyelinated CLTMR, that is, thin myelinated afferents (Aδ) which innervate certain kinds of hair follicles (Brown and Iggo 1967; Li et al. 2011). So far, Aδ tactile afferents have not been identified in man, whereas mechanoreceptive Aδ afferents of presumed nociceptive function have been described on the basis of microneurography recordings (Adriensen et al. 1983).

The interest in the unmyelinated tactile system has expanded markedly in recent decades once the idea was launched that the functional role of CT is not in the sensation of tickle as earlier assumed but rather in more fundamental limbic functions, notably in relation to affective touch (Vallbo et al. 1993, 1999). A large number of studies on CT and CLTMR systems have appeared in recent decades using a variety of methods ranging from molecular biology, genetic labeling, and pharmocogenetic activation in rodents, to microneurography, psychophysical investigations, and functional brain imaging in humans (Morrison et al. 2010; Olausson et al. 2010; Vrontou et al. 2013; McGlone et al. 2014). The various experimental approaches have been mutually fertilizing in expanding our knowledge, allowing a deeper understanding of the slow tactile system.

The primary purpose of the present chapter is to give a survey of properties of human CT primary afferents, particularly in relation to current ideas on their functional significance, notably the hypothesis of their role in affective and social touch. The chapter includes due references to data from studies of nonhuman species. This seems appropriate because human CT and CLTMR in furry animals appear to be homologs. On the other hand, studies in rodents indicate that the population of

CLTMR in animals is not homogenous but may include several subgroups, an issue that has not been explored in man.

History

As an introduction, the present chapter starts with a short tracing of the scientific history of the slow tactile system starting with furry animals and proceeding to man.

CLTMR in Furry Animals

Evidence for the existence of a slow tactile system (CLTMR) in animals was first presented almost 75 years ago. In 1939, the Swedish physiologist Zotterman proposed that light touch activates not only large afferents but also small unmyelinated afferents (Zotterman 1939) (Fig. 1.1a). Recording from thin strands of the cat saphenous nerve he noticed that touching the skin on the lower leg produced impulses of three different sizes, designated A beta (β), A delta (δ), and C in accordance with the Erlanger–Gasser scheme (Erlanger and Gasser 1924). He concluded that the C-spikes represent impulses in unmyelinated afferents, although his experimental approach did not allow him to prove this proposal by assessing their conduction velocities. Zotterman emphasized a unique and striking response feature of the low threshold C mechanoreceptive afferents, that is, a prominent and long-lasting after-discharge which was not seen in large diameter tactile afferents. On the basis of this finding, he suggested that unmyelinated tactile afferents might account for the sensation of tickle: "The itching after-sensation to light touch is most probably due to fibers conducting at C rates" (Zotterman 1939). The tickle hypothesis then remained unchallenged for almost five decades.

An important step was taken about 20 years later when Douglas and Ritchie (1957) demonstrated a number of fundamental properties of the slow tactile system using an elegant spike collision technique (Fig. 1.1b). Using a cat saphenous nerve preparation with intact connection to the skin Douglas and Ritchie (1957, 1962) monitored the compound C fiber volley produced by repetitive electrical stimuli. When light tactile stimuli were simultaneously delivered to the innervation zone of the nerve they found a dramatic decrease of one major component of the compound C fiber volley. Their conclusion was that the extinction observed was due to collision of impulses traveling in opposite directions in the same fibers, that is, impulses initiated in sensory terminals by the touch stimuli and impulses elicited by the electric stimuli delivered to the nerve trunk. Thus, they showed beyond doubt that the slow tactile afferents conducted impulses at a speed of about 1 m s^{-1} indicating nonmyelinated axons. In addition, their study demonstrated that these nerve fibers are abundant in nerves innervating hairy skin of the cat.

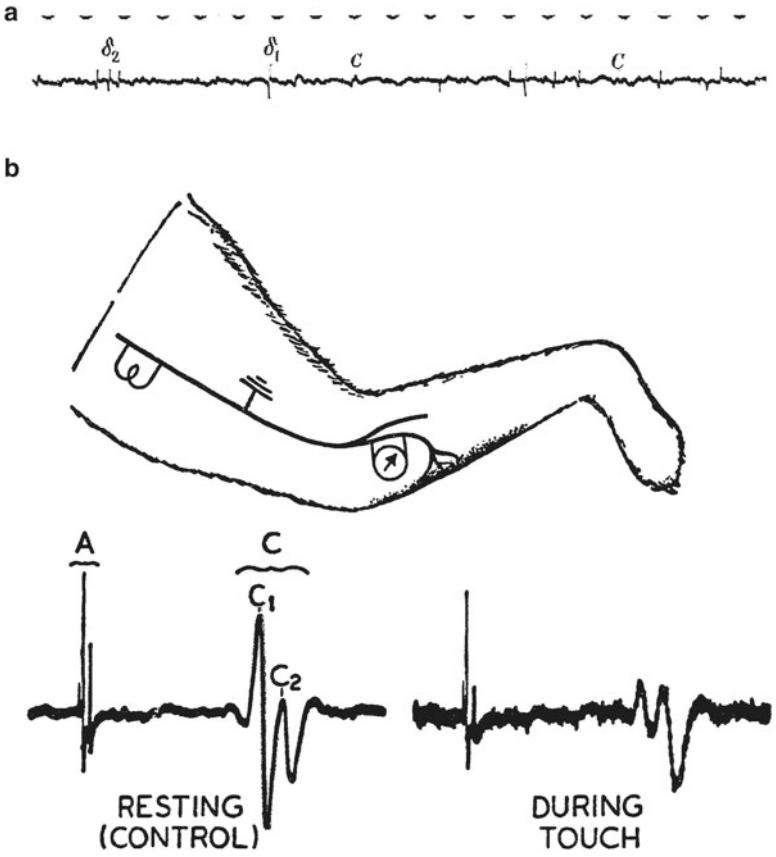


Fig. 1.1 Primary recordings of CLTMR. (**a**) A record from Zotterman's paper 1939 showing Aδ, and C impulses in cat saphenous nerve responding to skin deformation. This publication represents the first recordings ever of single unit impulses in mammalian C fibers. Time 1/50 s. (**b**) Douglas and Ritchie's collision experiment. The cat saphenous nerve was electrically stimulated above the knee to produce a compound action potential which was recorded distally at the level of the knee. The peripheral end of the nerve was kept intact and connected to the skin. Records show the compound action potential consisting of two A components (Aβ and Aδ) and two C components, C1 and C2 as seen in the resting (control) situation (left-hand record). The long latency proves that the C volleys were conducted at a speed of about 1 m s^{-1}. Right-hand record was collected while the innervation zone of the nerve on the lower leg was stimulated continuously with light touch. It may be appreciated that the C1 component markedly decreased in size proving that its constituent fibers responded to innocuous touch. In contrast, the C2 component remained invariant indicating non-tactile functions

Douglas and Ritchie (1957, 1962) were the first to observe another key feature of tactile C axons of interest in relation to recent studies in man. They noticed that the propagation velocity of one component of the compound C fiber volley markedly decreased as a result of preceding activity. Remarkably, the slowing was prominent in nontactile C axons (component C2 in Fig. 1.1b), whereas it was not seen in tactile

axons (component C1 in Fig. 1.1b). (Note that the slowing is not illustrated in Fig. 1.1b.) They concluded that postactivation slowing of impulse propagation is a prominent feature of several kinds of C fibers, whereas it is largely lacking in tactile C afferents. The relevance of this difference for microneurography studies in man will be further discussed in a later section.

Single unit analysis of CLTMR was pioneered by Iggo and coworkers who presented detailed descriptions of response properties to innocuous touch, for example, high sensitivity to skin deformation, large response to hair movements, intermediate adaptation, and pronounced postactivation fatigue effect of the sense organ, which may last up to 30 min (Iggo 1960; Iggo and Kornhuber 1977). In 1971, an important publication from Perl's group (Bessou et al. 1971) emphasized a distinct difference between CLTMR and Aβ tactile afferents with regard to their dynamic response properties. They wrote that as the velocity of a glass rod "stroked across the receptive field … is progressively decreased, the frequency (of the discharge) … first increases and then declines". In myelinated tactile afferents, on the other hand, impulse rate increases monotonously with velocity of touch movement. In spite of the detailed information on functional properties of tactile C afferents extracted in these studies, Zotterman's tickle hypothesis was continuously accepted as it seemed supported by consonant demonstrations of long-lasting after-discharge (Bessou et al. 1971; Nordin 1990). A singular deviation from the tickle idea was advanced already by Douglas and Ritchie in their 1957 paper where they speculated in passing, without advancing any arguments that central effects of tactile C afferents might be at subconscious levels rather than in contributing to conscious percepts.

Identification of CT in Man

For some time low threshold C mechanoreceptors were thought to be lacking altogether in man. Twenty years of microneurography investigations failed to demonstrate them in human nerves, in spite of many studies focused on unmyelinated afferents. Hence, it was generally assumed that the tactile C-system had vanished altogether in the evolutionary progression to man, an idea supported by the finding that CLTMR afferents are less numerous in monkey than in cat nerves (Kumazawa and Perl 1977). The interpretation that human skin is not innervated by tactile C afferents was supported by studies of two different kinds. Psychophysical tests in normal subjects indicated that touch sensibility disappears when large afferents are blocked by pressure (Torebjörk and Hallin 1973; Mackenzie et al. 1975). Similarly, it was reported that the neuronopathy patients have "a total loss of the senses of touch, vibration, pressure and kinaesthesia" (Fourneret et al. 2002; Forget and Lamarre 1990). Neuronopathy is a rare condition when the cell bodies of the large myelinated afferents in dorsal root ganglions have been destroyed bilaterally over many spinal segments either as a complication to a virus disease or from repetitive attacks of polyneuropathy. As a result, only small diameter afferents remain from skin, muscles, and other deep structures. These studies all seemed to support the

prevailing view that tactile information is carried exclusively in large myelinated Aβ afferents. The problems that these patients are facing have been well described in a book written by a physician who carefully studied one of the neuronopathy patients (Cole 1995).

The first description of low threshold C-mechanoreceptive afferents in man was based on recordings from the face area. Nordin (1990) presented a decent sample, although one single unit had been described already 2 years earlier (Johansson et al. 1988). The interpretation that human tactile C afferents (CT) seemed to be present in the face area alone invited speculation that they might have a role in the pathological condition of trigeminal neuralgia (Nordin 1990). However, soon afterwards it was demonstrated that CT afferents are, in fact, quite numerous in hairy skin of upper and lower extremities, suggesting a wide distribution over the human body (Vallbo et al. 1993, 1999; Edin 2001).

It may be asked why microneurography failed to identify CT units during 20 years of intense studies of mechanoreceptive afferents starting in the late 1960s. It seems that two experimental selections were particularly relevant for this odd neglect. First, a major number of microneurography studies on tactile mechanisms were focused on the glabrous skin of the hand where CT afferents were never seen (Johansson and Vallbo 1983). Successively it has become more and more evident that CT are, in fact, lacking altogether in glabrous skin as they have not been reported from any microneurography laboratory. On the other hand, psychophysical findings in studies of mechanisms behind allodynia have suggested that there are afferents that share some properties with CT afferents (Nagi and Mahns 2013). Second, a large number of detailed studies of C afferents were pursued using a particular modification of the microneurography method, that is, the marking technique, described in more detail below (Hallin and Torebjörk 1974; Schmidt et al. 1995). The marking technique has a disadvantage in this context in that it largely fails to catch CT afferents, whereas it is well suited for analysis of nociceptive afferents. This strange effect is due to a unique axonal property of CT afferents as mentioned above, that is, their resistance to postactivation slowing of impulse propagation after repetitive firing. In addition, CT afferents seem to be scarce in the distal parts of the lower leg, which for many years was the region used in studies of nociceptive C afferents.

Microneurography Technique

Our present day knowledge of CT afferents' properties in man is largely based on recordings of impulse trains in single afferent using the microneurography technique developed by Hagbarth and Vallbo in the 1960s (Hagbarth and Vallbo 1968; Vallbo and Hagbarth 1968). A tungsten needle electrode, insulated to the tip, is inserted though the intact skin (Fig. 1.2a). Its position is manually adjusted until the tip attains an intrafascicular position and finally until the electrode discriminates impulses in a single nerve fiber of the kind you intend to study. Examples of single unit recordings from C afferents are shown in several illustrations, for example,

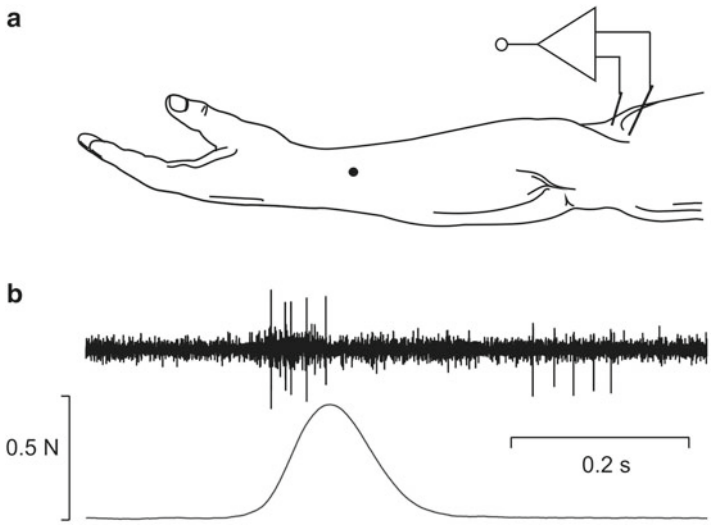


Fig. 1.2 Microneurography recording of tactile afferents. (**a**) Schematic illustration indicating location of touch stimulation on the forearm and recording device with the tungsten needle electrode in a cutaneous branch of the musculocutaneous nerve (lateral cutaneous antebrachial nerve). (**b**) Responses of an Aβ and a CT afferent to a tap stimulus. The two units had overlapping receptive fields located 274 mm from the recording site as schematically indicated in (**a**). The long latency of the CT response indicates a conduction velocity of about 1 m s^{-1}

Figs. 1.4, 1.8, 1.9, and 1.10. The electrode is freely floating in the soft tissue of the target region and it is only manipulated by hand. No micromanipulators or anesthetics are used. It might seem tempting to take advantage of the precision offered by micromanipulators to adjust electrode position, but they have not been found helpful. This is largely due to continuous movements of the target region with cardiac and respiratory cycles. If the electrode was fixed to an external micromanipulator, the tip would continually move within the nerve fascicle making impossible a stable recording of impulses from a single nerve fiber. Figure 1.2b shows a recording, which is unique because the electrode tip has appropriate contact with two tactile afferents having overlapping receptive fields. One is a myelinated Aβ afferent, whereas the other is an unmyelinated CT afferent. The difference in delay from the tap stimulus to impulse arrival at the recording site is striking. The difference in delay from skin deformation to impulse arrival in the brain suggests fundamental functional differences between the fast and the slow tactile system.

Although the microneurography technique is theoretically straightforward, it is in practice demanding, particularly in recordings of impulse trains from identified single nerve fibers. To attain an intrafascicular electrode position and, specifically, to discriminate impulses in a single nerve fiber of the kind you are interested to study may involve hours of manipulation under high mental concentration. Needle adjustments must be repeated in minute steps, guided by high-gain display of signals in the microvolt scale displayed on the computer screen. Important guidance is further

offered through a high-quality audio output from the amplifier where the faint sound of distant impulse trains in contrast to the continuous background of electronic noise and multiunit activity can be discerned. The experimenter is facing a particularly demanding task when exploring afferents from the hairy skin because most of the suitable nerves are very thin and therefore difficult to find and penetrate.

Impulse Shape Distinguishes Unmyelinated Fibers

An interesting and important feature of the microneurography recordings is that impulse shapes of myelinated and unmyelinated afferents are distinctly different. The predominant phase of C fiber impulses is always negative, whereas it is mostly positive in A fiber impulses (Fig. 1.3). C fiber impulses are triphasic suggesting a true extracellular recording. A similar triphasic shape is occasionally seen with myelinated afferents, presumably when the electrode tip is close to the regenerative membrane of a node of Ranvier. However, in the vast majority of single unit recordings from A fibers, impulses are diphasic with the initial and predominant phase in the positive direction. As impulses in multiunit recordings of A fiber activity seem to have similar diphasic shapes, the most reasonable interpretation is that the electrode sees, from an extracellular position, the current flowing through the myelin of the internode.

It should be noted that the electrical equivalent of the microneurography electrode in body tissues is a small capacitor rather than a resistance, in contrast to what one might intuitively presume (Westling 1972). Hence, we have, very likely, a capacitive coupling through the myelin. When impulses of a single A afferent stand out from the background activity by size (Fig. 1.2), the high amplitude is probably a consequence of reduced myelin thickness due to pressure from the electrode.

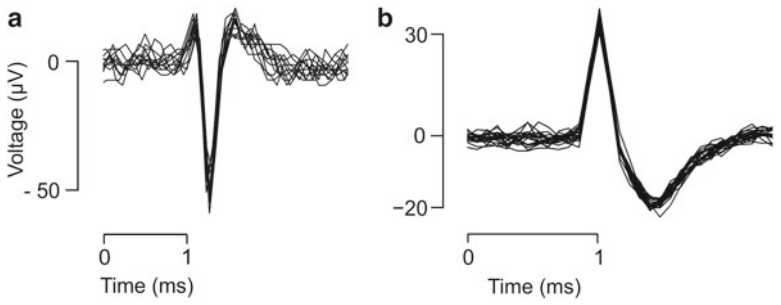


Fig. 1.3 Shapes of C and Aβ impulses in microneurography recording. Typical contours of nerve impulses in unmyelinated (**a**) and myelinated (**b**) nerve fibers. The former are always triphasic with a dominant negative phase, whereas A spikes are nearly always diphasic with the dominant phase in positive direction

More complex shapes are occasionally seen. In long-lasting recordings, the predominant phase of A fiber impulses may develop two peaks, due to a local conduction delay. The phenomenon is consistent with the interpretation that the electrode causes a thinning of the myelin to the extent that a fair amount of the depolarizing current is lost to the outside at the electrode site (Vallbo 1976; Inglis et al. 1996). Similar phenomena are never seen with C fibers.

Marking Technique

An important modification of the original microneurography technique was introduced by Hallin and Torebjörk (1974). The modification has been denoted the marking technique. It is based on a unique feature present in most kinds of unmyelinated axons; a pronounced decrease of conduction velocity in the wake of preceding impulses. Separate classes of unmyelinated nerve fibers exhibit different degrees of postactivation axonal slowing allowing clear identification.

The marking technique is highly rewarding in analyses of C afferents as it allows the identification of several units in a single recording. On the other hand, its potential is limited compared to impulse train recordings in analysis of stimulus response relations, dynamic characteristics of sense organs, and psychoneural correlation studies.

Moreover, as pointed out above the marking technique is ineffective with CT afferents because they exhibit very little axonal slowing and therefore cannot readily be identified.

Subject Care in Microneurography Experiment

In microneurography experiments, it is important to pay proper attention to the subject's emotional state and reactions. Although pain is seldom intense, there is still a risk of vagal reactions with unpleasant dizziness, or occasionally even fainting, probably more related to subject's worry in combination with exotic sensations rather than sheer pain. It is important that the experimenter strives to establish a confident relationship and prepare the subject in detail for the sensations to come when the needle electrode goes through the skin, the subcutaneous tissue, and through the nerve sheath. Ideally, the experimenter should have the experience of being a subject herself/himself to be able to give a well-informed introduction. Although pain is not prominent, the demand on the subject is considerable because she/he must keep an almost identical position for hours. Small and relatively slow movements of limbs are acceptable, whereas electrode position is jeopardized by many moderate limb movements.

Psychoneural Potential

An essential advantage of the microneurography technique is that anesthetics are not involved. Hence, sense organs and afferents are unaffected and, as subjects are fully awake, they may report in detail their sensations and cooperate in psychophysical and psychomotor tests while impulses in a single afferent are monitored. An illustrating example concerns the tickle hypothesis. Subjects' reports of their cutaneous sensations during microneurography recordings have amply demonstrated that there is no correlation between CT-firing and tickle sensation (Wiklund-Fernström 2004). This provides a direct argument against the tickle hypothesis which had been cherished for decades in the literature.

An additional tool for psychoneural correlation analyses is offered by the combination of microneurography recording, microstimulation, and psychophysical tests. Microstimulation of an identified afferent allows the assessment of effects of an individual afferent in the alert human brain, perceptive as well as neurophysiological (Trulsson et al. 2001; Ochoa and Torebjork 1983; Vallbo et al. 1984). This approach has been successful with large myelinated nerve fibers, whereas microstimulation of single unmyelinated afferents has not been accomplished. This is very likely related to the well-known fact that the threshold for excitation with electrical pulses is inversely related to fiber diameter. The high intensity required to excite an unmyelinated nerve fiber will inevitably excite a number of adjacent myelinated fibers as well.

Distribution, Terminal Organization, and Axonal Properties

The presence of the slow tactile system has been verified in the skin of face, forearm, and leg. More specifically, afferent impulses in unmyelinated CT fibers have been recorded in the small supra- and infraorbital nerves innervating facial skin, in lateral and dorsal ante-brachial cutaneous nerves innervating the hairy skin of the forearm and hand dorsum, and in the lateral cutaneous femoral and peroneal nerves innervating the thigh, lower leg, and the foot (Johansson et al. 1988; Nordin 1990; Vallbo et al. 1993, 1999; Edin 2001; Wessberg et al. 2003; Löken et al. 2007, 2009). On the other hand, nerves innervating the skin of the trunk have not been exploited so far. Although these findings strongly suggest that CT innervation of human skin is ubiquitous, a distinct exception is indicated by the fact that CT has never been encountered in recordings from the glabrous skin of the hand in spite of extensive analyses of tactile afferents in this skin area. Further, there is no indication that the lack of CT recordings from the glabrous skin can be ascribed to experimental factors because an identical approach and recording technique was used in explorations of hairy and glabrous skin. Moreover, the difference between hairy and glabrous skin in man is consistent with findings in cats, rodents, and nonhuman primates where the slow tactile system, that is, CLTMR afferents have never been found in nerves supplying foot pads or monkey glabrous skin. As in humans,

CLTMRs are abundant in hairy skin of these species (Bessou et al. 1971; Kumazawa and Perl 1977; Georgopoulos 1976; Liu et al. 2007). However, interspecies correlations must not be stretched too far in these respects considering that animal CLTMR include several functional groups of different properties and recent psychophysical studies argue that CT functional homologues might be present in human glabrous skin (Nagi and Mahns 2013).

Why No CT in Glabrous Skin?

It seems tempting to search the explanation in evolution for the difference between glabrous and hairy skin regarding CT innervation in man.

The pad skin of furry animals which is the homologue of human glabrous skin was primarily designed to take the wear and tear of walking and running. It was equipped with fast-conducting mechanosensitive afferents with the prime role to provide information required for the control of muscle actions, whereas it is not used in affective touch in most species as far as we know. Hence, CT innervation would be superfluous in pad skin of many nonprimate mammals. The human hand, on the other hand, has achieved a number of additional and more complex tasks, one being caressing gestures in affective conspecific touch. It seems that the primary mechanoreceptive innervation of the pad skin consisting of fast-conducting Aβ afferents alone has been preserved during evolution in spite of the potential role of human glabrous skin in affection. However, the quality of pleasant sensation that humans experience when being touched on glabrous and hairy skin differs to some extent as demonstrated in psychophysical tests and neuroimaging studies (Löken et al. 2009; McGlone et al. 2012; Ackerley et al. 2014a, b; Guest et al. 2014).

Density of CT Afferents

Although microneurography is not suited for the assessment of proportion of separate types of mechanoreceptive afferents in a nerve, a qualitative statement seems warranted on the basis of the common experience that CT afferents are encountered roughly as often as Aβ units in forearm skin nerves (Vallbo et al. 1999; Löken et al. 2009). This finding suggests that the density of CTs is at least as high as the density of Aβ units. This conclusion seems particularly justified since the microneurography technique should favor large nerve fibers. A monkey study indicates a proximodistal gradient with fewer CLTMR in the distal parts of the extremities (Kumazawa and Perl 1977). A similar gradient is suggested in a human study focused on distal hairy skin (Löken et al. 2007). Only a few CT afferents were found on hand dorsum and in lower leg in recordings from the radial and peroneal nerves. For instance, in the peroneal nerve only 3 CT were identified in 14 experiments. As considered in a previous section, the shortage of CTs in the distal parts of the lower extremities might be one factor why CTs failed to be recognized in man for so long.

To summarize, present data suggest that CTs are abundant in the hairy skin of the human body, scarcer in the distal parts of the extremities and seem to be lacking altogether in the glabrous skin.

The human findings on this point fit with recent studies in rodents using genetic labeling and visualization of axonal endings in skin and spinal cord. Cell counts revealed that CLTMR cells constitute a very large proportion in dorsal root ganglions (DRG), by far outnumbering low-threshold Aβ mechanoreceptive afferents (Li et al. 2011). Higher densities of CLTMR cells were found in DRG innervating proximal limb areas and trunk than in segments innervating distal limb areas. Interestingly, CLTMR cells are particularly numerous in sacral segments which innervate the genital region although CLTMR afferents seem to be lacking in the nonhairy skin of rodent genitalia (Li et al. 2011, suppl. material). Moreover, it was shown that CLTMR terminals are absent altogether in rodent pad skin, as considered above.

Receptive Field Characteristics

The receptive field of a cutaneous mechanoreceptive afferent is usually defined as the skin area where adequate stimuli are effective to produce afferent impulses. It should be noted that this definition is not very distinct because the extent of the effective skin area is dependent on stimulus characteristics. For instance, in the study to be described below, a doubling of indentation force increased measured field size, on the average, by a factor of 2. Receptive fields have often been assessed using von Frey bristles (Iggo 1960; Bessou et al. 1971; Iggo and Kornhuber 1977; Kumazawa and Perl 1977; Shea and Perl 1985; Nordin 1990). A widely accepted convention is to define the field as the area where a four to five times threshold stimulus is effective (Johansson and Vallbo 1980). The von Frey approach is informative, but it is not optimal for a more detailed analysis of field topography. The findings presented below and in Fig. 1.5 are based on a more sophisticated technique. A light probe was made to move in closely adjacent tracks over the relevant skin area of the subject's forearm while single unit impulses were continuously captured for offline analysis (Fig. 1.4) (Wessberg et al. 2003). Using this approach it was found that human CT fields ($n=9$) vary considerably in size and complexity (Fig. 1.5). It may be a single spot, about 0.25 mm^2 in size or it may include up to

Fig. 1.5 Topography of sample receptive fields in human hairy skin. Field maps are based on data collected with the scanning method illustrated in Fig. 1.4. The two left-hand panels show the smallest and the largest CT field encountered. The other panels show typical fields of four kinds of Aβ tactile afferents identified in human hairy skin, that is, SAI (Merkel), SAII (Ruffini), hair, and field units. Note scale differences demonstrating larger receptive fields of hair and field units. One kind of mechanoreceptive afferent is lacking, that is, Pacinian type which is encountered only occasionally in hairy skin nerves. The procedure to produce the color-coded plots involves a certain degree of smoothing of contrasts. Hence, the true fields are more ragged than shown in the illustration

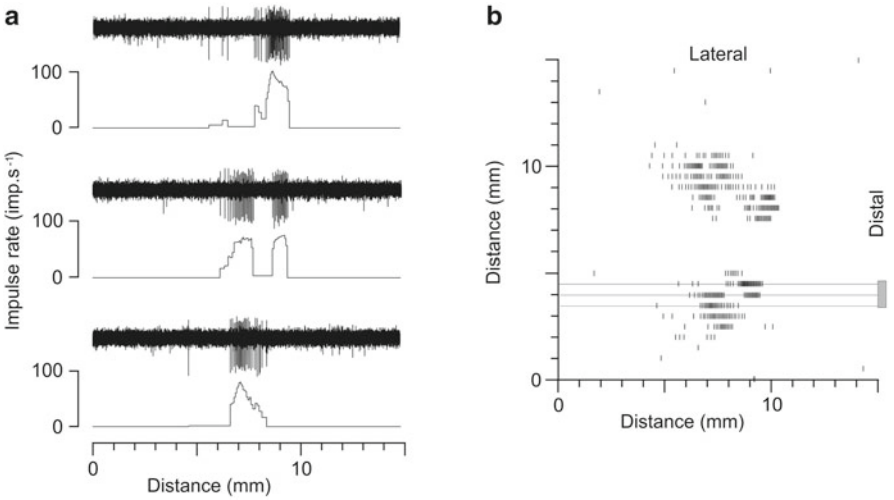
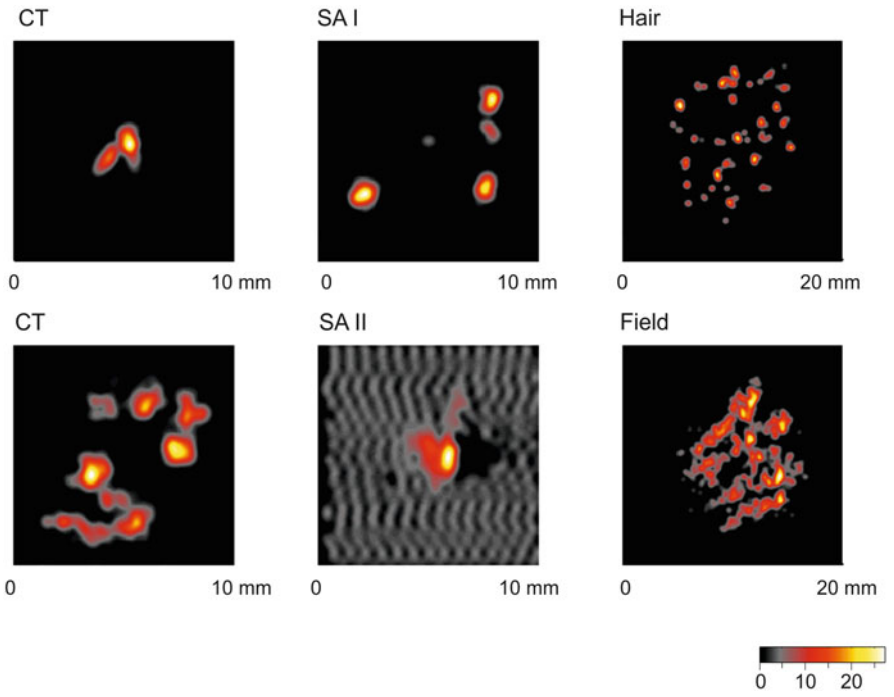


Fig. 1.4 Scanning procedure to explore receptive field topography. (**a**) Responses of a CT afferent to a scanning probe moving over the skin surface in three adjacent tracks, 0.23 mm apart. Indentation force was 2.2 mN. (**b**) XY plot of total scanned area of a CT field. Impulses are indicated by *vertical lines*. The three traces shown in (**a**) are indicated with *thin lines* in (**b**)



nine hotspots distributed over an area of 35 mm^2; mean field size was 7 mm^2 (s.d. 8 mm^2). The separate hot-spots within an individual field varied to some extent in sensitivity, as well as in size as illustrated in Fig. 1.5. Fields are roughly oval in shape with no preferred orientation. No dependence on location along the forearm emerged. This field analysis indicates that the stem fiber of a CT afferent commonly branches to terminate with a varying number of clusters of sensory terminals irregularly distributed within a relatively small area, rather than providing a continuous mesh of responsive terminals as suggested by many previous studies based on hand-held field exploration. Fields of similar structure and size have been described for presumed CLTMR afferents in the mouse hairy skin on the basis of histochemical methods (Liu et al. 2007). On the other hand, studies in rodents indicate that the population of CLTMR in animals is not homogenous but may include several subgroups, an issue that has not been explored in man. Hence, it is not valid to stretch interspecies uniformities too far.

Conduction Velocity

The slow impulse propagation in CTs is readily demonstrated in microneurography recordings using tap stimuli where the long latency from stimulus to impulse response is easily perceived through headphones or loudspeakers. Particularly striking is the contrast between CT and myelinated responses where the latter are perceived to occur right at the onset of stimulus, whereas CT impulses occur much later due to a 30–50 times difference in propagation velocity (Fig. 1.2). Conduction velocity of CT afferents is about 1 m s^{-1} (0.6–1.2 m s^{-1}) as assessed from the unit's response to mechanical stimuli. Activation of the afferent by electrical pulses which bypasses several peripheral processes gives a slightly shorter latency and hence a higher conduction velocity (about 10%). Data from the two modes of stimulation correlate well ($r=0.8$), indicating that distinct tap stimuli are adequate to demonstrate conduction velocity in the C fiber range. Neither significant correlation has been found between conduction velocity of individual afferents and location of receptive field along the extremity, nor with other functional properties of CT units.

Conventional Test Stimuli Demonstrate Functional Differences Between Aβ and CT Systems

A traditional approach to assess physiological properties of cutaneous mechanoreceptors is to explore responses to perpendicular skin indentations. A number of fundamental features are usually assessed with this technique, for example, threshold, sensitivity, response characteristics to static and dynamic skin deformations, adaptation, and dependence on previous history. This approach is adequate to investigate basic properties and define distinctive characteristics suited for comparison

with other kinds of mechanosensitive units, that is, nociceptive and Aβ afferents. However, analyses of CT response to perpendicular indentations fail to capture essential features of the CT system which are significant for the current hypothesis on its role in affective and social touch. Accordingly, we consider separately conventional analyses using local skin indentations, on the one hand, and analyses which are largely driven by the social touch hypothesis, on the other.

Sensitivity

One aspect of mechanoreceptor sensitivity is the absolute threshold, that is, the minimal stimulus required to evoke a response. This is most easily explored using handheld von Frey bristles providing threshold values in terms of indentation force. A sample of C mechanoreceptive afferents is illustrated in Fig. 1.6 (Vallbo et al. 1999). The primary inclusion criteria were conduction velocity in the C range and response to innocuous finger stroking over the skin surface. The fact that the histogram of Fig. 1.6 is bimodal suggests that innocuous touch activates two types of C afferents. As will be further considered below, several findings indicate that the left-hand group represents CT afferents, whereas the right-hand group represents non-CT afferents. Thresholds of the CT sample are 0.3–3 mN with a median of 1.3 mN ($n = 24$). Values

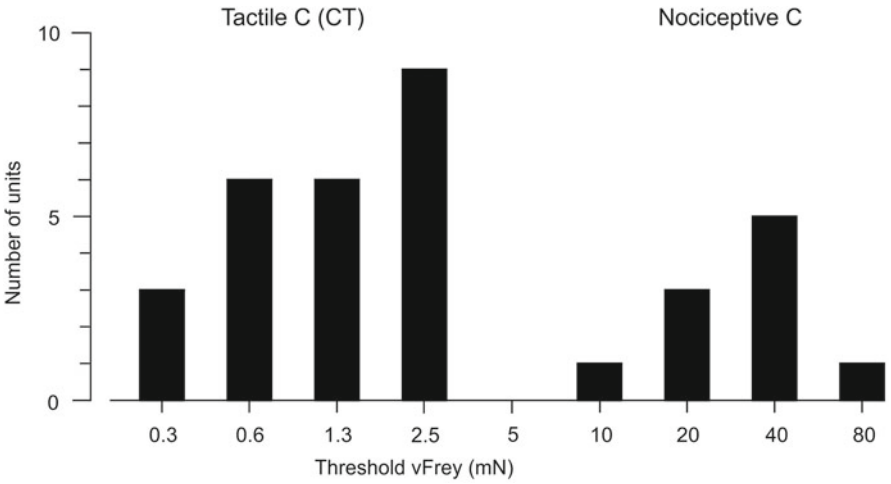


Fig. 1.6 Absolute thresholds of C mechanoreceptive afferents. Thresholds of 34 unmyelinated afferents as assessed with von Frey bristles. Inclusion criteria were any impulse response to innocuous touch beside conduction velocity in the C range. Left-hand group represent CT afferents. Their thresholds ranged from 0.3 to 2.5 mN with a median of 1.3 mN ($n = 24$). The right-hand group represents non-CT afferents usually denoted nociceptive mechanoreceptive afferents

above 5 mN suggest non-CT afferents which are commonly classified as nociceptive units. They do respond to innocuous touch but just weakly, producing one or a few impulses to finger stroking.

Although the von Frey bristle approach to assess force threshold is simple in principle, the procedure requires due experience as well as attention to the possible fine grain topography of the receptive field. Obviously, if the bristle fails to hit the most sensitive spot within the receptive field, a higher value than the minimal is collected. Therefore, it might be misleading to emphasize moderate discrepancies between threshold data collected in different laboratories (Nordin 1990; Vallbo et al. 1999).

It is of interest to compare sensitivities of CT and Aβ afferents. Unfortunately, strictly comparable observations are scant but available data suggest average force thresholds of CTs are roughly twice that of Merkel and presumed Meissner's in the hairy skin (SAI and RA/FAI). More specifically, Meissner and Merkel thresholds of 0.5 mN have been reported in studies of facial and forearm skin respectively (Meissner, facial skin, $n = 6$, median; Merkel, forearm skin, $n = 10$, mean) (Johansson et al. 1988; Vallbo et al. 1995).

It should be evident from the threshold data presented above that light touch will excite both myelinated and unmyelinated afferents. Hence, stimuli targeted for CTs must be based on other response properties than sensitivity to local indentation.

Impulse Rates

Although the sensitivity is similar in the slow and the fast tactile systems in terms of threshold to von Frey bristles, the response properties differ between CT and Aβ afferents in many other respects as will be exposed in the following sections. A striking difference refers to the range of impulse frequencies. Maximal rate is much lower in CT than in Aβ afferents which may produce 800–1500 impulses s^{-1} as shown in animal experiments (Burgess et al. 1968; Iggo and Muir 1969). Figure 1.7 illustrates that stroking with a soft brush across CT receptive fields evokes peak impulse rates between 50 and 100 s^{-1} in a majority of the afferents. Although these rates are not very impressive compared to firing of Aβ afferents, they are, in fact, relatively speaking very high considering that maximal rate of C mechanoreceptive afferents as found in animal experiments is 100 impulses s^{-1} (Iggo 1960). Incidentally, the bottleneck is probably not the axon because it has been found that cat CLTMR afferents may carry about three times higher impulse rates when stimulated with electrical pulses (Franz and Iggo 1968).

As might be expected from interunit variation in force threshold of CT afferents, response to suprathreshold stimuli varies between individual CT afferents as well. Figure 1.7 shows that maximal firing rate to the semistandardized stimulus (brush stroking) is higher the lower the threshold of the unit as assessed with von Frey bristles. Thus, it seems that these two measures essentially capture the same property of the individual afferent. The histogram of Fig. 1.6 shows that threshold difference between borderline CT and borderline nociceptive afferents is not large. Moreover, the scatter plot of Fig. 1.7 might suggest a continuum between the two

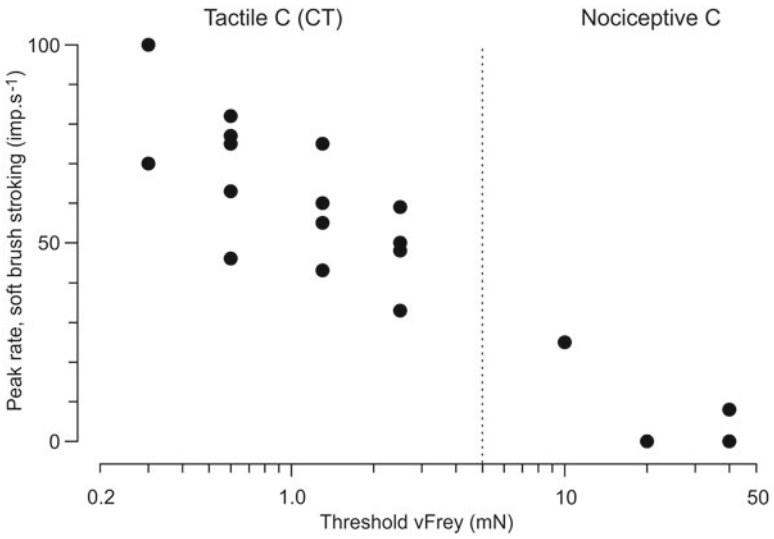


Fig. 1.7 Impulse rate to light touch stimulus versus afferents' thresholds. Peak rates to soft brush stroking over the receptive field versus von Frey thresholds. Units with thresholds above 5 mN are classified as nociceptive afferents. Subsample of the material shown in Fig. 1.6

kinds. However, a distinct difference emerges when responses to noxious and innocuous stimuli are compared (Nordin 1990; Vallbo et al. 1999). The left-hand traces in Fig. 1.8 illustrate that CT responses are similar with the two kinds of stimuli in spite of the marked difference in sensation produced by the pointed and rounded probe employed. In contrast, responses of the nociceptive afferent differ substantially because the response to the noxious stimulus is prominent, whereas the innocuous stimulus gives no response in this test (Fig. 1.8, right-hand traces). The examples of Fig. 1.8 are representative. Moreover, the difference is supported by statistical analyses, although the sample is small (Wilcoxon $P<0.01$, $n=5$). A further analysis with focus on borderline afferents would be of interest to test the suggestion that CTs regularly fail to distinguish between noxious and innocuous stimuli, whereas another set of C afferents (nociceptive) readily do.

Fatigue and Recovery

A distinguishing response feature of CT-units versus myelinated tactile units is that sensory endings of CTs exhibit a pronounced postactive depression. This fatigue effect is illustrated in Fig. 1.9a, showing a marked decrease of the response after a single stimulus. When a series of successive indentations are delivered, the response usually decreases with the first 2–4 stimuli to settle around a submaximal level which is dependent on interstimulus interval, as illustrated in Fig. 1.9b. Incidentally,

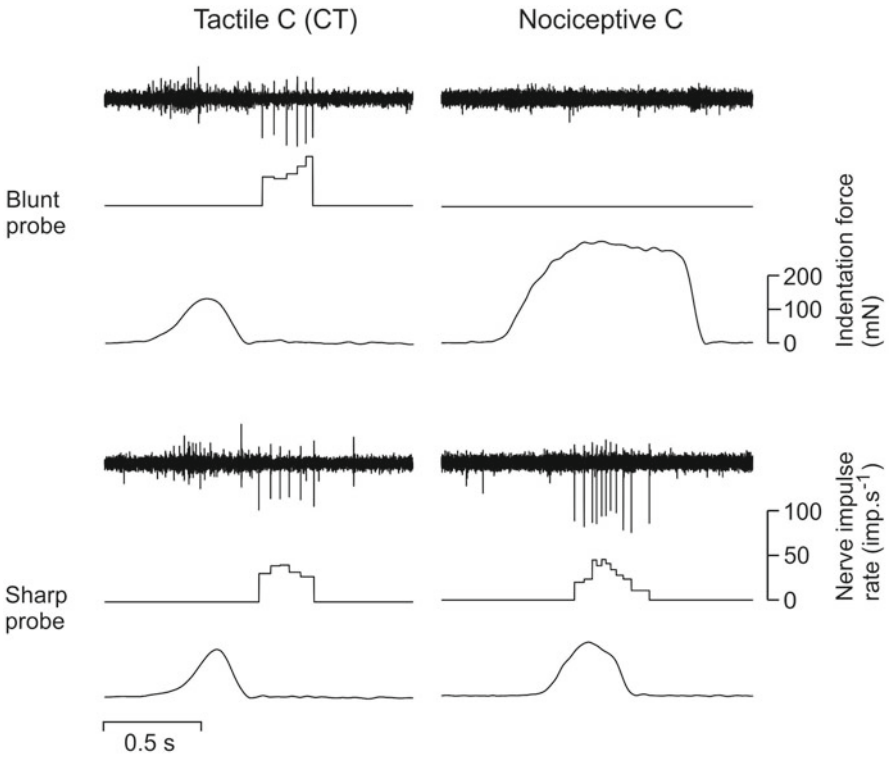


Fig. 1.8 Difference between CT and nociceptive C response to mechanical stimuli. Stimuli were local skin indentations delivered with a blunt probe (*above*) and a pointed probe (*below*), both connected to a handheld strain gauge device

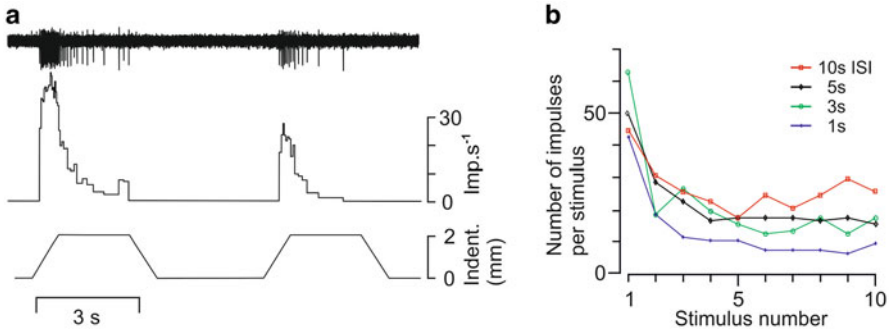


Fig. 1.9 Fatigue in a CT afferent. (**a**) Record shows the marked difference between the response to the initial stimulus and the second one delivered shortly (3 s) later. A resting period of about 60 s preceded the first stimulus. (**b**) Fatigue curves of a CT afferent repeatedly stimulated as in Fig. 1.9a at varying intervals. *Blue*, *green*, *black*, and *red curves* represent data with pauses of 1, 3, 5, and 10 s between stimuli, respectively

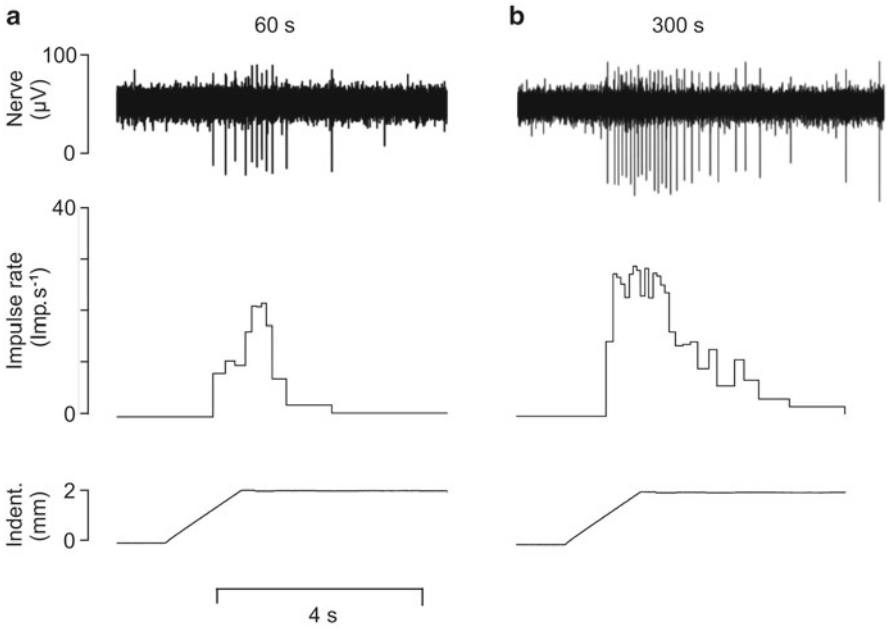


Fig. 1.10 Long-term postactivation recovery. Records show responses of a CT afferent to identical stimuli delivered after resting periods 60 and 300 s length

the curves in Fig. 1.9b illustrate a phenomenon consistently encountered in studies of CT afferents in man, that is, that the response to identical stimuli varies substantially from one test stimulus to the other for reasons which remain to be explored.

Another unique property of CT afferents is that the postactivation fatigue may be very long lasting. This is illustrated in Fig. 1.10 by the difference in response to identical stimuli which are delivered after a recovery period of 60 s versus 300 s. It may be appreciated that the response after the longer resting period is substantially larger in terms of impulse rate, number of impulses, as well as duration of discharge. There are indications that full recovery may take several minutes. However, systematic analyses regarding development of fatigue and time course of recovery remain to be pursued in man. In studies of cat CLTMRs, it has been pointed out that restoration may take several (4–30) minutes (Iggo 1960; Iggo and Kornhuber 1977). Mechanisms accounting for the depressant effect of preceding mechanical stimulation have not been explored in man. However, an analysis of cat CLTMRs suggests that important factors are transducer-bound events rather than events in conducting elements of the terminal arborization (Iggo and Kornhuber 1977). The slow recovery process implies that CT afferents are substantially more responsive to an initial touch stimulus than to succeeding stimuli. It may be speculated that the system is designed to make us more inclined to appreciate a friendly touch when first perceived. It remains to be explored if larger hedonic effects can be documented in psychophysical tests and in fMRI explorations when a skin area has remained untouched

long enough to have the CT population fully recovered. In addition, the pronounced and long-lasting fatigue in CT afferents may have significant implications of relevance for interpretation of certain microneurography findings. It seems likely that most, if not all, published CT data have, in fact, been collected from fatigued units considering that the search procedure in the experiments involves continual stroking of the test area. As a result, it must be assumed that CT units are depressed from maximal responsiveness already in the initial part of the experiment. Hence, the probability is low of encountering an unfatigued CT afferent. Occasional observations seem to support this interpretation. In a small minority of experiments, we have encountered a dramatically deviant activity, that is, a uniquely strong response to a light touch followed by an intense and long-lasting after-discharge. This kind of response has been rarely seen and only in the very beginning of an experimental session. Unfortunately it has not been possible to document this impressive response.

Adaptation

Another clear difference between the slow and fast tactile afferents concerns the response to sustained skin deformations. Aβ afferents fall in two distinct groups in this respect. Fast adapting units respond to dynamic events alone, but not to steady-state deformation, that is, they lack all static sensitivity. This is true with Pacini, Meissner, hair follicle, and field units. Slowly adapting Aβ afferents (Merkel and Ruffini), on the other hand, provide a continuous discharge during sustained skin deformation for minutes or more, albeit at a decreasing impulse rate over time. CT afferents, on the other hand, differ from both types, because they have intermediate adaptation properties in the sense that they respond initially with a burst of high impulse rate which successively decreases to zero after a few seconds of sustained indentation as illustrated in Figs. 1.9, 1.10, and 1.11a. Occasionally, an even more deviant response of CT afferents has been seen, that is, a late resumption of firing while a steady indentation is maintained. Figure 1.11b shows a representative example of delayed acceleration. It may be appreciated that the activity decreased to nearly null for a few seconds after the initial response to skin deformation. Then firing reassumed and continued for about a minute. The impulse rate was first highly irregular followed by a period of more regular discharge. Impulse rate increased to a peak of about 50 impulses s^{-1} and then fell to zero within 40 s after the peak. Among the CT afferents that exhibit delayed acceleration, the time course varies between tests and units. The example in Fig. 1.11 is an extreme whereas the duration is shorter in most cases. As the response to long-lasting steady indentation has not been systematically tested, the proportion of units exhibiting delayed acceleration is not clear, but it seems to be present in only a minority of units.

The mechanisms and the functional significance of delayed acceleration remain to be explored. On the other hand, the finding is of some interest from psychoneural point of view because the subjects consistently reported no change of the sensation when the intense firing of the CT afferent occurred. Thus, it seems that activity in a single CT afferent fails to influence the sensation of sustained skin deformation.

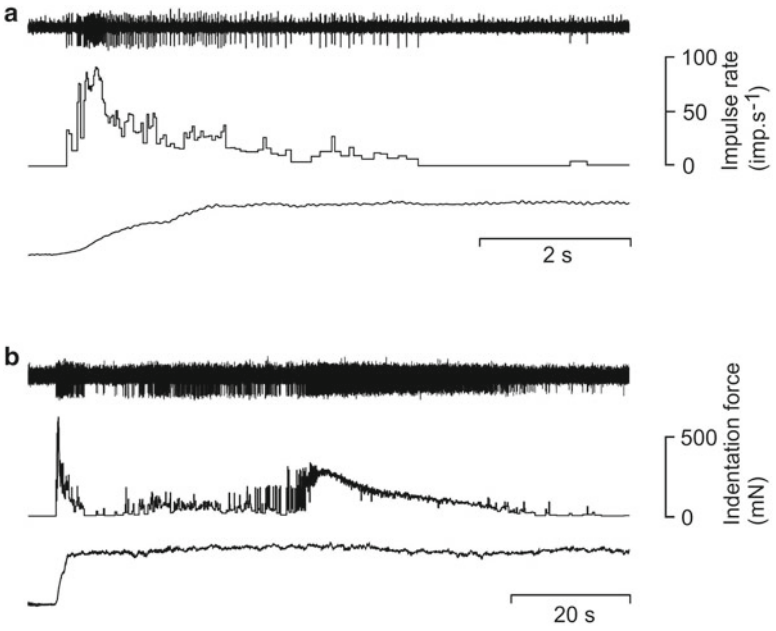


Fig. 1.11 CT response to sustained indentation. (**a**) Sample record to illustrate intermediate adaptation typical for CT. (**b**) Delayed acceleration of impulse discharge started after about 10 s. (**a**, **b**) Originate from the same recording displayed on different time scales

After-Discharge and Tickle Hypothesis

Long-lasting after-discharge in thin mechanoreceptive afferents was originally described by Zotterman (1939) in the cat and led him to formulate the tickle hypothesis, that is, that an essential role of unmyelinated tactile afferents is to account for the ticklish sensation associated with light touch. Microneurography studies confirm that there is a marked difference between the fast and the slow tactile systems in man with regard to after-discharge. In Aβ afferents, there is usually no activity after stimulus removal, whereas a prominent and sometimes long-lasting after-discharge is seen in CTs as illustrated in Fig. 1.12. On the other hand, after-discharge in CT afferents is highly dependent on temperature, as it is more frequent and more prominent at lower than neutral temperatures. In a sample of 15 CT units, after-discharge was seen in 80 % at 15 °C, but in only 13 % at higher temperatures (32 and 42 °C) (Wiklund-Fernström 2004).

Qualitative observations on psychoneural correlations, including delayed acceleration considered above, suggest that there is no correlation between tickle sensation and discharge in CT afferents. Moreover, it has been repeatedly observed that neuronopathy patients who lack large mechanoreceptive afferents cannot be tickled (Cole et al. 2006). These two findings seem to provide strong evidence for the interpretation that tickle sensation is not dependent on unmyelinated CT afferents but rather on Aβ afferents.

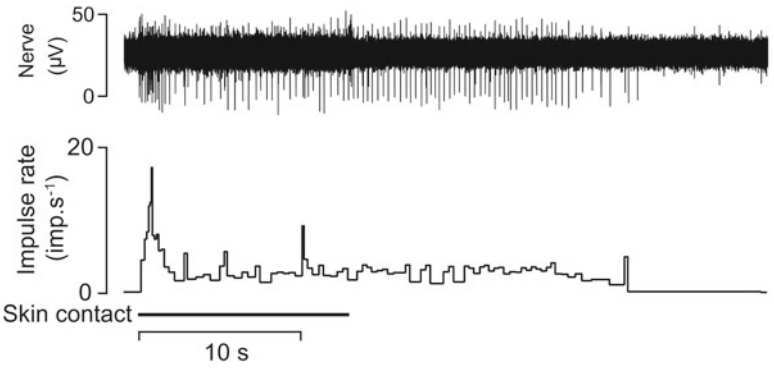


Fig. 1.12 After-discharge at low temperature. Sustained indentation indicated by bar was followed by an unusually long-lasting after-discharge which usually occurs with low temperature only. Skin temperature 15 °C

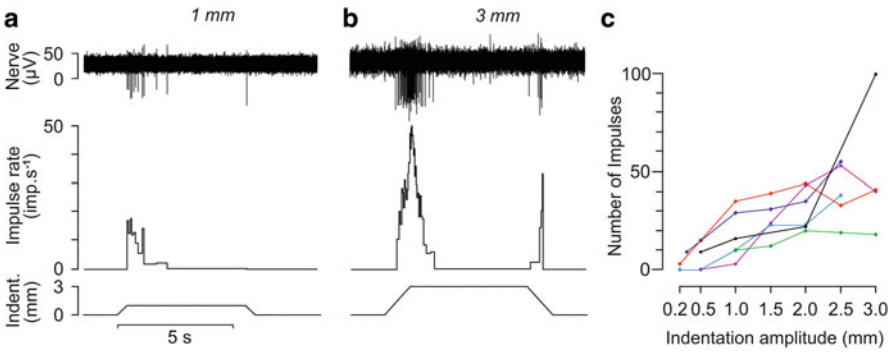


Fig. 1.13 Dependence of CT response on indentation amplitude. (**a**, **b**) Sample records from an afferent stimulated with two different indentation amplitudes. Note off responses. (**c**) Stimulus response curves for six CT afferents demonstrating effect of indentation amplitudes

Response to Amplitude of Skin Deformation

As with other kinds of cutaneous mechanoreceptive units, CT afferents are sensitive to the amount of local skin indentation as illustrated in Fig. 1.13. However, a difference is that CT afferents tend to respond less consistently to local indentations than Aβ mechanoreceptive afferents. Hence, stimulus response relation curves often emerge as irregular, nonmonotonous, and highly varying between individual CT units (Fig. 1.13c). No attempt has been made to explore which factors may account for the poor consistency of the CT response in man. However, it is noteworthy that the finding shown in Fig. 1.13c seems to clash with data from a study of CLTMR afferents in the cat where high correlations are reported between indentation amplitude and unit response (Iggo and Kornhuber 1977). To what extent this difference is related to heterogeneity of CLTMRs in furry animals remains to be explored.

Response to Hair Movements

Qualitative observations indicate that human CT afferents do not regularly respond to hair movements. A small response may be seen with large hair movements, possibly due to deformation of the skin outside the hair follicle. Whether CTs are excited by movements of the small vellus hairs has not been specifically tested, although it seems unlikely because air puffs are generally not effective (Ackerley et al. 2014a, b). These observations are in marked contrast to findings on CLTMR response in furry animals. A number of electrophysiological studies emphasize response to hair movements (Iggo 1960; Iggo and Kornhuber 1977; Douglas and Ritchie 1957) although there is a single exception (Bessou et al. 1971). Moreover, recent morphological studies using molecular-genetic labeling show that CLTMR regularly innervate hair follicles in rodents (Li et al. 2011; Zimmerman et al. 2014).

Psychoneural Analyses Indicate Hedonic Potential of the CT System

In response to a moving touch stimulus most mechanoreceptive afferents respond with higher impulse rate the faster the movement. However, this is not true with CT afferents. A unique feature of particular significance for the hedonic touch hypothesis is their relatively poor response to fast-moving stimuli (Nordin 1990; Vallbo et al. 1999). Figure 1.14 illustrates that human CTs respond with a similar impulse rate when a probe is moving across the skin at a low speed and at a five times higher speed. A more detailed analysis of CT impulse rate as a function of speed of a touch stimulus moving over the skin surface is illustrated in Fig. 1.15a.

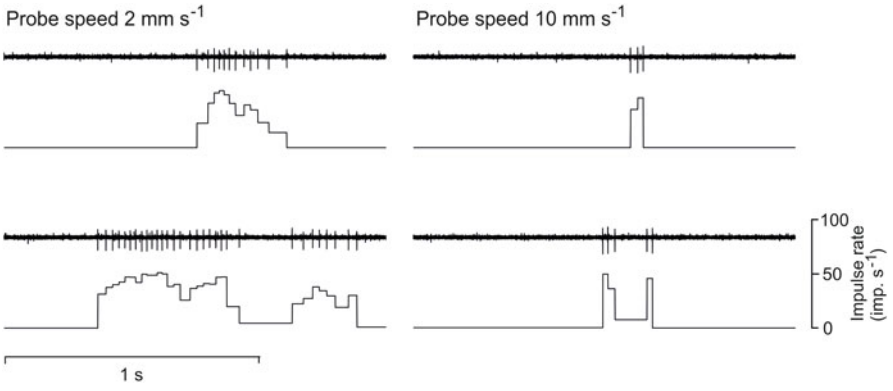


Fig. 1.14 Low sensitivity of CT afferents to speed of a moving stimulus. Responses of two afferents (upper and lower records) to touch stimuli moving over the skin surface at two different speeds. Indentation force was 2 mN. Stimulus delivered with a rounded probe

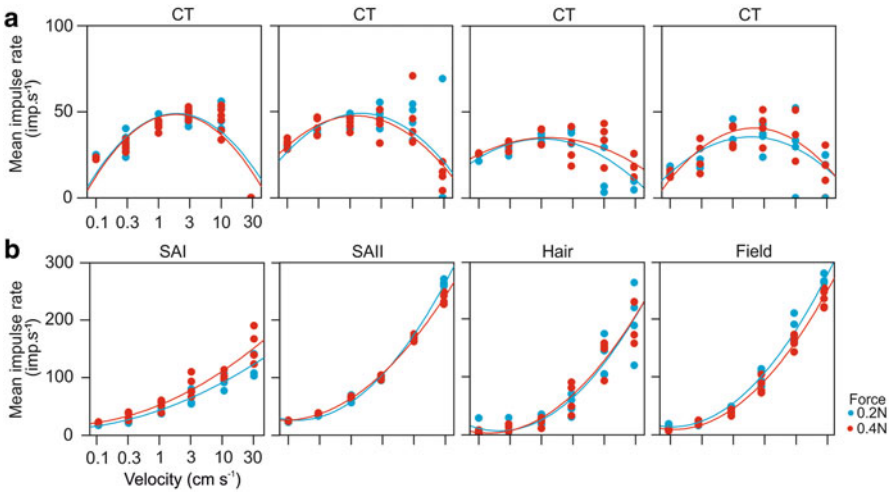


Fig. 1.15 Responses to moving touch stimuli. Contrast between Aβ and CT afferents. CT exhibit tuning to intermediate speeds of movement, whereas all types of Aβ afferents exhibit monotonous increase of impulse rate with speed of movement. Panels show data from individual units. Two different indentation forces (0.2 and 0.4 N) as indicated by *color code*. Stimulus was delivered with of a soft water color brush moving along the skin surface. Note difference in Y-scales with CT and Aβ units

The response increases to a peak at stroking velocities in the range 1–10 cm s^{-1}, whereas it levels off at higher and lower speeds. Hence, human CT afferents are tuned to a relatively slow speed of movements across the skin (Löken et al. 2009; Ackerley et al. 2014a, b). In contrast, impulse rates in Aβ mechanoreceptive afferents increase monotonously with the speed of a touch stimulus moving over the skin surface as illustrated in Fig. 1.15b for four different types of tactile afferents in the hairy skin.

For most people, a caring hand slowly moving over your skin surface gives a more pleasant sensation than a fast movement (Essick et al. 1999). A pertinent question is to what extent our feeling of pleasantness may match the impulse rate of the CT afferents. Figure 1.16 illustrates that subjects' estimates of pleasantness (middle diagram) are similarly tuned to the speed of movement as the response of CT afferents (left-hand diagram). The correlation between the two measures is highly significant (right-hand diagram) (Pearson's linear regression, $R^2 = 0.70$, $P < 0.001$) (Löken et al. 2009). On the other hand, there is a striking mismatch between the estimate of pleasantness and impulse rates of the myelinated tactile afferents as is obvious from data in Figs. 1.15 and 1.16. The difference between firing of CT and Aβ mechanoreceptive afferents in relation to subjects' estimates of pleasantness provides a direct support for the role of CT afferents as a system of significance for boosting the hedonic aspect of skin contact.

It is noticeable that the tuning of unmyelinated tactile afferents to relatively slow velocity of stimuli moving across the skin surface was described in the cat already in

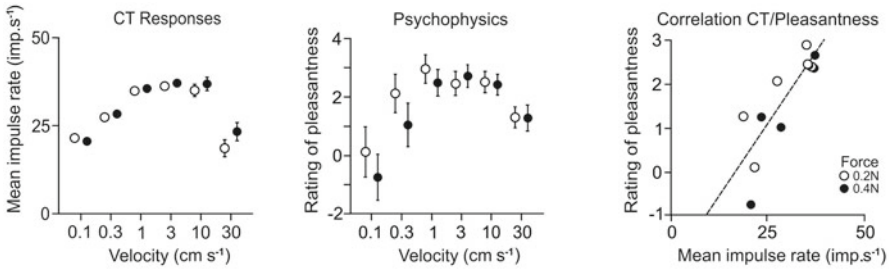


Fig. 1.16 Psychoneural relations between CT afference and pleasantness. Plot in *left-hand panel* demonstrates tuning of CT afferents ($n = 16$) to intermediate velocities of soft brush stroking. *Middle panel* shows subjects' estimates of pleasantness as a function of speed of soft brush stroking ($n = 10$). *Right-hand panel* demonstrates that the correlation between subjects' estimates of pleasantness and CT impulse rates is highly significant (Pearson's linear regression $R^2 = 0.70$, $P = 0.00063$)

1971 by Bessou et al. They pointed out that "the receptors respond more vigorously to an object moving at certain slow speeds across the skin than to one which moves more rapidly. … Whether central sensory systems utilize this peculiarity of responses is unknown." Obviously, time was not ripe at that time for a discussion of this observation in relation to the emotional impact of skin-to-skin contact. In fact, hypotheses of affective touch were never considered in animal studies of unmyelinated tactile afferents. In contrast, up to the 1990s, studies of cutaneous mechanoreceptive mechanisms were highly focused on discriminative touch (Kanel et al. 2013).

The hedonic effect of a caressing movement is dependent not only on the mechanical and kinetic characteristics of the stimulus but also on the temperature of the touching object. Obviously, in most situations one would not feel a cold or a hot object as very pleasant. The significance of the temperature was explored to assess whether CT response and estimates of pleasantness would be consistent with the affective touch hypothesis. When responses to slowly moving objects of three different temperatures were tested, a very pertinent response pattern emerged that seems not only consistent with the hedonic touch hypothesis but also, in fact, directly supporting it (Ackerley et al. 2014a, b). Left-hand diagram of Fig. 1.17 illustrates that a slowly moving object of neutral temperature was more effective than a warmer or cooler object in activating CT afferents. Moreover, subjects' feelings of pleasantness were optimal when the temperature of the moving object was neutral but suboptimal when the moving object was warmer or cooler (middle diagram). In fact, the correlation between CT firing and subjects' estimates of pleasantness was highly significant with neutral temperature (right-hand diagram), whereas the correlation was nonsignificant when the object was cooler or warmer (not illustrated). With Aβ afferents there was no such effect of temperature because their response was basically identical at the three different temperatures.

To sum up, two key features of caressing gestures were tested in the studies illustrated in Figs. 1.15, 1.16, and 1.17. The findings demonstrate significant correlations between CT activity and estimates of pleasantness when two different stimulus parameters were varied, that is, the speed of an object moving over the skin surface

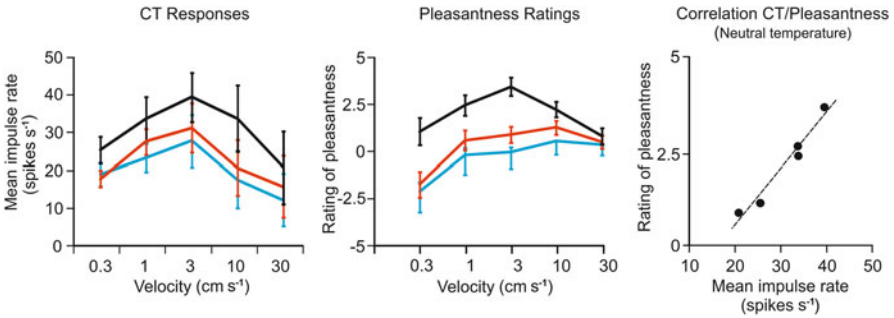


Fig. 1.17 Dependence of psychoneural relation on temperature of moving touch stimuli. Left-hand plot shows CT response ($n = 8$) to an object moving over the receptive field at different speeds. Three different object temperatures are color coded: *black*—neutral, *red*—warm, and *blue*—cool. *Middle plot* shows subject's estimates of pleasantness with the same stimuli. *Right-hand plot* shows correlation between estimates of pleasantness and CT firing rates with the object having neutral temperature. The correlation was highly significant ($R^2 = 0.96$, $p = 0.003$). whereas correlations were insignificant with warm or cool object stimulation (not shown)

as well as the temperature of the moving object. It seems that these two sets of correlations provide a strong support for the hedonic touch hypothesis which argues that the role of CT afferents, within the realm of perception, is to boost the feeling of pleasantness when touched by a friendly human being.

Functional Role of the CT System

The human CT system has attracted a remarkable interest in recent years. In contrast, its homolog in furry animals, that is, the CLTM system, was not much discussed until the CT system was identified in man. The interest in the human CT system is probably not only due to a new sensory system having been discovered. Even more important might be the nature of the hypothesis advanced regarding the functional role of the CT system, that is, the affective touch or social touch hypothesis. This working hypothesis ascribes to the CT system a unique role very much different from ideas previously considered among sensory physiologists.

The role of the CT system is not primarily to satisfy the need of a wide range of factual information about distinct features of mechanical events at the skin surface. This kind of information is amply provided by the fast Aβ system. The role of the CT system is rather to capture the particular features of skin deformation which indicate gentle bodily contact with an amiable individual. Thereby the system would boost the emotional effects of closeness to a friendly conspecific. The system would be of significance in supporting feelings of pleasure (reward), confidence, comfort, and security as you are close to your parents, lover, kin, or friends. Moreover, it may have a role in hormonal responses as well as in bonding individuals emotionally together.

The attraction as well as the problems with this hypothesis is to a great extent related to the idea that the CT system is conceptually deeply embedded in the complex emotional system of the human brain.

The hypothesis claims tight links between sensory input provided by a seemingly superfluous sensory system, on the one hand, and emotional responses which would contribute to the mental and physical well-being of the organism, on the other. Hence, the hypothesis puts the CT system side by side with a number of other small fiber systems which have the role to report the state of physical and chemical variables in the body which are essential for the control systems guarding the well-being of the individual (Craig 2002, 2008).

Scientists engaged in the CT system are facing demanding and exceptional problems due to the nature of the central effects ascribed to the CT system. The effects are obscure and diffuse compared to those commonly discussed in relation other cutaneous afferent systems. The complex mechanisms involved in emotional response to intersubject skin contacts make the task of pinpointing the exact role of the CT system particularly demanding. This is partly due to the response to touch by another individual being highly dependent on a number of contextual factors, for example, the social relation between the two and the actual emotional state of the person being touched. Moreover, the fact that another sensory system, that is, the Aβ system, is always activated along with the CT system and has the potential to capture all details of cutaneous stimuli, even those that seem relevant for social touch, is another complication for understanding and clarifying the exact role of the CT system.

With regard to the strict sensory effect, it is important to emphasize that selective stimulation of human CT afferents does not produce a clear and vivid sensation of pleasant touch as demonstrated in neuronopathy patients (Olausson et al. 2002). These patients report weak, vague, and inconsistent sensations of touch, sometimes reported as pleasurable, when innocuous skin stimuli are delivered. Hence, it seems obvious that the full sensation of pleasant touch by a close and amiable individual is dependent on sensory input in the two tactile systems. When considering the affective touch idea as a working hypothesis, it seems important to point out that only two alternative hypotheses have been discussed during the 75 years since the unmyelinated system was first identified in furry animals and then later in humans First, the tickle hypothesis, which has been refuted by observations in microneurography experiments showing lack of correspondence between CT activity and tickle sensation, and neuronopathy patients who lack large myelinated afferents are not aware of being tickled, indicating that the sensation of tickle is dependent on large myelinated afferents rather than unmyelinated nerve fibers. The other alternative hypothesis that has been aired in informal discussions is that the CT system might be essential in shaping somatotopic maps in the sensory cortex. The idea stems from studies in nonhuman species indicating that unmyelinated mechanoreceptive afferents may play an essential role in these complex processes (Calford and Tweedale 1991). Importantly, these studies emphasize that the C afferents involved in body surface mapping are sensitive to capsaicin, suggesting nociceptive afferents. Animal studies indicate that CLTMR are not sensitive to capsaicin (Foster and Ramage 1981; Kenins 1982; Vrontou et al. 2013) as is true with human CTs (Wiklund-Fernström 2004).

To sum up, there is essentially no experimental support for the two alternatives to the social touch hypothesis. Rather, available data speak against them. In contrast, a number of observations are consistent with the social touch hypothesis. Evidence from psychoneural correlation studies strongly suggest that CT activation is associated with hedonic effects. Moreover, supporting findings are provided by studies of CLTMR system in rodents. Particularly interesting is the demonstration that pharmacogenetic activation of one part of the CLTMR system has a positively reinforcing effect on behavior suggesting an anxiolytic potential (Vrontou et al. 2013).

At present, the affective touch hypothesis is the most promising and most stimulating interpretation of the functional role of the CT system. In spite of the difficulties to design conclusive tests, it seems important to explore further the CT afferents and their central connections. The more we know about the system the more we will be able to test and refine the social touch hypothesis—or any alternative idea that might eventually be proposed to explain the survival value of a seemingly superfluous tactile system.

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Chapter 2
Functional Properties of C-Low Threshold Mechanoreceptors (C-LTMRs) in Nonhuman Mammals

Mark Pitcher, Claire E. Le Pichon, and Alexander Chesler

As the methods of recording the activity of the nerve fibers now have been developed to such a degree that even the smallest afferent fibers have to yield to our curiosity, further experiments may provide more quantitative data required for the analyses of the nervous mechanism of cutaneous sensations.

Yngve Zotterman; Touch, pain and tickling: An electrophysiological investigation on cutaneous sensory nerves (1939)

Abstract In humans, unmyelinated C-tactile fibers, referred to as C-low threshold mechanoreceptors (C-LTMRs) in nonhuman mammals, are found exclusively in hairy skin and preferentially respond to slow moving gentle touch, such as that produced by lightly stroking the skin. While substantial species differences exist in the proportion of C-LTMRs to the total C-fiber population, C-LTMRs appear to be expressed more densely in proximal regions of the limbs and the trunk. Functionally, C-LTMRs are specifically tuned to relatively low velocity (~0.1 cm/s) cutaneous stimulation, respond with biphasic adaptation to a single sustained stimulus and exhibit prolonged fatigue in response to repeated stimulation. While a molecular marker of the global C-LTMR population is lacking, subtypes expressing MrgprB4, VGLUT3, and TH have been identified. Considering that C-LTMRs terminate in lamina II of the spinal dorsal horn, there is increasing evidence supporting their involvement in the modulation of spinal responses to nociceptive input.

Keywords C-Tactile • C-Low threshold mechanoreceptor • Unmyelinated C-fiber • Sensory afferent • Touch • Pain • Hair follicle

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The purpose of somatosensory afferents and their peripheral transduction organs is to inform the central nervous system about events occurring at the interface between the surface of the organism and the outside world. At this interface, sensory afferent terminals in the skin distinguish between multitudes of different stimuli, from vibration to temperature, from gentle touch to actual or potential tissue injury. Each class of touch sensitive end organ is tuned to detect a specific type of input while the associated sensory afferents transmit this information as faithfully as possible. Since Adrian pioneered the electrophysiological techniques to record activity in sensory afferents in the early twentieth century, neuroscientists have been working ceaselessly to establish how the functional differences among the rich tapestry of sensory fibers define each of their specific roles. At the macro level, the myelinated Aβ and Aδ fibers generally fulfill a sensory-discriminative role in that they confer the ability to rapidly detect and faithfully transmit critical information about the physical nature of the stimulus as well as its precise location on the body, permitting prompt guidance for motor activity. On the other hand, the slow conduction velocity that characterizes unmyelinated C-fibers renders them poor discriminative sensors. In accord with the suggestion that pain, like hunger and thirst, serves a homeostatic function (Craig 2003), C-fiber-mediated signaling appears to serve an affective-motivational function (Weiss et al. 2008). An interesting example of the emotional impact of nociceptive C-fiber activation is ischemic pain. Both visceral and muscle nerves have a higher proportion of nociceptive C-fibers than cutaneous nerves (Cervero and Laird 1999; Mense and Schmidt 1974). As such, ischemic block of the forearm with a blood pressure cuff rapidly produces an ischemic block of Aδ fibers followed later by C-fiber blockade. As any graduate student in an upper level pain neurophysiology course will attest, the pain from ischemic block of C-fibers is much more unpleasant than that from Aδ fibers. Along a similar line, sensitivity to ischemic blockade of C-fibers is increased in depressed subjects (Suarez-Roca et al. 2003).

While it has been long recognized that both Aδ- and C-fiber nociceptors contribute to pain perception, myelinated Aβ-fibers are held to be the main nonnociceptive "touch" fibers. For these reasons, the existence of a class of unmyelinated C-fiber that appears to be specifically tuned to gentle stroking of the hairy skin (Olausson et al. 2010) with objects at body temperature (Ackerley et al. 2014) is striking. Activation of these fibers in humans evokes pleasant sensations and, as such, has been posited to subserve affective touch, consistent with the putative affective-motivational role of C-nociceptors. In fact, slow, gentle stroking evokes oxytocin and endorphin release in rodents (Uvänas-Moberg et al. 2005). To the best of our knowledge, it would seem that no other sensory fiber type is as well adapted to an affective-motivational role as the C-low threshold mechanoreceptor (C-LTMR). It appears that the survival benefits of prosocial contact (i.e., caressing/grooming) have conserved the C-LTMR, but that is a subject for another chapter.

Zotterman (1939) was the first to record electrophysiological activity in C-LTMR fibers. While he concluded that they subserve the sensation of tickle, more recent work suggests a grooming phenotype based on their robust response to gentle, slowly moving stimulation of hairy skin (Bessou et al. 1971; Kumazawa and Perl 1977; Li et al. 2011). Perhaps due to these unique properties they have only recently

garnered the attention of the wider neuroscience community as well as the public. In this chapter, we will review the functional characteristics of C-LTMRs. Of note is that most of the functional characterization derives from mid-twentieth-century classical electrophysiological studies in anesthetized rats, cats, and monkeys. Each section of this chapter will briefly summarize a distinct facet of C-LTMR function. We then turn to more recent work integrating genetic modification in mice in order to discuss how different subtypes fit into the classical definition of C-LTMRs, followed by reviewing the evidence supporting a potential modulating role of C-LTMRs in nociceptive processing.

Peripheral Terminations and Receptive Field

While early studies were generally unable to study the anatomical and structural characteristics of C-LTMRs due to technical constraints, careful electrophysiological characterization showed that these fibers are associated with one or a few hair follicles (Douglas and Ritchie 1957; Iggo 1960; Iggo and Kornhuber 1977). Recent evidence suggests that at least a subset of peripheral C-LTMR terminals form longitudinal lanceolate endings in a palisade formation around the base of Zigzag and Awl/Auchene hair follicles (Li et al. 2011), rendering exquisite sensitivity to even the slightest deflection of the hair shaft. C-LTMR receptive fields (RFs) are found exclusively in hairy skin of mammals (Iggo and Kornhuber 1977; Sassen and Zimmermann 1971; Takahashi et al. 2003). A single C-LTMR fiber has multiple peripheral terminals in a relatively uniform field that is ovoid in shape and measures approximately 1 mm^2 in mouse (Liu et al. 2007; Seal et al. 2009) and 18 mm^2 in cat (Iggo 1960; Bessou and Perl 1969; Kumazawa and Perl 1977; Shea and Perl 1985). Humans appear to have larger RFs, on the order of 35 mm^2 (Wessberg et al. 2003). However, C-LTMR RF size may be overestimated if more intense stimuli are used (Bessou and Perl 1969; Iggo and Kornhuber 1977). For example, the center of the RFs were found to be more sensitive than the edges, hence stimulation at perithreshold intensity yielded smaller RFs than suprathreshold stimulation (Iggo 1960; Iggo and Kornhuber 1977) (Fig. 2.1). Species differences in C-LTMR expression have also been noted, where cats generally appear to have a higher proportion of C-LTMRs compared to other mammals. Specifically, in cat distal nerves C-LTMRs represent 25–50 % of all C-fibers sampled (Douglas and Ritchie 1957; Iggo 1960; Bessou et al. 1971; Traub and Mendell 1988). However, in rodents such as rats, guinea pigs, and rabbits, approximately 8–15 % are classified as C-LTMRs (Lynn and Carpenter 1982; Shea and Perl 1985; Fang et al. 2005; but see Takahashi et al. 2003 for a higher estimate) and approximately 10 % in monkey (Kumazawa and Perl 1977). The proportion in humans is unclear. It must be noted that these estimates may not represent the actual numbers for reasons including sampling bias. In terms of C-LTMR density in skin, monkeys (Kumazawa and Perl 1977), cats (Bessou and Perl 1969), and mice (Liu et al. 2007, 2011; Delfini et al. 2013) exhibit more C-LTMRs in proximal nerves than distal.

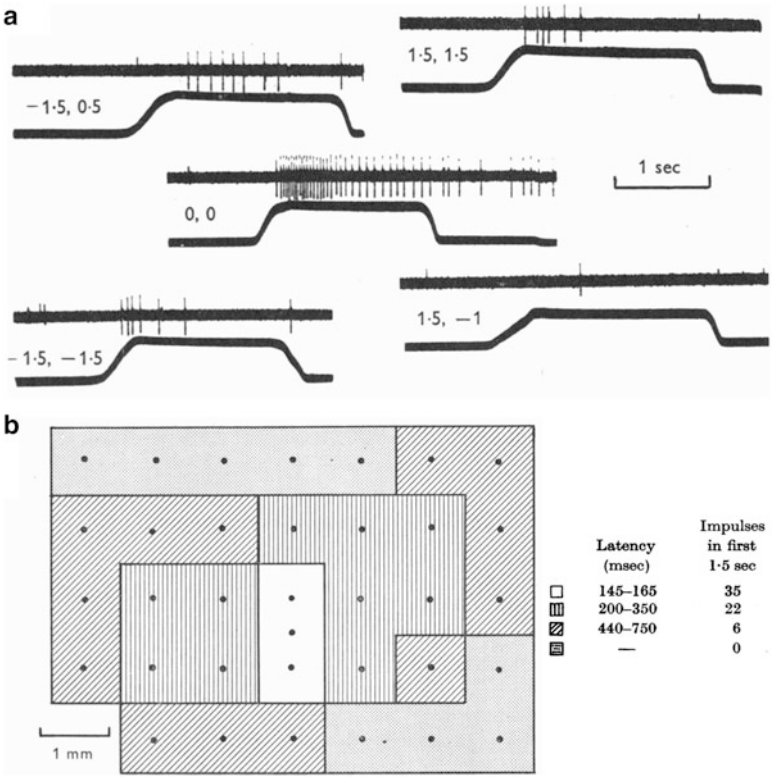

Fig. 2.1 The receptive field of a C mechanoreceptor. (**a**) shows five records obtained when different spots on the skin were touched with the probe. The final load is nearly the same (2 g weight) for all positions. The distances of the probe from the most sensitive central position are indicated in millimeters. (**b**) is a diagram summarizing all the results for the same unit. The skin was stimulated on a 1 mm grid and each spot is indicated by a *filled circle* in the diagram. The latency of the first impulse at each position is shown by the *shading*. At the centre of the field the latency was least, the rate of firing was highest and the persistence of the discharge was longest (Adapted from Iggo 1960)

Optimal Stimuli

The specific input required for maximal action potential output by the sensory fiber is defined by response properties of both the peripheral terminal organ (i.e., Pacinian corpuscle, Ruffini ending, etc.) and the axon (i.e., unmyelinated vs. myelinated fiber, etc.). For example, for a sensory fiber to faithfully follow high frequency vibration of the skin, the response properties of the terminal ending and the associated fiber must allow for rapid adaption to the input as well as fast conduction velocity. Pacinian corpuscles and their associated myelinated Aβ fibers amply fulfill these requirements, yielding increasing spike rates with increasing stimulation frequencies. Regarding C-LTMRs, considering the remarkable sensitivity of longitudinal

lanceolate endings situated around the base of the hair follicle together with the slow conduction velocity typical of unmyelinated C-fibers, human C-tactiles (Nordin 1990) and nonhuman C-LTMRs appear to be well suited to gentle, slowly moving stimulation of hairy skin (Zotterman 1939; Maruhashi et al. 1952; Douglas and Ritchie 1957; Iggo 1960; Bessou and Perl 1969; Kumazawa and Perl 1977). Single fibers can respond to barely perceptible mechanical stimuli such as the bending of a single guard or down hair (Douglas and Ritchie 1957; Iggo and Kornhuber 1977) or less than 4 mg punctate stimulation with a von Frey filament (Iggo 1960; Bessou and Perl 1969; Kumazawa and Perl 1977; Lynn and Carpenter 1982), which is consistent with C-tactile sensitivity in humans (Vallbo et al. 1999).

A remarkable characteristic of these fibers is their specific tuning to a velocity range: Using in vivo electrophysiological recordings from cat DRG, Bessou et al. (1971) demonstrated that C-LTMRs respond in an inverted U-shaped curve to increasingly rapid stroking of the skin with a glass probe (Fig. 2.2). Specifically, C-LTMRs show increasing spike rates to gentle stroking with a glass probe up to approximately 0.1 cm/s, with lower spike rates at higher stimulation velocities.

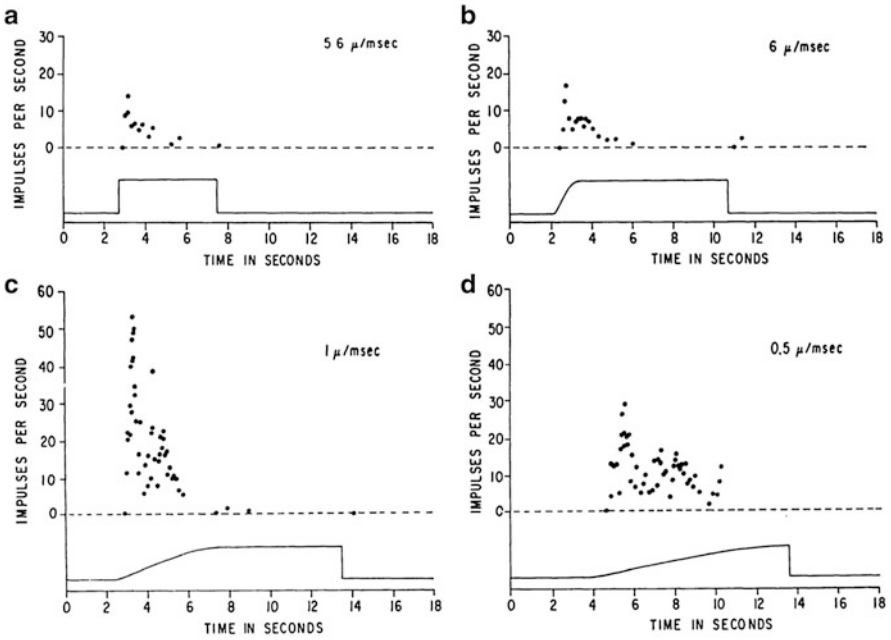

Fig. 2.2 Response of a C mechanoreceptor to a smooth stimulator moving across the skin at the indicated velocities. *Upper portion* of each graph shows the evoked discharge expressed as an instantaneous frequency vs. time. Instantaneous frequencies were obtained from the time intervals between successive pairs of impulses and marked by a *dot* placed on the horizontal axis at the time of occurrence of the second impulse of each pair. *Lower portion* of each graph indicates movement of the stimulator parallel to the skin surface. At the beginning of the movement, the stimulator was positioned on one side of the receptive field and had traversed the field when movement ceased (Adapted from Bessou et al. 1971)

In support, Kumazawa and Perl (1977) found that C-LTMRs respond optimally to stroking between 0.05 and 0.2 cm/s and others have noted similar velocity-dependent responsiveness (Shea and Perl 1985). Maximal C-LTMR spike frequency in response to stroking can be up to 100 spikes/s, which is significantly lower than the 300 spikes/s possible in nociceptive C-fiber axons (Franz and Iggo 1968) and in stark contrast to myelinated A-fibers that can maintain an output up to 800 spikes/s (Iggo 1960; Lindblom and Tapper 1967; Merzenich and Harrington 1969). Vallbo et al. (1999) found similar spike rates in C-tactile fibers recorded from humans. Interestingly, Douglas and Ritchie suggested that C-LTMRs were only able to fire up to approximately 10 spikes/s. However, this low estimate may be related to the limited time resolution available from their experimental setup. As mentioned earlier, in addition to slow, gentle stroking, C-LTMRs also respond to punctate stimulation, exhibiting a spike threshold of approximately 10 μm skin indentation with linear increases in spike activity up to approximately 500 μm indentation (Iggo and Kornhuber 1977). C-LTMRs typically exhibit little or no spontaneous ("background") activity (Bessou and Perl 1969; Takahashi et al. 2003).

Vibration

C-LTMRs are unable to follow 1 Hz mechanical stimulation frequencies applied to the skin for more than a few stimulations (Iggo 1960; Bessou et al. 1971); however, they can follow a 0.1 Hz frequency moderately well for up to 90 s (Bessou et al. 1971). Nonetheless, Gee et al. (1996) showed that C-LTMR fibers could follow 20 Hz electrical stimulation for up to 20 s. The inability to maintain consistent spike output in response to repeated mechanical stimuli to their RF reflects fatigue, to be discussed in more detail later.

Cooling

Kumazawa and Perl (1977) showed that while C-LTMRs do not respond to warming of the skin, they respond robustly to progressive cooling of the skin. Hahn (1971) demonstrated that cooling the skin attenuates responses to mechanical stimulation, such that cooling appears to produce cross-modal fatigue. Many other studies support C-LTMR responsiveness to cooling (Iggo 1960; Hensel et al. 1960; Bessou and Perl 1969; Hahn 1971; Iggo and Kornhuber 1977; Takahashi et al. 2003); however, the functional significance of this is not known.

Conduction Velocity

Conduction velocity (CV) is a measure of the speed of action potential propagation along the axon. CV is directly related to the degree of myelination of the fiber, where the most thickly myelinated fibers exhibit the fastest CV. Measurement of CV

usually involves measuring the time to arrival of an electrically evoked action potential to reach the recording electrode from the stimulating electrode a known distance away. A cardinal property of all C-fibers is that they are unmyelinated and thus display the slowest CVs. C-LTMR CV is between 0.55 and 1.25 m/s (Iggo 1960; Gee et al. 1996; Djouhri et al. 1998; Takahashi et al. 2003); however, some have been measured from 0.4 m/s (Iriuchijima and Zotterman 1960; Fang et al. 2005) to up to 2.5 m/s (Iggo and Kornhuber 1977). Gee et al. (1999) showed that there are some species differences in C-LTMR conduction velocity: In pig, C-LTMR CV is the fastest of all C-fiber types, sampled at approximately 1.2 m/s. However, rat C-LTMR CV is similar to other C-fiber types (0.87 m/s). Interestingly, C-tactile fibers, proposed to be the human equivalent of mammalian C-LTMRs, exhibit CVs between 0.8 and 1.3 m/s (Wessberg et al. 2003). A number of studies show that C-nociceptors exhibit similar CVs as C-LTMRs (Djouhri et al. 1998; Fang et al. 2005).

A common feature of repeatedly activated C-fibers is activity-dependent CV slowing, where action potentials conduct progressively slower with increasing number of stimuli. In terms of C-nociceptors, this phenomenon has been suggested to underlie some forms of persistent pain in rodents (Shim et al. 2008). However, C-LTMRs also exhibit CV slowing. Gee et al. (1996) showed that C-LTMR CV slows by approximately 14 % in response to 20 Hz electrical stimulation of the fiber for 20 s, whereas nociceptive C-fibers slow by 27–29 %. Interestingly, while other C-fibers show a stable rate of slowing over time, C-LTMR CV slows more abruptly over the first 6 s followed by a plateau. This initial period of acute slowing approximates the time required for adaptation, to be discussed later in this chapter.

Spike Properties

Using in vivo electrophysiological techniques in cats, Bessou et al. (1971) recorded intracellularly from C-LTMR cell bodies in the DRG. The membrane potential of C-LTMR DRG neurons was typically between 60 and 80 mV, similar to Aδ cell bodies. However, in guinea pig, Djouhri et al. (1998) found that the membrane potential was approximately 40–50 mV in both C-nociceptor and C-LTMR cell bodies.

In cat, the amplitude of action potentials (APs) evoked by suprathreshold peripheral electrical stimulation averaged 90 mV, higher than APs in Aδ DRGs (Bessou et al. 1971). However, in rat the AP amplitude was 61 mV in C-LTMR and 75 mV in C-nociceptors (Fang et al. 2005).

In recordings from the DRG cell bodies in cat, Bessou et al. (1971) found that C-LTMR AP duration was approximately 5 ms, much wider than the 0.6–0.8 ms width of Aδ APs. However, Djouhri et al. (1998) found that AP duration was much shorter in guinea pig C-LTMR cell bodies than in C-nociceptors (2.5 ms vs. 7 ms, respectively), similar to findings in rat (Fang et al. 2005). On the other hand, Traub and Mendell (1988) found that both C-fiber types in DRG cell bodies from cat had similar AP durations of approximately 7 ms. Recording from the saphenous nerve in pigs, Gee et al. (1999) showed that C-LTMRs had narrower spikes than nociceptive C-fibers; however, spike duration in rat was similar across all C-fibers.

In terms of AP rise time, fall time and after-hyperpolarization duration, Djouhri et al. (1998) and Fang et al. (2005) demonstrated that C-nociceptors were generally longer than C-LTMRs. Specifically, AP rise time was approximately 2.5 ms in C-nociceptors and 1 ms in C-LTMRs. AP fall time was approximately 3.5–4.75 ms in C-nociceptors and 1.5 ms in C-LTMRs. Finally, duration of after-hyperpolarization to 80 % of baseline was approximately 15–20 ms in C-nociceptors and 5 ms in C-LTMRs. As discussed in Fang et al. (2005), these differences may be linked to differential expression of voltage-gated sodium channels (NaVs) as well as voltage-gated calcium (CaVs) and potassium (KVs) channels. For example, nociceptive neurons, but not low threshold mechano-receptive neurons, typically express greater TTX-resistant NaV1.7, NaV1.8, and/or NaV1.9 channels that contribute to the greater rising phase and duration of the action potential.

Adaptation

Gradual decreases in neuronal output in response to a sustained, unchanging stimulus is referred to as adaptation. Rapidly adapting A-LTMRs are specially attuned to rapid movement or vibration, responding with short spike bursts that correspond to the onset/offset characteristics of the stimulus. On the other hand, slowly adapting A-LTMRs (i.e., indentation or stretch detectors) often exhibit two components of adaptation, comprised of a brief initial burst followed by relatively stable firing for the duration of the ongoing stimulus. Interestingly, C-LTMR activity in response to a sustained stimulus appears to share the two-component adaptation of slowly adapting A-LTMRs, with a brief burst of approximately 100 spikes/s followed by relatively stable spiking in the 20–65 spikes/s range (Iggo 1960; Iggo and Kornhuber 1977; Kumazawa and Perl 1977) (Fig. 2.3) that lasts approximately 5–10 s followed by virtually complete cessation of firing by 20 s (Bessou et al. 1971; Douglas and Ritchie 1957).

Fatigue

Whereas adaptation refers to decrements in response to a single sustained stimulus, fatigue is a related phenomenon characterized by a decreased output to repeated stimuli. While A-LTMRs generally exhibit little change in spike output to repeated stimuli with interstimulus intervals (ISIs) of 2 s or more, C-LTMR output drops dramatically (Iggo 1960; Hahn 1971; Kumazawa and Perl 1977; Iggo and Kornhuber 1977), even if adaptation to the first stimuli has not yet occurred (Bessou et al. 1971). The time until recovery from fatigue, where the C-LTMR response to the second stimulus is similar to the first in terms of magnitude and duration, can take several minutes if the initial stimulus was brief (i.e., approximately 10 s). However, longer or more intense stimulation may require up to 15–30 min to recover (Iggo 1960). Considering that C-fiber receptive fields are comprised of multiple, closely

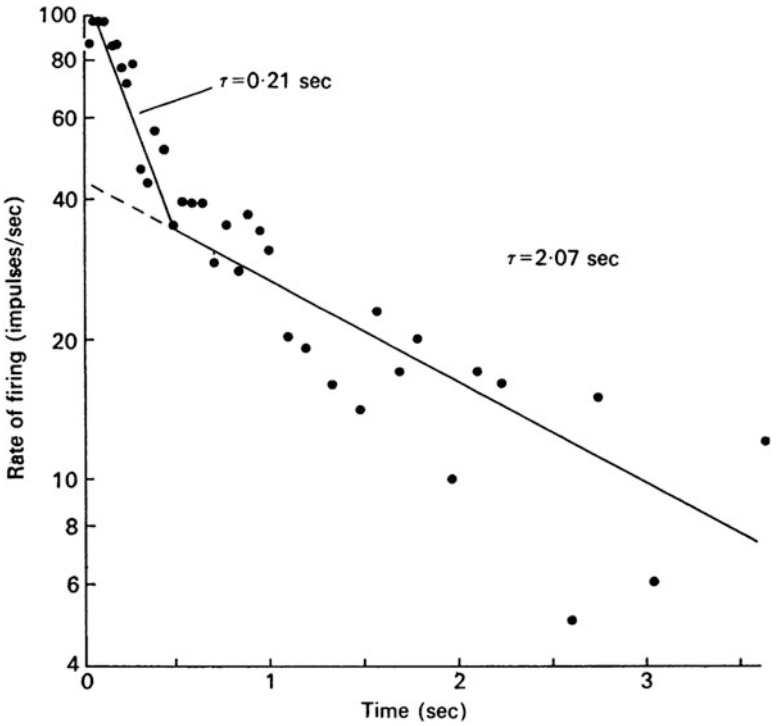

Fig. 2.3 Adaptation of a C-mechanoreceptor to a skin indentation of 476 μm. The rate of firing fell continuously from a maximum of 100 impulses/s and when plotted on semilogarithmic coordinates, two time constants could be fitted (Adapted from Iggo and Kornhuber 1977)

apposed terminal branches (Cauna 1969, 1973), Iggo and Kornhuber (1977) used multipoint discrimination in single C-LTMR receptive fields to determine if fatigue to repeated stimulation depends on the peripheral terminal organ or the sensory fiber axon. They showed that punctate stimulation of one point in the field did not affect responses to subsequent stimulation of another point 1 mm away within the same RF, suggesting that reduced responsiveness to repeated stimulation likely depends on end organ failure. Moreover, antidromic activation did not result in fatigue to subsequent mechanical stimulation of the RF, further supporting the end organ failure hypothesis (Iggo and Kornhuber 1977).

Similar to their observations that repeated stimuli reduce subsequent spike output, Bessou et al. (1971) observed that the minimal contact time to elicit a spike was also reduced by previous stimulation. Specifically, within 30 s of strong activation, the stimulation probe had to remain in contact with the skin for 500 ms to evoke a spike. If the receptor had not been stimulated for 5–10 min, 100–150 ms contact time was required. If 20–30 min separated the stimuli, 40–80 ms were required to evoke a spike. In contrast, A-fibers required stimulus durations of 3 ms or less to evoke robust responses (Bessou et al. 1971).

After-Discharge

After-discharge refers to the ability of a neuron to produce impulses after cessation of the stimulus. Zotterman (1939) was the first to observe after-discharge in stroking-activated C-LTMRs. Many others have substantiated Zotterman's finding (Douglas and Ritchie 1957; Hensel et al. 1960; Lynn and Carpenter 1982). Kumazawa and Perl (1977) also demonstrated that C-LTMRs exhibit prominent after-discharge, especially when not fatigued by previous activation. C-LTMRs appear to produce lengthy after-discharge following stroking of the receptive field, whereas perithreshold punctate input may not result in any after-discharge (Iggo 1960), suggesting that this phenomenon may reflect restorative changes to the skin after indentation (Iggo and Kornhuber 1977). In other words, they interpret C-LTMR after-discharge to reflect an inverse stimulation, where it is the indented skin returning to its original position that activates C-LTMR terminals, thus producing after-discharge.

Central Terminations

Using the plant lectin *Phaselus vudgans* leukoagglutinin (PHA-L) or Horseradish peroxidase (HRP) iontophoresed into the cell body, C-LTMR fibers innervating the guinea pig ear were found to terminate in lamina II of the spinal dorsal horn, similar to the termination zone of C-nociceptors (Sugiura et al. 1986; Sugiura 1996). Recent studies using modern viral vectors and genetic modification have substantiated this finding and will be discussed in the next section.

Molecular Characterization

Until the advent of genetic modification techniques, the sole source of information on the identity C-LTMRs was based on the classical electrophysiological experiments discussed in previous sections. As such, C-LTMRs were long thought of as a homogeneous population. However, recent work has identified a number of putative markers of C-LTMRs with some degree of nonoverlapping expression. Therefore, in this section, these potentially heterogeneous C-LTMR populations will be discussed sequentially.

Before discussing C-LTMRs, a brief description of C-nociceptors is in order. C-nociceptors terminate in the epidermis with free nerve endings that respond preferentially to noxious mechanical or thermal stimuli (Bessou and Perl 1969; Cain et al. 2001) and can be found in both glabrous and hairy skin. C-nociceptors are neurochemically classified by their neuropeptide content: Peptidergic C-nociceptors terminate deeper in the epidermis and contain substance P and CGRP, while nonpeptidergic C-nociceptors (often identified as isolectin B4-positive) terminate in more superficial layers of the epidermis (Perry and Lawson 1998; Ribeiro-da-Silva et al. 1989). Functionally, nonpeptidergic C-nociceptive fibers are associated with transduction

of noxious mechanical stimuli (Cavanaugh et al. 2009; Zylka et al. 2005) whereas peptidergic fibers transduce thermal stimulation in the noxious range (Cavanaugh et al. 2009). Mas-related G protein-coupled receptors (Mrgprs) comprise a family of receptors that are found specifically in small diameter sensory neurons (Dong et al. 2001; Lembo et al. 2002; Han et al. 2002; Zylka et al. 2003). Mrgprs are differentially expressed in subsets of sensory afferents suggesting functional specificity of these subsets.

Liu et al. (2007) demonstrated that MrgprB4-expressing neurons represent less than 2 % of dorsal root ganglion (DRG) neurons and do not coexpress CGRP, P2X3, or TRPV1. However, they do express isolectin B4 (IB4) and c-RET, indicating that MrgprB4$^+$ neurons are indeed nonpeptidergic but distinct from the nociceptive nonpeptidergic C-fibers. Consistent with findings from classical studies described earlier, peripheral terminations of MrgprB4$^+$ neurons are found only in hairy skin and are less dense in skin of distal limbs. The RFs in these mice are small, roughly 1 mm^2 with 1–3 arborization fields per terminal. These terminations are closely apposed to hair follicles and are absent from structures such as blood vessels and muscle. Centrally, MrgprB4$^+$ neurons coterminate in Lamina II$_{outer}$ with other IB4$^+$ neurons. Using two-photon calcium imaging of genetically labeled MrgprB4$^+$ neurons in the mouse spinal cord, Vrontou et al. (2013) observed increased fluorescence following application of α,β-methylene (Me) ATP to hairy and, unexpectedly, to glabrous skin of the hind paw. Importantly, gentle stroking of the hairy skin at 0.5–2 cm/s (0.2–0.5 Hz) also enhanced calcium transients whereas punctate stimulation with von Frey filaments and noxious pinching did not. Considering the pleasant sensations evoked by C-tactile input in humans (Olausson et al. 2010), Vrontou et al. (2013) used the DREADD (Designer Receptor Exclusively Activated by Designer Drugs) approach to activate MrgprB4$^+$ neurons in the conditioned place preference (CPP) assay to find that MrgprB4$^+$ neuronal activation is indeed positively reinforcing, suggesting a role in motivational reward processing.

The vesicular glutamate transporter (VGLUT) family is comprised of three isoforms (VGLUT1-3), involved in intracellular transport of glutamate to synaptic release sites. VGLUT3 is the least abundant isoform, found in sensory afferents terminating in spinal lamina II$_{inner}$ as well as some projections to lamina I and III (Seal et al. 2009). Specifically, VGLUT3$^+$ terminals correspond closely to PKCγ-expressing interneurons but not nonpeptidergic IB4 afferents, suggesting that VGLUT3$^+$ neurons represent a different population than MrgprB4$^+$ neurons. VGLUT3$^+$ neurons belong to the small/medium sized, unmyelinated neuronal population, and account for approximately 10 % of DRG neurons in mice. These cells are largely IB4-negative and do not express CGRP, SP, or TRPV1. Conduction velocity of VGLUT3$^+$ axons is approximately 0.6 m/s, consistent with C-fibers. In addition, these neurons are more responsive to slowly moving stimuli and exhibit clear adaptation to ongoing stimulation. RF size of VGLUT3$^+$ peripheral terminals is identical to MrgprB4$^+$ RF's at approximately 1 mm^2 with 1–3 sensitive spots. In contrast to findings from Liu et al. (2007) and others (Kumazawa and Perl 1977; Bessou and Perl 1969) showing reduced C-LTMR density in distal nerves, VGLUT3$^+$ neuron density appears to be equal in thoracic and lumbar regions of the spinal cord (Seal et al. 2009).

A somewhat distinct subset of mouse C-LTMRs specifically expresses tyrosine hydroxylase (TH; Li et al. 2011). TH^+ neurons comprise a large group of small caliber, unmyelinated neurons (Brumovsky et al. 2006; Rice and Albrecht 2008) that do not express common markers of peptidergic nociceptors, yet are also Mrgpr negative (Dong et al. 2001; Molliver et al. 1997) and do not bind isolectin B4 (Li et al. 2011). On the other hand, virtually all TH^+ neurons express cRet and Gfrα2, markers of nonpeptidergic nociceptors (Molliver et al. 1997) and over 80 % also express VGLUT3 (Li et al. 2011). Using the skin-nerve electrophysiological preparation, Li et al. (2011) demonstrated that functional characteristics of TH^+ neurons are consistent with C-LTMRs. Specifically, they exhibit CVs of approximately 0.6 m/s, respond to low intensity mechanical stimulation (1–5 mN), adapt to stationary mechanical stimulation and respond to cooling but not warming. Moreover, peripheral terminations of TH^+ neurons form longitudinal lanceolate endings on zigzag and awl/auchene hairs, but not guard hairs (Fig. 2.4). The RF size was small, approximately 0.2–0.4 mm^2, and found only in hairy skin. Finally, TH^+ DRG neurons were more prominent in nonlimb regions (i.e., trunk and genitalia). As such, both VGLUT3 and TH appear to label overlapping subsets of C-LTMRs. Lou et al. (2013) showed that Runx1, a transcription factor involved in the development of a wide variety of unmyelinated fibers, controls VGLUT3 and TH expression in C-LTMRs, as well as the formation of their longitudinal lanceolate terminations and, via Piezo2, mechanosensitivity.

In another study, Delfini et al. (2013) identified a putative marker of C-LTMRs that predominantly coexpresses both VGLUT3 and TH. TAFA4, a chemokine-like secreted protein, is found in approximately 19 % of thoracic and 8 % of lumbar DRG neurons that do not express TRKA nor bind IB4. In addition, these neurons contain neither MrgprD nor MrgprB4. Their central terminations are found in Lamina II_{inner} while peripheral terminations are exclusive to hairy skin. TAFA4 neurons exhibit electrophysiological properties similar to C-nociceptors such as small cell capacitance, high input resistance, short AP duration, and expression of Nav1.8 and a number of low threshold-type currents. However, these neurons do not respond to capsaicin, menthol, or other agents known to activate nociceptors. They show slowly adapting mechanosensitive currents that best respond to slow moving stimuli (Delfini et al. 2013). Taken together, VGLUT3- and TH-containing neurons appear to be strong candidates for specific markers of most C-LTMRs (Seal et al. 2009; Li et al. 2011; Lou et al. 2013; Delfini et al. 2013); however, MrgprB4 seems to define a separate class (Vrontou et al. 2013).

Nociceptive Processing

The spinal termination pattern of C-LTMRs places them in a privileged place to be involved in nociceptive processing: Lamina II neurons are well known to contribute to processing injury-induced hypersensitivity (Malmberg et al. 1997). In humans, inhibition of C-tactile input has been suggested to promote tactile

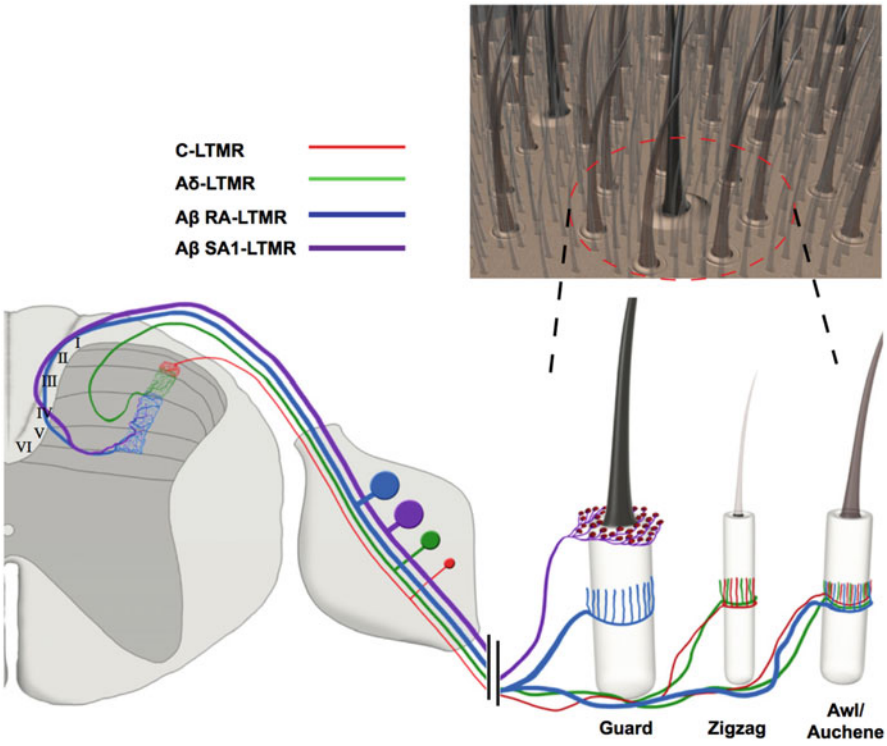

Fig. 2.4 The organization of LTMR endings in hairy skin and the spinal cord dorsal horn. The peripheral endings of Abeta-LTMRs, Adelta-LTMRs, and C-LTMRs associate with either one or two of the three types of hair follicles of trunk and proximal limb hairy skin. At zigzag hair follicles, C-LTMRs (*red*) and Adelta-LTMRs (*green*) form interdigitated longitudinal lanceolate endings; At awl/auchene hair follicles, Abeta RA-LTMRs (*blue*), Adelta-LTMRs (*green*), and C-LTMRs (*red*) form inter-digitated longitudinal lanceolate endings; Guard hair follicles are associated with longitudinal lanceolate endings formed by Abeta RA-LTMRs (*blue*) and clusters of Merkel cells, or touch domes and thus Abeta SA1-LTMRs (*purple*). The central terminals of LTMRs that innervate the same or adjacent hair follicles within a peripheral LTMR unit are aligned to form a narrow LTMR column in the spinal cord dorsal horn (Adapted from Li et al. 2011)

allodynia (Kramer et al. 2007; Linde et al. 2004), and activation of C-tactile fibers attenuates experimental pain (Kramer et al. 2006) in a manner reminiscent of Melzack and Wall's gate control theory (Melzack and Wall 1965). However, as described later, recent rodent studies suggest that C-LTMRs may play either pronociceptive or antinociceptive roles in persistent pain states (Seal et al. 2009; Lou et al. 2013; Delfini et al. 2013).

VGLUT3 is selectively expressed in unmyelinated sensory fibers that do not express markers of nociceptive neurons. Considering their role in synaptic glutamate release, mice lacking VGLUT3 would be expected to show deficits in sensory transmission. Seal et al. (2009) showed that mice in which VGLUT3 has been genetically deleted (VGLUT3$^{-/-}$) are indistinguishable from wild-type littermates in

terms of innocuous thermal and mechanical sensitivity; however, responses to higher intensity mechanical stimuli are blunted. Spinal wide dynamic range (WDR) neurons are well known to respond in a graded fashion to graded mechanical stimuli (Pitcher and Cervero 2010). In VGLUT3$^{-/-}$ mice, WDR neuronal responses to mechanical stimulation of the RF mirrored behavioral findings in that they exhibited normal responses to innocuous stimuli but had reduced firing to more intense mechanical stimulation. Accordingly, in mice with intact VGLUT3, VGLUT3^{+} fibers responded more intensely to higher intensity than lower intensity mechanical stimulation. In response to carrageenan-induced inflammation of the hind paw, nerve injury as well as a hind paw model of postsurgical pain, VGLUT3$^{-/-}$ mice exhibited attenuated mechanical hypersensitivity but normal thermal hypersensitivity. In contrast, after intraplantar formalin they showed similar responses to wild-type littermates (Seal et al. 2009). Based on this data, Seal et al. suggest that the C-LTMR activity may have pro-nociceptive effects, particularly in persistent pain states. As aforementioned, Runx1 controls VGLUT3 and TH expression in neurons with unmyelinated axons. Behavioral findings based on the global VGLUT3 knockout approach used by Seal et al. (2009) are difficult to interpret due to the wide expression pattern of VGLUT3 in other tissues. Using mice deficient in VGLUT3 specifically in Runx1-lineage neurons, Lou et al. (2013) explored C-LTMR involvement in nociceptive processing. In contrast to Seal et al. (2009), they found no changes to heat or mechanical sensitivity at baseline, after intraplantar capsaicin, CFA, and following spared nerve injury. However, similar to Seal et al. (2009), these mice had subtle yet statistically significant increases in mechanical thresholds (i.e., reduced mechanical hypersensitivity) after carrageenan-induced inflammation of the hind paw. Together, these studies suggest that C-LTMRs may play pro-nociceptive role in persistent inflammatory pain signaling.

Other studies have also focused on molecular markers related to VGLUT3-expressing DRG neurons. TAFA4 is strongly coexpressed with VGLUT3 and TH, and completely distinct from MrgprB4 neurons (Delfini et al. 2013). TAFA4-deficient mice have normal baseline thermal responsiveness but baseline mechanical sensitivity was not tested. Interestingly, in response to intraplantar formalin, while TAFA4 nulls exhibited a similar number of nociceptive behaviors during the first 5-min period (first phase) compared to wild types, they had increased behaviors during the second phase (10–60 min postformalin). Similarly, in both carrageenan-inflamed and nerve injured TAFA4 null mice, mechanical hypersensitivity was dramatically prolonged, an effect that was reversed with exogenous TAFA4. Moreover, excitability of lamina II_{inner} neurons in TAFA4-deficient mice was increased, suggesting that under normal conditions endogenous TAFA4 is antinociceptive.

To reiterate, mice deficient of VGLUT3 in C-LTMRs exhibit blunted nociceptive responses whereas mice deficient in TAFA4, found mainly in VGLUT3 neurons, show enhanced nociceptive responses. The same neurons appear to express molecules that promote nociceptive signaling (VGLUT3) and resist nociceptive signaling (TAFA4). Delfini et al. (2013) address this apparent contradiction by proposing that C-LTMRs may corelease glutamate and TAFA4, and it is the balance created by this corelease that tips either in favor of pro-nociceptive or antinociceptive effects.

They go on to suggest that under pathological conditions, increased C-LTMR activity may result in elevated TAFA4 release that suppresses nociceptive output to nociceptive neurons in the superficial dorsal horn. There is evidence to support increased C-LTMR activity in persistent inflammatory pain states: Using the intraplantar CFA model of peripheral inflammation, Takahashi et al. (2003) showed that electrophysiologically characterized C-LTMRs exhibit an enhanced responsiveness to cooling the skin as well as increased spontaneous activity. Considering the complex tangle of excitatory and inhibitory interneurons, intrinsic spinal neurons as well as peripheral terminals of sensory afferents, more work is required to understand just how C-LTMRs contribute to pain processing.

Final Statements

C-LTMRs are clearly involved in detecting gentle, slowly moving mechanical stimuli and, in contrast to myelinated A-fibers, are not ideally suited to sensory-discriminative functions. Thus, under normal conditions, C-LTMRs may serve affective-motivational purposes underlying social bonding. Considering the relatively small number of studies addressing C-LTMRs in pain processing as well as the technical differences between these studies, it is difficult to draw conclusions. An added confound may be related to the virtually universal approach to testing pain in rodents: The hind paw. C-LTMRs are not found in glabrous skin. As such, assessing C-LTMR involvement in pain processing using hind paw injections of irritants or nerve injury to distal limb nerves may not be optimal. For these reasons, Lou et al. (2013) also injected capsaicin into the hairy skin of the dorsal hind paw in VGLUT3-deficient mice, but found no difference compared to wild types, perhaps due to the generally smaller numbers of C-LTMRs in distal nerves innervating the limbs. With this in mind, as well as the generally greater number of C-fibers in visceral and deep muscle tissues, perhaps future studies using visceral or muscle pain models may be more fruitful. Moreover, considering the putative role that C-LTMRs play in social bonding, as well as mesolimbic pathway involvement in both reward and analgesia, it is surprising that only one study has probed their role in reward: Vrontou et al. (2013) demonstrated that DREADD-induced activation of C-LTMRs produced conditioned place preference. Future studies may also incorporate potential C-LTMR-induced changes in reward-motivational circuitry. Overall, C-LTMRs represent a small but fascinating class of sensory fibers that require additional experimentation.

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Chapter 3
Cell Biology of Tactile Afferents

Rebecca P. Seal and Ellen A. Lumpkin

Abstract This chapter reviews our current understanding of the cellular and molecular basis of sensory transduction and neurotransmission in mammalian tactile afferents. Recent advances from in vitro studies and rodent models have provided important insights into the cell biology of tactile afferents. The chapter covers fundamental mechanisms of mechanotransduction in cells, how these mechanisms relate to C-tactile afferents, and mechanisms of neurotransmission in these neurons.

Keywords Lanceolate ending • C-tactile afferent • C-LTMR • MrgB4 • Mechanotransduction channel • Peizo2 • Tether • Vesicular glutamate transporter

Tactile afferents are polarized cells with subcellular domains that carry out mechanosensory transduction and synaptic transmission. In mammals, these neurons have a somewhat unusual pseudounipolar morphology (Fig. 3.1). The basolateral compartment encompasses the neuron's soma, which is found in sensory ganglia of the dorsal root ganglia (DRG) or trigeminal ganglia. The apical compartment is composed of a branching axon, or afferent. The central branch, which projects to the dorsal horn of the spinal cord, forms presynaptic zones specialized for neurotransmitter release. The peripheral branch, which innervates the skin, terminates in specialized endings where mechanosensory transduction occurs. This chapter discusses fundamental mechanisms of mechanotransduction in cells, how these mechanisms relate to mammalian C-tactile afferents, and cellular mechanisms of neurotransmission in these neurons.

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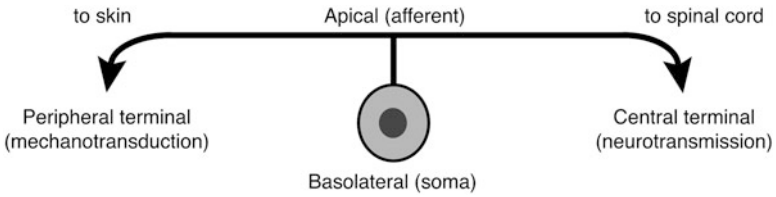

Fig. 3.1 Mammalian tactile afferents are polarized, pseudounipolar neurons. The basolateral compartment is made up of the soma (*light gray*), which localizes to dorsal root ganglia and contains the nucleus (*dark gray*). The apical compartment contains a branching afferent (*black line*). In C-tactile afferents, the peripheral branch projects to the skin, where terminals are specialized to mediate mechanotransduction. The central branch projects to the dorsal horn of the spinal cord, where terminals release neurotransmitters to activate second-order neurons

Cellular Force Sensing Is Ancient and Ubiquitous

The ability to detect mechanical stimulation is a fundamental feature of all cells, which are bombarded by physical forces in their environment. Single-cell organisms are subjected to fluid flow as well as fluctuations in solution osmolarity, which can trigger cell swelling, plasma-membrane stretch or changes in turgor pressure. The mechanical microenvironment is even more complex for eukaryotic cells in multicellular tissues. Along with fluid flow and osmotic shock, these cells can experience tissue stretch, compression, vibration, and adhesion forces at cell–matrix or cell–cell attachments.

To cope with this assortment of mechanical stimuli, cells have evolved a variety of structurally unrelated molecular force sensors. For example, integrins are mechanosensitive adhesion molecules that trigger intracellular signaling cascades critical for cell-fate determination, cell migration, and tissue morphogenesis (reviewed in Mammoto et al. 2013). In bacteria, stretch-activated channels of the MscL and MscS classes evolved independently to serve as pressure relief valves during osmotic downshock (reviewed in Kung et al. 2010). This redundancy highlights the indispensible nature of force sensing to an organism's survival.

With the evolution of the metazoan nervous system, elaborate mechanosensory systems developed to selectively encode mechanical inputs into neural signals. Within each sensory modality, specialized receptor cells are tuned to rapidly convert specific types of mechanical stimuli into electrical impulses, a process known as mechanoelectrical transduction. In the auditory and vestibular systems, mechanosensory hair cells transduce sound waves, gravitational forces, or rotational accelerations due to head movements. In the somatosensory system, primary sensory neurons that innervate the skin, musculature, and other organs initiate the senses of touch, itch, proprioception, and pain.

Models of Force Gating in Mechanosensitive Ion Channels

Sensory receptor cells transduce stimulus energy into electrical signals through the gating of transduction channels. In some cases, such as photoreceptors and olfactory neurons, transduction is an indirect process: a photon or volatile chemical activates a G-protein coupled receptor, which triggers an intracellular signaling cascade to open or close ligand-gated ion channels. The advantage of indirect gating is signal amplification, which affords sensitivity and reliability at the expense of speed. On the other hand, mechanosensory transduction typically occurs with submillisecond latencies, which is faster than known signal transduction cascades (Chalfie 2009). Because of this remarkable gating speed, mechanotransduction channels are thought to be directly activated by mechanical forces.

Two gating models have been proposed for mechanosensitive ion channels. First, stretch-sensitive ion channels are activated by membrane deformations, such as changes in membrane thickness or curvature (Kung 2005). Stretch-sensitive conductances, which can be activated by applying suction directly to the plasma membrane, are widely found in prokaryotic and eukaryotic cell types. A hallmark of stretch-sensitive channels is that they retain their mechanosensitivity when heterologously expressed or reconstituted in lipid bilayers. Examples of bona fide stretch-sensitive channels include the bacterial MscL channel mentioned above and eukaryotic channels of the recently discovered Piezo family, discussed below (Volkers et al. 2014).

A second model posits that mechanotransduction channels require tethers for efficient force gating (Chalfie 2009; Kung 2005). In this model, the transduction channel is at the core of a mechanosensitive protein complex anchored either to the extracellular matrix (ECM), the cytoskeleton, or both. Heterologous transduction channels expressed without tethering subunits are expected to display little or no mechanosensitivity. A wealth of biophysical and genetic evidence indicates that transduction channels are tethered in some mechanosensory cells (Chalfie 2009). For example, hair cells of the inner ear require extracellular filaments called tip links for proper transduction. In *Caenorhabditis elegans* body touch neurons, a multi-subunit complex called the MEC-4 complex mediates mechanotransduction. Consistent with the tether hypothesis, MEC-4 complexes expressed in heterologous cells form functional ion channels, but they lack mechanosensitivity. Moreover, genes encoding ECM and cytoskeletal proteins are required for organization and localization of MEC-4 complexes in vivo (reviewed in Lumpkin et al. 2010). Nonetheless, it is unclear whether putative tethers are directly involved in gating mechanosensory transduction channels, or whether they instead position transduction channels to respond to subtle changes in membrane forces. Moreover, with the exception of the MEC-4 complex, which comprises degenerin/epithelial sodium channel (Deg/ENaC) subunits, the molecular identities of tethered mechanosensory channels are still fiercely debated (Fettiplace and Kim 2014; Kawashima et al. 2015).

Identification of C-Tactile Afferents in Mice

Mammalian skin is innervated by mechanosensory neurons that differ in their cellular architectures, neurophysiological properties and sensory submodalities. The exquisite sensitivity of mammalian C-tactile afferents to innocuous mechanical stimuli makes them unique among the unmyelinated sensory neurons that innervate skin. These fibers exhibit a number of other defining physiological properties such as vigorous response to slow, but not fast brush strokes, response to cooling but not heating of the skin, an intermediate adaptation of their firing rate to sustained indentation, and the innervation of hairy but not glabrous skin (reviewed in Olausson et al. 2010). Variation in some of their properties such as conduction velocity (0.6–1.3 m/s) and the presence of delayed acceleration suggests the existence of more than one subtype of C-tactile afferent (Olausson et al. 2010).

In fact, two molecularly distinct populations of neurons unmyelinated sensory respond to light touch in mice. One population was identified by the expression of the Mas-related G-protein-coupled receptor, MrgB4 gene (Liu et al. 2007). MrgB4 belongs to a large superfamily of receptors, many of which are uniquely expressed by distinct populations of somatosensory neurons (Dong et al. 2001; Zylka et al. 2003). Mapping the peripheral projections of MrgB4$^+$ neurons, Liu et al. demonstrated that these afferents exclusively innervate hairy skin with receptive field sizes similar to those measured for human C-tactile afferents (Liu et al. 2007). This cell population makes up just 1–2 % of all DRG neurons, binds the lectin IB4, and projects to the same region of dorsal horn lamina II as the larger IB4$^+$ population (Liu et al. 2007). The functional role of these cells in somatosensation was recently demonstrated by Vrontou et al., who used the mrgb4 locus to selectively target expression of excitatory Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in these cells (Vrontou et al. 2013). Tested in a conditioned place preference paradigm, the mice showed a preference for the environment paired with DREADD-mediated activation of the MrgB4$^+$ population, consistent with the hypothesis that the cells encode a positively reinforcing sensation such as pleasant touch. Consistent with the proposed functional role, MrgB4$^+$ cells respond to light stroking and not to noxious punctate, mechanical stimuli (Vrontou et al. 2013). However, a more detailed analysis of their response properties is needed to clarify their relationship to human C-tactile afferents.

A second population of unmyelinated primary sensory neurons that responds to light touch are known as C-low threshold mechanoreceptors (C-LTMRs). These cells do not express MrgB4 or bind the lectin IB4 and they project to a more ventral part of lamina II, which is populated by interneurons expressing protein kinase C gamma (Seal et al. 2009). Similar to MrgB4$^+$ neurons, C-LTMRs also exclusively innervate hairy skin, forming longitudinal lanceolate endings around hair follicles (Li et al. 2011). Consistent with this innervation pattern, the cells represent 5–10 % of all DRG neurons innervating the fore and hind limbs and a higher percentage (15–20 %) of the DRG neurons innervating somatic regions containing hairy and not glabrous skin (Seal et al. 2009; Li et al. 2011). To date, three proteins expressed

specifically by C-LTMRs and not other primary sensory neuron populations have been identified in the adult mouse: the vesicular glutamate transporter (VGLUT) 3 (Seal et al. 2009), tyrosine hydroxylase (TH) (Li et al. 2011), and TAFA4 (Delfini et al. 2013). VGLUT3 packages glutamate into secretory vesicles for regulated release. In the brain, the carrier is expressed by a number of neuronal populations better known for signaling with a different classical transmitter such as raphe serotonin neurons and striatal cholinergic interneurons (Fremeau et al. 2004). Interestingly, TH is the rate-limiting enzyme for the synthesis of dopamine and norepinephrine, suggesting the possibility that C-LTMRs may also release a catecholamine. Finally, TAFA4 is a member of the Fam19A/TAFA family of chemokine-like proteins that was recently shown to prevent or suppress mechanical hypersensitivity through a spinal cord mechanism in chronic models of pain (Delfini et al. 2013).

The physiological response properties of C-LTMRs have been characterized in some detail using an ex vivo somatosensory preparation with thoracic DRG, nerves, and skin intact. To identify the cells, one group used the *vglut3* gene locus and another group the *th* locus to express fluorescent reporter proteins (Seal et al. 2009; Li et al. 2011). In both of these studies, the neurons responded to mechanical stimulation of the cutaneous receptive field with the lightest von Frey (0.07 mN) filament, with slow, but not fast, brush stroking, and with cooling but not heating. The conduction velocity of the fibers was ~0.6 m/s. These properties are consistent with those of human C-tactile afferents; however, the physiological role of C-LTMRs in normal touch has not yet been demonstrated.

The two populations of murine C-tactile afferents share several basic characteristics, including sensitivity to light stroking, small receptive fields, and exclusive innervation of hairy skin. They differ however in other characteristics such as the expression of molecular markers and their central projection patterns. Despite these differences, evidence thus far supports the possibility that these two fiber types convey similar sensory percepts, likely pertaining to affective aspects of touch. A detailed physiological characterization of the MrgB4$^+$ cells and evidence demonstrating the behavioral role of C-LTMRs in normal touch would help resolve whether these two fiber types have overlapping or distinct roles in mechanosensation.

The Cellular Architecture of C-LTMRs

C-tactile afferents respond to very gentle stroking of the hairy skin. Thus, the peripheral structure of C-LTMRs endings around hair follicles almost certainly plays a role in setting the response properties of these afferents to mechanical stimuli. In mice, C-LTMRs form longitudinal lanceolate endings that surround the shafts of awl, auchene, and zigzag, but not guard, hair follicles (Li et al. 2011). Zigzag-type hair follicles comprise ~80 % of pelage hairs, whereas awl and auchene hairs, which are morphologically similar, comprise ~20 % of pelage hairs. Interestingly,

D-hair Aδ primary afferents interdigitate with C-LTMRs as longitudinal endings around all three types of hair follicle. In addition, one type of Aβ afferent also forms longitudinal lanceolate endings and are interspersed with the C-LTMRs around only the awl/auchene hairs. As would be expected from such an arrangement, all three afferent types respond to hair movements and light touch. D-hair Aδ afferents also respond cooling, but not heating of the skin receptive field and have a rapid to intermediate adaptation rate, whereas Aβ afferents that innervate hair follicles show a very rapid adaptation rate (Li et al. 2011). These findings suggest that activation of C-LTMRs is likely to occur in concert with at least two other fiber types and is consistent with many studies suggesting that adaptation rates are set by factors distinct from the arrangement of the lanceolate complex (Li and Ginty 2014).

The afferent endings of LTMRs form important structural and functional relationships with terminal Schwann cells at the outer root sheath of the hair follicle (Li and Ginty 2014; Banks et al. 2013). Schwann cell processes surround longitudinal lanceolate endings of C-LTMRs and ablation of the Schwann cells in adult mice produced a loss of C-LTMR terminals around hair follicles. Thus, type-II Schwann cells are required to maintain the integrity of the C-LTMR lanceolate ending (Li and Ginty 2014). Whether lanceolate endings are required for maintaining Schwann cells seems less clear due to a potentially more complex relationship. In adult mice, denervation of the skin around hair follicles does not affect Schwann cell number (Li and Ginty 2014). However, consistent with an important role for the Schwann cell, reinnervated lanceolate endings find and form interactions with the Schwann cells indicating a potential role for the latter in the regeneration of the nerve endings (Li and Ginty 2014).

Mechanotransduction Mechanisms in Tactile Afferents

Since the late 1970s, intensive research efforts have aimed to identify genes that encode mechanotransduction channels in touch receptors. Numerous transduction channel candidates have emerged from genetic screens in *C. elegans* and *Drosophila melanogaster*. To date, all of these candidates fall into two gene families: Deg/ENaCs and transient receptor potential (TRP) channels. Interestingly, the TRP channels TRPM8 and TRPV1 serve as thermosensory transduction channels in mammalian somatosensory neurons. Several TRP channels and Deg/ENaC subunits (encoded by *ACCN* genes) are also expressed in mammalian touch receptors, leading to the hypothesis that they function as mechanotransduction channels. Genetic disruption of some of these mammalian candidates cause subtle changes in the physiological responses of touch receptors (Lumpkin et al. 2010; Kwan et al. 2009; Quick et al. 2012; Vilceanu and Stucky 2010); however, individual mutations do not severely impair touch sensitivity, as they do in invertebrate neurons. It is possible that genetic redundancy contributes to these subtle touch phenotypes. Alternatively, TRP channels and Deg/ENaC channels might modulate the responsiveness of mammalian touch receptors rather than act as transduction channels.

A recently discovered class of mechanically gated ion channels encoded by *Piezo* genes has generated substantial excitement in the field (Volkers et al. 2014). In a technical *tour de force*, Patapoutian's group identified Piezo1 and its only mammalian homolog, Piezo2, as necessary and sufficient components of stretch-activated channels in mammalian cells (Coste et al. 2010). Piezo-dependent channels can be activated either by membrane suction or by direct displacement of the plasma membrane. Piezo genes encode massive transmembrane proteins that are conserved in many eukaryotic species. Consistent with the broad distribution of stretch-activated ion channels in mammalian cell types, *Piezo1* and *Piezo2* are widely expressed in both mechanosensory and nonmechanosensory tissues.

Do *Piezo* genes encode mechanotransduction channels in sensory receptor cells that initiate touch and pain? Consistent with this hypothesis, genetic disruption studies have shown that *Piezo* genes are required for mechanical nociception in *Drosophila* and for responses to gentle touch in zebrafish larvae (Faucherre et al. 2013; Kim et al. 2012). Although *Piezo1* shows little to no expression in mammalian somatosensory neurons, *Piezo2* is expressed by 60 % of unmyelinated and 28 % of myelinated dorsal root ganglion (DRG) neurons (Coste et al. 2010). In cultured DRG neurons, focal membrane displacement evokes mechanosensitive currents with rapidly adapting (RA), intermediately adapting (IA) or slowly adapting (SA) inactivation kinetics. RA currents correlate with large-diameter LTMRs, whereas SA mechanosensitive currents are found predominantly in small-diameter, putative nociceptors (Lechner et al. 2009). Interestingly, the physiological properties of RA mechanosensitive currents closely match those of heterologously expressed Piezo2 channels. Moreover, *Piezo2*-directed short interfering RNAs severely attenuate RA currents without altering IA or SA responses in cultured DRG neurons (Coste et al. 2010). A recent study suggests that the mechanical threshold of Piezo-dependent RA currents is set by an accessory subunit, STOML3, mutations in which cause a dramatic loss of touch sensitivity in vivo (Poole et al. 2014; Wetzel et al. 2007). Finally, recent rodent studies provide functional evidence that *Piezo2* is required for mechanotransduction in mammalian Merkel cells and for proper mechanically evoked responses from these gentle-touch receptors in the intact skin (Ikeda et al. 2014; Maksimovic et al. 2014; Woo et al. 2014). Together, these data not only support Piezo2 as a candidate mechanotransduction channel in some types of touch receptor cells, but also suggest that additional mechanotransduction channels remain to be discovered.

The mechanical responsiveness of C-LTMRs might be due in part to the expression of *Piezo2*. Deletion of the *runx1* transcription factor in C-LTMRs of mice produced a loss of *Piezo2* expression, which was accompanied by a loss of mechanical responsiveness of the cells when tested in culture (Lou et al. 2013). Confirmation of Piezo2 as the principal mechanoreceptor of C-LTMRs will require further evaluation of mechanosensitivity in a more intact system and with selective deletion of Piezo2.

Do touch transduction channels require extracellular tethers analogous to cochlear hair-cell tip links? Tip links are calcium-dependent, heteromultimeric adhesion molecules composed of cadherin 23 and protocadherin 15 (Fettiplace and Kim 2014). Evidence from ultrastructural studies indicates that such filamentous

structures exist at the peripheral endings of some LTMRs in vitro (Hu et al. 2010). The newly described tether binds laminin, is sensitive to cleavage by subtilisin, and is calcium-independent, but the molecular identity has not yet been reported. Based on biochemical and functional analyses, it is molecularly distinct from hair-cell tip links. Whether this structure is required for mechanosensory functions in other populations of touch-sensitive neurons including the C-tactile afferents of rodents and humans has not been determined.

Thermal Transduction Mechanisms in C-LTMRs

Along with gentle brushing, C-tactile afferents respond to innocuous cooling; however, the response is much less robust than that of somatosensory neurons known to express the thermotransduction channel TRPM8. Measured in the ex vivo somatosensory preparation, a decrease in temperature of the skin receptive field from 32 to 4 °C produced action potentials in C-LTMRs that began at ~26 °C (Seal et al. 2009). This value is within the same range as the activation threshold measured for TRPM8 and is considered a response to cooling rather than cold. The mechanism underlying C-LTMR activation by decreasing temperature is still not known, but may be due to the low level expression of TRPM8 or the expression of other channels gated by cooling. For example, the cool sensitivity might reflect the thermal sensitivity of leak channels that set resting membrane potential or of voltage-activated ion channels that generate action potentials in somatosensory neurons (reviewed in McKemy 2013). Alternatively, activation of C-LTMRs may not involve cooling-gated channels, but rather, a drop in temperature may induce a structural rearrangement of the hair follicle-longitudinal lanceolate ending complex that activates the mechanosensitive channel.

Neurotransmitter Signaling by C-Tactile Afferents

Somatosensory neurons transmit information to the brain and spinal cord, and likely also to their peripheral target tissues, primarily through the regulated release of vesicular glutamate. This excitatory amino acid is packaged into secretory vesicles by a family of transport proteins that reside on the vesicle membrane and specifically recognize glutamate. The three members of this family (VGLUT1-3) exhibit a largely nonoverlapping expression pattern throughout the mammalian nervous system. VGLUTs 1 and 2 are the predominant isoforms, whereas VGLUT3 is more sparsely distributed. In adult somatosensory neurons, VGLUT1 is expressed by most large, myelinated neurons and VGLUT2 is expressed by a few myelinated and likely all unmyelinated neurons (reviewed in Brumovsky 2013). It therefore appears that both MrgB4$^+$ and C-LTMRs express VGLUT2 while C-LTMRs also express VGLUT3. Neither MrgB4$^+$ neurons nor C-LTMRs express the neuropeptides CGRP

or substance P (Dong et al. 2001; Seal et al. 2009). Thus, except for the potential synthesis of catecholamines by C-LTMRs, both MrgB4$^+$ and C-LTMRs likely rely strictly on glutamate for neurotransmitter signaling.

Given the largely nonoverlapping distribution of VGLUT isoforms, the presence of VGLUTs 2 and 3 within C-LTMRs suggests distinct roles for the two transporters. In recombinant systems, all three VGLUTs exhibit similar transport properties. However, in neurons, VGLUTs 1 and 2 interact with different proteins and traffic to distinct synaptic vesicle pools (Voglmaier et al. 2006). Less is known about VGLUT3, but unique sequences within the N- and C-termini suggest the transporter has discrete protein partners. The influence of these protein–protein interactions and modes of vesicle recycling on synaptic function is still not fully understood. One hypothesis suggests that these properties allow VGLUTs to influence probability of neurotransmitter release and synaptic plasticity (Voglmaier et al. 2006; Weston et al. 2011). In the brain, synapses with a high probability of release typically rely on VGLUT2. The probability of release at synapses that express VGLUT3 is more variable, making it less clear whether the two vesicular transporters would have a distinct impact on synaptic signaling and plasticity in C-LTMRs due to this criterion.

The VGLUTs also undergo different patterns of subcellular trafficking. VGLUT 1 and VGLUT2 traffic almost exclusively to nerve terminals and are rarely observed in cell bodies or dendrites. By contrast, VGLUT3 is found not only in nerve terminals, but also in somatodendritic compartments of a number of neuronal populations and has been shown to mediate retrograde release in the cortex (Harkany et al. 2004). Interestingly, as somatosensory neurons are pseudounipolar, proteins within their axonal compartment are typically trafficked both centrally and peripherally (Fig. 3.1). In the case of C-LTMRs, VGLUT3 but not VGLUT2 has been detected in central terminals (Seal et al. 2009). VGLUT2 may be expressed at low levels in central terminals as has been observed for other unmyelinated DRG neuron subtypes or more interestingly, the transporter may traffic only to the periphery, as has been proposed to occur with TH in these cells (Brumovsky et al. 2006).

As mentioned earlier in this chapter, the expression of TH suggests that C-LTMRs potentially synthesize and release catecholamines; however, other molecules required for catecholamine synthesis and release are not detected in C-LTMRs, including vesicular monoamine transporters (VMAT) 1 and 2, plasma membrane dopamine (DAT), norepinephrine transporters (NET), and amino acid decarboxylase (AADC) (Seal, unpublished data). Expression of TH in the absence of other catecholamine markers occurs in scattered neuron populations throughout the brain and its role in these cells is still not understood. It may be that certain conditions, such as nerve or tissue damage, upregulate the genes encoding the other catecholamine-related proteins. Alternatively, the cells may produce and release the product of TH enzymatic activity, L-dopa. A less exciting hypothesis posits that TH expression in such cases is vestigial. Interestingly, a larger percentage of DRG neurons are immunoreactive for TH during embryogenesis suggesting a developmental role for this enzyme in the DRG (Li et al. 2011). Whether this larger population is capable of releasing catecholamines has not been reported.

Concluding Remarks and Future Perspectives

Recent advances from in vitro studies and rodent models have provided important insights into the cellular and molecular basis of sensory signaling and neurotransmission by tactile afferents. Nonetheless, fundamental aspects of C-tactile afferent function and physiology remain unanswered. It remains to be determined whether the mechanotransduction in these afferents is mediated by Piezo2 or by other mechanosensitive channels that have yet to be described. In addition, essential molecular elements that work in concert with the mechanosensitive channel to shape the sensitivity, strength, and adaptation rate of the response are still not known. The mechanisms that regulate glutamate release by central and also likely peripheral endings of C-tactile afferents, as well as the impact of this neurotransmitter on affective touch, remain to be determined. Finally, to understand cell biological mechanisms of affective touch, the wealth of genetic and molecular data gleaned in rodents must be extended to studies of human C-tactile afferents.

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Chapter 4
Visualization of the Cutaneous Axonal Endings of CLTMs

Vincenzo Donadio

Abstract Affective touch is hypothesized to be driven by unmyelinated low-threshold mechanoreceptors that are often abbreviated as CLTMs in animals and CTs in humans. Despite numerous neurophysiological studies, morphological identification of CLTMs has been reported in only a few animal studies, but with contrasting data.

In the first mouse study, CLTMs were identified with a rare subpopulation of unmyelinated sensory fibers denominated Mas-related G-protein-coupled receptor B4 (MrgprB4) which encircled the neck of hair follicles. By contrast, a different mouse study supported the correspondence of CLTMs with tyrosine hydroxylase (TH) positive fibers which were found to form longitudinal lanceolate endings associated with hair follicles. A morphological study of CT skin endings in humans is needed to explain species-related difference or to define if CLTMs described in animals represent only one class of human CTs.

Keywords C-tactile unmyelinated nerve afferents • Affective touch • MrgprB4 • TH • Microneurography • Hair follicle

The sense of touch is essential for determining the location of a stimulus on the skin surface, for haptic exploration, and for object manipulation. However, these discriminative aspects of touch are complemented by an affective aspect that has only recently begun to be scientifically investigated (McGlone et al. 2007, 2014). The "skin as a social organ" involves interindividual contact, affective behavior, and the formation and maintenance of relationships hypothesized to be driven by C-tactile unmyelinated nerve afferents (CTs) which may represent a first stage for encoding the affective dimension of touch (Vallbo et al. 2007; Olausson et al. 2010; Morrison et al. 2010).

Many functional characteristics of unmyelinated low-threshold mechanoreceptors were defined by using a neurophysiological approach in animals (CLTMs:

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Bessou et al. 1971; Kumazawa and Perl 1977) and humans (CTs: Nordin 1990; Vallbo et al. 1999; Olausson et al. 2002; Wessberg et al. 2003).

CTs respond specifically well to slow, gentle touch, such as that which occurs during close social interactions, whereas they are not involved in temporal or spatial discrimination of touch (Essick et al. 2010; Morrison et al. 2010). These fibers are slow-conducting, easily fatigued, and often show after-discharge, that is, they may continue to fire for several seconds after stimulus withdrawal (Vallbo et al. 1999). They preferentially respond to stroking over the skin surface within a velocity range (1–10 cm/s) that is also rated as most hedonically pleasant, as opposed to slower (0.1 and 0.3 cm/s) or faster (30 cm/s) speeds (Loken et al. 2009). Psychophysical studies find that the same stroking velocities correlate with the highest subjective magnitude of pleasant touch (Loken et al. 2009; Essick et al. 2010). In mammals, including humans, CTs have been identified in the face and in the hairy skin of the body (Bessou et al. 1971; Kumazawa and Perl 1977; Shea and Perl 1985; Nordin 1990; Edin 2001; Light and Perl 2003), but not in the glabrous skin of the palm/paw (Georgopoulos 1976; Johansson and Vallbo 1979; Johnson et al. 2000). Additionally, CTs do not respond to capsaicin and they do not express the TRPV1 (transient receptor potential vanilloid 1) (Olausson et al. 2010). In cats, a subpopulation of CLTMs is very sensitive to hair movements (Iggo 1960). A comparison with humans is difficult since CTs in man does not respond to guard hairs movements which are not connected to CLTMs in animals, whereas the CTs response to thin hairs has not been tested (Olausson et al. 2010). However, the receptive fields of human CTs are roughly round or oval in shape with no preferred orientation. Detailed analyses revealed a large field consisting of one to nine small responsive spots distributed over an area up to 35 mm^2 (Wessberg et al. 2003).

Cumulative evidences support the hypothesis that CTs constitute a second cutaneous system serving slow C afferent low-threshold mechanoreceptors (LTMRs) in addition to that served by myelinated A-beta afferents conveying information from fast LTMRs (Vallbo et al. 1999; Olausson et al. 2002; Cole et al. 2006). The prevalent hypothesis is that pleasant touch from hairy skin, mediated by CTs, is processed in the limbic-related cortex and represents an innate nonlearned process. In contrast, pleasant touch from glabrous skin, mediated by A-beta afferents, is processed in the somatosensory cortex and represents an analytical process dependent on previous tactile experiences (McGlone et al. 2012).

Neurophysiological characteristics may help to identify the morphology of unmyelinated low-threshold mechanoreceptors in the skin which was hampered by a lack of markers for specific subtypes, the high degree of complexity of the myriad axonal skin endings, and the long distance between skin fibers endings and their connections in the spinal cord and brainstem.

Despite numerous neurophysiological studies, morphological identification of CLTMs has been reported only in few animal studies, but with contrasting data. Additionally, a systematic morphological study of CTs into the human skin has not been reported so far.

Liu et al. (2007), using a genetically encoded tracer, described in mice the peripheral representation of a rare subpopulation of unmyelinated sensory fibers

denominated Mas-related G-protein-coupled receptor B4 (MrgprB4). Mas-related G-protein-coupled receptors (Mrgpr), also called sensory neuron-specific receptors, are specifically expressed in subsets of small-diameter sensory neurons (Dong et al. 2001; Lembo et al. 2002). According to these authors, several similarities suggested that MrgprB4 correspond to CLTMs. MrgprB4 axons were unmyelinated, negative for CGRP and TRPV1, and positive for Griffonia simplicifolia isolectin B4 (IB4) suggesting the nonpeptidergic nature of these fibers. The density of MrgprB4 terminals increased proximally and they were absent in the genitalia. They exclusively innervate hairy skin showing a large receptive size with scattered distribution reflecting extensive branching in individual terminal arbors, remarkably similar to human CTs as reported by microneurography. The pattern of MrgprB4 arbors was bilaterally asymmetric and distinct between different animals (Fig. 4.1). MrgprB4 fibers) appeared to encircle and penetrate the necks of hair follicles and the adjacent epidermis. They were absent from all specialized cutaneous sensory structures, as well as from muscle arrector pilorum and blood vessels, and appeared to be aligned with a different subsets of Mrgpr (MrgprD) and CGRP fibers. However, the role of MrgprB4 fibers is not clear. Ligands for MrgprB4 have not yet been identified although some other Mrgpr family members are known to encode neuropeptide receptors (Dong et al. 2001; Lembo et al. 2002). There is also the possibility that MrgprB4 marks a rare population of nociceptors, such as C mechanoinsensitive cells (Schmidt et al. 2002). Nevertheless, in a recent study from the same research group (Vrontou et al. 2013), a better functional characterization of these fibers was reported. This study was based on a calcium imaging model to record physiological responses of primary sensory neurons to cutaneous stimulation in an intact animal. During peripheral stimulation, spinal projections of MrgprB4 fibers were selectively activated by massage-like stroking of hairy skin, but not by noxious punctate mechanical stimulation. By contrast, a different population of C fibers expressing MrgprD was activated by pinching but not by stroking. These important data pointed out that the two classes of cutaneous C fibers marked by expression of MrgprB4 and MrgprD respond to distinct types of mechanical stimulation in vivo. The reason why MrgprB4 fibers are not activated by pinching is not clear, but could reflect their specific tuning to moving stimuli (Vrontou et al. 2013). However, MrgprB4 neurons could not be classified as LTMRs according to the electrophysiological criteria established for CTs since they were not activated by von Frey filaments (Vrontou et al. 2013). Additional studies will be required to determine whether sensory neurons with similar properties exist in humans and to establish if MrgprB4 neurons may constitute at least one class of CLTMs. However, one important property of these neurons is related to behavioral responses. Pharmacogenetic activation of MrgprB4-expressing neurons in freely behaving mice promoted conditioned place preference, indicating that such activation may have a positive affective valence that is positively reinforcing and/or anxiolytic.

The conclusion of these studies on the morphological identification of CLTMs in mouse was not confirmed by Li et al. (2011). They reported an integrated study to identify peripheral and central projections of LTMRs which are classified as Aβ, Aδ, or C based on their action potential conduction velocities (Horch et al. 1977).

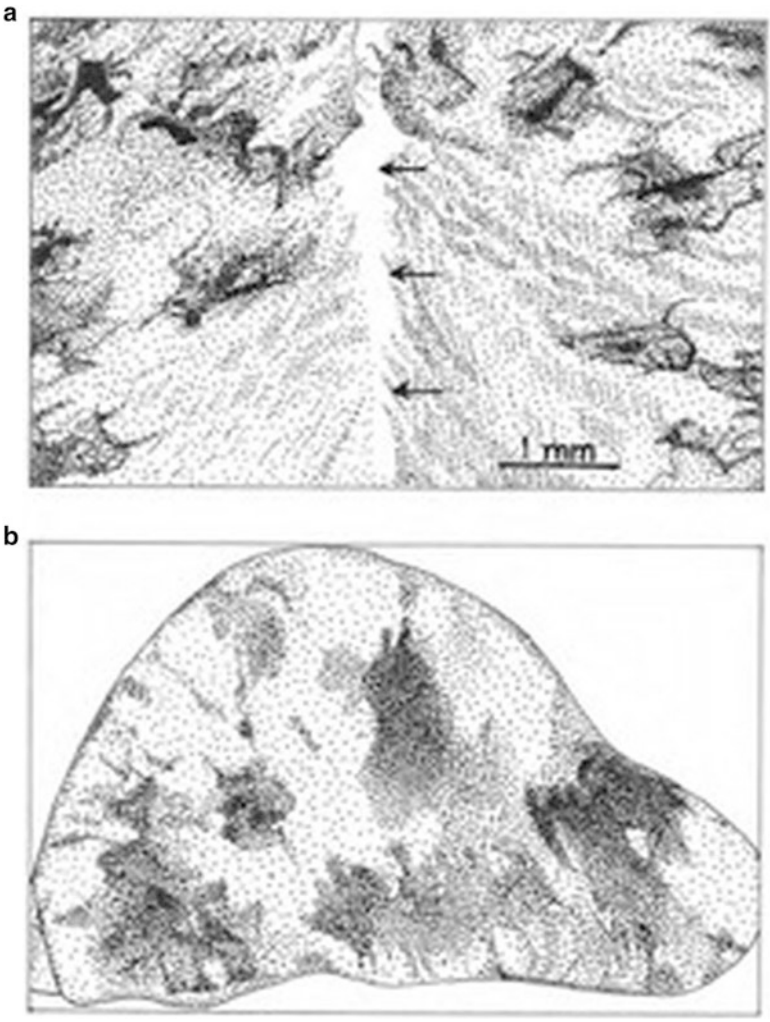

Fig. 4.1 Schematic representation of hairy skin MrgprB4 nerve terminals in mouse. (**a**) MrgprB4 endings show large and asymmetric arborizations (*dark staining*) in ventral thoracic skin. *Arrows* indicate midline; (**b**) MrgprB4 peripheral projections in the ear of mouse

C-LTMRs or CLTMs are unmyelinated and thus have the slowest conduction velocities, whereas Aδ-LTMRs and Aβ-LTMRs are lightly and heavily myelinated, exhibiting intermediate and rapid conduction velocities, respectively. Using a molecular-genetic labeling and somatotopic retrograde tracing approaches to identify Aβ, Aδ, and CLTMs, they described the pattern of organization of these axonal fibers in the skin and spinal cord of mouse (Li et al. 2011). Physiological intracellular recordings of CLTMs showed classically defined features of CTs: slow conduction velocities (CV = 0.58 ± 0.02 m/s), trains of spikes in response to

application of light mechanical force (1–5 mN); intermediate adaptation to stationary stimuli; and robust responses to rapid cooling but not warming of the skin. Additionally, as CTs CLTMs showed a large cutaneous receptive field of a single unit, exclusive innervation of hairy skin without fibers in the glabrous skin, and a prevalent innervation of proximal limb skin. The molecular characterization of CLTMs in adult mouse dorsal root ganglion (DRG) disclosed the expression of tyrosine hydroxylase (TH), which catalyzes the production of L-DOPA from tyrosine in the catecholamine biosynthesis pathway. TH is expressed in a large population of small-diameter DRG neurons (Brumovsky et al. 2006) which do neither express neurofilament (NFH), a marker for sensory neurons with myelinated axons (Rice and Albrecht 2008) nor CGRP, tropomyosin receptor-kinase A (TrkA) or TRPV1, which are markers for peptidergic nociceptors (Molliver et al. 1997). Rather, nearly all TH neurons express the nonpeptidergic nociceptor markers cRet and *Gfra2* (Molliver et al. 1997). Different from the unmyelinated nerve fibers described by Liu et al. (2007) and Vrontou et al. (2013), these TH positive neurons do neither bind the lectin IB4, nor do they express MrgprA1, MrgprA3, MrgprA4, MrgprB4, MrgprC11, or MrgprD all of which are expressed in nonpeptidergic nociceptors (Dong et al. 2001; Molliver et al. 1997). Thus, the TH DRG neurons are a molecularly unique population of nonpeptidergic, small-diameter sensory neurons. The peripheral axonal branches of individual TH positive CLTMs were found to arborize and form longitudinal lanceolate endings that are intimately associated with hair follicles on the hairy skin of the back. There are three major types of hair follicles on back hairy skin of mice (Driskell et al. 2009; Li and Ginty 2014): guard or tylotrich hairs (the longest and least abundant type with two rows of medulla cells); Awl/auchene hairs (shorter than guard hairs with three or four rows of medulla cells), and zigzags (the finest and most abundant type with a single row of medulla cells). Each of the three hair follicle types receives a specific combination of peripheral endings of LTMR subtypes. Furthermore, axons of select LTMR subtypes are intimately associated with one another, having entwined projections and interdigitated lanceolate endings that innervate the same hair follicle. Indeed, guard hair follicles are uniquely associated with a combination of Aβ-LTMR; Awl/auchene hairs are innervated by Aβ-LTMR and CLTMs; and Zigzag hair follicles are innervated by both CLTMs and Aδ-LTMRs (Fig. 4.2). In addition, because the three hair follicle types exhibit different shapes, sizes, and cellular compositions, they are likely to have distinct deflectional or vibrational tuning properties. Thus, guard, awl/auchene, and zigzag hairs are likely physiologically distinct mechanosensory end organs. The data from this study suggested that CLTMs are an abundant mechanosensory neuronal population providing rich innervation of trunk and proximal limb hairy skin associated exclusively with zigzag and awl/auchene hair follicles where their lanceolate endings are interdigitated with Aδ-LTMR fibers in a similar percentages: ~20 % of both C- and Aδ-LTMRs are associated with awl/auchene hair follicles, whereas ~80 % are associated with zigzag hair follicles. Remarkably, the tight morphological correlation between the endings of these two types of fibers around individual hair follicles suggested a common mechanism of excitation, which is supported by considering that both CLTMs and Aδ-LTMR fibers are highly

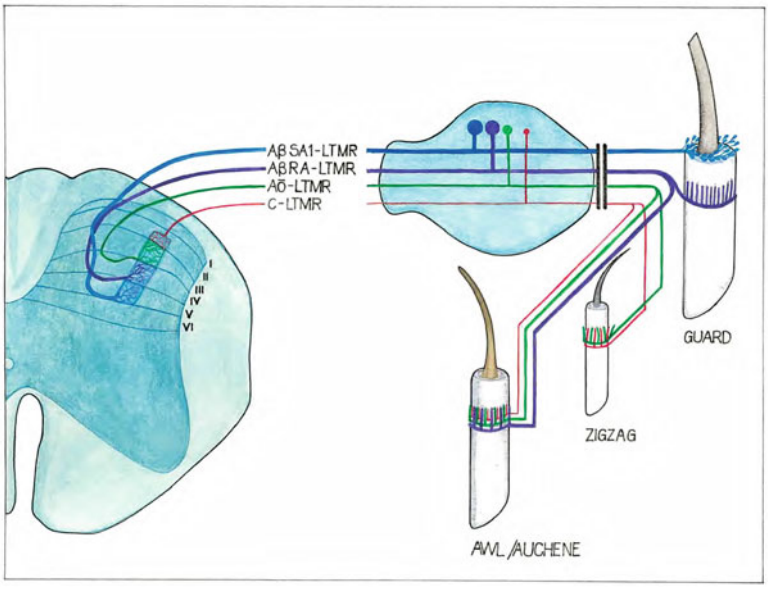

Fig. 4.2 Schematic LTMR organization in hairy skin and spinal cord dorsal horn in mouse. The peripheral endings of slowly adapting (SA1) and rapidly adapting (RA) Aβ-LTMR, Aδ-LTMR, and C-LTMR (or CLTMs) fibers are associated with either one or two of the three types of hair follicles of trunk and proximal limb hairy skin. At zigzag hair follicles, C-LTMRs (*red*) and Aδ-LTMRs (*green*) form interdigitated longitudinal lanceolate endings; awl/auchene hair follicles display Aβ RA-LTMR (*blue*), Aδ-LTMR (*green*), and C-LTMR (*red*) fibers interdigitated longitudinal lanceolate endings; guard hair follicles are associated with longitudinal lanceolate endings formed by Aβ RA-LTMR (*blue*) or Aβ SA1-LTMR fibers (*purple*). The central terminals of a peripheral LTMR unit innervating the same or adjacent hair follicles are aligned to form a narrow LTMR column in the spinal cord dorsal horn

sensitive to skin stimulation, responding to the finest von Frey filament and also to rapid cooling of the skin (Li et al. 2011).

Based on a molecular characterization and the von Frey filament response, the CLTMs described by Li et al. (2011) (i.e., TH positive fibers) did not correspond to that one described by Liu et al. (2007) and Vrontou et al. (2013) studies (i.e., MrgprB4 positive fibers). Furthermore, the analysis of DRG sensory neurons confirmed that TH and MrgprB4 belong to different peripheral nerve fiber populations (Lallemend and Ernfors 2012). A functional and morphological characterization of DRG sensory neuron types can be delineated by the expression of neurotrophic factor receptors, TrkA, TrkB, TrkC, Met, and Ret receptor tyrosine kinases, which serve as receptors for several neurotrophic factors (Bourane et al. 2009; Luo et al. 2009; Gascon et al. 2010). The unmyelinated populations are divided into four main categories: the late TrkA (lTrkA), the late Ret (lRet), the TrpM8 (Transient potential menthol receptor), and the TH lineages showing different ancestors (Lallemend and Ernfors 2012). Mrgpr class of receptors are expressed in the lRet line as nonpeptidergic neurons containing TrpC3 (Transient receptor potential subfamily C) and

IB4 and they include MrgprB4, MrgprA3 (acting as receptors for histamine independent itch), and MrgprD (polymodal pain-sensing nociceptors). By contrast, unmyelinated TH neurons do neither express TrkA, TRPV1, or Mrgpr, nor do they bind IB4 (Seal et al. 2009). They likely represent CLTMs, but the ancestors are still unknown and not connected to any early studied immature neuronal population (Lallemend and Ernfors 2012). In conclusion, available morphological studies in animals mainly described CLTMs around awl/auchene or zigzag hair follicles, substantially confirming neurophysiological data (Iggo 1960). However, these data only partially explain human neurophysiological findings which shows that CTs are not usually sensitive to movements of thick hairs although the CTs response to thin (i.e., awl/auchene or zigzag) hair follicles has not been tested (Olausson et al. 2010). A morphological study of CT skin endings in humans should be needed to explain species-related difference or to define if CLTMs described in animals represents only one class of human CTs.

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Chapter 5
The Peripheral Processing of Pleasant Touch in Mice

Sophia Vrontou

Abstract All social animals exhibit behaviors during which pleasant touch actions take place. That is also true for rodents including mice, which represent an experimental organism with genetic accessibility. Therefore, it is of great interest to study the processing of gentle touch in mice and clarify how these organisms detect and respond to such actions. Lately, a lot of advances have been made toward the peripheral processing of pleasant touch in mice. In humans, the C-Tactile (CT) fibers are believed to constitute the putative neurobiological substrate for rewarding touch processing. Whereas it was long believed that the C-Low Threshold Mechanoreceptors (C-LTMRs) in mammals represent the equivalent of the CT fibers in humans, these fibers have not been genetically identified until recently. Fortunately, several genetic markers for C-LTMRs have been identified in mice, enabling a deeper understanding of the encoding for pleasant touch in these organisms. Interestingly, a subpopulation of C-fibers that are stimulated by massage like stroking exhibit a positive valence effect when they are artificially activated and have been also identified in these experimental models. These particular fibers that do not belong in the C-LTMR family could constitute a distinct subclass of CT fibers in mice, offering another genetic handle for the elucidation of pleasant touch processing.

Keywords C-Tactile fibers • C-low threshold mechanoreceptors (C-LTMRs) • Mrgprs • MrgprB4 • Pleasant touch • Stroking

Introduction

All social animals experience during social interactions a broad spectrum of tactile stimulations, by their conspecifics. These actions occur either during parent–offspring interactions, or during sexual and aggressive encounters, but also during affiliative

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behaviors (McGlone et al. 2014; Carter et al. 1997). Interestingly, the tactile inputs during most social interactions (except those during aggression events) are "rewarding" (Hertenstein et al. 2006; Insel 2003).

On the other hand, all organisms should have circuits and functions that allow them to operate in the most optimal way in any given situation, circumvent any inconveniences, and capitalize any given opportunity (LeDoux 2012a, b). Therefore, they should also have neural pathways for processing "rewarding touch" actions, occurring during social interactions. As a result we could study the unconscious processing of rewarding tactile stimuli in any organism, analyze how these stimuli are detected and responded to, and ultimately develop general principles for the coding of "pleasant" touch (LeDoux 2012b; Stanley and Adolphs 2013; Adolphs and Anderson 2013). Mice are an ideal organism to study the neural processing of rewarding touch where, apart from sexual and aggressive behaviors, they display a series of social behaviors that are characterized by innocuous and dynamic tactile stroking actions by their conspecifics. These include nurturing (maternal grooming), but also affiliative behaviors such as such as side-by-side or huddling tactics, allogrooming, group sleeping, hugging, social proximity, and social play. In addition, several lines of evidence show that such social interactions in mice are rewarding (Insel and Young 2001; Panksepp and Lahvis 2007), suggesting that the sense of touch, which is so notable during these interactions, could be actually rewarding. Furthermore, seemingly beneficial tactile actions also occur in mice, for example, during scratching or rubbing to relieve pain or itch that provide a more functional benefit. Interestingly, an indirect measure of the affective state of mice could arise from approaches, using operant learning behaviors, such as conditioned place preference (reward) or avoidance (punishment) (Panksepp and Lahvis 2007) (Fig. 5.1). Nevertheless, despite the fact that the mammalian brain is anatomically and neurochemically equipped to generate emotional responses it is not possible to study directly the emotional aspect of such stimuli in these organisms and analyze how they are experienced by them since these states are not accessible to humans, as noted by Nico Tinbergen (Bateson and Laland 2013). Lastly, the ability to perform genetic manipulations in mice and the recent technological innovations that enable manipulation and activity recordings of their neurons at single cell level make them ideal for such studies (Packer et al. 2013; Scanziani and Hausser 2009).

MrgprB4 Neurons and Their Association with Pleasant Touch

MrgprB4 neurons belong to a family of G-protein-coupled receptors (GPCRs) that are related to the proto-oncogene MAS1 and are called Mrgprs (Dong et al. 2001). In mice, this subset comprises more than 50 GPCRs, including 6 single-copy genes (*MrgD* Zylka et al. 2005, *MrgE*, *MrgF/RTA*, *MrgG*, *MrgH/GPR90*, and *MAS1*), as well as three large subfamilies (*MrgA*, *MrgB*, and *MrgC*), each consisting of ten highly duplicated genes (Dong et al. 2001; Zylka et al. 2003). Interestingly, only *Mrgs D–G* have clear human orthologs (Fig. 5.2).

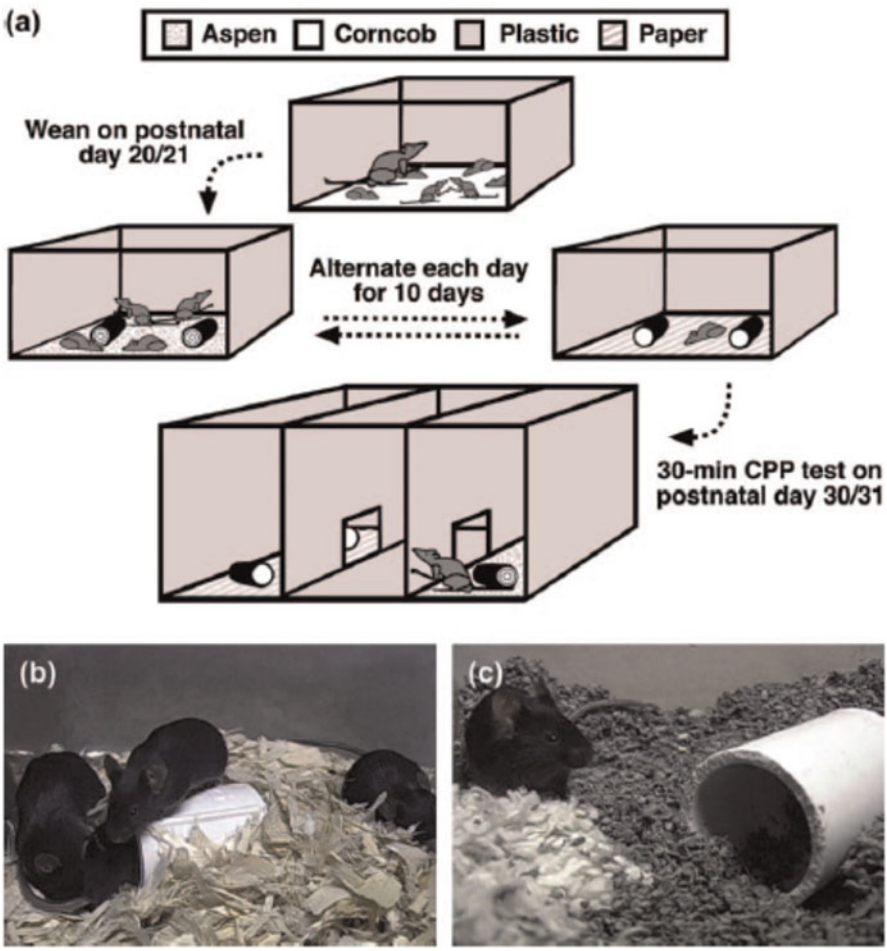

Fig. 5.1 Conditioning procedure for evaluating the social preferences of juvenile mice. (**a**) Following 24 h of social housing in a distinct home cage environment, mice were socially isolated in a second novel home cage environment for the next 24 h. The conditioning context (social or isolate housing) was always counter-balanced relative to its pairing with the home cage environment (aspen or paper bedding). Mice were alternately housed in each environment every 24 h for a total of 10 days. Following the last day of conditioning, which entailed 24 h of social isolation, the spatial location and locomotor activity of individual mice were monitored during a 30-min test session. (**b**) Photograph of socially housed juvenile B6 mice in an aspen environment. (**c**) Photograph of an isolated juvenile B6 mouse housed in a paper environment (figure taken from Panksepp and Lahvis 2007))

At this point it is worth mentioning that in the adult mouse Mrgprs neurons constitute a glial cell line-derived neurotrophic factor (GDNF)-dependent subset of dorsal root ganglia (DRGs) that expresses the (GDNF) receptor c-Ret and also binds the Griffonia simplicifolia isolectin, IB4 (Dong et al. 2001). This subset is further

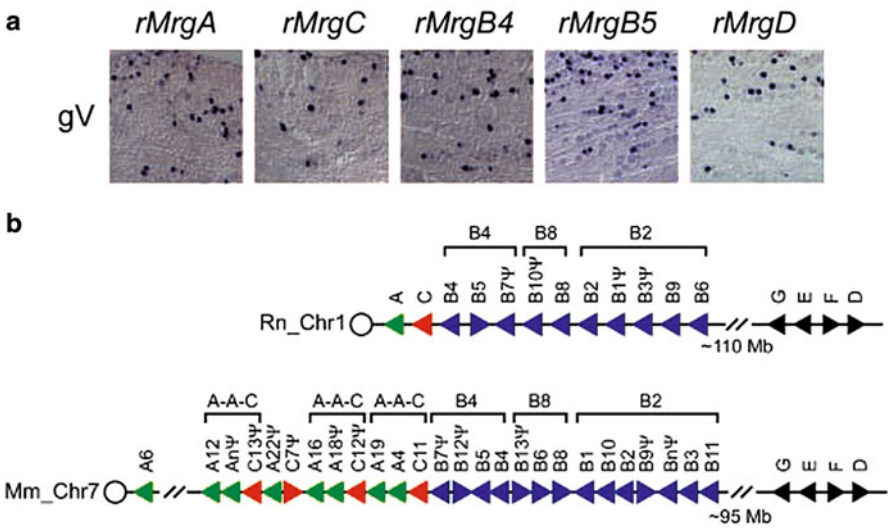

Fig. 5.2 Correlated expression and chromosomal localization of rodent Mrgs. (**a**) Expression analysis of rat Mrgs in adult trigeminal ganglia (gV). In situ hybridization was performed with antisense digoxigenin-labeled riboprobes. (**b**) Chromosomal arrangement of rat and mouse Mrgs. Analyses of the January 21, 2003, assembly of the rat genome and the February 24, 2003 (National Center for Biotechnology Information mouse build 30), assembly of the mouse genome revealed that most of the Mrg family members were located within two discrete regions of rat chromosome 1 and mouse chromosome 7. These two regions encompass the MrgABC cluster (760 kb in size from rat assembly NW 043369; 1.2 Mb in size from mouse assemblies NT_039420-NT_039423) and the MrgDEFG cluster (1.9 Mb in size from rat assemblies NW_043404-NW_043405; 1.6 Mb in size from mouse assembly NT_039437). The *circle* marks the relative position of the centromere. *Triangles* denote the direction of transcription and indicate the relative position of each gene on the chromosome. This figure is not drawn to scale. *Brackets* indicate the location of the three MrgB subdivisions. Several of the mouse A-A-C repeats are also highlighted. The mouse A-C cluster begins with MrgA6 and ends with a misassembled fragment of MrgC11. We did not plot all of the mMrgA and mMrgC genes because of obvious inaccuracies in the mouse assembly. Figure taken from Zylka, M.J., Dong, X., Southwell, A.L. & Anderson, D.J. Atypical expansion in mice of the sensory neuron-specific Mrg G protein-coupled receptor family. Proc Natl Acad Sci U S A 100, 10043-8 (2003). Copyright (2003) National Academy of Sciences, USA

divided in multiple distinct subpopulations with unique expression profiles, which implies that each one of them might subserve alterative functions (Dong et al. 2001). As far as the protein structure of the Mrgpr receptors, it has been shown that they have short and divergent extracellular N-termini (3–21 amino acid), with no signal peptide and highly conserved transmembrane and intracellular domains. Unfortunately, the majority of the endogenous ligands for the Mrgprs remain elusive, rendering them as orphan receptors (Dong et al. 2001; Han et al. 2002).

Members of the Mrgpr family in mice (by employing knock-in and knock-out technology and by performing appropriate functional studies) have so far been associated with mechanical pain, tissue damage (Cavanaugh et al. 2009; Qu et al. 2014), and itch (Liu and Dong 2015; Liu et al. 2011) sensation.

Morphological and Anatomical Characteristics of MrgprB4 Neurons

MrgprB4 neurons represent a very small population of DRGs and trigeminal neurons, comprising approximately less than 2 % of their total (approximately 4000 neurons per mouse). MrgprB4 is completely absent from enteric neurons, sympathetic ganglia, the central nervous system, and other tissues examined. Interestingly, the expression of MrgprB4 in DRG neurons is initiated after birth, at barely detectable levels at P1, getting stronger from P4 and persists through adulthood, suggesting that it may not be required for the embryonic neural development (Liu et al. 2007). More detailed anatomical studies, using a knock-in line that replaces the MrgprB4 coding region with the axon tracer human placental alkaline phosphatase (PLAP), has showed that the MrgprB4 neurons mark a small subset of small diameter, unmyelinated, nonpeptidergic, IB4+ cells. Interestingly, this subset is more abundant in the thoracic than in the lumbar and cervical level. Additionally, it was demonstrated that the MrgprB4 neurons lack a series of protein markers, abundant in other DRG subsets, as the neurofilament 200 kD, the calcitonin gene-related polypeptide (CGRP), the purinergic receptor X3 (P2X3), and the transient receptor potential cation channel V1/vanilloid receptor 1 (TrpV1/VR1), but on the other hand they exhibit low levels of the GDNF receptor c-Ret (Liu et al. 2007) (Fig. 5.3). The identification of the expression profile of the MrgprB4 neurons is very important, since these proteins markers could be revealing for their function, as has been shown for other subpopulations of DRGs (Cavanaugh et al. 2009).

The peripheral organization of the MrgprB4 projections (using PLAP histochemistry and immunostaining in several diverse peripheral tissues) revealed that they exclusively innervate the hairy skin of mice, whereas their central nervous system (CNS) innervation was restricted to the spinal trigeminal nucleus that receives projection from trigeminal ganglia. Additionally, the MrgprB4+ fibers were observed in the dorsal hairy skin of the paws, but their endings could not be detected in the plantar surface of both hind paws and front paws, as they were completely absent from the glabrous skin. In particular, the MrgB4$^+$ innervation density varied across different regions of the hairy skin, with highest innervation density observed in the ear and body skin (including both the dorsal and ventral skin) and substantially less innervation in the tail skin. Although MrgB4$^+$ nerve terminals can be observed in the mystacial pad, no innervation was found in the mystacial vibrissa follicle–sinus complex. In addition, MrgprB4+ nerve endings could not be detected in the genitalia that lack hairy skin. Astonishingly, the MrgprB4+ peripheral projections exhibit an innervation topography characterized by large, discontinuous patches with extensive branching, covering 50–60 % of the hairy skin. The size of each such patch/arbor ranged from 0.27 ± 0.04 mm^2 (in body skin) to 0.838 ± 0.068 mm^2 (in ear skin) and as a result given the fact that there are 4000 MrgprB4+ neurons per animal and 60 cm^2 of skin per mouse, each MrgprB4+ fiber terminates in 1–3 such arbors. At this point it is worth mentioning that MrgB4$^+$ fibers showed asymmetrical patterns of innervation along the midline in the same mouse and demonstrate random projection footprints in the hairy skin of different animals (Liu et al. 2007) (Fig. 5.4).

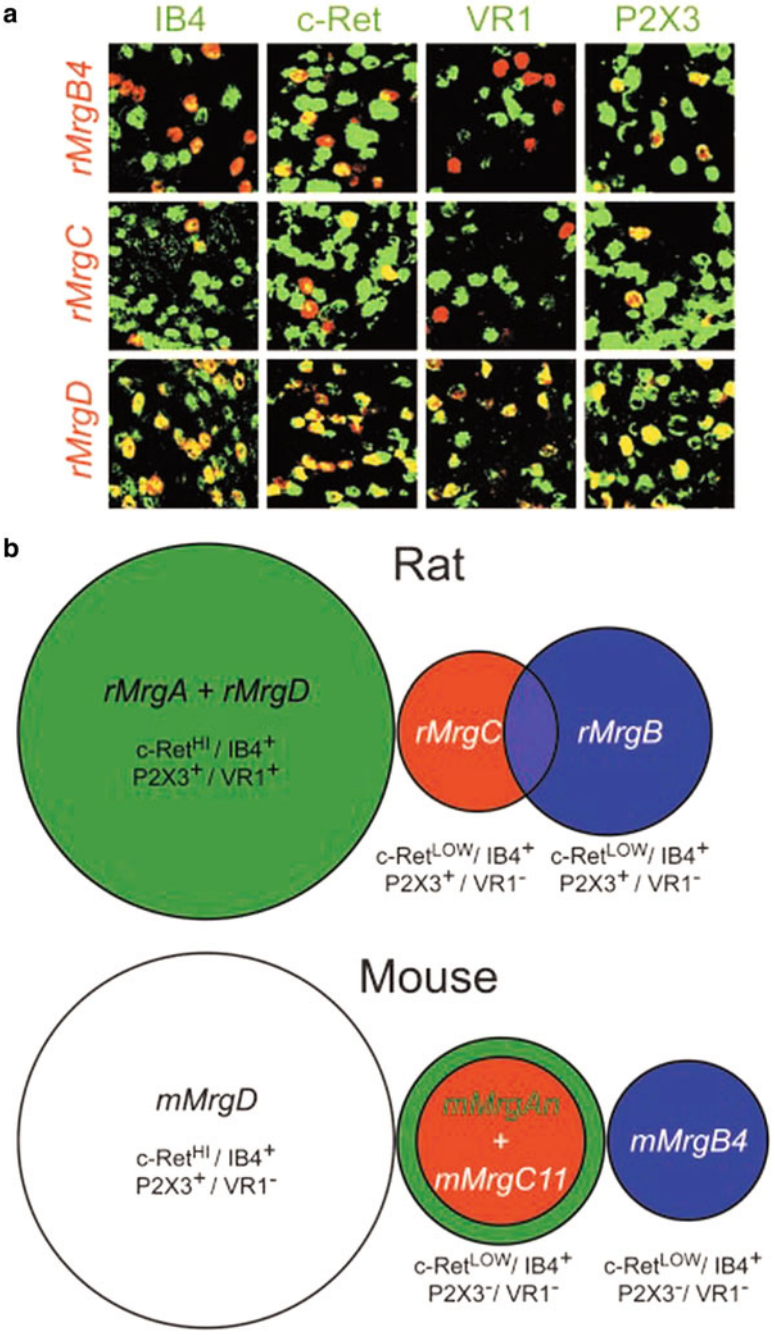

Fig. 5.3 Analysis of Mrg expression in adult rat and mouse DRG neurons. (**a**) Coexpression of rat Mrgs with various sensory neuron markers. With the exception of IB4, all gene combinations were detected by double-label in situ hybridization (ISH) with the indicated antisense cRNA probe. Fluorescein conjugated G. simplicifolia IB4-lectin was applied to sections after the ISH procedure to detect IB4-binding cells. (**b**) Summary of the rat and mouse Mrg expression domains in adult DRG sensory neurons. The sizes of the *circles* in the Venn diagrams are proportional to the sizes of the cell populations. Our results of double-label ISH among mMrgAs, mMrgB4, mMrgC11, mMrgD, and several nociceptive sensory neuron markers are also indicated (Bateson and Laland 2013; Scanziani and Hausser 2009). Figure taken from Zylka, M.J., Dong, X., Southwell, A.L. & Anderson, D.J. Atypical expansion in mice of the sensory neuron-specific Mrg G protein-coupled receptor family. Copyright (2003) National Academy of Sciences, USA

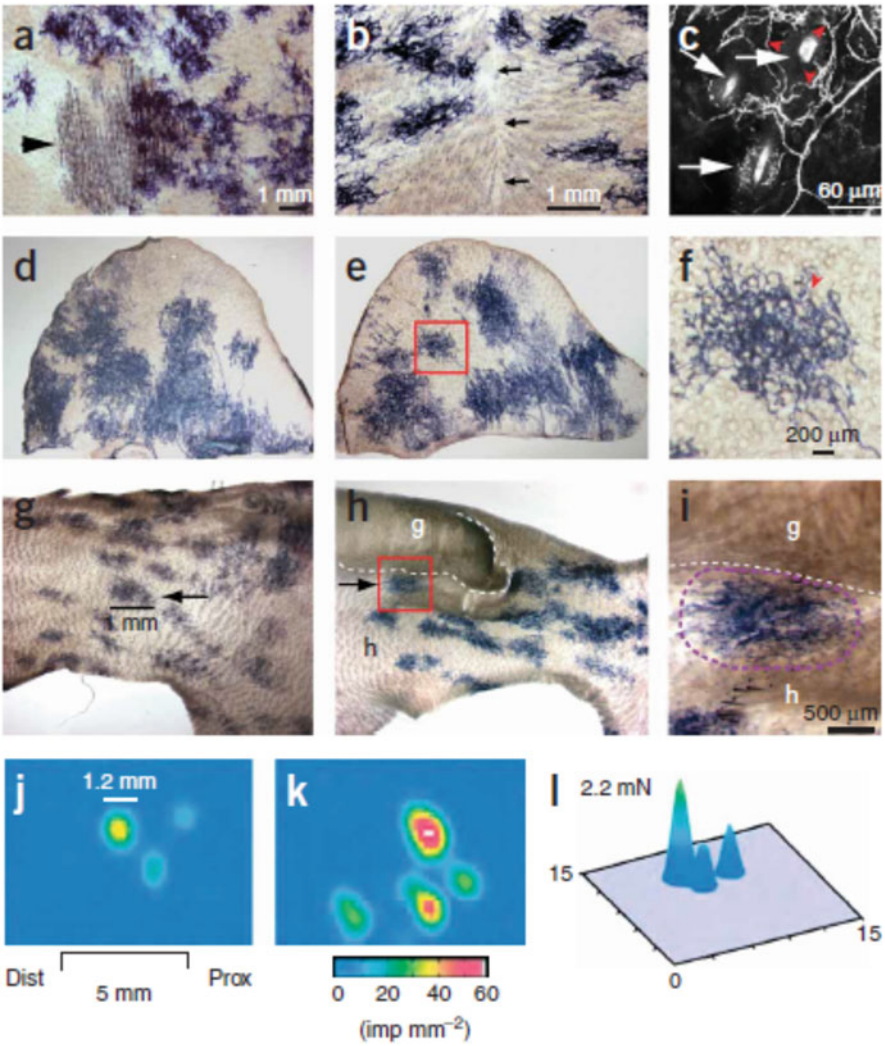

Fig. 5.4 MrgprB4+ peripheral terminals exclusively innervate hairy skin and show large arborizations. (**a**, **b**) Dorsal (**a**) and ventral (**b**) thoracic skin from MrgprB4ΔPLAP mice stained by whole-mount PLAP histochemistry. *Arrowhead* indicates hairs (**a**) and *arrows* indicate midline (**b**). (**c**) Whole-mount immunofluorescent staining of PLAP expression in thoracic skin (flat-mount view); *arrows* indicate hair follicles. (**d**, **e**) Right ears from two MrgprB4ΔPLAP mice. (**f**) Higher magnification view of *boxed area* in (**e**). (**g**–**i**) Whole mounts of total hindlimb skin (proximal to the right). Note the patchy MrgprB4+ innervation (*arrow*). (**h**, **i**) MrgprB4+ fibers were present in hairy (**h**), but not glabrous (**g**), skin. (**i**) Higher magnification view of *boxed area* in (**h**). (**j**–**l**) Receptive fields of C-fiber tactile afferents defined by microneurography. Note the similar size and distribution of individual touch-sensitive spots and MrgprB4+ arbors (1.2-mm scale bar in (**j**); 1-mm bar in (**g**)). (**l**) Three-dimensional density plot of the receptive field shown in (**j**) (figure taken from Liu et al. 2007)

More detailed characterization of the morphology and termination zones of MrgprB4+ free nerve endings within the epidermis of the hairy skin revealed that they encircle and penetrate the upper part of the hair follicles, as well as the contiguous epidermis (Fig. 5.4c). In addition, they were absent from all cutaneous specialized sensory structures, including Meissner corpuscle, Merkel cells, sweat gland, and vibrissa follicle–sinus complex, as well as from muscle and blood vessels within the skin. Interestingly, MrgprB4 neurons do not seem to play a role in cutaneous axon guidance, given the fact that their homozygous knockouts exhibit an analogous innervation pattern (Liu et al. 2007).

Correlation of MrgprB4 Neurons in Mice with the CT Fibers in Humans: Functional Analysis of MrgprB4 Neurons

As mentioned in the previous chapters, there is a category of unmyelinated afferents in human skin, called tactile C-afferents (CT) that is believed to mediate the pleasant affective touch sensation. This hypothesis is based on microneurography studies (that reveal the nature of the activating stimuli of these fibers), on psychophysics (that discloses their perceptual impact) and on fMRI data (that pinpoint their central projections in humans) (McGlone et al. 2014; Olausson et al. 2010). The low threshold mechanoreceptive afferents (C-LTMRs) in mammals, first identified in cat almost 70 years ago (McGlone et al. 2014), are considered to be the animal equivalent of the CT fibers in humans. But interestingly, several striking morphological and anatomical similarities suggest that also the MrgprB4 fibers may constitute another "unique" class of CT afferents in mice, distinct from C-LTMRs. Initially, MrgprB4+ axons, as revealed by electron microscopy, are small diameter and unmyelinated and therefore could be classified as C-fibers. In addition, immunostaining analysis revealed that they are negative for the markers CGRP and for the capsaicin-sensitive channel TrpV1, as are the CT fibers in humans. Most importantly, the MrgprB4+ fibers, as with CT afferents, innervate exclusively the hairy part of the skin. Additionally, their size (~0.3–1 mm^2), their scattered distribution, and the number of arborization fields per each MrgprB4 terminal (~1–3) are remarkably similar to those of touch-sensitive spots within human CT receptive fields (as has been determined by microneurography studies). Furthermore, the density of the MrgprB4 projections is higher in the ear than in the lower limb, where in addition there is a proximally biased allocation, all notably consistent with the topography of CTs. Last but not least, $MrgprB4^+$ central projections terminate in lamina II, which is in agreement with the cortical processing of CT stimulation, as identified by functional magnetic resonance imaging (fMRI) studies (Liu et al. 2007).

All these morphological and anatomical lines of evidence neither certify the involvement of MrgprB4 neurons in the peripheral processing of pleasant touch, nor exclude alternative roles of function for these neurons. For example, these fibers could mark nociceptors (as has been shown for other members of the Mrgprs family Cavanaugh et al. 2009; Qu et al. 2014). Nevertheless, MrgprB4 neurons do not express nociceptive signaling molecules such as the TRPV1 or the P2X3.

Alternatively, this subpopulation of C fibers could belong to the subclass of the mechano-insensitive nociceptors (which are also called "silent nociceptors," since they are not excited even by von Frey hairs of 750 mN). The silent nociceptors become mechano-responsive upon inflammation (Schmelz et al. 2000) and are believed to participate in the encoding of painful stimuli, such as the intracutaneous capsaicin injection and tonic pressure, and are also implicated in the induction of primary and secondary hyperalgesia (Schmidt et al. 2000). However, the mechano-insensitive units are characterized by large innervation territories, which are an order of magnitude bigger than the receptive fields of CT afferents (Olausson et al. 2010) and consequently of MrgprB4 axons. On the other hand, the MrgprB4 neurons could be involved in the axon reflex vasodilation. Interestingly, the axon reflex flare seems unlikely to be associated with the MrgprB4 fibers. This is based on the fact that these neurons do not express CGRP, which is involved in the production of this erythema. Lastly, as with other members of the Mrgprs family (such as the MrgprA3 Liu et al. 2009), these fibers could be associated with itch sensation.

Therefore, functional studies are necessary in order to provide some insight of the role of MrgprB4 neurons. The first effort toward this goal was initiated by applying the conventional and established method of ex vivo skin-nerve preparation (Woodbury et al. 2001; Koerber and Woodbury 2002), that has been used successfully to assign modality to several populations of somatosensory neurons (Li et al. 2011; Rau et al. 2009). For this method the spinal cord of mice is hemisected, and up to ten contiguous dorsal cutaneous nerves (DCNs), along with a longitudinal rectangular patch of dorsolateral skin, are dissected in continuity with their DRGs. The resulting isolated preparation consists of the spinal cord, the DRGs nerves, and a piece of intact skin with no underlying tissue. Unfortunately, this approach failed to produce any responses in MrgprB4 neurons, when directly applying mechanical, thermal, and chemical stimuli (inflammatory soup). Nevertheless, these negative results indirectly diminish the possibility that MrgprB4 fibers could potentially function as mechano-insensitive neurons or as mechanical and thermal nociceptors. In general, since the ex vivo skin preparation is the principal method to attribute distinct discriminatory functions to somatosensory neurons, the lack of MrgprB4 responses with this approach might imply that these fibers do not have an explicit discriminatory function. Under these circumstances, in order to enlighten the function of MrgprB4 fibers an in vivo technology of recording activity of somatosensory neurons was considered (Vrontou et al. 2013). This novel procedure enabled the application of more "natural" stimuli in the periphery of an intact organism in vivo, which might be necessary in order to uncover more qualitative than quantitative/localized functions for cutaneous peripheral neurons. More specifically, it allows the detection of calcium responses at the central projections of specific subsets of somatosensory neurons in the spinal cord, expressing genetically encoded calcium indicators (Akerboom et al. 2013) (GECIs). By establishing and applying this novel technology, it was revealed that the MrgprB4 neurons are excited by a gentle, dynamic stroking of the hairy skin of mice with a paintbrush, while concurrently mildly pressing their underlying tissue (Vrontou et al. 2013). These specific tactile stimulations are reminiscent of massage stimulations in humans (Fig. 5.5).

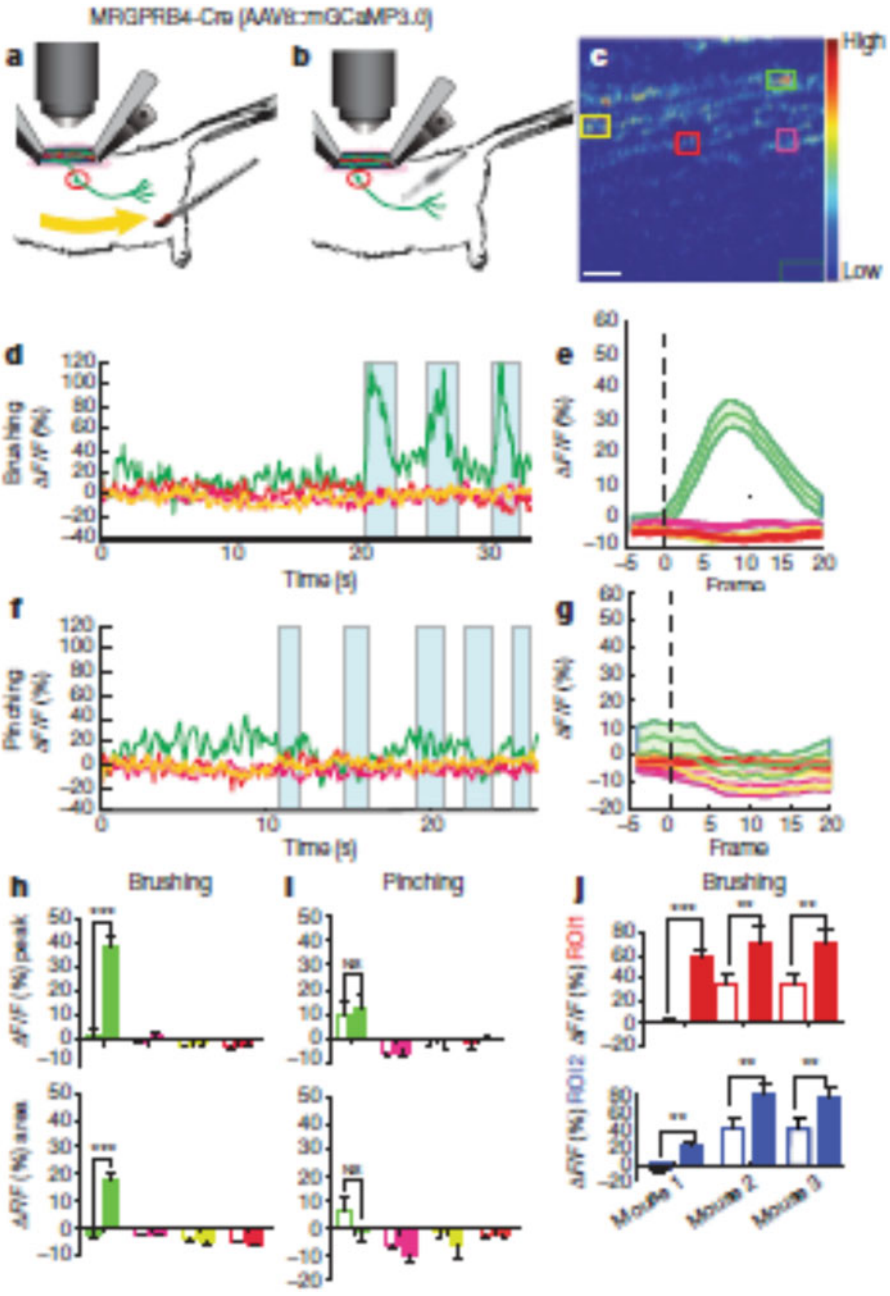

Fig. 5.5 Activation of MRGPRB4 fibers by stroking. (**a**, **b**) Schematics illustrating brushing (**a**) and pinching (**b**) stimuli. (**c**) GCaMP3.0 fluorescence in one imaging frame during stimulation and ROIs used for imaging in (**d**–**i**). The dark-green rectangle (*lower right*) is the region used for background subtraction. Scale bar, 8.5 μm. (**d**) Superimposed traces from different color-coded ROIs (**c**) in a single trial of three brush stimuli (*turquoise bars*). (**e**) Average response to brushing from

Furthermore, a positive valence effect was attributed to these neurons using an operant learning behavioral assay (conditioned place preference CPP), which has been employed successfully to study social reward in mice (Panksepp and Lahvis 2007; Dolen et al. 2013). More specifically, during this assay the MrgprB4 neurons were artificially activated in a distinct but otherwise neutral environmental context, whereas their activation was withheld upon another environmental context. Upon completion of this conditioning, it was shown that the mice urge a preference for the specific location where the activation of MrgprB4 neurons has occurred, when they were allowed to move freely in a three chamber apparatus, containing the two above environmental contexts on the edges and a middle neutral plastic enclosure. Therefore, their manipulation can serve as a reward, promoting a CPP (Fig. 5.6). The artificial activation of MrgprB4 neurons was achieved pharmacologically by targeting DREADD receptors (designer receptors exclusively activated by a designer drug) in these neurons (Vrontou et al. 2013; Alexander et al. 2009). It is noteworthy that these two aforementioned functional results, (the stimulation of the MrgprB4 neurons by gentle stroking and the concomitant rewarding effect of their activation), represent the first demonstration in mice of a relationship between a rewarding outcome and coding at the level of somatosensory neurons in the peripheral nervous system.

In conclusion, the nature of the mechanical stimuli that activates the MrgprB4 fibers (stroking stimuli), in combination with their perceptual impact (positive valence effect upon their activation) suggests that this subpopulation of C-fibers could share some similarities with the CT afferents in humans. But interestingly, the MrgprB4 neurons cannot be classified as C-LTMRs, which are believed to be the corresponding CT fibers in mammals, since no responses could be detected using the ex vivo skin prep for these neurons. Nevertheless, this subpopulation of C-fibers could represent "one unique class" of CT afferents in mice and therefore could contribute to pleasant touch sensation in mice. Consequently, conserved principles for the organization of the peripheral coding for pleasant tactile stimulation could be derived from studying the circuitry initiated from these neurons.

On the other hand, the protein markers, TH (Li et al. 2011), TAFA4 (Delfini et al. 2013), and VGLUT3 (Seal et al. 2009), which designate almost overlapping neuronal subpopulations in mice (Abraira and Ginty 2013) have been recently categorized as C-LTMRs and as a result they share one very important characteristic with

Fig. 5.5 (continued) a single mouse ($n=5$ trials, ~3–6 stimuli per trial). See also Supplementary Fig. 5g–j. (**f**) Response to five pinching stimuli (*turquoise bars*) in brush-sensitive region (**d**), in same ROI (**c**). See also Supplementary Fig. 9a–f. (**g**) Average response to pinching from the same animal ($n=2$ trials, ten stimuli total). (**h**, **i**) MPI ΔF/Fpeak (*upper*) or integrated area (*lower*) calculated from the curves in (**e**, **g**), respectively. *Open* and *filled bars* are 5 frames before and 20 frames after stimulus delivery, respectively. *NS* not significant. (**j**) MPI ΔF/Fpeak in two different ROIs (*red* and *blue* graphs) from each of three independent mice. *Open* and *filled bars* as in panels (**h**, **i**). $^{**}P<0.01$; $^{***}P<0.001$. All data are mean ± s.e.m. Reprinted with permission from Macmillan Publishers Ltd: NATURE. Vrontou, S., Wong, A.M., Rau, K.K., Koerber, H.R. & Anderson, D.J. Genetic identification of C fibres that detect massage-like stroking of hairy skin in vivo. Copyright 2013

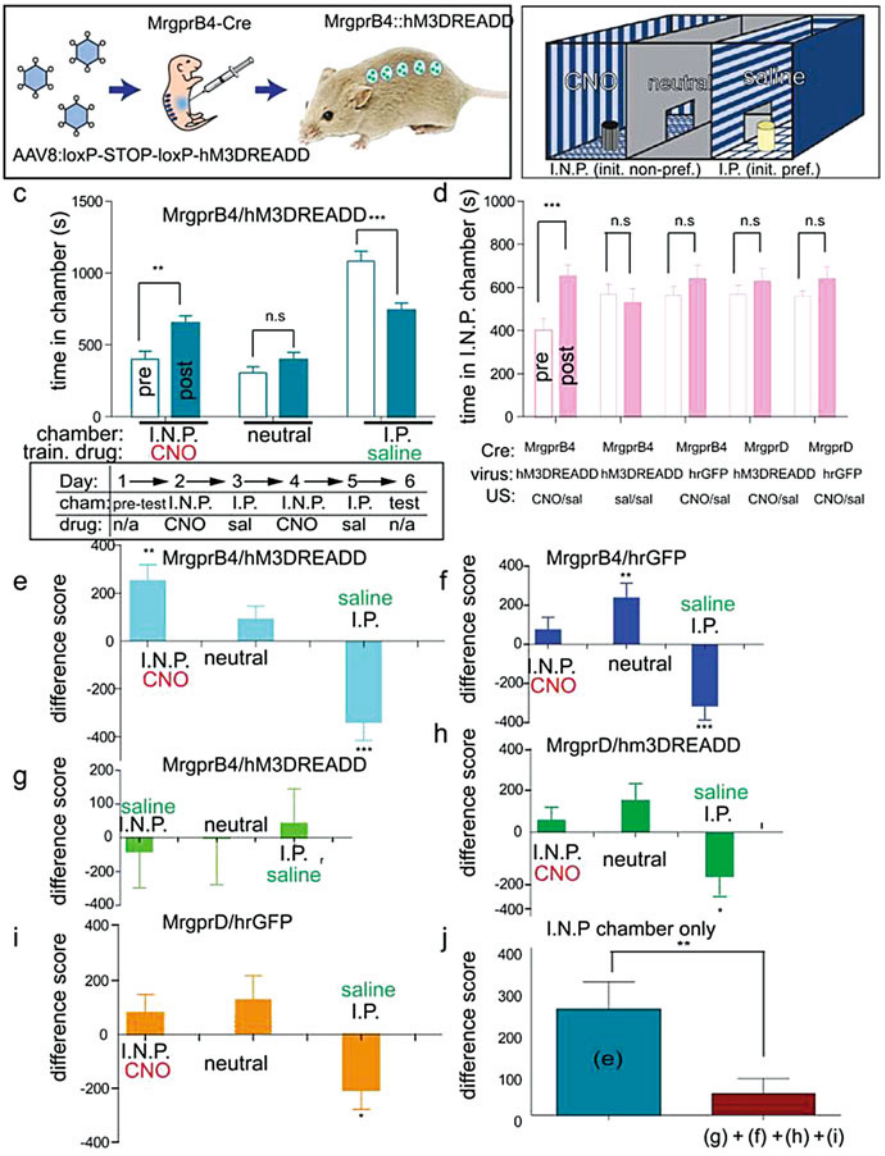

Fig. 5.6 Activation of MRGPRB4 neurons promotes conditioned place preference. (**a**, **b**) Schematic of experiment (**a**) and CPP apparatus (**b**). I.N.P. and I.P. indicate initially nonpreferred and preferred chambers, respectively (**c**, schematic, 'pre-test'). (**c**) *Top*: absolute time (s) in each chamber before (*open bars*; 'pre') versus after (*filled bars*; 'post') conditioning for the experimental group. Train. drug indicates CNO or saline paired with the indicated chamber. *Bottom*: schematic of experimental design. *Cham.* chamber. (**d**) Time in I.N.P. chamber for experimental (replotted from *panel* (**c**) for direct comparison) and control groups. $^{**}P<0.01$; $^{***}P<0.001$; *NS* not significant. (**e**–**i**) Difference scores ((time in indicated chamber after training) − (time in chamber before training)) for experimental (**e**, $n=15$) and control (**f**, **g**, **h**, **i**, $n=9$, 6, 8, 10, respectively) groups.

the CT fibers in humans. Despite this similarity, their corresponding neurons have not been associated yet with any positive valence sensation experimentally and therefore their association with CT fibers relies only on their innocuous discriminative quality. Notably, the notion stated earlier, that the MrgprB4 neurons might not transmit absolute discriminatory, but rather qualitative information of positive valence, might actually offer an explanation for the discrepancy in the results between the ex vivo and the in vivo recordings of MrgprB4 neurons and could explain the requirement of in vivo approaches to reveal their function. In addition, the excitation of the MrgprB4 neurons might entail the concurrent existence of several mediators, appearing only in an intact organism. For example, their activation could depend on descending information from the brain following the prior processing of other sensory stimuli, olfactory, visual, and tactile. Furthermore, the stimulation of MrgprB4 neurons might rely on signals emanating from the arousal of the vasculature, connective and fat tissue that underlies the skin of intact mice being stimulated by stroking actions. Therefore, the participation of such factors in the activation of MrgprB4 neurons demands the need of an intact organism and the use of in vivo approaches to measure their activity.

Nevertheless, the findings described earlier cannot reveal the natural behaviors during which the MrgprB4 neurons are normally excited. In order to elucidate the real physiological behaviors that MrgprB4 neurons participate, and to clarify their specific role, loss of function studies, as well as recordings in freely behaving animals are needed (Ghosh et al. 2011; Flusberg et al. 2008). In addition, it should be emphasized that we lack at the moment information about the central processing of MrgprB4 neurons, which could potentially provide some insight of whether their coding engages limbic cortical areas, as is the case for the brain activation during stimulation of CT fibers in humans. Despite that, natural behaviors that share stroking actions with recompensating effects are primarily those associated with social interactions, such as during parent–offspring interactions or during affiliative behaviors. But on the other hand, rewarding tactile actions could happen during scratching or rubbing, to relieve pain or itch. According to this latter view, the MrgprB4 neurons could be also involved in pain and or itch modulation. This second alternative is enhanced by the fact that other members of the Mrgpr family are associated with the sensation of pain and itch, as mentioned earlier. Interestingly, the CT fibers in humans have also been associated with pain modulation (Liljencrantz and Olausson 2014; Liljencrantz et al. 2014) and the same is true for CLTMRs in mice (Seal et al. 2009).

Fig. 5.6 (continued) (**j**) Comparison of mean difference scores for the I.N.P. chamber for the experimental (**e**) and the pooled control (**f**, **g**, **h**, **i**) groups. There was no significant difference between control groups. $*P<0.05$, $**P<0.01$; $***P<0.001$. All data are mean ± s.e.m. Reprinted with permission from Macmillan Publishers Ltd: NATURE. Vrontou, S., Wong, A.M., Rau, K.K., Koerber, H.R. & Anderson, D.J. Genetic identification of C fibres that detect massage-like stroking of hairy skin in vivo. Copyright 2013

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Chapter 6
The Touch Landscape

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Abstract Somatic sensation comprises four main modalities relaying tactile, thermal, painful, or pruritic (itch) information to the central nervous system. These input channels can be further classified as sub-serving sensory functions, such as spatial and temporal discrimination, and the provision of essential information for controlling and guiding exploratory manual behaviours, or affective functions that include the provision of the subjective experience of affective or emotional pleasurable touch. Signalling in fast-conducting myelinated peripheral nerve fibres (Aβ afferents) is important for the discriminative properties of tactile sensations, whereas signalling in unmyelinated peripheral nerve fibres, C-tactile (CT) afferents seems to be important for the rewarding, emotional properties of touch. CT afferents have specific biophysical, electrophysiological, neurobiological and anatomical properties to drive the temporally delayed affective somatic system. This chapter explores step by step the differences between the discriminative and affective touch systems, from the first stage of encoding touch in the skin to the neural pathways in the brain. The below quote from Bentley (Am J Psychol 11:405–425, 1900) reiterates the complexity of the skin and the wonder in the phenomenon of somatosensation:

> *'The skin is burdened with offices. One of the surprises of physiology is the revelation of the multitude of functions performed by this apparently simple organ. As a rind it is not only the container, but the warder-off, and also the go-between for the organism and its world; tegument, buckler, interagent. It is small wonder that its work is represented in mental process; that many of our most worn and useful perceptions are made up of cutaneous sensations.'*

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Keywords Affective touch • Discriminative touch • Somatosensation • C-tactile • Afferent • Mechanoreceptor • Somatosensory cortex • Insula • Myelinated • Unmyelinated

Introduction

The activation of cutaneous receptors gives rise to somatosensation, which has been classically divided into four main sub-modalities: mechanical (touch), thermal (temperature), nociceptive (pain) and pruritic (itch) pathways. Each of these pathways has further sub-divisions and there is some overlap in functions between the main distinctions. Here, we focus on the peripheral signalling of tactile input and compare the properties of the fast-conducting, *discriminative* touch system with those of a more recently characterised sub-modality comprising a slowly conducting, *affective* touch system, in humans. The majority of this research in humans has been carried out using the technique of microneurography: in vivo, axonal nerve recordings from single afferents in awake humans (Vallbo and Hagbarth 1968; Vallbo et al. 2004). This has provided a wealth of information about the functioning of the peripheral tactile system across the body, including responses from the skin of the hands, arms, face, tongue, mouth, legs and feet. In essence, the sensation of touch occurs when a specialised mechanoreceptor in the skin is activated by a contact stimulus. This can be a little as a gentle breeze over the arms, to the high force exerted from trapping a finger in the door. A single mechanoreceptive afferent can encode many aspects of the stimulus (e.g. force, speed, direction and roughness), and when activated together with other mechano- and somatosensory afferents, specific percepts are generated (e.g. wetness and oiliness; see Bentley 1900). Furthermore, this somatosensory information is combined with information from other sensory modalities (e.g. visual, olfactory, auditory and gustatory) and with cognitive mechanisms (e.g. previous experience, context, learning, memory, expectations, predictions and assumptions) to produce a percept that can be interpreted and acted upon.

The reception of a tactile stimulus starts with the mechanoreceptor end-organ(s), or free nerve endings, coding specific qualities of the stimulus. The mechanoreceptive afferent, a *single tactile unit*, may be composed of a number of end-receptors, all connected to a single axon (Lumpkin et al. 2010). The mechanoreceptors and their axon constitute the first neuron in the pathway: the primary afferent or first-order neuron. The receptor is situated in the dermis or epidermis of the skin and the cell body is located in a dorsal root ganglion close to the spinal cord, or the trigeminal ganglia from facial skin input. Signals from the periphery enter the spinal cord where there is at least one synaptic interruption in the spinal cord or brainstem, before the signal ascends into the cerebral cortex. A distinction can be made about the type of somatosensory information that enters the brain, namely from exteroceptive, discriminatory inputs (e.g. fast-conducting signals from myelinated mechanoreceptive afferents and proprioceptors), as compared to interoceptive, affective inputs (e.g. slowly conducting signals from nociceptive, thermal, itch, muscular, visceral as well as tactile afferents). Each of these inputs has specific pathways from

differences in the myelination of the afferents in the periphery to the projections in the brain, where the exteroceptive touch information from Aβ fibres is processed in the primary somatosensory cortex (S1) and the interoceptive signals from C-tactile fibres project to the insula (Craig 2002, 2003). This distinction between touch systems can also be viewed as the perceptual difference between sensing (discrimination) and feeling (affect) (McGlone et al. 2014). However, the 'bottom-up' distinction between the discriminative and affective processing of tactile stimulation is subject to higher-order cognitive influences, depending on factors such as experience, context and expectations, where there is predictive coding in the interpretation of afference (Büchel et al. 2014; Ackerley and Kavounoudias 2015).

Tactile afference can be divided into discriminative touch, signalled mainly by the fast-conducting (30–75 m/s), myelinated mechanoreceptive afferents, and affective touch, signalled predominantly by the slowly conducting (~1 m/s), C low-threshold mechanoreceptors (CLTMs in animals), or so-called C-tactile (CT) afferents in humans. Unmyelinated C-fibres make up ~80 % of the axons in peripheral nerves, accounting for tactile, thermal, nociceptive and sympathetic innervations (Ochoa and Mair 1969; St John Smith et al. 2012). Recent work using unbiased sampling and modelling of transcriptional states in single dorsal root ganglion cells (Usoskin et al. 2014) has identified a distinct population of CLTM neurons, whereas the cell bodies of fast-conducting myelinated mechanoreceptors are encoded by the integration of neurons with different transcriptional states. The discriminative touch system processes high-precision spatial and temporal information about a stimulus, for example what, when and where. On the other hand, the affective system processes the affective or hedonic experience of touch, like how pleasant the contact was. This emotional information is delayed in comparison to the discriminative touch information due to the slow conduction velocity of C-fibres.

Unmyelinated mechanosensitive afferents—CLTMs—were first described by Zotterman (1939) in the cat. A human equivalent of such unmyelinated mechanosensitive afferents was believed to have disappeared during evolutionary processes (Kumazawa and Perl 1977) until the discovery of CT afferents using the technique of microneurography (see Fig. 6.1 for the recording setup and example responses from CT and hair afferents). The first evidence of a human C-fibre low-threshold mechanoreceptive afferent was found in the late 1980s, when Johansson et al. (1988) published a single finding of a putative low-threshold mechanoreceptive C afferent in the skin of the face, innervated by the infraorbital nerve. Nordin (1990) gave the first conclusive evidence of CT afferents in the human face and this line of research was taken further by Vallbo et al. (1993, 1999) and Wessberg et al. (2003), who described CT physiology in much more detail.

Mechanoreceptive afferents signal specific aspects of tactile events; therefore, certain features of touch are encoded preferentially over a wide range of parameters, such as the duration and force of the stimulus. Currently, nine types of mechanoreceptive afferents have been physiologically described in relation to tactile sensations in humans (Table 6.1), although it is likely that in certain areas, such as the mouth and the genitalia, additional types of mechanoreceptors exist due to anatomical and/or physiological specialisations (Jaeger 1944; Gairns 1955; Johnson and Kitchell 1987; Johnson and Halata 1991; Trulsson and Essick 1997). There has long been an association of tactile afferents with hair follicles (Weddell et al. 1954) and newer

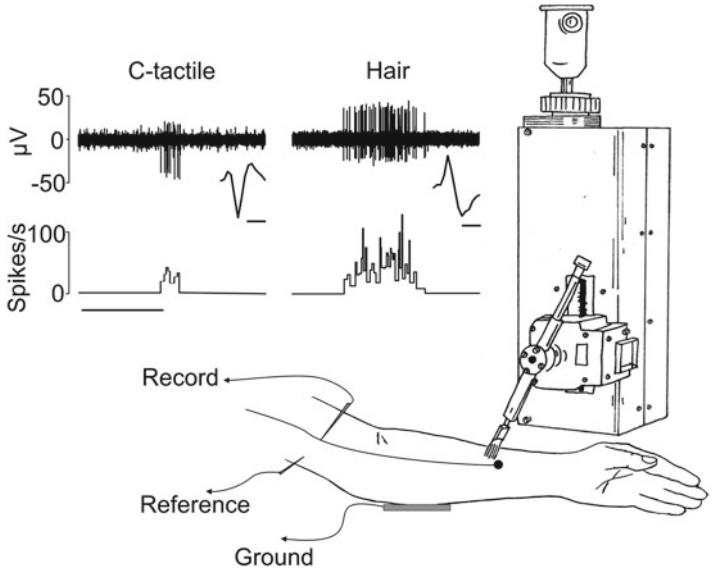

Fig. 6.1 Microneurography recording from single afferents unmyelinated and myelinated afferents with tactile stimulation. The setup and microneurography recording from an unmyelinated C-tactile (CT) afferent and a myelinated hair afferent are shown. The single afferents were both stroked at 3 cm/s (with a force of 0.4 mN), which demonstrates differences in the number of spikes produced and their firing frequency. The unmyelinated CT afferent produces negative-going spikes, whereas the myelinated hair afferent gives positive-going spikes. The *horizontal scale bar* denotes 1 s duration for the nerve recordings and 0.5 ms duration for the inset spikes (which have the same vertical scale as for the nerve recordings)

genetic labelling techniques have provided further evidence for the subdivision of mechanoreceptive afferents (Usoskin et al. 2014), including the exact relationship between mechanoreceptive afferents and hairs (Li et al. 2011). The mechanoreceptive afferents can be classified by a number of factors, including the myelination of the axon, the conduction velocity of the signals, the skin site innervated, the putative encapsulated end-organ or free nerve receptor, whether they continue to respond to sustained tactile indentation (adaptation), and their projection pathways through the central nervous system. The myelinated, Aβ mechanoreceptive afferents generally encode the more discriminative aspects of touch, whereas the unmyelinated C mechanoreceptive afferents are important for the affective components of touch.

Discriminative Touch

Myelinated mechanoreceptive afferents are not distributed evenly over the skin, with the highest innervation density being found in the digit tips and the perioral regions. There are around 17,000 mechanoreceptors in the human glabrous skin of the hand, where fast-adapting type 1 (FA1) afferents account for 43 % of the total number of mechanoreceptors, slowly adapting type 1 (SA1) for 25 %, fast-adapting

Table 6.1 Overview of mechanoreceptive afferents from different types of skin

Class	Sensory tactile unit	Putative receptor	Axon	Skin type	Receptor depth in skin	Type of touch
Aβ	Fast-adapting type 1 (FA1)	Meissner's corpuscle	Myelinated	Glabrous	Superficial	Discriminative
Aβ	Slowly adapting type 1 (SA1)	Merkel's discs	Myelinated	Glabrous, hairy	Superficial	Discriminative
Aβ	Fast-adapting type 2 (FA2)	Pacinian corpuscle	Myelinated	Glabrous, hairy	Deep	Discriminative
Aβ	Slowly adapting type 2 (SA2)	Ruffini's endings	Myelinated	Glabrous, hairy	Deep	Discriminative
Aβ	Field	?	Myelinated	Hairy	Superficial?	Discriminative
Aβ	Terminal hair	Hair	Myelinated	Hairy	Deep	Discriminative
Aδ	Vellus hair	Hair	Thinly myelinated	Hairy	Superficial?	Discriminative/affective
C	C-tactile (CT)	?	Unmyelinated	Hairy	Superficial?	Affective
C	High-threshold mechanoreceptive C fibre	Free nerve endings	Unmyelinated	Glabrous, hairy	Superficial?	Affective

Touch is transduced by either myelinated, fast-conducting Aβ mechanoreceptive afferents, which are more involved in discriminative touch or unmyelinated, slowly conducting C fibres, which contribute to affective touch

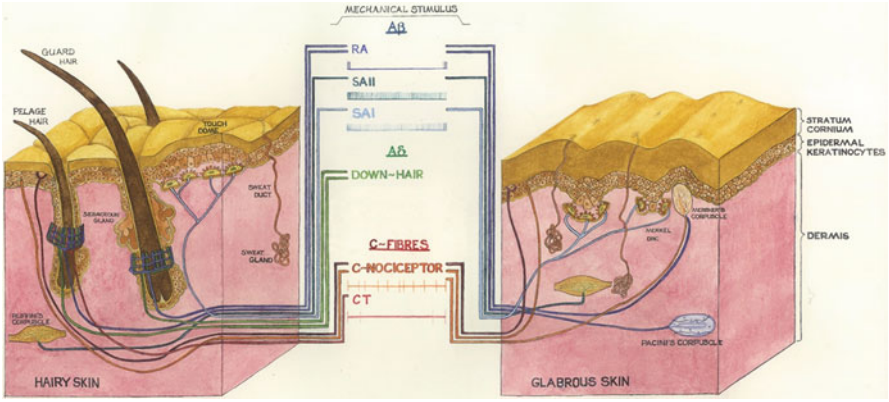

Fig. 6.2 Tactile afferents in hairy and glabrous skin. An overview is shown of the different types of mechanoreceptive afferent in the hairy skin (left side of picture) and glabrous (right side of the picture) skin. The different conduction velocity ranges are shown in *blue* for myelinated afferents, *green* for thinly myelinated afferents, and *red* for unmyelinated afferents. The type 1 myelinated mechanoreceptive afferents are located at more superficial locations, whereas the type 2 afferents are deeper in the dermis of the skin

type 2 (FA2) for 13 % and slowly adapting type 2 (SA2) for 19 % (Vallbo and Johansson 1984). The large number of mechanoreceptors allows for high discrimination of surfaces during manual exploratory behaviours, and particularly with the finger tips. This is in contrast to the hairy skin; where the density of myelinated mechanoreceptive afferents is much lower (Fig. 6.2). The innervation differences between glabrous and hairy skin can be demonstrated in two-point discrimination tests where it is possible to distinguish between two points at a distance of 2 mm on the fingers, whereas on the back, the distance is around 45 mm (Weinstein 1968). However, this is a generalisation, as the hairy skin of the face is very sensitive and it is possible to distinguish between two-point distances of around 5 mm on the nose (Weinstein 1968). There is also a difference between tactile discrimination and tactile sensitivity, where the sensitivity relates to whether something can be felt or not and discrimination relates to spatial tactile acuity (e.g. differentiating between two points—you could feel a fly that landed on your back but you would not know how many legs it had!). The whole of the skin is sensitive to a tactile event; the upper half of the body is generally more sensitive than the lower half, where the lips, cheeks and nose are maximally sensitive to pressure (Weinstein 1968).

Mechanoreceptive Afferents in Discriminative Touch

Fast-Adapting Type 1 (FA1) Afferents

The FA1 afferent unit has Meissner corpuscles as putative end-organs, which are only present in glabrous skin and cluster in the finger tips (Johansson and Vallbo 1979). The Meissner endings are found in the papillary ridges of the dermis (Miller

Table 6.2 Characteristics of human glabrous skin mechanoreceptive afferents

Sensory tactile fibre	Typical receptive field size (mm^2)	Receptive field shape	Receptive field borders	Typical no. points of maximal sensitivity	Force activation threshold (mN)	Optimal frequencies for activation (Hz)
Fast-adapting type 1 (FA1)	13	Round, oval	Distinct	14	0.6	6–100
Slowly adapting type 1 (SA1)	11	Round, oval	Distinct	5	1.3	2–32
Fast-adapting type 2 (FA2)	101	Round, oval	Not distinct	1	0.5	64–400
Slowly adapting type 2 (SA2)	59	Oval	Not distinct	1	7.5	<8

Information from Iggo and Ogawa (1977), Johansson (1978), Johansson et al. (1980), Johansson and Vallbo (1980), Johansson et al. (1982) and Vallbo and Johansson (1984). Note that the optimal frequencies for activation of mechanoreceptive afferents are given, although all of the four types of afferent will respond somewhat to frequencies between 0.5 and 400 Hz

et al. 1958) and compose a coil in an oval-shaped mass (right of Fig. 6.2). The receptive field of an FA1 unit is small and is readily activated with any light touch (Table 6.2), showing characteristic on and off responses. FA1s are best activated at higher frequencies of skin deformation and are involved in how objects are perceived, such as their curvature, compliance, vibrational qualities and texture (Johansson and Birznieks 2004; Weber et al. 2013; Pruszynski and Johansson 2014; Condon et al. 2014). Their small receptive field, high temporal resolution and increased density in the finger tips make them perfect candidates for use in discriminative, exploratory touch.

Slowly Adapting Type 1 (SA1) Afferents

The SA1 mechanoreceptive afferent is found in both glabrous and hairy skin, although is present at a higher density in glabrous skin. Its putative end-organ is the Merkel cell complex, which adapts slowly to tactile indentation. When the SA1 is activated with a sustained indentation using a monofilament, it shows an initial high firing frequency in response to the onset of the pressure, then continues to fire in an irregular manner throughout the indentation (as shown in Fig. 6.3a). A single SA1 mechanoreceptive unit may have 25–75 Merkel discs in an area of 25 mm^2 in the undersurface of the epidermis in the glabrous skin of the hand (Miller et al. 1958).

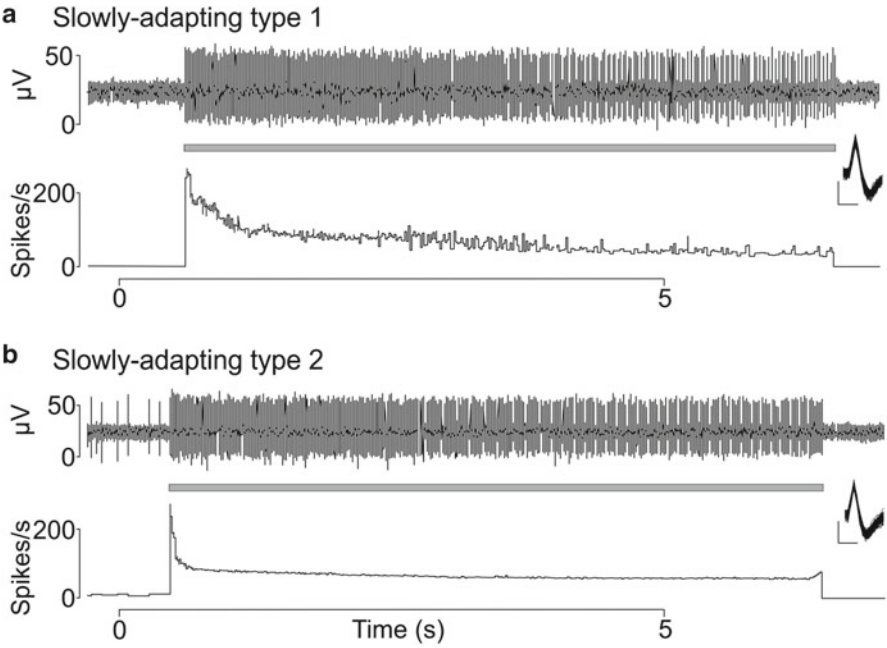

Fig. 6.3 Firing of slowly adapting afferents (**a**) type 1 and (**b**) type 2 to long-lasting indentation. (**a**) The firing of a slowly adapting type 1 (SA1) afferent to a sustained, constant, long-lasting indentation at 12 mN. (**b**) The firing of a slowly adapting type 2 (SA2) afferent to a sustained, constant, long-lasting indentation at 30 mN. Both the SA1 and SA2 were located on the hairy skin of the dorsal forearm. The *grey rectangles* denote the duration of touch. Note the irregular firing pattern from the SA1, as compared to the regular firing frequency of the SA2. An overlay of the spikes ($n = 100$ for each response) is shown as an *inset* for both (vertical scale 20 μV, horizontal scale 0.5 ms)

Like the FA1 afferent, the SA1 has a small receptive field and a low threshold for mechanical activation (see Tables 6.2 and 6.3). Merkel cell complexes form 'touch domes' in the hairy skin, which are very small swellings at the skin surface, whereas in the glabrous skin, there are no surface features of the receptor. Recent work has demonstrated that the Piezo2 ion channel is required for Merkel cell mechanotransduction and that it is both the Merkel cell, as well as the innervating afferent, that act together as the mechanical encoder in SA1s (Maksimovic et al. 2014; Woo et al. 2014). SA1s provide high-resolution information due to their small receptive fields and capacity for high firing frequency. Mechanical stimuli are encoded in different ways by the Merkel cell (which signals static pressure) and its afferent (which signals dynamic stimulation) to produce a sophisticated afferent unit with high spatiotemporal acuity (Maksimovic et al. 2014; Woo et al. 2014). These afferents are able to resolve fine details about a surface, such as its shape, texture and compliance (Maricich et al. 2012; Weber et al. 2013; Pruszynski and Johansson 2014; Condon et al. 2014), so play a pivotal role in discriminatory touch, especially exploratory touch using the hands.

Table 6.3 Characteristics of human hairy skin mechanoreceptive afferents

Sensory tactile fibre	Typical receptive field size (mm^2)	Receptive field shape	Receptive field borders	Typical no. points of maximal sensitivity	Force activation threshold
Fast-adapting type 2 (FA2)	56	Round, oval	Not distinct	1	1 mN
Slowly adapting type 1 (SA1)	11	Round, oval	Distinct	3	0.5 mN
Slowly adapting type 2 (SA2)	2	Round, oval	Not distinct	1	1.3 mN
Hair unit	113	Oval, irregular	Relates to hairs	20 (hairs)	N/A
Field unit	78	Oval, irregular	Not distinct	11	0.1 mN
C-tactile (CT)	20	Round, oval	Distinct	4	<5 mN
High-threshold mechanoreceptive C fibre	50	Round, oval	Distinct	3	>5 mN

Note that the characteristics here represent the general findings from the arm skin, but include other areas (e.g. dorsal hands). There is great diversity in the properties of mechanoreceptors in the hairy skin, much more so than those in the glabrous skin. From Järvilehto et al. (1981), Johansson et al. (1988), Nordin (1990), Vallbo et al. (1995, 1999), Trulsson (2001), and Wessberg et al. (2003). N/A—not applicable as the hair units are activated by hair movement, rather than skin indentation; therefore, the force required for activation cannot be reliably measured

Fast-Adapting Type 2 (FA2) Afferents

The FA2 afferent has Pacinian corpuscles (PCs) as a putative end-organ. FA2s are found throughout the glabrous and hairy skin, in the deeper layers of the dermis. It encodes the onset and offset of tactile stimuli, as well as providing information about vibrations. The Pacinian FA2 end-organ is either found singly or in groups of up to four corpuscles connected to one axon (Miller et al. 1958). The study of the PC has been ongoing for over 80 years, originating from the findings of Adrian and Umrath (1929), who identified onion-like layers in the receptor ending that in total is as large as a pinhead. There are approximately 300 PCs in the glabrous skin of each hand, where the end-receptors tend to cluster close to nerves and blood vessels (Stark et al. 1998). The density of PCs is less in the hairy skin. Due to the deep location of the receptor, it has a large receptive field on the skin (i.e. providing the brain with relatively poor spatial information about the touch location), as with sufficient force, a tap to the arm can activate an FA2 in the hand. This receptor is an excellent change detector in the temporal domain and responds to a large range of frequencies (Table 6.2). It has a very low force activation threshold, so that even blowing on the receptive field readily produces responses. The properties of this mechanoreceptive afferent play an important role in discriminative touch, especially detecting small vibrations such as would occur if a grasped tool slipped, although less so in the

localisation of touch. Vibration is especially important in everyday tactile interactions as small differences in complex, broad-spectrum frequency patterns, which are induced through vibrations of the skin, allow us to discriminate easily and rapidly between a wide range of surfaces and textures (Mackevicius et al. 2012).

Slowly Adapting Type 2 (SA2) Afferents

The SA2 unit is putatively connected to the Ruffini (or Ruffini-like) end-organ and is found in both glabrous and hairy skin in humans. There have been numerous microneurographical recordings from SA2s from the glabrous skin of the hand in humans (Vallbo and Johansson 1984) and human histological work shows the presence of Ruffini end-organs (Miller et al. 1958; Paré et al. 2003; Chikenji et al. 2010, 2011); however, SA2s or Ruffinis have not been found in the glabrous skin of monkeys (Coleman et al. 2001). It should be noted that the histological evidence suggests there are very few SA2s in the glabrous hand; the microneurography physiological recordings may overestimate the numbers of SA2s, as there is an innate sampling bias from finding spontaneously active units, which the SA2s very often are. The Ruffini end-organ is located deep within the dermis and consists of a long, fusiform, fluid-filled capsule that responds to changes in tension of surrounding collagen fibres (Chambers et al. 1972). In the glabrous skin, SA2s are uniformly distributed throughout the hand, although they are often found near joints or the nail bed.

Due to their location and high force threshold, they are thought of as stretch-sensitive mechanoreceptors and often show a directional preference. They have large, indistinct receptive fields in the glabrous skin, but these are smaller in the hairy skin (Tables 6.2 and 6.3). They also have much higher force activation thresholds in the glabrous skin, whereas they can be activated much more readily in the hairy skin. SA2s in both the glabrous and hairy skin are often spontaneously active at a low and regular rate of around 5 Hz. When the SA2 is activated with a long-lasting indentation using a monofilament, it will show an initial high firing frequency in response to the onset of the pressure, then it will continue to fire in a regular way throughout the indentation (as shown in Fig. 6.3b). This regularity of firing distinguishes it from the SA1s (cf. the flatter firing frequency in Fig. 6.3b to the more irregular pattern of the SA1 in Fig. 6.3a). Although the SA2s differ in their physiological properties between the glabrous and hairy skin, it is likely that they play similar roles in detecting changes in skin through larger deformations. They provide highly discriminative information about the direction and magnitude of skin stretch and tension. The SA2s in the hand may be involved in proprioception (Edin 1992), with those located near the nail in the glabrous skin playing a specific role in the encoding of fingertip forces during exploratory touch (Birznieks et al. 2009).

Hair Afferents

Hairs on the skin can be classified based on their length and thickness. They can also be classified depending on the type of fibre innervating and/or associated with their axon. Humans have two main types of hairs: the long, thick, pigmented terminal

hairs and the short, thin, non-pigmented vellus hairs, which dominate in number over the terminal hairs. The border between hairy and non-hairy skin is not clear, where a gradual change occurs between the thicker glabrous skin, and the thinner hairy skin in humans, such as between the ventral and dorsal hand, respectively. Moving more proximally, the terminal hairs are far easier to identify on the dorsal forearm and on the head. With the loss of a fur layer in humans, skin thermoregulatory mechanisms have developed to combat our susceptibility to environmental stressors; however, the density of hair follicles on humans is similar to that of an equivalent-sized animal (Schwartz and Rosenblum 1981). Physiologically, terminal hairs are connected to myelinated Aβ afferents (Vallbo et al. 1995), whereas it has been postulated that the vellus hairs are connected to thinly myelinated Aδ afferents, which conduct more slowly (Adriaensen et al. 1983; Halata 1993). Here, we define a hair afferent as the fast-adapting axon that directly signals the position and velocity of movement of the hair. However, many of the mechanoreceptors in hairy skin are related to the hairs themselves (Li et al. 2011), but do not signal hair movements.

A great deal of research has been conducted on hairs in the mouse; however, there are large inter-species differences in hair thickness and length, and pelage hair can be further sub-classified (Burgess et al. 1968; Horch et al. 1977). In mice fur, there are four different anatomical types of hair: guard (also called tylotrich or monotrich hairs, which are straight and long in length), awl and auchene (medium length, where the auchene has a bend) and zigzag (also called down hair; short in length with multiple bends) that are the most abundant (>70 %) (Burgess et al. 1968; Horch et al. 1977; Schlake 2007; Driskell et al. 2009; Lechner and Lewin 2013; Abraira and Ginty 2013). The guard hairs are innervated by Aβ fibres and are also associated with SA1 Merkel cells, the awl/auchene hairs are innervated by Aβ, Aδ and C fibres and the zigzag hairs are innervated by Aδ and C fibres. Sharp bends in hairs are absent in humans; thus, it seems that humans do not have zigzag hairs (Schlake 2007). The hair follicle is innervated directly by low-threshold mechanoreceptors, which form collars around the hair and include longitudinal lanceolate endings (that are sensitive to hair deflection and touch to the skin) and circumferential endings (with unknown function) (Zimmerman et al. 2014). The different lanceolate endings are very similar anatomically in their innervation of the hair, yet are transmitted by Aβ, Aδ and C fibres. We can make inferences about hairs and their innervation when taking together the human and animal literature. Overall, the thicker hairs are innervated by myelinated, fast-conducting Aβ afferents, which signal changes in hair movement with high temporal resolution, and the smaller hairs are innervated by thin afferents and conduct information more slowly to the brain, signalling emotional information (Zimmerman et al. 2014).

The typical hair unit responses recorded in human microneurography are usually from the fast-conducting terminal hairs (Fig. 6.1). On the forearm, there are around 20 individual hairs connected to one axon, which composes the hair unit and it has a large receptive field over 100 mm^2 (Table 6.3; Vallbo et al. 1995). For thicker terminal hairs, such as in a beard, a one-to-one relationship between a single hair and axon has been found (Trulsson and Essick 2010). These afferents are excellent at encoding *when* a tactile event occurred, but poor in encoding other qualities, such as force. They are neither spontaneously active, nor do they show thermal sensitivity (Ackerley

et al. 2014a). They also fire more to movements against the hair direction, rather than in the direction of the hair (Vallbo et al. 1995). Very few microneurographical recordings are available from Aδ afferents; however, a low-threshold, mechanosensitive Aδ grouping has been tentatively identified (Adriaensen et al. 1983), which they relate to vellus hair. In essence, the hairs on the skin signal the occurrence of all tactile events very well and play a pivotal role in the mechano*sensitivity* of the hairy skin.

Field Afferents

Much less is known about the anatomical and physiological properties of field afferents, as they are only found in the hairy skin and few papers have documented them. These mechanoreceptive units are fast-adapting and are larger in their receptive field (~80 mm^2), than most mechanoreceptive units (Table 6.3). Their receptive field resembles that of the hair, where there are sensitive hotspots; however, there appears to be no correlation in firing activity to hair movements and their end-organ is unknown (Vallbo et al. 1995). In other mammals, it may be possible to divide the field afferents into sub-classes based on their physiological properties (Burgess et al. 1968), but this has not been established in humans. As field afferents are fast-adapting and resemble hair responses, they may be connected to vellus hairs, or terminal hairs that are in the early stage of development.

Spinal Pathways in Discriminative Touch

The vast majority of discriminative touch information comes from myelinated Aβ afferents and the canonical view is that they constitute a direct pathway or 'labelled-line' for touch information to the brain. These first-order neurones have cell bodies in the dorsal root ganglia, where the axon enters the spinal cord through the dorsal root. A principle branch of the axon ascends in the dorsal column, whereas collateral branches terminate in the spinal cord locally, or within a few segments. The ascending dorsal column input is topographically organised, where fibres near the midline originate from the caudal, sacral spinal cord and progressively rostral levels are represented further laterally (e.g. genitals, leg, trunk, arm, shoulder and neck). The axon terminates in either the cuneate (input from the upper body) or gracile (input from the lower body) parts of the dorsal column nuclei (DCN). This afferent contacts ~1700 DCN neurons and each DCN neuron receives input from ~300 afferents (Johansson and Flanagan 2009). This synaptic interruption of the discriminative touch pathway provides a sub-cortical nucleus for tactile processing. A single DCN neurone can have similar receptive fields and response properties to other DCN neurons, yet each neuron responds to a unique combination of discriminative tactile inputs (Jörntell et al. 2014). The specificity found in the DCN means that haptic features have already been extracted before information progresses to the brain. This demonstrates great divergence and convergence of afference already at

the spinal cord and hindbrain, as well as the beginning of tactile processing. Second-order neurons in the DCN send projections across the midline, at the level of the medial lemniscus, which terminate in the thalamus. Similarly, input from facial skin is sent via the trigeminal nucleus to the thalamus. Third-order neurons then project from the thalamus to the somatosensory cortex, where tactile information is processed and integrated cortically (Mountcastle 1957).

Although this direct pathway for discriminative touch information exists, it is likely that the first point of integration for somatosensory input occurs in the dorsal horn (Abraira and Ginty 2013). This is based on the finding that all mechanoreceptive afferents have at least branching terminations in the dorsal horn (Petit and Burgess 1968), which are somatotopically organised. Ginty and co-workers have described, in a mouse model, how hair follicles and associated neurones are organised relative to one another (Li et al. 2011). This organisation, they state, enables us to think about how mechanosensory information is integrated and processed for the perception of touch. In mice, there are three types of follicles each of which has a distinct combination of mechanosensory endings that send signals to the spinal cord in a series of narrow columns, which each gathers input from a particular area of the skin. The local termination of the Aβ afferent information is mainly in lamina III, although also in lamina VI (Brown 1977; Brown et al. 1980; Semba et al. 1983, 1984, 1985). The microcircuitry present in the dorsal horn allows for the integration of intra- and inter-modality somatosensory information; therefore, tactile input will be influenced by temperature and nociceptive inputs. The principle ascending branch from Aβ input has a large contribution to discriminative touch; however, various studies have looked at the extent to which damage to the dorsal columns disrupts discriminative touch. In the nineteenth century, it was found that when the dorsal column was sectioned, tactile sensations disappeared and ataxia occurred (Bell 1832; Schiff 1894), whereas others found no sensory disturbances (Bellingeri 1823; Martinotti 1890) (in Wall 1970). Wall and Noordenbos (1977) found that when the dorsal columns in man were totally sectioned through injury, tactile sensations were still felt, but these were numb and tactile localisation was poor. Further, the patients failed in any task where simultaneous integration of temporal and spatial characteristics of the stimulus was necessary such as identification of numbers drawn on the skin or determining the movement direction of a tactile event on the skin. This implies that the local dorsal horn terminations may contribute to touch. Nevertheless, this distinction between the direct dorsal column pathway and the branched dorsal horn pathway leads us to concluding that *discriminative* tactile information travels via the dorsal columns, whereas the branching may provide tuning for additional spinal processing of touch, for example with slowly conducted information.

Cortical Processing in Discriminative Touch

It is well-established that a network of cortical areas is involved in tactile processing and classically, the contralateral primary somatosensory cortex (S1), bilateral secondary somatosensory cortices (S2) and the contralateral posterior parietal cortex

(PPC) are activated. There has been a long-running debate as to whether incoming somatosensory information from the thalamus is processed serially or in parallel in these areas. In humans, the latest opinion is that parallel thalamo-S1 and thalamo-S2 connections exist, although there are reciprocal connections between the S1 and S2. It seems that the first cortical activity is registered in the contralateral S1, ~20 ms after electrical nerve stimulation, and at ~90 ms in both the contralateral and ipsilateral S2 (Wegner et al. 2000). This pertains to the myelinated input, due to the very short latency. Animal work has shown similar findings where there are separate thalamic pathways to the S1 and S2, where these cortical areas are hierarchically equivalent in tactile processing (Murray et al. 1992; Rowe et al. 1996; Zhang et al. 1996, 2001).

S1 receives somatotopic projections from third-order neurons originating in the ventral posterolateral nucleus of the thalamus (and ventral posteromedial nucleus for facial input). S1 is divided into four separate Brodmann areas (BA) 3a, 3b, 1 and 2 (rostral to caudal); however, it has been suggested that only BA3 should be referred to as the 'primary somatosensory cortex' as it receives the bulk of the thalamocortical projections from the sensory fields (Kaas et al. 1984). Thalamic inputs to S1 terminate mainly in layer IV and in turn, neurons in this layer project on to other cortical areas. BA3b receives the densest thalamic input and shows specific responsivity to FA1, SA1 and SA2 afferents, hence is key in processing discriminative touch. BA1 has inputs from FA1 afferents and BA2 is more sensitive to proprioceptive inputs. BA1 and BA2 receive reciprocal input from BA3b, where texture and size/shape are transmitted, respectively (Randolph and Semmes 1974). The somatotopic organisation of S1 has been known since the historic mapping of the human cortex by Penfield in the 1930s and 1940s (Penfield and Boldrey 1937; Rasmussen and Penfield 1947). A sensory homunculus is found in each BA of S1, and the relative sizes of the body-part representations reflect the density of myelinated mechanoreceptive afferents on that skin area.

Each BA in S1 contains a continuous somatotopic body representation, where BA3b and BA1 are mirror representations of the body. However, on closer inspection, the bodily representation is somewhat fractured and there are multiple body areas, which are different on an individual level (Kaas et al. 1979). Advances in human neuroimaging have enabled the precise mapping of S1 with respect to digital representations. Using ultra-high field (7 T) functional magnetic resonance imaging (fMRI), Sanchez-Panchuelo et al. (2012) found four distinct maps in each BA of S1, which contained somatotopic representation within- and between-digits. Overall, the vast amount of myelinated tactile afference that is sent to S1, coupled with the over-representation of glabrous and perioral skin areas, reveal its critical role in the interpretation of discriminative touch information. An example of this type of discriminative assessment is roughness estimation. There is a flow of texture information from S1 to S2, where S1 computes differences in firing between SA1s in close proximity and S2 integrates this information to form the basis of texture perception (Hsiao et al. 1993).

S2 contributes to discriminative somatosensory processing, but does not contain the precise maps found in S1. Typically, tactile stimulation on one side of the body

produces bilateral activations in the S2, although with a larger response in the contralateral S2 (Hagen and Pardo 2002). The receptive fields in S2 are larger and can span many areas on multiple digits, as well as showing some selectivity for object orientation (Hsiao et al. 2002). S2 appears to also encode more cognitive aspects of tactile processing, such as showing representations of present and past sensory information, modulations with attention, comparisons between stimuli, correlations with behavioural decisions and tactile discrimination learning (Murray and Mishkin 1984; Romo et al. 2002a, b; Hsiao et al. 2002). The overlap of cortical representations and bilateral activation of S2, as well as its role in the cognitive processing of touch, highlights its role in the dissection of tactile information, but also its importance in integrating touch in the current situation.

Other cortical areas are activated during discriminative touch, such as BA5 and BA7 in the PPC, and the insular cortex, although these are more implicated in the integration and multi-sensory processing of tactile information. The PPC has been found to integrate visual and motor signals with touch information (Pasalar et al. 2010; Azañón et al. 2010; Padberg et al. 2010; Ackerley et al. 2012), whereas the insula is a hub to functionally connect information from the other senses and regulate homeostatic mechanisms (Craig 2009), and is more involved in the affective processing of touch due to its input from CT afferents.

Affective Touch

Mechanoreceptive Afferents in Affective Touch

C-Tactile (CT) Afferents

CT afferents, and their animal homologue CLTMs, have very low mechanical thresholds (<5 mN) and are exclusively found in hairy skin. The detailed physiological and anatomical aspects of CT afferents are covered in Chap. 1. CLTMs were first defined in cats, where delayed responses to touch were seen, relating to their slow conduction velocity and unmyelinated axon (Zotterman 1939). There came a wealth of studies investigating CLTM function in animals, which defined their properties, such as conduction velocity of <2 m/s, high sensitivity to touch, intermediate adaptation to mechanical indentation, lower frequency discharges (<100 impulses/s), small receptive fields, fatigue to repeated stimulation and a propensity for displaying after-discharge following brief mechanical stimulation (Douglas and Ritchie 1957; Iggo 1960; Iggo and Kornhuber 1977; Kumazawa and Perl 1977; see also Chap. 2). The properties of human CT afferents have been found to be very similar (cf. Nordin 1990; Vallbo et al. 1993, 1999; Wessberg et al. 2003). Their exquisite sensitivity is shown in Fig. 6.4 where responses from a CT afferent are elicited from small, brief, gentle taps to the receptive field. CT fibres also show stroking velocity-dependence, where optimal firing frequencies are found to stimulation in the range 1–10 cm/s, which also correlates with hedonic ratings of the same stimuli (Essick

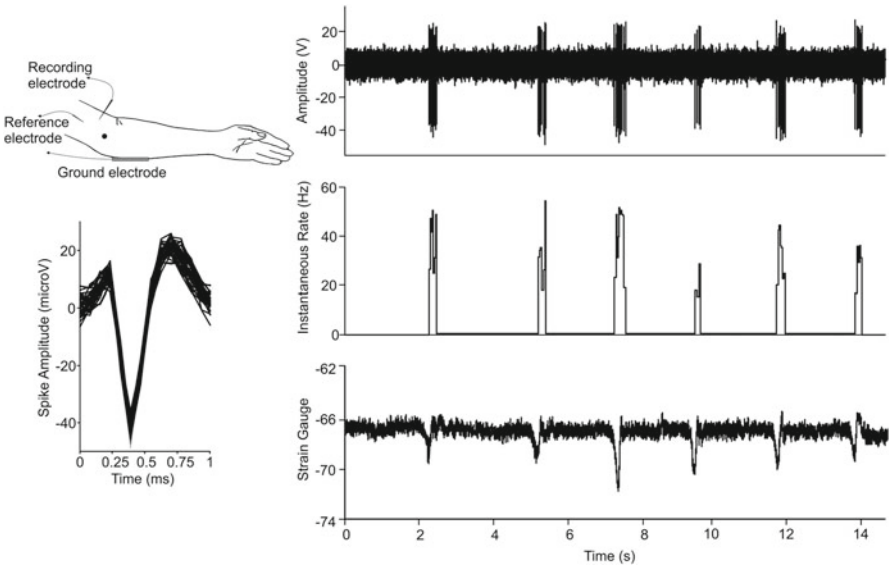

Fig. 6.4 Physiological responses from a sensitive C-tactile (CT) afferent. (**a**) Location of single CT unit receptive field and electrodes. (**b**) Overlaid CT responses ($n = 40$ from (**c**)). Responses of CT to tapping in the receptive field (**c**) CT negative deflections, (**d**) instantaneous rate and (**d**) recorded forces on blunt strain gauge. Threshold for activation was 68 mg Von Frey monofilament. Negative deflections are found from CT recordings, which reflect the unmyelinated nature of the axon

et al. 1999, 2010; Löken et al. 2009; Ackerley et al. 2014a, b). Furthermore, CTs appear to have an optimal thermal range, where the highest frequencies of firing are found to tactile stimuli delivered at normal skin temperature, responding less to warmer or cooler stimulation (Ackerley et al. 2014a).

C High-Threshold Mechanoreceptive (CHTM) Afferents

CHTMs signal touch, but at increased forces compared to CTs, as they have force activation thresholds of typically >10 mN. Although this higher activation threshold is not painful (i.e. normal forces involved in everyday touch will employ this force and higher), the CHTMs encode forces well into the painful range. CHTMs are usually classified as Type 1A polymodal nociceptors (C mechano-heat responsive units), as they signal both mechanical and thermal (heat, and sometimes cold) events, but purely high-threshold C-mechanical afferents are also present (Schmidt et al. 1995). Microneurographical studies have found CHTMs in both hairy and glabrous skin (Ochoa and Torebjörk 1989; Vallbo et al. 1999; Serra et al. 1999; Weidner et al. 1999; Bostock et al. 2003). As it takes a higher mechanical force to activate the CHTMs, they are not thought to be involved in pleasant touch, rather are likely to transmit nociceptive affective touch.

Spinal Pathways in Affective Touch

Contrary to the dorsal column pathway in discriminative touch, unmyelinated afferents terminate directly in the spinal cord and are subject to mass convergence with other somatosensory information, before the information is sent to the brain. Details of the spinal processing of CLTMs are covered in Chap. 9. Regarding CT fibres, animal work has shown these have projections to the inner lamina II of the spinal dorsal horn and neurons are found here that are exclusively responsive to slow brushing stimuli with input from unmyelinated afferents (Light et al. 1979; Sugiura 1996). There are connections from lamina II to wide dynamic range projection neurons in lamina I; these neurons respond to low- and high-threshold touch, as well as noxious heat and are different to the nociceptive-specific lamina I projection neurons (Andrew 2010). In humans, it is likely that the projection from lamina I ascends in the spinothalamic tract, synapsing in the posterior ventromedial thalamus (Craig 2002).

Cortical Processing in Affective Touch

The way in which affective touch information is processed centrally is very different to that in discriminative touch. The unmyelinated C fibre afference is massively delayed, compared to the almost-instantaneous myelinated Aβ input. The exact brain processing of CT-targeted touch is covered in Chap. 11 and we briefly describe the main pathways here. A lot of what we know about the processing of CT input comes from work on two neuronopathy patients, who lack myelinated afferent input from the majority of the body and describe very little conscious sensations of touch (Olausson et al. 2002, 2008). These patients have grossly elevated touch detection thresholds on their palms (in line with a lack of low-threshold myelinated afferent input), but they have only moderately elevated touch detection thresholds on their arms (Cole et al. 2006). Regarding the type of touch felt by these patients, they report no real sensation of touch in everyday life; however, Olausson et al. (2002) described that a soft stroking on the skin was reported as a faint pressure that was clearly pleasant, while failing to provide a percept of intensity (Olausson et al. 2002). Furthermore, this stimulus activated the insula cortex bilaterally, a nucleus known for integrating somatosensory and homeostatic signals, as well as the contralateral premotor cortex and ipsilateral BA44.

In a follow-up study, skin stroking in the neuronopathy patients evoked significant decreases in the fMRI activity in somatosensory cortex, supporting the notion that the CT input does not provide discriminative touch information. In healthy humans, a number of studies have found other cortical areas and signatures that relate to pleasant touch, via stroking stimuli that preferentially activate CT afferents. The S1, bilateral S2, superior temporal areas, anterior cingulate, prefrontal cortex and orbitofrontal cortex (OFC) have all been implicated in processing

pleasant touch applied to CT-innervated skin (Ackerley et al. 2012; McGlone et al. 2012; Gordon et al. 2013). A complementary electroencephalography study has shown correspondence between the progression of incoming CT input with an ultra-late, slow cortical potential found over the middle, frontal cortex (Ackerley et al. 2013). Although CTs do not seem to send an excitatory signal to S1 (Olausson et al. 2008), various studies have implicated S1 in the emotional processing of touch in relation to understanding the sensations of others (Keysers et al. 2010; Gazzola et al. 2012; Bolognini et al. 2013).

Relating Activity in the Periphery to Touch Sensations

There is a distinction between the mechanotransduction of a tactile event and the actual sensation of touch, where activity in the periphery may lead to a number of interpretations centrally. This is akin to the sense of pain, where nociceptive afferents may be activated in the periphery, but this may or may not be interpreted centrally as pain. For example, mechanosensitive C nociceptors may be activated with as little as 10 mN punctate force (Vallbo et al. 1999); in tactile terms, this is not felt as painful. This exemplifies the complexity of the somatosensory system: 'pure' input signals can be interpreted in different ways, depending on other concurrent sensory input and in relation to top-down cognitive influences. In the case of painful touch, there are two aspects to the stimulus that are paid attention to: the discriminative aspect (where, how long and size of contact) and the affective aspect (how unpleasant it is and how it impacts my well-being). These percepts can be generalised to all somatic sensations, where the discriminative and affective aspects are present in different degrees.

The synchronisation between an event transduced at the periphery and the central decoding of it is virtually instantaneous for myelinated mechanoreceptive input, but it is temporally mismatched for C fibres. This means that the information conducted by CTs is far better suited to the *consequences* of touch, pertaining to affect. An analogy can be made between functioning in the nociceptive and tactile systems, where there are first and second sensations to a stimulus. With pain, the first sensation is felt as sharp and intense (discriminative qualities from thinly myelinated afferents), whereas, there is a dull, burning second sensation (affective qualities from C nociceptors). The first sensation is fast, whereas the second sensation has a slower onset, which may outlast the stimulus itself. The tactile system is also similar, with fast-conducting Aβ input, then slowly conducting CT input, both relating to discriminative and affective aspects, respectively. The temporal dissociation relates to the discriminative 'What happened?' system, to alert the body to touch, and the 'How do I feel about it?' affective system to reflect on its consequences. The CT afference is postulated to convey pleasant tactile signals and socially relevant touch (McGlone et al. 2014). It is clear that the Aβ afferents also contribute to the emotional side of touch, because gentle touch to the palm, where CT afferents are lacking, can be perceived as pleasant (Löken et al. 2011; Ackerley et al. 2014b).

Similarly, the pleasantness of an object can be easily rated during active touching using the fingers (Klöcker et al. 2012); for example, it is enjoyable to stroke the soft fur of a pet using your hand. It seems that affective touch can be signalled by the myelinated mechanoreceptive afferents in the glabrous skin, but it is likely that the affective component is centrally derived and not peripherally encoded.

A question remains about where pleasantness is represented in the brain and if there are separate or shared areas for touch from CT-innervated and non-innervated skin, which constitute a pleasant tactile network. Brain imaging studies have shown that affective aspects of tactile stimuli on the glabrous skin of the hands elicits responses in the OFC (Francis et al. 1999; Rolls et al. 2003; McGlone et al. 2012), which is known for its role in emotion and reward. It has been suggested that this specific activation of the OFC may be due to the evaluation of the affective component of touch, although CT activity may also activate different parts of the OFC (Hua et al. 2008; McCabe et al. 2008; McGlone et al. 2012). Therefore, it seems that the affective processing of touch in the OFC occurs from both glabrous and hairy skin, but it can differ under the circumstances. Hence, there are many mechanisms that will allow the processing of pleasantness in tactile inputs without CT afference. Touch on glabrous and hairy skin is largely perceptually similar, and gentle stroking on both sites is described as pleasant. However, it is likely that the evaluation of the tactile input is qualitatively different from skin containing and not-containing CTs, where touch on hairy skin sites produces higher affective consequences. This has been shown using a touch perception task, where participants used more sensory descriptors for tactile stimuli to glabrous skin, and more affective descriptors on hairy skin (Guest et al. 2011; McGlone et al. 2012; Ackerley et al. 2014c), further implying a role for CTs in emotional tactile evaluation.

Conclusion

There are similarities and differences in the discriminative and affective touch systems, and it appears that CT afferents have a special role in signalling the inherently affective and emotional qualities of light stroking touch. It is apparent that the unmyelinated system has a poor temporal resolution and does not directly contribute to discriminative touch; however, the signals from CT fibres will likely interact with the myelinated mechanoreceptive input to shape tactile perception. On the other hand, the myelinated fibres can signal the conscious aspects of affective touch, although no obvious encoding for this is seen in their firing characteristics. Pleasantness of touch can be felt from the myelinated mechanoreceptive afferents in the glabrous skin, where CTs are not present; however, it is likely that this information is decoded in the brain—learned—rather than being coded directly in the myelinated afferent firing.

It is important to study and understand how all mechanoreceptive inputs combine, which allows us to gain insights into the normal functioning of the somatosensory system and what happens in clinical conditions and how to treat them. In patients

lacking myelinated touch fibres, the deficits are obvious: they have little perception of conscious touch and tactile stimulation only elicits a weak sensation. However, in patients lacking C-fibres, the clinical symptoms are often more related to aberrant pain reactions. Although they also have a deficit in the CT system, they nevertheless can feel pleasant touch, albeit somewhat different to a typical person. Hence, both the myelinated and unmyelinated tactile systems are required for a functioning and complete sense of discriminative and affective touch.

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Chapter 7
Some Historical Aspects of Cutaneous Psychophysics

Ulf Norrsell

Abstract The subject called psychophysics reflects an ambition to explore the mostly human characteristics of neurophysiology for both theoretical and medical purposes. It may be traced from the first half of the nineteenth century, starting with advocates like Johannes Müller and Ernst Weber. The historical development of the issue's cutaneous subdivision may be followed through publications of a restricted series of findings. Their authors as well as their messages are still recalled in many instances. The development followed the creation of new techniques. Nevertheless, it was not always the case. Some important observations were overlooked in the beginning and thus some possible developmental strategies were delayed for decades.

Keywords Cutaneous psychophysics • Touch • Temperature • Pain • Pleasure • Specificity

The term psychophysics appeared in the middle of the nineteenth century and denotes a branch of science dealing with the interaction between mental states and physical events. It dates from a period when a neurophysiological foundation for our present understanding of sensory perception was being shaped, notably by Johannes Müller and Ernst Weber.

The Architects

Johannes Müller (Fig. 7.1) introduced a concept which was called "specific nerve energy". It signified that reflex responses and/or conscious sensory qualities depended on the identity of the operative sensory system, not on the physical properties of the causative stimuli (Müller 1838). He provided some drastic, real life,

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Fig. 7.1 *Johannes* Peter Müller (1801–1858) studied medicine at Bonn, and defended his doctoral thesis on animal locomotion in 1822. He also studied philosophy, and medicine at the Berlin University, notably under Carl Asmund Rudolphi (1771–1832), the professor in Anatomy, and Physiology, who initiated Müller's interest in comparative anatomy. He returned to Bonn in 1824, and eventually became accredited professor in 1830. Following Rudolphi's death he was called to the chair in anatomy and physiology in Berlin. During the time in Bonn, he published anatomical and physiological observations on vision, and reproduction, and started the work on his renowned Handbook of Physiology, which kept him busy until 1840. His studies of the cellular structure of pathological tumours has been suggested the beginning of the subject pathological histology. He worked with the comparative anatomy of marine animals until the end of his life. Hence, he spent vacations on the Mediterranean or Norwegian coasts, and almost drowned once following a shipwreck outside Norway. He trained a number of eventually famous scientists, notably including Hermann von Helmholtz, and Rudolf Virchow (Anonymous 1859; Encyclopedia Britannica 2013). Image by courtesy of Wellcome Library

examples. Transection of the human optic nerve, for example, caused a vivid experience of light. However, this transection did not evoke any pain comparable to the agony experienced when a somatosensory nerve of equal thickness is divided. The individual sensory nerves were activated physiologically by restricted varieties of physical or chemical stimuli. Nevertheless, a conscious percept was not a reproduction of a peripheral event itself, but a product of the neural processing of the nerve energy discharged by the stimuli in question. Hence, electrical stimulation or compression of an afferent nerve could only evoke sensations which recognizably belonged to one or the other of the different sensory organs. Müller suggested two

alternative explanations for the condition (Müller 1842, translated from German by W. Baly, p. 1072):

> Either the [afferent] nerves themselves may communicate impressions different in quality to the sensorium, which in every instance remains the same; or the vibrations of the nervous principle may in every nerve be the same and yet give rise to the perception of different sensations in the sensorium, owing to the parts of the latter with which the nerves are connected having different properties.

He included the following qualities in the somatosensory system (Müller 1842, translated from German by W. Baly, p. 1059):

> By feeling, or touch, we understand the peculiar kind of sensation of which the ordinary sensitive nerves generally—as, the nervus trigeminus, vagus, glossopharyngeus, and the spinal nerves,—are susceptible; the sensations of itching, of pleasure and pain, of heat and cold, and those excited by the act of touch in its more limited sense, are varieties of this mode of sensation.

He discussed, and rejected the idea, that somatosensory percepts originating from internal organs belonged to a separate so-called *Gemeingefühl*/(cœnæsthesis, common feeling) category. He concluded that there was nothing essentially different between subjective and objective sensations for any sensory organ. Nevertheless, the expression "a feeling of touch" was understood to refer to something belonging to the body surface.

Ernst Weber (Fig 7.2), in contrast to Johannes Müller, promoted the concept *Gemeingefühl*. The title of his nowadays possibly best remembered publication is *Tastsinn und Gemeingefühl* (Weber 1849). The section on *Gemeingefühl* embraces one-third of the publication and commences with the following introduction (Weber 1849, p. 562, translated from German):

> Most of the physiologists use the word *Gemeingefühl* [common feeling] to indicate our possession of an ability to register a sensory condition, e.g. pain, while simultaneously experiencing an objective percept, which we consider to be distinct from the other. The objective percept could be e.g. a colour or a tone. Thus our capacity does not indicate the existence of an odd sensory organ. Many physiologists have also accepted that all sensory nerves may produce the same phenomena under certain conditions. There are sensory nerves without links to any particular sensory organ, and without ability to evoke any individual sensations, but only common feelings. Some physiologists even think that we from the beginning register different stimuli merely as events. We then gradually learn to identify particular sensory impressions as objects, by means of comparison and interpretation.—The common feeling [*Gemeingefühlsempfindung*], and the sensory percept often appear together. In that case, they are a product of one and the same influence like e.g. the disgust evoked by an odour. The same is true for any feeling of pleasure or revulsion, which is not the result of comparisons, and which appears immediately, and at the same time as the objective percept.

On the following page Weber courteously described his disinclination for Müller's dismissal of the *Gemeingefühl* (Weber 1849, p. 563, translated from German):

> By means of surgery on humans, and vivisection on mammals one has become convinced that more pain is evoked, compared to lesions of other nerve structures, when the tactile organs and their nerves are destroyed. This makes Joh. Müller's admitted thinking attractive,

Fig. 7.2 *Ernst* Heinrich Weber (1795–1878) studied medicine at Halle and Leipzig. He was promoted to Dr. Med. at Halle 1815, and habilitated in comparative anatomy at Leipzig 1817. His entire future career was achieved at Leipzig University. He upheld the chair in Anatomy of the Medical Faculty 1821–1840, and 1866–1871, and the chair in Anatomy and Physiology of the Medical Faculty 1840–1866. He is nowadays best remembered for his work on auditory and tactile sensory physics and physiology. Nevertheless, he has also been considered the founder of physically oriented physiology, and his findings depended on close observations of the relationship between structure and function. He also studied the autonomous nervous system, as well as human locomotion. His famous successor on the physiology chair, Carl Ludwig (1816–1895), considered Weber to be exceptional in his ability to find the links between the details and the theory (Hildebrand 2005). Image by courtesy of Wellcome Library

> i.e. we can perceive pain only through the agency of nerves of somatic sensibility. The sense of touch depends on the somatosensory nerves. The nerves of somatic sensibility are supported by special tactile organs, and are plentiful in the tactile organs for that reason. These nerves could, except for the common feelings [*Gemeingefühlsempfindungen*] provide us with the sensations of pressure, warm, and cool.—Despite the power of this proposition, it is not at present free from all reservations.

Weber's idea was that the emotional part of sensory percepts, if any, was generated by means of a separate mechanism, which was activated or not depending on the circumstances; a general sensory system, the "*Gemeingefühl*". His major argument was based on the observed disconnections of touch and temperature feelings from those of pain. He described how pain caused by high or low stimulation temperatures developed only after a shorter or longer delay following the feeling of hot or cold. In addition, the feeling of pain covered a larger area than the causal stimulation. According to Weber, a possible explanation could be that it took some time for the causal temperature change to spread and activate adjacent nerve fibres

covering a larger area in the brain. He noted that transections of body musculature during amputations without anaesthesia failed to evoke noticeable pain, in contrast to the cutting of nerves. Muscle tissue itself had been found to be generally insensitive, i.e. without the sensitivity to mechanical stimuli found in the skin (Bichat 1801). Nevertheless, Weber (1849) had personally experienced that persistent contraction of limb musculature caused a strong and long-lasting pain. This pain was located in muscles, which were known to be without the pain sensitivity found in the skin. In addition, his opinion was influenced by a number of descriptions of selective disconnections of pain from touch. For example, Beau (1848) had described lead poisoned patients with completely analgesic skin areas which, at the same time, retained a normal sensitivity to light touch.

Weber is sometimes called the parent of the psychophysics, a label well supported by the abundant references to the '*Tastsinn und Gemeingefühl*' on the internet. His findings regarding the objective functions of the tactile sense initiated the creation of the two point discrimination method, as a tool for studying tactile spatial, sensory resolution. He also described the non-linear correlation between the magnitude of stimulation intensity and the evoked subjective sensation. This finding later became known as the Weber–Fechner's law following a mathematical revision by Fechner[1] (1877). He thought that the tactile sense included two separate specific types of sensory organs, which independently provided a sense of touch and a sense of temperature. However, this idea was enfeebled by his own finding that an object's temperature influenced the feeling of its heaviness (Weber 1849). One silver thaler (≈27 g), or more on top of one another, had been placed on the skin of the forehead. Subjects were asked to compare the weights. It was found that two thalers with body temperature felt the same as a single cooled (−7 to −4 °C) coin. Weber thought that his finding reflected a phenomenon caused by the physical properties of fluids. Cooling of the skin would cause a local shrinkage of the extracellular and intracellular fluid volumes, which would activate the pressure receptors. This hypothesis, however, was invalidated within less than two decades.

A nowadays little known Hungarian doctor Michael Szabadföldi had discovered that a subjective, albeit less marked, weight increase could also be felt with objects holding a temperature above that of the body (Szabadföldi 1865). In that case, a temperature increase would produce the opposite physical effect on the local fluid volumes. Szabadföldi (1865) had also found that the accuracy of localization on the skin improved for hot stimuli. Subjects' ability to describe the places of skin stimulation with a light pinprick became more accurate when the needle was heated to a temperature well above that of the skin. His general conclusion was that Weber's hypotheses regarding cutaneous innervation were untenable. Weber's (1849) and Szabadföldi's (1865) findings regarding the variable percepts caused by touch stimuli of different temperatures were being discussed at the time but eventually neglected. Nevertheless, they were revived, and expanded, and discussed in a number of publications by

[1] Fechner may have been the first to use the term psychophysics in 1858, according to the Oxford English Dictionary.

Stevens and coworkers in the second half of the twentieth century. No explanation for the improvement of spatial localization was found. However, it was suggested that the weight illusion might be caused by activation of primary afferents that were sensitive to both touch and temperature (cf. Stevens 1979, 1982, 1989).

Spinal Lesions, Sensations and Feelings

An alternative example of disconnection between touch and pain to that which was cited by Weber (1849) was published a decade later by Moriz Schiff (1823–1896). In lesion experiments he had found two separate ascending pathways for reactions to light touch and painful stimuli, in the cat's spinal cord (Schiff 1859). However, Schiff's hypothesis became obsolete following a great number of subsequent critical reports about lesion experiments in animals and clinical observations in human patients. Page May (1906) reviewed the numerous articles on the subject and noted the relative lack of coherence. Regarding cases in man, he referred (p. 778): "to the careful collection and analysis of 137 such cases by Petrén and the numerous references given by him in the literature of the subject". Petrén (1901, 1902) had concluded (Petrén 1901, p. 594, translated from Swedish):

> With regard to the sensory pathways of the spinal cord we have come to the following conclusion. All four of the cutaneous senses are transmitted via the contralateral, lateral column, and with great probability it is in its lateral half. Their course constitutes part, or the whole of the Gowers pathway [ventral quadrant]. In addition, the pressure sense embraces a second pathway in the ipsilateral dorsal column. This pathway, very probably, comprises direct extensions of the dorsal roots' ascending axons.

The various types of sensory defects following scheduled, neurosurgical lesions of the human spinal cord were later investigated by Otfrid Foerster (1873–1941), and colleagues. Histologically, transections of Petrén's anterolateral pathway were found to cut fibres belonging to neurons with cell bodies located in the dorsal horn on the side of the afferent input. Fibres from these cells crossed at the segmental level and could reach the brainstem and thalamus. The transections of this crossed anterolateral pathway produced a loss of painful and uncomfortable as well as pleasurable feelings. The sensory deficiency was located contralateral to the lesion and caudal to its level. In addition, the same lesion also generally caused a severe disturbance of the subjective, temperature sensitivity and a mild increase of the touch threshold of the same area. The magnitudes of these four different types of sensory defects varied between the patients. These variations were taken to indicate that the thermal and tactile sensitivity depended on ascending fibres located partially dorsal or ventral to those that were essential for the pain sensitivity. The thermal, sensory deficiency depended partly on the dorsal span of the lesion, i.e. whether reaching the level of the dentate ligament, or not. The tactile disturbance depended on the ventral span, i.e. a lesion reaching all the way down to the vertical midline.

In the case of the dorsal column, a unilateral transection likewise caused a mild, ipsilateral increase of the touch threshold below the level of the lesion, but ipsilater-

ally in this case. However, the most marked effect, of this lesion, was a deterioration of ipsilateral, cutaneous, spatial perception. The subject's ability to find a spot on the skin previously touched by the examiner was very poor. The directional sensibility was lost, i.e. the subjects were unable to tell any difference between the directions of two lines drawn on the skin, one after the other, in the form of a cross (Foerster and Gagel 1932; Foerster and Loewi 1932; Foerster 1936). Another notable sensory change following transection of the dorsal columns was the disappearance of the power to distinguish between different types of painful stimuli. They all felt the same, whether caused by a needle prick, by a strong pull of hairs, by squeezing of a muscle or a bone, or by a strong faradic current applied to the skin. In addition, the dorsal column lesions caused a kind of hypersensitivity. Touch stimuli applied below and ipsilateral to the lesion had started to feel unpleasant or even painful. Hence, Foerster (1936) suggested a functional interaction between the dorsal column of one body half and it's crossed, anterolateral pathway. For one, it suggested that the dorsal column contributed to knowledge of the objective, causal reason for the pain feelings which basically depended on the existence of the crossed pathway. This idea was congruent with Weber's (1849) description of the *Gemeingefühl*. For another, the dorsal columns (Foerster 1936, p. 366, translated from German): "held back the anterolateral system, so as to prevent the making of excessively strong or even, for the stimulus, inadequate feelings". This was a proposition, which became news only some 30 years later (Melzack and Wall 1965; Shealy et al. 1970).

Evidence for Cutaneous, Specific and Objective, Sensory Modalities

Some evidence of different nerves for the touch, and the warm as well as the cool sensibilities was found towards the end of the nineteenth century. Three different scientists then independently discovered a functional grouping of cutaneous perceptions (cf. Norrsell et al. 1999). Magnus Blix (1849–1904) was first out, and Fig. 7.3 illustrates his technique for demonstrating how sensations/feelings of warm and cool could be evoked independently from separate spots on the skin. Feelings of light tactile contact (not illustrated) could be evoked from a third set of separate spots. Electrical stimulation of these separate spots evoked the same sensations as would the adequate stimuli.

Of the three scientists, Blix had finished his publication with a statement, that there are three specific "nervous organs", one for cool, and another for warm stimuli, and a third for pressure on the skin. He then added that no specific cutaneous devices for pain had been found (Blix 1883, 1885). However, one of the others, Alfred Goldscheider (Fig. 7.4), was prepared to elaborate the pain problem. In contrast to the other two, he was a clinician, who eventually became a renowned neurologist (Holdorff and Winau 2001). His doctoral thesis was about *Gemeingefühl* and the specific nerve energies (Goldscheider 1898a), and had appeared before his discovery of warm, cool and tactile spots in the first half of the 1880s. Among other

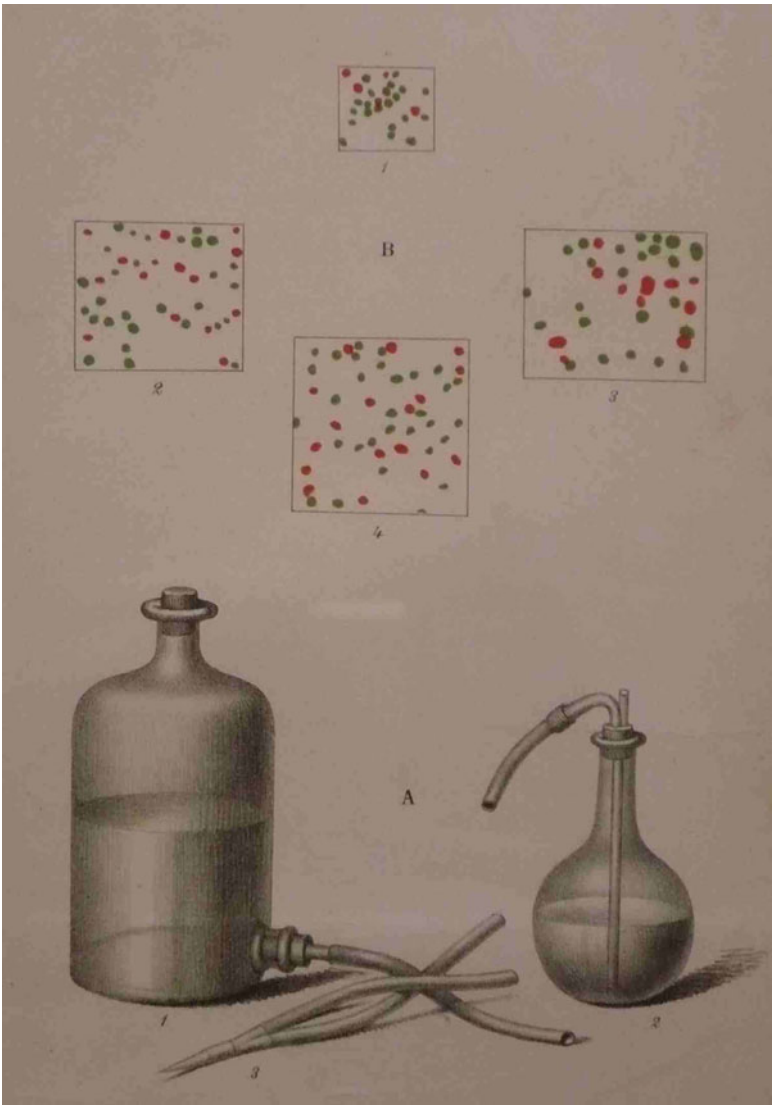

Fig. 7.3 (**a**) Blix's apparatus for temperature stimulation. The closed bottle to the left, with a tube protruding at the bottom contained cold water. The flask to the right was half filled with water and had two pipes penetrating the stopper: One short pipe providing passage of air between inside and outside. One long pipe with one end below the fluid level, and tubing attached to its bent upper end. The water in the flask was heated over a flame. The tubes from the two water bottles were joined at the Y-shaped, silver plated, hollow cone shown in the middle. When the bottle to the left was raised above the flask, cold water flowed through the metal tip decreasing its temperature. When this bottle was instead lowered, water would flow in the opposite direction, and the warm water from the flask would raise the tip's temperature. (**b**) *1* Cool (*green*) and warm (*red*) spots on the back of Blix's hand. *2* His wrist. *3* His elbow. *4* The back of J.H. Andersson's left hand. (From, Blix, M. (1883) *Upsala Läkareföreningars Förhandlingar*, vol. 18, Plate 11)

Fig. 7.4 Johannes Karl August Eugen *Alfred* Goldscheider (1858–1935) studied at the Kaiser-Wilhelm-Akademie for military physicians in Berlin and received his medical license in 1881. He defended his doctoral thesis in the same year. His supervisor was Emile Du Bois-Reymond (1818–1896). The training at the medical school included a subsequent, compulsory service as military physician, which was finished 1894 in his case. During that period he performed a series of experiments on cutaneous, and muscle sensibility which were published successively. These reports were republished 1898 in two volumes. After leaving the military service he pursued a career as clinical director, and extraordinary, and finally ordinary professor in internal medicine at Berlin University. He became a much admired clinical teacher, while still maintaining his theoretical interest (His 1928; Bergmann 1935; Kretschmer 1935). Photograph courtesy of Dr. Günter Grau, Humboldt Universität, Germany

things, he discussed the varied causes of pain feelings in his thesis. An obvious cause was strong mechanical stimulation of the skin. Nevertheless, pain would be caused by a light touch after application of an unspecified *rubefacient* [2] (possibly mustard oil). Moreover, a light touch on exposed tooth pulp would cause pain, without any preceding experience of mechanical contact. Hence, at the time, he considered the existence of a specific sense of pain to remain an open question.

In his subsequent experimental work, Goldscheider discovered points on the skin which he at the beginning had labelled "pain spots". This label was afterwards retracted, and the observation of "pain spots" was considered to be unrepresentative. He argued that any, depending on the circumstances, sufficiently forceful point

[2] Archaic term, a rubefacient was a substance, which caused redness of the skin following its application. For medical purposes rubefacients were formerly used as counterirritants.

stimulus on the skin would evoke a vivid afferent nerve activity. This activity would, if sufficient, exceed the threshold of a spinal pain pathway. He considered the pain felt in connection with ailments of inner organs, and tooth pulps to represent a separate, pathological category. He concluded that the skin contained four specific mechanisms for perception, and at the same time excluded the existence of a cutaneous, specific sense of pain (Goldscheider 1898b):

1. Impression nerves (*Gefühlsnerven*) responsible for evoking a feeling of being touched outside the pressure spots. Following very light stimuli they would contribute to feelings of tickle. Stronger stimuli would evoke a stinging feeling that could grow into a sharp pain.
2. Pressure nerves (*Drucknerven*) responsible for the feelings of particular spots being touched and which signalled stimulus magnitudes. They were found with the topographically densest distribution on the finger tips and the sparsest on the back. Following very light stimuli they would also contribute to the feelings of tickle. Strong stimulation would evoke a dull pain.
3. Warm temperature nerves. Warm stimuli would cause pain when exceeding a critical level. This pain feeling was higher at areas located in between the warm spots themselves.
4. Cool temperature nerves. Cool stimuli would cause pain when beneath a critical temperature. This pain feeling was higher at areas located in between the cool spots themselves.

Goldscheider's conclusions were fairly soon questioned by Maximilian von Frey (1896). Von Frey (Fig. 7.5) considered his own psychophysical findings to indicate the existence of specific, cutaneous, pain spots, i.e. specific, cutaneous pain nerves. The contrary opinions of the two endured. Sadly, they had both died before a paper appeared which provided a new trail for psychophysical pain studies. Clark et al. (1935) had found a theoretical neurophysiological link between the activity of slowly conducting C fibres in cats and pain feelings in humans.

An Intriguing Case of Allodynia

Goldscheider's work with the pain problem resulted in some, nowadays overlooked but conceivably relevant observations on experimental allodynia, which are summarized as follows. The term allodynia is a later creation (IASP 1979) for expressing what Goldscheider (1916, 1917) called "*Hyperalgesie*". The studies were performed while he was working as *Generalarzt der Landwehr* (surgeon general) on the western front in WW1. Many of his observations were obviously the results of autogenous procedures, but it appears probable that there also were results, which required the participation of other subjects. He warned, at the end of both papers, that military field conditions had curbed the procedures. In these wartime experiments he had returned to the problem of the above-mentioned changes of cutaneous sensitivity, which will appear outside, and apart from the cutaneous pain caused by application of mustard oil.

Fig. 7.5 Maximilian (*Max*) Ruppert Franz von Frey (1852–1932) studied medicine at Wien, Leipzig, Freiburg and München. He graduated 1877 in Leipzig. Contacts with Ernst von Brücke (1819–1892) in Wien, and Carl Ludwig (1816–1895) in Leipzig, while he was a medical student became decisive for his future occupation. 1874, he pursued his first scientific work on the innervation of salivary glands in Ludwig's laboratory. In 1880 he returned to Ludwig's laboratory and stayed until the death of the latter. During this period he worked with blood circulation, muscle metabolism and sensory physiology. The sensory physiology became his lasting interest, and he worked with muscle sensitivity, and the different cutaneous sensory qualities and their interaction. Following Ludwig's death he accepted a chair in Physiology at Zürich 1898, and the chair in Physiology at Würzburg in the following year. He stayed in Würzburg for the rest of his life (Rein 1933; Schriever 1961)

He had now evoked a controlled degree of local pain with a regulated start and duration by means of an adjustable clamp (pain stimulator), which is illustrated in Fig. 7.6a. Pain stimulation at a local point was found to make adjacent, normally non-painful stimuli immediately to become painful (hyperalgesic). Such hyperalgesic areas were located outside the region of the pain stimulus itself. This hyperalgesia vanished straight away, when the pain stimulation ceased. The hyperalgesic field was larger in the proximal direction relative to the pain stimulus (Fig. 7.6b). The magnitude of the intensity of the hyperalgesia, as well as the size of its area, was correlated positively to the pain caused by the primary pain stimulus. The topography of the hyperalgesic area did not correspond to the local field of innervation but to that of the relevant dermatome. This was found to be true, not only for the arm shown in Fig. 7.6b, but for all of the dermatomes which were investigated. Hyperalgesic fields on the torso stopped at the midline, and those on the thigh at the inguinal fold.

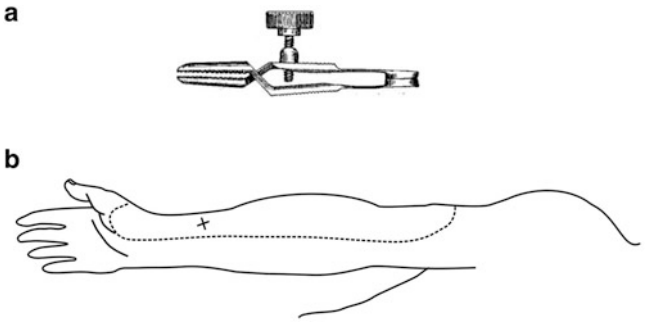

Fig. 7.6 (**a**) Goldscheider's adjustable, mechanical, pain stimulator (Fig. 1, Goldscheider 1916). (**b**) The interrupted line shows the allodynic area on the arm evoked by the pain stimulus when applied to the point on the forearm marked with a cross. Redrawn after Goldscheider (1916), Figs. 1 and 2

Goldscheider found that the above described principles likewise applied to a hyperalgesia which instead had been evoked by means of the application of a mustard plaster. He also performed the following heroic control experiment (Goldscheider 1916, p. 4, translated from German):

> While under way, the pathologically initiated pains spawn a widespread hyperalgesia, just like those evoked with the clamp. I initiated a personal burn injury pain by briefly touching my forearm with a powerfully heated piece of metal. This pain was not only being experienced for a long time, but also immediately initiated a widespread proximal (and in lesser extent distal) and equally enduring hyperalgesic field.

Goldscheider's basic idea was that pain was evoked when the activity of cutaneous touch fibres reached a sufficient level to exceed the thresholds of the neurons belonging to an ascending "pain" pathway, which were located in the grey matter of the spinal cord. His explanation of the experimental hyperalgesia was that a sufficiently strong pain stimulus would in addition, by means of "irradiation" lower the thresholds for afferent activity of adjacent neurons belonging to the same pathway. In that way normally innocuous cutaneous stimuli could become painful.

The term "irradiation" was used by both Goldscheider (1916) and von Frey (1926) and may be traced back to a paper by Quincke (1890). The latter had suggested that the activity of a primary sensory neuron could influence neighbouring neurons through centrifugal action (Quincke 1890, p. 443, translated from German):

> This irradiation usually occurs between closely neighbouring neuronal structures; for that reason it may be assumed that the saltation of the excitation occurs among peripherally located ganglion cells, e.g. in the nucleus of an ascending pathway in the dorsal horn of a spinal segment.

Goldscheider's (1916, 1917) findings about the mechanisms of hyperalgesia were cited in his own later publications, but appear otherwise to have made little impact. They were independently rediscovered towards the end of the century (cf. Treede et al. 1992).

Discovery of the Sensory Signal

Usage of the recently invented electronic amplifier had made it possible for Adrian and Zotterman (Fig. 7.7) to record the afferent signals of single cutaneous receptors for the first time. They recorded from a very thin nerve branch of the second digit of the hind foot of the decapitated cat. Touching of the toe pad evoked a discharge of separate impulses of equal amplitudes. An increase of the stimulation intensity caused an increase of the discharge frequency, whereas impulse amplitudes remained the same (Adrian and Zotterman 1926; Zotterman 1978). Technique permitting, from then on it had become possible to record objectively the nerve signals causing likewise objectively recorded reflex responses, as well as subjective feelings.

The subsequent technical development permitted neurophysiological identification of different categories of somatosensory, afferent nerve fibres. The receptivity of different sorts of peripheral, cutaneous receptors for different physical types of stimulation, now could be determined, e.g. pressure, frequency, tension or temperature. At first, this work was made in the form of animal experiments. Among other things, it was found that in the monkey there was solely one type of receptor which was able to transmit a specific type of information. In this case, it was the different frequencies of a flutter applied to the glabrous skin of the hand. This information was transmitted to the somatosensory areas of the cerebral cortex. Behavioural experiments showed that monkeys lost their ability to recognize this type of detailed information, after the cerebral somatosensory receptive areas had been removed. Nevertheless, this sensory deficiency did not include behaviour which depended on less demanding discriminations of cutaneous stimuli. The finding indicated that the individual information coming from a group of similar cutaneous receptors could be transmitted intact from the periphery to the cerebrum via a so-called labelled line (LaMotte and Mountcastle 1979).

The gap between animal experiments and human studies was narrowed to a great extent with the creation of the human, microneurographic technique (Hagbarth and Vallbo 1967). After an exclusive start, the human microneurography is now performed in a number of laboratories in several countries (cf. e.g. Macefield 2005; Schmelz and Schmidt 2010). The technique permits recording from single afferent cutaneous nerve fibres. It offers a possibility to determine the receptive field(s) of different types of receptors, as well as the frequency of impulse discharges evoked by different types, and intensities of adequate stimulation. A further technical improvement was the introduction of the microstimulation technique (cf. Ochoa 2010). In addition to offer the results of microneurography, this technique also provided evidence about the subjective sensations evoked by electrical stimulation of single identified axons. Hence, Torebjörk et al. (1987) could show that the activation of single fibres in the glabrous skin of the hand evoked individually unlike, subjective sensations. This happened with three receptor categories; it was true for the myelinated axons of the rapidly adapting Meissner receptors, with small receptive fields, and those of the rapidly adapting Pacini receptors with large receptive fields. It was also true for axons of the slowly adapting Merkel receptors with small receptive fields.

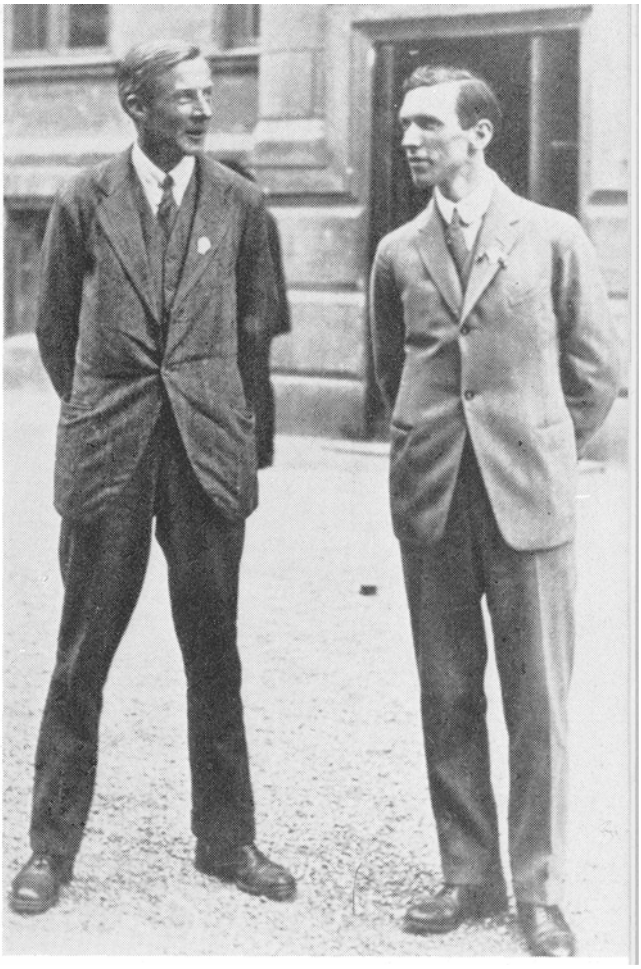

Fig. 7.7 E.D. Adrian (*left*) together with Y. Zotterman (*right*). *Edgar* Douglas Adrian (1889–1977) took his B.A. degree 1911 at Cambridge. In 1913, he was elected to a fellowship at Trinity College. He received his medical degree in 1915 and had pursued his clinical work at St. Bartholomew's Hospital in London. He became a Fellow of the Royal Society in 1923. In 1929, he was elected Fullerton Professor of the Royal Society, and became Professor of Physiology at the University of Cambridge in 1937. He was elected Master of Trinity College in 1951. He was raised to the peerage, and became Lord Adrian, Baron of Cambridge in 1955. He became Chancellor of Cambridge University in 1968. In Cambridge, before WW 1, he worked with Keith Lucas (1879–1916) who was a Fellow of Trinity College, and Lecturer in Natural Sciences. Keith Lucas died in a flying accident during the war. After having obtained his medical degree, Adrian spent the rest of the wartime working with casualties. He returned to Cambridge in 1919 and was able to take over Keith Lucas's laboratory. Together with Yngve Zotterman, and with use of Keith Lucas's capillary electrometer he was able to demonstrate the all-or-none principle of the axonal action potential. Adrian afterwards continued to investigate and demonstrate many of the basic principles of sensory neurophysiology. Together with Charles Sherrington, he received the Nobel Prize in Physiology and Medicine in 1932 (Zotterman 1978; Anonymous 2013). Gulle *Yngve* Zotterman (1898–1982)

When they were asked about the places of origin of such sensations, the subjects generally recognized the peripheral receptive field of the stimulated fibre. Thus, the findings indicated "labelled lines" from these peripheral receptors to a cerebrally induced consciousness. However, stimulation of the slowly adapting Ruffini receptors' afferents failed to evoke any conscious percepts. These receptors record the current states and eventual changes of local skin tensions. A number of these receptors' afferents therefore will be firing at any time. Behaviourally, they contribute to the subjective, tactile directional sensibility (Olausson et al. 2000), and to the spontaneous postural control (Backlund Wasling et al. 2005). These functions are based on the synchronized loading, and unloading of a number of receptors, i.e. a multifibre pattern of firing. Hence, a "labelled line" from a single Ruffini receptor to the subjective consciousness could be irrelevant.

Feelings of Pleasure

The fact that tactile stimulation may evoke pleasure is usually just mentioned in the early papers on cutaneous psychophysics, with some exceptions. Müller (1838) listed *Kitzel* (meaning tickle/titillation) and *Wollust* (meaning lust/pleasure) among the cutaneous, sensory qualities.[3] His brief comment on the subject was that feelings of *Kitzel* and the closely associated *Wollust* could be evoked from all parts of the body. They were most powerful when evoked from the genital parts, and less so from the female breasts, the lips, the skin and the muscles. Von Frey (1895, 1896) was more explicit. He noted that while the male sexual organ lacked any special facility for *Wollust*, it did possess the possibility to register temperature and pain, and touches, including *Kitzel* on its cutaneous surfaces. He regarded *Kitzel* to be a secondary phenomenon, which depended on multineuronal interaction in line with the above referred paper by Quincke (1890). In a later publication, he specified that *Kitzel* was a fickle sensation, which could not be captured unless the stimulus was

Fig. 7.7 (continued) studied medicine at Karolinska Institutet in Stockholm. In 1919, after obtaining the preliminary medical degree he visited Cambridge and studied physiology, and spent some time in Adrian's laboratory. After having obtained his medical license in 1925 he returned to Cambridge to work with Adrian on a Rockefeller Travelling Fellowship. He obtained a Doctorate in Medicine in 1933, and worked as senior lecturer, and afterwards reader in physiology at the Karolinska Institutet until 1945, when he got the chair in physiology, and pharmacology at the Royal Veterinary College in Stockholm. He is remembered for his work on the electrophysiology of the cutaneous, touch, pain and temperature sensitivity, as well as the chemo-sensitive afferents of the tongue (Zotterman 1971, 1978). Image from Zotterman (1971)

[3] The German nouns Kitzel, and Wollust together represent a variable significance with regard to a resulting experience ranging from sensations of being tickled, via enjoyment to delight.

moving. He noted that *Kitzel* required stimulation characteristics, which were similar to those of the tactile sensibility. However, the two kinds differed with regard to the evoked experience. The tactile stimulus was a signal of external stimulation, whereas *Kitzel* was a form of personal experience or condition. The latter was more a case of psychological attitude and the degree of disposition (von Frey 1926).

Zotterman (1939) was able to visualize the different, afferent action potentials which were evoked in thin branches of the cat's saphenous nerve following different types of cutaneous stimulation. His technique, to a certain extent, permitted a correlation between stimulus quality and the type of nerve fibre. The results indicated that tactile stimulation, which for human subjects would be termed tickling, were conducted via slowly conducting, and in some instances unmyelinated nerve fibres. Zotterman's suggestion was confirmed and expanded by Douglas and Ritchie (1957). Working like Zotterman with the cat's saphenous nerve they found that (Douglas and Ritchie 1957, p. 396):

> From our experiments in which we have examined directly the discharges of non-medullated fibres, it is clear that the bulk of such fibres in the cat's saphenous nerve respond to stimuli which cannot be thought of as painful; for these stimuli—light stroking with a cotton swab or the gentle pouring of liquid paraffin over the skin—gave rise to a sensation of tickling or of gentle touch when applied to the face or to the back of the hand of the experimenters.

This type of unmyelinated touch fibres was afterwards found in a number of mammalian species including primates. However, they were thought to be absent in humans for some time before eventually being discovered (cf. Vallbo et al. 1999). In addition, they were found to be critically involved in the pleasure evoked by a slowly moving, light touch (Löken et al. 2009). Hence, the type of stimulation which causes cats to purr depends on tactile afferents which contribute to analogous reactions in man.

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Chapter 8
Psychophysical Assessment of the Sensory and Affective Components of Touch

Steve Guest and Greg K. Essick

Abstract In this chapter, we address two issues. Initially, we consider how to assess the sensations and emotions that occur through touch. This is not a trivial problem, for there exists a wealth of potentially relevant language that one might use to construct appropriate psychometric instruments. After reviewing the limited number of prior tactile lexicons, we illustrate a method by which we have developed a new lexicon for touch. This 'Touch Perception Task' allows the assessment of relevant sensory and emotional components of perception. In the subsequent part of the chapter, we review two classes of devices for the study of touch. These devices either allow tactile stimuli to be delivered in a highly controlled manner, or allow the assessment of the physical interactions between skin and stimulus during tactile perception. The former robotic stimulators are of particular relevance to the study of C-tactile afferents, because they allow stimuli to be presented to hairy skin with velocities that are well- or ill-suited to stimulate such afferents. The other class of force-plate devices tends to be limited to assessing finger–surface interactions, which do not involve C-tactile afferents. However, active touch using the fingers is an important human behavior, which can certainly be replete with emotion. As such, it is important to reconcile C-tactile mediated affect, and the affect that derives from touch devoid of these afferents. Robotic and force-plate devices will both be of utility in this respect.

Keywords Affect • Emotion • Lexicons • Mechanical events • Perceptual space • Review • Sensation • Stimulus parameters • Touch

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Introduction

Sensations and emotions are distinct aspects of perception, and both are needed to fully describe a perceptual experience. Sensations—described by sensory words—are typically closely tied to definable, measurable stimulus properties. For example, the sensory word *roughness* has been shown to be associated with the magnitude of surface variation (Bergmann Tiest and Kappers 2006) and with timewise variations in friction between an exploring fingertip and underlying surface touched (Smith et al. 2002a). Similarly, for fluid-coated surfaces, perceived *viscosity* has been linked to the friction and vibrations that are recorded during a fingertip's exploration of the lubricated surface (Guest et al. 2012a). Although the link between each and every sensory word and its instrumentally defined basis is not understood, the potential exists to forge all such relationships. In contrast, emotions—described by emotional words—describe feelings that accompany sensations. Such words are not necessarily linked to instrumental measures in straightforward manner. For example, the feeling of *pleasure* can arise from very disparate physical stimuli. The sensations evoked by a physical stimulus may also be influenced by things other than the stimulus itself, such as global aspects of the perceiver's emotional state (viz. mood). In this way already present, or transiently occurring emotions, can alter the behavioral response to a physical stimulus, a critical component of commercial advertisements for example (Holbrook and Batra 1987; Laros and Steenkamp 2005).

This distinction between sensation and emotion is supported in validated psychometric tests (Melzack 1975; Melzack and Torgerson 1971), in social psychology (Osgood 1952, 1966; Osgood and Suci 1955), and also by neurophysiology. The latter work suggests that the sensory and emotional components of perception may be rooted in their transduction by different types of skin mechanoreceptor (Löken et al. 2006, 2009; McGlone et al. 2007, 2012; Olausson et al. 2002, 2008a, b). Specifically, it has been found that the magnitude of activity in low-threshold, unmyelinated mechanosensitive afferents, present in hairy skin, is closely associated with psychophysical ratings of pleasantness. That is, stimuli which strongly elicit C-tactile (CT) activity are expected to be judged as especially emotionally salient.

This discussion arrives at the purpose of the first half of this chapter, namely how best to assess the sensations—and especially—the emotions that occur through touch. It is not a simple task to relate afferent activity to perception if in the first place it is not clear what aspects of perception must be queried. For example, although CT afferents are often spoken of in the general context of 'pleasantness' (McGlone et al. 2012), it is not clear that pleasantness is the best descriptor of what is conveyed by CT activity; there may be more pertinent emotions. Pleasantness has been the default emotional tactile attribute studied from the earliest studies (Major 1895; Ripin and Lazarsfeld 1937) through to the present day (McGlone et al. 2012). However, although pleasantness is certainly important, it is not necessarily the 'best' or most veridical affective attribute for study; nor does the 'pleasantness' of something describe the full emotional experience that may occur during touch. The first half of this chapter highlights the incomplete picture that studying purely pleasantness might provide, and details the development of tools that allow a more complete

assessment of the emotional and sensory aspects of touch. Such tools allow presumptive CT afferent activity or indeed any other emotionally salient complex sensory input to be probed psychophysically with improved precision.

The second half of this chapter addresses tools that allow for better assessments of tactile hedonic perception to be made. In this text, we illustrate the development of devices that allow stimulus parameters to be tightly controlled for the application of stimuli to the skin. In particular, we note the development of a Rotary Tactile Stimulator (RTS; Essick et al. 2010) which can present materials to the skin with controlled speed, force, and direction of delivery. This is of clear utility in characterizing CT afferent activity in response to touch. Indeed, the RTS has been used in several recent microneurography studies to provide precise stimulus control (Löken et al. 2009, 2012). We also describe recent developments of devices that can characterize what occurs during free, active touch, specifically in terms of the forces and other 'mechanical events' that occur at the fingertip during touch. These devices are quite unlike those such as the RTS, which have traditionally been tailored so that an observer passively receives a carefully controlled stimulus. Devices that can characterize active touch allow for more ecologically valid experiments in emotional touch to be conducted.

Lexicons for Sensory and Emotional Touch

Language is the primary means by which we express our reactions to the things we touch and the things which touch us. In this respect, one might seek to assess a touch experience by asking the receiver of the touch to freely generate all words of relevance to the touch (e.g., the touch felt *soft*, *smooth*, *sexy*, etc.). However, freely generated, subjective descriptions of a touch experience make for poor data. This is for a few reasons: First, any individual might neglect to report a sensation or emotional reaction, even if it pertained to the touch. For example, the word *soft* might not be generated, but that does not mean the touch was not felt as *soft*. Second, the degree to which any word applied to the touch is not obtained from simple word generation. For example, if the touch indeed felt *soft*, how soft did it in fact feel? Third, the nature of each word is ambiguous; one cannot simply intuit the nature of a generated word, or rely on dictionary definitions to obtain robust data about touch. For example, does the word *silky* denote a sensory percept, or does it invariably carry with it emotional connotations? To what extent is *silky* synonymous with words such as *smooth* and *satiny*? Intuition does not lead to a reliable answer.

One way of characterizing a touch experience is to obtain a list of words which is stringently derived to allow a tactile, or other specific perceptual experience to be fully and accurately described (Bhushan et al. 1997; Osgood 1952; Stevenson and Boakes 2003). Such a set of words is what we term a *lexicon*. Until recently no attempt had been made to derive a touch lexicon, although lexicons for other modalities of perception have been reported previously (Bhushan et al. 1997; Dravnieks 1982, 1985; Harper et al. 1968). These are detailed below; they provide a context and base methods relevant to our development of a touch lexicon, which we describe in detail later.

Nontouch Perceptual Lexicons

The practical need for lexicons is universal across our various sensory modalities. For example, language to precisely describe odor perception is of utility for the evaluation of perfumes and beverages containing volatile odorants (Stevenson and Boakes 2003). A lexicon for (visual) texture perception could potentially allow spoken interactions with computer graphics systems for rapid generation of visual elements (Bhushan et al. 1997), for example, 'put a *granular*, *woven* texture on the red cube.' Similar arguments can be made for the utility of lexicons for audition and taste. Accordingly, lexicons have been developed and reported for some nontactile perceptual tasks. The nontactile lexicons are directly relevant to a touch lexicon: Their research has established basic principles for lexicon development, demonstrated important properties of descriptive word use and illustrated the practical utility of lexicons.

Any lexicon development must begin with the collation of an initial candidate set of all words that might be of relevance to the task. This is followed by culling these words by some method to product a final, manageable set of words. This final set forms an initial lexicon, which can be used as-is, or refined further. The overall idea here is simple, but there is no single method by which words might be selected and then culled. The initial candidate set of words is invariably subjective to a large extent, being necessarily produced using dictionary and literature searches, and introspection. For example, the (visual) texture lexicon (Bhushan et al. 1997) began with a candidate set of 367 texture-related words which were culled by removal of terms referring to interactions between light and a surface (e.g., *transparent*), and by removal of words used infrequently in American English (e.g., *ruched*). This led to a final lexicon of 98 words. Odor lexicons have tended to move toward a larger set of words over time and according to empirical needs. So, an odor lexicon of 44 words was proposed in the 1960s (Harper et al. 1968), later being expanded to a candidate set of over 800, which was reduced to 146 by 1982 (Dravnieks 1982, 1985). The rather labile nature of odor lexicons highlights that establishing a balance between a manageable number of words in a lexicon and the completeness of the lexicon is not an easy task.

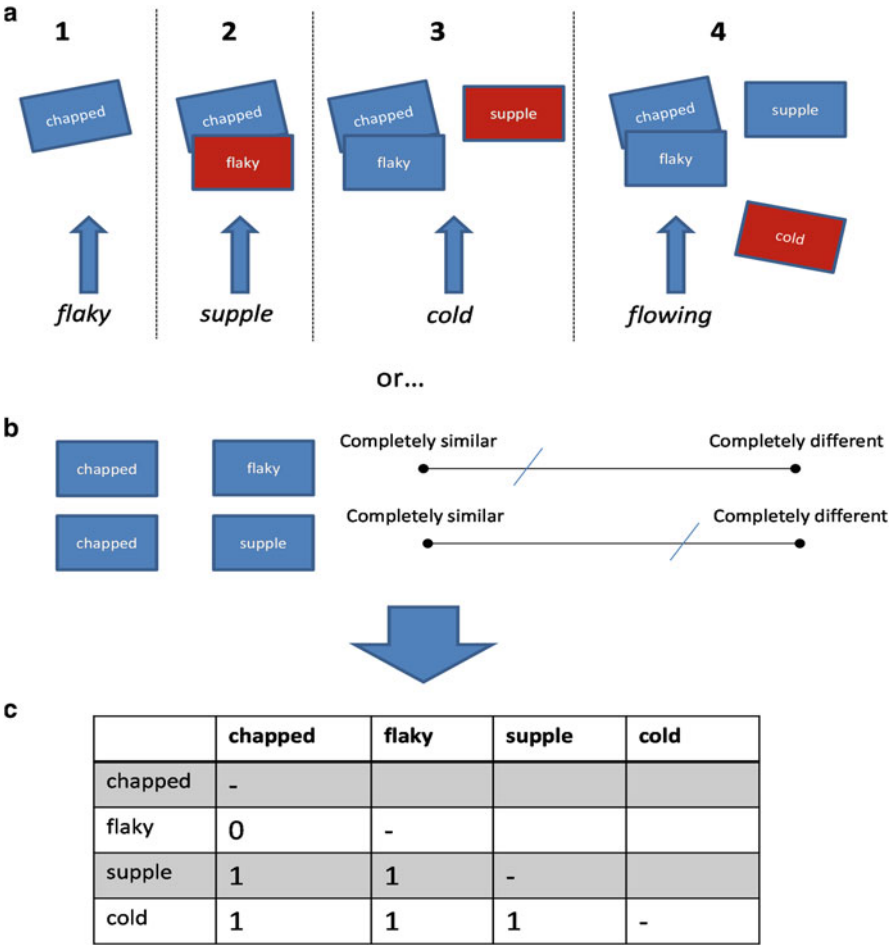
A more positive finding from the prior work is that descriptive language appears stable. That is, the degree to which a given descriptor applies to a stimulus is, on average, consistent. This was shown via empirical testing using a test set of odorants, some of which were quite perceptually similar (Dravnieks 1982). In simple terms, if an odorant is well-described as *sweet* and *yeasty*, then it will always be well-described by those words, at least over a sufficiently large sampling of respondents. Similar results have been shown for the visual texture lexicon by testing associations between actual, empirical textures and the texture lexicon words (Bhushan et al. 1997). Providing a set of texture lexicon words that applied to a given texture allowed the applicable texture to be successfully selected from a set of candidate textures. For example, one could correctly find a texture specified as *granular, well-ordered,* and so forth from a set of various example textures. It is reasonable to expect language to have similar properties over all sensory modalities, suggesting that a touch perception lexicon should also have a foundation in suitably stable descriptive language.

Semantic Relationships within Lexicons

The development of any lexicon would ideally include not only the production of a set of descriptive words, but would also quantify the semantic relationships among the words. The idea here is that any word could potentially be placed within a space, defined by orthogonal dimensions, where each dimension could be labeled with distinct concept or perceptual quality. Such a space is in essence a map, with cities replaced with words, distances between words representing their dissimilarity. For example, taking the words *slick* and *slippery*, how similar is the meaning of these words? Is the difference between *slick* and *slippery* akin to the distance between *sticky* and *glutinous*? A more sophisticated question might then be; are *smooth* and *slippery* words that simply describe different extents of some underlying quality, such as *smoothness*? The answers to these questions potentially assist lexicon development in allowing a principled culling of words. For example, a semantic map of words essentially allows the definition of the degree to which words are empirically synonyms (or empirically exceedingly different) to be defined. Neighboring words could potentially be quite different from dictionary-based synonyms.

The development of semantic maps may seem like a fairly abstract problem, but the actual process by which such maps are constructed is simple. Numerous experiments have produced similar maps, but for actual, physical materials assessed by touch. These experiments therefore provide maps of stimuli in a perceptual space, as opposed to maps of words in a semantic-perceptual space. However, perceptual map development is essentially the same, regardless of whether physical material or words are assessed. This development process is shown in Fig. 8.1 giving words as example stimuli.

Each experiment's first task has been to obtain measures of the dissimilarity of the different materials, via either free-sorting tasks (Fig. 8.1a) or via pairwise comparisons of stimuli (Fig. 8.1b). In the former, participants simply arrange stimuli into groups that 'belong' together in some (usually undefined) sense, with dissimilarities being defined based on group memberships. In the latter, participants rate each and every pair of stimuli in terms of how dissimilar the members of each pairing are felt to be. Regardless of how dissimilarities (Fig. 8.1c) are obtained, they are then analyzed using Multidimensional Scaling (MDS), a technique that explicitly produces an *n*-dimensional map that best replicates the empirical distances among items. These methods have established that (nonfluid) materials, such as manufactured textiles or natural materials, are well described by approximately three orthogonal perceptual dimensions (see Okamoto et al. 2013 for a review), namely, *Rough–Smooth* (Bergmann Tiest and Kappers 2006; Hollins et al. 1993, 2000; Na and Kim 2001; Picard et al. 2003), *Hard–Soft and a* less clearly defined tertiary dimension, perhaps consisting of *Springy-Inelastic* (Hollins et al. 1993), or *Sticky–Slippery* (Fig. **8.2**). For fluids, such as skin care products, quite different dimensions have been suggested, such as a primary component consisting of a combination of *residue*, *stickiness,* and *gloss* after application (Almeida et al. 2008). This illustrates another difficulty in formulating a successful touch lexicon, namely that it would need to be capable of describing all tactile experiences, including those that arise from the touch of both dry surfaces and wet surfaces.



c

	chapped	flaky	supple	cold
chapped	-			
flaky	0	-		
supple	1	1	-	
cold	1	1	1	-

Fig. 8.1 The basic procedures used in perceptual scaling experiments. First, the dissimilarity of stimuli is assessed, such as by freely sorting stimuli (**a**), or by making pairwise ratings of stimuli (**b**). This allows a dissimilarity matrix to be produced (**c**), in this case that shown is as derived from (**a**). Typically, the matrix is obtained by averaging responses made by many participants

Note that none of these touch-based studies explicitly considered the use of language in perception. Each study used sorting methods applied to physical materials with the axes of the perceptual space being labeled afterwards, based on the experimenters' intuitions or sometimes more sophisticated statistical methods; thus, none of these studies provided a lexicon. However, the studies did suggest some of the more important percepts, which should thus be included within a touch lexicon. Or, put another way, if a proposed lexicon lacked language related to roughness or smoothness, the lexicon would likely be incomplete. We know this because roughness and smoothness are unambiguously important aspects of touch perception.

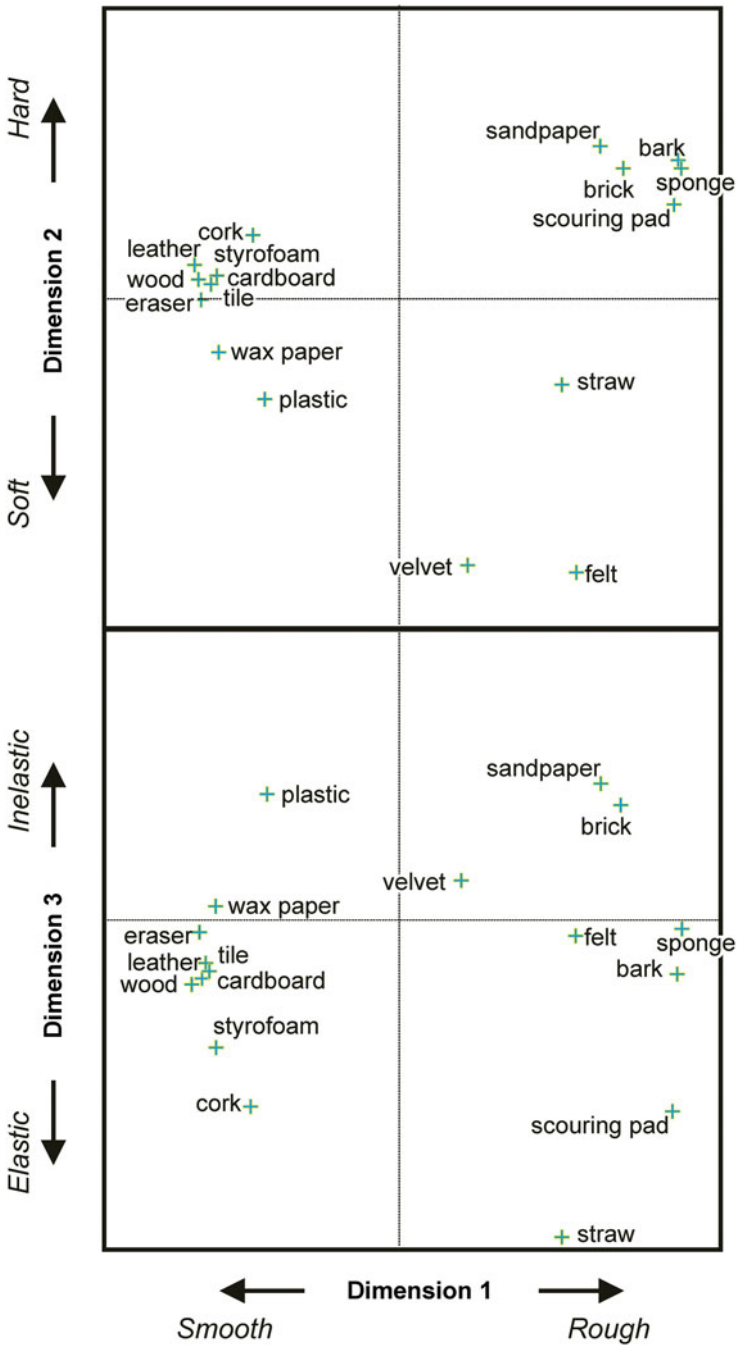


Fig. 8.2 The perceived similarities of different stimulus materials can be represented in *n*-dimensional perceptual spaces. Shown is a three-dimensional space derived by Hollins et al. (1993), depicting the perceptual distances for 17 common textured materials. Each dimension (i.e., axis) broadly represents a distinct type of perceptual change, for example, the first dimension encompasses stimuli varying from *smooth* to *rough*

Semantic mapping has been applied to some of the nontactile lexicons. For example, the 98 'final' words of the visual texture lexicon (Bhushan et al. 1997) were used in a sorting task, wherein participants sorted words into 'similar' groups, just as in the tactile material studies described above. Subsequent MDS revealed that in a three-dimensional space, explaining 82 % of the variance in word distances, the three axes were plausibly labeled as *Repetitive* versus *nonRepetitive*, *Linearly* versus *Circularly oriented* and *Simple* versus *Complex*. In this case, the semantic space was not used to reduce the lexicon further in size, although the space (and a related clustering analysis) was used to define which of a series of broader concepts a word described, such as which of the 98 words referred to the concept of *Granularity*. This allowed lexicon words to be assigned to groups for the purpose of scoring lexical ratings of textures.

Sensation Versus Emotion

The sensory aspects of touch have tended to be studied in far more depth than the emotions that arise from touch. However, the emotional qualities of any perceptual experience are very important. Touch has long been known to be critical in the physical (Meaney et al. 1991; Meerlo et al. 1999), social, and cognitive development of humans and other primates, possessing great emotional potential (Björnsdotter et al. 2000; Diamond and Amso 2008; Harlow 1958; Montagu 1986). Ongoing work into the role of CT mechanoreceptors suggests these are one means by which socially meaningful touch might be initially transduced (Löken et al. 2006, 2009; McGlone et al. 2007, 2012, 2014; Olausson et al. 2002, 2008a, b). This foundational role of touch aside, we clearly have an emotional response to many things we touch in daily life. Indeed, much commercial product development is tailored toward optimizing emotional feelings that arise from product use (Foxall and Greenley 1998; see Spence and Gallace 2011 for a review), especially in the context of foods and beverages (King and Meiselman 2010; Manzocco et al. 2013).

Just as prior work has determined the perceptual dimensions for the assessment of physical materials, so social psychology has suggested that any emotional experience is embodied with certain amounts of three independent qualities, namely *Pleasure*, *Arousal,* and *Dominance* (Osgood 1952; Osgood and Suci 1955; Russell and Mehrabian 1977; Russell and Steiger 1982). Figure 8.3 shows the spatial arrangement of some emotional terms, in much the same way as the physical materials shown in Fig. 8.2. The locations of the emotional words in the figure were derived from ratings made by people of actors depicting a single emotional state, for example, "To what extent does the actor appear *happy* versus *sad*?" The ratings were then analyzed in the same manner as the physical material data described earlier.

This background illustrates that the importance of the emotional qualities of experience have long been recognized, as has knowledge of the structure of emotional space in a wider context. In the specific context of sensory perception, the structure of emotional space has been quite sparsely studied, although emotional words have been used frequently in perceptual studies, as will be illustrated below.

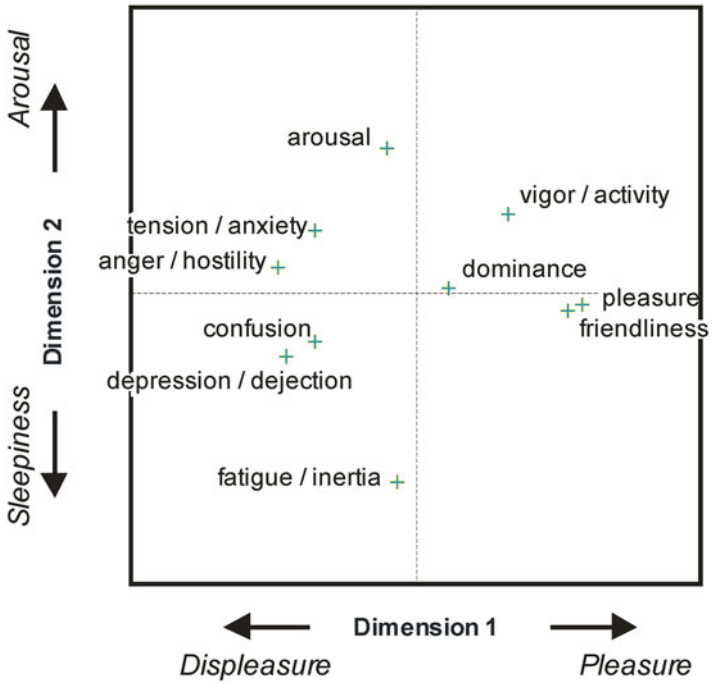


Fig. 8.3 Similar to physical materials, (emotional) words can be positioned in a semantic space that shows their similarities. The first two dimensions of the emotional space of Russell and Steiger (1982) are shown

Emotional Words in Perception

The words that describe emotional states in general (e.g. Fig. 8.3) are not necessarily the same as those used to describe tactile related emotions, and even words common to general emotional states and tactile-perceptual derived states will not necessarily be equally salient.

Pleasantness and allied percepts (e.g., comfort, Cardello et al. 2003; Guest et al. 2009) have been assumed to be important in tactile perception, an assumption that stretches back into the late 1800s (Major 1895) and continues to this day (Essick et al. 1999, 2010; Picard et al. 2003). Ratings of tactile pleasantness have often been shown to vary among materials (Essick et al. 1999, 2010). Additionally, pleasantness has clear face validity. However, it has never been explicitly tested whether pleasantness is the most salient emotional response to touch.

In counterpoint, the term *pleasantness* appears congruent with the primary dimension of general emotional experience, namely *Pleasure* (Fig. 8.3). Therefore, although the ubiquity of pleasantness did not arise though principled study, it happens that pleasantness is likely to be a very important tactile emotional quality given the importance of pleasantness in nontactile emotional responses.

Recently, an emotional lexicon (EsSense Profile) designed for the oral perception of foods has been reported, consisting of 39 words (King and Meiselman 2010). This lexicon was developed considering affect divided into three subsets: *attitudes*, *emotions,* and *moods*. Attitudes were defined as basic evaluations, such as "I like cheese." Emotions were defined as brief, intense, and focused on some specific object, such as "I hate cheese." Moods were defined as enduring, gradually formed, and not focused on a specific referent, such as "I feel content." Using three subsets, by referring to prior work on attitudes, emotions, and moods (e.g., the Profile of Mood States, McNair et al. 1971), the lexicon was produced.

Although this lexicon was intended for the assessment of foods, the emotional words selected are by no means exclusive to food perception (Table 8.1). Further, food perception has a strong tactile component, suggesting that this lexicon could inform a more widely applicable touch lexicon. Unfortunately, the words were not characterized in terms of their underlying perceptual structure; each word was grouped a priori as positive, negative, or uncertain. That said, the word selection procedure was reasonably principled, being based on the use of consumer-derived data to cull the lexicon. Therefore, a primary issue with King and Meiselman's lexicon is that it might not sample any underlying emotional–perceptual space well. Of course, it was—and remains—unclear as to how many underlying emotional dimensions exist with respect to an oral–emotional space. Indeed, until the development of the Touch Perception Task (see section below), it was unclear as to how many emotional dimensions exist with respect to tactile perceptual space in general, what emotional words describe those dimensions, and in what way such emotional dimensions are related to the established sensory dimensions. However, it is quite clear and implicitly understood that any touch lexicon must

Table 8.1 39 words that form the EsSense profile, designed specifically for assessing the emotions associated with foods

Active	Glad	Pleasant
Adventurous	Good	Polite
Affectionate	Good-natured	Quiet
Aggressive	Guilty	Satisfied
Bored	Happy	Secure
Calm	Interested	Steady
Daring	Joyful	Tame
Disgusted	Loving	Tender
Eager	Merry	Understanding
Energetic	Mild	Warm
Enthusiastic	Nostalgic	Whole
Free	Peaceful	Wild
Friendly	Pleased	Worried

incorporate words that describe sensation and emotion if any given tactile experience is to be described fully.

The Development of a Lexicon Explicitly for Touch

With the above context, we decided to produce a lexicon for tactile perception with the express purpose of allowing for the classification of sensory and emotional components of tactile perception. This lexicon was termed the Touch Perception Task, or TPT (Guest et al. 2011). No such comprehensive descriptive scheme for touch had been attempted previously. That is not to say that words of relevance to touch perception were unknown. For example, lists of 'Exploratory Procedures' or (EPs) had been classified and reported (Lederman and Klatzky 1987, 1990), although these were more an attempt to classify the important actions in active touch, rather than classifying the experience of touch in terms of its emotional and sensory content. Hints of other relevant tactile sensory concepts were present in prior tactile perceptual space work (Bergmann Tiest and Kappers 2006; Hollins et al. 1993, 2000; Na and Kim 2001; Picard et al. 2003), but as noted above prior work was of limited help in formulating a candidate lexicon given that it dealt with physical stimuli and not words per se.

We built upon the lexicon development methods not only as described for non-touch modalities, but also incorporating an important concept underlying development of the McGill Pain Questionnaire (MPQ; Melzack 1975, 1987; Melzack and Torgerson 1971). This was the realization that pain can have many qualities ("The pain of a toothache is obviously different from that of a pin-prick…" Melzack 1975, p. 278) which can be conveniently divided into those describing *sensory*/*discriminative*, *emotional,* and *evaluative* attributes of pain perception. We have described what is meant by the *sensory* and *emotional* aspects of perception earlier. *Evaluative* aspects of perception are those that refer to the significance, importance, or intensity of the sensory experience (i.e., pain, in the context of the MPQ). *Intolerable* is one example of an evaluative word listed in Melzack and Torgerson (1971).

We recognized that nonpainful tactile perception could also potentially be divided into sensory, affective and evaluative aspects. Therefore, combining ideas from prior lexicon development and the MPQ, we selected 262 initial candidate words (Table 8.2) via dictionary search. These were then rated by 49 individuals in terms of the extent to which each was considered emotional, sensory, or evaluative in nature. Ratings were collected using a four-point scale, where a rating of unity denoted the word had nothing to do with the aspect of touch under consideration whereas a rating of 3 or 4 indicated that the word referred moderately or strongly, respectively, to the aspect of touch.

This process revealed a few interesting findings. First, of the 262 candidate words, only 168 referred at least moderately overall to one or more aspects of touch. Second, whereas the MPQ development process upheld a distinction between *sensory*, *emotional,* and *evaluative*, the ratings of touch-related words

Table 8.2 262 words chosen as possible members of a touch lexicon

Abrasive	Decisive	Gelatinous	Meaty	Rugged	Taut
Achy	Dehydrated	Gentle	Moist	Sandy	Tender
Airy	Delicate	Glassy	Mushy	Satiny	Tense
Annoying	Demanding	Glossy	Nappy	Scabby	Tension
Arctic	Dense	Gooey	Nice	Scalding	Tepid
Arid	Desirable	Goopy	Nippy	Scaly	Textured
Arousing	Determined	Grainy	Notable	Scorching	Thick
Attending	Diffuse	Granular	Noticeable	Scraping	Thorny
Aversive	Dirty	Grating	Oily	Scratchy	Thrilling
Blissful	Discomfort	Greasy	Oozy	Searing	Tickling
Blunt	Distinctive	Grimy	Overheated	Sensual	Ticklish
Breezy	Distressing	Gritty	Painful	Sexy	Tickly
Bristly	Doughy	Grooved	Parched	Shaggy	Tight
Brittle	Downy	Gummy	Pat	Shallow	Tortuous
Bumpy	Drenched	Hairy	Pebbly	Sharp	Tough
Burning	Dry	Hard	Persistent	Significant	Tranquil
Bushy	Dull	Heavenly	Pert	Silky	Transient
Callous	Effervescent	Horny	Placid	Sinuous	Translucent
Calming	Elastic	Hot	Plastic	Slack	Trim
Chafed	Enjoyable	Hydrous	Pleasurable	Slick	Uneven
Chalky	Erotic	Icky	Pliable	Slimy	Unyielding
Chapped	Evocative	Icy	Plush	Slippery	Vague
Chilly	Exciting	Impacting	Pointed	Sludgy	Velvety
Clammy	Feathery	Important	Pointy	Slushy	Veneered
Clean	Filmy	Indented	Poked	Smear	Vibrating
Clear	Fine	Inflexible	Polished	Smooth	Viny
Coarse	Firm	Intense	Porous	Soapy	Viscous
Cold	Flabby	Irregular	Pounding	Soft	Vivid
Comfortable	Fleecy	Irritable	Powdery	Solid	Warm
Compliant	Fleeting	Irritating	Pressed	Soothing	Watery
Compressed	Fleshy	Itchy	Pressure	Spiky	Waxy
Consequential	Flexible	Jagged	Prickly	Spiny	Weird
Contact	Florid	Leathery	Provocative	Spongy	Wet
Cool	Fluffy	Light	Pulpy	Springy	Wiggly
Cottony	Fluttering	Liquidly	Purposeful	Squeezed	Woodsy
Crawling	Focused	Lively	Raw	Squishy	Woody
Creamy	Fragile	Localized	Relaxing	Steely	Wooly
Creepy	Freezing	Lumpy	Resolute	Sticky	Worn
Crispy	Friction	Luscious	Ribbed	Stringy	Wrinkly
Crumbly	Frigid	Lush	Rigid	Supple	Yielding
Crusty	Frosty	Malleable	Ripply	Sweaty	Yucky
Cushy	Furry	Matted	Robust	Sweeping	Yummy
Damp	Fuzzy	Mealy	Rough	Tactual	
Deadened	Gauzy	Meaningful	Rubbery	Tap	

showed that few tactile words were considered distinctly evaluative. Of the 168 words, 32 were evaluative in nature, but most of these were also considered additionally sensory (5 words), emotional (13 words), or sensory and emotional (6 words) in nature. Furthermore, such words were generally rated as more sensory or emotional than they were evaluative. Of the eight words remaining as predominately evaluative, only *important* revealed itself as strongly and unambiguously evaluative. On that basis evaluative was dropped as an aspect of touch considered during the lexicon development.

To cull the word list further, a dual ranking scheme was used. The sensory and emotional words were placed in order of decreasing sensory or emotional ratings, 'within word' and 'within aspect.' This is illustrated for the sensory words in Fig. 8.4; the same procedure was carried out separately for the emotional words. These ranking schemes considered how each word was ranked within the whole set

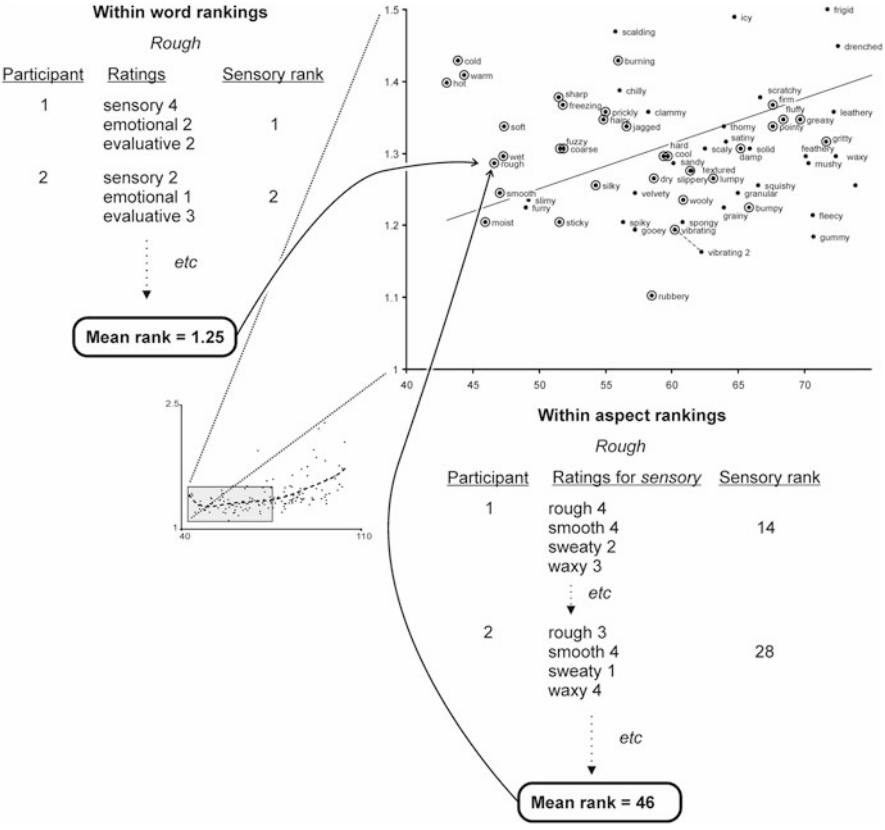


Fig. 8.4 When developing the Touch Perception Task, to form a lexicon of manageable size required choosing the best words from the many available. This was achieved by considering rankings of words in terms of the two schemes shown. The main figure is a subset of a much larger set of candidate words, per the small inset figure. Figure adapted from Guest et al. (2011). *Encircled points* are words that were selected for further consideration following this ranking phase

of sensory or emotional words, and within the three perceptual aspects (i.e., sensory, emotional, and evaluative).

After choosing the best ranked words, 97 words remained for a candidate lexicon, considered too many to be practicable for further study. Therefore a subjective culling was applied, with removal of retained synonyms (e.g., *scalding* and *burning* passed the ranking criteria, but *scalding* was excluded) and terms related to very specific materials (e.g., *furry* was excluded while keeping *fuzzy*). The original list of 262 was now winnowed down to 33 sensory and 16 emotional words.

Finally, similarity judgments of all pairings of the words were obtained, considering sensory and emotional words separately (see Fig. 8.1b, c), allowing perceptual spaces to be found for sensory and emotional words. The sensory and emotional spaces were both considered three dimensional. They are shown in Fig. 8.5.

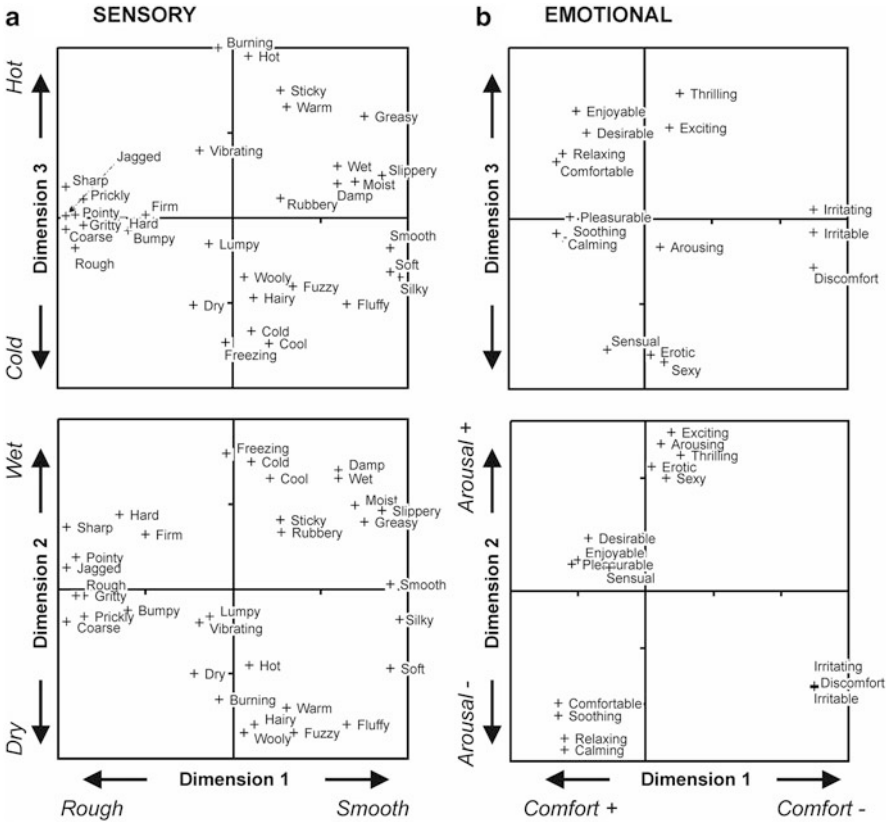


Fig. 8.5 The semantic relationships among sensory (**a**) and emotional (**b**) words pertaining specifically to touch. The third axis of the emotional space was not easily labeled and was considered to denote a difference in emotional quality among words, but possibly could be labeled as varying sensuality or eroticism

On inspection of the sensory word space we suggested the axes could be labeled *Rough–Smooth*, *Dry–Wet,* and *Hot–Cold.* Similarly, the emotional space axes were labeled *Comfort*, *Arousal,* and (more tentatively) *Sensory quality*. The relative locations of words allow one to determine which are similar enough that one or more might be omitted.

The Touch Lexicon in Use

After developing a touch lexicon, it is important to ask whether the lexicon 'works.' That is, does the lexicon successfully allow emotional and sensory responses to tactile stimulation to be assessed? And in the context of this book, do the responses to the sensory and emotional words of the touch lexicon support CT afferents' purported role in emotional touch?

We first used the TPT to collect subjective judgments of textiles stroked across a variety of body sites (Guest et al. 2011). The textiles were typical of those used in prior affective touch work (Essick et al. 1999), for which expected sensory properties were known and pleasantness ratings were available, allowing for some degree of validation of the TPT. The primary analysis method was to decompose the sensory and emotional word ratings of the TPT via Factor Analysis (i.e., the individual attributes of the TPT were not considered directly), although we have in other studies analyzed the individual attributes of the TPT (Guest et al. 2014). Four orthogonal sensory factors emerged describing, in decreasing order of importance, *Roughness*, *Slip*, *Firmness,* and *Pile*. The scores for the different textiles fell as expected within these factors. For example, a coarse hessian (burlap) material was scored as rougher than cotton t-shirt material. Two emotional factors emerged, approximating *Comfort* and *Arousal*. As for the sensory factors, the emotional factor scores fell as expected, although some interesting additional effects were found. For example, although silk was scored as very comfortable, this was far more the case when that material was moved over the finger or forearm as opposed to the underarm.

We subsequently extended this work to the tactile perception of a film surface coated with 15 different fluid skin care products (Guest et al. 2012b), again finding clear TPT-derived differences among the fluids, in this case the TPT attributes decomposing into five orthogonal sensory factors approximating *Wetness*, *Texture*, *Slickness*, *Silkiness,* and *Viscosity*—factors quite different in nature to those found for the assessment of textiles. In contrast, the factors describing the emotional experience of touch were similar for the tactile experience of fluid and textile stimuli (Guest et al. 2011, 2012b). However, in neither case did emotional experience of *Dominance* emerge, despite the common appearance of this factor in many social contexts. Perhaps, *Dominance* is only of consequence in interactions between, or assessments of, other humans (perception of body posture, Mehrabian 1970; perception of facial expression, Osgood 1966). In contrast, it seems that *Pleasure* (or *Comfort*) and *Arousal* are universal dimensions of any emotionally based judgment, emerging for social situations and for assessments of inanimate objects (i.e., textiles and skin creams).

Regarding use of the TPT in studying specifically CT-related psychophysical responses, McGlone and colleagues assessed the sensory and emotional components of touch (via TPT) in a study that investigated cortical activity (via PET) in response to touch of the forearm or palm (McGlone et al. 2012). The TPT revealed a complex of generally greater emotional responses at the forearm versus palm, consistent with the presence of emotionally relevant CT afferents in the forearm but not the palm side of the hand. However, one must exert caution in asserting that strong emotional responses, as measured using the TPT, unequivocally denote strong CT activity. For example, tactile stimulation of facial sites can lead to a large affective responses (Essick et al. 1999), but this is not necessarily a consequence of the nature and density of the facial innervation; the inherent role of facial touch in terms of its social meaning acts as a confound in this case (Heslin et al. 1983). Further, even if emotionally relevant touch is indeed primarily conveyed by CT afferents, we can clearly make emotional judgments to touch of– and by– the hands. Therefore, responses to the TPT combined with microneurography and brain imaging provide a compelling picture, unavailable from each source of information in isolation.

The TPT has also been used to investigate the sensory and emotional concomitants of delayed onset muscle soreness (DOMS; Nagi and Mahns 2013), although in this specific case the TPT did not garner notably more information than the MPQ which was also used. Interestingly, this work suggested a hitherto unknown role for CT afferents in DOMS.

In summary, in the short time over which the TPT has been available, it has proven useful in allowing a relatively detailed breakdown of the sensory and emotional perception of tactile materials. This type of detail, not available if one were to assess solely pleasantness, has illustrated the complexity of tactile perceptions, and has supported the purported role of CT afferents in conveying affect and the emotional significance of touch.

Questions Remaining for a Touch Lexicon

Regarding the TPT and other lexicons, an important question is how few attributes are needed to fully describe a perceptual experience? If perceptual experience is well described by an *n*-dimensional perceptual structure, one might propose rating attributes that anchor the axis extremes. So, if tactile emotional space has *Pleasure* (or *Comfort*) and *Arousal* as its cardinal axes (Fig. 8.5), then one might rate the attributes *comfort* and *irritation* (as anchors of *Comfort*), and *exciting* and *calming* (as anchors of *Arousal*). This assumes that one can rate intermediate points in the space as simply amounts of the anchors. The emotional space found in deriving the TPT seems quite amenable to this, because there are few intermediate attributes; *Pleasure* is anchored by *comfort*, with few attributes denoting intermediate amount of comfort present.

However, despite the enduring interest in producing orthogonal perceptual spaces, researchers have not tended use such spaces to optimize (minimize) the number of

questionnaire attributes in this way. In fact, it is not clear that a reductionist treatment of attributes generalizes. For example, consumer science research suggests that simple ratings of the most basic emotions miss information about the emotional experience of consumer goods (Laros and Steenkamp 2005). That is, attributes may not always be well described as amounts of an anchoring attribute. Regardless, the question of how many attributes are required for any perceptual lexicon remains.

Development of Devices for CT Study

A primary issue with any psychophysics is how to adequately control the parameters of stimulation. For tactile perception, a variety of methods have been developed to enable such control. The most common approach has been to precisely engineer the surface that contacts the skin during testing. This engineering is a fundamental part of common tactile detection and discrimination testing tasks. For example, precision gratings and other shapes of various types have been developed to study tactile spatial acuity (Lederman 1974; Lévêque et al. 2000; Morley et al. 1983; Patel et al. 1997), embossed letters have been reported as useful for the assessment of lingual tactile acuity (Essick et al. 2003), and calibrated filaments (Von Frey hairs/Semmes-Weinstein monofilaments) are popular in the assessment of light touch (see Jerosch-Herold 2005 for a review of such tasks in a clinical context). Some examples of these are shown in Fig. 8.6. More sophisticated variants on these established devices have been developed recently, such as those which allow vibrotactile

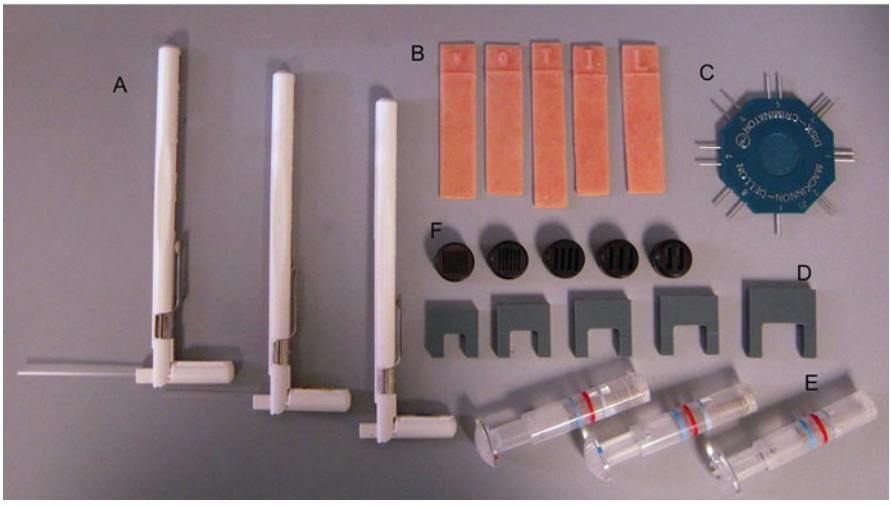


Fig. 8.6 Typical stimuli used to assess the discriminative properties of touch (**a**) VonFrey hairs for light touch detection tasks; (**b**) embossed letters for assessment of lingual tactile acuity; (**c**) two-point discrimination tool (Mackinnon Disk-Criminator); (**d**) gap detection stimuli; (**e**) JVP domes for the assessment of spatial acuity on sensitive skin sites (e.g., fingertip); and (**f**) grating stimuli with a similar purpose to (**e**)

stimuli to be delivered to two nearby skin sites with good, independent control of the two stimulator tips (Tannan et al. 2005).

However, the study of emotional touch requires the control of different and potentially rather more complex stimuli. The tactile emotional impact of an engineered plastic grating is unlikely to be great. In contrast, one of the most obviously emotionally impactful touches is a caress; in more prosaic terms, a stimulus gently brushed across the skin. Therefore, devices to effectively study emotional touch must be able to provide an 'ecologically relevant' brushing stimulus, while allowing for good control of the parameters of the brushing.

Early Approaches to Affective Stimulus Delivery

Early approaches to studying tactile affect did not use good stimulus control, because that type of control was beyond the engineering available to researchers. Commonly, stimulus materials to be assessed have been freely manipulated, such as by rubbing or pinching fabrics between fingers and thumb (Major 1895). These methods have established some of the basics of emotional touch, in terms of what tends to feel pleasant, although such methods are not able to determine how stimulus manipulation alters emotional judgments.

However, even in recent years very approximate stimulus control has been accepted for the study of emotional touch, with hand application of soft cosmetic or artist's brushes being commonly used as a prototypically pleasant stimulus (Cascio et al. 2008; Olausson et al. 2002, 2008b). This is acceptable in the sense that a pleasant stimulus, such as a soft cosmetic brush, remains pleasant almost regardless of how it is moved across the skin, even if it is not delivered with the optimal stimulus parameters. Therefore, if one wishes to simply deliver 'something pleasant,' barely controlled manual brushing is often a pragmatic choice, requiring no sophisticated engineering beyond that available by default in the experimenter's hand.

Automated Stimulus Delivery Control

One of the early attempts to provide improved stimulus control was via a brushing stimulator that allowed different materials to be moved across the skin with controlled velocity (Essick et al. 1999). The development of this robotic device was a primary step in CT-related work, not only to provide hitherto unavailable stimulus control, but also to control for experimenter-induced effects. For example, the physical attractiveness of the experimenter can influence the responses he/she obtains from participants (Donley and Allen 1977; Hartnett et al. 1976), and males and females can respond differently to 'objective' stimuli, contingent on the sex of the experimenter (Levine and De Simone 1991). The pressure exerted against the skin was controlled to a limited extent by mounting stimulus materials on a resilient

foam pad, but it was not explicitly characterized. This system allowed the authors to be the first to demonstrate that pleasantness has a curvilinear relationship with stimulus speed, with the greatest pleasantness being perceived for stimuli moved over the skin at c. 5 cm s^{-1} (Fig. **8.7**). Additional findings showed that replicate pleasantness ratings were reasonably reliable (intraclass correlation of 0.45), and confirmed that unpleasantness was the inverse of pleasantness.

The basic concept underlying the brushing stimulator was used in subsequently engineering a more sophisticated device, termed the 'Rotary Tactile Stimulator' (RTS). The early construction and programming of the RTS was described by

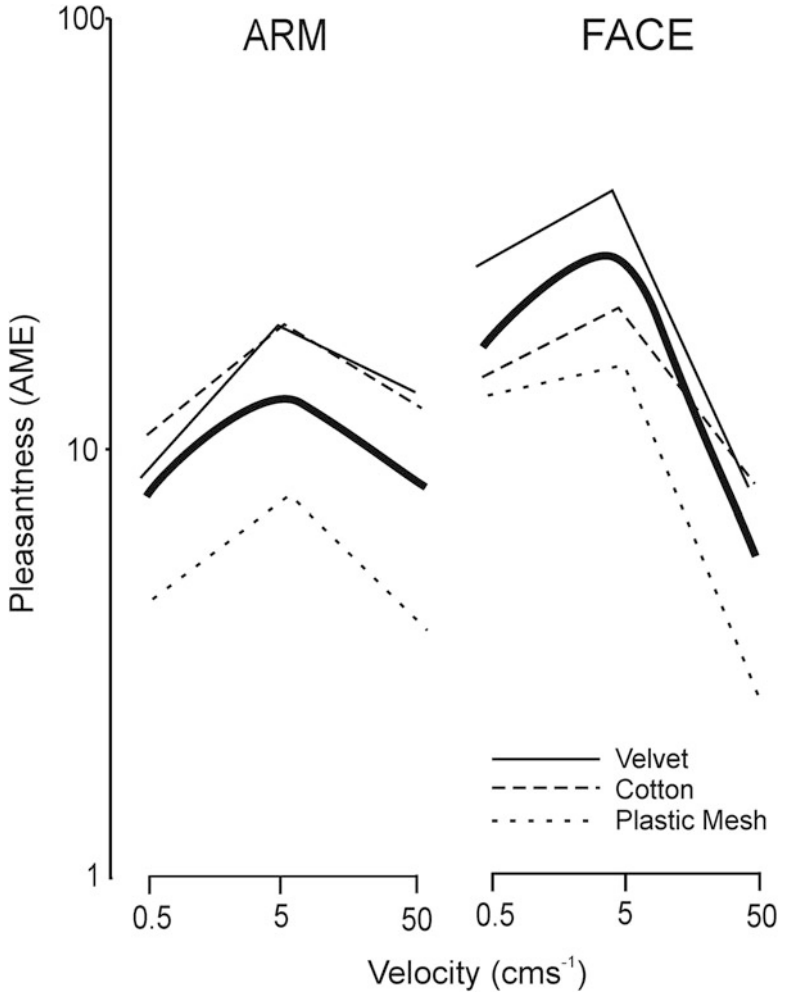


Fig. 8.7 The relationship between pleasantness and the speed a stimulus is moved against the skin is approximately the same regardless of stimulus or body site. Redrawn from Essick et al. (1999)

Fabricant (2000) and Ragin (2002), with the most recent iteration detailed by Essick et al. (2010), although other researchers had used the device to good effect prior to its full description in 2010 (Löken et al. 2006, 2009; McGlone et al. 2007).

The RTS allows stimuli to be brushed onto, across, and then off the skin with control of brushing direction, speed, and force of indentation into the skin, and with continual readings of the forces and torques occurring during delivery (Fig. 8.8). Up to four stimuli can be studied in the same experiment, each mounting on one of four arms. Rotation of the arms is dealt with by a brushless DC motor, reduction drive, and position encoder located in the head of the device. Interposed between the shaft of the DC motor assembly and the hub, is a 6-axis force/torque transducer. The DC motor and transducer assembly is mounted on a linear stepper motor, which allows

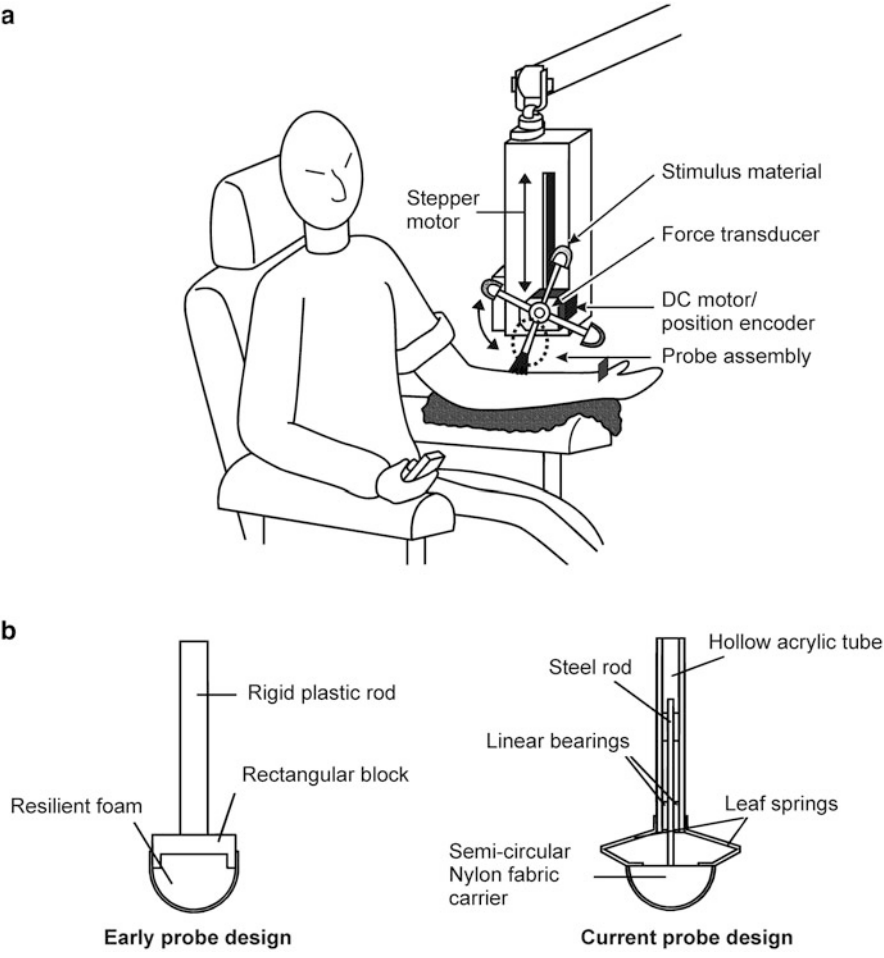


Fig. 8.8 The Rotary Tactile Stimulator (RTS), a device designed to provide highly controlled brushing stimuli to the skin (**a**). Different probe designs are shown in (**b**) and (**c**)

it to move perpendicularly to the skin surface. Both the DC and stepper motors are under computer control.

Any device that interacts with the skin requires calibration. The RTS is no different. The weight of all four probes and the hub contribute to the forces sensed by the transducer, and therefore each probe must be aligned perpendicular to the skin with the static forces and torques recorded and subtracted from all subsequent force and torque measurements. A second calibration stage is needed to enable each textured material to be delivered at a targeted normal force level. In this case, for any given probe and force combination the distance must be determined that the linear drive needs to move toward the skin from its home position to compress the probe and skin sufficiently to achieve the targeted force level. In actual use, the peak normal force level attained when the probe moves across the skin is typically twice the peak force level observed during vertical movement alone. This is primarily due to the different mechanical responses of the skin to tangential versus vertical displacement.

The design of the probes was critical to delivering as accurate and reproducible forces to the skin as possible. Ideally, the head of the probe that carries the stimulus should be compressible in the normal direction, with a reproducible force/distance curve, but should not move at all in the tangential or lateral directions. An early probe design consisted of a rigid plastic rod, at the end of which was a rectangular block, onto which was mounted a block of foamed plastic with a semicircular outer profile (Fig. 8.8b). Side-cheeks of thin plastic held the foam block in place and prevented lateral movement. The stimulus (fabric) sample was stretched over the semicircular outer edge of the foam block. It was recognized that this design suffered from the drawback that at higher forces the foam block was prone to distortion and lateral movement. Also, the repeatability of compression of the foam was unknown. In recognition of these shortcomings, an improved design was produced.

The most recent design is very similar to a motorcycle's front fork suspension: The probe assembly consists of a hollow acrylic tube inside of which are two miniature linear bearings (Fig. 8.8c). A steel rod travels freely in these bearings. At the end of the rod is fixed a rigid semicircular nylon fabric carrier. Two steel V-shaped leaf springs attach the ends of the fabric carrier to the sides of the acrylic tube. The springs provide resistance to compression and also hold the fabric carrier in the direction of rotation. This design is better than the older 'foam block' design in that the actual peak normal force recorded during a sweep for a given set of sweep parameters is quite consistent, and the leaf springs are not subject to losing their mechanical performance, at least for any biologically reasonable force delivery.

The main psychophysical study that has used the RTS was relatively complex, assessing pleasantness responses to multiple fabric materials, at multiple body sites, for both sexes (Essick et al. 2010). Experiments using the two probe designs were reported, although the two probes were used to deliver different combinations of normal force levels and stimulus materials, rendering direct assessment of probe performance difficult. The study primarily illustrated the complex nature of the pleasantness response. The simplest take home message was confirmation of the basic curvilinear nature of the pleasantness response with stimulus speed (viz. Fig. 8.7). A more complex finding was that increasing stimulus normal force

decreased pleasantness to a different extent among body sites, with the greatest effect observed on the face, the least on the calf. Although males and females responded in a broadly similar way, differences between the sexes were observed, too. For example, fast, high force stimuli were rated as more pleasant when moved over the male versus female body. The basis of this might have been mechanical, such as in frictional differences attributable to differences in body hair coverage under the moving stimulus, or in social–cognitive effects unrelated to the physical stimulus per se (Hertenstein et al. 2006a, b; Heslin et al. 1983; Koutantji et al. 1998; Lautenbacher and Rollman 1993).

The RTS is eminently suited to any psychophysics that requires highly controlled brushing stimuli. This suitability means that it has been an ideal tool for the study of CT afferent activity with microneurography, for both characterizing the CT-spike firing rates versus velocity tuning curve (Löken et al. 2009) and for delivering stimuli designed to maximize CT afferent activity, if that were desired. It is also possible to use the RTS in rather novel and informative ways, exemplified by Ackerley and colleagues (2012) who used the RTS to move fabric samples soaked to different extents in water to investigate how veridical wetness perception is, and how this type of perception varies over the body.

Recently, a linear tactile stimulator (LTS) has been derived, primarily for use within an MRI environment (Fig. 8.9). The device is in many ways a return to the brushing stimulator noted earlier, albeit with more sophisticated design and engineering. The small size of the LTS and its MRI-compatibility allow for experiments that would be impossible to conduct using the RTS.

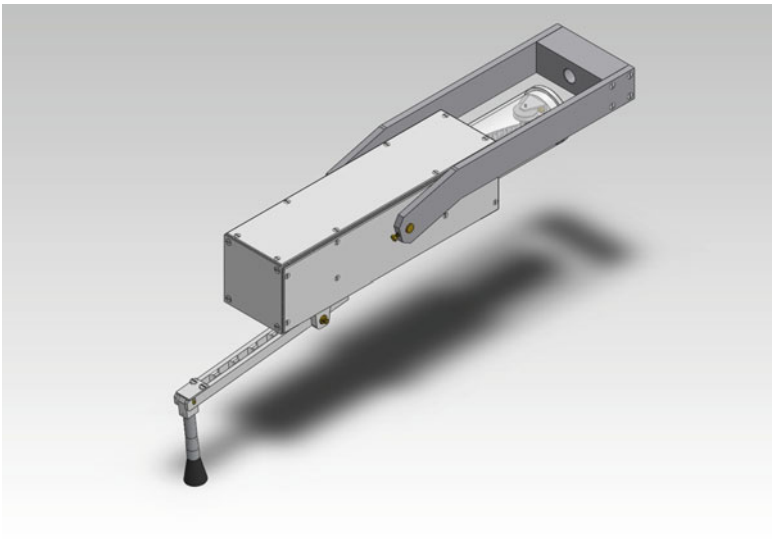


Fig. 8.9 The Linear Tactile Stimulator (LTS), engineered by Dancer Design (UK), of utility in MRI environments

Stimulus Characterization for Free Exploration

The RTS and similar devices take the approach of trying to provide a very precisely controlled, accurate stimulus to the skin. Such an approach forces very rigorous experimental setup, with any participants generally required to stay in a fixed position, often with the assistance of straps, foam pillows, and other restrictive devices. Devices such as the RTS are tailored to deliver stimuli which are passively received by an individual. The RTS is not equipped to address or characterize active manipulations of stimuli by a perceiver. However, passive receipt of a stimulus might not be the best way of assessing affect. Indeed, it is well known that affective attributes of touch are influenced by the nature of the touch well beyond its simple parametric nature; interpersonal touch cannot be truly replicated by simply replicating the speeds and forces that occur during the touch. For example, one tends to assess one's own skin (intrapersonal touch) as feeling less pleasant than the interpersonal touch of someone else's skin (Guest et al. 2009). The basis of this difference could be in the sensory receptors involved in the two types of touch (Von Békésy 1963) or in the social meaning that may be conveyed by interpersonal (but not intrapersonal) touch (Hertenstein et al. 2006a, b). Similarly, it is not possible to tickle oneself (Blakemore et al. 2000; Weiskrantz et al. 1971), probably because information regarding the tickling motions are available to the self during 'attempted self-tickle' but not when tickled 'conventionally,' that is, by someone else (Wolpert 1997). All of these observations show that passive receipt of stimulus is unlikely to provide a complete story of—in particular—emotional touch perception.

A different approach to the study of affective touch is to provide limited stimulus control, but to characterize the forces that occur at the skin site during stimulation. This approach allows the active explorations of a perceiver to be characterized and has the potential to allow more ecologically relevant touch to be investigated. For example, we know that CT afferent activity tends to be greatest for received touches that stroke the skin at circa 5 cm s^{-1} (Essick et al. 1999; Löken et al. 2009). However, we do not know whether individuals naturally choose to assess materials using this speed of touch. If someone is to assess the pleasantness of a piece of velvet, do they tend to gravitate toward stroking at 5 cm s^{-1}? Although this is the speed one would expect if the observer aimed to maximize CT afferent activity, there are no such afferents known in the finger. Therefore, there is no clear neural reason why the preferred touch speed should be the same for active touch by the finger and touch received by hairy body sites. Thus, as well as active touch being of interest and ecological importance in its own right, it also allows one to compare the responses of CT-innervated and CT-void body sites.

To this end, several devices have been reported that allow the frictional and other forces that occur during naturalistic touch of a surface to be recorded (Gee et al. 2005; Guest et al. 2012a; Skedung et al. 2010; Smith et al. 2002a). All in essence consist of a rigid plate which is coupled to sensitive force transducers. Figure 8.10 shows the 'force plate' used in our work, which is based on the type of force transducer used in the RTS. In use, each device is potentially very simple: as something

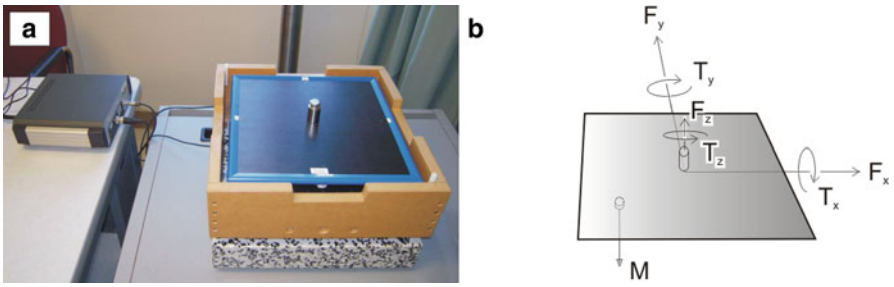


Fig. 8.10 A 'force plate' device, suited for collecting mechanical event data during active touch. Forces along, and torques around three axes are recorded, along with vibrotactile information (M)

on the force plate surface is touched, a continual reading of the forces and torques applied to the plate is obtained. So, an observer could be asked to freely assess something on the force plate, with the plate showing what actually happened at the fingertip during the assessment, in terms of finger movements and the forces and torques generated between the moving finger and the surface. The forces and torques can be used to derive further quantities of interest, such as the coefficient of dynamic friction at any point during the time course of the touch exploration. We have used the phrase 'Mechanical Events' (MEs) to refer to the various forces, torques, and derived quantities that might be considered.

Although these devices are not specifically for the study of affective touch, they are clearly well suited to the task. For example, the friction measurement system described by Gee et al. (2005) was proposed as a good way to "…provide information so that attractive, desirable products can be designed." One way this might happen is to allow consumers to assess a surface (textile or perhaps a skin analog coated with a cosmetic cream) and then attempt to link subjective ratings of the surface to the concurrent recordings of surface friction or other relevant measures.

In reality, entirely free exploration of a surface is problematic in that it could provide a relatively sparse data set if explorations were but fleeting. Indeed, no studies are available to date that consider entirely free assessment of surfaces while recording the mechanical events that occur. A partial exception to this are studies conducted by Smith and colleagues that looked at the strategies used during tactile search for a small asperity on the force plate surface (Smith et al. 2002b), and at the role of friction and forces at the fingertip in assessing roughness (Smith et al. 2002a). However, the former study did not investigate links between perception and mechanical events. The latter study investigated such links, and of all comparable studies, is probably the one that has allowed participants the most freedom in terms of their behavior. The restriction placed on participants was that each person could make a single, unidirectional traverse over a stimulus surface of fixed length; however, their chosen stroking speed and force were unconstrained.

A pragmatic compromise we have taken in our most recent experiments is for participants to continually explore a surface but use every ecologically relevant touch speed and force (Guest et al. 2012a; Hopkinson et al. 2008). In practice, this

involves providing continual feedback to the participant as they explore a surface, in terms of what speed and force they should use, and how well they are managing to achieve the target speeds and forces.

This approach has enabled some links to be found between the sensory perception of a surface and the nature of the stimulus at the fingertip, but has been less successful in linking affective judgments to the physical stimulus. For example, fluids that feel more viscous when explored on a skin-like surface tend to be those that have (perhaps unsurprisingly) greater friction (Guest et al. 2012a). However, we have found no such links between emotional attributes such as pleasantness or sensuality and the physical nature of the stimulus. This negative finding could be due to the lack of a strong emotional response for the active assessment of inanimate materials, as opposed to the active assessment of one's own or another's body (Guest et al. 2009, 2014). A second possibility is that the 'exhaustive exploration' paradigm is too far divorced from naturalistic touch to provide a strong emotional impetus. Yet, another possibility is that the analysis methods used for these complex datasets have not been optimized. It is also true that we have used the force plate only to assess lubricated surfaces and it may be that these surfaces are especially difficult to study. For example, different lubrication regimes allow any underlying surface texture to influence perception to differing extents, with regimes potentially changing within a single touch episode (see Guest et al. 2013 for a review). Finally, one should keep in mind that the lack of CT-innervation for the fingertip might underlie some of these weak emotional responses.

Conclusions

Methods and devices for the study of emotional touch have developed considerably since the inception of the field. These developments have included both what perceptual attributes should be studied, and how to best deliver stimuli to be rated in terms of their emotional content.

In terms of lexicons for touch, we have arrived at a tool—the TPT—that allows for principled and successful study of the sensory and emotional components of touch. Refinement of this tool is still desirable, if at all possible; empirically, for any given stimulus, typically few of the 40 attributes of the TPT are considered to be applicable. Unfortunately, it is not clear a priori as to what attributes will not apply to a given stimulus, especially any stimuli that are hitherto unexplored. As such it is unclear how streamlined the TPT might become. It is even possible that multiple TPT variants will exist, tailored for different gross classes of stimuli. Indeed, we have traveled this path to a limited extent by swapping in and out a limited set of attributes when studying the perception of lubricated surfaces (Guest et al. 2012a, b).

In terms of devices, one major challenge for the field is reconciling the technical and data complexity of studying naturalistic touch. It is clear that we can obtain 'good' psychophysical data from highly controlled, passively received stimuli—and for electrophysiological studies this will probably remain a necessary gold standard.

Otherwise, there is a need to be able to characterize what people actually do, and what mechanical stimulus consequently occurs, when making tactile judgments, especially those with an affective component. It is technically feasible to record mechanical event data from the naturalistic assessment of a subset of stimuli (e.g., anything that can be explored over a hard, planar surface). However, how to deal with the complex data that arise is a work in progress.

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Chapter 9
Processing of C-Tactile Information in the Spinal Cord

David Andrew and A.D. (Bud) Craig

Abstract Functional brain imaging places C-tactile (CT) fibres within an interoceptive network that is important for the sensation of pleasurable touch and emotional well-being, but the circuits that relay this information from periphery to forebrain are not well understood. In vivo single unit recordings from projection neurons in lamina I of the rat spinal cord showed that the activity of CT fibres is integrated with that of nociceptors before being relayed to the brainstem parabrachial nucleus. There is at least one interneuron in the pathway that relays CT activity from mechanoreceptor to lamina I output neuron, with preliminary data suggesting that such interneurons express the γ isoform of protein kinase C and receive inputs from vesicular glutamate transporter three-labelled primary afferents. A role for CT fibres in mechanical allodynia is also suggested, as pilot data shows that these fibres can provide low-threshold inputs to sensitized nociceptive-specific lamina I projection neurons. Thus, the homeostatic signal provided via CT fibres can be directly modulated by pain, placing the CT system firmly within an interoceptive network that regulates the body's internal environment.

Keywords Spinal cord • Lamina I • C-fibre • Mechanoreceptor • Spinoparabrachial

Introduction

The discovery of low-threshold mechanoreceptors with unmyelinated axons was inextricably linked with early studies of nociceptors (Perl and Kruger 1996). For example, Zotterman (1939) showed that discharges characteristic of unmyelinated fibres could be evoked by gentle mechanical stimulation of the skin in cats, as well as by thermal and strong mechanical stimuli. Subsequently, Douglas and Ritchie (1957)

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demonstrated that activity in low-threshold fibres was sufficient to reduce the amplitude of the early part of the C-fibre component of the compound action potential in peripheral nerves, with intense stimuli required to abolish the slower components of the C-wave. The single unit studies of unmyelinated fibres in cats by Iggo (1960) and by Bessou and Perl (1969) unequivocally established the existence of cutaneous mechanoreceptors with C-fibre axons. These unmyelinated mechanoreceptors were only found in hairy skin, their incidence differed in different species and they were more numerous proximally rather than distally (Iggo 1960; Bessou and Perl 1969; Iggo and Kornhuber 1977; Kumazawa and Perl 1977; Lynn and Carpenter 1982). Some years later, the presence of C-fibre mechanoreceptors in human skin was confirmed with microneurography (Nordin 1990; Vallbo et al. 1999). In the following text, we discuss how sensory information from C-tactile fibres is transmitted from skin to brain; specifically we consider the central terminations of C-tactile afferents, the identity of central neurons that transmit C-tactile information rostrally and how processing of C-tactile information can be modulated.

Spinal Terminations of C-Tactile Fibres and Transmission of C-Tactile Information to the Forebrain

C-fibre mechanoreceptors are virtually exclusively activated by gentle mechanical stimuli, although several reports have noted that they can be excited phasically by cooling stimuli (Bessou et al. 1971; Kumazawa and Perl 1977; Nordin 1990). Functionally, C-tactile fibres can be distinguished from A-fibre (myelinated) mechanoreceptors by their preferential response to slowly moving mechanical stimuli (Bessou et al. 1971), whereas A-fibre mechanoreceptors increase their discharge linearly as stimulus velocity increases (Greenspan 1992; Vallbo et al. 1999; Löken et al. 2009). This preferential sensitivity to slowly moving versus rapidly moving stimuli has been exploited in several types of studies that investigated peripheral and central pathways activated by brushing stimuli (e.g. Löken et al. 2009; Andrew 2010).

The anatomical distribution of the central terminals of C-fibres is technically difficult to study at the single cell level because the axons are very fine and virtually impossible to label with an intra-axonal microelectrode in the spinal cord. However, Sugiura and colleagues (Sugiura et al. 1986; Sugiura 1996) developed a technique where either horseradish peroxidase or the selective anterograde neuroanatomical tracer *Phaseolus vulgaris* leucoagglutinin was intracellularly injected into single guinea pig dorsal root ganglion neurons and recovery permitted to allow transport of the tracer into the central axonal terminals of the labelled cells. Prior to filling, each cell was characterized with natural and electrical stimuli thus enabling identification of receptor type and conduction velocity. The axons of C-tactile fibres were located in Lissauer's tract, with collateral branches given off into the spinal grey matter that terminated in lamina II. Typically the terminal arborization occupied a characteristic location in inner lamina II (Fig. 9.1), where spinal neurons with similar receptive properties have been identified in physiological studies (Light et al. 1979; 1999).

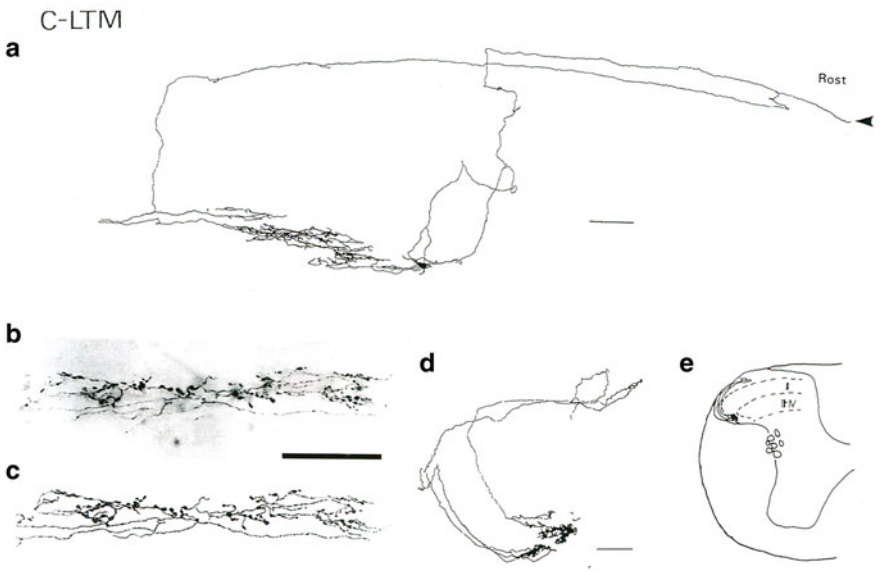

Fig. 9.1 Central projections of a C-low threshold mechanoreceptor in the C2 segment of the guinea pig spinal cord that had a receptive field on the ipsilateral pinna. (**a**) Sagittal view from 20 serial sections showing the fibre running through Lissauer's tract giving off collaterals that terminated in lateral lamina II. (**b**, **c**) Photomontage and reconstruction of the terminal arborization. (**d**) Rotated transverse view of the reconstructed fibre. (**e**) Transverse drawing of the fibre relative to the laminae of the spinal dorsal horn showing the terminal arborization in lamina II of the lateral dorsal horn. Bars = 100 μm. Reprinted from *Progress in Brain Research* vol 113, Sugiura Y Spinal organization of C-fiber afferents related with nociception or non-nociception, p. 328 © (1996), with permission from Elsevier

C-fibre mechanoreceptors are distinguished electrophysiologically from C-fibre nociceptors by their shorter duration action potentials (Fang et al. 2005), and they also lack the typical 'hump' on the descending phase of the action potential that C-fibre nociceptors exhibit. This suggests that C-tactile fibres express different types of ion channels than C-fibre nociceptors, and the type 2 hyperpolarization-activated cyclic nucleotide-gated channel (HCN2) may be one of the ion channels that accounts for the different action potential duration/profile in C-tactile fibres (Acosta et al. 2012).

The spinal neurons that are preferentially activated by slowly moving brush strokes (Light et al. 1979) have morphologies that correspond to two of the four anatomical classes of neurons identified in lamina II (Grudt and Perl 2002): central neurons with predominantly rostrocaudally directed dendrites of short length and vertical neurons with cone-shaped dendritic trees directed ventrally. Both of these cell types are thought to be excitatory on the basis of immunocytochemistry (Maxwell et al. 2007; Yasaka et al. 2010). However, virtually all the neurons in lamina II are interneurons, and how C-tactile activity was relayed to the forebrain was not well understood. A breakthrough occurred when two patients with large

fibre neuropathies were studied with functional brain imaging (Olausson et al. 2002, 2008). These patients lacked Aβ fibres, which subserve vibration and fine touch, but they performed equally well as normal controls in a two alternative forced choice psychophysical test of detection of a soft brush applied to the hairy skin of the forearm, but achieved no better than chance when the glabrous skin of the hand was tested. Interestingly, both patients used emotional cues for stimulus detection, as slow brushing evoked a pleasant sensation, rather than one of simple touch. Surprisingly, functional imaging showed activation of the contralateral dorsal posterior insula rather than the mechanoreceptive somatosensory cortices (Olausson et al. 2002). Posterior insular cortex activation has been described in many functional imaging studies that have used homeostatically relevant (i.e. interoceptive) stimuli such as pain, temperature, muscular effort, itch, etc. (reviewed by Craig 2002), including slow brushing (Olausson et al. 2002; Björnsdotter et al. 2009). Somatic input to the insula in primates is from a relay nucleus in posterolateral thalamus—the VMpo (posterior part of the ventromedial nucleus; Craig et al. 1994; Craig 2014). The inputs to VMpo are almost exclusively derived from lamina I neurons in the spinal and trigeminal dorsal horn (Craig and Zhang 2006). Projections from lamina I of the spinal cord are thought to be a series of modality-specific and anatomically distinct labelled lines that transmit homeostatically relevant sensory information rostrally (Craig 2002, 2003, 2015). Thus, it would be predicted that in primates C-tactile information is transmitted to the forebrain by lamina I spinothalamic neurons. In contrast, in sub-primates, including rodents, lamina I activity reaches the forebrain only after integration in the midbrain parabrachial nucleus (Cechetto and Saper 1990), and in the rat there are very few spinothalamic lamina I neurons in the lumbar cord compared to spinoparabrachial lamina I neurons (Almarestani et al. 2007; Al-Khater et al. 2008). Thus, in rats C-tactile activity ought to be relayed to the brainstem in the spinoparabrachial pathway.

This hypothesis was tested by recording from single spinal lamina I neurons that were antidromically activated from the contralateral parabrachial nucleus (Andrew 2009, 2010). Most neurons in the rat lamina I spinoparabrachial pathway are nociceptive, with several functionally and anatomically different sub-groups being recognized (Bester et al. 2000; Almarestani et al. 2007; Keller et al. 2007; Andrew 2009). Andrew (2009) identified a small group of cooling-sensitive neurons, which constituted about 4 % of the spinoparabrachial projection from lamina I of the rat lumbar cord. That differs from cat and monkey, in which about one-third of lamina I spinothalamic neurons are thermoreceptive (Dostrovsky and Craig 1996; Craig et al. 2001; Craig and Zhang 2006) and about 15 % of lamina I spinoparabrachial neurons are cooling-sensitive thermoreceptive neurons (Light et al. 1993). The sparseness of hindlimb thermoreceptive lamina I projection neurons in the rat lumbar cord may be due to the major role of the tail and scrotum in thermoregulation (but, see Almarestani et al. 2007).

Each lamina I spinoparabrachial neuron was tested with innocuous and noxious stimuli, and neurons receiving low-threshold mechanoreceptive inputs characterized quantitatively using graded velocity brushing stimuli. This approach was used to distinguish A-fibre mechanoreceptor inputs from C-fibre mechanoreceptor inputs, as

measurements of primary afferent conduction velocities can distinguish myelinated from unmyelinated fibres, but cannot confirm the identity of any particular class of inputs. The use of graded velocity brushing is justified as early physiological studies had emphasized that C-fibre mechanoreceptors were activated by slowly moving brushing stimuli (Bessou et al. 1971), and stimulus–response curves of velocity encoding have an inverted U-shape (Löken et al. 2009), with peak discharge occurring at velocities of 1–10 cm/s. In contrast, the relationship between discharge and velocity is linear for all classes of myelinated mechanoreceptors (Greenspan 1992; Löken et al. 2009), and this difference in velocity encoding was used to infer the conduction velocity classification of the mechanoreceptors that provided the low-threshold inputs to a cell. Out of 95 lamina I spinoparabrachial neurons 67 received inputs from heat and/or mechanical nociceptors and were classed as nociceptive specific (NS), 14 were activated by noxious heat, pinch and noxious cold and were classified as polymodal nociceptive (HPC), 4 were activated by innocuous cooling (COOL neurons) and 10 received inputs from low-threshold mechanoreceptors and nociceptors and were categorized as 'wide dynamic range' (WDR). Surprisingly, there were no cells identified that received inputs exclusively from low-threshold mechanoreceptors. The WDR neurons were characterized with graded brushing, thermal and noxious stimuli; as expected all of them received convergent inputs from heat/mechanical nociceptors as well as innocuous mechanoreceptors, but none were activated by cool/cold stimuli (Fig. 9.2a). Maximal responses to graded brushing stimuli (6.6–126 cm/s) occurred at slow brush velocities (mean 9.2 cm/s SD 5.0) and firing rates decayed exponentially as brush velocity increased (Fig. 9.2b, c).

Fatigue in the responses of individual cells to repeated brushing stimuli was also observed, which is a well-known property of C-fibre mechanoreceptors (Fig. 9.2b; Bessou et al. 1971; Nordin 1990; Vallbo et al. 1999).

By chance it was also possible to record from two other spinoparabrachial neurons, but these cells were located in lamina III of the dorsal horn rather than in lamina I. One of these cells received inputs from both low-threshold mechanoreceptors and nociceptors, and was therefore classified as a 'wide dynamic range' neuron. This cell was characterized with graded velocity brushing stimuli, and in contrast to lamina I neurons the velocity dependence of this cell was linear and monotonic as stimulus velocity increased, similar to the velocity dependence of myelinated mechanoreceptors (Greenspan 1992) which terminate in laminae III–V of dorsal horn (Li et al. 2011; Abraira and Ginty 2013) and are assumed to provide the low-threshold inputs to lamina III neurons.

The findings regarding velocity dependence of lamina I vs. lamina III spinoparabrachial neurons indicate that C-mechanoreceptor activity is relayed to the brainstem by lamina I spinoparabrachial neurons, but that this information is conveyed by an ascending channel that can also be activated by noxious stimuli. This suggests that the homeostatic response to C-tactile activation occurs when C-mechanoreceptor activity is integrated with activity transmitted by nociceptive ascending channels, that is the affective value transmitted by C-mechanoreceptive fibres can shift from positive when only lamina I WDR neurons are activated, to negative when both WDR and NS/HPC neurons are activated.

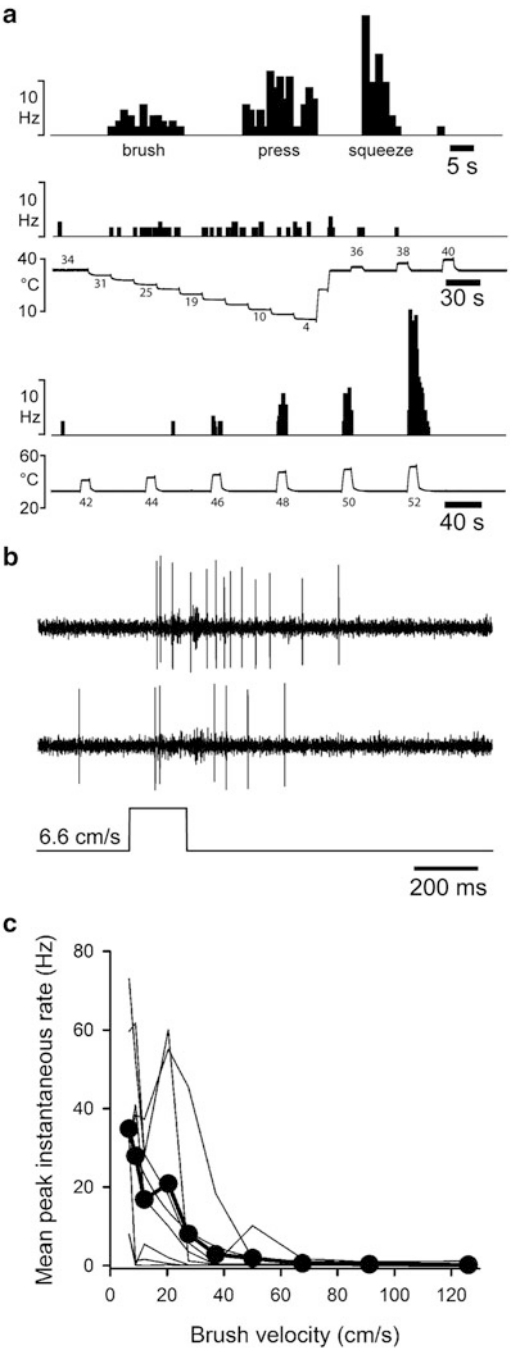

Fig. 9.2 Physiological properties of lamina I spinoparabrachial neurons that received inputs from low-threshold mechanoreceptors. (**a**) Characterization of a neuron with innocuous (brushing with a camel's hair paintbrush by hand ≈ 1 cm/s) and noxious mechanical stimuli, graded cool/cold stimuli and graded heat stimuli. The peri-stimulus time histograms (1 s bins) show that this cell responded to innocuous mechanical stimuli as well as noxious mechanical and heat stimuli applied to the skin, but not to cool/cold stimulation. (**b**) Responses to two trials of brushing (indicated by the *bottom trace*) at a brush velocity of 6.6 cm/s. The first and ninth responses to a series of ten repeated stimuli are shown; note the fatigue of the response. (**c**) Stimulus response curve of velocity encoding for individual neurons as well as the population mean (•, *thick line*), which was fitted by a first order exponential function that had the form $y = 48.7e^{-0.06x}$ ($r^2 = 0.93$). Reproduced from Andrew (2010) with permission from Wiley

Spinal Circuits That Process C-Tactile Impulses

Latency measurements in response to electrical skin stimulation showed that the C-fibre inputs to the circuit that relays low-threshold mechanoreceptor inputs to lamina I spinoparabrachial neurons are polysynaptic (Andrew 2010). As mentioned in the preceding text, lamina II neurons that were activated by slowly moving brush stimuli (Light et al. 1979) had morphologies similar to central or vertical neurons (Grudt and Perl 2002). Central and vertical neurons have axons that arborize in lamina I (Maxwell et al. 2007; Yasaka et al. 2010), where they can contact projection neurons, and there is evidence for modular circuits in the superficial dorsal horn that are functionally distinct (Lu and Perl 2005; Zheng et al. 2010; Lu et al. 2013). Studies on genetically modified mice (Seal et al. 2009) suggested that C-fibre mechanoreceptors express vesicular glutamate transporter 3 (VGLUT3) and that VGLUT3-labelled terminals show dense overlap with spinal interneurons that express the γ isoform of protein kinase C (PKCγ) in inner lamina II. Mice lacking PKCγ have reduced behavioural signs of neuropathic pain (Malmberg et al. 1997), and thus the PKCγ neurons may be important in integrating both C-tactile and nociceptor inputs in health and disease, and they may be one of the classes of interneurons within the C-mechanoreceptor-to-lamina-I-spinoparabrachial-neuron circuit (Lu et al. 2013). This possibility was investigated in pilot studies in Andrew's laboratory that were performed with Dr. David Hughes (University of Glasgow, UK), where hindlimb hairy skin was repeatedly stimulated with slowly moving (6 cm/s) brushing stimuli for 60 min in lightly anaesthetized rats. Sections of lumbar spinal cord were then processed immunocytochemically to identify the nuclei of neurons activated by the brushing stimulus as well as to label VGLUT3-positive axons and PKCγ-positive neurons. As can be seen from Fig. 9.3 there is preliminary evidence that C-fibre mechanoreceptors do indeed innervate and activate PKCγ-labelled neurons in inner lamina II, and this may represent the first synapse in C-tactile pathways.

Modulation of C-Tactile Processing

A role for C-fibre mechanoreceptors in persistent pain was suggested by Seal et al. (2009), as mice lacking VGLUT3 did not develop mechanical allodynia after capsaicin injection into the ankle or in the spared nerve injury model of neuropathic pain. Anecdotal reports also suggest that C-mechanoreceptor inputs to nociceptive lamina I spinothalamic neurons can be unmasked by repeated noxious stimulation in both cat (Craig and Kniffki 1985) and monkey (Dostrovsky and Craig 1996; Craig, unpub.). Although physiological studies indicate that all of the VGLUT3-expressing dorsal root ganglion neurons are C-fibre mechanoreceptors (Seal et al. 2009), these fibres are widely accepted as being absent from glabrous skin. Therefore, the development of mechanical allodynia in the glabrous skin of

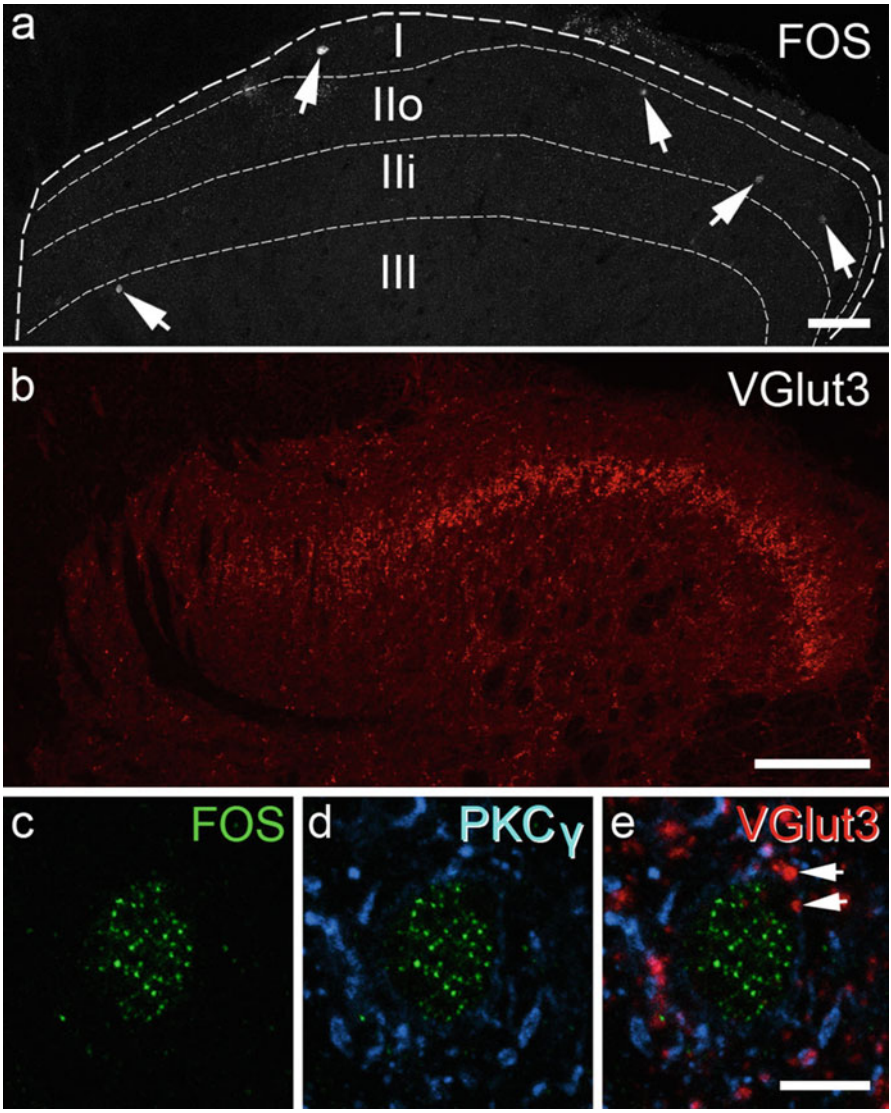

Fig. 9.3 Identification of putative central neurons that receive inputs from C-fibre low threshold mechanoreceptors. (**a**) Fos-expressing cells (*arrowheads*) in the L3 spinal segment after repeated slow brushing of the rat hindlimb. (**b**) VGLUT3-immunolabelled axons terminate principally in lamina III. (**c**–**e**) Example of a Fos-positive neuron (*green*) in inner lamina II that is labelled for PKCγ (*blue*) that receives putative synaptic inputs from VGLUT3-labelled afferents (*red*, *arrowheads*). Scale bars: $A = 50$ μm; $B = 100$ μm; $E = 5$ μm. Figure kindly provided by Dr. D.I. Hughes, University of Glasgow, UK

wild-type mice indicates that fibres other than C-fibre mechanoreceptors are important in allodynia. Indeed this is alluded to in the study of Seal et al. (2009) as VGLUT3 knockout mice showed reduced responsiveness to noxious mechanical stimuli compared to wild-type controls, suggesting that the VGLUT3-positive fibres include both nociceptors and C-fibre mechanoreceptors. Others studies in mice have provided evidence that the G-protein-coupled receptor MrgprB4 is a molecular marker of C-fibres that innervate multiple skin spots, are activated by slow brushing, produce positive affective conditioning, and terminate in outer lamina II (Liu et al. 2007; Vrontou et al. 2013). Evidence from a different study suggests that C-fibres that innervate hair follicles express tyrosine hydroxylase but not MrgprB4 and terminate in inner lamina II (Li et al. 2011). However, the pattern of tyrosine hydroxylase immunostaining in the spinal cord (Brumovsky et al. 2006) does not match the central terminations of intracellularly labelled guinea pig C-fibre mechanoreceptors (Sugiura et al. 1986), and labelling was also found in glabrous skin as well as hairy skin, suggesting that the tyrosine hydroxylase positive fibres are different from the C-fibre mechanoreceptors labelled by Sugiura (1996, 1986) and those identified in humans. Nonetheless, more than 80 % of tyrosine hydroxylase-labelled dorsal root ganglion neurons also express VGLUT3 mRNA (Li et al. 2011), suggesting that the VGLUT3 and tyrosine hydroxylase positive cells are largely overlapping populations of cells.

Regardless of the molecular identity of C-tactile fibres, if they are involved in the mechanical hypersensitivity (allodynia) that occurs in inflammatory and neuropathic pain then it would be predicted that spinal neurons that become sensitized to brushing stimuli should show the velocity dependence that is characteristic of slow-brush C-mechanoreceptors (Löken et al. 2009; Andrew 2010). It is interesting to note that only about 10–20 % of lamina I spinoparabrachial neurons normally receive inputs from low-threshold mechanoreceptors (Keller et al. 2007; Andrew 2009), but this proportion increased significantly to almost 60 % in a rat model of neuropathic pain (Keller et al. 2007). The prediction that C-fibre mechanoreceptors contribute to mechanical allodynia has been tested in preliminary in vivo experiments in Andrew's laboratory by recording from nociceptive-specific lamina I spinoparabrachial neurons before and after injection of dilute capsaicin close to their receptive fields. Cells with receptive fields only in hairy skin were studied and any novel brush-evoked responses that developed post-capsaicin were characterized with graded velocity brush strokes (Fig. 9.4).

As can be seen from the example in Fig. 9.4, a nociceptive-specific lamina I spinoparabrachial neuron developed a novel sensitivity to brushing post-capsaicin, and the stimulus–response curve was remarkably similar to that shown by naïve 'wide dynamic range' spinoparabrachial neurons. Thus, there is initial evidence from single neuron recordings that C-fibre mechanoreceptors contribute to mechanical allodynia. By comparison, lamina I spinoparabrachial neurons with receptive fields only in glabrous skin were sensitized to light touch after capsaicin, but they did not display the slow-brush sensitivity that neurons with hairy skin receptive fields did (Fig. 9.5).

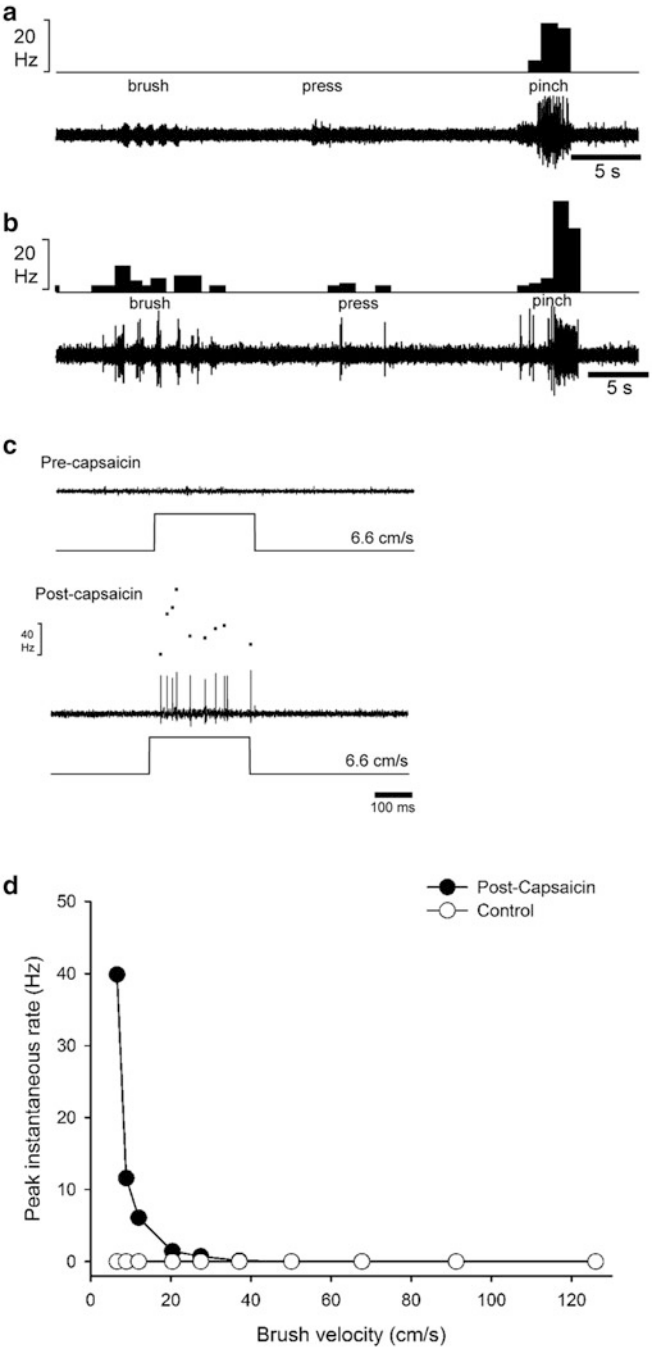

Fig. 9.4 Sensitization of a nociceptive-specific lamina I spinoparabrachial neuron unmasks novel low-threshold mechanoreceptors inputs from C-fibres. (**a**) Extracellular responses from a nociceptive-specific lamina I spinoparabrachial neuron to graded mechanical stimulation of its hairy skin receptive field shows that it only responded to pinch. (**b**) Responses of the same neuron to mechanical stimuli after injection of 5 μL of 0.1 % capsaicin adjacent to its receptive field. Note the new responses to brushing, as well as increased responses to pinch. (**c**) Responses to individual brushing stimuli at 6.6 cm/s before and after capsaicin, showing the novel brush-evoked discharge. (**d**) Stimulus–response curves before and after intradermal capsaicin show the velocity dependence of the brush-evoked responses are identical to those described for 'wide dynamic range' neurons in naïve rats

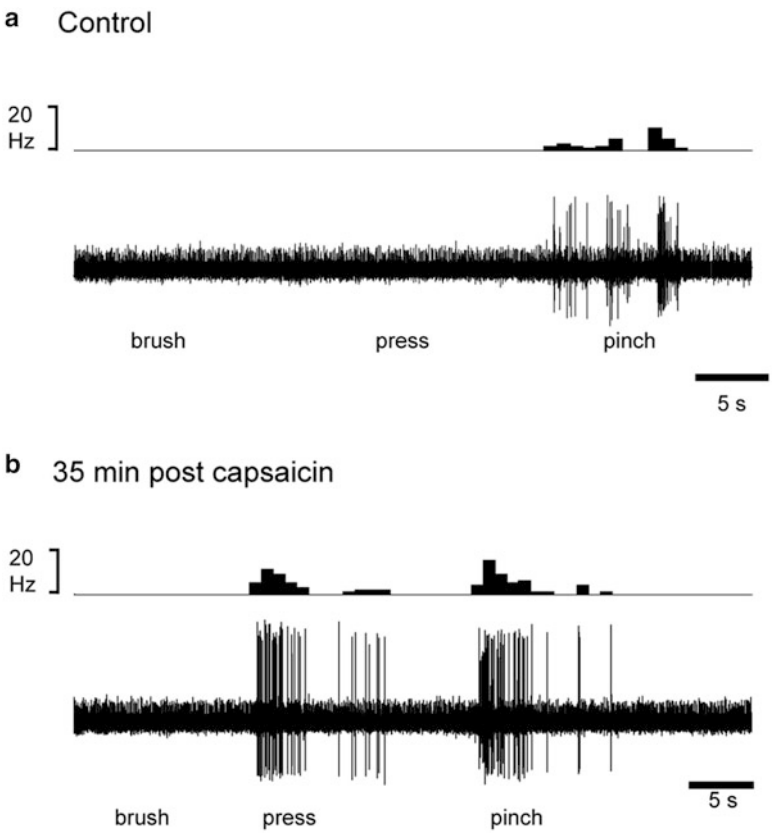

Fig. 9.5 Responses of a nociceptive-specific lamina I spinoparabrachial neuron with a glabrous skin receptive field before and after capsaicin injection. (**a**) Qualitative characterization using innocuous and noxious mechanical stimuli. The unit was responsive to pinching the glabrous skin of the tips of digits 4 and 5 of the hindpaw but was not excited by stimulation of the hairy skin of the paw. (**b**) Thirty-five minutes after injection of 5 μL of 0.1 % capsaicin into the pad of digit 4 the cell became responsive to gentle pressure applied to all of the glabrous skin of digits 4 and 5 as well as the skin of the medial half of the plantar foot, from the digits to the heel. Nonetheless it was not possible to excite the unit with innocuous brushing stimuli of the hindpaw skin. Note the after discharge to pinch following capsaicin

Functional Significance of C-Tactile Pathways

On the basis of the functional anatomy of the C-tactile system, it is thought that C-mechanoreceptors underpin the sensation of pleasurable touch and emotional well-being in humans (Löken et al. 2009; Björnsdotter et al. 2010); in animals these fibres would be important for maternal bonding with offspring. What is surprising from a physiological perspective is that all of the lamina I

spinoparabrachial projection neurons that receive C-fibre mechanoreceptor inputs in rats also receive inputs from nociceptors—they were all 'wide dynamic range' neurons and it was not possible to identify any neurons that only received C-tactile inputs. Other studies of lamina I trigeminothalamic and spinothalamic neurons in carnivores and primates have also failed to identify specific low-threshold projection neurons (Price et al. 1976; Ferrington et al. 1987; Craig et al. 2001; Dostrovsky and Craig 1996), despite the consensus that ascending projections from lamina I neurons constitute a series of modality-specific 'labelled lines' that relay interoceptive information rostrally (Craig 2003, 2015). Nonetheless, such 'C-tactile only' cells are found in lamina II (Light et al. 1979; Graham et al. 2004), but as all lamina II neurons are thought to be interneurons their activity must be integrated with that of nociceptors before being transmitted rostrally by lamina I projection neurons. Thus, the homeostatic inputs to the brainstem that are provided by C-tactile fibres seem to be inextricably bound with nociceptor inputs. To functionally de-couple C-tactile inputs from nociceptive inputs there must be a neuronal comparator that receives the output of both lamina I 'wide dynamic range' neurons as well as nociceptive-specific neurons. In rodents, this is presumably located within the brainstem, or perhaps within the posterior triangular nucleus of the thalamus (Gauriau and Bernard 2004). Interestingly, lamina I spinoparabrachial WDR neurons were also reported in earlier studies in cats, although slow-brush responses were not distinguished (Hylden et al. 1985; Light et al. 1993); and in studies in cats and monkeys in Craig's laboratory, WDR lamina I neurons were identified that were not spinothalamic neurons, some of which clearly responded to slow-brush stimulation (Craig et al. 2001; Dostrovsky and Craig 1996; see also Craig and Kniffki 1985; Craig, unpub.). These findings are consonant with anatomical evidence that (bilateral) spinobulbar and (contralateral) spinothalamic lamina I terminations originate from two distinct subpopulations of cells (cats: Andrew et al. 2003), while (predominantly contralateral) lamina I terminations in the parabrachial area seem to overlap with both subpopulations (cats: Panneton and Burton 1985; Hylden et al. 1989; rats: Li et al. 2006).

There is also data (Seal et al. 2009; Fig. 9.4) to support a role for C-fibre mechanoreceptors in mechanical allodynia, but the evidence is unclear as to whether these findings are applicable in humans. On the one hand, Nagi et al. (2011) showed that intramuscular infusion of hypertonic saline caused slow-brush-evoked pain from the overlying skin that persisted after compression block of conduction in A-fibres. Conversely, a recent study by Liljencrantz et al. (2013) showed that a patient with a large fibre neuropathy (and hence lacking large myelinated fibres) failed to develop tactile allodynia after treatment of the hairy skin with noxious heat/topical capsaicin. In the study of Liljencrantz et al. it was shown that when allodynia was present in normal controls there was decreased activation of medial prefrontal cortex by slowly moving brushing stimuli, implying that during brush-evoked allodynia the affective quality of C-tactile fibres had changed. This would be consistent with our suggestion that the homeostatic/emotional response to C-tactile activity is a product of the integration of C-mechanoreceptors and nociceptors.

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Chapter 10
Insights from A-Beta or C-Fibre Denervated Subjects

Jonathan Cole, India Morrison, Irene Perini, and Håkan Olausson

Abstract CT afferents have been known for years, since 1939 when Zotterman suggested they might contribute to itch. But their study has been hampered because any low threshold tactile stimulus will also activate large numbers of Aβ afferents. To investigate the psychophysics of CT afferents has recently become possible through microneurography, allowing selective recording from groups of these nerves, (Löken et al., Nat Neurosci 12(5):547–548, 2009 and this volume), and through the study of two rare cohorts of people who have lost either large fibre afferents due to disease or have selective loss of C afferents themselves due to hereditary neuropathy. This chapter details this latter work, and though comparisons between those with neurological conditions and control subjects must always be done with caution, such work can allow some insights into the normal functioning of the CT system.

Slow stroking on the hairy skin of deafferented subjects is poorly localised, but described, during forced choice experiments, as pleasant, and leads to activations in insula cortex but not sensory cortex. Since Ct activation is perceived poorly, if at all in deafferented subjects this suggests that a role for CT afferents may be to—in some way—set, or prime, information through Aβ pathways with affective valence.

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Introduction

CT afferents have been known for years, since 1939 when Zotterman suggested they might contribute to itch sensation, (Zotterman, 1939). But their study has been hampered by the fact that any low threshold tactile stimulus would also activate large numbers of Aβ afferents. Investigating the psychophysics of CT afferents has recently become possible through microneurography, which allows selective recording from them during carefully controlled cutaneous activation (Löken et al. 2009, and this volume) and through another line of work which has involved the study of two rare groups of people who have lost either large fibre afferents due to disease or have selective loss of C afferents themselves due to hereditary neuropathy. This chapter details this latter work, and though comparisons between those with neurological conditions and control subjects must always be done with caution we hope that such work can allow some insight into the normal functioning of the CT system.

Severe large fibre sensory peripheral nerve loss had been known following the use of some drugs (e.g. cisplatin and overdose of pyridoxine) for many years, but it was in 1979/1980 that Herb Schaumburg and colleagues first described an apparently new condition, the acute sensory neuronopathy syndrome:

> 'Four to twelve days following antibiotic treatment for a febrile illness, three adults suddenly experienced numbness and pain over the face and entire body. Signs appeared rapidly and included profound sensory ataxia, areflexia, and widespread sensory loss, primarily of large fibre modalities (proprioceptive sensibility). Slowed or absent sensory conduction was found. There was no weakness, and electrical study of muscle and motor nerve conduction was normal in all. Presently, all have a severe, static, residual sensory deficit. During follow-up of 5 years, no evidence of neoplastic disease or immunological disorder has appeared. Because of the rapid onset, widespread and pure sensory involvement, and poor recovery, the lesion is most likely confined to the dorsal root and Gasserian ganglia (sensory neuronopathy). We designate this previously unrecognised disorder the acute sensory neuronopathy syndrome and suggest that it represents a distinct, readily identifiable clinical entity'. (Sterman et al. 1980)

Since then a number of these subjects have emerged. One, 'Christina', was described by Oliver Sacks as 'The Disembodied Lady' (Sacks 1984). The two main subjects investigated by neuroscientists, IW and GL, emerged in the late 1970s and early 1980s, (for details on GL see Forget and Lamarre, 1987 and for IW see Cole and Sedgwick, 1992). But most of the papers have focussed on their capacities for movement without proprioception or movement and position sense. Detailed sensory testing of these subjects appeared to have to wait. Sterman et al. described loss of sensation over the whole body, but the two main subjects who have been studied in the literature, GL and IW, have preserved large fibre sensory function over the face and head allowing comparison of their sensory perceptions in deafferented and normally innervated skin.

Subjects with reduced C fibres, associated with a rare hereditary neuropathy (hereditary sensory and autonomic neuropathy type V) have been studied by Morrison et al. (2011). Cognisant of CT fibre function they studied the psychophysical and

functional imaging responses of ten subjects with the condition to a range of tactile stimuli designed to activate receptors linked to CT and Aβ afferents, as well as their responses to seeing tactile stimuli applied to others.

'Dual Tactile Innervation of Human Hairy Skin'

Subject IW (AN in earlier work) was found to have perception of a von Frey probe of a surprisingly low force, 40 mN, which was perceived as sharp (Treede and Cole 1993). It was presumed that this perception, which classically was thought to activate light touch receptors conveyed through Aβ fibres, reflected the sharp edges of the wire activating remaining Aδ or C fibres, though the low force required was unexpected. Since subject IW had neither perception of light touch, nor of a slowly increasing but large force applied to the hand, it was presumed that the von Frey monofilament result showed that a pre-pain sensation was being elicited. Further investigation awaited the 2002 study from Montreal (Olausson et al. 2002).

This study not only revealed something of what CT afferents might do, but also as the authors wrote, these experiments could only be done in subjects like those with acute sensory neuronopathy syndrome since in control subjects any low threshold cutaneous stimulus would activate Aβ afferents and drown out CT inputs.

In Olausson et al.'s study of subject GL, they found normal thresholds for perception of warmth and cold over all skin areas, but a reduced perception of cool stimuli over hairy skin suggesting some of the small fibres had been affected. She could not detect a vibration stimulus (selective for light touch Aβ inputs) on the forearm back of hand or palm but—when challenged in a two alternative force choice paradigm—could detect a soft brush stroked across the skin on the hairy skin sites (but not the palm which is thought devoid of CT afferents). When she concentrated, she said that she could feel a 'faint and diffuse touch sensation described as a 'pressure". The percept had no sensation of pain, temperature, itch, or tickle. Despite not knowing the nature of the stimulus, which she described it as being weaker in touch than controls, she clearly said it was pleasant and indeed as being as pleasant as controls' percepts when quantified. She could not however detect the direction of movement of the brush across the skin, whereas controls could.

They went on to study the areas of the brain activated during light stroking using functional magnetic resonance imaging. They found no activation in S1 or S2 cortex, unlike controls, but clear activation in two areas of contralateral insula cortex and one area of ipsilateral insular cortex.

They concluded that the human hairy skin has two systems for touch: the fast Aβ light touch one and a second for slow stroking touch involving CT afferents and which projects not to sensory cortex but to the insula and which is involved in 'emotional, hormonal and affiliative responses to caress like skin to skin contact between individuals'.

Subsequently IW has been studied with essentially similar results (Olausson et al. 2008). In addition, however, it was also seen that caressing on the arm in IW was followed by significant deactivations in the area of the arm representation of S1 cortex contralateral to the stimulation. Following this, data from the same experiment in

GL was reanalysed and also showed widespread deactivation in contralateral S1 (arm representation), bilateral S2, ipsilateral posterior insular cortex, bilateral anterior cingulate cortex, motor cortices, parietal association cortex, prefrontal cortices, and thalamus.

The fMRI activations and deactivations were weaker in IW, which reflect the smaller database from IW; GL underwent six runs with brushing (120 stimulation blocks in total), whereas IW had three runs with caressing (60 stimulation blocks in total). In addition, other experiments with IW have suggested he may be partly C-fibre denervated.

That deactivation in somatosensory cortices (contralateral S1 in IW, contralateral S1, and bilateral S2 in GL) offers further support for the suggestion that CT afferents are not involved in discriminative touch. It is known that there is continuous and fluctuating activity in somatosensory cortices during rest, evident as a time-variant BOLD signal; CT activation may inhibit this spontaneous activity. Since these CT stimuli were only just perceived, this is unlikely to be due to a form of selective attention by the subjects and might be a form of afferent or corticocortical inhibition. In control subjects, CT afferents are activated in parallel with Aβ afferents with strong excitatory projections to somatosensory cortices. It may be speculated, therefore, that CT afferents modulate information processing in somatosensory cortices in control subjects.

Reduced C Fibres and Pleasant Touch

The absence of Aβ fibres allowed crucial insights into CT projection and percept associated with them, but can only be part of the jigsaw of how we perceive pleasant or hedonic touch. Löken et al. employed microneurography to record from CT afferents in control subjects. Using different rates of stroking across the skin, they found that the perception of pleasantness of a stroke was greater for slow strokes (3 cm/s compared with 30 cm/s) and that this paralleled the discharge of CT afferents, which was greater for slower strokes and reduced for faster ones, than for Aβ afferents, which responded with increasing discharge with increasing stroke velocity (Löken et al. 2009).

Given these results it was logical to search for subjects with selective deficits in CT afferents to see whether their perception of slow stroking was different, and reduced, compared with controls. Morrison et al. (2011) studied a group of consanguineous subjects from northern Sweden with a condition called hereditary sensory and autonomic neuropathy (HSAN type V) who all have a mutation in the beta subunit of the nerve growth factor (NGF) gene. Severely affected mutation carriers have reduced pain perception, especially deep pain, resultant joint deformities, and bone fractures, (with the joint deformities and bone fractures only seen in the most severe, homozygous subjects). Their perception of light touch was normal, as were neurophysiological tests of large fibre function (nerve conduction studies). Sural nerve biopsy showed normal Aβ afferents but a severe reduction in C fibres. They offered the opportunity to study Aβ fibre function in the presence of reduced CT afferent activity.

In the subjects, brush strokes were clearly perceived—they have normal light touch—but they rated a slow brush stroke significantly less pleasant than controls.

In addition, and differently from controls, their ratings across velocities did not match the discharge pattern of CT fibres. Morrison et al. also imaged five such subjects and found a lack of insular cortex activation for the slow brush stroke compared with controls. Interestingly when the subjects viewed video recordings of stroking of other subjects via a screen they rated that similarly less pleasant than did controls. Their 'empathy for touch' ratings were lower, but then so were their 'self' ratings under similar conditions. When this was taken into account, the subjects' 'other' and 'self' ratings closely matched, as was the case for controls. Despite their atypical evaluation patterns, these subjects appeared to 'empathise' with the touch similarly to others.

Von Frey Monofilaments

A comparison was made of monofilament perception and other small fibre function between GL and IW and controls, since the two subjects appeared to have slightly different responses to tests of CT afferents. Von Frey testing was performed by forced choice and a threshold for perception taken when four out of five monofilaments of a certain force were felt.

It was seen that whereas controls have no difference in threshold for monofilament perception between glabrous and hairy skin, both GL and IW have a low but still slightly elevated threshold over hairy skin, presumed to be mediated through CT afferents, but a grossly elevated one over the palm, glabrous skin without CT fibres. In such skin, in the absence of Aβ and CT afferents, it is presumed perception becomes possible only when high threshold C-medicated pain receptors are activated (Cole et al. 2006) (Table 10.1).

Table 10.1 Psychophysical test results

Subject/test	GL	IW	Controls (mean +/- SD)
Monofilament thresholds (mN)			
Forearm	**23**	**46**	7.6 +/- 3.4
Palm	**200**	**200**	6.0 +/- 0
Cool thresholds (temp.–baseline, °C)			
Forearm +/-	4.0 +/-	4.1 +/-	2.1 +/- 1.3
Palm +/-	2.9 +/-	**5.1** +/-	1.8 +/- 0.8
Warmth thresholds (temp.–baseline, °C)			
Forearm	2.2	**3.8**	2.3 +/- 0.7
Palm	**3.9**	2.5	1.6 +/- 0.6
Cold pain thresholds (°C)			
Forearm	**16.4**	**<0**	6.0 +/- 1.8
Palm	10.3	<0	7.5 +/- 1.8
Hot pain thresholds (°C)			
Forearm	40.8	50.0	45.2 +/- 3.1
Palm	45.2	50.0	45.6 +/- 3.1

Figures in bold are outside normal ranges (mean +/- 2 SD)

The slightly elevated thresholds for perception in GL and IW in hairy skin are above those known to activate single CT afferents. This suggests that more than single afferents are required to reach perception (or that there is some clinically inapparent CT fibre dysfunction as well, which seems unlikely given the robust activations in insula cortex).

Localisation from CT Afferents and Sympathetic Responses

One of the roles suggested for CT afferents is in autonomic function and affective or emotional aspects of touch rather than in the discriminatory aspects of localisation and perception of touch quality (see Morrison this volume). It was of interest, however, to determine the limits of spatial localisation possible with the CT system alone.

GL and IW, together with controls, were stroked on a limb and asked to say whether or not they had been touched using a forced choice paradigm and to localise any brush stroke to the right or left arm or leg. Controls could correctly localise the brush on 100 % of trials but for GL it was reduced to 72 % and for IW to 53 %, both reduced but above chance of 25 %. GL localised all strokes she perceived but IW managed to dissociate localisation and perception of the brush stroke, localising six strokes correctly, but mislocalising one. When he could not discriminate, a feeling of being touched but made to guess where the brush stroke was he localised 11 correctly and 14 incorrectly. This is further evidence that the CT systems are functioning differently in GL and IW, suggesting that IW's CTs might have been affected by the neuropathy as well. But it also shows that IW can make what—for him—appears to be an ill-informed guess about a localisation of a brush stroke which he is not even sure he feels, and reach a level of success above chance.

In the same study, we also looked at the sympathetic skin responses after brush stroking. Since CT afferents are thought to be involved in social touch between conspecifics, the expectation was that CT-mediated input following a gentle brush stroke would also activate sympathetic responses. This was confirmed, though again there were differences between GL and IW. GL's responses appeared each time and with a latency, 1.1 s, only just above normal. In contrast, IW's had a later latency, 2.9 s and were inconsistent, occurring only 50 % of the time. These differences may be explained in part by GL and IW's comparative heights, with GL being shorter, and by our suspicion that IW's CT system may not be working entirely correctly and therefore may need greater temporal summation for a response to be elicited.

Since CT afferents do not seem to have excitatory projections to S1 or S2 cortex, but to the insula cortex, and because GL at least can localise brush strokes to a given limb, there might be a somatotopically organisation of pleasant touch in the insula. This was confirmed by a study with GL (Björnsdotter et al. 2009). They gave her a brush stroke to either the right arm or leg, which she correctly localised 31 times out of 32. There was also a somatotopic activation in contralateral insular cortex with the activations following arm stroking being anterior to those of the thigh. The authors suggested that this somatotopy followed that of pain and temperature in the insula and was further evidence of these being part of a system related to the autonomic body and affective self.

Hedonic and Nociceptive Processing: CT Interactions Within the Brain

The work done with GL and IW has all been related to a model in which CT afferents are involved in affective or affiliative touch. But what of the other C fibre inputs related to pain?

An early experiment by Treede and Cole used allodynia as a paradigm (Treede and Cole 1993). They showed that hyperalgesia to light touch (allodynia) does not develop after the production of a secondary allodynic area in IW after acute intradermal injection of capsaicin, but that hyperalgesia to punctuate stimuli, 200 mN in force, was present. It was concluded that the mechanisms for punctuate hyperalgesia and light touch allodynia were different. Presumably punctuate hyperalgesia is mediated through nociceptive afferents (C fibres) and it is pertinent that the von Frey monofilament used was one which IW and GL could perceive even without introduction of allodynia.

More recently allodynia was induced in control subjects, by a combination of heat and capsaicin, and the same procedure was done in GL and IW. In this condition, in controls, light touch and stroking are no longer felt as pleasant but rather as unpleasant and painful. The classical explanation for this is that after neuronal injury spinal cord sensitisation [in some way] enables Aβ afferents to access pain pathways.

Liljencrantz et al. (2013) used the heat/capsaicin model to produce tactile allodynia in 43 controls and also tested GL and IW with the same paradigm. Each subject was assigned two areas of forearm skin, one which was subjected to the capsaicin cream and to heat and the other, acting as a control, which was left alone. Then around the allodynic area and the control one light stroking was performed. The control subjects all reported tactile-evoked pain. In contrast, stroking in the allodynic zone was neither unpleasant nor painful for GL and IW. Instead, they reported that their C-touch percept (faint sensation of pleasant touch) was significantly weaker in the allodynic zone compared to untreated skin. These subjective reports were quantified in 2-afc testing; GL perceived stroking as being weakest in the allodynic zone for 10/10 stimulations ($p < 0.001$, binomial distribution), and IW perceived stroking as being weakest in the allodynic zone for 15/16 stimulations ($p < 0.001$, binomial distribution). Whereas their ability to perceive this light touch stimuli had been poor and uncertain in previous experiments, now they appeared to have no such problem in comparing stroking on their allodynic area and the control one. The former was clearly weaker to them.

Functional magnetic resonance imaging under these conditions was done in 18 controls and in GL (IW has agreed that it is explained that his claustrophobia prevented him entering a scanner). Stroking in the allodynic and control zones evoked different responses in the primary cortical receiving area for thin fibre signalling, the posterior insular cortex. In addition, reduced activation in the medial prefrontal cortices, key areas for C-tactile hedonic processing, was identified. These findings suggest that dynamic tactile allodynia is associated not only with nociceptive activations, but also with reduced C-tactile mediated hedonic touch processing. Nevertheless, because the patients did not develop allodynic pain, this pain seems dependent on Aβ signalling, at least under these experimental conditions.

Remember also that pleasant C-tactile afferent activation led to reductions in BOLD signal in S1 as well, so that this system has complex cortical interactions during both positive and negatively valenced cutaneous activation.

Plasticity

One concern in studying GL and IW has been that after 30 years without Aβ afferents below the neck that there may will have been extensive plasticity centrally in their brain, casting doubt on the utility of comparison with controls. Two recent imaging studies with GL have looked at this by analysing the topographical representation of stroking touch in the insular cortex (Björnsdotter et al. 2009) and by employing structural magnetic resonance imaging and resting-state functional magnetic resonance imaging scans (Čeko et al. 2013).

In the first study, soft brush stimuli to the right forearm and thigh of GL and six healthy controls were performed during functional magnetic resonance imaging (fMRI) to look for body-map topography in relation to gentle touch. A somatotopic organisation in the left (contralateral) posterior insular cortex was consistently demonstrated in all subjects, including GL, with forearm projecting anterior to thigh stimulation. Once more, despite denying any sense of touch in daily life, GL correctly localised 97 % of the stimuli to the forearm or thigh in a forced-choice paradigm. The authors suggest that the consistency and similarity in activation patterns across GL and the control subjects suggests that the identified organisation reflects the central topographic projection of CT fibres. They also point out that the similarities in insular activation for gentle touch with that described for noxious and cooling stimuli adds support for the hypothesis of a sensory-affective role of the CT system in the maintenance of physical well-being as part of a thin-afferent homeostatic network. But it is also possible to suggest that the similarities in insular projection of CT afferents between GL and controls argue against large-scale plastic change. Since the insula region received afferents in relation to hunger, thirst, air hunger, sexual function as well as affective touch, and these are small fibres functions and since GL's small fibres appear intact, one might not expect much plastic change in any case.

But elsewhere in the brain changes have been shown. In the structural scan by Čeko et al., there was widespread cortical thinning in GL compared with 12 age-matched female controls, in large parts of frontal, temporal, and parietal cortices. Primary somatosensory cortex (S1) was significantly thinner on the left, with a similar trend on the right side. In contrast, GL's insular and cingulate cortices were significantly thicker than controls, with the largest difference observed in the right anterior insula (aINS). Seed-based resting-state analysis revealed that her right anterior insula had increased connectivity to bilateral posterior insula. A separate independent component analysis revealed increased connectivity between the insula and visual cortex in GL. Since the insula is an important processing area for temperature and C-fibre tactile information, the increased intra-insular and insular-visual functional connectivity could be related to the patient's increased use of C-fibre temperature in monitoring her body and its movement, as well as her increased use of vision.

The largest region of thicker cortex was in the right aINS, an area particularly important for perception of cool and warmth, and interoceptive awareness (Craig et al. 2000; Craig 2002; Critchley et al. 2004; Olausson et al. 2005). GL reports that she uses temperature in daily living as a substitute for her lost sense of touch. She wears short sleeves at all times and uses the coolness of room-temperature objects compared with skin temperature to know when her arms or hands are touching something, without having to constantly look. An enhanced use of visual information is unsurprising since these subjects use vision of their bodies as partial replacement for lost proprioception. Examination of the insula network revealed an increased functional connectivity between the insula and visual cortex in the deafferented subject. Other functional neuroimaging studies have shown that the insula is activated during tasks involving cross-modal integration of tactile and visual information (Hadjikhani and Roland 1998; Banati et al. 2000). Along with her increased use of thermal information, GL reports using vision as much as possible to know the position of her limbs, including keeping her environment lit day and night. Such compensatory behaviour could strengthen the visual-insular integration.

Thus far, these results might be said to reveal consequences of GL's top-down training and attention to movement and cutaneous sensation in new ways. But there is one way in which she may have developed a genuine plastic change. She, uniquely, appears able to attend to and perceive pure C-tactile stimulation (Olausson et al. 2002), and this could be related to the increased thickness and functional connectivity of the insula. Control subjects cannot perceive pure C-tactile stimulation, losing all sensation of touch when their myelinated afferents are blocked, at least acutely (Mackenzie et al. 1975).

Conclusions

Work on these two groups of subjects without Aβ and with reduced CT function has shown that there is a CT afferent pathway underpinning the perception of pleasant touch, that this system projects to insular rather than sensory cortex and that there are complex interactions between CT and Aβ sensory systems in the elaboration of pleasant or hedonic touch. With reduced CT function touch appears to be felt as less pleasant, even though pure CT inputs are scarcely perceived in isolation. Indeed, one of the most curious aspects of this CT work in subjects GL and IW is that in activities of daily living, though they have maximised their remaining sensory percept, using heat, pain, 'pre-pain', and vision, they were not aware of any sense of remaining light touch before these experiments stimulating CT afferents and using alternative forced choice conditions. Despite this the system seems very robust. For instance, IW has not done many functional imaging experiments because he is severely claustrophobic and he also lives, almost permanently, with a bad back. Being in a scanner was not a comfortable experience for him. Despite these distractions, his results were similar to those for GL in showing activation in the contralateral insular cortex but not in S1 or S2. This result not only reinforced the results from GL but also showed how secure they were. Despite IW having little or no reliable perception of having been touched, and with his concerns about his back and his claustrophobia, his insula cortex was activated.

The results suggest that though CT afferents are not usually perceived when stimulated in isolation, they do appear necessary for hedonic touch processing. In contrast, Aβ afferents are also necessary for pleasant touch but are not sufficient. How these two systems interact is not yet clear. CT afferents activate insular cortex, and deactivate sensory cortex, Aβ afferents activate sensory cortices but not the insular. Just as there is crosstalk at a spinal cord level between Aβ and C afferents underpinning allodynia, so there must be complex interaction between the central connections of these two afferent types during hedonic touch and presumably also during nociception. Though, as yet uniquely, GL seems to have developed perception of CT afferents, in others we may have to consider that some cutaneous small afferents have sensory functions despite being not perceived directly. This parallels skin stretch receptors (Ruffini organs), in which stimulation of their Aβ afferents produces little sensation.

Despite stimulation of CT afferents being so poorly perceived, when forced to make a perceptual judgement, those judgements were above chance, to the surprise of both GL and IW. But there was one situation when this uncertainty all but disappeared. When asked in the allodynic experiment which stroke was stronger, the control one or that in the allodynic zone for controls, they responded easily and were near perfect in responding that the allodynic zone was less intense. For IW particularly, this meant that a stimulus on the skin of stroking which on its own was perceived very poorly, became more easily perceived when compared with an area felt as even more faint. The mechanism for this is unclear. The judgement may have been easier by the allodynic site being down-regulated since the experiments provided evidence for reduction in hedonic processing with allodynia associated with the nociceptive input.

Aβ afferents respond to all rates of skin stroking, but less to slower ones. Maybe with CT input associated with the slower stroke conditions, the larger light touch system interprets this touch as being pleasant, in a way as yet not known. Other top-down factors will also be important however; stroking by a loved one is pleasant whereas a similar stroke by a stranger or inappropriately familiar other may be distinctly unpleasant and unsettling.

CT afferents may also be less important to any pleasant feeling associated with faster strokes across the skin. Slow light touch is also still felt as pleasant on the glabrous skin of the palm and soles, areas in which CT afferents are absent (though some people find light touch to the feet ticklish and is unpleasant). It is not known why CT fibres are not found on these areas, but it may be relevant that CTs are stimulated by passive touch, whereas the feet and palm are usually used for active, exploratory touch. But the mechanism of affective touch from the palm may be different in afferent pathway to those from hairy skin. One should also keep an evolutionary perspective; CT afferents may be even more important in mammals and non-human primates in whom interpersonal grooming is hugely important for social group reinforcement and for development (Morrison, this volume). In this situation, grooming will be felt passively by the individual being groomed.

It is interesting that neither GL nor IW have ever experienced phantom limb or body sensations. Either the presence of continuing vision and movement of their limbs, or the intact small fibre functions have prevented this.

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Chapter 11
Brain Processing of CT-Targeted Stimulation

Malin Björnsdotter

Abstract CT afferents, together with other types of unmyelinated and thinly myelinated afferents, likely project via the spinothalamic tract to a specific posterior/basal ventral medial nucleus of the thalamus in primates. Functional imaging studies in patients with selective denervation of unmyelinated or myelinated afferents and in healthy subjects suggest that CT-targeted stimulation activates the insular cortex in the hemisphere contralateral to stimulation. This area shows a somatotopical response to CT stimulation, supporting the idea that it is a primary cortical target for CT afferent projections. This chapter reviews findings related to the insular cortex.

Keywords fMRI • MRI • Brain • Insular cortex

The poetic name of the insular cortex (*insula* means island in Latin) stems from its isolated position deep within the Sylvian fissure of the brain, snugly tucked in under the lid formed by the operculum (Fig. 11.1).

As a whole, the insular cortex is associated with an astonishing array of functions, ranging from basic processing of sensory and visceral information (Augustine 1985) to complex processing of emotion and self-awareness (Craig 2009, 2011). The insula is a cytoarchitectural heterogeneous area, however, and it can be divided into distinct regions within the ventrodorsal plane: the granular region in the posterior part to a granular area in the anterior part. The posterior, granular insula (Ig) is the putative primary target for the system of thin afferent fibers—including CT fibers—which project information related to the physiological condition of the body (Craig 2002). This region can be further divided into three distinct cytoarchitectural regions: one dysgranular (Id1), and two granular regions (Ig1 and Ig2) (Fig. 11.2) (Kurth et al. 2010).

The notion that the Ig region receives primary input from thin afferents is supported by a growing body of literature on pain and temperature sensations. Studies

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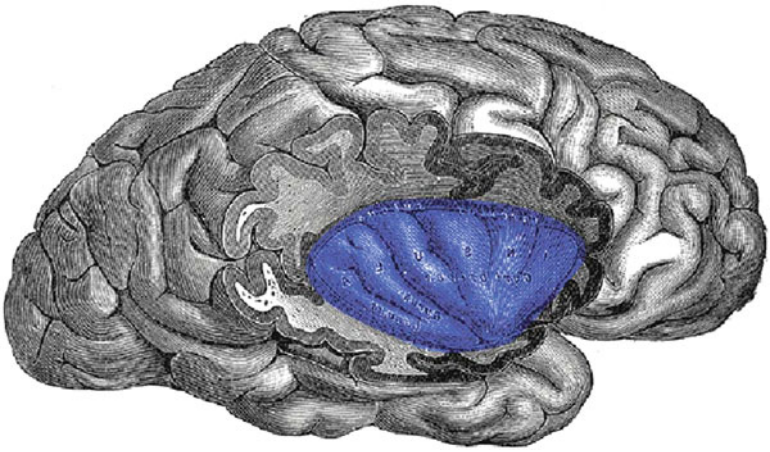

Fig. 11.1 The insular cortex of the human brain, highlighted in *blue*. Adapted from Gray's Anatomy of the Human Body, 1918

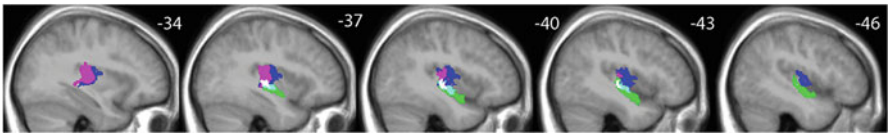

Fig. 11.2 Right hemisphere probabilistic representation of the granular posterior portion of the insular cortex; Id1 (*green*), Ig1 (*violet*), and Ig2 (*blue*). Overlap is indicated in *white* and *turquoise* (Kurth et al. 2010)

in awake humans have found that electrical stimulation of the posterior portion of the insula elicits sensations of temperature changes (warmth and cooling) and pain, mainly on the contralateral side of the body to the stimulated hemisphere (Ostrowsky et al. 2000, 2002; Penfield and Faulk 1955; Stephani et al. 2011). Corroborating the electrophysiological findings, neuroimaging studies have shown that painful stimuli and temperature changes activate the insular cortex in humans (Apkarian et al. 2005; Craig et al. 2000). Interestingly, electrical stimulation in the posterior insular cortex also elicited sensations of less well-defined, innocuous sensations, described as "tickling" (Ostrowsky et al. 2002; Penfield and Faulk 1955). These responses were attributed to the proximity of the insular cortex to the secondary somatosensory cortex (Penfield and Faulk 1955) and the reciprocal connections between posterior insular and somatosensory areas (Stephani et al. 2011). An alternative explanation, however, is that these sensations reflect primary processing of tactile information mediated through CT fibers.

Central projections of CT afferents are notoriously difficult to study since the CT preferred stimuli—slow, soft, and caress-like strokes—also vigorously co-activate thick, myelinated Aβ afferents which activate multiple brain regions (most notably the primary and secondary somatosensory cortices). How can the brain projections

Table 11.1 Somatosensory and insular brain activations during CT-targeted stimuli in neuronopathy patients GL (left forearm) and IW (right forearm) (Olausson et al. 2008)

Region		Patient GL	Patient IW
S1 (arm area)		n.s.	n.s.
S2		n.s.	n.s.
Insula, contralateral	Posterior	5.0 (−38, −14, 8)	4.3 (44, −12, 6)
			3.9 (40, −18, 6)
	Mid/anterior	3.6 (−46, 6, 0)	n.s.
		4.2 (−36, 12, −2)	
		3.9 (−34, 16, 6)	
Insula, ipislateral		4.6 (44, 8, 12)	3.8 (−40, −4, −10)

The table indicates peak *T*-values and associated coordinates in the MNI atlas. *n.s.* nonsignificant

of CT and Aβ input be dissociated? The first answer to this question came in the form of a landmark study by Olausson and colleagues (Olausson et al. 2002). During his research work at McGill University, Olausson came across a unique patient: GL. At the age of 31, GL suffered permanent specific loss of large-diameter myelinated afferents—including Aβ fibers—below the level of the nose. Her unmyelinated and small-diameter myelinated afferents—including CT fibers—were intact, however (Forget and Lamarre 1995). As a consequence, she can readily feel pain and temperature changes but not touch (Olausson et al. 2002, 2008). GL provided a unique opportunity to selectively study the behavioral and brain correlates of CT afferents, unshadowed by Aβ fiber input. Olausson and colleagues examined GL's brain responses to CT stimuli using a combination of psychophysics and functional magnetic resonance imaging (fMRI). During scanning, GL was gently stroked on the left forearm with a soft brush. Analyzing GL's brain responses to stroking, Olausson found that the somatosensory cortices were not activated (Table 11.1). In stark contrast, the same stimuli vigorously activated both the primary and the secondary somatosensory cortices in healthy control volunteers.

Instead, the patient's insular cortex was activated (Fig. 11.3). Similar activations in the insular cortex were found in healthy control volunteers, suggesting that GL's brain responses to CT stimuli were not a specific result of the neuronopathy. Olausson later replicated the findings in a second, similarly deafferented subject (IW), who was stroked on the right forearm (Olausson et al. 2008). Also in IW, the insular, but not somatosensory, cortices were activated (Fig. 11.3, Table 11.1).

The lack of activations in primary and secondary somatosensory cortices suggests that posterior insular processing of touch sensations occurs independently of Aβ afferents, which, in turn, casts doubt on the theory that insular activations are a consequence of connections to somatosensory cortices. Particularly consistent brain activations, across both patients and healthy control volunteers, were found in the posterior Ig2 region of the insular cortex in the hemisphere contralateral to the stimulated limb (Figs. 11.3 and 11.5a, Table 11.1). This finding suggests that the putative primary representation of bodily sensations in the posterior insula also includes CT-mediated information, similar to nociception and thermoception. Moreover, the CT

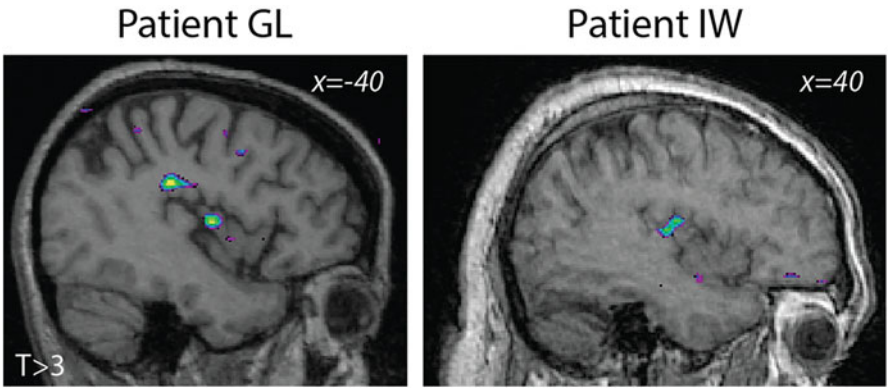

Fig. 11.3 Contralateral insular activations during CT-targeted stimuli in neuronopathy patients GL (*left forearm*) and IW (*right forearm*). Data from (Olausson et al. 2002, 2008)

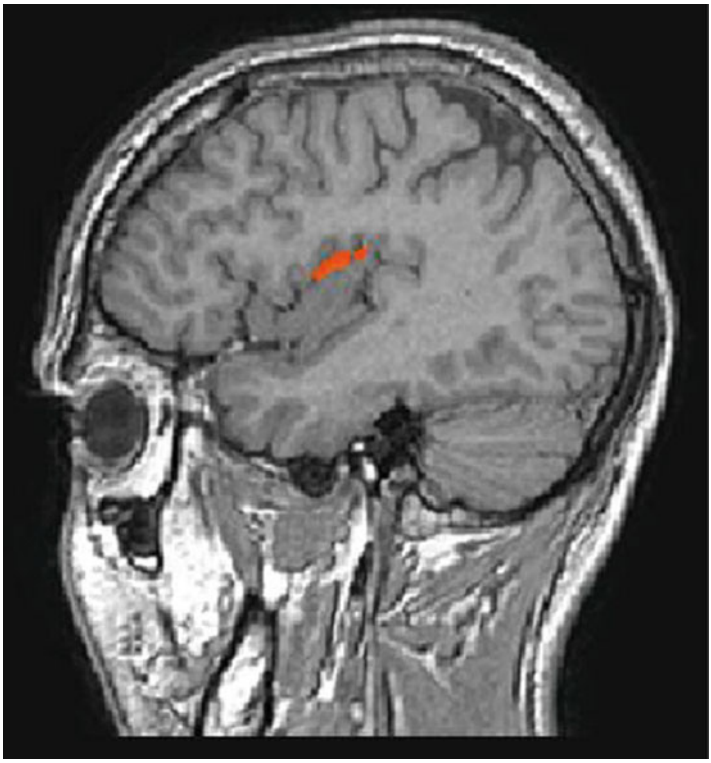

Fig. 11.4 Insular activations to CT-targeted stroking (velocity 3 cm/s) compared to Aβ-targeted stroking (30 cm/s) in the posterior insular cortex contralateral to the stimulated limb. Data from Morrison et al. (2011a)

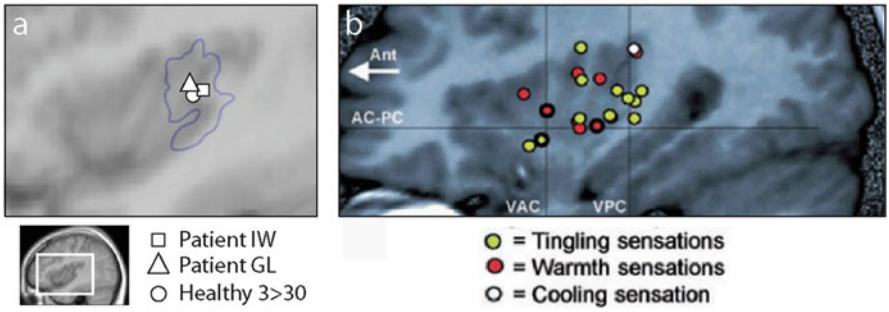

Fig. 11.5 (**a**) Loci of insular responses to CT-targeted stimuli in neuronopathy patients GL (*triangle*) (Olausson et al. 2002) and IW (*square*) (Olausson et al. 2008), and brain responses to 3 cm/s > 30 cm/s stroking in healthy volunteers (*circle*) (Morrison et al. 2011a). The Ig2 region is outlined in *blue*. (**b**) Locations of electrodes that elicited an innocuous tingling sensation shown in *green* (Ostrowsky et al. 2002)

loci correspond well to the locations of electrodes that elicit tingling sensations reported in the electrophysiological studies (Fig. 11.5b), supporting the idea that these sensations may be associated with the CT pathway.

Further support for the idea that the posterior insular cortex is the primary projection site of CT fibers comes from studies that dissociate Aβ and CT input using *velocity control*. A peculiar feature of the CT system is the distinct manner in which the afferent nerve discharge frequency is modulated by the velocity of the stroking stimulus. CT afferents vigorously respond to strokes with a velocity in the range of 1–10 cm/s, and less to slower or faster strokes (Löken et al. 2009). This velocity profile stands in sharp contrast to that of thick afferents, whose discharge frequency increase monotonically with stroking velocity. If the posterior insular cortex represents a primary target for CT input, the brain responses should reflect this velocity modulation. In order to examine this issue, Morrison and colleagues studied brain responses in 14 healthy volunteers to CT optimal slow (3 cm/s) and nonoptimal fast (30 cm/s) stroking by a soft goat hair brush (Morrison et al. 2011a). The results confirmed the hypothesis: the analysis identified a cluster of voxels in the contralateral posterior insular cortex where the 3 cm/s strokes elicited a larger brain response than the 30 cm/s strokes (Fig. 11.4). This cluster was located near the posterior insular cortex activations reported in the neuronopathy patients (x, y, z = 31, −15, 5), also within the granular Ig2 region (Fig. 11.5a). Again, this activation locus corresponded well with the reported locations of electrodes that elicit tingling sensations (Fig. 11.5b).

In a second study, Morrison examined the effects of stroking velocity in the insular cortex in a group of patients with reduced C fiber density. These patients suffer from a heritable disorder associated with a mutation affecting the nerve growth factor beta gene (Morrison et al. 2011b). Affected carriers exhibit reduced density of thin and unmyelinated nerve fibers, including C afferents. If the previously demonstrated insular responses to skin stroking are in fact contingent on CT afferents, decreased C fiber density should lead to selectively reduced activations of the posterior insular cortex. Morrison examined five patients and five gender and age-

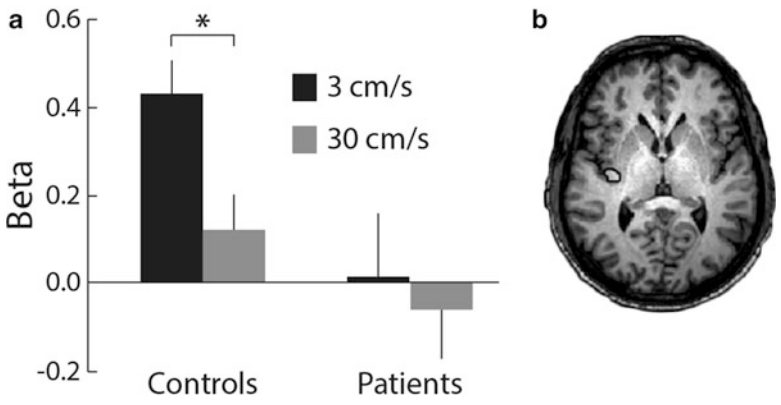

Fig. 11.6 Brain responses to CT-optimal (3 cm/s) and nonoptimal (30 cm/s) stroking in healthy controls and patients with reduced C-fiber density (**a**) in a posterior insular region of interest (**b**)

matched controls using fMRI, and applied brush strokes on the forearm at a CT-optimal stroking velocity (3 cm/s) and at a nonoptimal stroking velocity (30 cm/s). In the healthy control group, the contralateral posterior insular cortex in the healthy participants showed the greatest response to 3 cm/s stroking on the forearm. In patients, however, no significant responses to 3 cm/s stroking were found in the insular cortex. In order to verify the lack of response, a region-of-interest (ROI) mask created from the healthy group's activation cluster, was applied to the patient group's data. Mean brain responses (beta-values) were extracted for each voxel time course. In the patient group, there was no difference between 3 and 30 cm/s (Fig. 11.6). These results suggest a necessary role for CT input in posterior insular modulation to stroking stimulation.

Primary processing regions tend to have well-defined topographies, such as the somatotopy of the primary somatosensory cortex. Supporting the role of the posterior insula as a primary processing region, a growing number of studies of innocuous cooling and painful stimuli demonstrate that the posterior insular cortex is organized in a somatotopic fashion. Neuroimaging has demonstrated that upper body stimuli activate regions anterior to those of the lower body (Baumgärtner et al. 2010; Brooks et al. 2005; Henderson et al. 2007, 2011; Hua et al. 2005) (Fig. 11.7), and this organization has been identified also during electrical stimulation in patients (Mazzola et al. 2009). In order to assess whether CT responses are organized somatotopically, the neuronopathy patient GL was reexamined (Björnsdotter et al. 2009). In this study, soft brush stimuli were applied to the right forearm and thigh of GL and six healthy subjects during fMRI, and brain responses in the contralateral (left) insular cortex were analyzed. Similar to the findings in pain and temperature studies, it was found that forearm and thigh tactile stimulation activated distinctly separate clusters of voxels in the posterior insular cortex in GL (Fig. 11.7). The same organization was consistently found in all healthy subjects with forearm stimuli activating a region anterior to thigh stimulation. Again, the activations were located

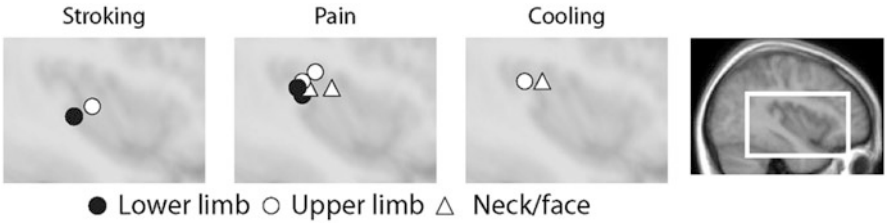

Fig. 11.7 Somatotopic organization with upper body limb stimuli projecting anterior to lower body stimuli in CT-targeted stroking in healthy controls (Björnsdotter et al. 2009), painful stimuli (Mazzola et al. 2009; Brooks et al. 2005), and cooling (Hua et al. 2005). Note that axial and coronal plane coordinates are represented as projections onto the sagittal plane $x = 40$ for display purposes

to the Ig2 region of the insular cortex. This somatotopic projection pattern is consistent with that found in thermosensation and nociception (Fig. 11.7), providing further support for the notion that the posterior insular cortex represents a primary target area for CT input.

Taken together, the studies examined in this chapter provide compelling support for the idea that the posterior insular cortex is the primary cortical target of information projected through CT afferents. Nevertheless, the central projection pathway of CT afferents remains unclear. A recent study suggests that, in rats, CT afferent signals merge with wide dynamic range neurons in the spinal cord (Andrew 2010) and brain responses to CT stimulation are modulated by tactile allodynia (Liljencrantz et al. 2013). Further research efforts are required to elucidate whether the posterior insular cortex contains a CT-selective neural representation, or whether the processing associated with CT-targeted stimuli is a generalized reflection of thin fiber sensations.

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Chapter 12
CT Afferent-Mediated Affective Touch: Brain Networks and Functional Hypotheses

India Morrison

Abstract Investigating the role of C-tactile (CT) afferents in affective touch requires exploration of the subcortical and cortical brain regions which receive information from the CT afferent pathway. This chapter summarizes the major known cortical targets and wider networks associated with CT-mediated touch, particularly the posterior insula and parietal operculum. It concludes with an outline of three hypotheses regarding the possible function of CT afferents. A central feature of each is the idea that C mechanoreceptive afferents contribute to physiological regulation, particularly of the sympathetic nervous system, in a manner which can extend to the social domain.

Keywords Neural processing • Affective touch • CT-mediated touch • C-tactile (CT) afferents • Cortical brain • Subcortical brain • Cortical targets

Introduction

Neural processing of affective touch starts in the skin. As evidence presented in other chapters in this volume demonstrates, mechanoreceptive CT afferents contribute to the signaling of light touch, associated with affectively valenced percepts. However, this implies neither that CT afferent signaling directly *codes* such affective qualities of tactile stimulation, nor that affective touch is *limited* to CT signal processing at any level of the nervous system. To explore how CT-mediated touch attains hedonic value, and what role CTs play in such processes, it is important to investigate the neuroanatomical details of higher-level cortical networks. The discussion in this chapter will address this, hinging mainly on a distinction between "cortical targets" and "cortical networks."

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In the following sections, cortical targets are considered as the earliest synapses from thalamic nuclei conveying the signal from the periphery, spinal cord, and brainstem—thus reflecting a high, though not exclusive, specificity for peripheral tactile information. These first cortical synapses are generally third-order neurons from spinothalamic projections. From these cortical targets, subsequent processing of the signal is elaborated in highly interconnected cortical networks, which extend throughout the brain and which are less likely to be domain specific for touch. These networks involve fourth-order connections and beyond. The identification of cortical targets involves tracing a pathway, either physically (by following axons) or functionally (by tracking responses to a stimulus). The identification of cortical networks, on the other hand, involves a less direct, more inferential approach—partly because of their complexity and multidimensionality, and partly because they are less experimentally accessible, especially in humans. Because a cortical target is also part of a cortical network, the distinction between the two is mainly heuristic.

Cortical Targets

One of our best tools for probing both CT cortical targets and networks in the brains of human volunteers is neuroimaging, especially MRI (magnetic resonance imaging). This technique can measure both structural and functional properties of the brain. Structurally, it can provide contrast images between grey matter and other types of brain tissue, such as white matter and cerebrospinal fluid. It can also highlight white matter tracts. Functionally, it provides measurements of regional changes in cerebral blood flow, which indirectly reflect changes in neurovascular regulation as a result of localized neuronal metabolic activity. However, it is important to note that the low temporal resolution of functional MRI (fMRI) makes it impossible to distinguish between early and late processing in the brain—though in some cases it is possible to infer the likelihood that an activation reflects a "cortical target" based on other considerations, such as the anatomical pathways established by research in nonhuman mammals. This section focuses on data obtained by MRI measurements relevant to affective touch in general, and CT stimulation in particular.

On the way to the brain, unmyelinated C afferents (including CTs) synapse in neural populations in the dorsal horn of the spinal cord (e.g., Craig 1995; Andrew 2010; this volume). There is little direct evidence about where CTs might go from there, especially in humans, but it is likely that the CT pathway ascends to the thalamus via the spinothalamic tract (STT; but see Abraira and Ginty 2013; Zimmerman et al. 2014). In contrast, Aβ tactile afferents associated with discriminative function follow a pathway up to the brain via the dorsal column of the spinal cord. These two pathways terminate in relatively distinct sets of thalamic nuclei, which project in turn to relatively distinct sets of cortical regions (Dum et al. 2009; Friedman and Murray 1986). Human neuroimaging cannot shed light on the exact course the CT pathway takes before the level of its thalamic projections, but CT signaling properties and tactile stimulation of hairy skin can be used to probe hemodynamic responses in the brain using functional fMRI.

fMRI gives us a small but growing toolkit for inferences about cortical targets of the CT pathway. First, we can use known CT properties as a "probe" to investigate related hemodynamic responses in the brain. The more we know about CT afferents, the more precisely we can tailor stimulation likely to elicit responses from the cortical targets. For example, we can manipulate the speed of stroking, to which CTs are sensitive (Löken et al. 2009; Björnsdotter, this volume). We can also exploit the differential innervation of hairy and glabrous skin: tactile stimulation of hairy skin activates both CT and Aβ fibers, whereas glabrous (e.g., palm) stimulation activates Aβs only. We can investigate populations with pathologies or disturbances in either their CT or Aβ innervation. We can also focus on experimental manipulations that change the participants' subjective experience or behavior related to affective touch stimulation. Finally, we can mine the existing published reports and apply inferential statistics for the meta-analytical picture across larger data sets.

Each of these approaches has yielded evidence pointing to posterior insula as the prime candidate for a first cortical target of the CT pathway (see also Björnsdotter, this volume). First, posterior insula shows preferential activation to "CT-optimal" stroking speeds of 1–10 cm/s (peaking at about 3 cm/s), compared to "CT-nonoptimal" speeds of 30 cm/s (Morrison et al. 2011a, b) and 0.3 cm/s (Perini et al. 2015), consistent with peripheral afferent response profiles (Löken et al. 2009; Ackerley et al. 2014). Second, comparing arm and palm stroking stimulation reveals partly distinct activations for each, with arm (hairy skin) responses limited to posterior insula (Perini et al. 2015). Third, Aβ-denervated patients with preserved CT afferents show insula activation when stroked on the hairy skin (Olausson et al. 2002, 2010; Cole, this volume), suggesting that CT signals reach this region of cortex in the absence of Aβ-mediated tactile information. In patients with a rare mutation resulting in a selective reduction in C-afferent density, on the other hand, posterior insula shows no modulation by stroking speed (Morrison et al. 2011a, b).

In a recent study investigating stroking preferences and behavior, posterior insula activation increased for stroking speeds that the participants preferred at above-chance levels (Perini et al. 2015). Finally, a recent meta-analysis created a spatial map of brain areas highly likely to be reported as active for pleasant touch in the existing fMRI literature, using activation likelihood estimate (ALE) analysis (Morrison, 2016). The posterior insula showed the highest probability of selective activation by pleasantly rated gentle touch, as opposed to tactile stimulation in the context of detection or discrimination tasks. The weight of the above evidence thus supports the posterior insula as a cortical target for the CT afferent pathway. This is consistent with a proposed pathway for all thin-diameter, unmyelinated C afferents in rodents and nonhuman primates (Craig 2004; see Andrew, this volume).

The posterior insula is activated by a broad range of visceral, somatosensory, and nociceptive stimulation in humans (e.g., Kurth et al. 2010; Segerdahl et al. 2015) and is highly interconnected with parietal sensorimotor cortices (Deen et al. 2011; Cauda et al. 2011; Cerliani et al. 2012). Distinct cytological subdivisions have been identified in insular cortex, with posterior granular areas Ig1 and Ig2 implicated in somatosensory and nociceptive processing (e.g., Kurth et al. 2010; Segerdahl et al. 2015). Granular insular cortex responses to affective touch fall predominantly around the long gyri and within the insular central sulcus (Morrison et al. 2011a).

This region also exhibits distinct somatotopic responses for stroking on the arm and thigh within the range of CT afferents' preferred speed (Björnsdotter et al. 2009, 2010; this volume). The granular region of posterior insular cortex might therefore provide a fundamental, early contribution to such stimulus processing, and may be critical for the efficient integration of affectively relevant somatosensory information (Lovero et al. 2009; Lucas et al. 2014; Perini et al. 2015).

Apart from the posterior insula, there are also parallel or minor cortical targets for affective touch. These may receive a proportionally smaller or less selective contribution of input from the CT-spinothalamic pathway than posterior insula, but could likewise reflect early projections to cortex. One such region may be the secondary somatosensory (SII) cortices on the parietal operculum. These can be regarded as cortical targets by virtue of major input from the STT via anatomical projections from ventroposterior inferior (VPI) nucleus, and minor input from the posterior-suprageniculate complex (Po-Sg; of which posterior ventromedial nucleus, VMpo, is considered a part; but see Willis et al. 2002, Graziano and Jones 2004). In the macaque monkey, parietal opercular cortex receives 29 % of STT inputs, in second place behind granular posterior insular areas which receive 41 % (Dum et al. 2009). In contrast, primary somatosensory cortex (SI) receives 4 % of the projections from STT. The parietal opercular regions most relevant for affective touch are discussed further in following section.

Cortical Networks

So far, then, granular posterior insula is the region most likely to be selectively activated by affective touch in fMRI studies and is anatomically well-situated to be a cortical target for a CT afferent pathway. However, it is improbable that activation of posterior insula singlehandedly exhausts any hedonic content of affective touch. For example, its selectivity for stroking speed outweighed pleasantness differences between soft- and coarse-haired brushes (Morrison et al. 2011a), and its activity consistently fails to correlate with subjective ratings (e.g., Morrison et al. 2011a; Ebisch et al. 2011; Perini et al. 2015). Despite this, posterior insula is doubtless a robust participant in a brain-wide network of different areas specializing in various aspects of tactile and affective processing. Specific relationships among such nodes in a wider network have not yet been experimentally tested, but several candidates have been identified as consistently implicated in affective touch processing.

As mentioned in the foregoing section, parietal opercular somatosensory areas may be parallel or minor cortical targets of the CT-spinothalamic pathway, alongside posterior insula (Fig. 12.1). Alternatively—or additionally—these regions may form part of a wider network that contributes to the processing of gentle, dynamic touch by virtue of its direct corticocortical connections (Friedman et al. 1986; zu Eulenburg et al. 2013; Ebisch et al. 2011; Morrison et al. 2010; Wei and Bao 2013). In fact, the term "operculo-insular cortex" has been used to capture the functional similarity among these areas. Yet although these insular and opercular

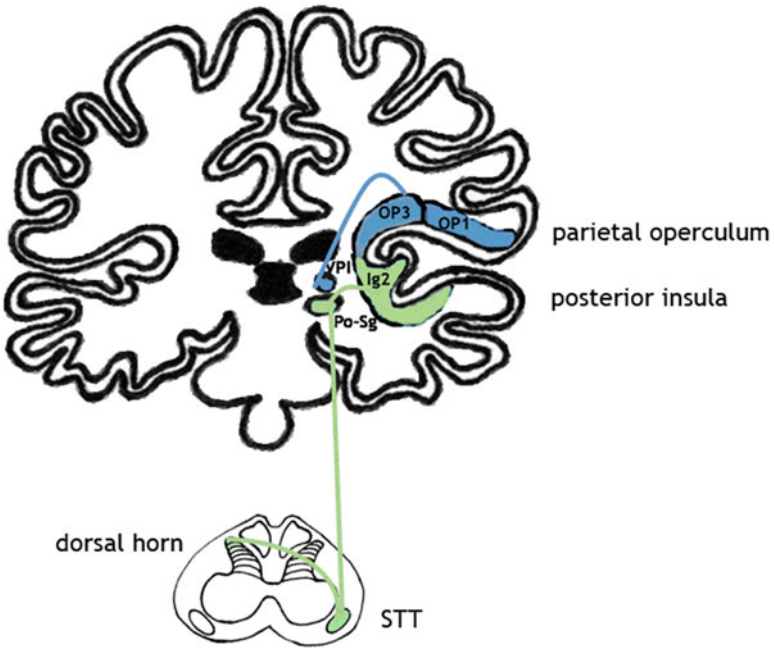

Fig. 12.1 Cortical targets of the CT-spinothalamic pathway. Schematic coronal section of the human brain showing pathway from the dorsal horn of the spinal cord, continuing to thalamic nuclei via the spinothalamic tract (STT), and onward to posterior insular and parietal opercular cortices. *Green* indicates the predominant STT projections to posterior insula via posterior suprageniculate complex (Po-Sg). *Blue* indicates the predominant STT projections to parietal opercular areas OP1 and OP3 via ventroposterior inferior nucleus (VPI). *Note*: *for simplicity of illustration*, *OP1 and OP3 are pictured in the same plane*, *though OP1 lies posterior to OP3 on the human parietal operculum*. For a discussion of the cortical networks in which these targets participate, see the section "Cortical networks"

areas are closely adjacent and highly interconnected—as well as being frequently interchangeably labeled—their receptive fields and cytological characteristics are distinct (Evrard et al. 2014).

Like granular insular cortex, primate opercular somatosensory areas have cytoarchitectonic subregions (Krubitzer and Kaas 1992). Within the parietal operculum, four relatively distinct somatosensory regions have been probabilistically mapped, using evidence from histologically stained postmortem human brains, alongside functional imaging evidence (Eickhoff et al. 2006; Baumgärtner et al. 2010; Kurth et al. 2010). The subregions OP1 and OP3 are particularly relevant here because they are commonly activated across both affective touch paradigms as well as in tasks which involve tactile stimulus detection and/or discrimination (Morrison).

Region OP1 lies posterior to OP3 and is the likely human homologue of "classical" secondary somatosensory (SII) cortex in the monkey (Eickhoff et al. 2006). OP1 responds to noxious tactile stimuli as well as tactile, nociceptive, and vestibular stimulation (zu Eulenburg et al. 2013). OP3 lies deeper in the Sylvian fissure and is

the likely homologue of the primate "ventral somatosensory" area VS, which is not functionally well-characterized (Eickhoff et al. 2006; Krubitzer and Kaas 1992). In nonhuman primates such as the macaque (*Macaca mulatta*) and the marmoset (*Callithrix jacchus*), both SII and PV receive major projections from VPI (Qi et al. 2002), whereas this is not clearly the case for VS. It has been speculated that thalamic inputs to S2 and PV are modulatory rather than relaying strictly sensory response properties (Krubitzer and Kaas 1992; Qi et al. 2002).

Primary somatosensory (SI) areas associated with the discriminative aspect of touch may also contribute to the processing of affective or social touch stimuli in humans. Although the CT pathway may privilege certain information based on specific ranges of speed (Löken et al. 2009) and temperature (Ackerley et al. 2014) variables, any tactile stimulation anywhere on the body will also activate the large myelinated Aβ afferents that project predominantly to somatosensory cortices. The potential involvement of SI is suggested by its ability to use visual cues to distinguish between videos of male and female strokers during tactile stimulation of the leg (Gazzola et al. 2012). Similarly, transcranial magnetic stimulation (TMS) over right SI selectively slowed reaction times on a go–no go task following affective touch (Bolognini et al. 2011). SI has also been activated alongside SII and posterior insula for palm (glabrous skin) stroking, whereas arm (hairy skin) stroking was limited to posterior insula (Perini et al. 2015; see also McGlone et al. 2012). Together with the palm-specific activation in SI, this incomplete overlap between arm and palm stroking activation suggests a general bias toward hairy skin (CT+Aβ input) in posterior insula and a bias toward glabrous skin (Aβ input) in somatosensory cortices.

Other areas implicated in affective touch networks include the superior temporal gyrus and sulcus (STG and STS; Gordon et al. 2011; Bennett et al. 2014). Neurotypical individuals who nonetheless score high on some measures associated with autism spectrum disorder (ASD) show reduced activation in STS during skin stroking (Voos et al. 2013), as do children and adolescents diagnosed with ASD (Kaiser et al. 2015). The role of superior temporal areas may lie in the integration of tactile information with sensory and spatial information from other modalities. A role in processing socially relevant stimuli was first revealed by neurons in the macaque STS, which responded to the eye gaze direction of other primates, especially in conjunction with congruent head orientation (Perrett et al. 1985). This area is also involved in processing convergent auditory and visual facial information (Ghazanfar et al. 2008). In addition to an involvement in processing movement-direction information and in polymodal integration (Beauchamp et al. 2008), STS/STG plays a role in sensory imagery (Berger and Ehrsson 2014). These functional properties are consistent with the fact that during a standard fMRI experiment, participants can feel but not see the tactile stimulation. STS may thus contribute to structuring a coherent representation of the touch by working to "fill in" missing visual and spatial information via imagery (e.g., Kilintari et al. 2014).

Since CT-associated touch can be experienced as pleasant, it may have intrinsic reward value. That is, people might not only *like* social touch but *want* it for its own sake, resulting in active seeking behavior (Berridge and Robinson 2003). Perini et al. (2015) used a feedback-based experimental paradigm in which the subjects

could determine which stroking speed they would receive in a given trial. The speeds that subjects preferred and actively sought above chance level were CT-optimal speeds, which activated both posterior insula and dorsolateral prefrontal cortex. The idea that affective touch networks interact with reward- and decision-related networks is consistent with several findings that implicate orbitofrontal cortex in affective touch processing (Francis et al. 1999; Disbrow et al. 2000; Rolls et al. 2003; McCabe et al. 2008; McGlone et al. 2014). The orbitofrontal cortex is associated with reward-related behavior (Rolls and Grabenhorst 2008; Padoa-Schioppa and Cai 2011) and may work together with posterior insula to evaluate affective touch in ways that guide such behavior. Studies involving tactile massage have implicated another important limbic region, the perigenual ACC, associated with emotional processing (Lindgren et al. 2012; Sliz et al. 2012).

Hypotheses of Role and Origin

Presumably, the wider function of CT signaling is not merely to indicate the presence of a certain stimulus type (for example, "warmish, medium-speed movement"), but to enable certain behaviors instigated by that stimulus. Such processes must take place at the level of cortical networks simply because this is where integration of tactile information with crucial higher-level factors—such as memory, context, and intention—occurs. Integration at this level underpins the complex affective dispositions which translate into behavior. This section therefore discusses and evaluates three hypotheses regarding wider functional roles for the CT pathway. Each revolves around the distinct physiological and functional properties of the afferent pathways followed by CTs, and each is likely to enlist cortical-level integration of various types of information. These hypotheses are (1) the "social touch" hypothesis, (2) the related "interoceptive" hypothesis, and (3) the "thermoregulatory" hypothesis.

These hypotheses have arisen because the functional neuroanatomy of CT-mediated touch invites conjecture as to its wider evolutionary role, and even its origin, in mammalian species. This necessarily involves a degree of speculation, and it is worth emphasizing that direct empirical tests of these hypotheses are lacking. However, they do tend to orbit around a distinct cluster of plausible and testable ideas. The most salient of these is efferent *regulation*, especially brain-level regulation of bodily processes (e.g., cardiac, respiratory, visceral, etc). More specifically, hypotheses of CT function postulate that CTs are part of a segregated afferent–efferent pathway influencing physiological regulation in the face of external perturbation. An implication of this view is that such regulatory mechanisms can extend beyond the individual organism to include social interactions.

The central pillar of the "social touch" hypothesis is the idea that affective touch operates mainly in the domain of social interactions and has an impact on behavior (Olausson et al. 2010; Morrison et al. 2010; McGlone et al. 2014). It proposes that human touch is a specific, distinct category of tactile experience that is inherently hedonic and rewarding, with possible functional roles in fostering and maintaining

social relationships. Such affective touch may thus constitute a domain of touch that draws on a qualitatively different category of information than that coded by Aβ afferents. This may even involve specialized functional organization in both the periphery and the central nervous system.

CT response properties appear to square very nicely with the proposition that they are tuned to stimulus features that typically occur in social interactions, such as caressing. First, the intermediate, caress-like speeds that give rise to the highest mean CT firing frequency are the most hedonically potent (Löken et al. 2009). Second, more recent findings suggest that the unique profile of CT responses to different stroking speeds can interact with temperature (Ackerley et al. 2014). Namely, their mean firing increases most to 3 cm/s stroking by a skin-temperature (32 °C) probe, compared to stroking at other speeds and by warmer or colder probes. This suggests that CT afferents prefer caress-speed stroking at a "creature" temperature, which is also rated as most pleasant. Less directly, the slow conduction velocity of CTs (around 1 m/s) and their diffuse perceptual correlates (e.g., Olausson et al. 2002) point away from a role in fast, high-acuity discriminative processing. On the "social touch" view, signaling in the CT afferent pathway flags tactile stimulation that is likely to signal close, affiliative body contact with others, making it available for further affective evaluation in the brain networks discussed in foregoing sections.

The "interoception" hypothesis dovetails with the social touch hypothesis, but places its emphasis on the physiological effects of affective touch on bodily processes. Historically, the classical view of interoception hinged on a distinction between "interoceptive" tissues within the body, for example, those involving visceral innervation, and "exteroceptive" tissues on the body surface, such as those involving cutaneous innervation. This view has recently undergone a paradigm shift away from a literal "in–out" distinction in favor of one based more on the physiological properties of the relevant nerve pathways. The currently prevailing view of interoception involves the coding and perception of physiological state changes in body tissues (Craig 2002; Migliorini et al. 2013). Craig has redefined interoceptive pathways as those of unmyelinated and thinly myelinated afferents synapsing in lamina I of the dorsal horn and ascending via the STT to medial thalamic nuclei (Craig 2003, 2009; see also Andrew, this volume). In this respect, CTs have more in common with "interoceptive" pathways, both physiologically and functionally, than "exteroceptive" tactile pathways, despite innervating the skin (Björnsdotter et al. 2010, see also Björnsdotter, this volume).

Importantly, Craig classed this pathway as an "afferent limb" of the sympathetic nervous system (Craig 2003). This implies a relationship with efferent autonomic regulation of bodily states via sympathetic and parasympathetic channels, for example, those which influence heartbeat, breathing, and muscle readiness (e.g., Seth and Critchley 2013). However, any such physiological relationships need to be further illuminated by experimental findings, especially in the case of CT-mediated touch in humans. Nonetheless, the plausible idea that small-diameter afferent traffic influences sympathetic outflow can be viewed from the perspective of homeostatic regulation. Homeostasis refers to a set of regulatory processes that defend a system from

deviations from a certain set point. The classic analogy for this is a thermostat, which turns on only when the ambient temperature falls outside a fixed limit.

But the problem with this is that very few complex regulatory loops are likely to involve a thermostat-like set point (Schulkin 2011). Moreover, multiple regulatory systems must operate together throughout the body to achieve and maintain a stable overall dynamic. To complicate matters further, many of these regulatory processes act in an anticipatory manner, especially those which rely on cortically mediated predictions involving context, memory, conditional learning, and so forth. A more accommodating model, then, is "allostasis" (e.g., Sterling 2012; Schulkin 2011). In contrast to strictly homeostatic models, allostatic models emphasize the requirement for energy efficiency in the operation of regulatory systems, and supply a role for predictive modulation as well as flexible input–output ranges among multiple interacting systems. Here, stable dynamics reflect optimized balances among energetic costs, not necessarily defense against deviations from a given set point. This allostatic view has generated a specific model of "interoceptive inference" implicating anterior insular cortex (Seth 2013).

A third, "thermoregulatory," hypothesis is proposed here (see also Morrison, in press). Its focal point is the somatosensory correlates of warmth-seeking behavior in mammals. The thermoregulatory hypothesis does not assume that affective, social touch confers survival benefits that have been directly selected for in our phylogenetic past. Rather, it postulates that CT coding may be an outcome (or "exaptation," Gould and Vrba 1982) of thermoregulatory-related traits that have themselves been more directly shaped by selection pressures. In this scenario, the present functions of mechanoreceptive C afferents have been scaffolded in phylogenetic history by thermosensitive C-mediated mechanisms of thermoregulatory behavior in young mammals, in the context of huddling (e.g., in litters) and counterparts to huddling in dyadic interactions (e.g., parent–offspring "snuggling").

Cold-sensitive subtypes of cutaneous C afferents signal decreases in temperature. This signaling can ultimately result in shivering or nonshivering thermogenesis, or changes in behavior to seek external heat sources. For example, in newborn mammals, nonshivering thermogenesis is mediated by sympathetic vagal efferents which can instigate the burning of brown adipose fat (BAT; Ryu et al. 2015). Though the physiology is less well understood, skin temperature decreases can also drive huddling behavior, a means of social thermoregulation that allows reduction of heat loss as well as lowering energetic metabolic costs of endothermoregulation (Gilbert et al. 2012; Morrison et al. 2008). Huddling in newborn porcupines (*Hystrix africaeaustralis*), for example, lowers the critical temperature at which they can effectively thermoregulate by endogenous means (Haim et al. 1992). Importantly, these decreases enable gains in energy allocation for other important processes, such as growth and repair (vital from an allostatic perspective, as discussed above).

Huddling involves active behavior to maximize its effects, which results in continual movement patterns as individuals nuzzle their way to the center, displacing and being displaced by littermates (Gilbert et al. 2012). It also generates predictable, stable signatures of somatosensory stimulation on hairy skin surfaces: gentle, moving

touch at skin temperature. This opens up an opportunity for mechanoreceptive coding to stand in for thermoreceptive coding in the allostatic regulatory loops, perhaps especially those most relevant to the efficient driving of specific, proximity-seeking behaviors. This is evolutionarily plausible because cutaneous sensory afferents show relatively wide scope for adjusting molecular receptor profiles according to species-level environmental pressures (Gracheva and Bagriantsev 2015). Both in development and phylogeny, genetic regulatory mechanisms determine specific response profiles of C afferent subtypes by differential expression of receptor channels (Lou et al. 2015; Ma 2010, 2012). Such genetic regulation could produce tuning shifts in afferent phenotype and function without requiring large genetic changes. Thus turning "on" or "off" the expression of certain receptor channels (such as MrgprB4; Lou et al. 2015) could result in modality-selective sensory neurons, or even response properties signaling in a combinatorial fashion with other subtypes (Lou et al. 2015; Ma 2010, 2012; Prescott et al. 2014). Importantly, such shifts could also provide energy efficiency gains in allostatic terms, potentially making tactile input energetically "cheaper" than thermoregulatory processing in this context. Via such phylogenetic and developmental mechanisms, the stable temporal coincidence of somatosensory and thermosensory processing in young mammals might thus favor a shift from a general thermoregulatory function to one more tuned to somatosensory aspects of close social contact. This in turn would create a platform for wider possibilities in the domain of social interaction.

Whatever the phylogenetic relationship between C afferent subtypes, though, both thermosensation and somatosensation during close proximity essentially signals that the organism is in a "safety zone." On this basis, these sensory processes can ultimately serve to signal other benefits of social proximity beyond the thermoregulatory realm, such as reduced risk for predation exposure. Social touch then becomes a parsimonious way to sound the "all clear" to the central nervous system with respect to metabolically expensive sympathetic arousal (see also Porges 2007). Conversely, it provides the neural means by which acute stress or anxiety can trigger a motivation to seek proximity in order to dampen arousal, just as being cold can drive behavior to huddle close to others to restore warmth. There is growing evidence that social and C-mechanoreceptor-mediated touch can buffer autonomic and behavioral signs of stress and anxiety (Coan et al. 2006; Vrontou et al. 2013; Schirmer et al. 2013). In this way, thin-fiber-mediated systems may have expanded into further aspects of social interaction and its multiple benefits in social animals.

The ultimate outcome of the "social touch," "interoceptive," and "thermoregulatory" scenarios of CT function is that social factors and events become incorporated into systems for physiological regulation of individual bodily economy. This is brokered by the brain's generation of motivated, adaptive behavioral changes. Future research will follow these various leads to arrive at more direct tests of CT afferent function (Fig. 12.2). In the end, these leads are likely to take us from the body to the brain, and back again.

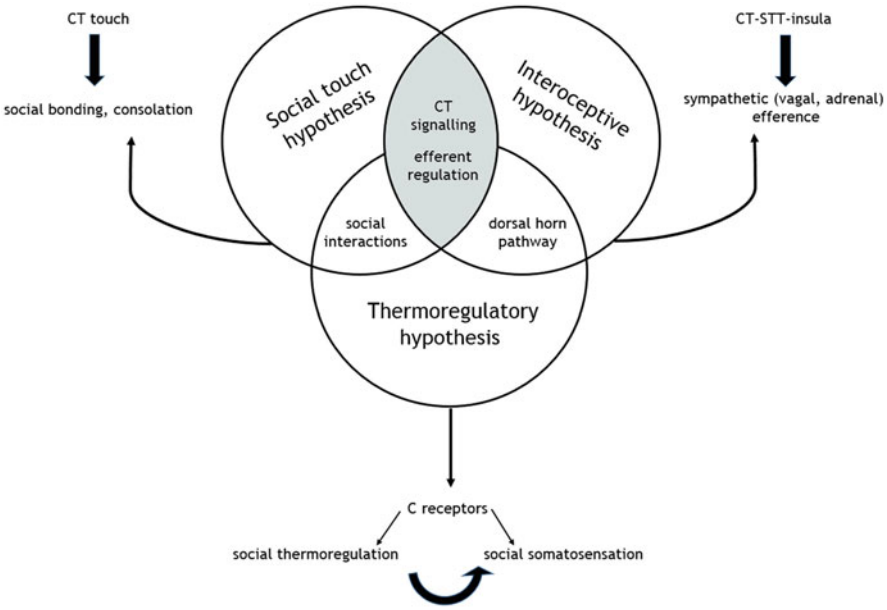

Fig. 12.2 Three hypotheses of CT afferent function. *Left top circle*: the "social touch hypothesis" postulates a relationship between CT-mediated touch and roles in interpersonal bonding, consolation, and other social phenomena (e.g., Morrison et al. 2010; McGlone et al. 2014). *Right top circle*: the "interoceptive hypothesis" postulates a physiological influence of CT afferents on physiological regulation via relationships between STT pathways and the sympathetic nervous system (e.g., Craig 2003). *Bottom circle*: the "thermoregulatory hypothesis" (proposed in this chapter) raises the possibility that a role for C-afferent-mediated circuits in social thermoregulatory behavior (e.g., huddling) may have scaffolded a role for mechanoreceptive C-afferent-mediated circuits in social tactile interactions, via changes in C receptor profiles. These three hypothesis variously share the general features of CT signaling and efferent regulation (*shaded area*), as well as dorsal horn pathways and social interactions

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Chapter 13
Brain Processing of Reward for Touch, Temperature, and Oral Texture

Edmund T. Rolls

Abstract Some of the principles of the representation of affective touch in the brain are described. Positively affective touch and temperature are represented in parts of the orbitofrontal and pregenual cingulate cortex in which other neurons represent the reward value of taste, olfactory, and/or visual stimuli. The orbitofrontal cortex is implicated in some of the affective aspects of touch that may be mediated through C fibre Touch afferents, in that it is activated more by light touch to the forearm (a source of CT afferents) than by light touch to the glabrous skin of the hand. Oral somatosensory afferents implicated in sensing the texture of food including fat in the mouth also activate the orbitofrontal and pregenual cingulate cortex, as well as the insular taste cortex. Top-down cognitive modulation of the representation of affective touch produced by word labels is found in parietal cortex area 7, the insula and ventral striatum. The cognitive labels also influence activations to the sight of touch and also the correlations with pleasantness in the pregenual cingulate/orbitofrontal cortex and ventral striatum.

Keywords Affective touch • Temperature • Cognitive modulation • Attention • Biassed competition • Taste • Fat texture • Pleasure • Emotion

The aim of this chapter is to consider the principles of the representation of positively affective touch, temperature, and oral texture in the brain, and the ways in which cognitive factors influence the representation of touch in the brain. Touch can be a primary (unlearned) reinforcer for actions, and as a goal for action, is one of the foundations of emotion and motivation (Rolls 2005, 2014). By positively affective touch is meant touch that is a reward, i.e. it will be worked for, and is rated as pleasant by humans. By negatively affective touch is meant touch that is a punisher, i.e. work will be performed to avoid or escape from it, and it is rated as unpleasant by humans (Rolls 2014). Touch can be negatively affective without being painful; an

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example is a cool surface applied to the hand, which is just unpleasant. Much social and affiliative behaviour, as well as behaviour directed towards comfort and a feeling of well-being, is directed towards pleasant touch.

First, the representation in the brain of the affective value of somatosensory stimuli including touch and temperature is described (Rolls 2010). Representations in the brain produced by light pleasant touch that activates C-tactile (CT) afferent fibres are included. Then cognitive modulation of the affective value of touch by word-level descriptions is considered, and the brain regions in which the affective modulation is evident are described. Then the brain regions that respond to the sight of touch being applied are described, and how these representations can be modulated by cognitive inputs that alter the affective interpretation of the sight of the touch. This evidence about the affective representations of somatosensory stimuli and their cognitive modulation comes mainly from neuroimaging with functional magnetic resonance imaging (fMRI). This evidence is complemented by single neuron studies that show how another set of somatosensory and temperature inputs, from the oral cavity, provides information about the texture and temperature of stimuli in the mouth, which are important in the palatability and affective value of food, and thus in appetite control.

The Representation of Positively Affective Touch and Temperature in the Brain

While there have been many investigations of the neural representations of pain (Kobayashi 2012; Wiech and Tracey 2013; Brodersen et al. 2012), there have been fewer investigations of the representation of pleasant touch in the brain.

In one study, the cortical areas that represent affectively positive and negative aspects of touch were investigated using fMRI by comparing activations produced by pleasant touch, painful touch produced by a stylus, and neutral touch, to the left hand (Rolls et al. 2003b). It was found that regions of the orbitofrontal cortex were activated more by pleasant touch and by painful stimuli than by neutral touch, and that different areas of the orbitofrontal cortex were activated by the pleasant and painful touches (see Fig. 13.1). The orbitofrontal cortex activation was related to the affective aspects of the touch, in that the somatosensory cortex (S1) was less activated by the pleasant and painful stimuli than by the neutral stimuli (as shown by a two-way analysis of variance performed on the percentage change of the BOLD signals under the different stimulation conditions in the different areas). Further, it was found that a rostral part of the anterior cingulate cortex was activated by the pleasant stimulus and that a more posterior and dorsal part was activated by the painful stimulus. Regions of the somatosensory cortex, including S1, and part of S2 in the superior temporal plane at the mid-insula level, were activated more by the neutral touch than by the pleasant and painful stimuli. Part of the posterior insula was activated only in the pain condition, and different parts of the brainstem, including the central grey, were activated in the pain, pleasant, and neutral touch conditions.

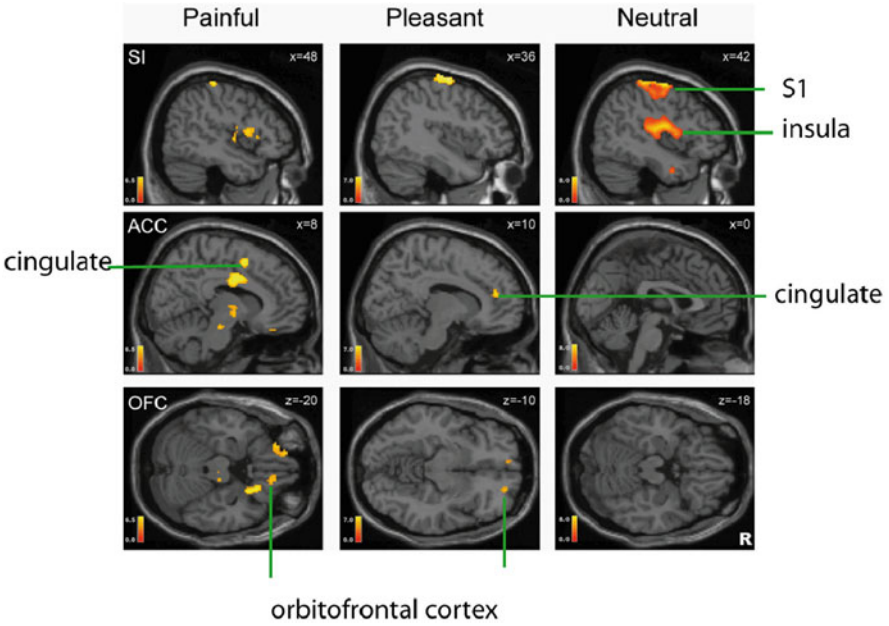

Fig. 13.1 Brain activation to painful, pleasant, and neutral touch of the human hand. The *top row* shows strongest activation of the somatosensory cortex S1/insula by the neutral touch, on parasagittal sections (parallel to the midline). The *middle row* shows activation of the most anterior part of the anterior cingulate cortex by the pleasant touch, and of a more posterior part by the painful touch, on parasagittal sections. The *bottom row* shows activation of the orbitofrontal cortex by the pleasant and by the painful touch, on axial sections (in the horizontal plane). The activations were thresholded at $p < 0.0001$ to show the extent of the activations (After Rolls et al. 2003b)

The results provide evidence that different areas of the human orbitofrontal cortex are involved in representing both pleasant touch and pain, and that dissociable parts of the cingulate cortex are involved in representing pleasant touch and pain (Rolls et al. 2003b).

Warm and cold stimuli have affective components such as feeling pleasant or unpleasant, and these components may have survival value, for approach to warmth and avoidance of cold may be reinforcers or goals for action built into us during evolution to direct our behaviour to stimuli that are appropriate for survival (Rolls 2014). Understanding the brain processing that underlies these prototypical reinforcers provides a direct approach to understanding the brain mechanisms of emotion. In an fMRI investigation in humans, we showed that the mid-orbitofrontal and pregenual cingulate cortex and the ventral striatum have activations that are correlated with the subjective pleasantness ratings made to warm (41 °C, rated as pleasant) and cold (12 °C, rated as unpleasant) stimuli, and combinations of warm and cold stimuli, applied to the hand (Rolls et al. 2008). Activations in the lateral and some more anterior parts of the orbitofrontal cortex were correlated with the unpleasantness of the stimuli. In contrast, activations in the somatosensory cortex and ventral

posterior insula were correlated with the intensity but not the pleasantness of the thermal stimuli (Rolls et al. 2008). Temperature may also be important for social touch, in that slow soft touch that activated CT afferents produced the best responses when the touch stimulus was at a typical skin temperature (32 °C), rather than colder or warmer (Ackerley et al. 2014).

A principle thus appears to be that processing related to the affective value and associated subjective emotional experience of somatosensory and thermal stimuli that are important for survival is performed in different brain areas to those where activations are related to sensory properties of the stimuli such as their intensity. This conclusion appears to be the case for processing in a number of sensory modalities , and the finding with such prototypical stimuli as pleasant and painful touch, and warm (pleasant) and cold (unpleasant) thermal stimuli, provides strong support for this principle (Rolls and Grabenhorst 2008; Grabenhorst and Rolls 2011; Rolls 2012, 2014, 2015). An implication of the principle is that by having a system specialised for the affective or reward aspects of stimuli it is possible to modify goal-oriented behaviour, and to do this independently of being able to know what the stimulus is (its intensity, physical characteristics, etc.). Thus, even if a stimulus has lost its pleasantness because of, for example, a change of core body temperature, it is still possible to represent the stimulus, recognise it, and learn about where it is in the environment for future use (Rolls 2014). This is a fundamental aspect of brain design (Rolls 2005, 2008b, 2014).

Decision-making about whether to select an affective stimulus may involve a further tier of representation beyond that involved in representing the affective value of the stimulus. Indeed, representing the affective value of a reward on a continuous scale may occur before and separately from making a binary, for example yes–no, decision about whether to choose the reward (Rolls and Grabenhorst 2008; Grabenhorst and Rolls 2011; Rolls 2014). To investigate whether these are separable processes, we used fMRI to measure activations produced by pleasant warm, unpleasant cold, and affectively complex combinations of these stimuli applied to the hand (Grabenhorst et al. 2008b). On some trials the affective value was rated on a continuous scale, and on different trials a Yes–No decision was made about whether the stimulus should be repeated in future. Decision-making contrasted with just rating the affective stimuli revealed activations in the medial prefrontal cortex area 10 implicating this area in binary decision-making. Activations related to the pleasantness ratings and which were not influenced when a binary decision was made were found in the pregenual cingulate and parts of the orbitofrontal cortex implicating these regions in the continuous representation of affective value. When a decision was yes vs. no, effects were found in the dorsal cingulate cortex, agranular (anterior) insula, and ventral tegmental area, implicating these areas in initiating actions to obtain goals (Grabenhorst et al. 2008b).

Thus, decision-making about whether to select a stimulus may be a process implemented in the brain separately from the representation of the continuous affective value of a stimulus (Rolls 2008b, 2014, 2015; Grabenhorst et al. 2008b; Rolls et al. 2010; Deco et al. 2009; Rolls and Deco 2010; Rolls and Grabenhorst 2008; Grabenhorst and Rolls 2011). It is important to be able to represent the current

affective value of a stimulus on a continuum, and indeed the exact affective value on a continuum is an important input to the decision-making mechanism. However, the implication of the findings in that the decision-making mechanism is separate, for on a given trial, a binary decision, such as 'yes' vs. 'no' must be taken, and the outcome must be represented in a binary way. Indeed, decision-making is probabilistic, so that for two stimuli that are equally pleasant on a continuous scale, the decision on each trial will be different on a probabilistic basis. The understanding we have of this process is that each decision is represented in an attractor network by a separate attractor state, and that on an individual trial, the continuous value of the evidence biases the two attractors, and which attractor wins the competition depends on the probabilistic spiking of the neurons in the network (Wang 2002; Deco and Rolls 2006; Rolls 2008b, 2014; Rolls and Deco 2010; Deco et al. 2013).

C-Tactile (CT) Afferents and Light Touch

Light touch to hairy skin such as the forearm can activate CT afferents (i.e. C fibres with low mechanical thresholds) and can be pleasant, and such afferents are thought not to be present in glabrous skin such as the palm of the hand (Olausson et al. 2002; McGlone et al. 2007; Bjornsdotter et al. 2010). In an fMRI study, a contrast of the effects of rubbing the forearm vs. rubbing the glabrous skin of the hand revealed activation in the mid-orbitofrontal cortex (see Fig. 13.2) (McCabe et al. 2008). The implication is that the orbitofrontal cortex may be especially activated in relation to CT afferents vs. afferents from the glabrous skin. (The activation of the orbitofrontal cortex by this contrast was of significance, in that the effects of rubbing the glabrous skin of the hand were for most somatosensory cortical areas much larger than those produced by rubbing the forearm, which has a smaller cortical representation than the hand.)

In a different study, Olausson et al. (2002) showed in a neuronopathy patient who specifically lacks A-beta afferents that CT afferent stimulation can activate the insula, and such patients can have feelings of a pleasant touch, and sympathetic responses produced by the touch (Olausson et al. 2008). In our study, the contrast rubbing the arm vs. rubbing the hand also showed a region of activation in the insula ([−30 26 0]), though this was not significant ($Z = 2.04$) (McCabe et al. 2008).

An implication of these findings is that the pleasantness of CT stimulation may be related to activation of the medial/mid-orbitofrontal cortex, a region in which many other pleasant sensory stimuli are represented (Rolls and Grabenhorst 2008; Grabenhorst and Rolls 2011; Rolls 2014), and that CT stimulation can also produce activation of the insula (Olausson et al. 2002). It will be of interest to explore the role of CT afferents in pleasant touch further, though I note that they cannot have an exclusive role in affective touch, in that touch to the glabrous skin of the hand can be pleasant (McCabe et al. 2008). Indeed, it has been suggested that the pleasantness produced by stimulation of the glabrous skin of the hand is mediated by A-beta afferent fibres (McGlone et al. 2012).

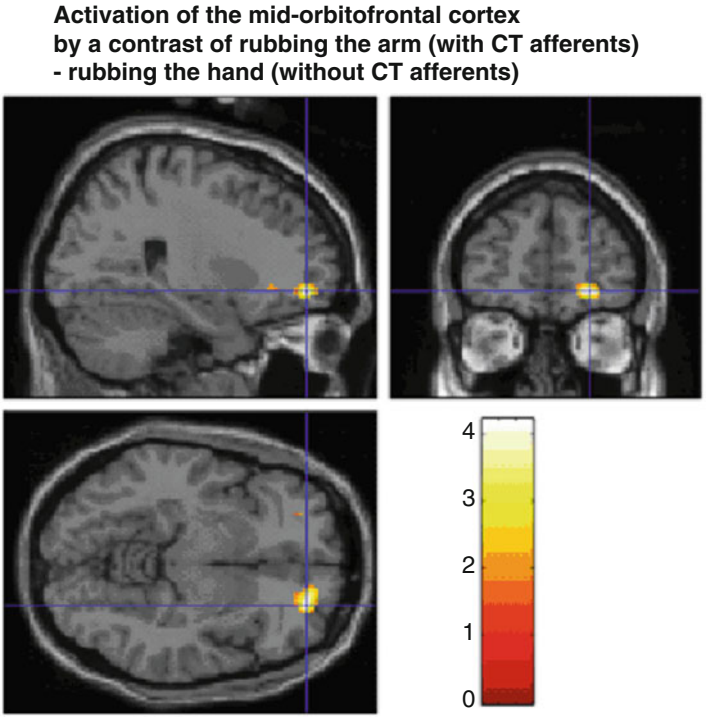

Fig. 13.2 A region of the mid-orbitofrontal cortex ([26 50 −8] $Z=3.18$, $p=0.035$ svc) was activated more by light touch to the forearm, which has CT afferents, than by light touch to the glabrous skin of the hand, which does not. The right of the brain is on the right of the coronal sections in this and subsequent Figures (After McCabe et al. 2008)

Cognitive Modulation of Affective Touch Processing

There have been many studies of the top-down attentional modulation (Rolls 2008b, 2013) of touch, with effects typically larger in secondary somatosensory and association cortical areas (e.g. parietal area 7), and smaller in S1 (Johansen-Berg and Lloyd 2000), and seeing unpleasant pictures can influence somatosensory evoked responses (Montoya and Sitges 2006). However, there has been little investigation of where high-level cognition influences the representation of affective touch in the brain.

To investigate where cognitive influences from the very high level of language might influence the affective representation of touch, we performed an fMRI study in which the forearm was rubbed with a typical skin lotion, but this could be accompanied by a word label that indicated that it was a rich moisturising cream (pleasant to most people) vs. a basic cream (McCabe et al. 2008).

We found that cognitive modulation by a label at the word level indicating pleasantness/richness ("rich moisturising cream" vs. "basic cream") influenced the representation of tactile inputs in the orbitofrontal cortex (McCabe et al. 2008).

(The cream was identical in all conditions in the study: it was only the word labels that were changed. The cream was rubbed onto the ventral, volar, surface of the arm, as illustrated in Fig. 13.4). For example, a negative correlation with the pleasantness ratings of the touch as influenced by the word labels was found in the lateral orbitofrontal cortex, a region shown in other studies to be activated by less pleasant stimuli including unpleasant odours, and losing money (O'Doherty et al. 2001; Rolls et al. 2003a, b). A positive correlation with the pleasantness of touch as influenced by the word labels was found in the pregenual cingulate cortex (McCabe et al. 2008). Convergent evidence on the functions of this region is that the pregenual cingulate region is close to (with peaks mm apart, and frequently with overlapping activations) where in different studies another somatosensory stimulus, oral texture, is represented (de Araujo and Rolls 2004), correlations with pleasantness ratings are found to food and olfactory stimuli (Kringelbach et al. 2003; de Araujo et al. 2005), and pleasant touch produces activation (Rolls et al. 2003b). We also found that activations to touch in the parietal cortex area 7 were influenced by the word labels, in that there was more activation when the rich label than when the thin label was present (as shown by a contrast analysis at the group level) (McCabe et al. 2008).

Activations to the Sight of Touch and Cognitive Modulation

The sight of touch can influence some areas involved in somatosensory processing including S1, S2, the inferior frontal gyrus and the parietal cortex (Blakemore et al. 2005; Schaefer et al. 2006). Indeed, it has been shown that somatosensory perception can be activated without actual touch but by imagery or empathy (Yoo et al. 2003; Singer et al. 2004; Bufalari et al. 2007) and also by the intention/anticipation of a touch (Carlsson et al. 2000).

We found that S1 was activated by the sight of the arm being rubbed with cream, in a region that overlapped with that activated by actually rubbing the arm. However, interestingly, activations were not produced by the sight of the arm being rubbed in the insular somatosensory areas in the mid-insula activated by the arm actually being rubbed (see Fig. 13.3) (McCabe et al. 2008). In the rubbing condition the stimulation will be related to one's own body, whereas in the sight condition it is less likely to be related to one's own body. The implication is that the insular activation is more closely related to body ownership, that is to the fact that one's own body is being rubbed, than is activation of S1. (However, under conditions of slow and social touch being seen to the arm, some insular activation has been found (Morrison et al. 2011).) It might be particularly interesting to follow up the finding of McCabe et al. (2008) in patients: are denials of ownership of a part of the body particularly related to damage to the insula as compared with damage to S1? Evidence using a rubber hand also suggests that insular activation may be related to body ownership (Tsakiris et al. 2007), whereas somatosensory cortex areas 1, 2, 3 was activated when the touch was not attributed to the self. Moreover, the study by Blakemore et al. (2005) showed that a synesthetic subject who felt touch whilst just observing

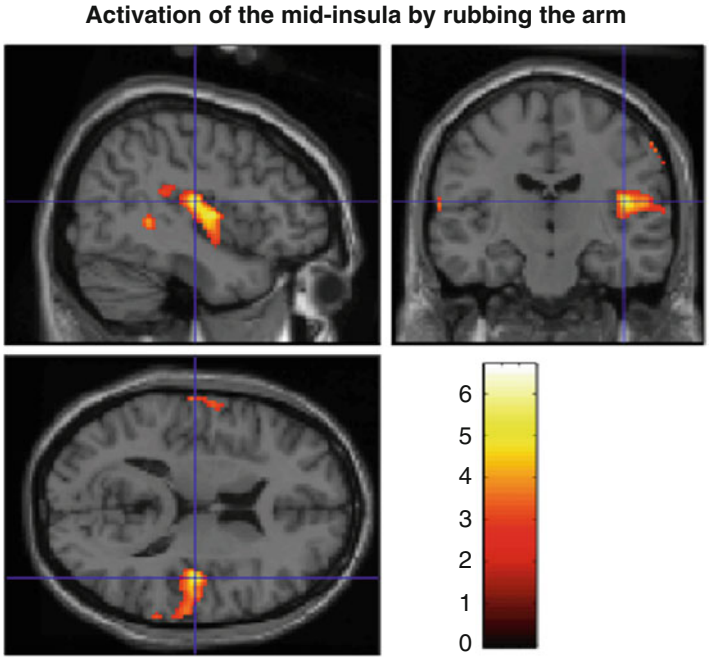

Fig. 13.3 Activations were produced by touch to the arm (rubarm condition) in the contralateral insula with peak at [44 −16 14] $Z = 3.83$ $p = 0.003$ fc. Activations were not produced in this region by the sight of the arm being rubbed (After McCabe et al. 2008)

touch had anterior insula activation whereas the control non-synesthetic subjects who did not feel touch as they observed touch did not have insular activation, again evidence for the insula being involved in recognition of touch to one's own body. The insula has also been described as a system involved in interoception (Craig 2002), but in our study the insular activation was produced by a thoroughly exteroceptive input, touch to the arm or hand. There was also activation in the lateral orbitofrontal cortex (area 47/12) which extended into the inferior frontal gyrus bilaterally (McCabe et al. 2008).

We may consider here the functions of some different parts of the insula. There are somatosensory areas that represent parts of the body in the mid- to posterior insula, as illustrated in Fig. 13.3 (McCabe et al. 2008; Baumgartner et al. 2010). The anterior and dorsal part of the primate including human insula includes the primary taste cortex (Pritchard et al. 1986; Yaxley et al. 1990; de Araujo et al. 2003; Kadohisa et al. 2005a; Rolls 2007a, 2015), but it also includes a representation of oral texture (Verhagen et al. 2004; de Araujo and Rolls 2004), so this might be thought of as an insular somatosensory area for the mouth which also contains the primary taste cortex. Having these taste and somatosensory oral representations in the same anterior insular cortex enables neurons to respond to combinations of oral texture and taste, which is important for enabling effects related to particular foods to be

computed (Rolls 2005, 2007a, 2008b, 2012, 2014, 2015). The anterior more ventral part of the insula may be a visceral cortical area, and consistent with this, this part of the insula has activations related to autonomic functions (Critchley et al. 2004; Critchley and Harrison 2013). Painful somatosensory stimuli, because they produce autonomic activity, may activate this anterior insular area.

To investigate how specific the sight of touch needs to be to evoke activity in somatosensory areas, we compared the sight of rubbing the forearm by a finger that was applying cream, with a close visual control condition which showed the finger moving 1 cm above the arm and clearly not touching the arm. This contrast showed effects in parietal area 7, the lateral orbitofrontal cortex perhaps continuing into the inferior frontal gyrus (see Fig. 13.4), and S1 (McCabe et al. 2008). This is of considerable interest, for it shows that these areas are activated particularly when the intention to touch is made clear in the stimulus, that is when the fingers are seen to be intentionally rubbing the arm, and not just moving facing upwards 1 cm above the arm clearly not intending to touch it. The close visual control we use provides evidence that these

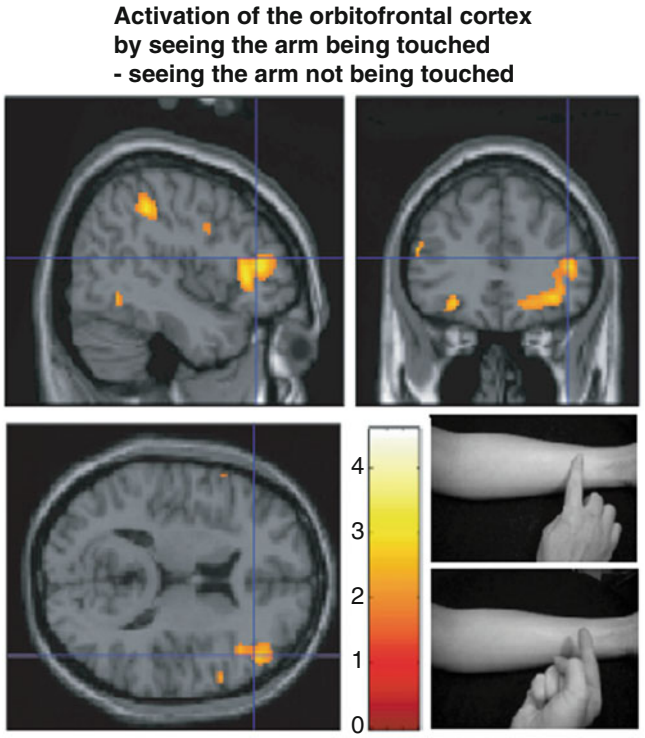

Fig. 13.4 The contrast Sight-Sightnotouch: a comparison of the effects of the sight of the arm being touched by an experimenter's finger vs. the sight of the arm not being touched in that the experimenter's finger was moved inverted and 1 cm above the image of the arm (as shown in the inset image). Effects were found in the contralateral orbitofrontal cortex area 47 at [42 30 −2] $Z = 3.45$ $p < 0.03$ and extended medially through much of the orbitofrontal cortex (After McCabe et al. 2008)

systems are very sensitive to whether intentionality to touch is implied by what is seen. Indeed, in our study the difference between the conditions indicated whether physical interpersonal contact was going to occur or not, and this could influence activations in all these areas. Because the moving stimuli were so similar, yet only one implied that touch was occurring, we interpret the effects as being related to the sight of touch, and not to the sight of the movement (McCabe et al. 2008).

Although other studies did not address so directly the issue of interpersonal touch, some investigations support our finding that intentionality can be important, by showing in the movement system that a movement seen in a context that implies an intention (to drink tea from a cup or clean the cup) produced more activation in the inferior frontal gyrus and premotor cortex than did seeing the same movement without a context-setting background (Iacoboni et al. 2005). A relation to intentionality is also implied by grasp-related mirror neurons in the macaque F5 that respond when a hand is reaching behind a screen to grasp a hidden object (Umilta et al. 2001), and by activation in the human inferior frontal gyrus occurring when there is a visible goal for a movement (Koski et al. 2002).

Interestingly, in our investigation this contrast, the sight of a finger rubbing an arm—the sight of a finger moving in a similar way but clearly not touching the arm—produced some activation in S1 (McCabe et al. 2008), implying that back projections from higher cortical areas (in e.g. the parietal cortex) can influence S1 when there is an evident intentionality to touch and touch is therefore being imagined. In another study without such a close visual control condition (because the contrast was between the sight of a body and the sight of an object being touched), S1 activations were found when touch to a body but not touch to an object was being seen (Blakemore et al. 2005). Consistent with the hypothesis that activation of S1 can be produced by imagining touch in our sight of touch condition, a neuroimaging study by Carlsson et al. (2000) showed that anticipation of tickling activated the primary somatosensory cortex. The visual input to the primary somatosensory cortex may have some useful functions, in that for example TMS of the primary somatosensory cortex impairs the usual visual enhancement of tactile acuity (Fiorio and Haggard 2005).

Positive correlations with pleasantness ratings to the sight of touch, which were being influenced by the cognitive word labels, revealed significant effects in the medial orbitofrontal cortex and the ventral striatum (see Fig. 13.5) (McCabe et al. 2008). Further evidence for cognitive modulation of affective representations of touch was found in a related area, the pregenual cingulate cortex, as shown by the contrast of the effects of the sight of touch when the label was "rich moisturising cream" vs. "basic cream". A negative correlation with the pleasantness of the sight of touch in the lateral orbitofrontal cortex bilaterally and extensively, and in the dorsal anterior cingulate cortex, was found (McCabe et al. 2008).

Interesting implications of these findings are that cognitive input produced by word-level descriptions can modulate the representations of the affective value of touch and of the sight of touch in areas such as the orbitofrontal cortex, anterior cingulate cortex, and ventral striatum (McCabe et al. 2008), where the pleasantness of many stimuli are represented. A similar modulation by cognitive labels that influence

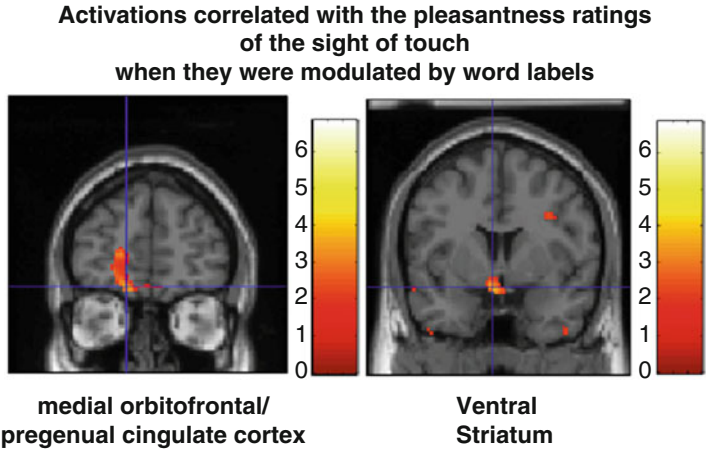

Fig. 13.5 Cognitive modulation of the affective value of touch. Correlations with the pleasantness of the sight of touch as influenced by the word labels "rich moisturising cream" vs. "basic cream" were found in the medial orbitofrontal/pregenual cingulate cortex ([−14 50 −16] $Z=2.97$ $p=0.02$) and ventral striatum ([−4 4 −14] $Z=2.95$ $p\approx0.05$) (After McCabe et al. 2008)

affective value is found for taste (Grabenhorst et al. 2008a), flavour (Grabenhorst et al. 2008a), and olfaction (de Araujo et al. 2005). What is fascinating here is that the cognitive modulation can reach right down into these sensory systems to modulate the activations at the first stage of processing that for several of these systems is the first stage at which the pleasantness is represented. Thus, the cognitive modulation appears to have a direct influence on the brain's representation of the affective value of stimuli, and these interactions are not left until purely cognitive or language-related processing systems in the brain, that is, there is a top-down effect of cognition on areas where the pleasantness of stimuli is represented (Rolls 2008b, 2013, 2014; Ge et al. 2012; Grabenhorst and Rolls 2010). The mechanism may be implemented by top-down biased competition in a way similar to that which appears to be involved in top-down attention (Rolls 2008b), though whole cortical processing streams may be biased by attention to affect vs. intensity (Rolls 2013, 2014; Ge et al. 2012; Grabenhorst and Rolls 2010). Further, affective cognitive modulation of sight of touch representations may help in processes such as empathy.

Oral Texture

Another somatosensory stimulus, the texture of food in the mouth, is also very important in perceived pleasantness. Neurophysiological studies have shown that the orbitofrontal cortex of primates is also important as an area of convergence for somatosensory inputs, related for example to the texture of food including fat in the mouth, with other sensory inputs. We have shown for example that single neurons

influenced by taste in the lateral and medial macaque orbitofrontal cortex (Rolls et al. 1990, 1996; Rolls and Baylis 1994; Critchley and Rolls 1996; Pritchard et al. 2005, 2007; Rolls 2008a, 2015) can in some cases have responses produced by the texture of the food. This was shown in experiments in which the texture of food was manipulated by the addition of methyl cellulose or gelatine, or by puréeing a semi-solid food (Rolls 1998, 1999), or by the astringent stimulus tannic acid (Critchley and Rolls 1996). It has been shown that some of these neurons with texture-related responses encode parametrically the viscosity of food in the mouth (using a methyl cellulose series in the range 1–10,000 cP), and that others independently encode the particulate quality of food in the mouth, produced quantitatively for example by adding 20–100 μm microspheres to methyl cellulose (Rolls et al. 2003c).

Texture in the mouth is an important indicator of whether *fat* is present in a food, which is important not only as a high value energy source, but also as a potential source of essential fatty acids. In the orbitofrontal cortex, Rolls et al. (1999) have found a population of neurons that responds when fat is in the mouth. The fat-related responses of these neurons are produced at least in part by the texture of the food rather than by chemical receptors sensitive to certain chemicals, in that such neurons typically respond not only to foods such as cream and milk containing fat, but also to paraffin oil (which is a pure hydrocarbon), and to silicone oil ($(Si(CH_3)_2O)_n$). Moreover, the texture channels through which these fat-sensitive neurons are activated are separate from viscosity sensitive channels, in that the responses of these neurons cannot be predicted by the viscosity of the oral stimuli (Verhagen et al. 2003; Rolls 2011). Behavioural evidence consistent with this comes from a study in rats (Ramirez 1994). Some of the fat-related neurons do though have convergent inputs from the chemical senses, in that in addition to taste inputs, some of these neurons respond to the odour associated with a fat, such as the odour of cream (Rolls et al. 1999). Feeding to satiety with fat (e.g. cream) decreases the responses of these neurons to zero on the food eaten to satiety, but if the neuron receives a taste input from, for example, glucose taste, the response to the taste of glucose is not decreased by feeding to satiety with cream (Rolls et al. 1999; Rolls 2014). Thus, there is a representation of the macronutrient fat in this brain area, and the activation produced by fat is specifically reduced by eating fat to satiety.

The pleasantness of oral fat texture is represented in the orbitofrontal cortex and anterior cingulate cortex, as shown in an fMRI investigation using high and low fat dairy products (Grabenhorst et al. 2010). The soft pleasant feel of fat in the mouth is reminiscent of the soft pleasant feel produced by gentle rubbing of the forearm that is associated with the activation of CT fibre afferents. It is an interesting hypothesis that the texture of fat in the mouth might involve CT afferents.

Fat texture, oral viscosity, and temperature, for some neurons in combination with taste, are represented in the macaque primary taste cortex in the rostral insula and adjoining frontal operculum (Verhagen et al. 2004).

These oral sensory properties of food, and also the sight and smell of food, are also represented in the primate amygdala (Kadohisa et al. 2005a, b; Rolls 2000; Rolls and Scott 2003). Interestingly, the responses of these amygdala neurons do not correlate well with the preferences of the macaques for the oral stimuli (Kadohisa

et al. 2005a), and feeding to satiety does not produce the large reduction in the responses of amygdala neurons to food (Rolls 2000; Rolls and Scott 2003) that is typical of orbitofrontal cortex neurons (Rolls 2006, 2007a). Multidimensional scaling analyses of the spaces encoded by neurons suggest that the amygdala emphasises texture (oral viscosity), and the orbitofrontal cortex sweet taste stimuli (Kadohisa et al. 2005a).

The viscosity of food in the mouth is represented in the human primary taste cortex (in the anterior insula), and also in a mid-insular area that is not taste cortex, but which represents oral somatosensory stimuli (de Araujo and Rolls 2004). In these regions, the fMRI BOLD activations are proportional to the log of the viscosity of carboxymethyl cellulose in the mouth. Oral viscosity is also represented in the human orbitofrontal and perigenual cingulate cortices, and it is notable that the perigenual cingulate cortex, an area in which many pleasant stimuli are represented, is strongly activated by the texture of fat in the mouth and also by oral sucrose (de Araujo and Rolls 2004).

Oral Temperature Representations in the Brain

It has been discovered that some neurons in the orbitofrontal cortex reflect the temperature of substances in the mouth, and that this temperature information is represented independently of other sensory inputs by some neurons, and in combination with taste or texture by other neurons (Kadohisa et al. 2004).

Until recently, no neuroimaging study had investigated whether changes in oral temperature activate these areas in humans, or the activity of middle or posterior insular cortex, the areas most frequently identified in neuroimaging studies for the encoding of temperature information from the human hand. To analyse the representation of oral temperature in the human brain, we conducted an fMRI study to identify areas of activation in response to temperature-controlled (cooled and warmed, 5, 20 and 50 °C) liquid introduced into the mouth (Guest et al. 2007). The results showed that the oral temperature stimuli activated the insular taste cortex (identified by glucose taste stimuli), a part of the somatosensory cortex, the orbitofrontal cortex, the anterior cingulate cortex, and the ventral striatum. Brain regions where activations correlated with the pleasantness ratings of the oral temperature stimuli included the orbitofrontal cortex and pregenual cingulate cortex. We conclude that a network of taste- and reward-responsive regions of the human brain is activated by intra-oral thermal stimulation, and that the pleasant subjective states elicited by oral thermal stimuli are correlated with the activations in the orbitofrontal cortex and pregenual cingulate cortex.

Thus, somatosensory and temperature inputs from the oral cavity provide information about the texture and temperature of stimuli in the mouth in a number of brain regions, and in regions such as the orbitofrontal cortex represent the palatability and affective value of the food, and are thus important in appetite control (Rolls 2005, 2007a, b).

In conclusion, exciting discoveries are being made at present about the affective representations of touch and their cognitive modulation. The affective value of touch is represented particularly in brain regions such as the orbitofrontal and anterior cingulate cortices. In these regions, cognitive inputs from as high as the word level can influence the affective representations, showing that cognition can influence the pleasantness or unpleasantness of touch by modulating activations to touch in some of the first cortical regions where the affective value of touch is represented. The same regions can be influenced by the sight of touch, emphasising the contribution of the visual as well as the somatosensory modality to the affective value of touch and how this is represented in the brain. Multimodal inputs have been shown to be very important for oral aspects of touch, with somatosensory inputs that contribute to the texture and mouth feel of food including fat being combined in these orbitofrontal and anterior cingulate cortical areas, and also the insular taste cortex, with taste and oral temperature inputs (Rolls 2007a, 2008a). All of these somatosensory and taste inputs combine further with visual and olfactory inputs in the orbitofrontal cortex to produce a multimodal representation of the affective value (pleasantness) of the sensory properties of food. These representations of affective value are in turn important in decision-making (Rolls 2008b, 2014).

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Chapter 14
Social Touch

Alberto Gallace and Charles Spence

Abstract The more social aspects of touch, despite their relevance to numerous domains of human behavior, from cultural anthropology to cognitive neuroscience, and from virtual reality through to linguistics, have not been extensively studied by scientists. That is, psychologists and neuroscientists are only now beginning to uncover some of the neurocognitive mechanisms responsible for these important real-world interactions. In this chapter, we summarize the latest developments in this field of research. In particular, we highlight a number of studies where touch, no matter whether direct or mediated by technological devices, has been shown to affect our behavior, as well as our physiological reactions. We show how this sensory modality often acts as a powerful interface allowing us to interact socially and emotionally with the world around us. The available research also suggests that touch plays an important role in supporting our well-being.

Keywords Touch • Interpersonal • Well-being • Neuroscience • Technology • Social

Introduction

It takes nothing more than a caress, be it tender or erotic, to remind us of the importance of social touch to our everyday lives. That said, experimental psychologists and cognitive neuroscientists are only now beginning to uncover some of the cognitive and neural mechanisms underpinning this most important aspect of our behavior. Surprisingly, however, this increased scientific interest in the study of the more social aspects of touch has been paralleled by a global trend toward there being less social touch in our everyday public interactions. Indeed, it has long been suggested

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that many industrialized societies are drifting toward a state of 'touch hunger' (see Field 2001), where tactile interactions are limited and often actively inhibited or even prohibited (for fear of harassment claims or litigation).

The study of the more social aspects of touch is relevant to many different disciplines, including cultural anthropology, social psychology, physiology, the neurosciences, and linguistics among many others. Given such a complex array of relevant research fields, and the fact that a truly interdisciplinary approach to the study of touch still has not been fully developed, it is not so surprising to observe that social touch has received far less attention than the study of many other topics in psychology. Moreover, it should also be borne in mind that touch is actually one of the least well studied of the senses (especially if one compares it with the far greater number of studies that have been conducted on vision and audition; see Gallace and Spence 2014, for a review). Even today, it would seem as though many of the same factors that have prevented us from increasing the incidence of tactile social interactions in public social situations have also been responsible, at least in part, for the slow rate of progress of academic research in this field. That is, asking people to touch each other in order to study the neurocognitive mechanisms underpinning tactile social processing can be seen to be a rather delicate matter, at least from an ethical standpoint (not to mention the limited ecological validity of a study where people are not free to touch or be touched by whomever they want). Surprisingly, however, there are perhaps more studies on the topic of sexual behavior than there are on the topic of public social touch. Moreover, even within the tactile modality itself, there has been far more research on the sensory/discriminative properties of touch, than on the more social/hedonic properties (see Gallace and Spence 2010, 2014; Kitada et al. 2010a, b).

The possibility of using machines that are capable of reproducing, at least electromechanically, certain patterns of tactile stimulation across the surface of the human skin has certainly provided a promising starting point for the development of this field of research (e.g., Essick et al. 2010). Note, however, that while we are now, at least in principle, able to simulate certain kinds of tactile sensation successfully (e.g., the amount of pressure, the speed, etc.), our knowledge on this topic is still far from sufficient when it comes to knowing what cues need to be provided or what exactly should be simulated and how, in order to deliver certain specific sensations. At the moment, it is not even clear whether certain kinds of tactile stimulation can exert the same effects within a social context when reproduced mechanically/digitally (e.g., Haans et al. 2007; Haans and IJsselsteijn 2006; Haans et al. 2008; see also Gallace and Spence 2010, 2014 for reviews).

Over the last few decades, many studies have addressed the cognitive and neural correlates of tactile information processing (see Gallace 2012; Gallace and Spence 2014; Hertenstein and Weiss 2011, for reviews), demonstrating that touch and the skin provide an important means of differentiating ourselves from the external world. Where touch begins we are, one might say. However, touch not only provides a protective function (together with the pain system) by informing us about potentially dangerous stimuli, it also acts as a powerful interface that allows us to interact socially with the world at large. In this chapter, we will examine how this occurs and what the putative mechanisms are that allow us to interpret, at least from a social point of view, those signals impinging upon the body surface.

Social Touch from Birth (and Earlier) Through to Old Age

Touch is the first sense to develop within the womb (e.g., Montagu 1978). In fact, a 6-week-old embryo can already perceive and respond to various tactile stimuli (e.g., Atkinson and Braddick 1982; Bremner et al. 2012). This early development is especially impressive if one considers the fact that many more weeks of maturation are required before the other senses really start to develop. Early tactile interactions have also been reported to occur between twin fetuses in the womb itself (Castiello et al. 2010). In fact, Castiello and his colleagues documented the occurrence of movements aimed at touching the co-twin starting from the 14th week of gestation. Even after birth, when the newborn's sight is still very poor (e.g., Atkinson and Braddick 1982), touch offers the very first means of contact and interaction with the outside world. The very first examples of pleasant and comforting sensations in our life are mediated by touch. Given that the human baby is, from a functional and anatomical point of view, critically undeveloped with respect to other mammals (and thus requires a much higher level of parental care), it is natural that these early forms of interaction must be social in nature. The automatic hand closure response seen in babies in response to those objects that are placed in their palm is certainly an important mechanism for helping the developing newborn to determine the nature of external stimuli. However, the fact that this behavior can also be observed when the feet of a newborn baby is touched (e.g., Zappella 1967) would seem to suggest a somewhat different evolutionary role: That is, this behavior might also carry an important social function. In fact, baby primates use this automatic grasping behavior in order to cling on to their mother's fur. Thus, maintaining the physical contact with the caregiver (and the level of comfort mediated by that) can probably be seen as one of the most important functions in the early stages of human development.

The possible importance of touch in human babies has been hinted at by a series of controversial studies conducted by Harry Harlow (e.g., Harlow 1958; Harlow and Zimmerman 1959). Harlow and his team removed baby rhesus monkeys from their mothers, and assigned them to a couple of surrogate mothers, one made of terrycloth (that did not provide any food) and the other, of metal wire, that did provide sustenance. He observed that the baby monkeys spent the majority of their time on the terrycloth mother, even though it didn't provide them with any nourishment. Moreover, those baby monkeys who were assigned to wire-only mothers suffered from diarrhea more often, and what is more, had more trouble digesting their milk. On the basis of these results, Harlow went on to conclude that the lack of social tactile contact is extremely stressful, at least for this mammalian species (but, by extension, for others too). Even if one ignores the oft-cited ethical concerns related to this study, whether or not its results can be extended to humans remains rather unclear (see also Edelmann et al. 2013, for a recent study on the role of maternal touch on the juvenile social play behavior of rodents).

Different studies have attempted to investigate the role of early tactile deprivation on different biological, cognitive, and social functions. It is important to note here that regardless of the results obtained, all of this research has tended to concentrate on

those unfortunate children who have had to live for some period of time in orphanages that were deemed to have provided a very substandard level of care. As a consequence, it is impossible to determine whether any difference between these children and those who had been raised in a more standard and socially rich environment might have been due to the lack of tactile contact, or rather, to the more general sensory, social, and cognitive deprivation that they suffered. Therefore, on the basis of these studies, no scientific conclusions can be drawn regarding the importance of early tactile interactions on the cognitive and social development of humans.

Evidence regarding the importance of tactile contact at an early stage of life in humans comes from the study of the 'kangaroo care method.' This technique is commonly used in developing countries. The method was developed back in the 1970s by one Dr. Edgar Rey Sanabria in Bogotà, Colombia, in order to address a shortage of incubators and medical personnel and it mainly consists of maintaining skin-to-skin contact between the newborn baby and the mother or father (see Rodgers 2013, for a recent review). Even if its initial purpose was to provide warmth, nutrition, and to enhance the likelihood of an early hospital discharge for low-birth-weight babies, further research studies have demonstrated that it results in improved neonatal signs in terms of heart rate, respiratory rate, sleep, pain relief, and neurobehavioral general development (e.g., Ludington-Hoe et al. 2008). That is, early tactile social contact seems to provide a very important role in the normal functioning of the organism during the earliest stages of human development.

Interestingly, tactile social contact is not only relevant at this point in human development, but throughout the lifespan, that is, from childhood through to old age (Field 2001). For example, it has been suggested that in adults social touch may contribute to the maintenance of longer lasting relationships (probably due to its effect on oxytocin release; see the section below; e.g., Gulledge et al. 2007; Holt-Lunstad et al. 2008). Tactile stimulation also seems particularly relevant to the growing aging population, who often complain about the fact that fewer and fewer people want to touch them as they become old and wrinkly (note how this contrasts with the desire to touch the skin/cheeks of new born babies; e.g., see Field 2001). So, for example, one study reported by Eaton et al. (1986) hints at the important role that social tactile contact might play in improving the condition of institutionalized elderly individuals. They found that when the service staff who were caring for these patients combined their verbal encouragement to eat with tactile contact, the individuals concerned consumed significantly more calories and protein.

Social Touch at Work

It has been demonstrated that tactile social interactions, even if they go unnoticed (or else are not particularly relevant to the context in which they occur), can exert a very powerful effect in a person's evaluation of a given situation, or else in eliciting certain kinds of behavior. For example, people become more

compliant with requests when they are touched by another person than when they are not touched (this phenomenon is known as the 'Midas touch effect'; e.g., Crusco and Wetzel 1984). However, within certain contexts, touch can obviously also have negative consequences on our behavior or judgments. So, for example, Martin (2012) reported that those individuals who were touched by another customer when examining the merchandize in a store evaluated the products more negatively than did those customers who weren't touched. That is, the context in which touch takes place can have a powerful effect on the evaluation of the tactile stimulation itself (Gallace and Spence 2014). Interestingly, this seems to apply both to the more perceptual and to the more social aspects of touch (see McCabe et al. 2008; for an elegant study showing how the affective experience of touch and the sight of touch can be modulated by higher order cognitive evaluations).

The role of context (e.g., where the touch originates from) in affecting the perception of social touch has been highlighted by an intriguing study by Gazzola and her colleagues. These researchers delivered the same pattern of tactile stimulation, consisting of a series of caresses administered to the shin and calf to a group of male participants while they viewed different visual displays (Gazzola et al. 2012). In particular, the participants were told that the touch was administered by the person that they could see in the video. In one condition, the video portrayed an attractive woman wearing a black evening dress and high heels, while, in the other, a man was shown wearing a black tank top and jeans. These researchers reported that not only was the tactile stimulation perceived differently (in term of its pleasantness) as a function of the context in which it appeared to have been presented, but that even the activity of one of the brain areas involved in the early processing of tactile information (i.e., the somatosensory cortex) was modulated by these higher order cognitive factors.

The observations reported in this section clearly highlight the important role that social touch can play in driving human behavior, whether we realize it or not. However, by analyzing these studies one cannot fail to notice that when attempting to study the topic of social touch, researchers need to move from more laboratory-based situations to more ecologically valid contexts. From a scientific point of view, this certainly becomes problematic. In fact, more ecologically valid situations are obviously going to lack the control over a number of important variables that might well be expected to affect one's results (such stimulus control can obviously be more easily guaranteed in the case of laboratory-based experiments). At the same time, one can only wonder about how a very controlled laboratory study, such as one in which the participant has to lie completely still and immobilized in a fMRI scanner (with their head clamped still), while a stranger touches them, can be considered as somehow being similar to any real life tactile social interaction (see also Komisaruk et al. 2004; Mallick et al. 2007; for examples of studies on human sexual behavior conducted in the fMRI scanner).

The Neural Basis of Social Touch

Despite of the fact that many different studies have investigated the neural basis of tactile sensory processing, a surprisingly small number of researchers have actually addressed the neural mechanisms underlying our perception of the more social aspects of touch. In one of the few examples of this kind of research, Schaefer et al. (2013), analyzed, by means of fMRI, the responses of the primary somatosensory cortex (S1) of their participants while they watched video clips showing simple nonpainful tactile stimulation being delivered to another person's hand. These researchers reported that a part of this brain area, one that generally responds to the tactile stimulation delivered to the participant's own body, would actually also respond to the observation of touch being delivered to another person (see also Blakemore et al. 2005; Bolognini et al. 2012; McCabe et al. 2008, for similar results). Previous studies have demonstrated that, in certain individuals, such neural activation can also give rise to a conscious perception of touch on their own body, a phenomenon known as mirror-touch synesthesia (see Blakemore et al. 2005; though see also Deroy and Spence, in press). Here, though, it should be noted that it remains somehow unclear whether the activation of S1 observed by Schafer and his colleagues was related to a 'social neural mirror system' that responds to the tactile stimulation seen occurring to another individual, or whether instead it may merely reflect the mental imagination of the effects that the touch seen on the screen might have on a participant's body (Spence and Deroy 2013). In fact, in a previous study, the same research team documented a correlation between the personality dimension of 'perspective taking' (the extent to which someone cognitively imagines a situation from the other person's point of view; e.g., Furlanetto et al. 2014) and the activation of S1 due to the sight of tactile contact (Schaefer et al. 2012).

Interestingly, Schaefer and his colleagues (2013) in their study also found that the observation of touch resulted in activation in the insular cortex, a part of the brain that is involved in self-awareness. That is, it would seem as though when people watch tactile stimulation in others the systems involved in differentiating the self from other needs to be actively maintained. Taken together, then, these results would seem to suggest the presence of an important link between the neural systems that are responsible for the processing of tactile information and those supporting the difference between self and others, a critical function at the basis of any social interaction (e.g., Moseley et al. 2012).

Indirect evidence on the role of social touch on neural processing comes from a study by Teneggi et al. (2013). Following on from the observation that a sound can affect tactile processing when presented within peripersonal space, these authors asked their participants to detect a tactile stimulus that was presented on their face while concurrent task-irrelevant sounds were heard to approach toward or recede from their face. They then calculated the critical distance at which auditory stimuli speeded up the participants' tactile reaction times (RTs) and considered this distance to be the boundary of peripersonal space. Taneggi et al. found that peripersonal space is modulated (i.e., shrinks) when another individual faces the participant. These results would therefore seem to suggest that social factors affect the functioning of

neural systems that are responsible for maintaining a representation of a person's peripersonal space (see also Graziano and Cooke 2006; Spence 2011).

One of the most promising fields of investigation within research on social touch is likely going to be related to the relatively recent discovery of a new class of tactile fibers in humans, known as C-Tactile (CT) afferents(e.g., see Löken et al. 2009; McGlone and Spence 2010). These fibers, which are found in the hairy, but not in the glabrous skin, respond optimally when the skin is stroked at a speed of about 1–10 cm/s, a stimulation that can resemble a caress (e.g., Bessou et al. 1971; Iggo 1960; Olausson et al. 2008). These fibers would seem to be associated with the perception of the more pleasant aspects of tactile stimulation. It has even been suggested that the C-Tactile fibers constitute part of a neural system responsible for the maintenance of physical and social well-being in humans (e.g., Björnsdotter et al. 2010; Morrison et al. 2009; see also Cascio et al. 2012; Marco et al. 2012; McGlone et al. 2007, for the possible link between tactile processing and autism—a disorder including abnormalities of social behavior—in humans). Interestingly, it has been shown that a reduction in the density of thin and unmyelinated nerve fibers, including the C afferents, can result in a perceived reduction in the pleasantness of tactile stimulation (Morrison et al. 2011b). Moreover, the patients affected by this lack of neural fibers rate tactile stimuli seen in short videos depicting the stroking of on another person's forearm as less pleasant.

The presence of the CT fibers in humans, and their apparent involvement in the perception of the more pleasant aspects of our behavior, certainly provides some evidence concerning the importance of affiliative social interactions in the tactile modality. This crucial role of tactile interactions in our social behavior is also supported by a number of studies that have been conducted on couples. It has been reported that those women who received physical contact from their partners before a stressful situation exhibit significantly lower cortisol and heart rate responses to stress (e.g., Ditzen et al. 2007). As far as the areas of the brain responsible for the processing of the signals resulting from the activation of CT afferents is concerned, a recent study by Gordon et al. (2013) has shown that the gentle stroking of the arm as compared to the stroking of the palm of the hand (an area of the body that isn't innervated by CT afferents) resulted in the activation of the posterior insula, as well as a network of areas that are known to be involved in social perception and social cognition (comprising the right posterior superior temporal sulcus, the medial prefrontal cortex, and the dorsoanterior cingulate cortex; see also McGlone et al. 2012; Morrison et al. 2011a).

Here, it is important to note that many effects of social touch on behavior and physiological responses are likely mediated by hormonal mechanisms. In fact, it has been demonstrated that tactile stimulation, be it of a sexual or nonsexual nature, induces the release of oxytocin (e.g., Shermer 2004; Williams et al. 1992), a hormone that has been implicated in human and animal bonding behavior (e.g., Bales and Carter 2003; Schneiderman et al. 2012). This hormone is also informally known as the 'cuddle hormone' (e.g., http://news.bbc.co.uk/2/hi/health/8653500.stm downloaded on 06/08/2013). Interestingly, the relationship between tactile processing and hormone release would appear to be a two-way one. That is, tactile sensations certainly affect the release of hormones, but the perception of touch can also be affected by hormone release. So, for example, during the refractory period (this is the name given to the period of time immediately following orgasm) males expe-

rience tactile hypersensitivity in the glans of the penis (Yilmaz and Aksu 2000; see also Humphries and Cioe 2009, for the report of a similar phenomenon in some women). This sudden change in sensitivity results in tactile stimuli applied to this region being perceived as highly aversive and seems to be related to the localized release of prolactin following orgasm (Krüger et al. 2003). Prolactin is sometimes referred to as the 'paternity hormone,' and its release seems to play an important role in limiting and controlling human sexual behavior.

The Development of Mediated Social Touch for the 'Internet Generation'

Many of our daily activities, such as buying groceries or consulting a library archive can be now performed from the comfort of our desk or sofa, that is, without the need to leave our own homes. The rapid growth of the internet has certainly changed our lives in many ways and especially our way to communicate with other people. There is nothing like a Tweet or a post on one's Facebook profile to spread the news about one's latest holiday exploits or even about a recent trip to the doctors. In fact, there isn't a single aspect of our life that cannot be shared with friends or strangers with the click of a mouse. That is, social media allow our thoughts to reach an incredible number of people more quickly than ever before (see Spies and Margolin 2014, for a discussion on the diffusion of social media among adolescents). Researchers have even shown that the use of the internet may be beneficial for reducing loneliness and increasing social contact among older adults in assisted and independent living communities (e.g., Cotton et al. 2013; Park et al. 2013). It should come as little surprise, then, that different kinds of media allow for the emergence of very different kinds of social interaction. Some of these interactions, such as, for example, internet chats, are limited to written contents. In this case, the lack, or insufficiency of the social context for interpreting certain expressions, has somehow been fixed by means of simple symbols that can immediately add some social or emotional meaning to a sentence, namely, the 'emoticons' (e.g., Ganster et al. 2012).

Other forms of internet-based communication provide the possibility of communicating by means of a virtual counterpart of our body, what is called an 'avatar.' This is the case for software such as 'Second Life,' where an individual can control his/her own customized avatar and use it in order to perform actions and communicate with other people's avatars within the context of a virtual world (e.g., Wagner 2008; see also Ward 2007). Despite the big improvement that the latter forms of interactions would seem to provide (they may offer the possibility of expressing ourselves by means of a virtual counterpart to our actual body), watching a mannequin shaking hands, nudging, or even making love with another mannequin is certainly far from what can be called a realistic and rewarding social interaction. That is, tactile contact is so far lacking in all forms of internet-based communication, comprising those occurring within virtual worlds.

Importantly, some attempts to fill this gap have started to emerge over the last decade. One example of a device that has been developed to provide mediated

social touch is certainly the hug-shirt. More recently, an internet-connected jacket, named "Like-A-Hug," which inflates to give the wearer a hug every time a Facebook friend "likes" a status update or photo has been developed (see http://www.huffingtonpost.com/2012/10/15/like-a-hug-jacket-embrace_n_1942421.html downloaded on the 08/08/2013).

As one can easily imagine, none of these devices has yet spread over a large section of everyday internet users. Most of them actually never hit the market and can only been described as advanced prototypes or perhaps as engineering case studies. The lack of appeal of these devices is probably not only due to their inadequacy in terms of delivering believable tactile social interactions, or to the fact that they fail to capture some fundamental aspects of social touch, but also to their inability to reproduce a multisensory context that is congruent with the large majority of our social interactions. That is, holding a mouse (even if it vibrates when someone else wants to communicate with us; see Gallace et al. 2007) is most likely going to activate our brain's memory networks related to PC working activities rather than memory traces related to embracing or caressing a spouse or partner.

Perhaps the only systems that have witnessed some form of success among the WWW population are those known as 'teledildonics.' These are electronic sex toys that can be controlled by a computer and allow physical tactile sexual stimulation to be transmitted over a distance (e.g., Machulis 2006; see also Bardzell and Bardzell 2011). However, the success of these devices is perhaps attributable more to their ability to create new forms of mediated sexual interactions than to their ability to reproduce all of those sensations that can be experienced during real intimate contacts. Think about one of the classic scenes in erotic literature or movies, the use of an ice cube to arouse someone (a scene that also appeared in the 2015 controversial but very popular movie '50 Shades of Grey'). Despite its clear power, to date no technology can so far allow to reproduce something similar to that. Even more importantly, the mechanisms eliciting such strong sensations are far from being fully understood by researchers. In fact, the majority of the teledildonics devices that have been developed so far limit the delivery of tactile stimulation to the genital regions. It should, however, be said that the stimulation reproduced by these devices is now more than ever before based on the results of those studies that analyzed the tactile innervation of the genitals and the neural responses to their stimulation.

Conclusions

As this brief review of the literature will hopefully have made clear, the area of social touch is important, albeit understudied, and what is more it plays a crucial role from long before our birth through to our last moments on planet earth. Researchers are still making many exciting discoveries regarding this understudied sense, be it CT afferent fibers, or the relationship between tactile contact and the release of hormones. These discoveries are now becoming increasingly important due to the diffusion of internet-based social media. In fact, most of these new means of communication

do not (at the moment at least) allow for the occurrence of tactile contact, with potentially important effects on our social relationships and even on our well-being. In order for significant progress to be made, a multidisciplinary approach will be extremely important within this field of research in the years to come.

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Chapter 15
The Neurochemical Basis of Motivation for Affiliative Touch

Guro Løseth, Siri Leknes, and Dan-Mikael Ellingsen

Abstract Affiliative touch interactions are often rewarding. They can on one hand alleviate stress and negative affect, while on the other hand induce intense feelings of pleasure. The behavioral nature of touch interactions (e.g., soothing soft touch or rough-and-tumble play) is often very different depending on whether the motivation for touch is primarily relief of negative affect or social exploration and joy, which is guided by the individual's underlying needs. Here we discuss the central neurochemistry involved in motivation for affiliative touch interactions, with a focus on the mu-opioid receptor (MOR) and oxytocin systems. While both of these neurochemical systems play critical roles in various aspects of social affiliation, there are inconsistencies regarding their specific role in driving motivation for social touch interactions. We discuss this in the light of test subjects' motivational state (distress or comfort) and appraisal of the situational context, and propose that many of these apparent discrepancies can be resolved by accounting for these factors.

Keywords Opioid • Oxytocin • Social motivation • Social touch • Affective touch • Affiliative touch • Neurochemistry • State dependent • Motivational state • Social reward

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Introduction

Throughout the life span of social animals, touch fosters and communicates intimacy and cooperation (Hertenstein et al. 2006). Even brief experiences of touch can increase pro-social behaviors in humans (Gallace and Spence 2010), and touching and mutual grooming between romantic partners are related to feelings of intimacy, relationship satisfaction, and trust (Gulledge et al. 2003; Nelson and Geher 2007). Tactile interactions such as grooming, huddling, and playing are common in most mammalian species and aid establishment and maintenance of social, romantic, sexual, and parental relationships across mammalian taxa (Figs. 15.1a–c and 15.2a–c). One candidate for transmitting affective touch signals from the skin is C-tactile afferents (McGlone et al. 2014). These low-threshold unmyelinated skin afferents activate primarily in response to light, gentle, slowly moving touch, and their firing rates correspond closely to pleasantness ratings across different velocities of slowly moving touch (Löken et al. 2009). Moreover, C-tactile afferents fire most vigorously in response to touch stimuli delivered at normal skin temperature, but less to colder or warmer stimuli, which again corresponds closely to pleasantness ratings (Ackerley et al. 2014).

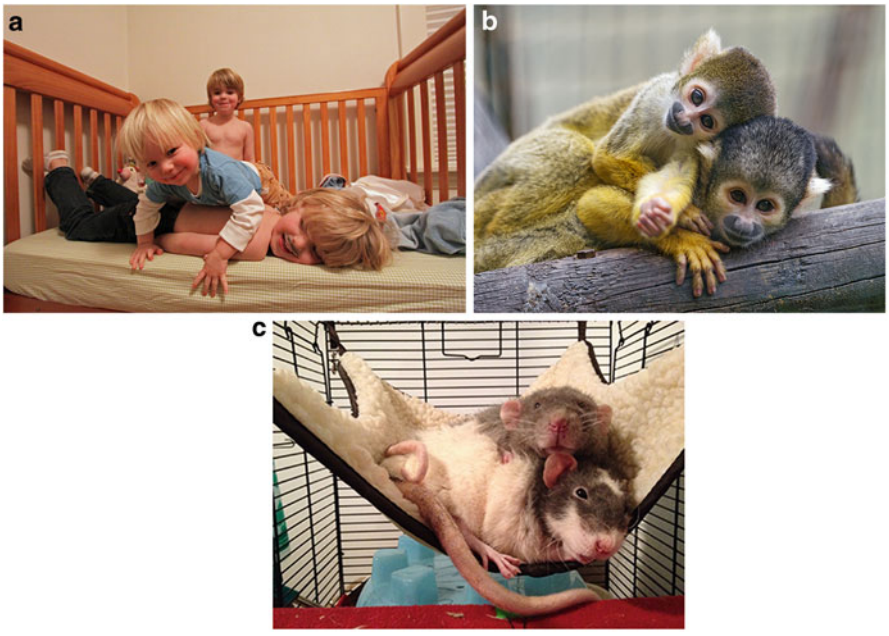

Fig. 15.1 (**a**–**c**) Touch and physical closeness is a central component in affiliative behavior for most mammalian species. (**a**) Lucia, Jessica. Puppies. Flickr.com. https://www.flickr.com/photos/theloushe/4366827800/in/photostream; February 18, 2010. Accessed January 28, 2016. (**b**) The Jaguar, Tambako (Keller, Emmanuel). Two cute friends! Flickr.com. https://www.flickr.com/photos/tambako/16009831076; December 16, 2014. Accessed March 30, 2016. (**c**) Clinesmith, Brad. Rats in a hammock. Flickr.com. https://www.flickr.com/photos/macgodbrad/6247055081; October 15, 2011. Accessed March 30, 2016

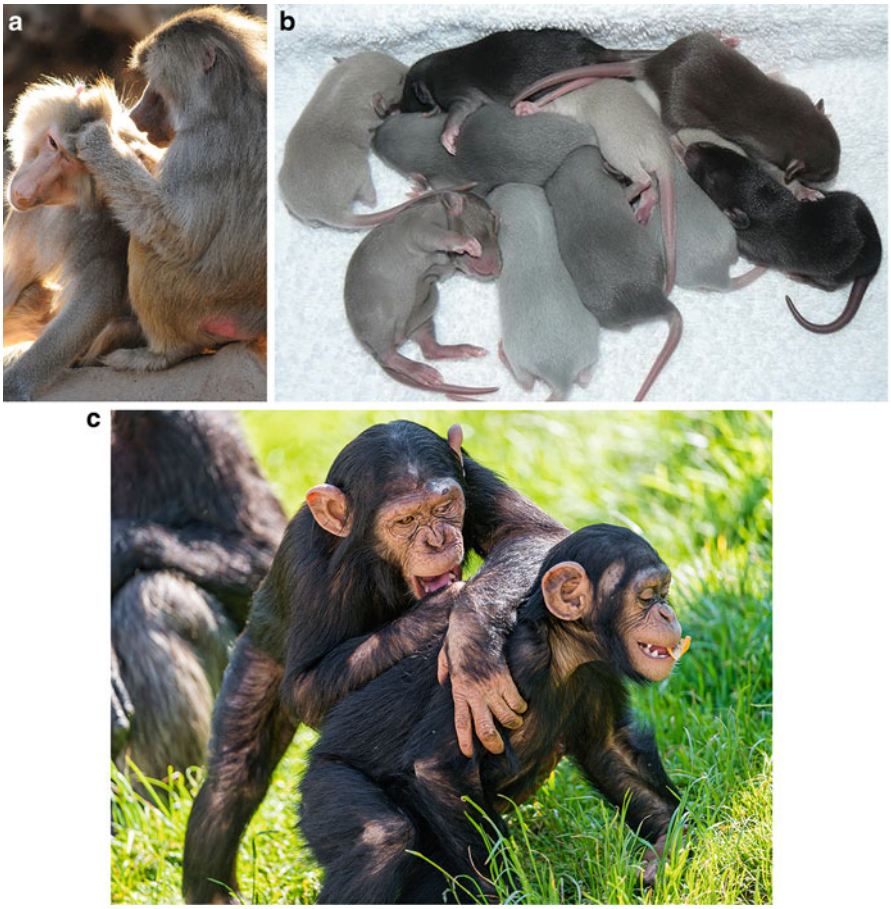

Fig. 15.2 Affiliative touch interactions in mammals. (**a**) Social grooming in primates involves sweeping through someone else's fur with hands and lips and removing impurities—the relaxing effect can be measured physiologically, e.g., reduced heart rate (Dunbar 2010), as well as behaviorally, e.g., reduced stress-related scratching (Schino et al. 1988). (**b**) Huddling (motionless physical contact) typically occurs when animals are resting side by side. This mediates pair bonding in adult prairie voles (Burkett et al. 2011) and sibling bonding in rat pups (Alberts 2007); aids infant well-being in primates (Harlow and Zimmermann 1959), and homeostatic regulation in infant rodents (Nelson and Panksepp 1998). (**c**) Social play, such as wrestling and tickling, involves a great deal of tactile contact, and inhibiting the sense of touch with a local anesthetic significantly reduces playing in juvenile rats (Siviy and Panksepp 1985). Play interactions involve expressions of positive affect, such as laughter (Vettin and Todt 2005; Davila Ross et al. 2009) and positive USVs (Panksepp and Burgdorf 2003, 2000; Burgdorf et al. 2005), and help establish social organization and interaction patterns in human and nonhuman primates (Maestripieri and Ross 2004; Palagi et al. 2004; Mancini and Palagi 2009; Cordoni and Palagi 2011; Norscia and Palagi 2011; Ciani et al. 2012; Shimada 2013) and in rodents (Meaney and Stewart 1981; Van Den Berg et al. 1999; Pellis et al. 2010). (**a**) Andy Blackledge. DSC_4593. Flickr.com https://www.flickr.com/photos/hockeyholic/8427240567; January 29, 2013. Accessed March 28, 2016. (**b**) braindamaged217 (Sutter, Audra). Group on Day Thirteen. Flickr.com https://www.flickr.com/photos/braindamaged217/2077113462; December 1, 2007. Accessed February 12, 2016. (**c**) The Jaguar, Tambako (Keller, Emmanuel). Two young chimpanzee playing. Flickr.com https://www.flickr.com/photos/tambako/9927267514; September 25, 2013. Accessed January 28, 2016

While touch can be a powerful reward signal that the animal works to achieve, its hedonic value is dramatically shaped by surrounding contextual information from other senses (McCabe et al. 2008; Ellingsen et al. 2013; Ellingsen 2015). For example, an otherwise sensual pleasant touch can be "hedonically flipped" to evoke displeasure and disgust if other sensory information tells us that the toucher is unattractive, a stranger, or unfriendly (Gazzola et al. 2012; Ellingsen et al. 2014; Scheele et al. 2014). Further, as is the case with other rewards, the motivation to engage in specific touch interactions depends on the internal homeostatic and affective state of the animal (Morrison et al. 2010; Triscoli et al. 2014; Ellingsen et al. 2015). When social contact is sought, the underlying motivation can be safety and relief of an aversive state, or enjoyment and social exploration. The motivational modes driving these two behaviors may be fundamentally different, and thus be underpinned by different neurobiological mechanisms (Georgiadis et al. 2012; Krahe et al. 2013; Løseth et al. 2014).

The μ-opioid system plays a central role in both avoidance and reward-seeking behavior (Dum and Herz 1984; Fields 2007; Berridge and Kringelbach 2008; Fields and Margolis 2015), and also in the corresponding subjective experiences of relief and pleasure (Leknes and Tracey 2008; Berridge and Kringelbach 2013). Accordingly, there is strong evidence for a central role of the μ-opioid receptor (MOR) system in social affiliation in mammals, which often involves substantial interindividual touch. However, there has been a hitherto unresolved inconsistency in the literature regarding the specific role of the MOR system for affiliative touch behavior, characterized by apparent opposite species-related function of MOR whereby stimulating MOR signaling reduces social contact seeking in primates, but increases it in rodents (Keverne et al. 1989; Trezza et al. 2010). We recently put forth a model of State-dependent μ-Opioid Modulation of Social Motivation (SOMSoM) to resolve this disparity (Løseth et al. 2014). The model proposes that MOR activation promotes or represses motivation for social contact depending on whether the animal is affectively content or distressed, respectively (Fig. 15.3). Importantly, these studies predominantly involve social isolation followed by reunion, which is profoundly distressing for animals that depend on social support for comfort, such as primates and infant rodents (Fabre-Nys et al. 1982; Keverne et al. 1989; Schino and Troisi 1992; Martel et al. 1995; Graves et al. 2002), but not for juvenile and adult rodents (Panksepp et al. 1985; Siegel and Jensen 1986; Vanderschuren et al. 1996; Trezza and Vanderschuren 2008b). According to the SOMSoM model, differential between-taxa effects of pharmacological MOR manipulation may therefore be due to differences in the experimentally induced motivational state rather than inherent species differences in MOR function.

In this chapter, we will discuss how close social interactions involving touch are differentially pursued for either (1) relief of negative affect or (2) for enjoyment and exploration depending on the initial motivational state of the animal. Furthermore, we will present evidence that the μ-opioid system plays a crucial role in this mode-dependent regulation of action. Finally, we will discuss the role of other neurotransmitters, such as oxytocin, in mammalian affiliative touch behavior.

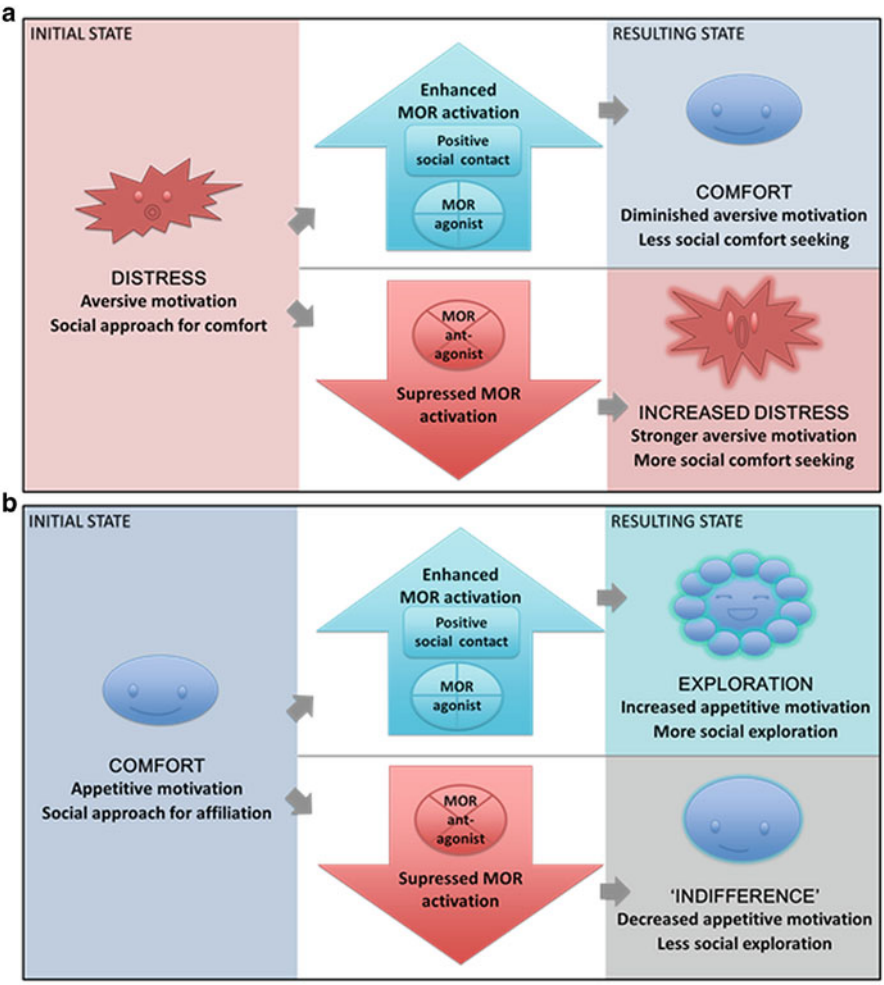

Fig. 15.3 The State-dependent μ-opioid Modulation of Social Motivation (SOMSoM) Model. (**a**) During a separation distress state, motivation is predominately aversive, and social contact is sought out for comfort and relief. Positive social contact or MOR agonist treatment enhances MOR activation, thereby providing relief. The result is a comfort state where the need for social support is diminished, thus reducing social approach behaviors. When the MOR system instead is blocked with an antagonist, the resulting state is one of increased distress and enhanced aversive motivation. Social approach behaviors are thus increased, since the need for social support is greater. A similar reaction would be expected from further social isolation. (**b**) During a normal state of homeostatic balance, motivation is predominately appetitive, and social interaction is sought out for exploratory or affiliative purposes. Increased MOR transmission through MOR agonist treatment or positive social interaction leads to a state of exploration with increased appetitive motivation and increased social exploration and approach. If the MOR system instead is blocked by an antagonist, the resulting state is one of "indifference," where appetitive social motivation is diminished and social approach is reduced. From: Løseth, G. E Front Behav Neurosci., et al. (2014). "State-dependent mu-opioid modulation of social motivation." **8**: 430

The MOR System Plays a Key Role in Affiliative Touch Behavior

Engagement in affiliative touch activities, such as social play, social grooming, and huddling (Fig. 15.2a–c), is associated with μ-opioid functioning in both primates and rodents (Beatty and Costello 1982; Trezza and Vanderschuren 2008a, b; Dunbar 2010). In juvenile rats, rough-and-tumble play leads to increased central *μ-opioid* receptor activation, as suggested by both in vitro (Panksepp and Bishop 1981) and in vivo studies (Vanderschuren et al. 1995e). Direct evidence of touch-related MOR activation in humans is scarce and somewhat inconsistent. Some currently unpublished results indicating that touch can induce MOR activation have however been communicated from a PET study where participants were stroked extensively by their romantic partner while in the scanner, but whether this activation was specific for affiliative touch or just a response to somatosensory stimulation is so far unclear (Nummenmaa et al. 2016, Soc. Neurosci., abstract). Some studies of the neuroendocrine responses to massage (Day et al. 1987; Kaada and Torsteinbo 1989; Morhenn et al. 2012), which may be better classified as "therapeutic" than affiliative touch, suggest involvement of MOR. One study reported a moderate and significant increase in blood plasma β-endorphin levels in pain patients following a connective tissue massage, possibly contributing to the subsequent pain relief (Kaada and Torsteinbo 1989). In contrast, another study observed significant *reductions* in plasma β-endorphins in a group of healthy volunteers receiving moderate pressure massage compared to a control group that were only resting (Morhenn et al. 2012). A third study observed no changes in blood plasma levels of β-endorphins in pain-free healthy volunteers following massage (Day et al. 1987). These inconsistencies may be due to differences in physical (pressure, speed) and contextual factors beyond the touch itself, making it difficult to draw general conclusions from these studies. Moreover, since these studies only assessed peripheral levels of β-endorphins, it is difficult to make assumptions about central mechanisms (although see Walker and McGlone 2013; Fell Gillian et al. 2014).

In nonhuman primates, social grooming can elicit endogenous μ-opioid release, as demonstrated in a study where large increases in cerebrospinal fluid levels of β-endorphins were observed following social grooming (Keverne et al. 1989). Social grooming, which involves sweeping through someone else's fur with hands and lips and removing impurities, has relaxing and stress-reducing effects, such as reduced heart rate (Dunbar 2010) and stress-related scratching (Schino et al. 1988). Grooming-induced MOR activation is thought to facilitate formation and maintenance of long-term relationships that provide social support and protection in species of nonhuman primates that frequently engage in mutual social grooming (Dunbar 1980, 2010; Seyfarth and Cheney 1984; Machin and Dunbar 2011). In rats the amount of licking and grooming received as an infant is associated with sociability in adolescence (Moore and Power 1992; Parent and Meaney 2008; van Hasselt et al. 2012). Furthermore, a series of studies report that adult mice engage more in social grooming when they interact with siblings, and subsequently display larger

μ-opioid-mediated decreases in pain sensitivity, as compared to mice interacting with unrelated cage mates (D'Amato and Pavone 1993, 1996; D'Amato 1998). This suggests that endogenous μ-opioid responses to social interactions vary according to the nature and quality of the relationship between animals engaging with each other. However, because touch always happens in combination with a rich multisensory context in these studies, it is difficult to ascertain what part of the observed involvement of the MOR system can be attributed to touch. Moreover, whether certain types of touch inherently activate the μ-opioid system, or if touch-related μ-opioid activation depends primarily on other influences, such as context and affective-motivational state, remains to be determined.

More generally, MOR activation has been found to mediate preference for the most valuable option when several rewards are available. For instance, blockade of μ-opioid signaling using antagonist treatment reduces consumption of palatable cookies in rats, but does not affect consumption of standard chow (Cooper and Turkish 1989). Conversely, enhancement of μ-opioid signaling with agonist treatment specifically enhanced male rats' sexual approach of female rats in estrus, while their interest in the nonestrus females diminished (Mahler and Berridge 2012). A parallel finding in humans showed that psychopharmacological treatment with μ-opioid agonist increased, while an antagonist reduced, the relative appeal of highly attractive over less attractive opposite-sex faces (Chelnokova et al. 2014). Partial μ-opioid agonism with buprenorphine also increased people's memory for smiling faces (Syal et al. 2015) and reduced sensitivity to fearful photos (Ipser et al. 2013). A recent study showed that μ-opioid receptors were necessary for formation of lasting bonds between monogamous prairie vole mates (Burkett et al. 2011). Another study found that blocking μ-opioid receptors in the dorsomedial nucleus accumbens shell (dmNAcS) effectively impaired partner preference formation without affecting mating behavior. The authors proposed that MOR in the dmNAcS mediated pair bond formation by eliciting positive hedonic feelings associated with mating (Resendez et al. 2013). In other words, MOR activation may mediate a 'hedonic marking' of available choices, making one partner stand out as preferable to the others.

'The Brain Opioid Theory of Social Attachment' (BOTSA), postulated by Panksepp et al. (1978), argued that, because pro-social behaviors such as parental care and altruistic behaviors are so important for survival in social species, affiliative behaviors may have evolved from more basic systems subserving pain perception, with a central role of MOR. The authors proposed that social contact alleviates isolation distress and induces positive emotions through the release of endogenous opioids, while separation or social isolation causes opioid withdrawal symptoms and thus negative affect. This way, the pleasant effects of endorphin release and the aversive effects of endorphin withdrawal are thought to motivate us to seek social contact and maintain proximity to individuals we are emotionally attached to (Panksepp et al. 1978, 1980b).

A series of psychopharmacological studies in infants of several species showed, consistent with BOTSA, that μ-opioid agonists like morphine reduced and opioid antagonists like naltrexone and naloxone exacerbated distress calls and social contact seeking during and following social separation and isolation. Without apparent sedative

effects, MOR agonists, such as morphine profoundly reduced isolation-induced crying, while blocking the receptors with an opioid antagonist exacerbated or even *induced* separation distress behaviors in isolated puppies (Panksepp et al. 1978; Knowles et al. 1989), infant guinea pigs (Herman and Panksepp 1978), rat pups (Panksepp et al. 1980b; Carden and Hofer 1990b), chicks (Panksepp et al. 1980a), and infant rhesus monkeys (Kalin et al. 1988). In rat pups, socially mediated reductions in distress vocalizations were completely blocked by the opioid antagonist naltrexone (Carden and Hofer 1990a), suggesting that social comfort was indeed mediated by the MOR system. This evidence consistently showed that across species, MOR *deactivation* increased the motivation to seek social contact for comfort in distressed infants, while MOR *activation* reduced this motivation and left the infant less distressed.

Studies of adult and juvenile nonhuman primates lent further support to the BOTSA postulations that exogenous opiates can replace the need for social contact, and that blocking the MOR system enhances overall motivation for social interaction. Following brief social isolation, animals injected with morphine engaged less in social grooming (Keverne et al. 1989), while those injected with μ-opioid antagonists such as naltrexone and naloxone made more solicitations and spent more time receiving grooming (Meller et al. 1980; Fabre-Nys et al. 1982; Keverne et al. 1989; Schino and Troisi 1992; Martel et al. 1995; Graves et al. 2002).

Species Differences in μ-Opioid System Modulation of Social Motivation?

One interpretation of these findings may be that animals engage in affiliative touch behavior in order to obtain MOR release, and that substitute MOR activation, by drug administration or consumption of other rewards, reduces the need for affiliative touch. With this in mind, it can seem surprising that social play in juvenile rats is *increased* by low-dose morphine injections and *reduced* by μ-opioid antagonist treatment (Beatty and Costello 1982; Panksepp et al. 1985; Siegel and Jensen 1985, 1986; Vanderschuren et al. 1995a, c, d, 1996; Trezza and Vanderschuren 2008a, b). Similar effects have been found in adult rats, where social grooming was increased by MOR agonists and decreased by MOR antagonists (van Ree and Niesink 1983; Niesink and van Ree 1984, 1989). One possible explanation for the apparent opposite involvement of the MOR system in affiliative behavior between these species may be that the MOR system plays fundamentally different roles in social reward for rodents and primates, and that species differences become evident through development. However, such an explanation seems unlikely when considering the striking neurobiological correspondence the rodent and primate reward systems in general (Berridge and Kringelbach 2008), and in μ-opioid effects on pain and social distress in particular (e.g., Eisenberger 2012). We recently argued that, rather than reflecting a fundamental species-based difference in MOR function, the observed differences between rodents and primates are due to differences in the animals' affective responses to the experimental conditions (Løseth et al. 2014).

Since social isolation is aversive to many social animals, experiments where the animal is taken away from its normal social setting before being reintroduced after a period of separation can be called *relief paradigms*. A large proportion of the experimental studies investigating the role of the MOR system in affiliation have applied such relief paradigms where animals are subjected to a stressor such as separation from their mother, offspring, mate or social group in primates (Meller et al. 1980; Fabre-Nys et al. 1982; Keverne et al. 1989; Schino and Troisi 1992; Martel et al. 1995; Graves et al. 2002) and rodents (Beatty and Costello 1982; Panksepp et al. 1985; Siegel and Jensen 1985, 1986; Vanderschuren et al. 1995c, d, 1996; Trezza and Vanderschuren 2008a, b). Following the separation period, the MOR system is manipulated by central or peripheral administration of a MOR agonist or antagonist, and subsequent effects on distress-related behaviors, physiological stress responses, and social interactions are observed.

Seeking social support is a central coping strategy for social animals facing some form of adversity (Cobb 1976). Animals that are more dependent on social comfort to handle adversities should react with greater distress during isolation. This mechanism is illustrated by age-related differences in social distress. All mammalian infants rely on parental care to survive and respond promptly to separation from the caregiver by emitting distress vocalizations and seeking physical proximity. The distress behaviors cease if comforting social contact is reinstated (Blumberg et al. 1992; Kalin et al. 1992; Hofer et al. 1993; Van Oers et al. 1998), and this comforting effect is thought to be mediated by MOR activation (Panksepp et al. 1980b; Kalin et al. 1988; Carden and Hofer 1990b).

Later in the life span, species differences in social dependence become more apparent. Juvenile and adult rats respond to temporary social isolation with few signs of distress (Nelson and Panksepp 1998) and no increase in stress hormone levels (Van Den Berg et al. 1999). Nonhuman primates on the other hand continue to display behavioral signs of distress upon social separation (Kalin 1995; Rilling et al. 2001; Levine 2005; Tardif et al. 2013). Depressive-like behavior similar to that observed in infant primates is displayed by adult primates separated from their family environment (Suomi et al. 1975), and physiological indications of stress such as increases in cortisol levels are observed in both juvenile and adult primates during social separation (Higley et al. 1992; Lyons et al. 1999; Ragen et al. 2013).

The discrepancy between MOR effects in rodents and primates could reflect a qualitative difference between social bonds in primates and rodents. Most rodents typically form transient bonds that serve to facilitate mating and nurturing of offspring, and that hinge on the hormonal context induced by copulation and parturition. They do not typically depend on enduring parental or social bonds for survival or successful offspring rearing (Broad et al. 2006). In contrast, primates are capable of forming long-lasting bonds even without such hormonal context (Broad et al. 2006). Primates live in highly complex social groups, on which they depend for protection from predators, as well as for cooperation on rearing of offspring and foraging for food (Dunbar 2012). While social separation is a potential stressor for all social mammals, the occurrence and intensity of distress should reflect the potential harm from social isolation. Thus, experimental "relief paradigms" may involve different levels of distress in primates compared to adolescent or adult rodents, accompanied by different motivational states.

State-Dependent μ-Opioid Modulation of Social Motivation

The meaning of a given pleasant or unpleasant (or rewarding or threatening) stimulus depends on the predicted role of this stimulus in achieving the goal currently kept in mind. The prediction of outcome value, or cost, of different actions is a constantly ongoing process, which affects hedonic experience (Friston and Kiebel 2009; O'Reilly et al. 2013). For instance, implicit or explicit expectations of pain relief from medical treatment often lead to a reduction in pain, even when the treatment itself does not involve an active analgesic ingredient (Benedetti 2014; Schedlowski et al. 2015). According to the Motivation-Decision Model of Pain, the MOR system plays an instrumental role in this ongoing prediction of subjective utility, through fine-tuned up- or down-regulation of pain signals in the brainstem (Fields 2006, 2007). This is part of a complex unconscious "decision-making" process, which takes into account the surrounding contextual (sensory) information, as well as internal homeostatic and motivational state, to guide how to act in the given situation. The model was initially put forward to explain modulation of pain, but the basic idea holds for all events that fall within a reward–punishment continuum. By using constructs of meaning to assign hedonic value (e.g., painfulness) to stimuli, the brainstem MOR system thus promotes safety- or pleasure-seeking behavior depending on the internal motivational mode. The state-dependent effect of MOR is illustrated by high-pain states, where MOR agonists provide pain relief, but with reduced impact of other effects commonly associated with opiate drugs during nonpain states, like respiratory depression (Borgbjerg et al. 1996) and addiction potential (Ballantyne and LaForge 2007).

The SOMSoM model suggests a corresponding bimodal role of the MOR system in social approach behavior, depending on whether the initial state of the animal is distress or comfort. First, in a *distressed state*, social animals will seek out social contact for safety from a threat or for healing and recovery. In this context, social contact relieves negative affect through μ-opioid release. Thus, in a distressed state, (a) stimulating MOR with opiates will relieve the animal's distress, and consequently diminish social contact seeking, while (b) blocking MOR will exacerbate distress, and thus increase contact seeking. Second, *in a comfort state*, social interaction has functions beyond comfort and safety, such as formation and maintenance of social bonds, testing the boundaries of social hierarchies, or exploring possible new mating partners. Thus, social contact can be a source of fun, joy, and pleasure, but also challenge and risk. In this motivational mode, (a) exogenous MOR agonists will promote approach for social rewards, whereas (b) MOR antagonism will inhibit the incentive salience of social rewards, and result in reduced interest in others.

Our model assumes a central role for the MOR system in the prioritization of needs. This is inspired by more generalized theoretical frameworks stipulating that motivation to meet higher needs is contingent on the prior fulfillment of more basic needs (Maslow 1943; Tay and Diener 2011). Specifically, during pain or distress, the μ-opioid system is employed to pursue relief of the aversive state, which may be critical to survival and health. When this basic need is fulfilled, and homeostatic equilibrium has been achieved, the μ-opioid system is instead involved in promoting reward-seeking and social exploration.

μ-Opioids Regulate Comfort Seeking and Social Exploration Depending on Motivational State

The State-dependent μ-Opioid Modulation of Social Motivation (SOMSoM) model postulates that the diverging and paradoxical findings showing that MOR agonists in some cases *reduce* and in other cases *increase* social approach are due to very different motivational contexts. Animals were socially isolated before testing in the majority of studies in this field. We argue that social separation leads to different motivational states depending on how much the animal relies on social contact for survival and emotion regulation. One central assumption of SOMSoM is that blocking MOR transmission should cause increased contact seeking only if the animal is in a distressed state.

As we have seen, studies of animals known to find social separation distressing, such as infant rodents; infant, juvenile, and adult primates; and infants from other species, consistently show the *comforting* effect social contact has on separation distress is blocked by MOR antagonism (Herman and Panksepp 1978; Panksepp et al. 1978, 1980a, b; Kalin et al. 1988; Knowles et al. 1989; Carden and Hofer 1990a, b). However, blocking MOR with an antagonist is not sufficient to induce separation distress in animals that are not already distressed. For instance, naltrexone failed to induce distress vocalizations in infant rats when they were allowed to remain together with their siblings (Carden et al. 1993). In primates, MOR antagonist treatment *reduced* maternal infant grooming in mothers who were never separated from their infant (Martel et al. 1993). These findings indicate that MOR blockade itself does not increase the need for social comfort or induce distress in a context where there is no prior stress. Instead, blockade of the MOR system attenuated social interaction in animals that remained unstressed.

Although juvenile and adult rats do not typically show distress from social isolation, there is ample evidence that MOR agonism relieves pain and conditioned fear and distress (Davis 1979; Westbrook et al. 1991), while MOR antagonism exacerbates acquisition of fear and safety seeking (Fanselow and Baackes 1982; Helmstetter and Fanselow 1987). Similarly, in humans, blocking MOR transmission with naloxone inhibits the extinction of (recovery from) fear conditioning, when a conditioned cue no longer predicts a threat (Eippert et al. 2008). The role of the MOR system appears to be generalizable across both social and nonsocial rewards (and punishments). We speculate that μ-opioids may be involved in a common language of hedonic utility used by social and nonsocial basic and abstract rewards (Leknes and Tracey 2008).

A similar context-dependent MOR mechanism was recently demonstrated in humans through measures of endogenous MOR activity. Using molecular imaging, Hsu et al. (2013) identified separable MOR mechanisms for modulation of negative and positive affective states caused by social interaction. Participants underwent a social feedback task in the scanner, where they were exposed to acceptance or rejection from persons they had rated as highly attractive and considered likely to reciprocate romantic interest. Social distress from being rejected was associated with increased MOR in the amygdala, periaqueductal gray (PAG), and right ventral striatum. This may

reflect a coping mechanism, since higher MOR activity was mirrored by lower negative affect, perhaps analogous to a coping mechanism for physical pain that is activated in stressful or threatening contexts (Zubieta et al. 2001; Fields 2004). Interestingly, during acceptance, increased MOR signaling was also associated with positive affect, but in different circuitry: the right anterior insula and left amygdala. Moreover, MOR activation in the ventral striatum during acceptance was higher in those who were more motivated to seek social contact. This may point to separate opioidergic subcomponents involved in social distress and social exploration. A follow-up study employing the same paradigm in depressed patients reported decreased MOR activity during both rejection and acceptance, consistent with disrupted ability to self-comfort and reduced social motivation even during social acceptance (Hsu et al. 2015). Future research should address questions of specificity and generalizability of putative MOR subsystems for motivation. For example, in humans, social isolation or loneliness may lead to overindulgence in comfort food or addictive drugs, suggesting that other (nonsocial) rewards may serve as substitutes for social support and affiliation (Bruce and Agras 1992; Cacioppo and Hawkley 2009).

If, as assumed by SOMSoM, the MOR system promotes social exploration during nondistressed states, then MOR antagonism should *reduce*, while MOR agonism should *increase* social contact seeking. Since social play generally occurs only when an animal is free from physiological and social stress, it provides a useful behavior for investigating MOR effects in the absence of distress (Loizos 1967; Baldwin and Baldwin 1976; Fagen 1981; Siviy and Panksepp 1985; Vanderschuren et al. 1995b; De Oliveira et al. 2003). By the time rats have become juveniles, social separation is no longer associated with distress (Nelson and Panksepp 1998; Van Den Berg et al. 1999). The observation that social separation leads to subsequent increases in social play interactions upon reunion (Panksepp 1981) is therefore likely to reflect primarily an appetitive motivation for social exploration and joy (Panksepp and Burgdorf 2003), rather than for consolidation and safety, as is seen for primates (Meller et al. 1980; Keverne et al. 1989) and infant rodents (Panksepp et al. 1980a, b). As we have reviewed, pharmacological MOR agonist treatment has consistently been found to increase social play in rodents (Beatty and Costello 1982; Trezza and Vanderschuren 2008a, b). Further, social play is associated with strong increases in endogenous μ-opioid release in the rostral nucleus accumbens (Vanderschuren et al. 1995e), an area that is also central to processing of other appetitive rewards (Berridge and Robinson 1998; Trezza et al. 2011). A recent study in adolescent rats found that the injection of a selective MOR agonist into the NAc *increased* social play, while the injection of a selective MOR antagonist *prevented* the development of social play-induced conditioned place preference (Trezza et al. 2011).

Since most studies have examined modulation of MOR function during *either* distress *or* affective equilibrium, we do not yet know the temporal dynamics of how the MOR system transitions from promoting safety seeking to, once affective equilibrium has been obtained, promoting social exploration and pleasure seeking. Nevertheless, exposing young rats to novel environments normally delays social play due to exploration of the surroundings (Vanderschuren et al. 1995b),

but animals injected with low doses of morphine before being introduced to an unfamiliar cage immediately started social play interactions, which could indicate that MOR activation directs the attentional focus toward social rewards rather than exploring the environment (Trezza and Vanderschuren 2008a). An alternative interpretation could be that the enhanced MOR transmission increases confidence (Panksepp et al. 1985), and thus reduces the need to check whether there are potential dangers present. Given its function in establishing social hierarchies and dominance relationships, engaging in social play involves a level of risk that could make it a more challenging rather than comforting activity (Poirier and Smith 1974; Panksepp et al. 1985; Blumstein et al. 2013).

Few studies have investigated the effects of experimental MOR manipulation on play behaviors in primates, but the limited evidence suggests that the MOR system mediates social play in a similar manner to what is seen in rodents. A study where juvenile rhesus monkeys were socially isolated for 2 h found that the subsequent injection of naloxone, relative to saline, significantly decreased social play interactions when reunited with peers while contact with the mother increased (Martel et al. 1995). The authors hypothesized that the decrease in social play could reflect that MOR blockade decreased social confidence and reduced the young monkeys' willingness to risk social play while increasing their need for social comfort (Martel et al. 1995). In another study specifically designed to investigate MOR modulation of primate social play, marmoset juveniles living in a family group were injected with morphine, naloxone, or saline without prior social isolation distress. Here, morphine specifically increased social play behaviors compared to both saline and naloxone, while naloxone led to slight, albeit not statistically significant, decreases in play behaviors compared to saline (Guard et al. 2002). Similarly, a study of long-tailed macaques that also were allowed to remain in their social context throughout the experiment reported a decrease in social play after treatment with naloxone that approached statistical significance (Schino and Troisi 1992). The weak effects of naloxone point to the likely contribution of other neurotransmitter system for play behavior in primates.

A few studies have tried to detect changes in endogenous opioid transmission following tactile interactions in humans by measuring changes in β-endorphin in the blood plasma, but these provide only indirect evidence since correlations between opioid levels in peripheral blood plasma and opioid transmission in the central nervous system have yet to be established in humans. One study investigating endocrine responses to interspecies interaction found increases in plasma β-endorphin levels in cephalic venous blood in dog owners after they had played with, stroked, and scratched their dog. A similar opioid release was also measured in the dog following this interaction. Increases in oxytocin, prolactin, and dopamine and decreases in blood pressure were also measured in both humans and dogs (Odendaal and Meintjes 2003), suggesting that opioid release is only one part of a cascade of neuroendocrine responses to social interaction involving affiliative touch.

Contributions by Oxytocin and Other Neurochemicals

The nine amino-acid neuropeptide oxytocin (OT) plays a central role in social affiliation and attachment in mammals (Tops et al. 2007; Feldman 2012). In rodents, species differences in OT distribution in limbic brain areas have been associated with differences in social organization and bond formation (Young et al. 2011). The prairie vole, one of the few mammals classified as monogamous, has higher densities of oxytocin and vasopressin receptors in the ventral striatum than the closely related, but promiscuous, montane and meadow voles (Ross et al. 2009). Furthermore, the blockade of mesolimbic oxytocin signaling in prairie voles prevents the formation of both alloparental behavior (Cho et al. 1999; Olazabal and Young 2006) and the formation of long-term pair bonds (Insel and Hulihan 1995; Cho et al. 1999; Ferguson et al. 2000). In humans, oxytocin is involved in a range of social and emotional processing (Bartz et al. 2011; Leknes et al. 2013; Ellingsen et al. 2014) and is shown to have anxiolytic effects (Heinrichs et al. 2003; Kirsch et al. 2005), enhance parasympathetic responses (Gamer and Buchel 2012), and increase heart rate variability—an index of vagal control (Kemp et al. 2012).

The parasympathetic and anxiolytic effects of stroking touch in mammals have been proposed to be mediated by oxytocin (Uvnäs-Moberg 1997, 1998). Pharmacological administration of an oxytocin agonist increases social exploration in adult rats (Panksepp et al. 1997), and specific affiliative behavior such as social grooming (Drago et al. 1986; Pedersen et al. 1988; Witt et al. 1992) and maternal nurturing (Pedersen and Prange 1979; Pedersen et al. 1982; Bosch 2011). Relatively few studies have employed pharmacological modulation of oxytocin in primates. A recent study investigated pair bonding in marmoset monkeys and found that huddling behavior was increased by the administration of an OT agonist, but reduced by an OT receptor antagonist (Smith et al. 2010). Another study found that, in squirrel monkeys, intranasal oxytocin dampened stress-related increases of blood plasma adrenocorticotropic hormone (ACTH) induced by social isolation, although plasma levels of cortisol were not affected (Parker et al. 2005). Also, since behavioral changes were not assessed, it is difficult to directly relate this finding to affiliative touch behavior.

A series of studies have investigated peripheral levels of oxytocin during social interactions in primates, which provides indirect evidence for an involvement of oxytocin in affiliative touch behavior, albeit limited mechanistic details about central function. One study found increased urinary levels of oxytocin following social grooming interactions in wild chimpanzees, an effect that was mediated by bond strength (Crockford et al. 2013). In rhesus monkeys, the expression of grooming has been reported to correlate positively with plasma (Maestripieri et al. 2009) and cerebrospinal fluid (Winslow et al. 2003) levels of oxytocin. However, another study found no relationship between plasma oxytocin and social behavior in free-ranging macaques (Schwandt et al. 2007). A recent study, which studied pair bonding in cotton-top tamarins, reported that interindividual

levels of urinary oxytocin covaried closely with grooming and mutual contact in females and with sexual behavior in males (Snowdon et al. 2010). Another study reported that urinary levels of oxytocin were higher during social contact relative to social isolation (Seltzer and Ziegler 2007). In sum, these studies are in line with a notion that oxytocin release may relieve negative states induced by social isolation or rejection, and that low levels of oxytocin may promote seeking of social support (Panksepp et al. 1997; Tops et al. 2007), which is similar to the effects of MOR. Considering findings that administration of an oxytocin receptor agonist increases social exploration in adult rats (Panksepp et al. 1997) and aspects of social approach in humans (Kemp and Guastella 2011; Weisman et al. 2012), future research should address interactions between oxytocin and MOR to determine the relative contribution of these two neurotransmitter systems. The lack of an oxytocin antagonist for human use has hampered the understanding of this system in humans relative to other species.

Similar to the effects of μ-opioid system manipulations, the behavioral effects of oxytocin administration also seem to vary across contexts and affective states (Bartz et al. 2011). In rodents, oxytocin is associated with both protective behavior toward pups and aggression against intruders (Campbell 2008). Intranasal oxytocin in humans increases the recognition of both positive (Unkelbach et al. 2008; Marsh et al. 2010) and negative emotions (Bartz et al. 2010; Fischer-Shofty et al. 2010; Leknes et al. 2013), and increases empathizing and cooperation with in-group members, but may instead increase aggression toward threatening out-group members (De Dreu and Kret 2015). We recently found that oxytocin potentiated a social-touch induced "sharpening" of social impressions of others, relative to nonsocial touch, such that friendly faces were perceived as more attractive and friendly, while hostile faces were perceived as less attractive and friendly (Ellingsen et al. 2014). This modulation was not reflected in the participants' experience of the touch itself, which remained unaffected by oxytocin treatment. Interestingly, a recent study found that, in a group of heterosexual men, intranasal oxytocin increased the pleasantness of sensual caressing specifically when they were led to believe this was performed by a woman (Scheele et al. 2014). However, oxytocin had no effect on touch pleasantness when the participants believed the caresser was a man, highlighting the importance of context and meaning in oxytocin functioning. One view is that oxytocin may have a general role in promoting social approach behavior (in both positive and negative contexts), while inhibiting social avoidance (Kemp and Guastella 2010, 2011; Clark et al. 2013). However, while many of the studies using intranasal oxytocin in humans involve an experimental manipulation of context, they rarely assess—or manipulate—more profound changes in motivational or homeostatic state. Thus, it is not known whether oxytocinergic modulation of social approach/avoidance in humans depends on the individual's initial state.

Although the exact mechanism(s) are currently unclear, a series of studies have proposed a role for oxytocin in human affiliative touch (Feldman 2012). One study found that plasma oxytocin levels in mothers throughout pregnancy and the early postpartum period predicted maternal bonding behaviors such as eye gaze, high-pitched vocalizations, and affectionate touch directed at the infant

(Feldman et al. 2007). Another study found that in first-time parents, higher plasma levels of oxytocin were associated with more frequent infant-directed affectionate touch in mothers, but with more frequent stimulatory touch in fathers (Gordon et al. 2010). Unfortunately, this literature commonly quantified oxytocin in plasma using methods now considered questionable, and results may be driven by nonoxytocin substances (McCullough et al. 2013; Christensen et al. 2014). Perhaps for this reason, along with potentially fine-grained variations in context and motivational state across studies, overall findings of touch-induced release of peripheral oxytocin in humans are inconsistent. While some studies have found peripheral oxytocin release in response to touch (Light et al. 2000, 2005; Odendaal and Meintjes 2003; Holt-Lunstad et al. 2008), others have found no effect (Turner et al. 1999; Heinrichs et al. 2001; Wikstrom et al. 2003; Grewen et al. 2005; Ditzen et al. 2007). Moreover, methodological limitations like the lack of useful oxytocin antagonists for human testing, as well as the current inability to assess oxytocin release in the human brain with molecular imaging, limit the understanding of the functional neurobiology of oxytocin in humans. Finally, it is important to note that, like the MOR system, many of the functions of central oxytocin are not restricted to the social domain, but instead may reflect more fundamental mechanisms involved in generalized processing of salience, motivation, anxiety, and stress regulation (Churchland and Winkielman 2012; Harari-Dahan and Bernstein 2014).

Other neurotransmitters that modulate social touch behaviors in mammals are vasopressin (Winslow et al. 1993; Panksepp et al. 1997), serotonin (Insel and Winslow 1998; Depue and Morrone-Strupinsky 2005a), cannabinoids (Trezza and Vanderschuren 2008a, b; Trezza et al. 2012), and dopamine (Champagne et al. 2004). These neurotransmitter systems are likely to interact with opioid and oxytocin processing in key brain regions for social and emotional processing (e.g., Hagelberg et al. 2002; Liu and Wang 2003; Depue and Morrone-Strupinsky 2005b; Lintas et al. 2011; Colasanti et al. 2012; Tops et al. 2014). Understanding the nature of these interactions is an important challenge for future studies (Weisman and Feldman 2013).

Conclusion

Affiliative touch is a key ingredient in mammalian relationships and is often a powerful reward. The motivation for seeking touch can be broadly identified as rooted in either avoidance of negative affect (comfort, safety, and social support) or appetite for reward (social exploration and reward seeking). We have reviewed how the MOR system, which plays a central role in both pain regulation and social affiliation, may be differentially involved in these two motivational modes. An apparent contradiction in the literature is that MOR activation seems to reduce social contact seeking in primates and rodent pups, but increases social contact seeking in juvenile and adult rodents. We have proposed a model for State-dependent μ-opioid Modulation of Social

Motivation (SOMSoM), which addresses this disparity, suggesting that these differences may be due to differences in the animals' motivational state rather than species-related differences in MOR function.

The predominant experimental procedure in these studies is social separation followed by pharmacological treatment and then social reunion. Social separation is very distressing in animals with high social dependency, such as most primates and rodent infants (Kalin et al. 1992; Hofer et al. 1993), which may trigger a need for social comfort. In contrast, social separation does not evoke pronounced distress in juvenile and adult rats (Nelson and Panksepp 1998; Van Den Berg et al. 1999), which may leave them with more capacity for social exploration and play. In line with a general role for μ-opioid system in both avoidance based and appetitive reward seeking, we suggest that MOR activation promotes motivation for stress relief and social support during a distress state, but promotes motivation for social exploration and pleasure seeking during a comfort state (Løseth et al. 2014). The SOMSoM is supported by the reviewed evidence from a large literature of psychopharmacological studies in rats and a few key studies of nonhuman primates. When factors such as species and age differences in social dependency are taken into account, effects of pharmacological MOR manipulation on social approach behaviors are similar across species. Importantly, the consistent correspondence between species in the reviewed literature on MOR modulation of reward processing, emotion regulation, and affiliation in humans, nonhuman primates, and rodents substantiates an interpretation of the initial paradox as a result of differences in motivational state caused by affective responses to the experimental conditions, rather than differences in neurobiology.

Other neurotransmitter systems also play important roles in mammalian affiliative touch behavior. Oxytocin has been studied most extensively and likely interacts with MOR, dopamine, and other neurochemical systems to shape social and affective touch behaviors. Evidence from rodent and primate studies indicates that oxytocin agonism has both anxiolytic and antistress effects as well as promoting social approach and exploration, which is similar to the effects of MOR. How these neurotransmitter systems interact to regulate social affiliation is currently less known and poses an important challenge for future research.

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Chapter 16
Affective Touch and Human Grooming Behaviours: Feeling Good and Looking Good

Francis McGlone, Susannah Walker, and Rochelle Ackerley

Abstract Grooming behaviours, whether directed at the self or at others, are ubiquitous within the animal kingdom—from bees to bonobos. Having evolved for hygienic purposes, it is in primates that grooming behaviours supersede their original role to one in which there is a clear social element: nurture, control of dominance relationships, facilitating group cohesion, etc. In humans, grooming has been seen traditionally as providing a functional, plus an aesthetic, benefit—we keep clean and we look good. However, there may be another factor driving these impulses to groom ourselves: one which is less overt and a consequence of grooming that actually makes us *feel* good as well. It is axiomatic that grooming involves touching and, as the previous chapters in this book have described, there exists in the skin of the body a population of unmyelinated mechanosensory nerves that respond optimally to precisely the kinds of touch that typify many grooming behaviours—gentle moving touch.

Keywords Pleasant • Touch • Cosmetic • Industry • Neuroethology • Grooming • Behaviour • Primate

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Introduction

All animal species, including humans, to a greater or lesser degree engage in behaviours involving both intra- and inter-active touch for a variety of reasons including personal grooming, socialising and procreation. The evolutionary, ancient precedence of grooming behaviours is evident in its occurrence in all animal taxa. Amphibians, fish, birds, arthropods, reptiles and mammals all spend a significant part of their time grooming, an activity described collectively by neuroethologists as 'care-of-body-surface' (COBS) (Sachs 1988; Spruijt et al. 1992). However, beyond body surface maintenance, identical 'grooming' behaviours can confer a range of benefits, in courtship, social communication and emotional regulation. For example, in the rodent there is a well-described auto-grooming behaviour that comprises a sequence of paw lick, face wipe and body lick that can serve to counter irritation, aid thermoregulation, increase arousal, decrease arousal and/or signal quiescence to conspecifics (Sachs 1988). Given that maintaining the integrity of the body surface undoubtedly contributes to reproductive success, these behaviours will have played a part in driving natural selection and providing the behavioural building blocks for more species-specific functional adaptations. However, grooming behaviours have evolved to be more often driven by the contexts in which they occur rather than the condition of the skin (Spruijt et al. 1992).

Observational studies of grooming activity indicate it is often spontaneous, occurring between transitions from rest to activity (Fentress 1988), but can also be a displacement activity that typically comprises self-grooming movements, such as touching and scratching in response to stress (McFarland 1966; Kalueff 2000). Self-grooming behaviours can therefore be elicited by both comforting and stressful conditions. It is likely that allo-grooming (grooming others), a common practice in non-human primates, originated to confer the benefits of physical contact first experienced in the mother–infant relationship where, beyond hygiene, COBS serves to soothe and pacify the infant and build attachment bonds (Hofer 1994). Certainly, physical contact between conspecifics is often associated with coping strategies that serve to reduce stress by attenuating activity along the hypothalamic-pituitary-adrenal (HPA) axis, as indexed by the lowering of circulating glucocorticoid levels (cortisol and corticosterone) (Panksepp et al. 1980). A behaviour that requires focusing on one's own or a conspecific's body surface will necessarily be at the expense of other motivational or environmental influences, with Spruijt et al. (1992) speculating that a consequence of such behaviours is a reduction in exogenous attention, i.e. it has a calming or relaxing effect—it makes you feel good!

The key point here is that COBS repertoires have come to serve more than simply a body-maintenance role to one found in a highly heterogeneous group of behaviours that serve many functions. Given that the evolution of grooming behaviour is likely to depend on homologous neural mechanisms in humans and non-human primates (Dunbar 1997; Katz and Harris-Warrick 1999) a neuroethological approach to human grooming behaviour may also provide unique insights into aspects of human psychology and psychopathology. Here we focus on the less explicit secondary role of grooming, that in humans is posited to drive the growth of

the personal products industry which supports and/or promotes such behaviours. We will argue that COBS has transitioned to COS (care of self), a transition that is supported by a multibillion dollar global beauty industry.

Grooming: Beyond Hygiene

The purpose of applying cosmetics to the skin is generally understood to serve a dual function where their use either enhances perceived attractiveness and/or alters skin structure/integrity in some way. This can be anything from the application of skin-lightening formulations to the use of anti-ageing creams, and as such have a clear social purpose of enhancing self-confidence and self-esteem, as well as a less subtle role in attracting a mate (Cash and Labarge 1996; Sturrock and Pioch 1998; Craig Roberts et al. 2009; van Paasschen et al. 2015). It is axiomatic that such grooming behaviours involve the application of products to the skin during either allo- or auto-grooming, and often in a manner that uses slow, gentle touch. Here, it is proposed that grooming provides not only a functional benefit but, more importantly, an emotional/affective one that has as yet not fully appreciated consequences for mental health and well-being.

A 'secondary function' of COBS is proposed that relies upon a functional interplay between cutaneous nerves in the skin and a cascade of epigenetic, neural, physiological, behavioural and endocrine systems. An example of this 'secondary function' is the licking/grooming behaviours of rodent mothers to their pups, which have been shown to modulate responses to stress via the HPA axis in adulthood. Such maternal care plays a fundamental role in neurodevelopment and brain function, the effects of which influence the adult phenotype and are implicated in adult susceptibility and response to stressors, and in humans to the development of mood disorders (Meaney 2001; Sequeira-Cordero et al. 2013). Tactile stimulation has also been shown to lower stress and fear levels in fish; Soares et al. (2011), working with a cleaner fish model, found that tactile stimulation lowered basal cortisol levels in the recipient surgeonfish. Furthermore, Schirmer et al. (2013) report a reduction in an olfactory-induced fear response in zebrafish that had previously received tactile stimulation. These effects are not socially driven, but dependent on bottom-up sensory mechanisms—animals are 'wired' to respond to gentle touch, with grooming behaviours having evolved as a behavioural mechanism to stimulate specific populations of low threshold mechanoreceptors that function to modulate affective states.

It should also be recognised that a number of neurotransmitters, neuromodulators and neurohormones, that have traditionally been associated with arousal and stress responses, are also implicated with the 'secondary functions' of grooming behaviour. Spruijt et al. (1992) see the involvement of neuropeptides, hormones and opioids as providing evidence that COBS confers benefits beyond that of taking care of the body surface alone. Maestripieri et al. (1992) have noted that autogrooming is often observed during stressful situations in non-human primates, and that such behaviour is decreased by the administration of anxiolytic drugs and

increased by anxiogenics (Schino et al. 1996). Furthermore, when macaques are close to a higher ranking male the frequency of self-grooming increases (Troisi and Schino 1987), suggesting a complex and hierarchical role for auto-grooming which is closely tied to social dominance and relationships.

Animal studies have shown that in a stressful situation grooming behaviour is functionally linked with the neurobiology of stress mechanisms, manifesting as a reduction in arousal (D'Aquila et al. 1994). Studies in rodents suggest that licking and grooming behaviours have anxiolytic and rewarding effects, and that via epigenetic mechanisms, confer resilience to subsequent stressful events. A lack of grooming/nurturing touch in infancy has an adverse effect on such physiological responses (Champagne et al. 2003). Evidence for the acute stress reducing effects of grooming behaviour in captive macaques has reported heart rate slowing in the groomee (Boccia et al. 1989; Aureli et al. 1999) after bouts of grooming (Shutt et al. 2007). A number of studies, particularly in primates, emphasise the important social functions of such behaviours and have begun to unravel the ethological factors involved. There are clear parallels here with the use of soft-massage therapies in humans. Lindgren et al. (2012), using functional magnetic resonance imaging (fMRI), reported that it was slowly moving skin-to-skin contact, rather than touch with a rubber glove, that was rated as most pleasant, and that most strongly activated the pregenual anterior cingulate cortex—a region activated during other pleasant sensations and also activated during opioid analgesics. Of interest here are displacement activities; in non-human primates, by far the most common displacement activities are 'comfort behaviours' related to body care such as grooming, scratching, shaking, stretching or yawning. In humans displacement activities include both self-directed behaviours similar to primate grooming behaviour (e.g. head scratching, beard stroking) and aimless, iterative manipulation/fiddling of objects.

Neurobiology of Grooming

In mammals, grooming behaviours typically follow a head-to-toe (cephalo-caudal) pattern, described by Berridge et al. (1987) as an "idealised syntactic grooming chain", i.e. a behaviour that is rule-driven—scripted—where the temporal sequence of its elements "imparts a lawful predictability to the sequence as a whole" (Berridge et al. 2005). This is seen in early development through to adulthood where the functional units of a particular script are hierarchically organised, e.g. in rodents, the script controlling scratching with the hind paw appears to be separate from that controlling licking and face wiping. Although many brain areas are involved in controlling these highly ordered motor patterns, neuroethological studies have shown that the neostriatum, specifically the dorsolateral portion, is critical for implementing serial patterns of grooming behaviour (MacLean 1978; Meyer-Luehmann et al. 2002; Baxter 2003). The orchestration of such sequential patterns has also been posited to extend to higher order functions such as language and cognition, i.e. thought (Lieberman 2000), with Marsden (1984) proposing that "The sequencing of *motor action* and the sequencing of *thought* could be a uniform

function carried out by the basal ganglia". This argument sees the evolution of basal ganglia systems from one of coordinating patterns of the instinctive movements we see in grooming, to one of controlling the sequencing of cognition and language (Berridge and Whishaw 1992; Aldridge et al. 1993; Marsden and Obeso 1994; Lieberman 2001; Meyer-Luehmann et al. 2002; Kalueff et al. 2016). Although this speculation remains untested, it is already clear that studies of rodent self-grooming are likely to have implications that extend beyond the motor aspects of grooming, to include the sequential control of complex behaviours in general. These evolutionary links between grooming and higher order process in humans have been expounded on by Dunbar (2012) who further argues for an evolutionary pathway from grooming in non-human primates to the emergence of language in humans (but see Grueter et al. 2013 for a counter-argument).

Neuroethological models of grooming behaviour have demonstrated the critical role of dopamine projections from the substantia-nigra to the striatum in the generation of these instinctive fixed action patterns (Berridge et al. 2005). 6-OHDA lesions which deplete dopamine in this pathway have been shown to disrupt the production of grooming chains (Berridge 1989). While mice which lack D1 receptors in this nigral-striatal pathway are unable to complete grooming chains (Cromwell et al. 1998), systemic or intra-ventricular administration of a dopamine D1 agonist has been shown to enhance the stereotypic rigidity of grooming sequences (Berridge and Aldridge 2000a, b). Further evidence that a hyperdopaminergic state strengthens syntactic grooming chains, a mutant mouse bearing a knock down of the dopamine transporter gene (DAT), which enhances extracellular levels of dopamine in the striatum by 170 %, were reported to display more stereotyped and predictable grooming bouts which were less susceptible to disruption by external stimuli than those of controls (Berridge et al. 2005).

Pathologically intense and distorted grooming rituals are seen in a range of psychological disorders including obsessive-compulsive disorder and trichotillomania (Feusner et al. 2009). While the consciously experienced drivers of these excessive behaviours may differ (i.e. fear of contamination or relief of tension), neurobiologically, they appear to reflect dysregulation of basal ganglia circuitry responsible for action selection, resulting in a lack of inhibitory control over automated, habitual action sequences (Gillan and Robbins 2014). Consistent with the animal models discussed previously, dopamine agonists have been reported to increase these stereotyped behaviours exacerbating compulsions and tics (Goodman et al. 1990). Indeed, clinical cases of dysregulated grooming are also seen in animals (Feusner et al. 2009). For example, Canine-acral lick dermatitis is a condition typified by compulsive licking of the wrist or ankle in dogs. Although it can be triggered by allergies or presence of foreign bodies on the skin, licking continues long after the primary cause has been removed. Stressors, such as social isolation, are thought to contribute to the onset, intensity and frequency of the compulsive grooming condition. Of note, selective serotonin reuptake inhibitors, which are also used to treat obsessive-compulsive disorder and trichotillomania, have been shown to reduce symptoms. Putatively, these serotonergic drugs act by increasing ventromedial prefrontal inhibitory control over the dysregulated striatal regions responsible for generating habitual grooming responses (Graybiel and Rauch 2000). Further causal

evidence for the role of serotonin in control of grooming behaviours comes from a study by Welch et al. (2007) who developed an animal model of obsessive-compulsive disorder by breeding mice that lack a gene encoding SAPAP3 (a scaffolding protein that is highly expressed in excitatory synapses of the striatum). These mice displayed both excessive grooming (resulting in hair loss and skin damage) and high levels of anxiety-like behaviour, which were remediated by treatment with selective serotonin reuptake inhibitors. Taken together, the drivers of these aberrant grooming behaviours and their remediation by medications with anxiolytic properties further support the notion that grooming behaviours are reinforcing due to their stress relieving and calming effects.

The neuropeptide oxytocin (OT) is strongly associated with enhancing affiliative interactions and anti-stress effects. Indeed it has been proposed that OT provides a crucial biological link between the social world and HPA responsivity (DeVries et al. 2003). Unsurprisingly, given that OT is released in response to warm, low intensity stimulation of sensory nerves in the skin, it has also been implicated in grooming behaviour (Uvnäs-Moberg et al. 2015). For example, a study in chimpanzees reported an increase in OT levels following grooming, but only when the groomee and groomer have strong social/affiliative bonds (Crockford et al. 2013). Uvnäs-Moberg et al. (1993) showed in rats that non-noxious sensory stimulation leads to an increase in OT in blood and cerebrospinal fluid. Centrally, intracerebroventricular injection induced intense grooming in rodents (Meisenberg 1982; Pedersen et al. 1988) and monkeys (Winslow and Insel 1991). In humans, massage is also associated with stimulating endogenous OT release (Morhenn et al. 2002), as is skin-to skin contact between mother and infant (Matthiesen et al. 2001). Furthermore, Holt-Lunstad et al. (2008) reported increased OT salivary levels following a 4-week 'warm touch enhancement intervention' between couples who were in a romantic relationship. However, as with animal models, social context is important in modulating the effect of OT during tactile interactions. For example, Scheele et al. (2014) recently reported that OT, delivered via a nasal spray, increased the perceived pleasantness of female, but not male touch to the male participants.

In response to cutaneous sensory stimulation, OT is released from neurons within the paraventricular nucleus of the hypothalamus, which project to other regions of the brain critical for regulating positively and negatively motivated behaviours. While OT receptors are found throughout the brain, they are particularly prominent in limbic forebrain regions where they co-localise with and modulate the activity of monoaminergic neurons releasing dopamine, serotonin and noradrenaline (Walker and McGlone 2013; for a review, see Uvnäs-Moberg et al. 2015). Of particular pertinence to the current discussion on grooming, oxytocinergic projections to the nucleus accumbens modulate dopamine release, which is critical for signalling the incentive motivational value of environmental stimuli (Schultz and Dickinson 2000; Berridge and Kringelbach 2008), i.e. the rewarding value of grooming. Indeed, a microdialysis study in rats reported that gentle stroking touch with a soft brush, a stimulus which has been shown to mimic the long-term benefits of maternal licking and grooming, elicits dopamine release in the nucleus accumbens (Maruyama et al. 2012).

While the mesolimbic dopamine pathway is critical for the display of motivated behaviours (Wise 1996; Robbins and Everitt 1996; Berridge and Robinson 1998)

the hedonic impact or sensory pleasure derived following receipt of a reward is signalled by release of endogenous opioids (Berridge 1996). The mu-opioid receptor system interacts closely with the mesolimbic dopamine pathway and a range of studies evidence the fact endogenous opioid release during affiliative social interactions, like allo-grooming is necessary for signalling their rewarding effects (Panksepp et al. 1980; Dunbar 2010; for a review, see Loseth et al. 2014). For example, Keverne et al. (1989) reported that while low, non-sedative, doses of morphine reduced the frequency of grooming solicitation and receipt in talapoin monkeys following brief social isolation, naltrexone, an opioid receptor antagonist, increased grooming solicitation. Similar effects have been reported in rhesus macaques (Martel et al. 1995). In rodents too, consistent with the notion that exposure to mild stressors elevates grooming behaviour, Green et al. (1979) found that intra-peritoneal injections of naloxone dose dependently decreased self-grooming behaviour displayed by rats following either exposure to a novel environment or handling.

This brief overview of the neurophysiology and neurochemistry controlling grooming behaviours serves to highlight a key aspect of this complex behaviour of relevance here—the role of these systems in positive and negative reinforcement processes. Supporting the notion that grooming behaviour, both allo- and auto-grooming, is motivated by the seeking of pleasure or the avoidance of pain/stress. By analogy with feeding behaviours, where the maintenance of energy balance at homeostatic levels depends on the consumption of high energy foods (fats and sugars) associated with sensory attributes that are most rewarding, a similar reward-based sensory mechanism would be predicted to operate with grooming behaviours, which also serve a homeostatic function in COBS. Thus, the release of OT during social tactile interactions or self-soothing behaviours is likely, through its site specific interactions with monoaminergic and endogenous opioid receptors, to be a primary mediator of the stress buffering, de-arousing and social-bonding effects observed.

Rewarding Touch

COBS behaviours require high levels of motivation for their performance (Tinbergen 1963), the corollary of which is that there needs to be a physiological reward system driving the psychopharmacological endorphin release found with both allo-grooming and self-grooming (Keverne et al. 1989; Dunbar 2010). None of the aforementioned studies appear to have recognised that all grooming behaviours, whether allo- or self-grooming, stimulate touch receptors in the skin and in a manner that would selectively activate a population of C low-threshold mechanoreceptors (CLTMs), which in humans are termed C-tactile (CT) afferents. Understanding the structure/function relationships underpinning the control of grooming behaviours in mammals will provide insights into how these mechanisms have evolved to those we now observe in human primates, where they serve additional emotional, affiliative and affective functions, driving a multibillion dollar personal care industry. As described elsewhere in this book, the hairy skin of the body of mammals is innervated by two main classes of mechanosensitive nerves; in addition to the more

commonly described tactile nerves—the fast-conducting myelinated afferent fibres—there is a system of slowly conducting unmyelinated afferents that respond to gentle, dynamic touch, i.e. CTs. These two touch pathways are classified here as the first and second touch systems. An important distinction between them that relates to their function is the presence or absence of a myelin sheath surrounding the axon. Myelinated afferent nerves are required when sensory information needs to be transmitted rapidly to the central nervous system, such as in the dexterous manipulation of objects or tools. Without this rapid first touch system it would be impossible to control objects with the hands or perceive conscious, near immediate, feedback on which body sites have been touched, e.g. during COBS. The slow second touch system, however, cannot provide such rapid information about externally generated tactile events as the information arrives centrally with a temporal delay (Ackerley et al. 2013), which begs the question "Why has such a slow touch-sensitive system in the skin evolved?" Our current hypothesis is that this second touch system processes the affective, rewarding, properties of touch (Fig. 16.1).

Results from human microneurography, psychophysical, behavioural and neuroimaging studies described in detail in other chapters of this book all indicate that CTs contribute to pleasant touch sensations. CTs therefore provide an important sensory underpinning for a wide range of social behaviours from the nurturing touch of a mother to an infant, to the caressing and sensuous touch of lovers, through to the implicit rewarding nature of personal grooming. Of note here is another key difference between the first and second touch systems—CTs have never been found in glabrous skin during microneurography studies, although a recent report by Nagi and Mahns (2013), using a psychophysical approach, posit the presence of a functional

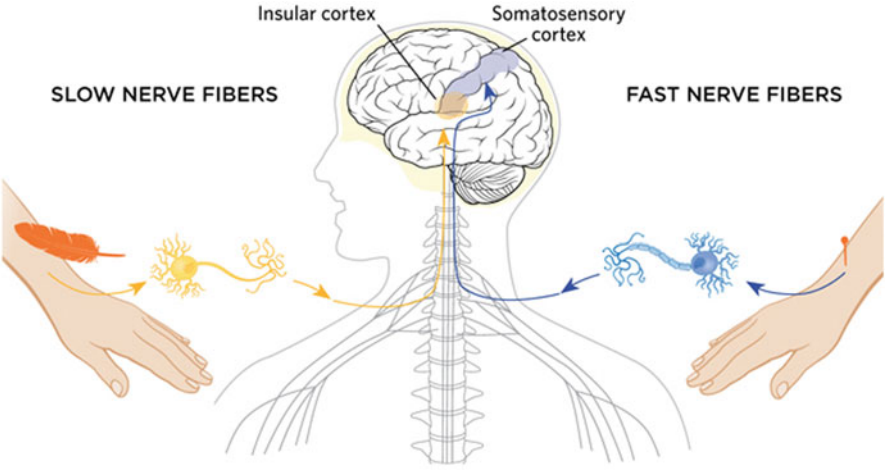

Fig. 16.1 The two touch systems. The slow nerve fibres are unmyelinated C-tactile afferents (CT), responding optimally to slow gentle touch and projecting to limbic systems in the brain. The fast touch nerve fibres respond to a wide range of mechanical stimuli and project to primary somatosensory cortex for rapid discrimination

homologue of CTs in glabrous skin. This poses some interesting questions about the mechanisms of self-touch during personal grooming, as the palmar surface of the hand acts as the 'applicator' of grooming products such as skin creams, emollients, soaps, etc. Where is touch felt? Here we need to introduce another property of touch that was first conceptualised by Katz (1989), which he termed 'dual-touch' describing the different sensations produced when individuals touch themselves or touch another—intra-active versus interactive touch (Verrillo et al. 2003). In intra-active touch, low-threshold mechanoreceptors (LTMs) are activated in two loci: the touching site (usually the fingers and/or hand) and the touched site (anywhere else on the body). If the touched site is anywhere other than glabrous skin, then in addition to LTMs being activated, CTs are also stimulated as this will be on hairy skin. As is typical with self-grooming behaviours, this often involves gentle stroking movements across the touched body site, i.e. at an optimal CT stimulation.

In interactive touch, the sensation is mediated only at the touched site when another person touches the subject or at the fingers of the toucher. Weber (1905; cited in Katz 1989) and (Katz 1989), recognising the clear differences between these types of touch, and basing their observations upon introspection, concluded that the sensations generated during self-touch depended on the anatomical distance of the touched skin site from the brain. The logic here was that when touching, e.g. the ankle, signals from first touch nerves in the fingers would arrive in primary somatosensory cortex (SI) before those from the ankle, leading to touch being sensed at the fingers, whereas when touching the face, the reverse would be the case, as signals in first touch trigeminal nerves would reach SI before those from the hand. However, a moment's introspection tells us this is not the case—we feel the touched body site when self-touching. By way of explanation we now know that glabrous-to-hairy skin self-touch will not only activate first touch neurones but also the slow second touch CTs—particularly if the touch is delivered at a CT preferred velocity typical of the speeds used when allo-grooming.

In order for touch **not** to be sensed by the touching fingers—the most densely LTM innervated body site—an inhibitory gating of LTMs in the touching hand is required. This may depend on 'efference copy' feedforward mechanism such as that posited to explain why we cannot tickle ourselves (Weiskrantz et al. 1971; Blakemore et al. 1998), but more intriguingly is the putative role of a somatosensory cortical mechanism. This hypothesis is based on data from single-unit recordings of pyramidal neurones in upper-layer area 3b/1 of somatosensory cortex in the monkey and cat (Dreyer et al. 1974; McKenna et al. 1982) which responded optimally to slowly moving (1–5 cm/s) brushing stimuli, and sub-optimally to brushing at high velocities. These velocity-tuned responses in layer I/II neurones in SI mirror those of the first-order CT neurones recorded in humans, as does their prolonged after-discharge to slow touch and their receptive field properties—poorly defined borders with non-uniform 'hot spots', similar to the properties described by Wessberg et al. (2003) with microneurography recordings from CTs in human skin. Slow touch activation of these upper layer (I/II) pyramidal neurones, as would occur during allo-grooming, is here hypothesised to inhibit the deeper layer pyramidal neurones that are traditionally regarded as the entry stage

of fast touch somatosensory cortical information processing—layers IV/IIIb. We therefore feel the body site being groomed—second touch inhibits first touch. And, more importantly for understanding why grooming is so pleasurable, the non-CT innervated hand delivers the rewarding touch.

A complete understanding of the behavioural and affective consequences of the differential innervation of CT afferents awaits a fuller understanding, but of interest here to auto- and allo-grooming behaviours in humans is whether the non-CT innervated palm used to apply grooming products confers a different response from the giver and receiver of such touch? A study in female Barbary macaques found significant relationships between physiological stress levels and the giving, but not in the receiving of grooming (Shutt et al. 2007), running counter to previous research that showed the more intuitive opposite effect that the receipt of grooming reduces stress levels, as measured by lowered heart rate (Boccia et al. 1989; Aureli et al. 1999; Fairhurst et al. 2014). Grandi and Ishida (2015) have also reported a cross-species effect of allo-grooming showing that grooming by a familiar human induced a lowering of heart rate and an increase in heart rate variability in housed male monkeys. It is also of interest to note that this autonomic response on heart rate was groomed body site dependent being largest when the mouth was groomed compared with the arm and chest. The giving and receiving of touch forms a complex relationship, where it is likely that the higher level cognitive implications of the social interaction play a key role in how the touch is perceived, as well as in the physiological effects produced. Differences have been found in the sensations generated from self- compared to other-touch with the emotional processing of touch being particularly susceptible to context (Ackerley et al. 2014). It has also recently been shown that cortical processing of tactile and visual input can be influenced by the apparent gender of the touching person (Gazzola et al. 2012), and this could also modify conscious perception of the touch received.

With both the pleasant and social aspects of gentle skin-to-skin contact in mind, a framework is proposed within which to consider CT afferent coding properties and pathways, and the behaviours and mind states elicited by their stimulation, that is encompassed by the ‘CT affective touch grooming hypothesis’. As first and second touch systems normally operate seamlessly together it has been difficult to ascertain their separate contributions to this wider sense of touch, but in studies carried out in a patient lacking large myelinated afferents—and hence first touch—it was found that activation of CTs by gentle stroking produced a faint sensation of pleasant touch. Neuroimaging (fMRI) revealed that in response to CT-preferred (gentle brushing) stimulation there was activation of the insular region, but a negative BOLD response in SI (Olausson et al. 2002). These findings identify CTs as a system for emotional touch driving hormonal and affiliative responses to caress-like, skin-to-skin contact between individuals, but also during self-touch. This system of unmyelinated afferents has topographical, electrophysiological and psychophysical response properties that correlate well with specific COBS repertoires—e.g. the slow, gentle stroking and rubbing movements typified by auto- and allo-grooming behaviours. A study on the pleasurable sensation of different tactile stimuli to various parts of the body reveals significant differences in pleasure ratings, with remarkable differences between men and women (Essick et al. 2010, see Fig. 16.2).

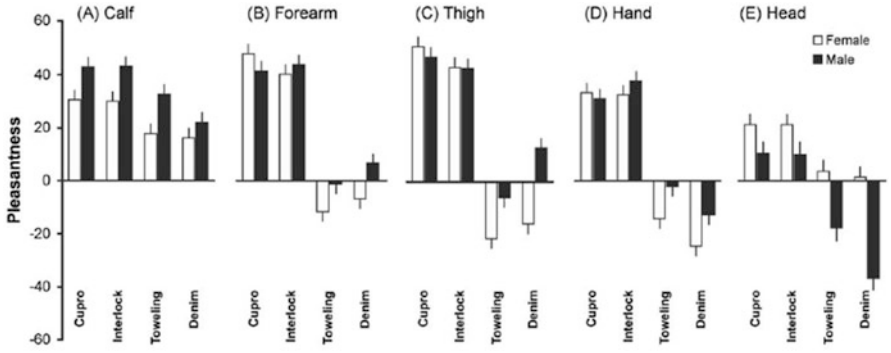

Fig. 16.2 Least squared means (+1 S.E.) of hedonic ratings for four textured materials, differing along a harsh–soft dimension, at each of five body sites. The materials and sites are each rank ordered left to right in overall, descending tactile pleasantness. Data are shown separately for female and male participants (Essick et al. 2010)

The attention given to individual body sites within a sequence may well be determined by the extent to which these sites are innervated by the fast and slow touch systems, which have been shown to be linked to the production of endogenous opioids as well as a 'hedonic homunculus' (Walker and McGlone 2014; Denworth 2015). Studies also confirm the intuitive notion that pleasant touch requires a light and slowly moving stimulus, and that the pleasurable effect from stroking a single body site decreases over time (Vallbo et al. 1999; Triscoli et al. 2014).

Functional brain imaging has shown that brush stroking of the skin activates the insular cortex, the part of the brain that represents the body's physiological condition and hence is associated with different aspects of 'feeling good' (Craig 2002; Olausson et al. 2002). From a commercial standpoint, these findings may help to identify formulations that activate CTs in order to improve the sensory properties of grooming products. Knowledge about the structure and function of the different cutaneous sensory nerves innervating the skin can help, for example, determine the tactile pleasure effects of fabric softening technologies (Essick et al. 2010), or to map the sensory nerves in the axilla (armpit) to develop deodorants that do not feel sticky (Guest et al. 2012). There is a risk also that some skin care formulations may harm the skin, inducing sting or itch, and here it is yet another population of C-fibres that generate these sensations—nociceptors and puriceptors (Rukwied et al. 2002, 2003).

Human Grooming and the Personal Care Industry

Extrapolating from Dunbar's statement (Dunbar 2010) that in non-human primates the amount of time spent mutually grooming indicated that the behaviour must confer substantial benefit beyond one of hygiene, we can now take this an evolutionary step further and apply the same analysis to human grooming. The amount of money

spent purchasing all manner of grooming products far outweighs any functional need from their use. In human primates COBS has evolved far beyond its equivalent role in lower animals to now drive a global body care and cosmetic industry predicted to reach $265 billion per year by 2017 (Lucintel 2012), with the skin care sector accounting for $115 billion in 2015 for the United States alone (Fig. 16.3).

Here it is important to make the distinction between allo-grooming and self-grooming. Most animals self-groom, but allo-grooming has been seen as more the province of non-human primates where it has been known for some time to control social hierarchies within colonies. The most commonly reported allo-grooming in humans is maternal grooming of offspring, but it also reported to be prevalent in adult dyads (Daly

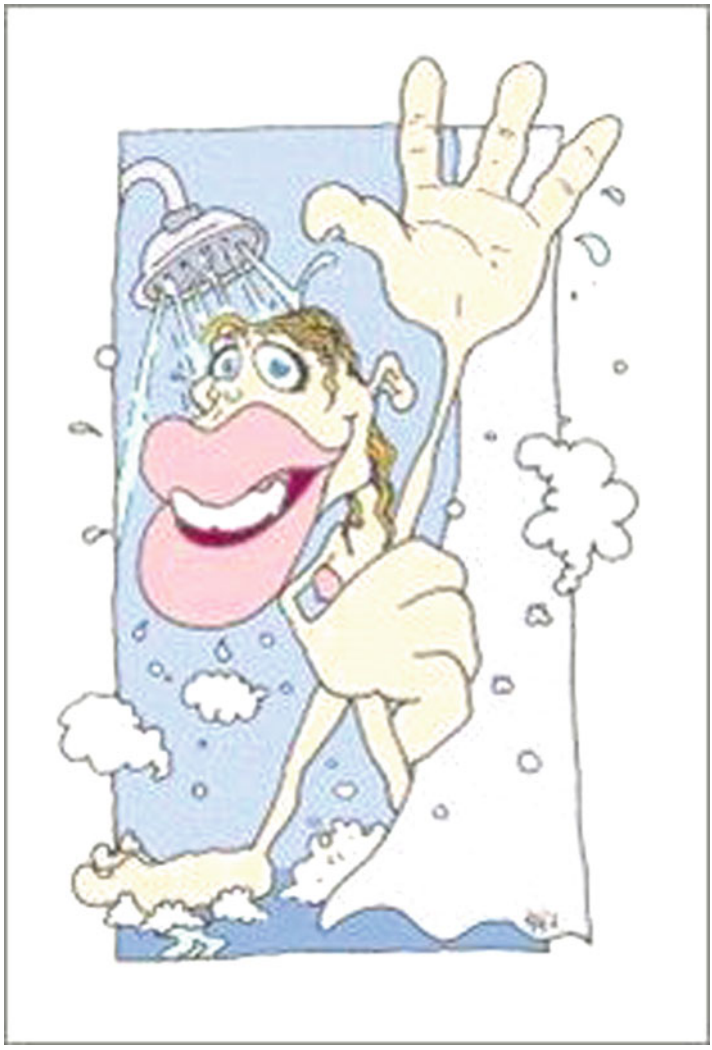

Fig. 16.3 The pleasure of grooming …

et al. 1983; Nelson and Geher 2007). Although this has the classic COBS function, it also plays a critical role in cementing the relationship between mother and infant, and of that between romantic dyads (Bowlby 1969; Lee 1983; Hazan and Shaver 1987). Allo-grooming of infants has a profound impact of the development of a well-adjusted social brain (see McGlone et al. 2014 for a review), and capitalising on how important touch is to a baby's growth and development, baby care companies are promoting such maternal behaviours with advertising campaigns that promote the importance of '*enhanced daily care rituals that help your loving touch gently stimulate your baby's senses and nurture their developing mind*' (http://www.johnsonsbaby.co.uk/sensorial-experiences). Also capitalising on how important touch is to adult intimate relationships, a major condom company is recognising that sexual behaviour has evolved beyond a solely procreative function to one of pure pleasure by marketing gels and oils claiming that '*Massage & Play Soothing Touch boosts pleasure and intimacy by inviting you and your partner to explore and experiment with what feels good*.' Of note here is that we do not currently know if CTs are present in the genitals, the only evidence for their absence coming from a study by Liu et al. (2007) in mice. However, feeling good is more than just a side effect of looking good: the very act of grooming inevitably activates CTs, leading to the release of endogenous peptides such as the endorphins which stimulate the intrinsic opiate system, and also OT, which also interacts with the endogenous opiate system (Panksepp 1998; Uvnäs-Moberg 1998).

Conclusion

By taking an ethological perspective on human grooming behaviour, we are able to see links with our evolutionary past that helps identify the initial drivers of such behaviours and to better understand the neurobiology and the psychology behind human '*grooming beyond cleaning*'. Evolution has led to the emergence of a neural circuit from the skin to the brain that codes for the affective as opposed to discriminative properties of touch, rewarding us with the pleasurable feelings associated with personal and allo-grooming. It is this hard-wired mechanism that the cosmetic industry has inadvertently hijacked and that explains how the ubiquitous use of grooming products generates not only a sense of personal well-being but also one of social connectedness: These effects are specific to the COBS behaviours, they have empirically validated health benefits—both physical and mental—and they have emerged from fundamental and evolutionary determined necessity for the human primate to groom self and other.

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Chapter 17
The Midas Effect: How Somatosensory Impressions Shape Affect and Other-Concern

Annett Schirmer, Maria Teresa Wijaya, and Siwei Liu

Abstract Studies exploring the influence of casual touch (e.g., a tap on the arm) on interaction partners identified a phenomenon called the Midas effect. In analogy to the Greek mythical figure Midas, whose touch turned everything into gold, casual touch promotes positive affect and other-concern. Compared to interactions without casual touch, those with casual touch leave touch recipients with more positive emotions and goodwill toward others. Here, we review the literature that established the Midas effect and explore a possible somatosensory basis. Specifically, we consider studies that independently modulated skin temperature, pressure, and velocity of tactile sensations and show that these modulations produced mental and behavioral changes in line with the Midas effect. Additionally, we discuss possible mechanisms by which somatosensory impressions affect emotional and social processing and outline existing links between both. Together, the literature reviewed here favors the idea that the Midas effect arises in a bottom-up manner from the stimulation of the skin and highlights the importance of interpersonal tactile exchanges for our personal well-being and the functioning of our social groups.

Keywords Midas effect • Somatosensory impressions • Casual touch • Positive affect • Physical contact

Our interactions with others tend to focus on verbal information and often leave us inattentive to the myriad of non-verbal signals that we both send and receive. This is particularly true for the casual tactile exchanges that accompany most friendly intercourse (Fisher et al. 1976). Often, do we gently tap a person's arm or shoulder without these actions springing from an obvious action plan or conscious strategy. Likewise, that we are touched by others often goes unnoticed and is afterward difficult to describe or recall. Is touch then insignificant—a mere accessory of human

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communication? In this chapter, we review evidence to the contrary and show that, despite a potential lack in awareness, interpersonal touch makes a significant contribution to interaction outcomes. Additionally, we characterize the nature of this contribution and shed light on potential mechanisms through which touch exerts its effect.

The Midas Effect

A now classic study by Fisher and colleagues revealed first evidence that casual touch in interpersonal interactions is more consequential than it seems (Fisher et al. 1976). In this study, the researchers instructed library clerks to either casually touch student customers or to avoid touch. Specifically, they asked these clerks to place their hand over the open palm of the customer's hand when returning the customer's library card or to extend the card without making physical contact. Afterward, an experimenter approached the customer under the pretext that the library was conducting a survey of its services and personnel. Customer reports that were obtained under this pretext indicated that those who had been touched by the clerk felt more positively and were more positively inclined toward the clerk than customers who had not been touched.

Many studies followed this original research and replicated the general results. In the context of commercial settings, the services of stores, restaurants, and their service personnel were rated more positively by customers who were touched as compared to customers who were not touched (Hornik 1992; Erceau and Guéguen 2007). Additionally, similar findings extend to other settings such as the classroom. Here it was shown that students touched by their instructor were more motivated in class and found the instructor more effective and engaging than students who were not touched (Legg and Wilson 2013).

Importantly, however, touch shapes more than just affective responses or attitudes. Research that explored behavioral consequences of touch found that it increases the likelihood of interaction partners complying with a request. For example, in a field study by Kleinke (1977), subjects used a public telephone-booth in which the experimenter had left a dime. After exiting the booth, subjects were approached by the experimenter who pretended to have lost the dime and asked whether the subject had found it. Subjects were significantly more likely to return the dime when the experimenter accompanied his request with a touch as compared to when there was no tactile contact. In line with this, other researchers reported that touch increases the likelihood that individuals participate in an interview or survey (Hornik and Ellis 1988), they follow advice for a meal (Guéguen et al. 2007), they share a smoke (Joule and Guéguen 2007), they leave significant tips (Crusco and Wetzel 1984), or they simply help someone in need (Guéguen and Fischer-Lokou 2002, 2003). Thus, the effect of casual touch on interaction partners has been described as the Midas effect in reference to the Greek mythical king who turned everything he touched into gold (Crusco and Wetzel 1984).

Research suggests that, on a psychological level, the Midas effect reflects an influence of touch on affect and impression formation. The term affect here refers to an underlying mental state that varies in valence from positive to negative and is hence a

more basic psychological property than emotions, which are more varied (Feldman-Barrett 2006). Impression formation, the process whereby we assess another's personality and intentions, has been postulated to occur along two dimensions termed warmth and competence (Fiske et al. 2007). When encountering others, so the theory goes, we first evaluate them as warm or cold depending on whether they appear sincere, trustworthy, friendly and helpful as opposed to false, scheming, hostile, and self-serving. In a second step, we are thought to evaluate competence as a means to assess how capable others are in following through potential positive or negative intentions.

That touching contributes to affect and impression formation especially with respect to warmth is implicit in the findings reviewed above showing that touch increases liking toward a toucher. Additionally, it is apparent from a recent study in which participants were presented with images of dyadic interactions that differed only in whether they involved touch. Those interactions that involved touch elicited higher likeability ratings for the toucher, the touchee, and the overall interaction than those that did not (Schirmer et al. 2014).

Why Touch Makes Us Kinder

Together psychological research provides compelling evidence that casual touch can bring out the best in us. However, it says little as to why and how this effect is achieved. Different possibilities present themselves. For one, many aspects of our nonverbal behavior may change when we touch as compared to when we do not touch others and it may be this change, rather than the touch itself, that makes others affectively more positive and obliging. One nonverbal behavior that does necessarily change is the physical proximity between interaction partners. Typically, we move physically closer when we touch and one may reasonably suspect that such closeness affects interaction partners.

Another possibility is that touch effects arise from the somatosensory impressions that physical contact leaves on the skin. Specifically, the stimulation of tactile receptors may relay information to the brain that is rewarding and that promotes attitudes and behaviors that promise future tactile rewards. In the following, we focus on this latter possibility. We provide a short review of the somatosensory system, which is followed by a discussion of existing research on the emotional changes elicited by stimulating components of the somatosensory system that seem particularly relevant for casual touch.

The Somatosensory System

The term somatosensory system refers to the nerves and tissue formations that enable proprioception (i.e., the sensing of one's body position in space) and cutaneous sensitivity. The latter, which is fundamental to our ability to perceive touch, comprises specialized receptors and processing pathways representing different kinds of information including the temperature, pressure, and movement of objects that come into contact with the skin.

Temperature information is conveyed via receptors with thinly myelinated and unmyelinated axons. These thermal receptors respond to changes in skin temperature with warmth receptors increasing their firing as the skin gets warmer and cold receptors increasing their firing as the skin gets colder. Thermal information from both receptors is sent via spinal fiber tracts that project to the thalamus and from there to the primary somatosensory cortex or, bypassing this region, to dorsal-anterior insula and anterior cingulate cortex (Kandel et al. 2000). Notably, the latter two areas are primary sites for emotional processing within the brain (Phan et al. 2004).

Pressure and movement parameters of touch are conveyed by a foray of thickly myelinated mechanoreceptors with different properties and functions. They include Merkel disks, Ruffini endings, Pacinian corpuscles, Meissner's corpuscles, hair follicle receptors, and free nerve endings. These receptors differ in whether they are located in superficial or deep aspects of the skin, whether they have small or large receptive fields, and whether they are slow or fast adapting.

Of much interest for the purpose of this book, however, is another type of mechanoreceptor called C-tactile afferent. It was discovered more recently than the other mechanoreceptors and it differs from them in important ways. First, CT afferents are found only in hairy skin and are thus absent from the palm of the hands and the sole of the feet. Second, they respond maximally to stroking rather than simple pressure and prefer velocities around 4 cm/s (Löken et al. 2009). Third, they are sensitive to temperature information in that they prefer tactile contact that is skin-warm (Ackerley et al. 2014). Fourth, they are unmyelinated and have, therefore, a slower conduction velocity than your typical mechanoreceptor. Fifth, their projections to the central nervous system appear to by-pass primary somatosensory cortex and, like some of the thermal projections, to travel directly from the thalamus to the dorsal, albeit posterior, part of the insula (Olausson et al. 2002). Lastly, their stimulation in the skin and associated brain activations are experienced not simply as touch but as pleasure whereby the amount of pleasure correlates with the receptor's firing rate. Based on these properties, it has been proposed that CT afferents play a special role in the interindividual tactile exchanges of humans and those of other hairy animals (Morrison et al. 2011a; Löken et al. 2009; Olausson et al. 2010).

Given the nature of casual touch and the basic organization of the tactile system, three somatosensory mechanisms may be responsible for the Midas effect. These include the neural pathways underlying the perception of temperature, pressure, and velocity. In the remainder of this chapter, we review studies that have recruited these three somatosensory mechanisms and linked their recruitment to positive affect and/or prosocial behavior.

Temperature

In most climates, interpersonal touch is associated with changes in skin temperature. Under ordinary conditions, skin temperature moves between 32 and 35 °C and is thus typically warmer than ambient temperature. Moreover, when ambient air is

cooling, skin-to-skin contact has a warming effect and excites warmth receptors in the skin to increase firing. Irrespective of ambient temperature, skin-to-skin contact furthermore activates CT afferents (Ackerley et al. 2014). Research suggests that the resulting increase in perceived physical warmth could contribute to the Midas effect.

The first fact in favor of this possibility is the close and potentially reciprocal relationship between skin temperature and emotions or affect. Emotions and affect regulate skin temperature from within the body through their impact on the sympathetic nervous system. Specifically, sympathetic arousal elicited from stress or threat leads to vasoconstriction of the blood vessels that innervate the skin and thereby reduces skin temperature (Kistler et al. 1998; Kuraoka and Nakamura 2011). Conversely, calm positive states such as those produced by the mental engagement with pleasant memories appear to increase skin temperature. Specifically, they were found to raise subjective feelings of warmth and to increase participants' tolerance for a noxious cold stimulus (Zhou et al. 2012).

In addition to research showing that emotions modulate skin temperature, there is also evidence that changes in skin temperature can modulate emotions. Sung and colleagues (2007) showed this by attaching a warm pack to the lower leg of their participants. Subjective reports from the participants indicated that the pack produced feelings of pleasure and comfort. Functional imaging measures additionally revealed increased brain activity in a range of structures including the somatosensory insula (Sung et al. 2007). In line with this, hot water or steambaths are a common recreational activity and have been used since antiquity as a means to treat various medical conditions including psychosomatic disorders (Lowry et al. 2009). It has been proposed that the positive relaxing feeling we associate with being warm relates to warmth sensitive brain stem neurons that trigger the release of serotonin (Lowry et al. 2009).

A second line of evidence that links temperature sensation to the Midas effects comes out of social psychology and entails a series of studies showing that physical warmth boosts psychological warmth and vice versa. Original evidence that increased skin temperature enhances psychological attributes along the warmth dimension comes from a study by Williams and Bargh (2008). In a first experiment, these authors asked participants to hold onto a hot or cold beverage. Afterward, the participants read the description of a person and had to rate that person's personality on traits that ranged from warm to cold. Holding a warm drink significantly increased warmth ratings relative to holding a cold drink. A second experiment was conducted under the guise of a product evaluation. Here, participants held onto a warm or cold therapeutic pad and were asked to subsequently evaluate the pad. After completing this mock evaluation, they were presented with two items one of which they could take home. Participants holding the warm pack were significantly more likely to pick the item that was framed as a gift for a friend over the item that was framed as a personal treat. Participants holding the cold pack showed the opposite effect.

Subsequent research from other labs corroborated these findings. For example, in a series of experiments, IJzerman and Semin provided evidence that the effect of changing skin temperature is similar to the Midas effect (IJzerman and Semin 2009). In a first study, these authors used the beverage approach introduced by

Williams and Bargh. Participants were given a hot or cold drink and subsequently completed the Inclusion of Other and Self Scale for a person they knew and themselves. Rating results indicated greater inclusion and thus closer psychological proximity between other and self after holding a hot as compared to a cold drink. In two further experiments, IJzerman and Semin manipulated skin temperature by changing ambient room temperature. Compared to a colder temperature, a warmer temperature was again associated with higher inclusion ratings. Additionally, participants' descriptions of geometrical figures contained more relational terms.

Apart from exploring whether changes in skin temperature affect psychological warmth, researchers also explored the opposite—namely whether changes in psychological warmth alter how warm or cold people feel. To this end, IJzerman and Semin invited participants to the lab and manipulated social proximity by spacing them either closely or distantly to confederates in a mock experiment (IJzerman and Semin 2010). Subsequently, participants were asked to judge ambient temperature together with other variables on a Likert scale. Those spaced more closely judged ambient temperature as higher than those spaced more distantly, even when there was no actual difference in the temperature as measured by the thermometer.

IJzerman and colleagues extended these results to situations in which social proximity was manipulated not by physical distance but by making participants feel similar or different from other participants or by making them feel socially included or excluded. For example, using a virtual ball-tossing game, they introduced participants to the notion that there were two other players with whom they were exchanging balls over the internet. After the participants engaged with the game, the researchers manipulated the behavior of the virtual players such that they excluded the participants from the game. This exclusion was felt by the participants and was accompanied by a reduction in skin temperature. Moreover, it could be alleviated when participants were given a hot but not a cold drink to hold after the game (IJzerman et al. 2012).

In sum, there is now a substantial literature pointing to a positive relationship between skin temperature perception on the one hand and affect and psychological warmth on the other. Important for the present purpose is the finding that warm somatosensory experiences appear to further positive affect and psychological warmth. Thus, the warmth of another person's touch may have a similar effect and contribute to emergent positive attitudes and prosocial behaviors.

Pressure

Aside from affecting skin temperature, casual touch produces changes in pressure on the skin that are registered via pressure sensitive tactile receptors. That such pressure changes in and of themselves might contribute to the Midas effect may be inferred from the positive psychological effects that come with pressure sensations. These effects are leveraged in the context of massages applied as a treatment not only for pain but also simply for relaxation and enjoyment. Of particular note are

deep pressure massages during which individuals are covered with weighted blankets and which hence focus on altering pressure as opposed to other somatosensory experiences (e.g., velocity) implicated in more ordinary massages. Such pressure treatment has been shown to decrease physiological markers of arousal and to increase psychological well-being by providing a sense of safety, comfort, and groundedness (Mullen et al. 2008). Notably, deep pressure massages are also employed in the treatment of autism. While individuals with autism find ordinary interpersonal touch everything but pleasant, they, like healthy individuals, feel less anxious and tense when their skin is weighed down by stationary deep pressure (Edelson et al. 1999).

There is little empirical research exploring pressure effects for the smaller body-area contact more typical of casual touch. One relevant study found that CT afferents respond preferentially to low pressure touch as may be employed during interindividual contact (Vallbo et al. 1999). Additionally there is a study that explored the effect of low pressure touch on emotion (Schirmer et al. 2011). In this study, participants came to the lab with a friend who served as the toucher in one of three experimental blocks. In the other two blocks, the participant was connected to an inflatable pressure cuff and told that inflation was machine controlled or controlled by the friend operating the cuff remotely from outside the experimental room. Within each block, the participant was exposed to emotionally negative and neutral images, half of which were viewed while the friend or the cuff exerted light pressure on the forearm, whereas the other half were viewed without such pressure.

Scalp recorded event-related potentials (ERPs) to the images indicated that pressure altered the participants' mental state (Fig. 17.1). Specifically, it increased the size of a well-established emotion effect between 300 and 500 ms following image onset. As had been shown before, emotional images elicited a greater positivity in this time window than did neutral images suggesting that they attracted more processing resources or attention. Notably, touch, irrespective of block, enhanced this condition difference indicating that participants became more likely to engage with the emotional images. Moreover, in line with the clinical work cited above, the authors proposed that the touch from both friend and machine made participants more comfortable such that they became less avoidant of the images' negative content.

One issue with interpreting the findings from massage studies cited earlier is that they may have invariably increased skin temperature. Thus, the resulting psychological effects may be a result of either pressure or temperature. Although no measurements of skin temperature were taken, the study by Schirmer and colleagues provides some indication that pressure alone may nevertheless be relevant. This is because participants in the pressure cuff block were wearing the pressure cuff continuously. On no-touch trials, it rested deflated on their skin and simply inflated on touch trials. Thus, one would presume that between these trials skin temperature was left more or less the same.

In sum, research implicates skin pressure in the Midas effect. Such pressure appears to calm and reassure recipients, which could help establish trust. Additionally, it seems to influence how recipients engage with concurrently presented information making them more receptive toward emotional content.

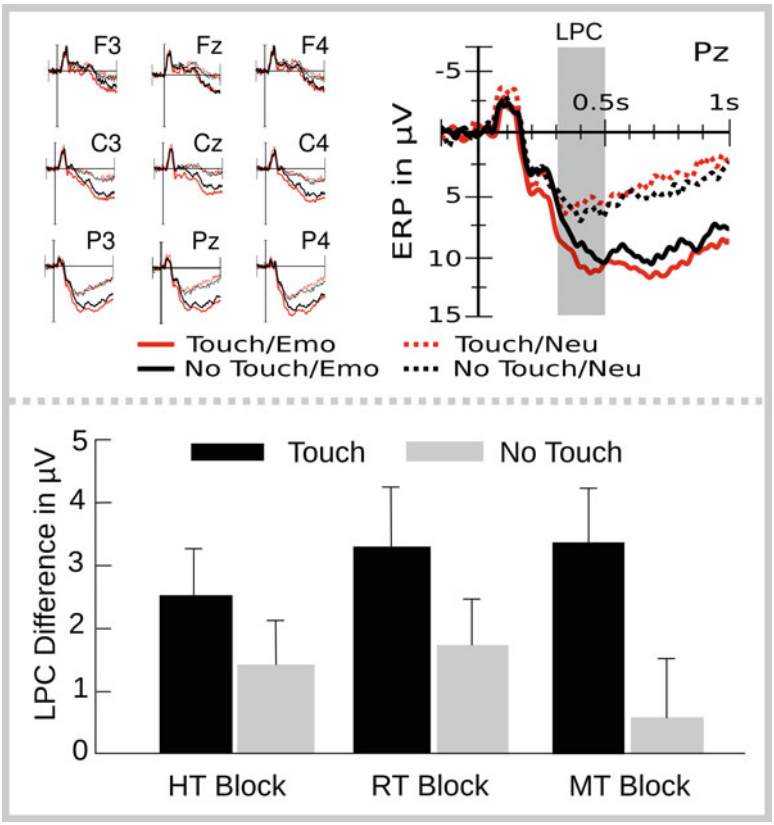

Fig. 17.1 (*Top*) ERP traces time-locked to picture onset. The time window for the late positive component (LPC) is the area shaded in *gray*. Touch enhanced the LPC amplitude difference between emotional (Emo) and neutral pictures (Neu) (*bottom*). This enhancement was seen across the three experimental blocks (*HT* Human touch, *RT* Machine touch attributed to the friend, and *MT* Machine touch attributed to the machine). In each of them, the mean LPC difference between emotional and neutral pictures was enhanced when there was touch as compared to when there was no touch

Velocity

Compared to other forms of interpersonal touch, casual touch as explored with the Midas effect appears fairly stationary. It comprises short instances in which the toucher's hand contacts relatively "public" body parts of the touchee such as the hand, forearm, or shoulder. Moreover, these contacts are so short that there seems barely time for the hand to touch, let alone for it to move across the skin. Yet, a case can be made that such movement occurs. Given that interaction partners are in motion, most casual touch probably has a short movement trajectory making touch velocity a potential contributor to the Midas effect.

Among the different sensory components involved when two individuals touch, velocity has received most attention to date with insights coming from both human and nonhuman animals. Like humans, many nonhuman animals find movements across the skin pleasurable. This is self-evident for anyone experienced with pets such as dogs or cats who enjoy being stroked and may even demand such stroking from their owners. Moreover, that the stroking motion is rewarding independently of the temperature or pressure of touch may be inferred from the fact that pets often become restless when a petter's hand remains stationary.

Actual scientific evidence for the pleasure of moving touch in nonhuman animals comes from a study in rodents in which the experimenter tickled the rodents' belly. Such tickling provoked ultrasonic vocalizations akin to human laughter. Additionally, it led the animals to follow the experimenter's hand if he stopped tickling and moved his hand to somewhere else in the cage (Panksepp and Burgdorf 2003). In addition to tickling, stroking has been shown to be pleasurable and to reduce stress. For example, in a study in dairy cows, stroking by a human handler over a few days reduced stress responses to medical examination (Schmied et al. 2010). In rats, stroking was shown to trigger the release of dopamine, a neurotransmitter involved in pleasure and reward (Maruyama et al. 2012).

Human research parallels these findings. A study in preterm infants employed stroking with the hand in combination with kinesthetic exercises and found that this decreased stress behaviors such as crying or startling and seemed to help pacify the child (Hernandez-Reif et al. 2007). In healthy adults, the effect of stroking was explored using a soft brush. After the stroking, participants had to rate their experience on different scales assessing pleasure and other affective and sensory qualities of the touch. These ratings indicated that stroking is perceived as pleasurable, comfortable, and calming among others (McGlone et al. 2012).

Given the nature of the somatosensory system, there are different ways in which velocity may be processed and represented in the brain. One of them invokes the contribution of CT afferents, which, as mentioned above, change their firing rate as a function of tactile velocity. CT afferents were first discovered in cats and more recently identified in other species such as humans and rodents. Their functional role is difficult to explore and was hence long debated. The difficulty rests with the fact that any stimulation of the skin activates multiple kinds of receptors apart from CT afferents. Thus, the effect of CT activation is in most cases impossible to dissociate from the effect of other receptors.

One step toward solving this issue came from investigations of patients with a peripheral neuropathy syndrome characterized by a lack of ordinary mechanoreceptors and intact CT afferents. Despite being seemingly void of all conscious tactile sensations, these patients were able to detect soft stroking across hairy skin with better than chance accuracy. Moreover, such stroking triggered sympathetic arousal as measured with the skin conductance response (Olausson et al. 2008) and was reported to be pleasurable (Olausson et al. 2002). Thus, it was proposed that CT afferents serve to mediate the pleasurable aspects of social touch.

Research in rodents corroborates this proposition (Vrontou et al. 2013). Like cats and humans, these animals possess unmyelinated mechanoreceptors that are found

specifically in hairy skin and that produce a pleasurable sensation when activated. The latter was demonstrated using a pharmacological manipulation in the context of a place conditioning procedure. Specifically, rodents were placed in an enclosure and given a receptor agonist any time they moved into a particular corner of this enclosure. Over time, the rodents developed a preference for being in that corner suggesting that they found the associated pharmacological stimulation rewarding.

Apart from CT afferents, myelinated mechanoreceptors contribute to the coding of velocity and their contributions are likely to augment the psychological benefits of moving touch. Multiple lines of evidence from both humans and nonhuman animals point to this. In the context of human research, such evidence comes again from neuropathic and healthy individuals. Neuropathy comprises different somatosensory syndromes affecting different fiber types. As mentioned above, it includes patients whose only mechanoreceptors are CT afferents. Additionally, it includes patients without thinly myelinated or unmyelinated but intact fully myelinated mechanoreceptors. If CT afferents alone were responsible for the pleasure that comes from stroking, these latter patients should be unable to experience such pleasure. This, however, is not the case. Although the pleasure experienced by these patients is not great, they are not entirely void of it (Morrison et al. 2011).

In line with this, a study in healthy individuals suggests that pleasure can be experienced from stroking parts of the skin that do not contain CT afferents. In this study, participants were stroked on the palm of the hand and the forearm with both evoking equal amounts of subjective pleasure (McGlone et al. 2012). Notably, however, this pleasure may be differently caused. Concurrently elicited brain activations in insula and orbitofrontal cortex were smaller for the palm relative to the forearm. Additionally, subjective reports obtained after the experiment indicated that stroking of the palm created stronger sensory perceptions than did stroking of the forearm. Specifically, individuals perceived palm stroking as more fluffy and hairy. Stroking on the forearm, in contrast, created stronger affective responses. Participants found it more comfortable and tendentially more relaxing.

In addition to human research, research in nonhuman animals suggests a role of myelinated mechanoreceptors in velocity induced psychological effects. Among others, such research was done in zebrafish, a species without hairy skin and thus presumably without CT afferents. Zebrafish are a small, tropical freshwater fish that move in fish shools with synchronized or coordinated behavior (Miller and Gerlai 2012). Like other fish they possess hair cell patches in their lateral lines that are referred to as neuromasts and that underpin mechanosensation (Dijkgraaf 1963; Montgomery et al. 1997). Some of these neuromasts are located in canals under the skin and presumably serve the perception of changes in water current such as those caused by sudden acceleration in the movements of the shool. Other neuromasts are located more superficially and have been linked to the general perception of water currents and the fish's ability to orient itself within such currents.

That a stimulation of lateral line neuromasts affects emotional aspects in zebrafish was recently demonstrated using a fear buffering procedure (Schirmer et al. 2013). To this end, individual zebrafish were exposed to a pheromone called Schreckstoff that is normally released by injured fish skin (Mathuru et al. 2012).

This pheromone serves as a threat signal and induces fear behaviors in nearby shoal companions. In the study, zebrafish exposed to Schreckstoff were subsequently moved into a beaker with clear water to help wash off the substance. Afterward, half the subjects were moved directly into an observation tank, whereas the other half were moved into a second beaker with water current prior to being moved into the observation tank. Water current in the beaker was induced via two valves through which water was flowing in and out. Throughout a 10-min observation period, subjects in the no-current condition showed significantly more fear behaviors than subjects in the current condition did. They dived to the bottom and froze, whereas subjects in the current condition behaved indistinguishably from fish that were unexposed to Schreckstoff. These behavioral findings were paralleled by whole body cortisol measurements.

It may come as a surprise that the tactile impression of flowing water calms fish. Unlike mammals, fish rarely come into physical contact with each other, which might make tactile sensations appear affectively irrelevant. Yet, this appearance is deceiving. Also, in fish does mechanosensation provide information that is behaviorally relevant and as such may carry a certain affective or social value. For example, flowing water brings oxygen and may contain edible materials. Additionally, it conveys tactile feedback that results from swimming in a shool and thus signals the presence of conspecifics. This perception, if it mimics that of a calm shool, could reduce fear and produce positive affect in a way that is similar to the actual presence of conspecifics (Schirmer et al. 2013).

In sum, research has linked the perception of movement across the skin to a number of positive psychological consequences. Apart from being perceived as pleasurable, such movements appear to reduce negative states and to bias ongoing mental processes toward social information. These effects depend on an array of mechanoreceptors both unmyelinated and myelinated that represent touch velocity. Given that casual touch, albeit fleeting, is likely to produce tactile motion, these processes potentially contribute to the Midas effect.

Why Do Tactile Temperature, Pressure, and Velocity Matter to Us?

As evident from the present review of the literature, the perception of interpersonal touch is a complex phenomenon that requires the integration of multiple somatosensory aspects including pressure, temperature, and velocity. Past inquiries into these aspects have shown that they each are linked to emotions and that they can increase positive affect and prosociality in touch recipients. In the following, we consider possible mechanisms through which this might occur.

Positive Affect. Warmth, pressure, and velocity antagonize affectively negative and promote affectively positive states. Why this should be the case is not immediately obvious. Of the myriad of tactile sensations that meet us every day most seem

behaviorally irrelevant. The wind brushing over our skin, the contact our body makes with fabric or furniture, or the instances in which we thoughtlessly touch ourselves seem hardly worth an emotion. Moreover, only a few tactile instances are of obvious consequence most of which probably arise from interpersonal interactions.

One reason why tactile sensations regardless of source may pull our emotional strings is that they may be more important than they seem. After all, touch is the sense most developed at birth and thus enables an individual's first exploration and representation of the world (Field 2003). Additionally, it serves to maintain the natural bond between infant and mother that emerges in the womb and that is critical for the infant to survive after birth. Through tactile contact with the mother, the infant can regulate his/her body temperature and secure food, protection, and body care. Thus, tactile sensations associated with these early necessities may be hard-wired to emotion centers in the brain. Such hard-wiring would ensure that infants find their mother's touch naturally rewarding and that they seek out or "demand" this reward.

In line with this idea, there is evidence that early maternal touch—or in nonhuman animals, grooming—is critical for offspring development. Epigenetic mechanisms exist whereby the frequency of touch modulates brain morphology and function. Licking and grooming of rodent pups by mothers or surrogates were shown to affect the expression of glucocorticoid receptors in the hippocampus a structure that is critical for downregulating HPA axis activity during stress (Liu et al. 1997). Maternal stroking has also been implicated in the development of what has been termed the "social brain." Compared to pups with a low-touch mother, pups with a high-touch mother were shown to develop more receptors for oxytocin, a neuropeptide that promotes bonding and prosocial behavior. Thus, the latter animals eventually turn into more socially apt adults (Champagne and Meaney 2001). Similar findings, albeit correlational, were obtained in humans with children showing greater interest in social information the more their mothers were observed touching them during a 10-min free play situation (Reece et al., 2016). Moreover, children receiving greater amounts of touch showed greater resting activity and connectivity in the right posterior superior temporal sulcus a major node of the "social brain" and a projection target of CT stimulation (Brauer et al., 2016).

In addition to a hard-wired relationship, touch may be linked to emotions through learning. Early developmental as well as subsequent tactile exchanges with other individuals during childhood and adolescence likely carry a particular temperature, pressure, and velocity signature. The close temporal association between this signature and positive interaction outcomes (e.g., nourishment, cleaning, protection, and sex) may create associations in memory via classical conditioning. Because intermittent reinforcements of such associations are more powerful than continuous reinforcements in producing an enduring affective response, it is easy to see how the occasional positive tactile encounter could create emotional links that eventually operate simply based on somatosensory experiences irrespective of the source of touch.

Finally, it is possible that the positive affect that comes with being touched is a secondary result of tactile sensations promoting prosociality (discussed below). There is much research linking the two and showing that kindness and goodwill conferred to others promotes an individual's own happiness (Lyubomirsky and Layous 2013). One such demonstration was made in 2-year-old toddlers who were rated as happier by independent observers after having bestowed a treat on a puppet monkey as compared to having received a treat for themselves (Aknin et al. 2012). Thus, the concern for others kindled by touch and the associated readiness to act on this concern may in and of themselves make us feel better.

Prosociality. Research that explored the relationship between touch and prosociality has focused primarily on temperature and velocity. Both were shown to enhance social interest and it is possible that prospective studies on pressure would do as well. Again, several mechanisms could account for this.

First, it is possible that prosocial touch effects are mediated by positive affect. As such they would depend on the first or second mechanism outlined in the previous section. In line with this possibility, studies have demonstrated that positive affect promotes prosociality (Isen 1970; Isen and Levin 1972). For example, in early work by Isen, participants performed a task after which they were told that their performance was well above or well below average. Subsequently, a confederate came into the room asking for donations. Compared to participants who considered themselves unsuccessful, those who considered themselves successful and were thus arguably in a happier mood donated more money. This and similar results were linked to the idea that in a happy state we consider our needs fulfilled and our resources sufficient, thus allowing us to extend consideration and support to others without significant costs to oneself (Isen 1970).

A second possible mechanism underpinning the relationship between touch and prosociality involves learning and operates independently of positive affect. It entails the possibility that in the course of development the somatosensory signatures of interpersonal touch attain a certain symbolic value. They may come to stand for a close and beneficial social relationship and implicitly affect our evaluation of others. As such others who touch us, regardless of their relational status, may be perceived as close and beneficial.

Lastly, the prosociality that springs from another's touch may be a by-product of more general principles that govern our representation of abstract concepts such as another's personality or mental state. These principles have been proposed to rely on processes that ground abstract concepts within actual physical experience (Barsalou 2008; Niedenthal et al. 2005). Such grounding, also referred to as embodiment, would mean that we map personality aspects or mental states such as approachability on actual body sensations such as being physically connected with someone. Within this framework then, touch could serve as a concrete experience that automatically informs our thoughts about more abstract interpersonal matters. A summary of this and the other mechanisms outlined here is presented in Fig. 17.2.

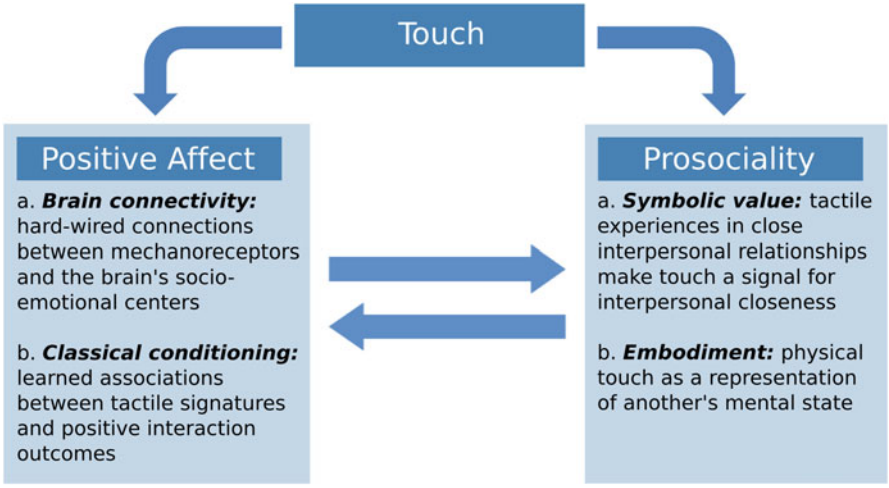

Fig. 17.2 Summary of possible mechanisms mediating the Midas effect

Summary and Outlook

Casual touch in interpersonal interactions is often performed and perceived unconsciously. Nevertheless, its impact on these interactions is substantial. Compared to individuals who are not touched, individuals who are touched feel affectively more positive and are more likely to extend goodwill toward interaction partners. Here, we show that this phenomenon, called the Midas effect, likely has a somatosensory basis. Touch produces sensations of warmth, pressure, and velocity on the recipient's skin and these sensations by themselves, irrespective of their source, can trigger positive affect and concern for others. At present, we can only speculate about the mechanisms that underpin these effects. Existing work highlights numerous possibilities ranging from hard-wired pathways that link tactile sensations with affective and social substrates in the brain to experience dependent learning. Additionally, there is evidence that positive affect and prosociality are tightly linked and are probably feeding off each other such that tactile effects on one might automatically affect the other.

Although extant research sheds much light on the effects of casual touch, many studies remain to be done. For one, studies are required that tackle the mechanisms by which touch alters affect and prosociality. Additionally, it would be interesting to explore whether vicariously experienced touch has similar effects. Does observing another person being touched improve the observer's affective state and does it increase other-concern? Neuroimaging research demonstrating somatosensory activations during tactile observations makes this a possibility (Morrison et al. 2011a). Another question worth investigating is whether the tactile sensations that produce the Midas effect need to be caused by others. The person who is touching us most is

probably the self and it would be interesting to determine whether such self-touch is equally potent in promoting positive emotions and prosocial tendencies.

Note that answers to these and related questions would not simply address mere scientific curiosity. They would be of practical value. In a society where interpersonal interactions become more and more impersonal by being conducted over the telephone or the World Wide Web, the consequences this has for our mental functioning need to be better understood. We need to know what we lose by making friends and "staying in touch" through remote messaging and what this form of socializing means for our emotions and actual social connectedness. The research outlined here does help with this and although it may not stop the advance of technology into our lives, it may inform policymakers to preserve critical interpersonal elements and engineers to find ways of incorporating them into emerging social platforms.

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Chapter 18
Intimacy and the Brain: Lessons from Genital and Sexual Touch

Janniko R. Georgiadis and Morten L. Kringelbach

Abstract The fusion of the male and female gamete is usually preceded by intense interpersonal touch, especially involving stimulation of parts of the genital tract. However, the effects of sexual genital stimulation reach beyond fertilization and reproduction, as shown by experimental evidence that the pleasure drawn from it drives sexual desire, mediates the formation of sexual preferences, and improves general well-being. The brain processes sexual stimuli like other pleasurable stimuli, which means that they go through a cycle where they are identified, desired, consumed, and devalued. Genital receptors and nerve fibers may thus primarily serve a proximal master—pleasure. In this chapter, we outline what is known about the peripheral and central processes involved in the perception of pleasurable sexual touch and intimacy. As sexual behavior is typically social (i.e., involves human stimuli), genital afferent input might well adhere to the principles of the social touch system.

Keywords Genitalia • Small diameter fibers • Central body maps • Sexual pleasure cycle • Erogenous zones • Incentive motivation • Psychophysics • Neuroimaging

How lucky we are that we can reach our genitals instead of that spot on our back that itches.
—Flash Rosenberg

I'll be a park, and thou shalt be my deer;
Feed where thou wilt, on mountain or in dale:
Graze on my lips, and if those hills be dry,
Stray lower, where the pleasant fountains lie.
—William Shakespeare

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Introduction

Historically, touch has been much less studied than other senses, which is perhaps surprising given how much pleasure and well-being can be drawn from it. In fact, touch is vital for the survival of the human species, playing a major role in the early parent–infant relationship which ensures the survival of a child to reproductive age. Reproduction, in turn, also relies strongly on the role of bodily intimacy and touch between sexual partners. It is thus vital to obtain information about how touch and intimacy help to promote the survival of our species. However, there clearly is much more touch and intimacy than is required for species survival, and most of us would readily admit that squeezing, biting, scratching, sucking, kissing, licking, or caressing enhance sexual pleasure. As a testimony to the hedonic and erogenic potential of interpersonal touch, much human art in the form of paintings, poetry, songs, movies, and literature have expressed the thrill and pleasure of intimate bodily contact. Indeed, skin touch may give rise to distinct erotic or sexual sensations, including autonomic manifestations as expressed in shivers—or even feeling as if one is fainting. Such distinct pleasurable sensations may well draw on small diameter fiber signaling (McGlone et al. 2014), as shown by studies of anterolateral (spinothalamic) tract transections resulting in loss of sensitivity to intimate touch (Lahuerta et al. 1994) and even anorgasmia (Beric and Light 1993).

Genital sensation (real or imagined) may well provide the basis for all erotic feelings, and its role in putative sexual reflexes (erection, lubrication, and ejaculation) and sexual development (through associative learning) has started to be investigated in more details (Pfaus et al. 2012; Georgiadis et al. 2012; Hoffmann 2012). The skin of the genitalia, as a pivotal point of entry into the brain's sexual system, may thus be of great importance in understanding the development of sexual behavior, from sexual dysfunctions like premature ejaculation to sexual preferences like a leather fetish and maybe even to malicious sexual preferences like child sexual abuse. Unfortunately, genital and erotic touch remain an understudied field of neuroscience.

In this chapter, we outline what is known about the peripheral and central processes involved in the perception of sexual touch and intimacy. While we acknowledge that any part of the human skin has the potential for erogeneity, and while, conversely, we accept that the erogeneity of genital touch depends on contextual factors (e.g., person, place, and time of day), we feel it is reasonable to define sexual touch primarily by genital sensation. A recent study demonstrated that the skin of the genitalia clearly tops the list of body areas that have erogenic potential (Turnbull et al. 2014).

Overall Structure of Sexual Behavior

Ultimately, reproduction requires the fusion of the male and female gamete, and usually this is achieved through sexual intercourse. This critical procreative consequence of sex has given rise to numerous sociosexual norms and taboos surrounding

sexual behavior. It has also resulted in a strong reproductive focus in the way people (including scientists) generally think about sex (Agmo 2007), blurring the basic structure of human sexual behavior. Yet, as already suggested, besides fertilization of the ovum, sex has another more proximal master: sexual pleasure.

Sex is fundamental reward for most healthy adult animals alongside that of food and social stimuli (in social animals). In order for the brain to optimize the allocation of resources, all rewards go through pleasure cycles where they are first desired, then liked, and finally devalued so that other rewards can be pursued (Fig. 18.1b) (Kringelbach et al. 2012; Georgiadis and Kringelbach 2012).

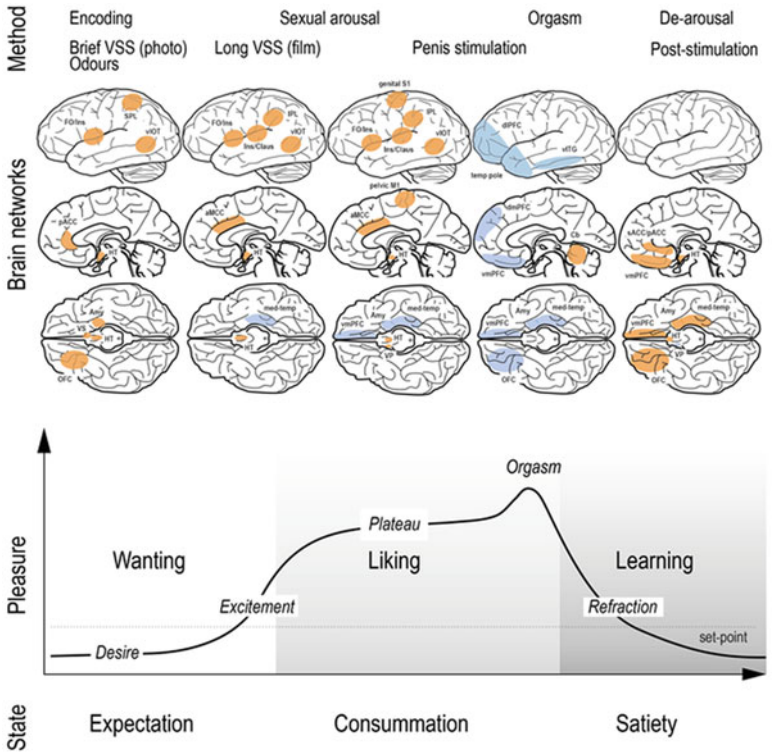

Fig. 18.1 Brain activity over the sexual pleasure cycle. The figure summarizes the findings from the neuroimaging literature as they relate to the different stages of the human sexual response cycle: desire, excitement, plateau, orgasm, and refraction (*bottom*). Note that the sexual response cycle can easily be reworked to conceptual frameworks that allow generalization to other motivated behaviors. Neuroimaging studies have elucidated the key nodes and hubs that are responsible for sustaining and switching between the different phases of the pleasure cycle which can lead to changes in behavior (*top*). Relative increases and decreases in brain activity during a particular phase are indicated by *red* and *blue* color, respectively. Please note that some regions have multiple roles at different points in the sexual response cycle, for example, activity in the amygdala is involved in different ways in encoding sexual salience, sexual arousal and orgasm, and poststimulation

The evidence shows that the largest human erogenous zone is in the brain integrating sensory and contextual information to bring about pleasure. However, different networks of brain regions are important during the different phases of the sexual pleasure cycle; in particular, for enabling the necessary state transitions (see Fig. 18.1a).

Motivation ("desire") is required for sexual activity to commence and can be seen in a wide range of courtship or appetitive behaviors. There is no general consensus as to what exactly drives this sexual motivation. The popular concept of libido holds that sexual desire results from a homeostatic drive (the need to reproduce), which would make it analogous to how eating is driven by the need to restore the energy balance. Sex hormones are necessary for sexual desire, and it is therefore often assumed that sex hormone levels could represent a sexual homeostatic signal. However, this view has been challenged by studies that point to the role sexual experience and that coin external stimuli as drivers of sexual desire (Spiering et al. 2002; Agmo and Berenfeld 1990; Parada et al. 2010). In recent years, it has become increasingly clear that sexual pleasure, especially when derived from stimulation of (engorged) genitalia, is a major driver of sexual responsiveness, and a key factor in the formation of sexual incentives (Pfaus et al. 2012; Georgiadis et al. 2012; Georgiadis and Kringelbach 2012). The actual sexual performance is usually highly pleasurable and requires high levels of general arousal and adequate genital function. A variable period of sexual performance can lead to sexual satiation which may temporarily kill further sexual desire. Presumably, it is the ejaculation that instates this refractory state in men. In women, sexual refraction is much more variable and the mechanism causing it much more difficult to determine (Levin 2009). Sexual unresponsiveness may also result from other factors, such as stress.

Sex is thus a true pleasure cycle: the different elements that constitute sexual behavior wax and wane in frequency over time as different goals are identified, desired, and consummated (Kringelbach et al. 2012). Recently, we proposed to structure it accordingly by using heuristics (wanting, liking, and inhibition) to describe the major behavioral phases (Georgiadis et al. 2012). In this way, sexual responses follow a pattern similar to other motivations, such as thirst, hunger, and drug addiction, in which an individual wants or craves, likes (or dislikes), and then experiences behavioral inhibition and diminished desire in the form of satisfaction (Kringelbach et al. 2012; Georgiadis and Kringelbach 2012). These conceptualizations allow researchers to draw direct comparisons between men and women, and across species, both in terms of the behavior that is expressed in each phase and the neuroanatomical and neurochemical systems that underlie them. For instance, wanting is driven by mesolimbic dopamine, whereas liking is driven by opioid systems (Georgiadis et al. 2012; Berridge and Robinson 2003; Pfaus 2009).

Touch is an important part of all the phases of the sexual pleasure cycle, and the sexual pleasure model predicts that its effect is likely to vary accordingly. In other words, touch may be the sexual incentive or it may enhance sexual desire during the wanting phase; touch may enhance the pleasure experienced during the liking phase; and touch might cause sexual aversion during the inhibition phase (note however that depending on, e.g., context or person touch may have opposite effects). Genital stimulation is important for genital responses and climax and may well be an unconditional sexual incentive.

Genital Touch

Anatomy of External Genitalia

The genitalia are organs designed for sexual activity, but not all of these organs are located on the body surface. Skin covers the penis, perineum, and scrotum in men, and the clitoris, perineum, and labia in women. The contact surface of the internal genitalia (e.g., vagina, prostate, and urethra) is lined with mucosa. This distinction can be traced back to the ectodermal versus endodermal origin of the external and internal genitalia, respectively. Take the example of the external genitalia: from about the ninth week of gestational age and starting from a common embryonic template, the external genitalia begin to differentiate under influence of androgens. The fetal labioscrotal walls give rise to the labia majora and scrotum, whereas the fetal genital tubercle gives rise to the clitoris and the penis. The common starting point results in very similar innervation and vascularization of male and female external genitalia. From the adult male and female genital appearance, this may be hard to imagine, but one has to bear in mind that conditions where a genetically female fetus is exposed to excess levels of androgens (e.g., congenital adrenal hyperplasia) sometimes give rise to a completely normal male external genital appearance. Some of these genetic women prefer to live as men (Lee et al. 2010).

The penis is made up of three cavernous bodies, which engorge with blood during erection. The two *corpora cavernosa* are paired cavernous bodies forming the dorsal aspect of the penis and the greater part of the shaft. These bodies are responsible for the quite extraordinary change in penile shape and size during erection. In the midline, the ventrally located *corpus spongiosum* contains the urethra. The distal portion of this body is generally perceived to be the most pleasurable of all body parts when stimulated sexually: the glans (or tip) of the penis. The shaft is covered by hairy skin, which may or may not extend all the way over the glans as the prepuce. The glans itself is covered by glabrous skin. The clitoris only differs from the penis with respect to length and size of the shaft, the size of the clitoral glans, and the position of the urethra which is between the clitoris and the vagina, and not inside the corpus spongiosum. As we will argue below, it is probably not unreasonable to consider the glans as a specialized "sex sensor" (which in the case of the penis is elongated). However, in contrast to other sensors in the human body, the glans is able to increases its sensitive surface transiently. This certainly does not imply that other parts of the genitalia would not be able to fulfill a role as sex sensors.

Innervation of Glans Penis and Clitoris

The central afferents of the receptors in the skin of the external genitalia course in the somatosensory pudendal or perineal nerves and enter the central nervous system (CNS) at the level of the sacral spinal segments S2–S4, whereas the sensory afferents from the internal genitalia use the sympathetic and parasympathetic nerve

fibers (Everaert et al. 2010). This means that visceral afferent information from the deep genitalia can enter the CNS in sacral segments (pelvic nerve), in high lumbar or low thoracic segments (hypogastric nerves), or even in the brainstem (vagal nerve). In terms of the receptors in the wall of the genitalia, not much is currently known but, as shown below, most of the present evidence concerns the glans penis and to a lesser extent the glans clitoris.

The neurophysiologist Max von Frey (1852–1932) famously stated that "no other area of the body is less sensitive to mechanical stimulation than a callus on the sole of the foot" (Von Frey 1894). His accurate observation was backed with empirical data many decades later. In a seminal ultrastructural study using penises amputated during sex change operations, the receptors in the human glans penis were mapped (Halata and Munger 1986). It was found that the constellation of receptors in the penis is rather unique. Classic corpuscles (encapsulated mechanoreceptors) and thick myelinated fibers appeared to be virtually absent. By contrast, the glans was packed with free nerve endings (FNEs) and thin myelinated or unmyelinated fibers. In fact, FNEs were estimated to account for 80–90 % of all axon terminals in the glans. This does not mean that corpuscular receptors were absent in the glans. Already in the nineteenth century, it was known that the glans penis houses an unusual type of large encapsulated receptor (Krause 1866) found nowhere else in the body, later coined genital end bulbs (Dogiel 1983), or lamellated genital corpuscles (Johnson and Halata 1991). Halata and Munger identified at least two subtypes, located at a variable depth in the skin of the glans, and moreover demonstrated that the inner core of these genital corpuscular receptors consists of "numerous axon branches that are indistinguishable in ultrastructural terms from free nerve endings" (Halata and Munger 1986, p. 225). In a recent study on the human glans clitoris, similar corpuscular receptors were found (Shih et al. 2013). Furthermore, the study suggested that their density is greater than that in the glans penis, but implications for clitoris versus penis sensitivity are unclear due to the descriptive nature of these studies. The authors concluded that "genital corpuscular receptors are […] a terminal collection of sensory nerve fibers twisted in a skein-like fashion resulting in an increase in surface area for the perception of pain, temperature, vibration, and touch." (Shih et al. 2013, p. 1788). This suggestion is both interesting and reasonable, but it may be added that these receptors have also been shown to be sensitive to filling of the penile cavernous bodies (Johnson and Halata 1991), suggesting a role in the sensation of sexual erection and engorgement. Moreover, sensitivity to (at least) penile touch is enhanced when the penis is erect (Johnson 1988) and warm (Johnson and Kitchell 1987).

These receptors might be especially sensitive to moving touch and friction, analogous to the FNEs that are held to process pleasant social touch in arm and leg (CT afferents; Vallbo et al. 1993; Bjornsdotter et al. 2010). The interesting finding that pleasant touch FNEs exhibit optimal function when the skin is warmed to temperatures reflecting interpersonal skin to skin contact (Ackerley et al. 2014) provides an intriguing possible connection to any FNE)social touch system in the genitalia. Indeed, genital contact between sexual partners may be seen as a form of intense social interaction (i.e., between sexual partners). Unfortunately, much remains

unclear from the present evidence, like the mediating role of lubrication or the receptors in the skin of shaft and prepuce (though some evidence seems to indicate that more classic mechanoreceptors would be present in the prepuce than in the glans (Taylor 2007)).

Psychophysical Studies

Important evidence of genital touch comes from psychophysical studies of sensitivity thresholds, either on the skin of the external genitalia, or on other parts of the skin under neutral or sexually aroused conditions. Assessing skin sensitivity thresholds may be performed in the context of clinical diagnosis of neuropathic conditions such as diabetes, but also of sexual dysfunction like sexual arousal problems or erectile dysfunction.

In a thorough study in 107 patients recruited from a large US urology clinic (Bleustein et al. 2003), sensory tests were performed on flaccid penises. About 80 % of the sample had some degree of erectile dysfunction, while the remaining men did not report experiencing sexual difficulties. Spatial discrimination, pressure, and vibratory thresholds were determined for the glans penis, the ventral aspect of the shaft (at least including the frenulum) and the base of the shaft. Thermal thresholds (warm and cold) were determined for the glans only. All temperature thresholds turned out to be higher (or in the case of cooling, lower) in men with erectile dysfunction, and glans thermal sensation was the most specific and sensitive predictor of the degree of erectile dysfunction. On average, patients with erectile dysfunction reported neither cold nor heat in the 25.3–39 °C range. In the male patients, *without* erectile dysfunction this nondetection range was on average 6 °C narrower (Bleustein et al. 2003). An even narrower nondetection range (29.9–34 °C) was found in healthy young men (Yarnitsky et al. 1996). Decreased thermal sensitivity is also seen after prostate resection (Lefaucheur et al. 2000), whereas sensitivity to vibrotactile stimulation is decreased in neuropathic (diabetic) patients (Morrissette et al. 1999). All in all, these psychophysical studies seem to reflect the receptor constellation of the penis and the clitoris as identified by physiological studies. In particular for the glans, the fact that thermal stimulation is the most sensitive indicator of glans sensation, and that prostatic surgery (which seriously affects thermal sensitivity) is most likely to damage small diameter fibers, is in line with the protopathic dominance of glans innervation (Halata and Munger 1986; Johnson and Halata 1991) and the mediating role of temperature in glans touch sensitivity (Johnson and Kitchell 1987).

Ecstatic exclamations during the sexual pleasure cycle such as “your touch makes me tingle” are not uncommon, and suggest that under aroused conditions skin sensitivity changes. An important question is how physiological (genital engorgement) and subjective sexual arousal modulate the sensitivity of the skin. During normal sexual arousal, there is a concordance between physiological and subjective sexual arousal, which then manifests as a unified feeling of sexual

arousal. This, however, is not necessarily the case in the laboratory. Pharmacologically induced penile erections have provided inconclusive answers: Rowland and colleagues found an enhanced detection threshold to vibrotactile stimulation in the erect versus the flaccid state, especially in men with erectile dysfunction under non-pharmacological conditions (Rowland et al. 1991). Another study failed to find an effect of genital engorgement (Rowland et al. 1991) on vibrotactile sensitivity in a group of men with premature ejaculation (Paick et al. 1998). On the other hand, penile sensory thresholds (assessed by mild electrical stimulation) have been found to increase immediately after ejaculation relative to baseline (Yilmaz and Aksu 2000), but it is unclear whether this is a characteristic of the postejaculatory state or of residual engorgement of the penis. These results do not provide clear evidence for the idea that the altered position of the receptors or the altered receptor shape underlies enhanced touch sensitivity during genital arousal (Halata and Munger 1986; Johnson 1988).

What about the effect of subjective sexual arousal? Jiao and colleagues showed that sexual arousal (induced by an erotic video) enhanced the sensitivity (i.e., reduced detection threshold) to 30 Hz, 60 Hz, and 100 Hz vibrotactile stimulation on the index finger relative to the nonaroused state (Jiao et al. 2007). Likewise, women who are unable to attain sexual arousal were found to have lower vibrotactile and thermal sensitivity in the clitoris and vaginal wall (Helpman et al. 2009). On the other hand, healthy young women did not show a difference for light touch detection thresholds on their vulva and clitoris between a nonaroused baseline and a state of high sexual arousal. The use of hormonal contraceptives had no effect on detection thresholds (Paterson et al. 2013). Women who cannot attain sexual arousal have decreased vibrotactile sensitivity in their index finger (Frohlich and Meston 2005), but the reverse (increased touch sensitivity during sexual arousal) has not been found in sexually asymptomatic women (Paterson et al. 2013).

Interpretation of these results is complicated by a number of problems. First, most studies make use of static vibrotactile stimulation, whereas moving touch or friction is a key element of actual sexual stimulation. Second, the mediating effect of lubrication is mostly neglected. Third, the most relevant of all thresholds may be the *hedonic* threshold (i.e., the pleasantness of stimulation) rather than the sensitivity threshold.

Paterson and coworkers tried to tackle some of these issues by allowing women to masturbate to orgasm or near orgasm, and by allowing them to use a lubricant. Besides testing factual ('neutral') touch sensitivity, the researchers also assessed pleasure and pain thresholds by applying pressure with increasing force. As we have described earlier, neutral touch sensitivity was not different across the sexual response. However, hedonic thresholds were. Specifically, pleasure thresholds only changed *after* masturbation, decreasing, and reaching their lowest rating 15 min after masturbation had ended (regardless of whether orgasm had been achieved). Intriguingly, pain thresholds showed dynamic changes *during* the period of masturbation, as women were more sensitive to pain relative to the nonsexual (and non-stimulatory) baseline state (Paterson et al. 2013). This does not fit earlier studies showing that deep vaginal penetration decreases pain sensitivity in both female rats

(Johnson and Komisaruk 1996; Gomora et al. 1994) and humans (Whipple and Komisaruk 1998). Yet, it does show that sexual pleasure can modulate incoming pain information from the genitalia. Such modulation would then most likely occur at the central level, which is interesting in the light of recent insights into interacting pain and pleasure pathways in the brain (Leknes and Tracey 2008).

In summary, though it seems clear that the glans is a sensor specialized for detecting stimuli that signal sexual reward, we do not yet have insight into the exact, intricate workings of this sensor. Importantly, however, much less is known in this respect about the glans of the clitoris, and this area could benefit from more research. One way of interpreting the sometimes conflicting psychophysiological findings outlined in this section is that encoding of genital pleasure is mostly happening in the brain, but it should be noted that this is still an outstanding issue.

Central Processing of Genital Touch: Animal Studies

Afferent sensory information from the genitalia can cause several primal sexual reflexes, including spinal cord reflexes such as contact erection, contact lubrication of the vagina, and reflexes related to ejaculation (Normandin and Murphy 2011). The same sensory information may also contribute to behavioral reflexes, that is, stereotyped sexual behaviors, like the female receptive posture (lordosis) or male mounting behavior. These reflexes basically equal sexual performance in all vertebrates, except a few primate species. Nevertheless, these reflexes may also be present in humans in a rudimentary form. What this would imply is that genital sensory information reaches centers in the brainstem and diencephalon that organize these reflexes, most notably the midbrain periaqueductal gray matter (PAG) and centers in the hypothalamus which are known to be linked to such behaviors in rodent and feline species (Pfaus 2009; Sakuma and Pfaff 1979; Hull and Dominguez 2007). However, the external genitalia are connected to many more brain areas. Using retrograde viral tracers injected in the external genitalia, Marson and colleagues showed that many areas were labeled in the brains of male and female rats, including the PAG and parabrachial nucleus in the brainstem, the amygdala, the hypothalamus, and the nucleus accumbens (Marson and Murphy 2006; Marson 1995). This common neuroanatomical network for male and female animals that is somehow connected to external genital structures clearly attests to their previously described anatomical similarities.

Another method is to identify neural activity during an actual sexual performance, and in the case of experimental animals this always involves genital stimulation. This can be achieved by injecting a tracer that labels neurons that express c-fos, an immediate early gene in neurons that are active, and to compare the c-fos activity during the different stages of sexual performance. It turns out that during penile–vaginal intercourse (which stimulates penis, vulva, and vagina) the hypothalamus, the amygdala, the bed nucleus of the stria terminalis, and the thalamus are active in both male and female rats. This activation is stronger than in a nonsexual

male–female social interaction (Coolen et al. 1998; Veening and Coolen 1998). There is currently very little information on the activity in the cortex which has been largely ignored in animal tracing studies, even when the cortex is also a likely target of genital sensory information in rodents.

Central Processing of Genital Touch: Human Studies

Brain areas related to the processing of genital touch in humans can be inferred from functional neuroimaging in healthy individuals or from patients with neurological problems. Whereas, animal studies are concerned with genital afferent input to subcortical structures like the thalamus and hypothalamus, human studies have a tendency to focus exclusively on the cortical representation of the genitalia. In particular, there is much debate about the exact location of the external genitalia on the primary somatosensory cortex in the postcentral gyrus (S1). Based on their seminal cortical stimulation experiments in neurological patients, Penfield and Rasmussen developed the iconic "homunculus," their representation of S1 topography (Penfield and Rasmussen 1950). On this sensory homunculus, the external genitalia were represented on the paracentral lobule, that is, the interhemispheric cortical surface dorsal to the cingulate gyrus, immediately ventral to the representation of the feet. One of Penfield's colleagues, J. Kershman, is known to have expressed his concerns about the homunculus' genitalia in a song that was sung during Penfield's 60th birthday party, stating that "his [the homunculus] happiness founded on things near his toes" (Feinsod 2005). The external genitalia indeed are represented more than fivefold smaller than the foot on the homunculus. The representation of the female external genitalia is similar, but appears to be based on the reports of a single patient, questioning its validity (Di Noto et al. 2013).

The "Penfield-location" of the penis and vulva has been corroborated (Allison et al. 1996; Guerit and Opsomer 1991; Mäkelä et al. 2003; Nakagawa et al. 1998; Komisaruk et al. 2011), but it has also been heavily disputed. First, a thorough anatomical study has demonstrated that the central sulcus does not even reach the midline in most people (Grefkes et al. 2001), which corresponds with a location on the dorsal convexity of the postcentral gyrus generally found by modern neuroimaging studies of genital stimulation (Bradley et al. 1998; Georgiadis et al. 2010; Kell et al. 2005; Michels et al. 2010; Mehnert et al. 2008). This location is found regardless of whether the study involved genital engorgement and sexual arousal or not.

A second major concern is the electrical stimulation used in most of the studies that identified the "Penfield" location. As remarked by Kell et al. (2005), electrical stimulation typically activates larger cortical areas than natural stimulation (Forss et al. 1994), whereas the cortical stimulation employed in the days of Penfield was probably hardly focal. The latter is relevant because Kell et al. (2005) showed that postcentral gyrus responses to toothbrush stimulation of the toe (hallux), the inguinal region, and the shaft of the penis largely overlapped in all of their eight subjects (Kell et al. 2005). A recent study from our lab using paintbrush stimulation has found very similar overlapping activity (Kortekaas et al., 2015).

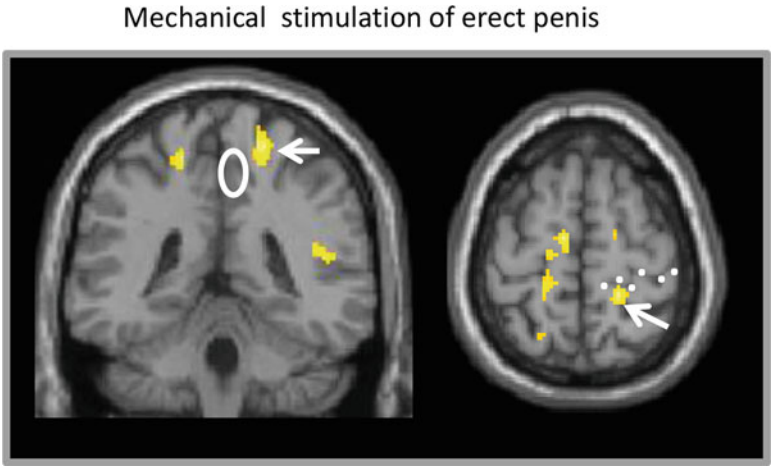

Fig. 18.2 Representation of the genitalia on human somatosensory cortex. The position of the genitals on the primary somatosensory cortex (S1; white oval) was originally described by Penfield and Rasmussen (1950) based on electrode recordings during brain surgery. This location has been heavily disputed, which is depicted here by activation in dorsal S1 in a group of 16 healthy men undergoing dynamic tactile stimulation of the erect penis (Georgiadis et al., 2010). The dotted line marks the central sulcus, the white arrow marks the alternative genital S1 location, and the black arrow marks the posterior insula. Note that despite bilateral stimulation of the penis, activity is primarily right-sided

The way the genitals are represented on the homunculus, and the suggestion that this representation reflects their sexual function, is neither satisfactory nor very intuitive, and discordant with the feelings that can be gained from stimulating these organs. S1 may produce genital feelings, but it is unlikely that it is sufficient to produce sexual feelings. Penfield himself is known for stating that that the cortical stimulation never elicited erotic sensations in his subjects (Penfield and Rasmussen 1950; Penfield and Kristiansen 1951), but this might also reflect the strict sexual mores of the time (Di Noto et al. 2013; Kell et al. 2005). In an fMRI study with partnered stimulation of the erect penis, genital S1 activity did correlate both with objective (penile tumescence) and subjective measures of sexual arousal (Fig. 18.2). However, sexual feelings may require genital S1 to have interplay with other brain areas. The auxiliary somatosensory areas are found in the parietal operculum and in the posterior insula, both of which have been shown to respond to penile touch (Mäkelä et al. 2003; Kell et al. 2005; Kortekaas et al. unpublished results), penile erection (Georgiadis et al. 2010; Georgiadis and Holstege 2005; Ferretti et al. 2005; Moulier et al. 2006; Redouté et al. 2000), and sexual genital stimulation (Georgiadis and Holstege 2005; Georgiadis et al. 2009, 2010). In a study focusing on vulvar pain, insula and parietal operculum activity tracked with the perceived discomfort of vaginal stimulation (Pukall et al. 2005), supporting the idea that emotional load modulates activity in the parietal operculum (Ploner et al. 2002). Indeed, in a design where touch and arousal/erection effects of sexual penis stimulation could be

disentangled, parietal operculum activity was found to depend on both (Georgiadis et al. 2010). The parietal operculum may be one of the nodes that creates a unified sexual experience depending on how genital sensory inflow is coupled to, for example, emotional information from the mediotemporal cortices (Friedman et al. 1986) and frontal motor areas (Eickhoff et al. 2010).

Despite the strong evidence provided by the animal work, no study to date has been able to reliably connect human genital touch or genital stimulation to subcortical areas. For the detection of distant sexual cues, this is different: the ventral striatum and amygdala in particular are highly responsive to visual sexual and olfactory incentives (for an overview see Georgiadis and Kringelbach 2012). Alongside S1 one would expect the somatosensory thalamus to activate, and the same logic could apply for medial thalamic nuclei which in primates are known to project to the somatosensory cortices (Cerkevich et al. 2013). It is unclear why these areas do not exhibit significant activity in the fMRI experiments of genital touch. The hypothalamus and ventral palladium showed involvement in a design using partnered sexual tactile stimulation of the penis, but their involvement seemed to be driven by the arousal—or maybe erotic—component of the feeling, rather than the somatosensory component (Georgiadis et al. 2010).

Clinical conditions may lead to (unwanted) genital and sexual sensations, which may give additional clues about the way sexual genital feelings come about. In rare cases, epileptic seizures may manifest such that the dominant ictal sign is sexual or erotic (sexual auras). Genital sensations may ensue from epileptic lesions in the postcentral gyrus (York et al. 1979), but sexual auras seem to be a key feature of temporal lobe epilepsy (TLE), especially originating from the right mesiotemporal lobe (Janszky et al. 2004; Aull-Watschinger et al. 2008; Remillard et al. 1983). The seizures and sexual ictal manifestations are usually resolved after resection of part of the affected mesial temporal lobe. This is interesting because sexual arousal in healthy, nonneurological subjects tracks with decreased activity in the medial temporal lobe, including the amygdala and hippocampus (Georgiadis et al. 2006, 2007, 2010; Redouté et al. 2000), suggesting that the seizures caused similar activity changes in the medial temporal lobe or affected the information processing between the medial temporal lobe and other areas in the brain. Interestingly, sexual auras (both orgasmic and nonorgasmic) are more common in women (Janszky et al. 2004).

Another interesting clinical condition in the light of genital and erotic feelings is Persistent Genital Arousal Disorder (PGAD), also known as REGs, Restless Genitals Syndrome (Waldinger and Schweitzer 2009; Leiblum and Nathan 2001). The condition seems to affect women more than men, is distressing and largely outside of the patient's control. Typically, it involves genital sensations and sensations of being aroused, including a genital engorgement that is clearly felt. Furthermore, a role for small diameter fibers in the etiology of this syndrome has been hypothesized (Waldinger et al. 2010, 2011). One interesting case study found an association between PGAD and an epileptic focus in the left posterior insula, and subsequently performed fMRI to study functional connectivity of the posterior insula before and after antiepileptic treatment (Anzellotti et al. 2010). During the pretreatment fMRI experiment, the patient experienced sudden waves of sexual

feelings and genital arousal, which did not occur during the posttreatment fMRI experiment when the symptoms had resolved. The results indicated that treatment had reduced functional connectivity especially among areas in the left hemisphere, such as the middle temporal gyrus, the inferior parietal lobule, and the superior and the inferior temporal gyrus. All these areas are usually found in fMRI studies of healthy (wanted) sexual arousal (Georgiadis and Kringelbach 2012; Stoleru et al. 2012). This would seem to suggest that the feelings reported by PGAD patients are largely neocortical and left-dominant, but besides the obvious potential problems with single case studies many questions remain. For instance, it remains unclear how the posterior insula feeds into these neocortical areas, and whether the analysis was sensitive to subcortical effects.

There is clearly a need for more, and more structured, human brain studies of genital touch, both under neutral and aroused conditions. Currently, fMRI experiments are underway that try to scrutinize the functional connectivity of the posterior insula; in particular, as the posterior insula is known to be sensitive to pleasant slowly moving touch (Morrison et al. 2011), different brush stimulations are being applied (fast and slow) to different parts of the penis (shaft and frenulum) in different groups of men (including men suffering from premature ejaculation). The results of these experiments are expected to provide new insight into the central processing of genital touch.

Nongenital Erotic Touch

Erotic sensations can be derived from body surfaces outside the genitalia. These so-called erogenous zones have long been a topic of popular interest, but have been largely neglected by science. Popular belief has it that certain body surfaces are more erogenous than others, for example, the feet, the inner thighs, the buttocks, the neck, and also the ears. The dominant explanation for the distribution of erogenous zones is currently provided by Ramachandran and Blakeslee (Ramachandran and Blakeslee 1998) who in their book hypothesize that certain body areas may more easily gain erogeneity by virtue of their representation of S1 adjacent to primary sexual organs (genitalia and nipples). In other words, touching body parts *adjacent* to genital S1 may produce *partial* activation of the genital S1 representation—producing low level erotic sensation. Such presumed crossover effects have been taken to explain that the most common fetish is that for feet or footwear (Scorolli et al. 2007), or that some people have strong sexual feelings associated with the desire to have a healthy leg amputated (xenomelia) (Hilti et al. 2013).

Unfortunately, this S1 hypothesis has not been tested empirically. In a very recent study, Turnbull and colleagues recruited college students for an online survey, asking them to rate (in terms of level of arousal) the ability of 41 different body areas to facilitate sexual arousal. The foot was listed as one of the least erogenous zones, which seems to disprove Ramachandran's hypothesis (Turnbull et al. 2014).

On the other hand, it is well possible that such rankings of erogenous body areas are highly contextual. The actual sexual arousal is likely to depend on factors such as

the person providing the stimulation and the level of sexual arousal. This may have profound impact even on S1 activity. Support for this notion comes from an fMRI study, where male, heterosexual subjects were led to believe that they were being touched on their inner thigh by a man or by a woman. In reality, however, it was always the same woman touching them. Thinking that someone of their sexual preference touched them led to much stronger leg S1 activity than when they thought a man was stimulating them, even when the stimulation, mechanically, was always the same (Gazzola et al. 2012). Further analysis revealed that brain responses already started to diverge when the cue was shown that predicted the 'male' and 'female' touch.

Sexual Development and the Role of Touch

Sexual pleasure is brought about by sexual stimuli and in particular genital touch and bodily intimacy. Usually touch stimuli only become important as a route to pleasure when sexual maturity is reached, but they can have this role earlier in development. Sexual stimuli are so potent that learning effects become very powerful. Such learning is very difficult to study in humans for obvious ethical reasons, but the implications of this learning are very important in the future well-being of individuals. Here, we briefly touch upon what is currently known of the role of touch in sexual development.

Touched for the First Time

Genital sensory input is instrumental in sexual development and the formation of sexual incentives, such that virtually any stimulus or feature can come to trigger sexual desire after association with genitally induced sexual pleasure (Pfaus et al. 2012; Hoffmann 2012). In principle, this is the same incentive motivational framework (Bindra 1974) that drives the formation of incentives for other pleasures, like drug (ab)use and eating (Robinson and Berridge 1993; Berridge 1996), and it has recently been shown that motivation (whether it is for drugs or sex) is mediated through a common neural platform, at least in rats (Pitchers et al. 2013).

Experimental studies conducted in rats have pointed out that touch is most important for crystallization of sexual behavior. Male rats who have their first sexual experience with a topical anesthetic (lidocaine ointment) applied to their glans penis do not reach ejaculation and most likely experience little sexual pleasure. On a subsequent test, they fail to show the sharp increase in sexual motivation that is typical of second sexual encounters. Quite to the contrary, an insensitive glans penis extinguishes subsequent sexual performance almost completely. Interestingly, prior experience with genital pleasure (i.e., without the ointment) seems to have a protective effect. As few as five prior sexual encounters with normal penile sensation lets males mount and intromit normally despite penile sensation being absent on the test. Ten prior normal sexual experiences even lets them ejaculate normally with an

anesthetized penis (Pfaus et al. 2012). Likewise, sexual experience protects against the effects of clitoris anesthesia. In female rats blocking of clitoral glans sensation (with a lidocaine ointment) during their first sexual experiences affects pacing behavior, the most reliable indicator of female sexual reward (Coria-Avila et al. 2005). Specifically, without clitoral glans sensation females spend less time with the male and show increased return latencies (female rats tend to 'pace' copulations by running away and hiding for the male). This effect is not seen when the anesthetic is applied in an animal with ten prior sexual experiences with intact clitoris sensation (Parada et al. 2014). This suggests that clitoris somatosensory inflow during copulation guides the development of sexual activity.

The role of touch in sexual development may begin well before the onset of puberty. Juvenile rats engage in rough-and-tumble play which has been shown to induce a reward state (Burgdorf and Panksepp 2001). This play, which obviously involves intense mutual somatosensory stimulation, can be mimicked experimentally by tickling (Burgdorf and Panksepp 2001). Female rats who as juveniles received tickling in the presence of a scented male, as adults turn out to pick out males bearing that same odor for their first sexual contact (Paredes-Ramos et al. 2012). These results are at least suggestive of the fact that prepubescent somatosensory experiences contribute to sexual development, even when these early experiences are not sexual. They furthermore support and underscore a long line of evidence showing the importance of sufficient early somatosensory stimulation for adult emotional, cognitive, and behavioral functioning (Ardiel and Rankin 2010). To the best of our knowledge, nothing is known about possible relationships between early touch deprivation (e.g., in orphans) and adult sexual behavior.

Out of Touch

If first experiences with sexual and genital reward guide sexual development in the way scientific data seem to indicate, we are faced with a problem. Obvious ethical constraints make it highly venturesome—if not outright impossible—to study first sexual experiences in youngsters, but this means that neuroscience is going to miss out on a critical time window in sexual brain development.

It might be possible to study people who experienced first sexual genital sensations when they were adults. Rather than ethically questionable experiments on virgins, it might be possible to study a human endophenotype for the condition of absent genital sensation. People with low spinal injuries may have lifelong absent or largely absent genital feelings as testified by their sexual health and satisfaction which are typically very low (McDonald and Sadowsky 2002). This is in a way reminiscent of the lidocaine-treated rats mentioned earlier (Pfaus et al. 2012).

Interestingly, a surgical technique, TOMAX, allows the restoration of genital feelings in male patients with low spinal lesions, by transposing a (lumbar) sensory nerve of the groin area (ilioinguinal nerve) to the dorsal nerve of the penis (Overgoor et al. 2006). In a trial of 27 patients, 11 patients gained groin feelings and 13 eventu-

ally gained glans feelings. Sexual activity became far more pleasurable and meaningful to them, and some of them reported feeling that they entered the vagina (which they had never felt before). Some patients even achieved orgasms for the very first time in their life (Overgoor et al. 2013). It is not unreasonable to think that some selected TOMAX patients could provide invaluable information about sexual development.

Conclusion

In this chapter, we have reviewed the evidence for peripheral and central processing of genital touch, which is an important source of pleasure during sex. The brain integrates the sensory information from the body and in particular from the genitalia to facilitate the necessary state transitions between the different phases of the sexual pleasure cycle. The evidence shows that genital touch is processed differently whether experienced during the initial arousal phase, during the consummatory phase or during the satiety phase. The scientific evidence for the peripheral information gathered by the genital sensors and transmitted to the brain throughout the sexual pleasure cycle is still very sparse and much remains to be discovered. It is clear, however, that contextual and learning effects play significant roles in mediating the pleasure obtained. Future research would be important for revealing the role of touch in sexual development with important implications for sexual dysfunctions.

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Chapter 19
Affective Touch from a Philosophical Standpoint

Matthew Fulkerson

Abstract This chapter offers a critical philosophical examination of recent work on pleasant (or affective) touch. After developing a distinction between two notions of perceptual affect, I argue that "emotional" and "affiliative" touch are best understood as causing affective reactions, and that affective touch is best understood as perceptually presenting us with affective qualities. In other words, affective touch, unlike other forms of hedonic touch, has a presentational character. On neither model does touch involve anything like a pleasantness detector, nor does it involve a direct relation to or representation of affective qualities understood as objective sensible features of external objects. I suggest an alternative, largely dispositional account of affective touch experiences. Taken together, these reflections aim to provide a detailed framework for better understanding the richness and diversity of affective touch experience.

Keywords Affect • Affiliative touch • CT fibers • Emotional touch • Pleasant touch

Introduction

Our experience of the world through touch is not merely descriptive or informational; it is also often evaluative and motivational. Offering an account of this richness provides an important component of our understanding of touch. In addition, a focus on the affective character of tactual experience reveals some interesting connections between perceptual touch and the rest of our mental lives. After

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all, pleasantness and pain play a central role in our judgments, emotions, feelings, desires, and motivations. Any advance in our understanding of affective touch will thus have multiple implications in our understanding of human experience. But first, we need to be clear about the explanatory target and the broader implications of our theoretical accounts of that target. This chapter seeks to make some progress on both fronts.

Here is my plan. I will first develop an important and often neglected distinction between two kinds of affective state: that between *affect-causing* and *affect-presenting* perceptual experiences.[1] The former states are those in which a perceptual experience, on the basis of its informational content, generates a secondary positive or negative reaction in a subject. The latter are those whose very felt character is itself positive or negative. In the following section, I will argue that touch is (sometimes) affect presenting in this way. Feeling a soft feather pulled gently across the arm is often quite pleasant, but this felt pleasantness is a quality of the experience, and cannot be generated through any of the other sensory modalities. Seeing a feather does not feel pleasant in that way, nor does being told that there is a feather near your arm, and so on. I will complete the chapter by considering, over the course of several sections, how recent empirical work on affective touch can be understood given this framework. I argue that "emotional" and "affiliative" touch are best understood as affect causing, and that "affective" touch is best understood as affect presenting. On neither model does touch involve anything like a *pleasantness* detector, nor can it be understood as involving the representation of (or a relation to) affective qualities understood as objective sensible features of external objects. The only sense in which touch represents or brings us into contact with the pleasant and the unpleasant is via a dispositional relation between affective touch experiences and the things in the external world that typically cause them. Taken together, these reflections provide a detailed philosophical framework for understanding the affective character of touch experience, one that can easily be generalized to the affective character of all sensory modalities.

Two Kinds of Perceptual Affect

Many perceptual experiences have a pleasant or unpleasant character. This component of an experience is often called its *affect*.[2] In this section, I argue that there are two distinct ways that a perceptual experience can possess an affective character. In

[1] To be clear, these are not the only kinds of affect, as emotions and pains can also have positive and negative affect. The distinction I'm invoking here is one between kinds of *perceptual* affect. Cutaneous pains, note, are neither affect presenting or affect causing, but they have an affective character. It is just one that is never associated with external features or derived from the operations of genuine perceptual modality.

[2] "Affect" as I use it here goes by different names in the psychological literature, including *valence*, *salience*, or *hedonic tone*. While there may be some subtle differences in these various uses, for my

the first instance, a perceptual experience comes to possess an affective character by appropriately causing a secondary affective response, where such a response involves some (nonperceptual) evaluative change in a subject.[3] Call perceptual experiences of this kind *affect causing*. Other perceptual experiences come to possess an affective character by presenting external objects through a particular sensory modality as having a pleasant and unpleasant quality. Call these sorts of experiences *affect presenting*.

While I will be focusing on pleasant touch, we can get a sense of what I mean by perceptual affect by briefly considering some vivid cases from other sensory modalities. Suppose Nina comes home to find the garbage has been left sitting out, and its stench is filling her small apartment. Before she realizes not to, she inhales through her nose, filling it with the putrid, rotting air. This is affect-presenting; she is presented with an experiential quality that itself is negatively valenced. This negative experience causes immediate reactions in her, from covering her mouth and face with her arms to holding her breath until she is outside the room. She moves immediately to open the windows and tie up the trash bag, all while breathing as little as possible through her mouth. If asked, she would have preferred to avoid this experience entirely, and in all likelihood she will take immediate steps to prevent its recurrence.

There is a crucial ambiguity in experiences like this, which we will discuss in more detail later. For now, not that when Nina says that the smell is bad or unpleasant, she could be referring to the quality of her experience, the quality of the garbage odor, or both. This form of ambiguity will be important when we turn our sights directly on pleasant touch. For now, note that however she describes it, it intuitively *seems* that the quality of her experience, and not the objective features of the odor-causing objects, will be the most fundamental factor in determining the affective character of her experience. This is because, however we vary the objective features in her vicinity, if her experience has a negative quality to it, she will judge her affective experience to be bad. If she dislikes the smell of cat litter, it will not ease her experience to learn that it is not *really* cat litter she is smelling but something else that merely smells like ammonia. It is the quality of her experience that seems to be the fundamental locus of her affective experiences and judgments. Call this intuitive claim the principle of *experiential priority*.

Hopefully the notion of perceptual affect, both positive and negative, is clear enough for our purposes. Now, I believe that there are good reasons for thinking there are two distinct classes of perceptual affect, which will help clarify the inherent ambiguity between applications of affective predicates. There are *affect-causing* perceptual experiences that involve a perceptual experience that generates an affective character by causing an amodal affective response (a response not tied to any particular modality), and *affect-presenting* ones that occur when a perceptual

purposes here I will make clear the target and exclusively use the terms "perceptual affect" and "affect presenting" to refer to them.

[3] This need not be understood as a serial process, for as we'll see, the perceptual experience can immediately cause a secondary reaction. I will make clear the nature of the distinction in what follows.

experience seems to present an external object as having an affective quality.[4] Both of these forms of affective character seem to involve pleasant and unpleasant feelings, but the nature of these feelings is quite different in each case. Let's see if we can motivate this distinction.

One way to mark the distinction is by appeal to the *modality-salient* character of our affective reactions. The notion of a modality-salience is invoked by Clare Batty, who suggests that "we must distinguish between those properties that are by-products of the operation of a modality and the properties that a modality is 'in the business' of presenting" (Batty 2010).[5] The modality-salient features of visual experience include colors, shapes, and texture; for smell they include the features and properties of odors and so forth. For each modality there is a set of modality-specific salient features. The observation, then, is that the affective character of some perceptual experiences is not captured by appeal to such features. Instead, the affective character seems rooted in some other nonperceptual reaction. In other words, the affective character of affect-causing experiences doesn't supervene on first-order sensory qualities.[6] The very same affective character could have been caused by a different perceptual experience or by an experience that is not perceptual at all. For example, unexpectedly seeing a loaded gun in your friend's bag might create a strong affective response, and you might describe the resulting visual experience as unpleasant. However, *feeling* the gun in the bag or *being told* that a loaded gun was in the bag would have generated the same response. What was unpleasant about the experience wasn't the way the gun *looked*. None of the visually salient properties of the gun were unpleasant. Rather, what was unpleasant was the fact that there was a gun in the bag, and this information could have been attained in a variety of ways. The response to the gun was heavily dependent on background knowledge. If you expected your friend to have a loaded gun in her bag (perhaps she is a police officer), then you would likely not be upset to discover the gun there. Yet it seems the gun would not *look* any different. While unexpectedly seeing a loaded gun can be an unpleasant experience, there is nothing essentially *visual* about the unpleasantness. This suggests a rough criterion for determining whether a perceptual experience is affect causing:

Affect-causing experience: An experience E is affect causing if its affective character does not depend on any modality-specific features of the experience.

[4] The locution "seems to present" is used here descriptively to pick out the sort of experience I have in mind, without thereby committing myself (yet) to the claim that sensible qualities are represented or presented by such experiences. As we'll see, I don't think affect-presenting states are best explained by appeal to strong representationalism; they are best understood as a modification of occurrent perceptual experience caused by objects and properties in the environment subject to evaluative processing.

[5] Interestingly, Batty (2010) uses this distinction to defend a version of representationalism, which I take to be false for affective experiences.

[6] Note that temporal relations are not relevant for this distinction; whether the perceptual experience occurs first or alongside the affective reaction is not at all what motivates this distinction.

Similarly, we can define an affect-presenting experience as one in which the affective character supervenes on modality-salient, indeed, on modality-*specific*, sensible features:

Affect-presenting experience: An experience E is affect presenting if its affective character depends on modality-specific features of the experience.

Unfortunately, it will not always be clear whether or not the affective character depends on modality-salient features in this way. And in some cases the criterion will rest upon intuitions that might be difficult to determine. Nevertheless, in many cases, the criterion will give a strong indication of whether or not an experience is affect causing.

Plausible examples of affect-presenting experiences are easy to find. Consider again Nina smelling the rotting garbage. Is it plausible to think that Nina could have the very same affective reaction if we removed her olfactory experience? This seems unlikely. It seems more plausible that the foulness of Nina's experience is an essential part of her olfactory experience; it is part of *how* she experiences the state of affairs in her home. For this reason, it is not simply a reaction in her. This experience could not be generated through any other modality; being told there is smelly garbage in one's apartment is not at all awful in the same way. No other nonolfactory experience is awful in just this way. The awfulness of certain smells seems dependent on olfactory experience. Its grounding in a particular modality is why it is both perceptual and externalized.

Affect understood in this way plays an immediate and powerful role in our conscious lives: it provides a rich felt awareness of the potential goods and harms in our environment, and it adds value and meaning to our experiential lives. Affect presenting is distinct from the other aspects of conscious awareness: it is not (I'll argue) simply an awareness of things around us, nor is it just an emotional or subjective reaction in us. Instead, this form of affect seems to present things to us in a certain way, bridging the gap between information processing and evaluative appraisal. Recall the ambiguity of affective experience. For Nina, both the olfactory experience of the rotting smell and the smelly garbage can be understood as bad. The experience is awful and unpleasant, and it takes priority in our affective judgments, but in a sense the foulness is also out there, a feature of the odor cloud in her home. This dual nature helps explain why she is motivated to remove the garbage from her apartment.

The foulness of the odor is a modality-specific feature of the garbage; it is part of her perceptual experience of the smells in her home. Similar things could be said for affective experiences that arise in each of the other modalities. The taste of rotting meat is not one that merely causes a general secondary reaction, one that could have been caused by any other modality; the awfulness of the meat must be tasted, and when tasted, the meat itself seems to possess a particular disgusting quality.

So far we have one clear way of marking the distinction: modality dependence. An affect-presenting experience is one that strongly depends on (indeed, supervenes on) the modality-specific features of perceptual experience. We can add another way of marking the distinction: consider what happens when we introduce the possibility of *phenomenally indistinguishable fakes*. Consider, for example,

what happens if my friend only has a realistic-looking prop gun in her bag. If I didn't know it was a prop, seeing it would be very disturbing. However, once I learn that it's a prop, it is no longer disturbing. In this case, changing a non-modality-salient feature of the example (i.e., the gun still looks exactly the same, and exactly like a real gun) completely alters the affective response. Contrast this example with a synthetic rotting odor. If I walk into a room filled with such an odorant, it would not lose its unpleasant aspect once I learn that it is synthetic. An unpleasant "fake" smell is just as unpleasant as the real thing, provided all of the modality-salient qualitative features are the same. Learning that it's a fake in this case would change nothing about the affective character (assuming the context remains the same). Mohan Matthen (2012) makes this point when he argues that while there can be fake oranges (objects that look and smell just like real oranges), there is no such thing as fake orange (the color). Anything phenomenally indistinguishable from the color orange (across different exploratory contexts) *is* the color orange. Similarly, anything that has the very same sensible features as a foul odor will smell just as foul (for a subject in a context). These examples lend support to the claim that the affective character of some perceptual experiences is modality dependent; to smell something foul is to experience some object or event as having an unpleasant or pleasant phenomenal quality.

This account leaves open the possibility that the distinction involves some fuzzy borders or overlaps between cases. Some experiences might skirt the line between the two forms of experience; a strong smell might seem more affect presenting than a beautiful statue. Others might involve overlap between the two forms of experience; a rare, expensive wine might taste pleasant both because of its inherent affect-presenting sensory features but also because of its rarity and high price, knowledge, and appreciation of which cause an overall positive emotion or mood.

In addition, marking this distinction here leaves open how we understand affect-presenting states. For example, a strong representationalist, who holds that all phenomenal character is identical with, or completely determined by, representational content, might explain affect-presenting states as involving the representation of genuine affective qualities, understood as the objective sensible features of external objects (this is the view defended most persuasively in philosophy by Michael Tye; see, for instance, Tye 1995; Cutter and Tye 2011). Others might deny strong representationalism but still maintain that sensory pleasures present things to us as good and bad, perhaps in virtue of a primitive relation of *feeling* good and bad (Smuts 2010) or through intrinsic links to motivational attitudes (Heathwood 2006).[7] So there is nothing at the moment that forces us to give a particular account of affect-presenting states. That said, it might be helpful to see where I will be going with it.

[7] While I will not discuss Heathwood's paper in much detail here, I believe it is actually best understood as an attempt to reduce affect-presenting states to affect-causing ones, where all sensory affect results from causing a secondary state or desire or motivation in a subject (where such desire is a subject-level state). Still, there is logical room for a view similar to Heathwood's, but importantly different in that it is largely automatic, *subpersonal* mechanisms of perceptual evaluation that essentially alter the character of incoming sensory signals, resulting in a single, unified perceptual experience with a felt positive or negative quality. It is just such a view that I defend here.

On my view, there is only a weak sense in which affect-presenting perceptual experiences represent the affective qualities of external objects, in that external objects are pleasant or unpleasant only to the extent that they have (somewhat) stable dispositions to cause pleasant experiences in subjects. Pleasantness and unpleasantness on this view are thus complex features connecting external objective properties with features of subjective experience. Externalized affect (the *presentational* element of affect) is thus highly relational, relating an experiential quality with an objective sensible feature. On this view, there is no pleasantness out there in the silk that we track or detect when we run our hand along it; instead, running our hand along silk generates an experience with positive qualities, and these qualities become derivatively associated with the silk itself.[8] Filling in the details of this account, I will propose that the experiential features can be reductively explained in terms of the subpersonal evaluative processing of the incoming sensory signals. This account of sensory affect is compatible with many versions of representationalism, but probably incompatible with a strongly externalist representational account of affective touch since it adverts in the first instance to introspectively available features of affective experience that are not themselves essentially representational. However, this is getting very far ahead of ourselves.

Touch as Affect Presenting

So far our discussion has been relatively general. We will now focus our attention specifically on the affective character of touch experiences.[9] It is obvious that some tactual experiences produce an affective response. We do have pleasant and unpleasant experiences through touch. Now, it's likely that all perceptual modalities equally feed into the general reactions that are marked as affect causing. As noted earlier, feeling a loaded gun inside a purse can cause an affective response, but there is nothing necessarily bad about the way the gun *felt*. None of its tangible qualities are implicated in the badness of the experience. Similarly, imagine that you lose your wedding ring down the drain and you reach your hand deep into the pipe to dig it out. After digging for a long time without luck, finally feeling the distinctive shape of the ring in your hands might generate a strong positive reaction. But your spouse might have the exact same reaction upon hearing you say "I got it!" Again, while the overall tactual experience is a good, pleasant one, there is nothing pleasant about the felt qualities of the ring. Both of these examples are cases of affect-causing tactual experiences. The question now is whether there are any affect-presenting experiences in touch.

Indeed there are, and they are not hard to find. Consider feeling a soft feather gently pulled across the arm. This experience is often quite pleasant, but this pleasant affect

[8] As we'll see, I believe the "positive quality" of experience can be reductively explained by appeal to certain specialized, evaluative, psychofunctional roles.

[9] These ideas are discussed in more detail in collaborative work with Murat Aydede (e.g., Aydede and Fulkerson 2013).

cannot be generated through any of the other sensory modalities (modality dependence). Seeing a feather does not feel pleasant in this way, nor does being told that there is a feather near your arm, and so on. Second, it does not remove the pleasantness if you are told that it is a synthetic feather. Since it feels exactly like the real thing, it will feel just as pleasant even after you know it's a fake (it passes the phenomenal fake test). Similar things can be said for things that feel really slimy or sticky. These are modality-specific experiences that cannot be generated in any other modality, and for many people such experiences are deeply unpleasant. Again, it would hardly matter if the slimy object were a phenomenal fake; it's not the object as such that is gross or unpleasant in these cases, it is the way it *feels*.[10]

So touch can be affect presenting. Touch can present objects and features in the external world as having a certain pleasant or unpleasant character. Now the question is how we ought to understand such examples. When touch is affect presenting, does it involve the detection or tracking of affective qualities, understood as objective sensible features of objects? Or does it involve something like a modality-specific emotional reaction? I will claim that neither of these views is by itself adequate. Instead, pleasant touch is best understood as a subpersonal *way of evaluating* tactual features, an experiential modification of incoming tactual information.

Emotional and Affective Touch

Before moving on to my positive account of affective touch, it will be important to consider recent empirical investigations into affective touch. Ample empirical evidence exists for a distinctive, modality-specific affective component in tactual experience. In recent work, Francis McGlone and his many collaborators have recently isolated and extensively studied a separate tactile channel that seems to mediate (some of) the pleasurable aspects of cutaneous touch (see, e.g., Bin Saif et al. 2012; Essick et al. 2010; Löken et al. 2009; McGlone et al. 2007, 2012). They call this the CT channel, which involves a novel unmyelinated C-fiber found on the hairy skin of the body. This channel codes for the pleasant aspects of touch, especially soft stroking motions of 2–4 cm/s along the skin. This channel is not located at all on the glabrous skin—the sensitive skin found on the palms, fingers, and lips—which is typically used for externally directed touch. The following is from McGlone et al. (2007):

> [T]here is growing evidence for what might be considered to be a separate channel for affiliative or emotional touch: A CT fibre channel, notably present only in hairy skin. These afferents are preferentially activated by slowly moving, low-force, mechanical stimuli. (p. 174)

[10] Of course, some sticky or slimy things are also unpleasant because of *what* they are. These might generate an experience that is both affect causing and affect presenting. Touching a pile of fake brains, for instance, might be unpleasant because of its slimy feel but also because it's thought to be *brains*. Finding out it's only fake brains might alleviate some of the unpleasantness, but not all; the slimy feel itself will remain gross.

They refer to this channel as coding for the "emotional touch system," which they contrast with the "discriminative touch system." This language is potentially confusing since it's not clear that affective reactions can all be understood as involving an emotional reaction, or, conversely, that the notion of an emotion is basic enough to offer an explanation of such experiences. Consider what Evan Thompson (2007) notes about emotion:

> Emotion involves the entire neuraxis of brain stem, limbic areas, and superior cortex, as well as visceral and motor processes of the body. It encompasses psychosomatic networks of molecular communication among the nervous system, immune system, and endocrine system. On a psychological level, emotion involves attention and evaluation or appraisal, as well as affective feeling. Emotion manifests behaviorally in distinct facial expressions and action tendencies. Although from a biological point of view emotion comprises mostly nonconscious brain and body states, from a psychological and phenomenological point of view it includes rich and multifaceted forms of experience. (p. 363)

Our best account of affect-causing states will be situated in this complexity, offering a rich account of how perceptual experience connects with emotions, moods, and a range of distinct but interacting subpersonal states and cognitive processes. In other words, much detailed philosophical and empirical work is required to fully explain the nature of affect-causing perceptual experiences. They are deeply interesting. Still, they are distinct in character from affect-presenting states. It seems plausible that one could find the feel of silk pleasant in the absence of any strong emotional or motivational reaction. Such feelings seem more basic, more fundamentally sensory in nature.

For these reasons, I believe the term "emotional touch" should be reserved for affect-causing experiences, ones in which a touch experience generates an emotional reaction. The term "affective" touch can then be used exclusively to refer to affect-presenting touch, where external objects are felt to have an apparent pleasant or unpleasant character. One might resist this suggestion by pointing to the special nature of social or affiliative touch. If such reactions are affect causing, then the worry would be that we might lose some of the special character of social touch. This worry would be misplaced. Even if we reserve the term "emotional" or even "affiliative touch" to refer to instances of affect-causing touch, it will not mean that such touch is no longer special or interesting. This is because touch is a powerful conduit of emotional reactions, both because of the number and strength of its secondary projections but also because it often brings us into direct contact with another person (and the many strong social and cultural meanings associated with such forms of contact). Just think of the many taboos and norms attached with human contact. Even if they are affect causing, instances of emotional touch would still be just as powerful, interesting, and worthy of investigation. And indeed, many such interactions may be best understood not as just emotional or affiliative touch but as emotional and affiliative touch that also has an affect-presenting character. Intimate or sensual touch may be best understood as such a complex interaction of distinct forms of tactual affect. In a single complex experience there is a general emotional and motivational response caused by sensory inputs available through touch but also more direct pleasures presented to us through touch.

This framework gives us a way to conceptualize and move forward in our understanding of emotional and affiliative touch. However, what about affective touch? The empirical details are well covered in this volume (see especially Chap. 2.a). Löken et al. (2009) used an experiment where precise measurements of activation patterns of the CT system were correlated with hedonic evaluation ratings provided by subjects. They found a significant linear correlation between mean firing rates of the C-tactile cells and ratings of pleasantness (p. 548). As they summarize,

> Soft brush stroking on hairy skin was perceived as most pleasant when it was delivered at velocities that were most effective at activating C-tactile afferents (1–10 cm/s), with a linear correlation between C-tactile impulse frequency and pleasantness ratings. In contrast, the response of myelinated afferents increased with faster velocities (30 cm/s) and showed no relationship with pleasantness ratings. (p. 548)

One might conclude from these findings that affective touch involves a kind of information processing that codes for pleasantness. That is, one might think that CT fibers carry information about pleasant and unpleasant features of objects in the environment. However, this would be a mistake. For one, it is clear that some pleasant tactual experiences can be felt through the hands, lips, and genitals, where there are no CT fibers. So the CT system isn't the whole story. But in addition, it isn't at all clear that the CT system is even carrying any information about pleasantness understood as an objective sensory quality of external objects.

Löken et al. (2009, p. 548) note that "[H]edonic ratings probably depend not only on bottom-up neural signaling but also on top-down factors related to context, previous experience, expectation, homeostatic state of the individual and culture."

This is a complex and nuanced view, highlighting the context sensitivity and fragility of most pleasant touch experiences. There isn't any single channel that simply detects and elicits experiences of tactual pleasures. While the correlations between gentle stroking and CT-fiber activations are strong in controlled laboratory settings, there is every reason to think that our feelings of pleasantness through touch are highly malleable. This accords well with work on cutaneous pains, which seem to have both a sensory-discriminative component but also an affective-motivational component. Affective touch also seems to essentially involve a discriminatory element (the A-beta fiber system must also be activated to generate pleasant experiences) combined with an affective-motivational component. How exactly this system functions (and the kinds of affective experiences it generates) depends on the present and prior state of the overall tactual system, as well as many other systems involved in the evaluation of tactual inputs.

McGlone et al. (2007) describe some of the larger meaning of this system by contrasting it with discriminative touch (see also Chap. 2.b, this volume).

The authors propose a largely social function for the CT system, which might explain how the system evolved and came to operate as it does. As they write:

> [T]here is possibly another purpose to touch that is more interoceptive than exteroceptive and that is less accessible to conscious self-report as evidenced by recent research findings that unmyelinated CT-afferents project towards the emotional systems (insular cortex, orbitofrontal

> cortex), but less or not at all towards the discriminative-cognitive systems (classical somatosensory areas S1 and S2). (pp. 179–180)

This helps make sense of the role played by touch in the development of the immune system and in the social bonding that occurs in infant development. This is all plausible, but for my purposes what is most interesting about the CT system is that it only performs this function when appropriately combined with the A-beta system (which codes for discriminative touch). In addition, the pleasantness generated by the CT system is extremely context sensitive. For these reasons, I think we can understand this channel as part of a larger system that functions to evaluate incoming tactual signals. Working alongside the many other sensory systems subserving tactual experience, the CT system looks for inputs of a certain kind (relative to appropriate contexts and conditions) and generates affective-motivational responses to them in the appropriate ways.

While there are certainly tactual sensations that feel pleasant or unpleasant (garden variety pains, warm baths, etc.), it's unlikely that tactual affect can be fully explained by appeal to any one sensory channel. There is reason to think that pleasant and unpleasant touch experiences are not simples, activated automatically by a single type of sensory fiber, but complexes built out of several interacting components. Murat Aydede (2000), relying in part on decades' worth of research on cutaneous pain, argues that pleasant and unpleasant bodily feelings typically involve a discriminatory component along with an affective-motivational component "fused" into a single experience. Even orgasm seems to involve a sensory component that can be dissociated from its pleasant aspect (Linden 2011). Affective touch on this model isn't simply the activation of any single system or circuit; it arises from the complex interaction of many different components, including context, mood, and state of arousal. It is beyond the scope of this short chapter to provide the details of all of these systems and how they interact. For my purposes here, it is important to emphasize that the discovery of the CT system only constitutes part of the explanation of tactual affect.

It is clear that a complete account of affective touch will ultimately involve a detailed functional story about the complex interactions between many interacting systems. Obviously, I don't want to make any predictions about where the empirical facts may lead. However, I think we can provide a general philosophical outline of the role and nature of affective touch that has a good claim to illuminate the many considerations outlined thus far: to explain the existence and nature of affect-presenting tactual experiences and to do so in way consistent with the known empirical facts.

An Account of Affective Touch

A natural question arises when thinking about affective touch: does the pleasantness arise as a property *out there* in the external environment, or is it a purely self-directed experience that arises in the ways suggested by recent work on affective touch? Our affective judgments and the phenomenology of affective perceptual

experience strongly suggest that pleasant touch is not simply a nonsensory emotional reaction in us: when we have a pleasant touch experience, we often partly attribute the pleasant aspect to the sensory features of the object. It is the *silk* that feels good, the *velvet* that feels pleasant. However, it is also unlikely that the pleasantness is anything like a detected objective sensible property of the silk (that is, pleasantness is not among the basic tangibles we encounter when touching silk). Standard arguments from inter- and intrapersonal differences and the extreme context sensitivity of affect, combined with their direct motivating influence on judgments and behavior, strongly suggest that affective qualities are highly relational, involving *both* a sensible quality and an experiential reaction. This explains why we can, over time and through training, learn to alleviate our affective responses. The first day on the job as a dishwasher will likely bring your hands into direct contact with many gross-feeling substances. After a busy summer working the dish line, those substances may have little to no affective character. What changes isn't the incoming sensory information; it's a change in how this input is processed and interpreted. It is a change in experiential character.

Affective touch does not involve a sensible tangible property to be treated in the same manner as the intensive features discussed earlier, nor is it a complex sensible feature arising from the systematic combination of more basic tangible constituents. Instead, I suggest that the pleasant aspect of touch experience arises as incoming tangible signals are evaluated by a complex, subpersonal affective-motivational system associated with touch. Because this account reduces the felt qualities of affective touch to the functioning of this evaluative system, the view is a version of psychofunctionalism. Psychofunctionalism is described by Block (1981) as a form of functionalism in which mental features are identified with a particular set of functional or causal roles derived from investigations in empirical psychology and neuroscience (as opposed to the roles taken from folk psychology that define analytic versions of functionalism).

The basic idea is that there are incoming signals being processed by the tactual system. This story is told in largely information-processing terms. However, affective touch is not a case where we have a receptor that codes for pleasantness or an information channel that is in the business of carrying signals about the objective pleasant or unpleasant qualities of external objects (despite the way it's sometimes described in recent empirical work). Instead, there is on one side an information-processing story, one in which information (often distal information) is reliably transmitted to our bodily surfaces. This information is processed by the peripheral transduction systems, often producing representations carrying information about the current state of the body (allowing for a robust notion of bodily awareness). From this changing and temporally extended flow of bodily information we are able to extract stable, coherent, and constant features from the distal environment. This extraction process thus far involves no evaluation. The pleasantness gets into the picture on my account in virtue of certain changes or alterations in the downstream effects of the incoming sensory stream in touch.

Perceptual experience provides information that is, in most cases, *flexible*. Such information is leveraged for forming beliefs, making decisions, and acting, but such

information does not *force* us into certain judgments or actions (cf. Matthen 2005). An organism uses perceptual information in combination with background knowledge, current goal and motivational states, and other aspects of the context to form judgments and initiate action. My claim is that conscious awareness of affective qualities just is to have a strong bias for or against the perceptual information, and this bias is realized by a complex functional property connecting the perceptual input with a complex array of evaluative and motivational brain regions. A smell with neutral affect is for a subject of experience maximally flexible; a smell with a strong negative affect will automatically set behavioral and epistemic parameters relative to that input. To feel a sheet of silk as pleasant just is to have an experience of the silk that is being actively processed by the relevant evaluative areas of the brain. This evaluation is directly attributed to the sensory features of the silk, forming a kind of complex phenomenal character, partly informational, partly evaluative (cf. Berridge and Kringelbach 2008; Panksepp 2004). This view, if successful, would reconcile the informational and motivational aspects of affective perceptual experiences, offering a robust explanation of how properties like *pleasant* can both be attributed to externalized sensory features but also play a crucial, subjective role in motivating perceptual judgments and behavior.

The account also handles some long-standing difficulties with previous accounts of sensory pleasures. For instance, there is the so-called *heterogeneity problem*, which arises because not all felt pleasures feel the same. There is a wide variety of felt pleasures, in different modalities, and there does not seem to be any stable component that is the pleasure. On my view, this variety is easily explained, as sensory pleasures are dependent on modality-specific features. This allows for pleasures in different modalities to have different characters while involving similar forms of subpersonal processing. In addition, the view holds that presented affect involves evaluations of specific incoming sensory signals, and the differences between these individual signals help explain why certain felt pleasures differ so much in their character. Feeling a warm, soft blanket involves a positive subpersonal evaluation of the warmth and softness; feeling the cooling spray of mist on your body on a hot day involves a positive subpersonal evaluation of the coolness. While both involve a kind of positive evaluative processing, what is being evaluated differs, resulting in tactual pleasures with heterogeneous characters. In addition, of course, there are the many overlaps and blends with affect-causing tactual experiences that can also provide richness and diversity of felt affective character.

Another worry that is sometimes raised for accounts of felt pleasure is the Euthyphro problem. This problem is especially vexing for those who take affective character to be explained by appeal to a subject's motivation or desire. The worry is that we seem motivated to like and seek out pleasures because they are *pleasurable*, not the other way around. If all it is for something to be pleasurable is for us to be motivated toward it, then we seem to lose the seemingly strong rational connection between motivation and pleasure. On my view, the motivating force of presented affect is easily accounted for: the subpersonal systems of evaluation (the affective-motivational systems partly comprised by the CT channel and related networks) provide, through their operation, a kind of biasing of incoming sensory signals.

These biases account for the felt quality of our experience and also provide prima facie reasons for or against certain actions with respect to the incoming signals. However, these prima facie reasons are easily overridden by other considerations and top-down processes. A subject can be overall motivated *against* a sensory experience that nevertheless would feel pleasant (for instance, a fasting devotee who refuses a hot meal, even though it would taste delicious). The view also easily handles the fragile and fickle nature of our affective experiences. The pleasant aspect of touch is highly context sensitive and variable. Pulling a feather across one's arm in a controlled lab setting might reliably elicit pleasant responses in subjects, but it does not follow from this that there is some objective feature of the feather which the pleasure channel is sensitive to. This should be especially obvious given that feeling pleasure from a feather depends a lot on who is doing the pulling, the context in which is occurs, and much besides. Consider Soft Feather Test:

Soft Feather Exam: You are taking a very important and critical exam that requires a lot of mental effort and concentration. During the exam, the person next to you, a stranger, keeps rubbing a feather across the back of your neck when the proctor is not looking.

Even though Soft Feather Exam involves the pulling of a feather across your nonglabrous skin, it will likely not invoke anything like a pleasant response. In fact, in such a scenario it is highly likely that it will generate a very unpleasant feeling, one that you would seek to end or stop as soon as possible. While other tactual features (and indeed, other perceptual features) are context sensitive in similar ways, the feeling of pleasantness through touch is far more fragile and contextualized than other sensory features. It differs not only among subjects but also within individuals in just slightly different contexts.

While there have been attempts to ground affective qualities so understood in objective features, these attempts do not offer a plausible account of an external property that is such that our tactual systems could possibly be sensitive to them. For instance, Cutter and Tye (2011) argue that the negative affective character of pain experiences (though they believe their view extends to all forms of both positive and negative affect) can be cashed out in terms of (a forward-looking, teleological form of) representing that a feature is apt to harm (or help) an organism. Thus, for instance, breaking of the skin historically has been apt to harm an organism, and so our feeling of pain when we are cut or scraped is a way of representing that possibility of harm (and this is so, even in those cases where the break does us actual good as when we get stitches or a vaccination). I don't want to discuss this possibility in too much detail here (for that, see Aydede and Fulkerson, 2014). Instead, I want to highlight the implausibility of this view as an account of affective touch. It is unlikely that there is going to be any fully objective account of affective qualities such as those involved in affective touch. Affective qualities are not properties *out there* in the distal environment, to be detected and tracked. Instead, they seem to critically involve something like the experiential character or way of taking in a sensory feature. For consider again Soft Feather, is it the case that the pleasant feeling of a feather gently pulled across the arm *represents* that the feather is apt to

benefit us? There are many complications here that I am setting aside, but the general idea is that it is going to be very difficult to account for the felt pleasantness by appeal to the experience representing some objective, nonexperiential bit of the distal environment. Such a view can perhaps be made more plausible by appeal to the historical importance of feathers for warmth and comfort in colder climates and the like. And all things considered, soft warm things are more likely to be a good than a harm. But what to make then of Soft Feather Exam? Here too the feather should be felt as pleasant since, again, it is something warm and soft, likely to be of benefit and not harm. If this is right, then there would be a kind of *misrepresentation* involved in feeling the unpleasantness of the distracting and unwelcome feather pull. Obviously, there are lots of moves people like Cutter and Tye can make here; invoking wider and more diffuse properties, like the tendency to harm that arises from strangers violating your bodily space and whatnot. However, these seem more and more like epicycles on an already implausible view. Once we look at the alternative, it should be clear that there is a much simpler and robust way to explain where the pleasantness lies. According to this view, when we feel a feather as pleasant, what we feel is a certain pleasant sensation (to be, I suggest, reductively explained in terms of psychofunctional role) that is caused by the feather. This relation is highly context dependent, and arises differentially in different subjects (for some a feather generates a strong tickle, in others it generates an entirely neutral reaction). However we fill in the details of this view, affect involves something about *the way* in which we experience the things around us, not just in us experiencing as they are in themselves.

The view I've sketched here seems to do a good job across a wide range of desiderata for a theory of affect. It has a representational component, holding that felt pleasantness is an experiential way of taking in a sensory property. Our sensory systems extract information from the distal environment and then evaluate it. When we feel a soft feather in a particular context as pleasant, we take in the sensory information about the feather and subject it to evaluation, generating a subpersonal proattitude toward the feeling and biasing motivational and motor parameters.

That is the proposed view of felt pleasantness. It is a downstream, functional modification of a subject on the basis of incoming sensory information. In what sense, then, does this component gets externalized? Why does it sometimes seem that there really is an objective fact of the matter about whether a feather feels pleasant or not? This can be accounted for in a rather traditional way, by appeal to a dispositional account of externalized features similar to John Locke's view of secondary properties. The general idea is that the external object felt as pleasant through touch comes to bear an affective quality in virtue of its disposition to create experiences of a certain kind:

An object *o* has a secondary property P if, and only if, *o* has the disposition to cause experiences of type F in subjects of type T in contexts of type C.

Specifying a dispositional account like this requires filling in the details concerning each of the type places. For example, silk has the disposition in many subjects and contexts of feeling quite pleasant; coagulated blood does not. Silk

has this power in virtue of having certain inherent textural and material compositional features (extreme smoothness and softness being of primary importance). Being relational, silk's having this disposition is contingent upon there being creatures with a certain perceptual apparatus capable of experiences of type F in response to coming in appropriate causal contact with silky substances. The dispositional view thus attributes to the silk a complex relational property. It is a relation between the objective sensible features of the silk (its smoothness and softness) and a particular phenomenal feature intrinsic to silky touch experiences. To be clear, I don't endorse dispositional accounts of genuine sensible properties, like texture, pressure, or even thermal properties. However, I do think such an account offers the best explanation of the affective character of affective touch experiences.

Conclusion

The view of affective touch I've offered here understands affect-presenting touch as primarily an experiential modification in a subject, and this is fundamentally a feature of the subject that cannot be fully cashed out or identified with some externally determined objective quality. Of course, it does have *something* to do with objective features, but it also involves an ineliminable subjective component. If it turns out that Bob finds the feeling of a feather pleasant, what makes his experience veridical has nothing to do with the external conditions that give rise to that experience. Because the accuracy of (the affective character of) his experience is insensitive to these conditions, the accuracy conditions cannot track anything in the objective, external environment. The conditions that make his experience veridical or accurate only concern the quality of his experience—whether or not he finds it enjoyable. This explains the intuitive experiential priority of affect described earlier.

I've argued that we can reductively explain this feeling in psychofunctionalist terms as a kind of evaluative inspector that scans for incoming signals and assigns something like values to those signals. However, this is just one among many possible ways of cashing out this account, and a lot will depend on the empirical details yet to be determined. For now, the best understanding of the CT fibers is that they play an important role in mediating inputs that typically have such effects on us. However, just as we shouldn't think of the taste receptors that code for the taste of chocolate as "pleasure detectors" or "deliciousness receptors," we also shouldn't treat the channels that code for affective touch to be in the business of detecting pleasantness itself. Instead, they play a role in generating experiences which have felt positive and negative qualities, and which thereby get associated with the objects and sensible qualities that cause them.

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Chapter 20
The Effects of Touch

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Abstract Interpersonal touch is renowned for playing a pivotal role in strengthening social bonds and communicating emotions. This chapter provides an overview of the effects of touch or lack of it early in life, and the tactile differences across cultures, as well as discussing the subconscious effects of touch and the role it plays in intimacy. Despite the obvious benefits of touch there is surprisingly little scientific research on the topic of interpersonal touch; however, the present chapter will highlight some of the recent advancements in the neuroscience and biology behind affective touch. Overall the chapter provides overwhelming evidence for the importance of touch in our everyday lives, and queries why it is not explored and utilised more in clinical contexts. A synergistic effort will be needed by researchers across varying disciplines in order to develop a more detailed understanding of interpersonal touch.

Keywords Touch • Emotion • Interpersonal • Communication • Affective • Tactile • Intimacy • Senses

Introduction

Touch is one of the most basic and innate of human needs; it is not solely a biological sense but also our most social sense. Touch has the power not only to communicate social messages and emotions but also to impact strongly on development in a way that affects the whole life course of an individual.

This chapter will describe the developmental benefits of touch, the subconscious social effects and the neuroscience behind it, as well as the ways in which it differs across cultures and relationships.

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Early Development of Touch in Animals

Tactile stimulation contributes to the well-being of the majority of mammals and is universally important across cultures and species. A feature of touch that is vital to animals is grooming; it is through this action that primates form bonds and communicate with each other (de Waal 1989; Dunbar 1996, 2008). Research has shown that infants who do not experience sufficient bodily contact become anxious and disturbed (Harlow and Harlow 1965; Schanberg et al. 1988).

Harlow and Harlow's famous experiment in 1958 explored the importance of touch in infant rhesus macaque monkeys (used because they share 93 % of their genes with humans). The infant monkeys demonstrated that the need for a soft feeling surrogate mother superseded that of a surrogate mother providing food; tactile comfort was more important. Harlow concluded, "These data make it obvious that contact comfort is a variable of overwhelming importance in the development of affectional response, whereas lactation is a variable of negligible importance" (Harlow 1958).

Those that had no real or surrogate mother developed patterns of clasping their own bodies and as the deprived monkeys grew older they did not develop typical grooming patterns and had reproduction difficulties. The infants required interactive, nurturing touch to help them become functional adults with normal development (Zur and Nordmarken 2011). The converging data from many sources strongly implicate touch as central to the development of attachment in primates (Harlow 1958; Jensen 1965; Mendoza et al. 1978; Mitchell and Tokunaga 1976; Hertenstein et al. 2006).

It was Harlow's experiments that sparked a plethora of strong empirical support for Bowlby's theories of attachment and the importance of loving interaction between a child and their primary caregiver (Bowlby 1969). It became widely accepted that intimate body contact strengthens bonds, and behavioural evidence corroborated this (Harlow 1958; Suomi and Leroy 1982; Rambaugh 1997). Although the experiments explored why touch was important, none of the theories ever explored the mechanisms behind the touch; the chain reaction of what happens in our body when touched, and the components in our skin that contribute to the interpretation of touch. The exploration of the science behind touch is something that has only recently been researched, and this will be discussed in more detail later in the chapter.

Epigenetic Inheritance

Early development in mammals can be effected by cues received from mothers or caregivers in the first days of their lives. Research has shown that well nurtured rat pups tend to develop into calm adults, whilst rat pups who do not receive a high level of nurturing early on tend to develop into anxious adults (Weaver et al. 2004).

More specifically, Weaver and colleagues discovered that the level of care a rat mother gives her pup changes the chemistry of the DNA in certain genes involved in the offspring's stress response. The highly nurturing behaviour of the mother contributes to the development of glucocorticoid receptor (GR) protein in her pups. Glucocorticoid receptors regulate genes controlling development, immune response and metabolism, and are the receptors to which cortisol and other glucocorticoids bind. Rats that have a lot of GR protein relax more quickly when stressed, and Weaver's research indicates that nurturing touch in infancy is one vehicle towards GR protein development.

Curley et al. (2008) further demonstrated that impaired maternal care leads to negative effects for offspring; in a study exploring genetic mutation versus epigenetic inheritance, Curley's team found that pups receiving impaired care exhibited increased neophobia (the fear of anything new) and decreased exploratory behaviour.

It may be difficult to directly correlate these findings in the animal world into that of the human realm. However, researchers are beginning to look at the correlation between the quality of early family life environments and health outcomes in later life in humans.

Early Development and Attachment

During early development, touch is the first sense to develop in a human foetus as the skin becomes sensitive to tactile stimuli after just 7 weeks in the uterus (Montagu 1986). Touch is the most developed sensory modality at birth and contributes to cognitive and socio-emotional development throughout childhood (Hertenstein 2002). The young child learns to explore the physical world through touch, and in a similar way to animals, they learn the many facets that touch can convey including grooming, hygiene, safety and self-preservation.

Unlike other senses, touch is not optional for healthy human development. People can be born blind and deaf and develop well functioning and satisfying lives, whereas, the research indicates that lack of touch early in life can have lasting damaging effects (Pollak et al. 2010; Feldman et al. 2014). In a longitudinal study researchers followed a group of Romanian children who lived as babies in orphanages (Nelson et al. 2014). The children were fed and cleaned but received very little in the form of psychological or tactile nurturance. They found that early institutionalisation affected both the structure and function of the brain in the form of reduced volume of grey matter and lower quality brain activity. Collectively these studies and others have contributed to a Western culture that encourages immediate skin-to-skin contact with newborns from both mothers and fathers as a way of stimulating healthy development.

Relatively little is known about the relation between touch and psychological attachment in human beings although studies have indicated that healthy growth and psychological well-being in children is dependent on the relationship with the primary caregiver much in the same way as it is in animals (Duhn 2010), and that the presence of nurturing touch is paramount in bonding and healthy attachment relationships (Hertenstein et al. 2006).

Exploring Physical Touch Across Cultures

Human communicative interactions are governed by a universal hierarchically organised system of rules which channel our social interactions, and it is no secret that the worlds in which we live determine how often we touch, who we touch, where we touch them and what form those touches will take. Cultural conventions specify our mode of interaction as etiquette, and cultural differences in touching within various communities have been widely reported (Montagu 1986).

Some cultures are consistently reported as touching more than others; for example, the French have been found to be part of a more touch-friendly culture compared to Americans or British people (Jourard 1966; Field 2001). Jourard (1966) visited cafés in different parts of the world and recorded the number of times two people who were sharing coffee touched each other. The tally in London was zero, Florida reported two cases, Paris reported 110 cases and more than 180 cases were reported in Puerto Rico. The wide array of research in this area suggests that Mediterranean countries are contact societies, whereas northern countries are predominantly non-contact societies. This is fitting with research by Watson (1970) who observed interactions and differentiated between 'contact' and 'non-contact' cultures. Contact groups were observed to be Arabs, Latin Americans and South Europeans because they were found to face one another more directly, interact closer to one another, touch each other more, look one another in the eye and to speak louder. Non-contact groups were observed to be Asians, Indians, Pakistanis, Northern Europeans and Americans because they did not initiate the close contact described earlier.

A number of studies have confirmed these findings (Dodd 1987; Jandt 1995), whereas others have disagreed (Remland et al. 1991), but what does it mean to live in a more tactile culture? One study linked more frequent touching acts with dominant and powerful personality traits (DiBiase and Gunnoe 2004). Another found that adult aggression is low in touching cultures, whereas adult aggression is high in cultures in which touch is limited (Prescott and Wallace 1976). The basis of Prescott's admittedly controversial theory was that the lack of sensory stimulation in childhood leads to an addiction to sensory stimulation in adulthood, resulting in drug use, crime and delinquency.

Culture clearly plays a large role in frequency of social touch, but many other factors play a role too; the amount and types of touch people communicate is closely linked with gender and context (DiBiase and Gunnoe 2004) as described further later.

Subconscious Effects of Touch

Touch has proved to have subtle social benefits, and socially relevant touch can be a powerful modulator of behaviour in a range of social settings (Gallace and Spence 2010). There is a plethora of research indicating the social benefits of touch when communicating with others; for example, a quick touch on a stranger's shoulder makes it more likely that they will help pick up dropped belongings (Guéguen and Fischer-Lokou 2003). Other altruistic behaviours include getting free bus rides and help with errands (Guéguen and Fischer-Lokou 2003); employees working for longer hours (Patterson et al. 1986); shoppers spending more time shopping, buying more goods and evaluating a shop more favourably (Hornik 1992) and applicants initiating a handshake at a job interview being deemed as more appealing (Walton 1989).

It is difficult to separate the influence on people's behaviour of tactile stimulation from the interaction of tactile stimulation with the addition of any other sensory components, for example facial expressions and voices. However, the overwhelming evidence indicates that simple touch contributes to more altruistic behaviour. But why? Taylor (2007) suggested that touch is an indication of charisma, whereas others have predicted that the positive effects of touch may be due to cognitive interpretational factors such as implied affiliation, trust and cooperation (Rose 1990). A somewhat different suggestion came from Reite (1990) who suggested that the early association between touch and stress reduction in early life creates a long-lasting positive response to being touched in later life.

Unsurprisingly many studies have shown that people touch those whom they like more often (Heslin and Alper 1983) and studies have demonstrated an interplay between different genders playing a role too; waiters and waitresses that subtly touch a customer when they return their change tend to receive larger tips but even more so when the customer is of the opposite gender (Hubbard et al. 2003; Guéguen et al. 2007).

The Role of Touch in Intimacy

Tactile signals are important in intimate relationships and studies with romantic couples have provided unique results. Studies involving flirtation behaviour between men and women in bars provide observational support on the superiority of nonverbal communication in the courtship process (Moore 1985; McCormick and Jones 1989). Most of the early signalling appears to be performed by women and most frequently observed behaviours include smiling, tossing one's head, grooming and a variety of seemingly 'accidental' touching of another person. Interestingly, Guerrero and Andersen (1991) found that opposite-sex touch varies between relational stages with the peak of touch taking place during steady dating or engagement stages. Not only does the level of touch differ but different neural mechanisms within the brain are utilised during the initiation and the maintenance of a relationship (Depue and Morrone-Strupinsky 2005).

Worldwide, romantic love plays a key role in courtship, suggesting that it evolved as a primary aspect of the human mating system (Fisher 1998). Heslin and Alper (1983) found that couples who were most in love also engaged most in touching, both sexual and non-sexual. For some, touch can be the most meaningful part of intimacy; in a survey of over 100,000 people, 72 % of respondents answered yes when asked, "Would you be content to be held close and treated tenderly and forget about the sex act?" 40 % of those answering 'yes' were under 40 years of age (Landers 1996).

In regard to married couples, Enochson and Wiseman (1999) found support for a positive relationship between similarities of touching behaviours of married couples and marital satisfaction. This is corroborated by research which found that relationship satisfaction and trust positively correlated with dynamic touch (Nelson and Geher 2007). Displays of emotion have evocative functions, eliciting complementary or matching emotions from relationship partners (Keltner and Kring 1998), and this is relevant regardless of the channel of emotional communication: facial, vocal or tactile.

In comparison to "simple touch", research has also explored the effects of "protracted" and "dynamic touch". Protracted touch involves longer and mutual contact, and dynamic touch involves continuous movement over the skin, such as stroking or caressing. Coan et al. (2006) carried out one of the first studies identifying the distress-alleviating effects of protracted touch on the neural circuitry supporting threat response. Women in highly satisfying marriages were subjected to the threat of electric shock while holding the hand of their spouse, a stranger or no hand at all. Spousal hand holding was particularly powerful in attenuating neural response to threat—more so than stranger hand holding, suggesting that attachment figures act as emotion regulators in ways that strangers do not. Coan and his team believe that supportive relationships allow the prefrontal areas of the brain used for regulating emotion to 'relax', enabling them to utilise their other resources for problem-solving. These findings support the view of Field (2006), founder of the Touch Research Institute, that massage therapy is more beneficial when given by a significant other. Furthermore, the quality of the relationship with the hand holder was also of great importance, suggesting that the effect of touch is sensitive to symbolic representations (e.g. good relationship vs. bad relationship) in the brain. Interestingly, Coan et al. (2006) suggested that these findings may not be applicable to relationships characterised by discord or of poorer quality.

Levels of the hormone oxytocin, sometimes called the 'love hormone', increase in intimate relationships and have been implicated in bonding behaviours (Young 2002; Bales and Carter 2003; Gulledge et al. 2007). Elevated levels of oxytocin in the brain are associated with an improvement in reading emotional expressions in faces and with being more trusting (Baron-Cohen 2007), and oxytocin contributes to more touching behaviour as witnessed by the increased grooming behaviour when administered to mice which do not produce the neurotransmitter (Amico et al. 2004).

Touch as a Form of Emotional Communication

Interpersonal behaviour involves accessing a comfortable balance between making enough contact whilst keeping enough distance at the same time. The nature of relationships between people can often be worked out by noticing what kinds of touch they communicate with one another.

Touch is used to create distinct forms of self-expression and can be utilised to reinforce or emphasise what has been said. Certain actions or movements seem natural or instinctive, for example, to draw close to or hold someone in distress or to hold hands with the person we love. When people refer to nonverbal behaviour, they are often referring to the signals (encoding) to which meaning will be attributed (decoding) (Knapp and Hall 1997).

The giving and receiving of messages through touch is often instinctual as people are used to being touched in the context of interpersonal relationships. The ever-growing literature on communicating emotion has paid little attention to the investigation of touching, and this has remained an almost disregarded area of psychological research until recently (Hertenstein et al. 2006; Thompson and Hampton 2011). Hertenstein et al. (2006) carried out the first experiment focusing solely on communicating emotion through touch. They investigated whether people could identify the emotions of another from the experience of being touched on the forearm by a stranger without any verbal or visual clues. Hertenstein et al. (2006) carried out the experiment in the United States and in Spain, with the latter being chosen as a culture that values touch more highly, and found that participants in both countries could accurately interpret anger, fear, disgust, love, gratitude and sympathy via touch at significantly above-chance levels. However, participants could not interpret embarrassment, envy, pride, surprise, happiness or sadness at significant levels. Hertenstein et al. (2006) referred to embarrassment, envy and pride as self-focused emotions, which could explain the lack of successful tactile communication.

Further research by Hertenstein's team (App et al. 2011) found that people have a preference for which nonverbal channel they use to convey differing emotions; participants favoured the body for expressing embarrassment, guilt, pride and shame; the face for anger, disgust, fear, happiness and sadness; and touch for love and sympathy. The researchers hypothesised that the social function of an emotion predicts its channel of communication, stating that the body promotes social status emotions, the face is used for survival emotions and touch is utilised for intimate emotions (App et al. 2011).

Thompson and Hampton (2011) replicated Hertenstein et al. (2006) to observe if the interpretation of emotional touch differed more for romantic partners than for strangers. The study compared the ability of romantic couples and strangers to communicate emotions solely via touch. Results showed that both strangers and romantic couples were able to communicate universal and prosocial emotions, whereas only romantic couples were able to communicate the self-focused emotions envy and pride. Despite the higher accuracy of communication shown by couples, analysis of the types of touch used revealed that couples and strangers tended to use

much the same touch actions for specific emotions, including the self-focused emotions that were decoded by couples only. The similarity in touching actions for couples and strangers and the disparity in their successful interpretation may indicate that more subtle differences in the manner of touch, not picked up by their coding scheme, were responsible for differences in success. However, it is more likely that the same cues are being interpreted differently due to relationship status, which is an exciting finding deserving of further exploration.

The Neuroscience and Biology of Affective Touch

As stated, the hormone oxytocin plays a role in interpreting emotional expressions and has been hypothesised to promote human affiliation through its calming and antinociceptive effects (Uvnäs-Moberg 1997). Studies have confirmed this by showing that intranasally administered oxytocin improves the ability to read emotions (Leknes et al. 2012; Van IJzendoorn and Bakermans-Kranenburg 2012). Higher levels of oxytocin also predict affectionate touch in mothers (Feldman 2012), and high frequency of touch between partners predicts higher levels of oxytocin (Light et al. 2005).

The experience of being touched is thought to intensify emotional displays from other sensory modalities (Knapp and Hall 1997). Understanding the brain processing that underlies affective touch may provide an understanding of the brain mechanisms of emotion, and functional magnetic resonance imaging (fMRI) studies have shown that different cortical areas are activated by different types of touch, e.g. pleasant, neutral and painful (Rolls et al. 2003). Studies have implied that activation of the orbitofrontal cortex may be related more to pleasantness and painful stimulation rather than by neutral touch (Olausson et al. 2002, 2008; McCabe et al. 2008), evidencing that the brain is able to differentiate between affective and neutral aspects of touch (McGlone et al. 2007; Olausson et al. 2008).

The neural processing of affective touch is being researched using a variety of experimental approaches to chart the neural pathways, from the periphery to central nervous system projections and neuro-modulation. An important finding in the realm of affective touch has been the characterisation of human nerve fibres (C tactile afferent) that are hypothesised to code for pleasant touch (McGlone et al. 2007). These nerve fibres are only found in hairy skin (the main body surfaces) and are not present in glabrous skin such as the palm of the hand (Olausson et al. 2002; McGlone et al. 2007). They show a partiality to stimuli that move gently over the surface of the skin, for example, a caress or stroke (Löken et al 2009; McGlone et al. 2014). The discovery of certain types of tactile receptors only being present in non-glabrous skin highlights the importance of testing different areas of the body when exploring the perceptual effects of interpersonal touch.

Relating Touch to Clinical Presentations

Touch serves an important function in social and emotional communication yet is rarely explored in relation to clinical pathologies. One well-known exception is the literature surrounding people with Autism Spectrum Disorder (ASD) evidencing a sensitivity to touch; however, there are few empirical studies exploring the effects of this in regards to communication. One study found that the tactile sensory system is foundational for social functioning in people with ASD with diagnosis and intervention implications (Lundqvist 2015), and it has been suggested that sensitivity to touch is not a perceptual sensory problem but emotional in origin (McGlone et al. 2007; Güçlü et al. 2007; Voos et al. 2012).

Another study suggests that perceived touch deprivation may play a role in body image pathologies (Gupta et al. 1995), and a more recent study proposes that major depression may be part mediated by overarching sensory abnormalities whereby normal sensory perceptions are no longer activating reward systems (Fitzgerald 2013).

Collectively, the few studies strengthen the claim that an abnormality or neglect in tactile sensitivity has an important impact on a person's social behaviours and may play a role in mental health. There is often little consideration of the benefits of touch in a clinical environment, but future work is needed to evidence the benefits of touch for clinical samples and varied pathologies, especially in contexts where touch is less circumscribed.

Conclusion

The need for touch, both to be touched and to touch, is one of the most instinctive of human needs. The pivotal message from all of the aforementioned literature is that the simple action of touch, especially early in life, can have profound effects on the way you relate to others and the way you respond to stressful situations.

The advancement of technology means that there is less opportunity for physical human contact. Video communication software such as Skype means people can have several meetings a day without being alongside another human being. Developers have tried to create various software that allows for a more personal feel to virtual communication in the form of; the 'inTouch' device which creates the illusion that two people are interacting with a shared physical object (Brave and Dahley 1997), a 'hug' that can be connected across devices (DiSalvo et al. 2003; Gemperle et al. 2003), and more recently a 'Keep in Touch' fabric touchscreen interface combining visual and tactile sensations to provide a physical intimacy (Motamedi 2007). Developers are attempting to incorporate tactile stimulation into virtual communication but moving in this direction may be moving further towards a culture that decreases much needed in-person tactile behaviours. As the evidence has clearly outlined, the effects of lack of in-person touch can be detrimental and long lasting.

Working in a psychology healthcare setting the topic of touch is an anomaly. Touching patients is not permissible for many reasons, for example, therapeutic boundaries, and potential liability for any misconstrued communication. However, if touch effects the way we evaluate others, heightens the sensitivity of our other senses and is scientifically proven to be beneficial both biologically and psychologically, why is it not factored into healthcare in a more formal manner? There is a wealth of research into the effects of lack of touch in early life, but more exploration is needed into the effects of touch in relation to pathology and in the context of clinical settings.

The scientific evidence is there, so when will practice follow?

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Chapter 21
The Touched Self: Affective Touch and Body Awareness in Health and Disease

Antje Gentsch, Laura Crucianelli, Paul Jenkinson, and Aikaterini Fotopoulou

Abstract This chapter focuses on how interpersonal, affective touch shapes our sense of self as embodied beings. In the first section, we highlight the centrality of bodily representations for our psychological sense of self, with special emphasis on the role of internal bodily signals in forming the emotional, core of selfhood. The second section focuses on affective touch as a domain of interoception and addresses its important contribution to healthy body representation and bodily awareness. Specifically, we present recent, accumulating evidence in healthy volunteers pointing to the crucial role of affective touch in the construction and maintenance of fundamental facets of bodily awareness, such as the sense of body ownership. Finally, in a third section, we discuss findings in neurological and psychiatric disorders of body representation and awareness, indicating the importance of affective touch and other affiliative, interpersonal signals for the construction of a coherent, efficient and resilient sense of embodied selfhood. Overall, our chapter draws on perspectives from multiple mind and brain fields in order to highlight how affective touch, a bodily modality by which we can communicate social affiliation and care, has a fundamental role in the constitution of selfhood.

Keywords Body ownership • Interoception • Bodily self • Affective touch • Self-awareness • Body representation • Selfhood • Insula • Rubber hand illusion

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Introduction

The ability to perceive our body as distinct from other entities in the world and our ability to move it intentionally relies on the capacity to form mental representations of its structure, states and possibilities in space and time. These representations are also linked with fundamental facets of our psychological self, in the sense that we locate our self within the boundaries of our physical body and we perceive this particular body as belonging to the self and as being under its volitional control. Most of the time in our everyday life, however, we are not aware of these mental representations. Instead, we seem to become aware only of a small proportion of them and under specific circumstances. For example, we do not routinely think about the position of our arms or legs in space but we may do so if we are asked to perform a complex task for the first time. Similarly, we do not usually think of the shape of our body as it appears from the outside, but we may suddenly become 'self-conscious' of our appearance if a particularly attractive individual enters the room. Given the preconscious and elusive character of these representations, their particular content and subdivisions, as well as their reflective or pre-reflective nature remain controversial (Gallagher 2000; see also later). Importantly, despite the centrality of these bodily representations for our sense of self, neuropsychology and experimental psychology have long demonstrated that our conscious awareness of the body is not infallible nor cognitively impenetrable. Indeed, psychologists have used several experimental 'tricks' to systematically manipulate sensorimotor signals, promote their integration, or generate conflicts and illusions, and hence study how the bodily self is constructed and maintained in the mind. In addition, while in such studies with healthy volunteers the particular manipulations of the bodily self are by necessity fully dependent on the duration and set-up of the experiment, neuropsychological and psychiatric disorders have revealed rich and long-lasting aberrations of body awareness. For example, brain damage to the perisylvian regions of the right hemisphere may deprive patients of their normal sense of body ownership for the affected, left body parts, so that they may feel that their left arm is no longer theirs and instead belongs to a different person. In this sense, such disorders represent an indispensable window of insight into the psychological and neural processes of body representation and awareness.

Several scholars further argue that the bodily self is not something that depends solely on mental and brain processes that belong to the singular individual and its body. Instead the self is socially or intersubjectively constituted. The notion of a socially constituted self has had many different voices in science and the humanities. A common denominator in these perspectives is the incompleteness of the view of an individual responding to a world populated only by inanimate things. The self, and particularly the bodily self, is according to some scholars shaped from the very beginning by the encounter with other living beings and hence our self is seen as intrinsically intersubjective (see Fogel 2013; Prinz 2012). In cognitive neuroscience, the once prevailing assumption that the human mind can be understood by examining exclusively cognitive functions and their neural correlates has undergone

considerable criticism. A diverse and growing community of researchers claim that mental abilities are embedded in the acting, sensing and feeling body and are subject to intricate couplings between organisms and their social environments (e.g. Damasio 1994; Decety 2009; Frith and Frith 2010; Panksepp 1998; Rizzolatti and Craighero 2004; Sebanz et al. 2006). In this chapter, we will focus on affective touch, as a specific modality of interoception (see later) that in juxtaposition to cutaneous pain has clear affective quality (pleasure vs. unpleasure) and natural social meaning (care vs. harm).

The Interoceptive and Emotional Core of the Bodily Self

What Constitutes the Bodily Self?

What is the bodily self and how does it emerge? Questions about the mental representation of the body in relation to the self have been of recurring interest throughout the history of sciences and the humanities and have recently regained attention in brain sciences. Although debates regarding the precise nature of self-representation are ongoing, growing evidence suggests that abstract, metacognitive notions of selfhood may depend on more fundamental, somatic sources. The mechanism of integration of somatic experiences with other signals from the environment is thought to contribute in the first place to a non-conceptual basic form of self-awareness, which is also commonly referred to as the 'minimal self' (Damasio 1999; Gallagher 2000). A multitude of experimental paradigms have documented the mechanisms of integrating visual, vestibular, proprioceptive and tactile input that give rise to higher level representations of our body (Blanke 2012). This multisensory integration is considered to be at the core of our most basic sense of selfhood. Accordingly, at least two levels of self-awareness have been proposed: (i) a pre-reflective, non-conceptual form of bodily self-awareness ('minimal self'), which can distinguished from (ii) a conceptual self-knowledge that is based on beliefs, intentions and social-contextual cues ('narrative self', Gallagher 2000). The 'narrative self' (or 'extended self'; Neisser 1988) can be conceived of as a continuous, coherent self that is derived and reconstructed from autobiographical knowledge (Conway 2001). In contrast, bodily self-awareness is regarded as an implicit internal, procedural model of the bodily self that operates primarily (but not necessarily) outside of conscious awareness. It is thought to rest on immediate sensory experiences associated with authorship for actions (sense of agency, i.e. the experience of initiating and controlling bodily movement and physiological states) and 'mineness' of the body (sense of body ownership). The 'acting' self and the associated sense of agency, certainly plays an important role in shaping the 'bodily self'. However, research on embodied self-awareness in the domain of action cognition is extensive and beyond the scope of our purpose here. Instead, this chapter will primarily explore representations of the bodily self in relation to affective touch.

What kinds of body representations do exist? Scientific research seems to suggest that there are "many bodies in the brain". Neuroimaging studies have found different cortical regions specialized for different facets of bodily awareness, with the strongest evidence for the posterior parietal cortex, the anterior insula and the extrastriate body area (for a review, see Berlucchi and Aglioti 2010). Moreover, many different conceptualizations have been proposed in an attempt to classify the various forms and sub-components of mental body representations (Berlucchi and Aglioti 1997; Dijkerman and de Haan 2007; Gallagher 2005). Most of these concepts, however, have been used rather vaguely or inconsistently across studies. This has contributed to partly divergent interpretations of research findings, which have led to much debate regarding their usefulness for understanding bodily self-awareness (see Berlucchi and Aglioti 2010). Of particular controversy is the classical dichotomous distinction between the concepts of 'body schema' and 'body image', which have been used by different authors in partly opposite ways (Gallagher 2005). The body schema has been defined by most authors to exclusively rely on proprioceptive input from muscles, tendons and joints and to provide the postural, kinaesthetic and tactile basis for sensorimotor capacities underlying action. The body image, in contrast, has mostly been referred to as the visual representation of the body as it appears from the outside, as an object in third person perspective, including the shape and length of limbs. It has often been used in relation to more declarative kinds of body-related knowledge and to contribute to a sense of body ownership and self-consciousness. Other alternative proposals that have been put forward distinguish between online (momentary) vs. offline (continuous) representations of the body (e.g. Carruthers 2008), or suggest a multi-component/multi-level organization (e.g. Giummarra et al. 2008).

For the present purposes, in order to elude conceptual vagueness, the structure of the chapter will not be based on distinct concepts of the bodily self, but we will focus more specifically on the experimental paradigms that have been used to study body representation. The terms bodily self or bodily self-awareness will be used here to refer generally to the implicit or explicit knowledge one may have of oneself as a bodily whole and of being localized within the bodily borders. The term body representation will be used to refer to a mental representation of the body that emerges from an integration of multiple sensorimotor signals and therefore is dissociable from the primary sensory representations.

The Role of Interoception in the Bodily Self

It has long been proposed that bodily self-consciousness relies on an integrated representation of multiple streams of sensory information, although findings are not fully consistent with respect to the precise weighing of the various sensory cues (Craig 2009; Critchley et al. 2004; Seth et al. 2011). Indeed, despite the important role of interoceptive signals for bodily self-awareness, scientific work has focused

almost exclusively on the integration of exteroceptive signals. Visceral afferent signals have long been neglected in this empirical and theoretical picture of body representation. Only recently has empirical research revealed and emphasized the importance of interoceptive (Craig 2002; Seth et al. 2011), emotional (Damasio 1999) and social (Prinz 2012) mechanisms underpinning bodily self-awareness.

Specifically, it has been proposed that interoception, the perception of the body from within, lies at the core of selfhood (Craig 2009; Critchley et al. 2004; Damasio 1999). Interoception refers to the perception of the physiological condition of the body. It is thought to rest on a separate specialized interoceptive system that is associated with the autonomic nervous system and has been related to the generation of subjective feelings and self-awareness (Craig 2009; Critchley et al. 2004; Damasio 2010; Seth et al. 2011). Interoception involves representations from multiple modalities such as temperature, itch, pain, cardiac signals, respiration, hunger, thirst, pleasure from sensual touch and other bodily feelings. It is distinct from the exteroceptive system, which refers to the classical sensory modalities for perceiving the external environment as well as proprioceptive and kinesthetic input informing about the movement of the body in space (Blanke and Metzinger 2009; Craig 2003; Critchley et al. 2004).

The mental representation of the internal physiological state of the body, such as the awareness of one's bodily pain or, heartbeat, has been associated with the insular cortex (Craig 2002, 2009; Critchley et al. 2004). More specifically, the dorsal posterior insula supports primary cortical representations of ascending interoceptive pathways reporting physiological states (e.g. mechanical, thermal or chemical) of skin, muscles, joints and internal organs (Craig 2003). The posterior insula also serves as the primary cortical area for projections of unmyelinated C-tactile (CT) afferents responding to gentle touch (Morrison et al. 2011; Olausson et al. 2002, 2008). These primary interoceptive representations are then re-represented and integrated with exteroceptive signals in mid-anterior portions of the insular cortex, where interoceptive awareness and bodily self-awareness is thought to emerge (Craig 2009).

Apart from interoceptive modalities such as pain and itch that can be assessed by stimulating nerve endings on the skin, there are different 'objective' methods for assessing the perception of 'visceral' interoception such as gastrointestinal distension, adrenergic stimulation and heartbeat perception. However, most attempts to quantify individual differences in the ability to perceive one's own internal bodily states have predominantly focused on cardiac activity perception. In heartbeat perception tasks participants are asked to detect and count their heartbeat silently under resting conditions (Pollatos and Schandry 2004; Schandry 1981). Quite stable interindividual, trait-like differences were found in these tasks in a plethora of studies (for review see Pollatos et al. 2005). The perception of cardiac signals, therefore, has been proposed as a measure of "interoceptive awareness".

Importantly, there is preliminary evidence that such measures of cardiac interoceptive awareness shape various body representations. In a series of studies on the sense of body ownership, Tsakiris and colleagues found that participants with lower cardiac awareness were more susceptible to experimentally induced

bodily illusions, such as the rubber hand illusion or the enfacement illusion (Tajadura-Jimenez et al. 2012; Tsakiris et al. 2011). These illusions involve self-identification with another person's face or hand induced by synchronous visuotactile stimulation between the own and the other's face or hand (see also section "How Touch Structures Body Representation"). Other evidence showed that providing visual feedback of the physiological state of the body, such as cardiovisual feedback presented synchronously with the heartbeat of the participants, can enhance the sense of ownership for a virtual hand (Suzuki et al. 2013), as well as self-identification with and self-location toward a virtual body (Aspell et al. 2013). Consistently with these studies in healthy volunteers, clinical studies in patients with disorders of body representation, such as somatoform and eating disorders have found reduced levels of interoceptive awareness, as perceived by heartbeat detection tasks (Mussgay et al. 1999; Pollatos et al. 2008; Schaefer et al. 2012; see also section "The Role of Touch in Pathological Bodily Awareness"). Conversely, improvements in cardiac awareness have been linked with reduction of distress associated with somatic symptoms in these disorders (Schaefer et al. 2014).

However, the relation between such measures of cardiac awareness and the perception of signals from other interoceptive modalities remains to be specified, and further explored in relation to multisensory integration and the bodily self. In the meanwhile, indirect support for the more general role of cardiac awareness in the bodily self can be found in the observed relation between cardiac, interoceptive awareness and emotion. For example, recent studies using heartbeat perception tasks have showed that cardiac awareness is positively correlated with the perceived intensity of emotional stimuli (Critchley et al. 2004; Pollatos et al. 2005). Clinical studies have also pointed to fact that patients with anxiety disorders have a higher interoceptive awareness (Domschke et al. 2010; Dunn et al. 2010; Pollatos et al. 2009; Stevens et al. 2011), while patients with depression typically show reduced cardiac awareness (Pollatos et al. 2009). These findings bring us to the relation between interoception, emotion and the bodily self which will be considered in the following section.

The Role of Emotion in the Bodily Self

The idea that bodily self-awareness is tied to signals that are important for homeostatic regulation has commonalities with theories that emphasize the perception of physiological, bodily states as the basis of emotion (Damasio 1994, 1999; James 1884, 1890). The precise role of bodily perception however, in relation to emotion and cognition is a classical (for review, see Sander 2013) and ongoing debate (Critchley et al. 2004; Niedenthal 2007; Seth 2013) that escapes the scope of this article. Here we refer merely to the relation between emotional awareness and certain sensory modalities as a prelude to our consideration of affective touch and its role in the bodily self.

The relation between emotion and body representation has been addressed in different sensory modalities. For example, paradigms involving visual bodily signals have revealed that body-selective cortical areas are modulated by emotional information and the socio-effective context in which the body is perceived (de Gelder et al. 2010; Van den Stock et al. 2014). These areas include the extrastriate body area (EBA; Downing et al. 2001) and the fusiform body area (FBA; Peelen and Downing 2005) that are typically activated by images of body parts. Furthermore, a strong relation has been proposed to exist between emotion and vestibular body signals (for review, see Carmona et al. 2009). The vestibular system plays an integral role in body ownership representation (Lenggenhager et al. 2007) and self-awareness (Simeon et al. 1997). The link to emotion is primarily based on the observation of a high co-morbidity of vestibular dysfunctions and psychiatric symptoms such as anxiety, depression and panic disorders (e.g. Balaban and Thayer 2001; Gazzola et al. 2009; Godemann et al. 2004). Finally, abundant examples for a strong interrelation between emotional disturbances and somatic symptoms can be observed in neuropsychiatric disorders. This relation is perhaps most obvious in conditions such as body integrity identity disorder (BIID; Sedda 2011) or misoplegia (Critchley 1974), in which patients report extreme dislike of and other strong, negative emotions towards an individual body part, even to the degree that they may wish that it is amputated. Moreover, the excessive preoccupation with body size and the perceptual overestimation of one's own actual body size in patients with eating disorders involves a strong negative emotional attitude towards the body. We consider examples of these pathologies and discuss the potential role of affective touch in the third section of the present chapter.

Strong effects of emotion have also been observed in the processing of nociceptive body-related signals. The affective modulation of pain has been examined at the spinal and cerebral levels and evidence was found for hyperalgesic and analgesic effects of negative and positive emotions, respectively (Duquette et al. 2007; Rainville et al. 2005). In a recent study, for example, emotions induced by pleasant and unpleasant images modulated spinal nociceptive responses to painful electrical stimulation and pain perception (Roy et al. 2009). The modulations of perceived pain were particularly correlated with activity in the right anterior insula, while a partially distinct brain circuit was involved in the modulation of spinal nociceptive responses. Interestingly, the anterior insula has been shown to code the affective component of pain (Kong et al. 2006; Schreckenberger et al. 2005), and it has been found to be sensitive to other emotional experiences associated with odours (Royet et al. 2003) and tastes (Small et al. 2003). These observations are consistent with current theoretical models proposing a dominant role of the anterior insula in both bodily (e.g. Tsakiris et al. 2007) and emotional awareness (Critchley et al. 2004).

Affective Touch and the Bodily Self

Touch and the Elusive Dualities of the Body

How does affiliative touch contribute to the bodily self? Which particular sensory, affective and interpersonal features convey relevant information for the construction of a sense of embodied selfhood? It appears that when we are touched at the physical boundary of the body, that is the skin, our brain forms two sets of partly independent representations about this single experience. On the one hand, the tactile stimulus is processed in terms of its exteroceptive, discriminatory processes in classical peripheral pathways and somatosensory cortical areas, while on the other hand, a specialized peripheral and central system seems to code for the affective properties of the same stimulus. Indeed, the recent neurophysiological evidence that is reviewed in this book suggests the existence of a dual touch system consisting of two parallel neural pathways: one for purely sensory touch, composed of skin mechanoreceptors projecting to the thalamus and primary somatosensory cortex (Johnson and Hsiao 1992), and another for affective touch (Olausson et al. 2002; Vallbo et al. 1999). The affective touch system is thought to rely on a distinct subgroup of mechanoreceptors, tactile C-fibres, responding only to slow (between 1-10 cm/s), caress-like touch, with activation being correlated with pleasantness ratings on visual-analogue scales (Löken et al. 2009). What is more, C-tactile afferents take a distinct ascending pathway from the periphery to a different part of the thalamus and then to the posterior insular cortex (Morrison et al. 2011; Olausson et al. 2002). As aforementioned, the latter pathway is considered as mediating an early convergence of sensory and affective signals about the body, which are then re-represented in the mid and anterior insula: the proposed sites of interoceptive awareness (Craig 2009; Critchley et al. 2004).

This duality at the neurocognitive level seems to lead to a number of psychological dualities at the core of our embodied self-consciousness. In this section, we will highlight two such dualities, namely the inside-outside and the self-other distinctions, and describe their elusive and interrelated character, as well as certain conceptual fallacies associated with them. In the following sections, we review research that has focused on how affective touch may be integrated with other sensory and motor modalities to shape our bodily self.

The Inside–Outside Distinction

Affective touch such as a caress is applied at the outer surface and boundary of the body, namely the skin. As aforementioned however, the signals conveyed via such dynamic, gentle touch provide information about both the internal state of the organism (‘this experience feels good’) and the external surface of the body (e.g. ‘I am touched on the right forearm’). This multiplicity of information and pathways poses conceptual challenges for any rigid, dichotomous distinction at

the level of awareness between sensation and emotion, interoception and exteroception, or, inner and outer body, or, body schema and body image. Since Sherrington, neuroanatomy categorizes senses into interoception, exteroception and proprioception. Recently, affective touch and pain were reclassified as interoceptive modalities (Craig 2003), given their aforementioned neurophysiological specificity and role in providing information about the physiological stability of the body (homeostasis). Yet unlike other interoceptive modalities, affective touch, itch and cutaneous pain are by definition linked with external stimuli (and frequently social agents, see later) and are applied on the outer surface of the body. It thus appears that such modalities may act as important mediators of the bodily inside and outside, possibly having a unique contribution to the coherent and unified character of body awareness (see section "How Touch Structures Body Representation").

The Self-Other Distinction

Affective touch seems to simultaneously capture information about 'the self' and the outside world, in the same way that it transcends the inner–outer body distinction. Specifically, gentle, slow stimulation of the skin provides information about one's own body (as described earlier), as well as about the external world (e.g. 'this is a soft material, moving slowly'). Importantly, research has now shown that the perception of affective touch can provide information about the emotions and thoughts of other individuals (Hertenstein et al. 2006a, b). We speculate that this rather unique, parallel activation of pathways relating to the internal representation of the body, as well as the external, social world, presumably acts as an early, developmental source of bodily information regarding the self-other distinction. Indeed, contrary to traditional assumptions, seminar studies in developmental psychology have established that even before their first birthday infants show unequivocal signs of primary self-other distinction and corresponding social interaction behaviours; they actively solicit their caregivers' attention and engage themselves in interactive practices that are attuned to the actions and gestures of other humans (for recent reviews see Braten and Trevarthen 2007; Fonagy et al. 2004; Meltzoff and Brooks 2001; Reddy 2008; Rochat 2009; Trevarthen 1993). There is already some evidence from developmental psychology suggesting that multisensory integration, including the integration of tactile stimuli with vision and proprioception, contributes to the establishment of the psychological distinction between one's body and that of others (Cascio et al. 2012). We speculate that given its dual, sensory-discriminatory and affective-motivational nature, social touch, an essential part of early mother-infant interactions, has a unique developmental role in establishing the physical boundaries of the psychological self.

The Self-Other Relation

Somewhat paradoxically, affective touch may be important not only in establishing and maintaining a healthy self-other distinction but also in mediating the psychological connection between self and other and related social cognition abilities (for the so-called social touch hypothesis; Morrison et al. 2010; Olausson et al. 2008). Seminar studies have established that humans, given their need for early nurturance and care by conspecifics, have developed an innate social attachment drive, unrelated to hunger or thermoregulation, and a corresponding lifelong need for social connection (Bowlby 1969; Harlow 1958; Panksepp 1998). Perhaps built upon the evolutionary foundations of grooming (Dunbar and Shultz 2007) and tickling (Panksepp and Burgdorf 2003) behaviours in other mammals, human tactile contact in early life is increasingly understood to be central to a healthy, emotional development (cf. Fogel 2013; Prinz 2012; Winnicott 1971). For instance, self-reported frequency of maternal stroking over the first weeks of life has been associated with reduced association between prenatal depression and adverse mental health outcomes in infancy (e.g. Arditi et al. 2006; e.g. Dieter et al. 2003; see also Sharp et al. 2012).

Similarly, the physical development of premature infants can benefit from skin-to-skin contact with caregivers (e.g. Dieter et al. 2003). It has been suggested that a decrease in cortisol levels, and stimulation of oxytocin and growth hormones underlie these touch effects (Field 2001). 'Kangaroo care' (KC) is by now a common intervention in neonatal care in many clinics with increased emergence of evidence-based KC guidelines (DiMenna 2006). KC allows the naked infant to have direct tactile contact with the parent's bare chest and to hear the parent's heartbeat. It has been shown to significantly reduce pain behaviour in full-term infants and stable preterm infants (for review, Warnock et al. 2010). Other evidence has shown that skin-to-skin contact following Caesarean section may help maintain temperature of newborns and reducing newborn stress (for review, Stevens et al. 2014). More generally, being held and gently stroked by caregivers is also associated with reduced pain and distress in infants (Esposito et al. 2013; Gray et al. 2000; Pelaez-Nogueras et al. 1996).

Moreover, these developmental effects seem to be mirrored by lifelong phenomena. Tactile interactions with significant others can help in regulating emotions, for example, in stressful or threatening contexts (Coan et al. 2006; Gallace and Spence 2010). A number of studies in healthy adults have demonstrated that warm, social, physical contact among couples can lead to decreases in blood pressure reactivity and cortisol release to stress (Ditzen et al. 2007; Grewen et al. 2003), and can reduce physical pain (Krahe et al. 2013). Recently, we have also found that the neuropeptide oxytocin, known for its role in social bonding and prosocial behaviour, and its analgesic effects in animals (Gu and Yu 2007), can reduce pain perception in humans.

More generally, such findings are consistent with the crucial role of grooming behaviours in mammals, particularly as regards the formation of social bonds and the development of lifelong healthy resilience to environmental threat and bodily pain (for review see Panksepp 1998). For example, early postnatal maternal tactile

stimulation in rats can modify prenatal adverse effects by reducing HPA axis reactivity to bodily stressors (Vallee et al. 1999) and increased postnatal sensory input from maternal care reduces excitation to stress-responsive hypothalamic neurons and even has beneficial epigenetic effects (Korosi et al. 2010).

In addition, recent neuroimaging studies have shown that neural regions such as the posterior superior temporal sulcus (STS) and the medial prefrontal cortex that are typically associated with the 'social brain' and a number of social cognition abilities, such as perspective taking and mind-reading, are selectively engaged by the processing of affective touch (Bennett et al. 2014; Bjornsdotter et al. 2014; Gordon et al. 2013). Interestingly, there is at least a female-specific developmental increase in the sensitivity of the posterior STS to affective touch (Bjornsdotter et al. 2014).

Although some of the above brain areas are also linked with self-related processing and embodied facets of perspective taking (Decety and Jackson 2004), to our knowledge, few systematic, developmental studies have focused on the role of affective touch in the formation of the bodily self. Yet indirect confirmation comes from studies on neurodevelopment in low birth weight infants (see also Gallace and Spence 2010). For example, Weiss and colleagues (2004) observed that infants of mothers who used more stimulating touch during feeding at 3 months had better visual-motor skills and more advanced gross motor development. Finally, the research application of multisensory integration paradigms to infant body perception (Cowie et al. 2013; Filippetti et al. 2013) suggests that the specific, developmental role of affective, social touch can soon be studied in early infancy and childhood. In one of these studies, multisensory integration of visuo-tactile and proprioceptive information did not lead to changes in the bodily self in children with Autism Spectrum Disorders (ASD) as fast as it did in children without ASD. Moreover, this effect was moderated by individual differences in social cognition abilities such as empathy, in the sense that higher levels of empathy were associated with greater changes in body representation following multisensory integration. These findings point to the tight link between attuned, social responses to infants' bodily needs and the development of both self- and other-related cognition.

How Touch Structures Body Representation

Before discussing the specific link between affective touch and the bodily self, we will briefly discuss the general dimension of touch in relation to body representation in order to better understand and integrate its affective aspects. Evidence for the general influence of tactile afferent signals and their reciprocal interaction with mental body representations has been provided by a range of different research paradigms (for review, see Serino and Haggard 2010). In these paradigms, most attention has been focused on the sensory discriminative component of touch.

One important piece of evidence for the impact of tactile information on body representation comes from the rubber hand illusion (RHI) in healthy participants (Botvinick and Cohen 1998). Observing a rubber hand being stroked and at the same time experiencing one's own unseen hand being stroked in synchrony typically elicits the sensation that the rubber hand is one's own hand. It was concluded that the concurrence of primary tactile and visual input strongly influences the incorporation of body parts within the psychological self. Other multisensory integration paradigms have observed changes in the bodily self in relation to isolated body parts such as fingers (Dieguez et al. 2009), arms (Fourneret and Jeannerod 1998) and the face (Sforza et al. 2010), or even the perception of the entire body (Ehrsson 2007; Lenggenhager et al. 2007). Other studies were able to induce the rubber hand illusion even when vision was not implicated, in the so-called somatic rubber hand paradigm (Ehrsson et al. 2005). Specifically, when blindfolded participants applied externally guided touch to an artificial hand and synchronously received touch on their own hand from the experimenter, they experienced the illusion that they were touching their own hand. This was observed even when they received incongruent visual feedback (White et al. 2010). That is, a match between touch and proprioception (i.e. active and passive touch) was shown to be sufficient to induce or change feelings of ownership for the artificial hand, as reflected in the illusion of self-touch.

Another important domain of touch that has been repeatedly shown to modify the structural representation of the body as a physical object is self-touch. In fact, phenomenological philosophy considers self-touch a basic form of self-awareness based on the integration of active and passive hand (Husserl 1989; Merleau-Ponty 1962). For example, Schütz-Bosbach and colleagues asked participants to touch several fingers of one hand with fingers of the other hand (2009a, b). By interleaving the experimenter's fingers with the fingers of the participant's passive hand they induced a discrepancy between the number of fingers touched on the active and passive hand. It was found that participants underestimated the number of fingers specifically in the self-touch conditions. These findings suggest that self-touch may influence the mental representation of body parts, in particular via somatic inputs (i.e. the passive experience of being touched) rather than sensorimotor signals associated with active aspect of touch.

A number of neuropsychological studies have investigated the influence of active- and self-touch on the processing of somatosensory signals and the structural representation of the body in relevant pathologies. Patients with right hemisphere lesions may suffer from severe loss of sensory function resulting in the inability to detect sensory stimulation administered to the affected limb. Importantly, in these patients it has been found that self-touch can enhance sensory processing and improve tactile detection (Valentini et al. 2008; Weiskrantz and Zhang 1987). In addition to this low-level sensory enhancement, beneficial effects of self-touch have also been reported in relation to higher order body representations such as body ownership. For example, White and colleagues (2011) used the somatic rubber hand paradigm (Ehrsson et al. 2005) to investigate whether self-touch enhancement can be observed even when the patient is unable to use knowledge about the position of

the limb. The patient's affected hand was stimulated, while the unaffected hand was guided by the experimenter to stimulate a prosthetic hand. If these two events were executed simultaneously, enhanced detection of the sensory stimulation was observed in the patient's affected hand. Since no visual or proprioceptive information was available to patients, it can be concluded that self-touch allowed them to *feel* rather than infer the tactile stimulation.

A recent study by Kammers et al. (2010) is important because it explicitly investigated the role of touch and body representation in relation to emotions. They induced an illusory feeling of painful heat in the middle finger by placing the participant's index and ring finger in hot water, and the middle finger in cold water ('thermal grill illusion'). This illusion has traditionally been explained by low-level interactions and disinhibition of C fibres signalling pain. The authors found that the perceived heat was reduced if the same fingers of the unstimulated hand touched the three corresponding fingers immediately after the stimulation. This suggests that self-touch may gate strongly negative affective signals and increase the coherence of the mental representation of the body. Moreover, it has been shown that touch is associated with changes in autonomic bodily functions, such as reductions in heart rate, blood pressure and hormone secretion (Ditzen et al. 2007; Grewen et al. 2003).

The important conclusion from the earlier reviewed evidence is that touch is a crucial factor contributing to mental body representation via its purely sensory-discriminatory component. Given this evidence and the role of emotions for the bodily self, it is reasonable to assume a specific influence of the purely affective and social components of touch on body representation, which will be discussed in the following section.

Figure 21.1 illustrates the various ways by which social, emotional touch experience may interrelate with the bodily self.

Affective Touch Modulates the Sense of Body Ownership

As we outlined earlier, most experimental research on the bodily self has thus far explored how the integration of exteroceptive and proprioceptive signals may give rise to changes in the habitual sense of body ownership (for review see Tsakiris 2010). By contrast, remarkably little attention has been paid to how the sense of body ownership can be modulated by interoceptive signals arising from the body itself. Previous research has shown that individuals who score lower on a trait measure of interoceptive sensitivity (the heart beat detection task, described previously) experience a stronger rubber hand illusion (RHI) compared to individuals who score higher on the same measure (Tsakiris et al. 2011). In addition, physiological regulation (e.g. temperature) of the body during the illusion can be influenced by exteroceptive, multisensory integration (Moseley et al. 2008). However, Schütz-Bosbach et al. (2009a, b) found no effect of using materials with different qualities (i.e. soft vs. rough) on body ownership during the RHI.

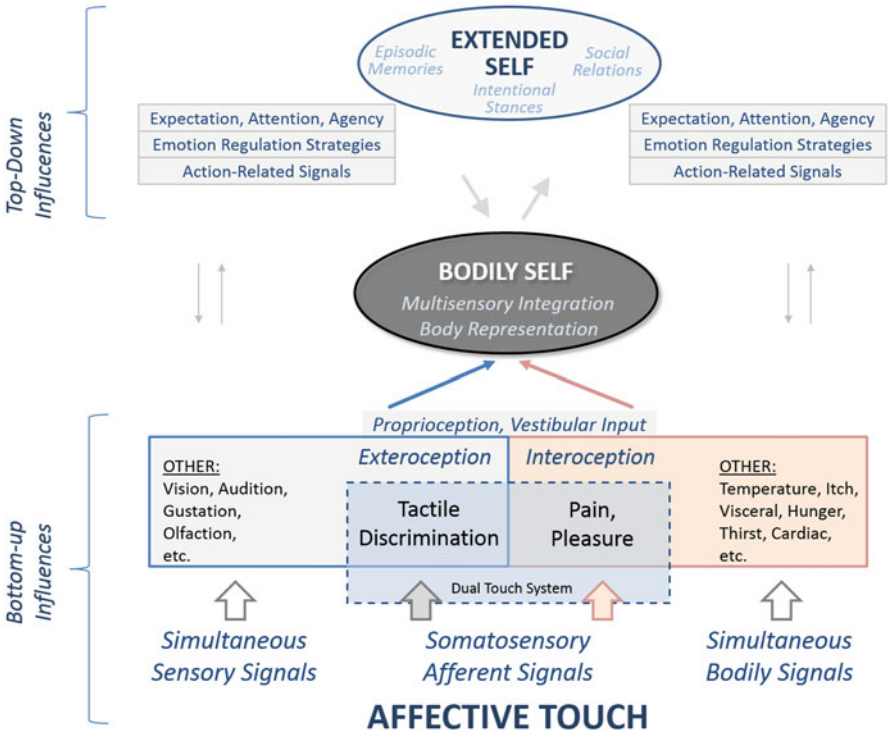

Fig. 21.1 Simplified schematic figure of the bottom-up sensory signals and the top-down mechanisms underlying mental representations of the bodily self. Multiple sensory and emotional signals, including those conveyed via affective touch, are integrated depending on top-down modulatory mechanisms in order to allow for the experience of bodily ownership and the location of our self-awareness inside our physical body. This mechanism of integration of somatic experiences with other internal and external signals is thought to contribute in the first place to a low-level pre-reflective form of immediate bodily self-awareness. This representation interacts with conceptual self-knowledge of the 'extended self', based on episodic memory, background beliefs and contextual cues. Note that there are intrinsic connections between sensory, cognitive and socio-emotional processes at each level of self-awareness, which, for reasons of simplicity, are not detailed here. Abnormalities in the weighing and integration of bottom-up and top-down signals may lead to 'body image' disturbances as in anorexia nervosa (see section "Affective Touch and Body Image Disturbances in Anorexia Nervosa"), or to a disturbance in the sense of body ownership as seen in asomatognosic patients following right-hemisphere brain damage (see section "Affective Touch and Body Disownership: Studies in Neuropsychological Disorders")

A recent study by Suzuki and colleagues (2013) specifically examined the role of interoception and exteroception on body ownership, by presenting cardio-visual feedback in time with the participant's heartbeat. This feedback enhanced ownership of a virtual hand, indicating that online integration of interoceptive and exteroceptive signals can modulate the sense of body ownership. Similar findings have been confirmed by other studies. Aspell and colleagues (2013) showed that cardio-visual signals modulate not only the sense of body ownership, but also tactile

perception. These recent data suggest that the integration of internal and external body signals is crucial for self-consciousness (Aspell et al. 2013). However, none of these studies have examined how affective (pleasant) touch, which provides a unique and direct source of interoceptive information about the state of the body, influences body ownership.

In light of the above, we examined body ownership during a RHI procedure that used different stroking speeds to deliver either pleasant (3 cm/s) or affectively neutral (18 cm/s) touch to participants' forearms (Crucianelli et al. 2013). Our results confirmed that slow touch on hairy skin is perceived as more pleasant than fast touch (Löken et al. 2009, Fig. 21.1a), and, more importantly, demonstrated for the first time that pleasant touch produces higher levels of subjective body ownership feelings and sensations (Fig. 21.2b).

Our findings were later confirmed by Lloyd et al. (2013), who also found that slow, caress-like touch, modulated subjective reports of pleasantness and body ownership during the RHI. Interestingly, Lloyd and colleagues found that stroking the palm of the hand (which contains no CT afferents, also elicited greater feelings of pleasantness and enhanced embodiment. This suggests that the perceived pleasantness of touch and its effect on embodiment may be mediated by a complex interaction of higher cognitive factors (such as beliefs, memory, motivation) and basic sensory and affective processes, which goes beyond the simple activation of skin fibres. Further evidence of this complexity can be found in the most recent study to examine the effect of affective touch on body ownership (van Stralen et al. 2014). Unlike previous studies (Crucianelli et al. 2013; Lloyd et al. 2013), van Stralen and colleagues found that pleasant touch did not affect subjective measures of body ownership (i.e. questionnaires), but did influence the perceived location of the real hand in relation to the rubber hand (i.e. the so-called proprioceptive drift). Contrary to Lloyd et al. (2013), this effect was specific to the use of a C-tactile optimal velocity applied to hairy skin. According to van Stralen and colleagues, these results suggest that C-tactile fibres modulate body representation in terms of multisensory

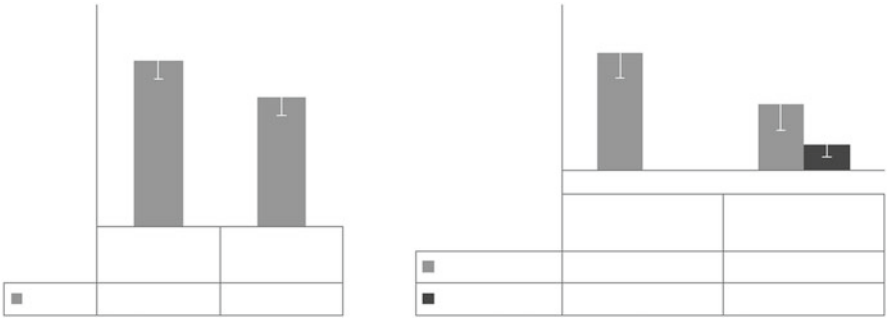

Fig. 21.2 (**a**) Median and interquartile range (*error bars*) of pleasantness rating scores for slow and fast stroking. (**b**) Median and interquartile range (*error bars*) of change in embodiment of the rubber/real hand for synchronous (*dark grey bars*) and asynchronous (*light grey bars*) stroking. This figure is reproduced from Crucianelli et al. (2013)

integration, rather than being involved in the conscious experience of body ownership. However, further studies are needed to fully explain these contradictory findings and determine the precise mechanisms by which affective touch modulates body ownership.

For example, research has begun to investigate individual differences in pleasant touch perception; however, it is currently unknown whether such differences might depend only on C-tactile stimulation. Moreover, to the extent that pleasant touch (Bermudez 2005; Bjornsdotter et al. 2009) and other interoceptive modalities such as pain (Krahe et al. 2013) are thought to convey important social signals of safety versus threat, future studies are needed that investigate the potential role of social, affiliative signals on the sense of body ownership and more generally, the malleability of the bodily self.

The Role of Touch in Pathological Bodily Awareness

The Role of Touch in General Mental Health

Affective touch seems to promote psychological and physical well-being. In this third part of the chapter, we will first briefly outline accumulating clinical and experimental evidence for the beneficial role of affective touch in healthy individuals, before focusing on psychiatric and neurological disorders that have been specifically linked with abnormalities in the bodily self. These disorders involve severe forms of dysfunctional and impaired body representation and are also assumed to have a significant socio-emotional component determining the development and severity of pathology. Therefore, gentle, caressing touch may potentially be an important remedy to these disorders.

Several studies have reported health benefits of light touch on a number of bodily conditions and autonomic functions such as blood pressure and heart rate, which have been taken to suggest enhanced parasympathetic nervous system activity and embodied self-awareness (see Fogel 2013). For example, clinical trials demonstrated beneficial effects of soft, interpersonal touch on bodily symptoms such as pain in fibromyalgia syndrome (Denison 2004), headache pain (Keller and Bzdek 1986), pain and sensory symptoms associated with neuropathy or degenerative joint diseases (Blankfield et al. 2001; Gordon et al. 1998), and on agitation in Alzheimer patients (Woods et al. 2005; Woods and Dimond 2002). These therapeutic touch interventions typically involve light touch, rather than massaging movements, which is applied to the tense or painful area of the body (for review see Kerr et al. 2007). Often they are coupled with attentional practices used in meditative traditions such as mindfulness meditation. Most of these studies, however, did not explicitly measure subjective bodily self-awareness or related neural markers, therefore, the exact pathways mediating the effects of this type of therapeutic touch are still unclear. It has been argued that touch activates the parasympathetic nervous

and embodied self-awareness, which in turn reduces pain and supports restoration (see Fogel 2013). Other findings support benefits of massage therapy for bodily self-awareness in eating disorders, by decreasing body dissatisfaction and levels of stress as reflected in lower cortisol (stress) hormone levels (Hart et al. 2001). In the following section we discuss the specific relation between anorexia nervosa and interpersonal, affective touch.

Affective Touch and Body Image Disturbances in Anorexia Nervosa

Disturbances in body representation and awareness are a core, clinical features in anorexia nervosa (AN), an eating disorder with unknown aetiology and the highest rate of mortality among all psychiatric disorders (Sullivan 1995). Patients with AN show restricted eating, an endless pursuit of idealized levels of thinness irrespective of actual body mass index and obsessive fears of becoming fat (Wagner et al. 2008). Given these clinical traits, a large number of studies have investigated whether patients with AN are dissatisfied with their own body, show any other negative attitudes towards it or overestimate their weight and shape. Such attitudes and tendencies are typically described as 'body image' disturbances. Several investigations and meta-analyses have claimed that such disturbances are mostly attitudinal and emotional, and do not entail low-level, perceptual deficits, such as body size overestimation (Cash and Deagle 1997; Cornelissen et al. 2013; Farrell et al. 2005; Smeets et al. 1998).

Nevertheless, the possibility that AN is accompanied by abnormalities in low or higher order perception of the body has recently captured the attention of cognitive neuroscientists. Accordingly, a number of perceptual tasks have been applied to AN samples, showing that AN patients overestimate their body size compared to healthy controls in visual, tactile and haptic perception (e.g. Grunwald et al. 2001; Guardia et al. 2012; Keizer et al. 2011; Urgesi et al. 2013), as well as in action-related tasks (Guardia et al. 2010; Nico et al. 2010). Furthermore, neuroimaging studies testing the visual perception of the body in patients with AN versus healthy controls have shown reduction of activation in middle occipito-temporal cortices, such as the extrastriate body area (EBA) and the fusiform body area (FBA), which are typically activated by viewing human bodies and body parts but not faces and objects (e.g. Suchan et al. 2010; Uher et al. 2005).

Interestingly, despite the clear clinical indications of abnormal emotional attitudes towards the body, as well as the more general emotional, abnormalities in AN patients, such studies on body perception have focused exclusively on the exteroceptive body, i.e. the body as perceived on the basis of classic sensations such as vision or sensory-discriminatory touch. Indeed, the so-called body image disturbance in AN is understood as a separate domain of study than the ample investigations of reward motivation and anhedonia (inability to seek and enjoy pleasurable

experiences) in AN (Friederich et al. 2006; Kaye 2008; Soussignan et al. 2011; Tchanturia et al. 2012; Wagner et al. 2007). This separation of topics seems not only arbitrary, but it also portrays a dualistic distinction between perception and emotion or, body (perceived from the outside as an object) and mind (based on disembodied notions of emotional subjectivity). As we outlined earlier, sensations such as affective touch challenge such rigid dichotomies. They instead call for an embodied understanding of subjectivity that is grounded in the integration of bodily signals deriving from multiple 'internal' and 'external' sources.

To our knowledge it is only very recently that multisensory integration paradigms have been applied to the study of body awareness in AN. Specifically, Eshkevari and colleagues (2012) found that AN patients are more susceptible to the Rubber Hand Illusion (RHI, see earlier) than healthy female volunteers, even in the asynchronous tactile stimulation (control) condition. These suggested that there may be an increased sensitivity for visual aspects of body perception in AN patients. Keizer and colleagues (2014) have recently replicated this finding and also showed that the experience of ownership over the rubber hand, as well as the mere visual focus on the rubber hand in the asynchronous (control) condition, were able to reduce the prior overestimation of (own) hand width shown in the AN group. These results are consistent with prior findings in healthy volunteers showing that the incorporation of the rubber hand into the body representation affected the similarity that participants perceived between their own hand and the rubber hand, while the reverse was not true, i.e. objective similarity (as measured by skin luminance, hand shape and third-person similarity ratings) did not appear to influence participants' experience of the RHI. Taken together, the earlier findings highlight that the bodily self is highly malleable in AN and also importantly suggest a direction of causality in the observed symptoms: it may be that the body image disturbances seen in AN patients are due to that abnormalities in the subjective sense of embodiment, rather than the other way around.

Interestingly however, none of the earlier studies have accounted for the role of interoception in the construction of the bodily self in AN. Apart from the aforementioned clinical reasons, this seems important as previous studies on AN have found altered subjective responses to interoceptive stimuli such as hunger and physical pain (e.g. Strigo et al. 2013) and a reduced capacity to accurately perceive one's heartbeat (Pollatos et al. 2008). Therefore, in a recent study we investigated the idea that AN patients may present reduced bodily pleasure, by examining the perception of pleasant touch in AN. Healthy and AN participants were asked to rate the pleasantness of light touch applied to the forearm at CT-optimal (3 cm/s; pleasant) and non-CT optimal (18 cm/s; neutral) velocities. Our preliminary data reveal that AN participants rate the pleasantness of the perceived touch as lower in both slow and fast velocities compared to healthy controls. This suggests a generally reduced bodily pleasure in AN subjects and a potentially dysfunctional CT afferent system, or an abnormal cognitive regulation of this system. Interestingly however, our results also show that pleasant ratings were influenced by social manipulations in similar fashion in AN patients and controls. Thus, these results indicate that perception of affective touch, rather than its social modulation maybe affected in AN. These

results are consistent with the more general social and emotional anhedonia in AN and corresponding hypotheses about the role of dopamine and other reward-related neural mechanisms in the aetiology of the disorder (Friederich et al. 2006; Kaye 2008; Soussignan et al. 2011; Tchanturia et al. 2012; Wagner et al. 2007). The precise role of affective touch and other interoceptive, as well as social signals in the construction of the bodily self in AN remains to be specified. Nevertheless, as aforementioned, there are some preliminary indications that massage therapy can reduce AN symptomatology, including a decrease in body dissatisfaction and a corresponding increase in dopamine levels (Hart et al. 2001).

Affective Touch and Body Disownership: Studies in Neuropsychological Disorders

The body is normally omnipresent in the mind. As such, identifying the factors that constitute the bodily self is particularly problematic, because it is hard to achieve a viable 'control' condition in healthy volunteers where the bodily self is absent or subjective 'disembodiment' exists. In spite of the progress in creating suitable, experimentally induced sensorimotor conflicts and illusions, it remains difficult to create convincing and stable states of disembodiment in healthy volunteers (for discussion see de Vignemont 2011; Longo et al. 2008). By contrast, neurological patients with disorders of body awareness may show clear, counter-intuitive and long-lasting, subjective experiences of disembodiment. Indeed, there is some initial neural (Zeller et al. 2011) and behavioural (Jenkinson et al. 2013) evidence suggesting that the subjective sense of body disownership seen in these disorders is caused by damage to neural mechanisms that are separate from those involved in paradigms such as the RHI. In this sense, neurological disorders of body awareness represent unique windows of insight into the psychological and neural mechanisms of the bodily self.

Such disorders may affect different facets of the bodily self, including, among others, self-location and first-person perspective (autoscopic phenomena; Blanke et al. 2004), body ownership (Vallar and Ronchi 2009) and motor agency and awareness (anarchic hand syndrome and anosognosia for hemiplegia; Fletcher and Fotopoulou 2014; Fotopoulou 2014). As in the case of studies with healthy volunteers, investigations of these disorders have mainly focused on the integration and representation of proprioceptive, vestibular and exteroceptive signals (vision and discriminatory touch). However, as evidence accumulated about the fundamental role of interoception in the bodily self in other fields (Craig 2003; Damasio 1999), a handful of neuropsychological studies have turned their attention to interoception.

In this chapter, we review such studies with particular focus on one, prototypical disorder of body awareness: asomatognosia (from the Greek, meaning 'lack of body knowledge'). Asomatognosia refers to the lack of recognition of the existence or ownership of one's limbs (Jenkinson et al. 2011). Patients may feel their contralesional arm is missing or they may perceive it as not belonging to themselves. The

disorder also has several 'constructive' variants (in the classical sense of 'positive' symptoms as compared to 'negative' symptoms). For example, patients may perceive their affected arm as belonging to someone else (somatoparaphrenia), as being duplicated (supernumerary phantom arm), or as having an identity of its own (personification). Direct confrontation by doctors does not improve awareness and, if anything, when patients are challenged they tend to become more ingrained in their false beliefs. Although such symptoms typically resolve spontaneously, they are of variable duration, lasting from days to years (Vallar and Ronchi 2009) and they constitute a considerable therapeutic challenge (Jenkinson et al. 2011).

Asomatognosia and its constructive variants (hereafter referred to as 'disturbance in the sense of body ownership', DSO, for brevity, see also Karnath et al. 2005) typically occur in patients with right-hemisphere lesions (although left cases have been noted; see Vallar and Ronchi 2009). DSO is frequently associated with primary and higher order motor, proprioceptive and tactile deficits. Nevertheless, these deficits do not seem sufficient for the occurrence of DSO, as primary sensorimotor loss and higher order deficits such as neglect typically do not produce the awareness symptoms seen in these patients. Furthermore, tactile perception can be improved in DSO without a corresponding improvement in body ownership (Bottini et al. 2002; Moro et al. 2004) and patients retain their delusional beliefs about their affected arm even when this is placed in the non-neglected hemifield (Moro et al. 2004).

Whether DSO should be considered a single disorder, and whether it is dissociable from motor, or sensory unawareness following right hemisphere lesions remain debated issues (e.g. compare Invernizzi et al. 2013; with Karnath and Baier 2010). Importantly, however, recent lesion mapping studies suggest that a number of brain regions associated with interoception and interoceptive salience may be selectively associated with DSO. Contrary to original assumptions about the role of the right premotor and parietal cortices in DSO, recent lesion mapping studies have revealed that right hemisphere areas such as the posterior insula, basal ganglia structures, certain limbic structures such as the amygdala and related subcortical white matter connections are selectively associated with DSO (Gandola et al. 2012; Invernizzi et al. 2013; Karnath et al. 2005; Zeller et al. 2011). Such areas and their connections have long been implicated in bodily salience, emotion and interoception, and as previously mentioned, the posterior insula has been critically implicated in the processing of primary affective touch signals.

Remarkably, however, only one systematic study has thus far focused on the role of interoception in DSO. Romano and colleagues (2014) measured anticipatory skin conductance responses to noxious, threatening stimuli approaching either the affected or the intact body side in patients with somatoparaphrenia. This was compared to a control group of patients with preserved ownership but decreased awareness of somatosensory deficit and to a control group of patients with no deficits of ownership or sensory awareness. Anticipatory skin conductance responses for the disowned arm were selectively reduced in the somatoparaphrenic patients, but were intact in patients that showed clear deficits in tactile perception and related unawareness. These results point to a dissociation between (anticipatory) interoceptive

awareness and awareness of discriminatory touch, and suggest that the sense of body ownership is tightly linked with the former and only to a lesser degree with the latter. To use the words of an asomatognosic patient reported long ago "But my eyes and my feelings don't agree, and I must believe my feelings. I know they [left arm and leg] look like mine, but I can feel they are not, and I can't believe my eyes." (C.W. Olsen, 1937, cited in Feinberg 1997).

Motivated by a single case study that found that self-touch increased both the sense of ownership and positive feelings towards the paralysed arm in a somatoparaphrenic patient (van Stralen et al. 2011), we recently became interested in investigating the role of affective touch in DSO. We administered soft, light, dynamic tactile stimuli in CT-optimal speeds (3 cm/s; known to elicit feelings of pleasantness) versus non-CT-optimal speeds, (18 cm/s; known not to elicit such feelings) to both arms of a group of seven patients with DSO, as well as ten control patients with similar lesions but intact sense of ownership for their affected arm. We measured their perception of pleasantness after each stroke, as well as patients' sense of body ownership for the touched arms before and after stimulation. Our preliminary findings suggest that patients with DSO have a disturbed CT-based affective touch system, in the sense that they do not seem to differentiate between the slow and fast speeds in their perception, and they seemed to rate both types of touch as more pleasant than the control group (see also previous section). Interestingly, however, we have noted that in most DSO patients, these touch trials have led to an increased sense of body ownership for the affected and previously, persistently disowned arm. This study is ongoing and the specificity, neural correlates and long-term effects of these manipulations remain to be tested. However, taken together the findings reviewed earlier provide preliminary indications that self- and other-touch that is experienced as pleasant and possibly linked with top-down, prior expectations of positive, supportive meanings, can enhance the sense of body ownership. This conclusion applies even in patients that have damage to brain areas critical for the processing of primary interoceptive signals. We may even speculate that it is precisely such impaired processing of primary interoceptive signals about the current state of the body that leads patients to adhere to past expectations of how the affected body parts should *feel from the inside*, leading to the ensuing aberrant beliefs about to whom the body parts belongs.

In sum, focusing on the role of affective touch in neurological disorders of higher order body awareness may reveal unique aspects of the bodily self. In particular, such studies highlight the potential role of the touched skin as the interface upon which the categories of self and other, inside and outside, are constructed and maintained in the mind and brain.

Concluding Remarks

In this chapter, we highlighted behavioural and neuroimaging evidence that interpersonal touch—through its affective component—influences and selectively enhances the mental representation of our body. Critically, empirical research has shown that the bodily self relies on mechanisms of multisensory integration, and interoceptive signals have a unique role in such integration. This knowledge may be used to advance our understanding of the crucial role of social embodied communication in the aetiology of disorders such as anorexia nervosa, and may stimulate the integration of touch and mindfulness interventions as therapeutic strategies. Now that there is converging evidence for the interrelation between affective touch and the bodily self, a particularly important area for future research will be examining not only how affective touch influences each domain of body representation but also how it affects the interaction among the different domains of the bodily self, and how our ability to regulate our emotions might influence what sensory signals are used to inform our perception of our own body.

Outstanding Question and Future Directions

- Through what mechanisms do different emotional components of affective touch influence multisensory integration processes underlying body representation? Emotion evoked or communicated by interpersonal affective touch has different components to it, including the emotional experience, motivational-behavioural tendencies, physiology reactions and social meanings. It is unclear whether these components exert a dissociable impact on different aspects of the bodily self.
- Extensive research has been conducted on the role of motor action, in particular the sense of agency, for the minimal, embodied sense of self (see Balconi 2010). The sense of agency is the subjective experience of being the source, initiator and controller of my own bodily actions and through them events in the external world. Similar to sense of ownership, this aspect of the bodily self is thought to be shaped through interactions in social contexts (see Prinz 2012), in which our actions are influenced by others or aim at influencing others. This assumption, however, needs to be experimentally addressed, in particular with respect to the affective dimension of social interactions for which affective touch appears to be an ideal research approach.
- How does our ability or need to regulate emotion and the supporting role of others in this, influence our mental body representation and capacity for self-other distinction? Research has demonstrated that interpersonal contact influences emotion regulation, but investigation into how the regulation of valence or intensity of emotional experience affects the bodily self are in their infancy. Understanding the link between emotion regulation strategies, social communication and embodied self-awareness may shed light on psychopathologies associated with the bodily self.

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Chapter 22
Moderate Pressure Massage Therapy

Tiffany Field

Abstract This chapter is a review of representative data (not an exhaustive review) on moderate pressure massage therapy effects and potential underlying mechanisms for those effects. They include (1) weight gain in preterm infants, (2) pain reduction and potential underlying mechanisms for pain reduction following massage, (3) enhanced attention, (4) reduced depression and its EEG correlates, and (5) enhanced immune function. Moderate pressure massage is necessary for these effects which, in turn, may be mediated by increased vagal activity and reduced cortisol. The fMRI data from one study suggest that touch when combined with movement simulates findings on other rewarding pleasant touch.

Keywords Moderate pressure massage • Weight gain • Depression • Vagal activity • Cortisol

Moderate Pressure Massage Therapy

Moderate pressure massage therapy (moving the skin) has been more effective than light pressure massage (lightly skimming the skin's surface) (see Diego and Field 2009 for a review). Although these different pressure massages have not been calibrated in terms of intensities and velocities, moderate versus light pressure massage has been noted to elicit a parasympathetic response in adults and infants (including decreasing heart rate) (Diego et al. 2004). And, in the one study that attempted to measure the pressure by the use of a sound-level meter placed on the skin, greater intensity touch by the mother (between +5 and +10 dB) was preferred by the infant (as measured by the infant's leg-kicking response) (Perez and Gewirtz 2004). Typically, lubricants (most often oils) have been used to reduce friction in both moderate and light pressure massage. Moderate pressure massage therapy has been primarily used to treat pain, although it has also been effective for reducing

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prematurity, ADHD, and depression, and for enhancing immune function, for example, in HIV and breast cancer (see Field et al. 2007 for a review). This chapter is a review of representative data (not an exhaustive review) on moderate pressure massage therapy effects and potential underlying mechanisms for those effects.

Moderate Pressure Massage Increases Weight Gain in Preterm Infants

Preterm infant massage has been noted to increase weight gain in studies from neonatal intensive care units around the world (see Field et al. 2010a, b for a review). After several studies we conducted showing preterm infant weight gain following massage, we noted increased vagal activity and gastric motility which may have contributed to more efficient food absorption and increased weight gain (Diego et al. 2007). In another study, we noted higher levels of insulin and IGF-1 growth factor when we compared a moderate pressure massage group who received three, 15-min massages per day for five days to a control group who received standard nursery care without massage therapy (Field et al. 2008). The moderate pressure massage groups had greater increases in (1) weight gain, (2) serum levels of insulin, and (3) serum levels of IGF-1. Weight gain was correlated with insulin and IGF-1 levels. Path analyses suggested that increased vagal activity was associated with increased gastric motility, which, in turn, was related to greater weight gain, and increased IGF-1 was related to greater weight gain. The change in vagal activity during the massage contributed to 49% of the variance in the change in gastric activity. And, the change in vagal activity during the massage explained 62% of the variance in the change in insulin. The change in gastric activity was not related to the change in insulin. This suggests two potential pathways by which moderate pressure massage can increase weight gain: (1) insulin release via the celiac branch of the vagus; and (2) increased gastric activity via the gastric branch of the vagus (Field et al. 2012).

Increased temperature is another potential underlying mechanism for moderate pressure effects inasmuch as decreased temperature can be associated with energy expenditure that results in weight loss. Temperature was assessed in preterm neonates randomly assigned to a control or moderate pressure massage group (Diego et al. 2008). Temperature increased more in the preterm neonates receiving moderate pressure massage, even though the incubator portholes were open during the 15-min massage therapy sessions (which would be expected to lower their temperature).

Another group explored reduced energy expenditure as a potential underlying mechanism in preterm neonates receiving massage (Lahat et al. 2007). During the treatment period, the same massage therapy protocol as the one used in our preterm infant studies was followed. Metabolic measurements by direct calorimetry suggested that energy expenditure was significantly lower in infants after the 5-day massage therapy period than after the period without massage. This decreased energy expenditure may be in part responsible for the enhanced growth associated with massage therapy.

Preterm infants receiving moderate pressure massage have also shown fewer stress behaviors (Field et al. 2006). In that study, the moderate versus light pressure (light stroking) massage group gained more weight per day, and during behavior observations that followed the massage they showed significantly less: (1) active sleep, (2) fussing, (3) crying, (4) movement, and (5) stress behavior (hiccupping). They also showed less deep sleep, lower heart rate, and greater vagal activity. All of these changes suggest lower arousal, which, in turn, could explain better immune function noted in preterm neonates following massage in another study. In that study, mothers massaged their infants on the face and limbs as well as passively exercised their upper and lower limbs four times a day (Mendes and Procianoy 2008). The incidence of delayed-onset sepsis was significantly lower in the massage group who also had a shorter hospital stay (by 7 days), probably related to their lesser illness. A potential pathway for the moderate pressure massage effects may be increased vagal activity, in turn decreasing cortisol, enhancing immune function and reducing sepsis. Inflated proinflammatory cytokines such as IL-1, IL-6, and TNF-alpha should also be measured for their contribution to sepsis and their potential reduction by moderate pressure massage.

Long-term effects of moderate pressure massage have also been shown, including better neonatal outcomes (less prematurity and low birthweight) following the use of moderate pressure massage during pregnancy (Field et al. 2010a). In addition, infants who received moderate versus light pressure massage from their mothers gained more weight and had better development over the first month of life (Field et al. 2004b).

Moderate Pressure Massage Reduces Pain

An example of pain-related research comes from a study entitled "Rheumatoid arthritis in upper limbs benefits from moderate pressure massage therapy" (Field et al. 2013). In that study, adults with rheumatoid arthritis in the upper limbs were randomly assigned to moderate pressure or light pressure massage therapy groups. The participants were massaged on the wrists, arms, and shoulders once a week for one month and the participants were also taught self-massage and asked to massage themselves once a day. The moderate versus the light pressure massage therapy group had less pain and greater grip strength following the first and last massage sessions. By the end of the one-month period the moderate pressure group had less pain, greater grip strength, and greater range of motion in their wrists, elbows, and shoulders.

Moderate pressure massage has also been effective for both immediate pain and mood in cancer patients (Kutner et al. 2008). In that study, adults with advanced cancer and moderate-to-severe pain who were enrolled in hospice received six 30-min massages or simple-touch sessions for 2 weeks. Massage was more effective for both immediate pain and mood. Some large cancer centers in the US have started to integrate massage therapy into their programs based on these positive effects of massage on cancer pain (Russell et al. 2008).

Moderate pressure massage has resulted in reduced pain in all the studies we have conducted on chronic pain conditions from lower back pain in pregnancy to labor pain, back pain, migraine headaches, fibromyalgia, and juvenile rheumatoid arthritis (see Field et al. 2007 for a review). Moderate pressure massage has also been provided for children and adolescents who were admitted to a chronic pediatric pain clinic (Suresh et al. 2008). After the therapy sessions, the children and adolescents reported significantly lower levels of pain, discomfort, and depressed mood. In a study on postoperative pain management in adults, back massages resulted in decreased pain intensity as well as lower anxiety levels (Mitchinson et al. 2007).

Laboratory research has also been conducted to assess the effects of moderate pressure massage on pain. For example, one group studied the effects of massage on mechanical hyperalgesia (pressure pain thresholds) and perceived pain using delayed onset muscle soreness as a model for myalgia (Frey Law et al. 2008). The participants were assigned to a deep-tissue (moderate pressure) massage group, a superficial touch group or a no-treatment control group. Exercises were then performed to induce delayed onset muscle soreness. The deep-tissue massage as opposed to the superficial touch group experienced decreased pain (by 48 %) during the muscle stretch.

Potential Underlying Mechanisms for Moderate Pressure Massage Reducing Pain

The Gate Control Theory is the mechanism that has been most frequently used to explain massage therapy effects on pain syndromes (see Field et al. 2007 for a review). In that theory, pain stimulates slowly conducting finely- and un-myelinated nerve fibers so that the pain signal requires more time to reach the brain than the pressure signals which are carried by fast conducting myelinated nerve fibers that are able to transmit the stimulus faster. The message from the pressure stimulation reaches the brain prior to the pain message and "closes the gate" to the pain stimulus. This metaphor has been used for the electrical and chemical changes that are thought to occur following a pain stimulus. However, this theory has been discredited (Inui et al. 2006).

Another theory relates pain to deep sleep deprivation. In deep sleep, less substance P is emitted and therefore less pain occurs because substance P causes pain. We directly tested the "enhanced deep sleep leading to less substance P" theory in our study on fibromyalgia (Field et al. 2002). Following a period of massage therapy, more time was spent in deep sleep, and lower levels of substance P were noted in the saliva samples taken. Reputedly, lamina I of the superficial dorsal horn contains the main concentration of spinal substance P responsive neurons (Craig 2003).

Still another theory is that increasing serotonin levels decrease pain (Field et al. 2002), serotonin being the body's natural antipain neurotransmitter. Serotonin is increased by massage therapy and also decreases cortisol and depression which are also important effects of massage therapy. And, serotonin is also noted to decrease

substance P, although further research is needed to test these models. Basic problems for hands-on therapy research like massage are the ethical problem of randomly assigning individuals to a no-treatment control group when a treatment is known to be effective and the inability to double-blind the study.

Moderate Pressure Massage Enhances Attentiveness

Moderate pressure massage has also increased attentiveness in a laboratory study by our group using 15-min chair massages (Field et al. 1996). An EEG pattern of heightened alertness/attentiveness occurred following the massage sessions including increased beta and theta waves and decreased delta waves. This EEG pattern was related to better performance after the massage on math computations including being able to perform them in less time with greater accuracy.

Moderate pressure massage effects on attentiveness might be mediated by increased vagal activity. The vagus nerve has a branch to the heart that slows heart rate (Porges 2001). In several studies, increased vagal activity has been associated with increased attentiveness and in others, increased attentiveness has been associated with decreased heart rate (see Field and Diego 2008b for a review). The stimulation of pressure receptors as in moderate versus light pressure massage is associated with slower heart rate and EEG patterns that are related to enhanced attentiveness (Diego et al. 2004). Increased vagal activity may mediate the effects of moderate pressure stimulation on attentiveness. This might also explain the enhanced attentiveness noted in children with autism and adolescents with ADHD following moderate pressure massage (see Field et al. 2007).

Moderate Pressure Massage Reduces Depression and Modifies EEG and Other Correlates

Moderate pressure massage reduces depression. Depressed individuals typically have greater relative right frontal EEG activation (Henriques and Davidson 1991). Greater relative right frontal EEG activation is associated with negative affect and withdrawal or less approach behavior (Henriques and Davidson 1991). Chronically depressed individuals show stable patterns of this asymmetry. And, depressed adults show greater relative right frontal EEG activation even when they are in behavioral remission (Henriques and Davidson 1991). Right frontal EEG has been noted as a physiological marker for chronic depression. Frontal EEG has shifted from right to left in depressed adolescents (Jones and Field 1999) and adults following moderate pressure massage (Field et al. 2006). Other correlates of depression that have also changed following massage therapy include increased vagal activity, that is, typically lower in depressed individuals (Field et al. 2004a, b). Low vagal activity could explain the flat facial expressions and vocal intonation contour noted in depressed individuals given that the vagus nerve stimulates the face and voice muscles (Porges 2001).

Cortisol levels that are typically high in depression have also decreased following moderate pressure massage (Field et al. 2005) as have norepinephrine levels (Field et al. 1992). In contrast, serotonin levels have increased following moderate pressure massage (Field et al. 2005).

Moderate Pressure Massage Enhances Immune Function

Children with cancer benefit from moderate pressure massage (Post-White et al. 2009). After four weekly massage sessions alternated with four weekly quiet-time control sessions, moderate pressure massage reduced heart rate and anxiety levels in the children, although immune function was only marginally improved in these children.

Natural killer cells and natural killer cell activity have increased following moderate pressure massage (Field et al. 2007). These data are promising given that natural killer cells in immune compromised individuals including those with HIV and breast cancer ward off viral cells, bacterial cells, and cancer cells. Natural killer cells increased following a 1-month period of moderate pressure massage for HIV-infected adolescents (Diego et al. 2001). CD4 cells also increased in the adolescents, suggesting an improved clinical condition. Natural killer cells and natural killer cell cytotoxicity (activity) also increased in our studies on breast cancer (Hernandez-Reif et al. 2004, 2005). These women would also be expected to improve clinically given that natural killer cells destroy cancer cells (Brittenden et al. 1996). Stimulation of pressure receptors, as in moderate pressure massage, increases vagal activity, which would reduce cortisol levels and thereby enhance immune function (Diego and Field 2009).

Cortisol is noted to kill immune cells, and natural killer cells are noted to kill bacterial, viral, and cancer cells. Other immune functions such as proinflammatory immune cells (cytokines) may also be involved.

Moderate Pressure Is Necessary for These Effects

Moderate pressure is apparently necessary for increased vagal activity and its effects (Diego and Field 2009). That moderate versus light pressure massage is effective suggests involvement of pressure receptors. Animal studies also indicate that stimulation of pressure receptors activates the vagus nerve (Pauk et al. 1986; Schanberg and Field 1987). And these data are consistent with our findings that lower heart rate and EEG patterns of lower arousal were associated with moderate versus light pressure massage (Diego et al. 2004). In this study comparing different pressure massage, three types of massage techniques were assessed in a sample of adults, who were randomly assigned to (1) moderate pressure massage, (2) light pressure massage, or (3) vibratory stimulation from a vibrating handheld massager (Diego et al.

2004). Anxiety scores decreased for the 3 groups, but the moderate pressure massage group reported the greatest decrease in stress, in heart rate and EEG changes including an increase in delta and a decrease in alpha and beta activity, suggesting a relaxation response. The moderate pressure group also showed increased positive effect, as indicated by a shift toward left frontal EEG activation. The light pressure massage group, in contrast, had increased arousal, as indicated by increased heart rate and decreased delta and increased beta activity. The vibratory stimulation group also showed increased arousal, as indicated by increased heart rate and increased alpha and beta activity.

In another study we conducted on different pressure massage, adults were randomly assigned to a moderate pressure or a light pressure massage group, and EKGs were recorded (Diego and Field 2009). The high-frequency (HF) and low-frequency (LF) components of heart rate variability as well as the low- to high-frequency ratio (LF/HF) were derived from the EKGs as markers of autonomic nervous system activity. The moderate pressure massage group experienced a parasympathetic response characterized by an increase in HF, suggesting increased vagal activity that peaked during the first half of the massage. In contrast, the light pressure massage group had a sympathetic nervous system response characterized by decreased HF and increased LF/HF. Another lab reported that moderate pressure massage increased oxytocin and reduced adrenocorticotropic hormone (Morhenn et al. 2012). For the massage group, the research team assessed 15 min of moderate pressure massage of the upper back. The control group rested quietly for 15 min. Pre–post blood draws were assayed: Massage was associated with increased oxytocin and decreased adrenocorticotropic hormone, nitric oxide, and beta-endorphin.

Some researchers have quantified the changes in muscle activity that occurred after massage. Compared with light pressure massage, deep pressure massage produced a greater reduction in the stretch reflex (Lidbeck 2002). As the author suggested, the fact that the stretch reflex is reduced by massage suggests that massage therapy may produce some of its beneficial effects by "reducing excitability in alpha motor neurons by 1a afferents from muscle spindles." A reduction in the stretch reflex would be desirable because spinal hyperexcitability is associated with chronic pain syndromes (Lidbeck 2002). Massage therapists often start by applying light pressure and then increasing to deeper pressures. When deep pressure was applied after conditioning the muscle with light and moderate pressures, there was no change in muscle activity, and when deep pressure was applied with no prior conditioning, the muscle became more active. The stretch reflex or nociceptive reflex pathways (or both) could have been inhibited by application of light and moderate pressures before the deeper pressure was applied. Parasympathetic versus sympathetic activity affects cutaneous pathways and cutaneous mechanoreceptors influence the magnitude of spinal reflexes which are, in turn, modulated by autonomic tone (Loewenstein 1956). The approach of gradually increasing pressures, as currently practiced by many massage therapists, seems to be more therapeutic than applying deep pressure with little warm-up.

Moderate Pressure Massage Increases Vagal Activity

Vagal activity increases after moderate pressure massage (Diego et al. 2004, 2007). In these studies, vagal activity increased after moderate pressure massage. This may have occurred via the stimulation of pressure receptors within and beneath the skin, which ultimately signal the limbic system including hypothalamic structures involved in autonomic nervous system regulation and cortisol secretion (Ouchi et al. 2006).

Anatomical studies suggest that baroreceptors, and to a lesser extent, mechanoreceptors within and beneath the skin (i.e., Pacinian corpuscles) transmit signals to the nucleus ambiguous and the dorsal motor nucleus of the vagus (Kandel et al. 2000). Research also indicates that electrical vagal stimulation reduces cortisol levels in depressed individuals (O'Keane et al. 2005). Also, as already noted, we recently showed that moderate pressure massage (but not light pressure massage) increased vagal activity in both infants and adults (see Field and Diego 2008a, b for a review). Data collected across several studies have suggested that massage therapy decreases heart rate (Diego et al. 2004; Kubsch et al. 2000), lowers blood pressure (Ahles et al. 1999; Hernandez-Reif et al. 2000; Kubsch et al. 2000), and reduces cortisol levels (see Field et al. 2005 for a review; Kim et al. 2001). And finally, an fMRI study showed that moderate pressure massage increased cerebral blood flow in several brain regions involved in depression and stress regulation including the amygdala and the hypothalamus (Ouchi et al. 2006), suggesting that moderate pressure massage involves hypothalamic regulation of autonomic nervous system activity, cortisol secretion, and limbic activity associated with emotion regulation.

Vagal Activity May Mediate the Effects of Moderate Pressure Massage on Cortisol

Increased vagal activity results in a slowing of heart rate and blood pressure as well as cortisol (Porges 2001). Reduced vagal activity has been associated with increased cortisol (Spangler 1997). Some have suggested that vagal activity has an inhibitory effect on hypothalamic pituitary adrenal function (Thayer and Sternberg 2006). The prefrontal cortex and amygdala seem to have significant effects on the regulation of emotion and hypothalamic pituitary adrenal function. The decrease in norepinephrine and increase in serotonin and dopamine might be mediated by increased vagal activity (Field et al. 2007). Further research is needed on how these changes interact with reduced cortisol and other biochemical changes.

Functional magnetic resonance imaging (fMRI) data have shown that activation of the orbitofrontal cortex during affective touch (pleasant touch) appears to be transmitted via unmyelinated C afferents (Rolls 2010). But pleasant touch can also "irritate instead of soothe" (Craig 2003). Although less fMRI research has been conducted on moderate pressure stimulation, at least one group has used functional magnetic resonance imaging and noted that moderate pressure massage was represented in the pregenual anterior cingulate cortex (Lindgren et al. 2012). They assessed four different

touch conditions including human touch with or without movement and rubber glove with or without movement. The force and velocity were held constant across conditions. Human touch was rated as most pleasant particularly when combined with movement. The fMRI results suggested that human touch with movement most strongly activated the pregenual anterior cingulate cortex. The authors suggested that these data were consistent with findings on other rewarding pleasant touch.

An extensive literature on rewarding pleasant touch and the class of low-threshold mechanosensitive (LTM)C fibers (CTs) that innervate the hairy skin has been recently reviewed by McGlone et al. (2014) and by Field (2014). While moderate pressure massage probably activates a large population of CTs (as it is considered pleasant by those who receive it), light pressure massage (although often experienced as a tickle stimulus) may also activate these fibers. Moderate pressure massage likely also activates the rapidly conducting large myelinated Alpha-beta afferents, as in firm holding and squeezing (McGlone et al. 2014). As McGlone et al. (2014) have suggested, "…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 Alpha-beta afferents is required for the complete feeling of pleasant touch…." (p. 749). The moderate and light pressure massage clearly needs to be calibrated for their intensities and velocities to determine the extent to which they activate CTs and/or alpha-beta afferents.

Summary

Moderate pressure massage has increased weight gain in preterm infants, reduced pain associated with several syndromes including rheumatoid arthritis and fibromyalgia, enhanced attentiveness, reduced depression and enhanced immune function, most specifically natural killer cells and natural killer cell activity. When moderate pressure has been compared to light pressure massage in several studies, moderate pressure reduced stress and heart rate, altered EEG patterns, and increased vagal activity, as in a relaxation response. Vagal activity may mediate the effects of moderate pressure massage on cortisol. Functional magnetic resonance imaging data suggest that moderate pressure massage was represented in the pregenual anterior cingulate cortex (Lindgren et al. 2012). Further research is needed to calibrate moderate pressure massage for its intensity and velocity, to identify underlying neurophysiological mechanisms and pathways associated with moderate pressure massage, and to determine the involvement of C fibers (McGlone et al. 2014) versus the more classically studied alpha-beta afferents (Kandel et al. 2013).

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Chapter 23
Psychiatric Conditions and Touch

Carissa J. Cascio

Abstract Touch is an understudied sensory modality that has a significant neuroregulatory impact on social and emotional behavior relevant to psychiatric conditions. In particular, the sense of touch has a profound impact on early social development and bonding which makes it particularly relevant for neurodevelopmental disorders such as autism spectrum disorder (ASD). This chapter reviews behavioral and neural studies of touch in two categories of psychiatric diagnosis: ASD and obsessive compulsive (OCD) and related disorders. In ASD, altered tactile perception seems to be heavily weighted toward affective, rather than discriminative touch, and relates significantly to core symptoms including social deficits and repetitive behaviors. In OCD and related disorders, body-focused repetitive behaviors are significant and debilitating clinical symptoms that often involve affective dysfunction of the somatosensory system, including diminished nociception and/or altered reward response to tactile stimuli. Animal models suggest the involvement of serotonergic, dopaminergic, and oxytocin neurotransmitters/neuropeptides and neuroimaging studies implicate the interface of sensory systems with networks for affect and arousal in both classes of psychiatric conditions, but much more research is needed to clarify the role of touch in these clinical conditions. In addition, our understanding of other psychiatric conditions such as psychotic disorders and mood disorders would benefit substantially from more research on the role of touch in their development and clinical presentation.

Keywords Autism • Somatosensory • Body focused repetitive behaviors • Obsessive-compulsive disorder • Trichotillomania • Sensory • Tactile • Touch • Developmental disorders

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Introduction

Relative to other sensory systems, the role of touch in psychiatric conditions has received little attention from researchers and clinicians. Two notable exceptions have emerged in recent years, which reflect the developmental significance of tactile experience, as well as the inextricable link between somatosensory and motor function that influences aberrant repetitive behaviors. This chapter will address tactile perception in two classes of psychiatric conditions: neurodevelopmental disorders (specifically, autism spectrum disorder) and obsessive-compulsive and related disorders.

Autism Spectrum Disorder

The DSM (APA, DSM-5) defines autism spectrum disorder (ASD) as a pervasive neurodevelopmental condition that develops during the first 3 years of life and is characterized by complex behavioral symptoms that include qualitatively impaired social communication and the presence of restricted or repetitive behaviors. These symptoms are sometimes accompanied by intellectual disability, although a wide range of cognitive functioning is seen in autism.

Among the specific symptoms that comprise the repetitive behavior subdomain is 'unusual response to sensory stimuli,' with hyper- or hypo-responsiveness to touch being a very common variant. Several studies have investigated basic somatosensory processing in ASD. Parent questionnaires that address sensory processing generally provide evidence that tactile hyper-responsiveness is more common in autism than in typical development (Tomcheck and Dunn 2007) or in other developmental disabilities, although rates may be similar to, or even lower than, those in Fragile X syndrome (Rogers et al. 2003). The relation between tactile hyper-responsiveness and the full complement of core features of autism remains unclear. Baranek et al. (1997), using parent questionnaires, reported that tactile hyper-responsiveness was significantly associated with certain kinds of rigid and stereotyped behaviors in young children with ASD. A study of older children found that while tactile hyper-responsiveness did not predict other core symptoms, tactile *hypo*-responsiveness was strongly associated both with social communication symptoms and other variants of repetitive behavior (Foss-Feig et al. 2012).

Aberrant responses to touch in ASD are not limited to tactile hyper- or hypo-responsiveness. Tactile-seeking behaviors (unusual interest in tactile stimuli) are often noted, such as repetitive rubbing of certain textures or surfaces, and an affinity for deep pressure input such as intense hugging or squeezing (Grandin 1995). Experimental studies also provide evidence of uniquely pleasurable responses to certain tactile stimuli (Pernon et al. 2007). Foss-Feig and colleagues also noted that, like hypo-responsiveness, tactile seeking was strongly related to social communication symptoms and other variants of repetitive behavior.

The range of unusual responses to tactile stimuli in ASD has prompted the investigation of tactile sensitivity using classic psychophysical approaches such as contact detection, texture discrimination, adaptation, and thermal detection. Blakemore et al. (2006) were the first to investigate tactile processing in adults with Asperger's syndrome and found that they had greater sensitivity to high frequency (but not low frequency) vibration when measured at the fingertip, a site often chosen for psychophysical experiments because of its dense innervation by various classes of mechanoreceptors. This result was interpreted as a putative difference in mechanoreceptor afferent function, as high- and low-frequency vibrations are signaled by different types of mechanoreceptors (Pacinian and Meissner's corpuscles, respectively). Both types of mechanoreceptor convey signals through large myelinated afferents (A-fibers), while unmyelinated afferents (C-fibers) convey primarily pain and temperature information (although see later for a description of C-touch afferents, which constitute an exception to this general rule). A subsequent study failed to replicate high-frequency vibrotactile threshold differences at the fingertip in children with autism spectrum disorders (Güçlü et al. 2007), but this study was limited by a small sample size, which may have reduced power to detect group differences. The authors of this study did, however, note significant correlations between tactile and affective responses of children identified through parent questionnaires, suggesting that aberrant responses to tactile stimulation may arise from emotional or even cognitive mechanisms, rather than from differences in physiological response of the somatosensory system.

This interpretation is supported in part by a study from Cascio et al. (2008) in which adults with autism were tested on a variety of somatosensory psychophysical tasks at two sites: the surface of the palm and the dorsal forearm. In addition to extending tactile psychophysics beyond the fingertip, an advantage of testing the forearm is its innervation by C-touch afferents (Olausson et al. 2002), which are believed to constitute a unique system for conveying affective or social touch signals (McGlone et al. 2007). C-touch afferents are theorized to be central to mother–infant bonding and early social communication (McGlone et al. 2007, 2014), and if aberrant in ASD, might partially account for very early divergence in the developmental trajectory of social reward as mediated through touch (Ferber et al. 2008; Neu and Robinson 2010) in infancy. Cascio and colleagues noted a lower threshold for low-frequency vibration at the forearm site, but not at the palmar surface, which has no innervation by C-touch afferents. In addition, greater sensitivity was observed for painful thermal stimuli, while there were no group differences in thresholds for innocuous thermal stimuli. Test–retest data from two sessions suggested that while the pain thresholds for the control group stayed relatively constant, pain sensitivity in the autism group was significantly lower at the second session than at the first. These data together support the idea that either a top-down emotional regulatory mechanism, an affective mechanism that includes C-touch afferents, or a combination of these two contributes to altered tactile sensitivity in autism, rather than solely a neurophysiological mechanism restricted to class A afferent subtypes.

While psychophysical studies of discriminative touch processing in ASD have yielded mixed results, the emotional aspects of touch are more consistently reported

to be affected in ASD. Cascio and colleagues investigated the perceived pleasantness of various textures in adults (2008, 2012) and children (2016) with ASD. While adults with ASD rated the perceived pleasantness of a range of textures very similarly to controls, their neural responses as assessed with functional magnetic resonance imaging (fMRI) differed starkly. Adults with ASD showed diminished neural response to touch in primary and secondary somatosensory cortices as well as in prefrontal regions (Fig. 23.1a). However, response in the posterior insula, posterior cingulate cortex, as well as thalamic and brainstem response to the most unpleasant stimulus was higher in the ASD group than the controls (Fig. 23.1b). The posterior insula is a site of projection for C-touch afferents and plays an important role in assessing the affective significance of touch. The heightened response to a mildly

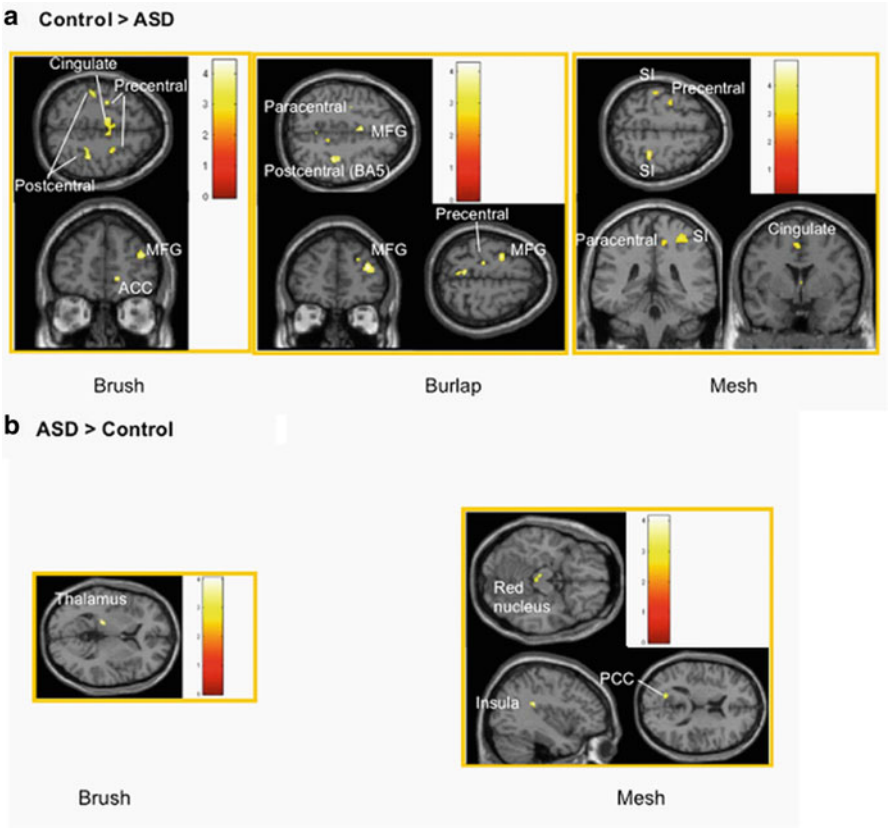

Fig. 23.1 Group differences in brain response to stroking touch with various textures in adults. (**a**) Widespread regions were more responsive in typical adults, especially for pleasant (*brush*) and neutral (*burlap*) textures. (**b**) Isolated regions were more responsive in ASD, particularly the posterior insula for unpleasant (*mesh*) texture. (Figure used with permission from Cascio et al. 2012, *Autism Research*, Wiley Periodicals. © 2012 International Society for Autism Research, Wiley Periodicals, Inc.)

unpleasant texture in this region may reflect an exaggerated response to emotionally negative touch, consistent with the hyper-responsiveness pattern, while the diminished overall response of somatosensory and attention regions to emotionally more pleasant and neutral touch is consistent with the hypo-responsiveness pattern. Of note, both patterns can be observed within the same individuals in ASD (Tomcheck and Dunn 2007). In an experimental study of texture perception in children with ASD, Cascio and colleagues (2016) noted that behavioral defensiveness was linked to the bodily site of stimulation, while explicit ratings of (un)pleasantness were linked to the textures themselves, underscoring the complexity of affective response to touch in ASD.

Additional studies of the neural response to touch in ASD support these findings of both early and later differences within the sensory processing stream. A recent fMRI study using similar stimuli in healthy adults showed an inverse relation between social and reward response to touch and a dimensional measure of subclinical autism traits (Voos et al. 2013), further supporting a role for higher order affective neural circuitry as an important determinant of tactile response in ASD. However, electroencephalographic and magnetoencephalographic studies of neural response to tactile stimulation in ASD suggest differences on the level of primary somatosensory (SI) cortex, reporting disorganized somatotopic mapping (Coskun et al. 2009, 2013) and diminished response amplitude (Miyazaki et al. 2007; Marco et al. 2012), which was associated with parent report of aberrant tactile processing, but without a distinction between hypo- and hyper-responsiveness. Further exploration is required to determine the extent and nature of both low- and high-level somatosensory differences in ASD.

While several studies of touch response have emphasized potential roles of different peripheral afferent populations, or distinctions between early sensory and later attentional/affective processing of touch, others have been driven by more global cortical models of ASD, such as the theory of a cortical excitatory/inhibitory imbalance (Rubenstein and Merzenich 2003) thought to be driven by reduced GABA-ergic tone (Fatemi et al. 2009; Buxbaum et al. 2002) impacting minicolumnar cortical structure (Casanova et al. 2002) and lateral inhibitory mechanisms in sensory cortex. Tommerdahl et al. (2007) tested adults with autism on a vibrotactile localization paradigm with an adapting stimulus. The presence of a preliminary adapting stimulus has been shown to improve tactile localization and is thought to do so via a spatial tuning mechanism in somatosensory cortex that depends on GABA-mediated inhibition of neighboring cortical minicolumns. This inhibition of surrounding cortex under extended stimulation is thought to sharpen the signal by limiting it to a localized area of cortex. The investigators noted that individuals with autism exhibited greater sensitivity to touch during baseline performance than the control group, a finding predicted by other studies demonstrating enhanced tactile perception in individuals with autism. Interestingly, the group with autism did not exhibit the improvement in the presence of the adapting stimulus that was observed for the control group. A recent study by Puts et al. (2014) provides further evidence that in children with ASD that is consistent with impaired lateral inhibition in the somatosensory cortex, including dimin-

ished vibrotactile adaptation and amplitude discrimination. This study also reported aberrant feedforward inhibition using a dynamic threshold detection paradigm, linking the deficit to possible poor sensory filtering in ASD.

The picture of somatosensory processing in ASD is a complex one that will require substantial additional study, with consideration for stimulus type, neural mechanisms, and relation of psychophysical and neural evidence to behavioral sensory response patterns as assessed by clinical or parent report. The cooccurrence of tactile hyper-responsiveness/defensiveness and hypo-responsiveness/touch seeking presents a challenge to experimental study. Current evidence suggests that touch with an emotional basis is more affected than discriminative touch, reflecting the potential import of social touch for ASD. However, specific patterns of enhanced and diminished discriminative ability may shed light on specific cortical mechanisms such as excitatory/inhibitory imbalance.

Pathological Grooming Behavior in Psychiatric Conditions

A common comparison group to ASD when considering repetitive patterns of behavior that can become maladaptive is obsessive-compulsive disorder (OCD). While repetitive patterns of behaviors in ASD are not necessarily associated with negative affect, the obsessive thoughts and accompanying compulsions in OCD are by definition experienced as intrusive and/or distressing. Touch can often play a central role in the repetitive behaviors that are common in OCD, including compulsions to touch objects in a particular way or a certain number of times, and excessive grooming (e.g., repetitive hand washing). A variety of related disorders also include excessive grooming behavior, such as skin picking (excoriation disorder), trichotillomania (hair-pulling disorder), and onychophagia (nail-biting), collectively known as self-induced dermatoses or body-focused repetitive behaviors (Teng et al. 2002), as well as body dysmorphic disorder (Bohne et al. 2002), which often includes compulsive grooming (Phillips and Diaz 1997) to ameliorate perceived bodily imperfections such as oily skin or unwanted hair. These disorders often cooccur with one another (Stein et al. 2008). The transition from DSM-IV-TR to DSM-5 has engendered a major shift for OCD and body-focused repetitive behaviors. Whereas in DSM-IV-TR, OCD was categorized as an anxiety disorder and body-focused repetitive behaviors as impulse control disorders, in DSM-5 OCD and related disorders occupy their own category, which includes body-focused repetitive behaviors. There is still some debate, however, about this reclassification, arising from a dearth of research on the behavioral and neural basis of body-focused repetitive behaviors.

While allocentric grooming is important for maintaining social structure in many nonhuman primate (Dunbar 2010) and other animal societies, the primary role of egocentric grooming is the maintenance of physical health and attraction of mating partners (Pruujit et al. 1992). While pathological egocentric grooming in animals (e.g., the Hoxb8 mutant mouse) has been widely viewed as a model system for

OCD, the difficulty in assessing complex cognitive patterns in affected animals limits the ability to link compulsive grooming to obsessive thought (Feusner et al. 2009), suggesting a broader interpretation of pathological grooming in animals that extends to other compulsive grooming behaviors in humans.

The question of what drives compulsive grooming behavior in psychiatric populations is an area of active investigation, but tactile sensation, perhaps as a modulator of anxiety or mood, is a key candidate. The possibility that body-focused repetitive behavior serves as a mechanism to regulate anxiety or mood has been proposed (Shusterman et al. 2009; Gupta 2013) and is supported by evidence such as pleasurable sensation from hair-pulling (Meunier et al. 2009). There is evidence that this pleasurable sensation might be mediated in some cases by digital-tactile stimulation (i.e., tactile stimulation of the fingers), by the hair (Rapp et al. 1999), as evidenced by the feature of rolling individual strands of hair between the fingers. A study of children with OCD with or without comorbid body-focused repetitive behaviors suggested that comorbid grooming is associated with increased tactile sensitivity (Flessner et al. 2009), and these behaviors are associated with increased somatic sensitivity in the general population (Teng et al. 2002; Dar et al. 2012). Thus, the majority of the available evidence in humans points to an association between compulsive grooming and increased tactile/somatic sensitivity.

The neurobiology of the association between compulsive grooming and tactile sensation is less clear. Animal models of compulsive grooming such as the Hoxb8 mutant mouse (Greer and Capecchi 2002) exhibit reduced nociception (Holstege et al. 2008), but this has been demonstrated to arise from a distinct mechanism that is unrelated to pathological grooming (Chen and Capecchi 2010). Hoxb8 codes for a transcription factor with various roles in neural development, thus there may be multiple neurobiological mechanisms for compulsive grooming in this animal model. In addition, there are other animal models of pathological grooming, such as the $SAPAP_3$ mutant mouse. The $SAPAP_3$ mutation affects cortico-striatal circuitry and leads to repetitive grooming behavior that is rescued by selective serotonergic reuptake inhibitors (SSRIs) (Welch et al. 2007). Effective treatment of OCD (Graybiel and Rauch 2000) and body-focused repetitive behaviors in humans with SSRIs (Phillips and Hollander 2008) (although at higher doses than for many other psychiatric disorders (Grant and Phillips 2005)) corroborates the involvement of the serotonin system seen in $SAPAP_3$ mice. Dopaminergic antagonists, however, have also been shown to have some efficacy (Skapinakis et al. 2007; Stewart and Nejtek 2003), and intraamygdalar injection of oxytocin has been demonstrated to increase grooming behavior in rats (Marroni et al. 2007). A role for oxytocin in compulsive self-grooming would be interesting in light of its established role in allocentric grooming and parental–infant tactile interactions (Feldman et al. 2010; Saltzman and Maestripieri 2011).

Dysfunction of striatal and limbic circuits may be central to body-focused repetitive behaviors (Stein et al. 2002; Feusner et al. 2010), although there is evidence for more widespread deficits of neural connectivity and organization (Arienzo et al. 2013). Neuroimaging studies of individual body-focused repetitive behavior disorders are limited, but ongoing and are expected to yield important information on

how they relate to each other and to OCD (Chamberlain et al. 2009; Grant et al. 2013). Given the associations between tactile sensitivity and body-focused repetitive behaviors, it will be important as these investigations continue that the roles of touch, pain, and other somatic systems are considered.

Conclusion

The impact of the sense of touch on mental health is garnering increasing attention from the psychiatry community, particularly with regard to developmental trajectories of mental health. This is evidenced by a recent large-scale longitudinal study investigating long-term cognitive and physiologic outcomes as a function of maternal touch in early infancy (Feldman et al. 2014). Developmental disorders (specifically autism spectrum disorder), OCD, and associated body-focused repetitive behaviors are characterized by aberrant response to and processing of touch, although the shared and divergent behavioral and neural mechanisms for this constitute a still emerging picture. The therapeutic role of touch in treatment and/or prevention of psychiatric illness such as depression (Field et al. 2009; Poland et al. 2013), anxiety (Sherman et al. 2010), and eating disorders (Field et al. 1998; Hart et al. 2001) is an area of active investigation and offers considerable promise for affected individuals. As the field of psychiatry moves toward a heavier focus on neurobiological mechanisms of discrete and observable behaviors that are common across diagnostic categories (Cuthbert and Insel 2013; Chung and Insel 2014), the well-characterized neurobiology of the somatosensory system and aberrant response to touch across multiple diagnostic groups will shed additional light on our current understanding of psychiatric conditions.

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Chapter 24
Pain and Touch: Roles for C-Tactile Afferents in Pain Inhibition and Tactile Allodynia

Jaquette Liljencrantz, Mark Pitcher, M. Catherine Bushnell, and Håkan Olausson

Abstract In humans there is a positive correlation between the pleasantness perception of soft skin stroking and the firing rate of unmyelinated C-low-threshold mechanoreceptive afferents (often abbreviated C-LTMR in animals and C-tactile and CT afferents in humans). CT-targeted touch reduces heat pain in humans suggesting that activation of the CT system modulates pain perception. This finding is supported by animal work which has shown that C-LTMRs inhibit nociceptive signaling at the spinal cord level, release a protein (TAFA4) with analgesic effects, and have positively reinforcing and anxiolytic behavioral effects. However, under pathophysiological conditions, research in mice and humans instead suggests a role for CLTMRs and CTs in tactile allodynia. There is a divergence in results with some studies pointing to CLTMRs/CTs driving tactile allodynia, whereas others suggest a modulatory role.

Keywords C-tactile • C-low threshold mechanoreceptor • Affective touch • Pain • Allodynia • VGLUT3 • TAFA4

Touch is known not only to console, as in a mother's gentle touch, but also to diminish pain, as in the natural reflex to rub or stroke a wounded body part. A neurophysiological explanation for this latter phenomenon is the Gate Control Theory (Melzack

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and Wall 1965; Mendell 2014) proposing that activation of myelinated mechanoreceptive (Aβ) afferents at the site of an injury activates inhibitory interneurons in the dorsal horn of the spinal cord, which in turn decreases the amount of information signaled to the brain from the nociceptive afferents. The theory proposes that cells in lamina II of the dorsal horn act as a gate control system to modulate the excitatory incoming nociceptive signals before they penetrate further into the central nervous system. This inhibitory effect is generally considered to be driven by signaling in large diameter (Aβ) afferents (Melzack and Wall 1965). At the time when this theory was presented, gentle touch was thought to be signaled only by Aβ afferents. The C-low threshold mechanoreceptive (C-LTMRs) afferents, found in animals, were believed to be nonexistent in humans (Kumazawa and Perl 1977). However, using the technique of microneurography, C-LTMRs were found to exist also in humans (Nordin 1990; Vallbo et al. 1993), where they were termed C tactile (CT) afferents.

Previous work in animals presents evidence of a potential pain modulatory role for C-LTMRs. C-LTMR-targeted input inhibits C-nociceptive signaling in the superficial dorsal horn (Lu and Perl 2003). C-LTMRs, when activated, may release the chemokine-like secreted protein TAFA4 that has analgesic effects (Delfini et al. 2013). In addition, pharmacogenetic activation of Mas-related G-protein-coupled receptor B4 (MRGPRB4^{+}) expressing neurons, thought to be another type of C-LTMRs, promotes conditioned place preference, indicating that activation of these neurons is positively reinforcing and/or anxiolytic (Vrontou et al. 2013).

In humans, the pain modulatory role of touch has been studied by comparing pain perception with and without associated touch stimuli typically targeted to activate Aβs (Mancini et al. 2014). Our group has found a significant decrease in pain perception when CT-targeted stimulation (slow brush stroking) is presented at the same time as heat pain stimulation as well as when CT-targeted stimulation is applied prior to the heat pain stimulation (Krämer et al. 2008; Liljencrantz et al. 2012; Spadoni et al. 2012; Strigo et al. 2011). Individual differences in CT-related pain reduction are significantly associated with state anxiety and calmness, that is, participants with large reductions in pain ratings following CT stimulation also report low anxiety scores and high calmness scores.

The mechanisms for pain reduction following CT stimulation may not be limited to the spinal cord. Since CT firing correlates significantly with the perceived pleasantness of the stimulus (Loken et al. 2009; Ackerley et al. 2014), CT stimuli may decrease pain perception in the same way as positive pictures (Kenntner-Mabiala and Pauli 2005), beautiful music (Roy et al. 2008), pleasant odors (Villemure and Bushnell 2009; Villemure et al. 2003), sweet tastes (Dum and Herz 1984; Reboucas et al. 2005), and positive expectations (placebo) (Ellingsen et al. 2013). By providing a pleasant opponent sensation, pain processing can be modulated; a concept known as pleasure-related analgesia (Leknes and Tracey 2008) (Fig. 24.1). In humans, psychological/emotional pain modulation is likely mediated not only by endogenous opioids activating descending pain inhibitory pathways from the periaqueductal grey (PAG) and rostral ventral medulla (Fields 2000) but also through direct opioid effects on cortical areas involved in pain processing such as the anterior cingulate cortex (Zubieta et al. 2001; Petrovic et al. 2002).

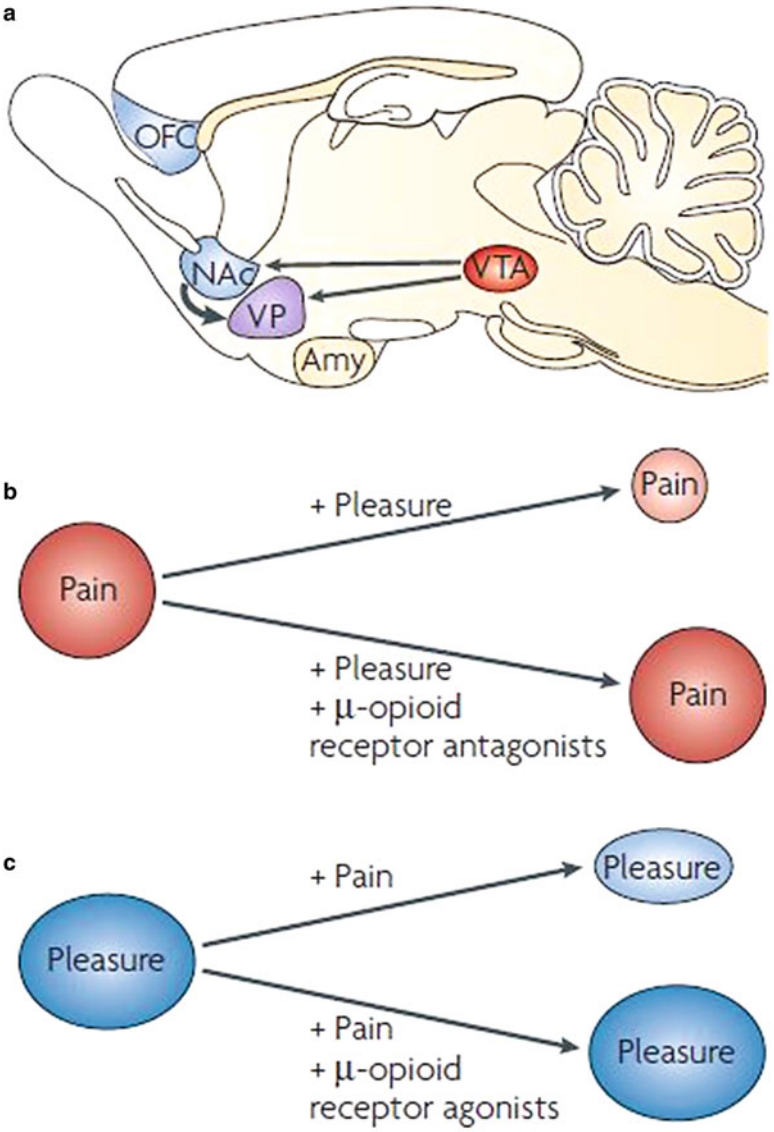

Fig. 24.1 (**a**) Illustration of brain areas involved in opioid release: orbitofrontal cortex (OFC), the amygdala (Amy), the nucleus accumbens (NAc), and the ventral palladium (VP). Endogenous opioids are suggested mediators of the psychological/emotional pain modulation observed by positive/pleasurable stimuli such as activation of CT afferents. (**b**, **c**) Representation of the concept pleasure-related analgesia and the reverse relation. Studies using μ-opioid receptor antagonists versus agonists confirm a role for opioids in this concept. Original publication: Leknes, S. and I. Tracey, *A common neurobiology for pain and pleasure*. Nat Rev Neurosci, 2008. **9**(4): p. 314–20

Following neuronal injury, gentle touch can elicit unpleasant sensations; a phenomenon called tactile allodynia. According to the International Association for the Study of Pain (IASP), allodynia is defined as "Pain due to a stimulus that does not normally provoke pain." The first studies on experimental allodynia were probably performed by Goldscheider (1916, 1917). Using an adjustable clamp fastened to the arm, he was able to evoke local, controlled pain. The novelty in the finding was that having the ongoing local pain rendered normally nonpainful stimuli painful in areas located away from it. Upon cessation of the painful stimulus, that is, removal of the adjustable clamp, this phenomenon disappeared immediately. Although Goldscheider originally termed this finding "hyperalgesia," it was later classified by the IASP as tactile allodynia (1979). People with tactile allodynia typically experience a burning, tender sensation during soft stroking of the affected skin (Rasmussen et al. 2004). Even a very light stimulus, such as a garment brushing against their skin, can evoke allodynia. The prevailing hypothesis involves altered tactile signaling in the spinal cord following central sensitization (Campbell and Meyer 2006; Woolf 1993) whereby Aβ-LTMRs signal to nociceptive neurons in the dorsal horn and on to pain processing areas in the brain (Woolf 1993; Iadarola et al. 1998; Koltzenburg et al. 1992; Torebjork et al. 1992; Campbell et al. 1988; Maihofner et al. 2003; Wasner et al. 1999). This view is based on human selective nerve block experiments demonstrating that tactile allodynia is abolished by compression or ischemic block of Aβ afferents (Koltzenburg et al. 1992; Torebjork et al. 1992; Cervero and Laird 1996; Gracely et al. 1992; Landerholm and Hansson 2011). However, these theories were established just as CTs were discovered in humans (Nordin 1990; Johansson et al. 1988) and were thus not taken into account. Over the last years, a number of studies have explored the role of CTs in mechanical hypersensitivity. Some studies indicate a prominent role for CTs in driving allodynia (Seal et al. 2009; Nagi et al. 2011), whereas others suggest a modulatory role (Lou et al. 2013; Liljencrantz et al. 2013, 2014).

The first study to investigate the role of C-LTMRs in allodynia used a vesicular glutamate transporter type 3 (VGLUT3) knockout mouse (Seal et al. 2009). Direct recordings in the dorsal root ganglion (DRG) from VGLUT3 neurons confirmed that they were C-LTMRs. This study demonstrated that the functional loss of C-LTMRs impairs mechanical hypersensitivity to normally innocuous stimuli (allodynia) that accompanies inflammation, nerve injury, and trauma (Seal et al. 2009). However, more recently it was found that VGLUT3 neurons can be divided into two groups depending on if the genetic cell fate of the sensory neuron is a transient or a persistent VGLUT3 expression (Lou et al. 2013). The VGLUT3-transient neurons are myelinated mechanoreceptors, whereas the VGLUT3-persistent neurons are unmyelinated neurons. In mice with a conditional knockout of VGLUT3-persistent neurons (C-LTMRs), both acute and chronic mechanical pain was largely, but not completely, unaffected (Lou et al. 2013) suggesting that VGLUT3-transient neurons (i.e., myelinated cutaneous afferents) signal tactile allodynia.

A recent study in human volunteers supports the idea that CTs mediate tactile allodynia. Nagi et al. (2011) demonstrated that muscle pain, induced in the tibialis anterior by hypertonic saline infusion, increases following CT-targeted touch, that is, slow stroking of the overlaying skin (Nagi et al. 2011) (Fig. 24.2). The effect survived

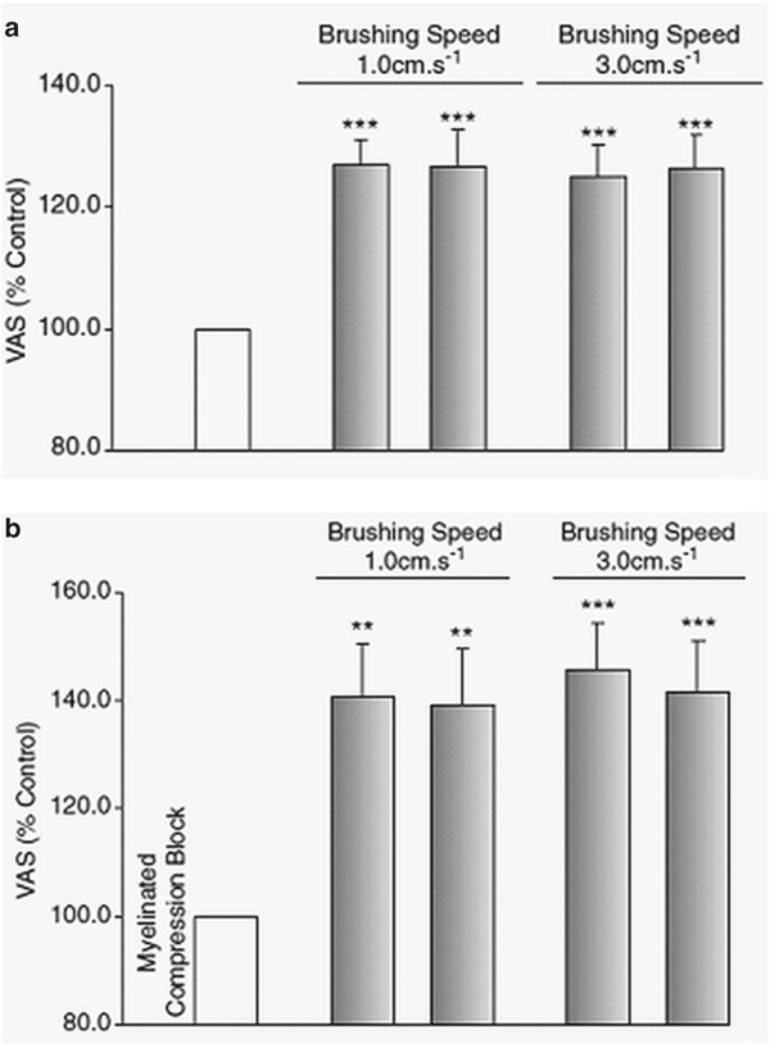

Fig. 24.2 Pain ratings recorded on a visual analogue scale (VAS) with *grey bars* indicating mean brush-evoked muscle pain responses expressed as percentages of baseline muscle pain indicated by the *white bar*. (**a**) CT-targeted slow brush stroking, at velocities of 1 and 3 cm s^{-1}, significantly increased the hypertonic saline-induced muscle pain ($n=9$). (**b**) Also during compression block of myelinated afferents slow brush stroking, at the same velocities, significantly increased the hypertonic saline-induced muscle pain ($n=5$). $^{**}P<0.01$; $^{***}P<0.001$. Original publication: Nagi, S.S., et al., *Allodynia mediated by C-tactile afferents in human hairy skin*. J Physiol, 2011. **589**(Pt 16): p. 4065–75

compression block of the sciatic nerve, that is, functional blockage of myelinated cutaneous afferents, thus demonstrating that this type of allodynia is mediated by CT afferents (Nagi et al. 2011). The slow skin stroking was reported as innocuous prior to the induction of the muscle pain and after its cessation.

On the other hand, there are numerous studies instead showing that Aβ afferents, rather than CTs, are responsible for tactile allodynia. As described above, several studies have observed that a compression or ischemic block of Aβ afferents eliminates tactile allodynia (Koltzenburg et al. 1992; Torebjork et al. 1992; Cervero and Laird 1996; Gracely et al. 1992; Landerholm and Hansson 2011). Further supporting this idea is a study of an Aβ-denervated subject who does not develop experimental tactile evoked pain following capsaicin injection. The Aβ-denervated subject develops normal pain, flare, and pinprick hyperalgesia but does not develop tactile allodynia to stroking with a cotton swab, as is seen in neurologically intact subjects (Treede and Cole 1993).

However, a potential role for CTs was further studied using the heat/capsaicin model of experimental tactile allodynia (Petersen and Rowbotham 1999). Our research group replicated the observation of no tactile allodynia in two participants lacking Aβ afferents. However, we also observed that these patients report that their CT touch percept (faint sensation of pleasant touch) is reduced for stroking in the cutaneous zone that, following the model application, is allodynic in control subjects. This finding suggests a possible contribution of CT afferents in the production of allodynia through a reduced CT-mediated hedonic touch processing. Functional magnetic resonance imaging (fMRI) was used to further explore this hypothesis. Differences in cortical processing between stroking in the allodynic and control zones were confirmed. When brushing on the allodynic skin (or the same site in the Aβ-denervated subject) is compared to brushing on normal skin, one Aβ-denervated subject and the neurologically intact subjects show reduced processing in medial prefrontal cortex (mPFC) (Fig. 24.3) as well as altered processing in the posterior insular cortex. Since the mPFC is implicated in a hedonic network of brain areas for CT-mediated affective touch (Gordon et al. 2013; Kringelbach and Rolls 2004) and the posterior insular cortex is a primary receiving cortical projection site for CT signaling (Bjornsdotter et al. 2009; Olausson et al. 2002), we suggest that the allodynic condition is indeed associated with reduced hedonic C-touch processing following alteration of CT signaling, perhaps in the superficial dorsal horn (Fig 24.4) (Arcourt and Lechner 2015). However, the sensation of allodynic pain seems to, at least under these experimental conditions, require Aβ signaling since the patients did not develop allodynic pain.

Further evidence of a disturbance in Aβ afferent processing comes from another study using the heat-capsaicin model of tactile allodynia in neurologically intact subjects (Liljencrantz et al. 2014). The findings show a consistent and significant decrease in tactile direction discrimination (TDD) accuracy in the allodynic zone. TDD is a function that is dependent on the integrity of Aβ signaling (Olausson et al. 1997; Essick 1988). The altered Aβ processing is explained in terms of rerouting of tactile peripheral input into nociceptive pathways (Magerl and Treede 2004). Physiological alteration of somatosensory processing due to pain has been demonstrated at the level of the spinal cord (Dougherty et al. 1998), the thalamus (Bruggemann et al. 1998), and the contralateral primary somatosensory cortex (Apkarian et al. 1992). Two point discrimination (TPD) and other measures of tactile acuity are typically reduced in chronic pain conditions with (and without) allodynia

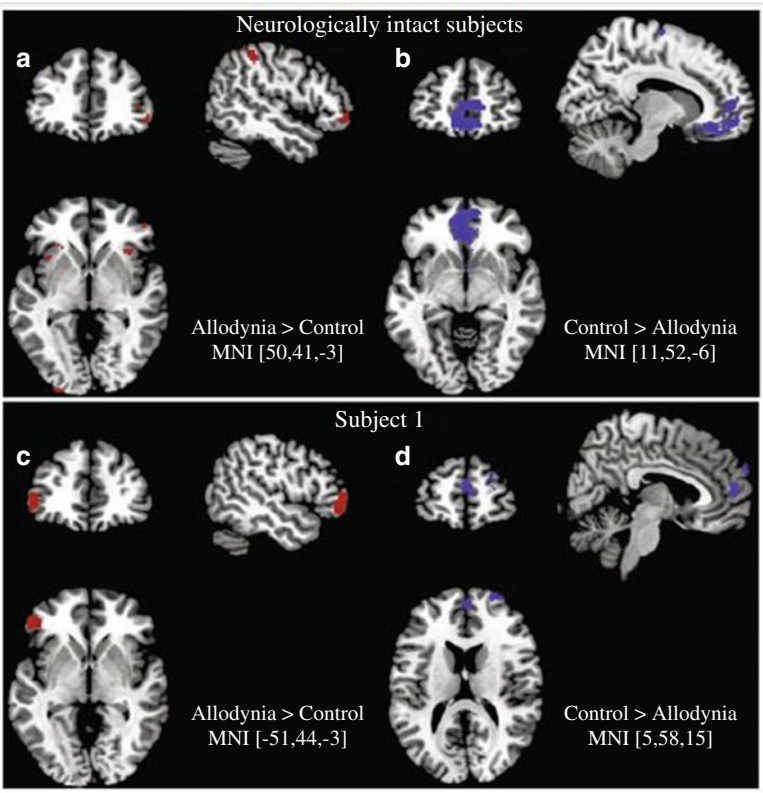

Fig. 24.3 Functional magnetic resonance imaging (fMRI) of gentle brush stroking in the heat/capsaicin mode suggesting a possible contribution of CT afferents in the production of allodynia through a reduced CT-mediated hedonic touch processing. (**a**, **b**) Neurologically intact subjects. Activation maps thresholded at $P<0.001$ uncorrected; k>16 voxels, corrected at $P<0.05$. (**a**) Stroking in the allodynic zone evoked significantly stronger activation than stroking in the control zone in multiple areas including inferior frontal gyrus and anterior insular cortex. (**b**) Stroking in the control zone evoked significantly stronger activation than stroking in the allodynic zone in large parts of the medial orbitofrontal cortices extending into prefrontal cortices. (**c**, **d**) Aβ-denervated, subject 1. Activation maps thresholded at $P<0.01$ uncorrected; k>46 voxels, corrected at $P<0.05$ (for complete activation lists, see original publication). (**c**) Stroking in the intended allodynic zone evoked significantly stronger activation than stroking in the control zone in the inferior frontal gyrus. (**d**) Stroking in the control zone evoked significantly stronger activation than stroking in the intended allodynic zone in the frontal superior medial cortex. All images are shown in neurological convention with the right side corresponding to the right hemisphere. Original publication: Liljencrantz, J., et al., *Altered C-tactile processing in human dynamic tactile allodynia*. Pain, 2013. **154**(2): p. 227–34

(Hollins and Sigurdsson 1998; Maihofner et al. 2006; Moriwaki and Yuge 1999; Moseley 2008; Lewis and Schweinhardt 2012; Stanton et al. 2013). Chronic pain patients may have a reorganization of the somatosensory cortex and the extent of this reorganization correlates with their pain intensity as well as their reduced tactile

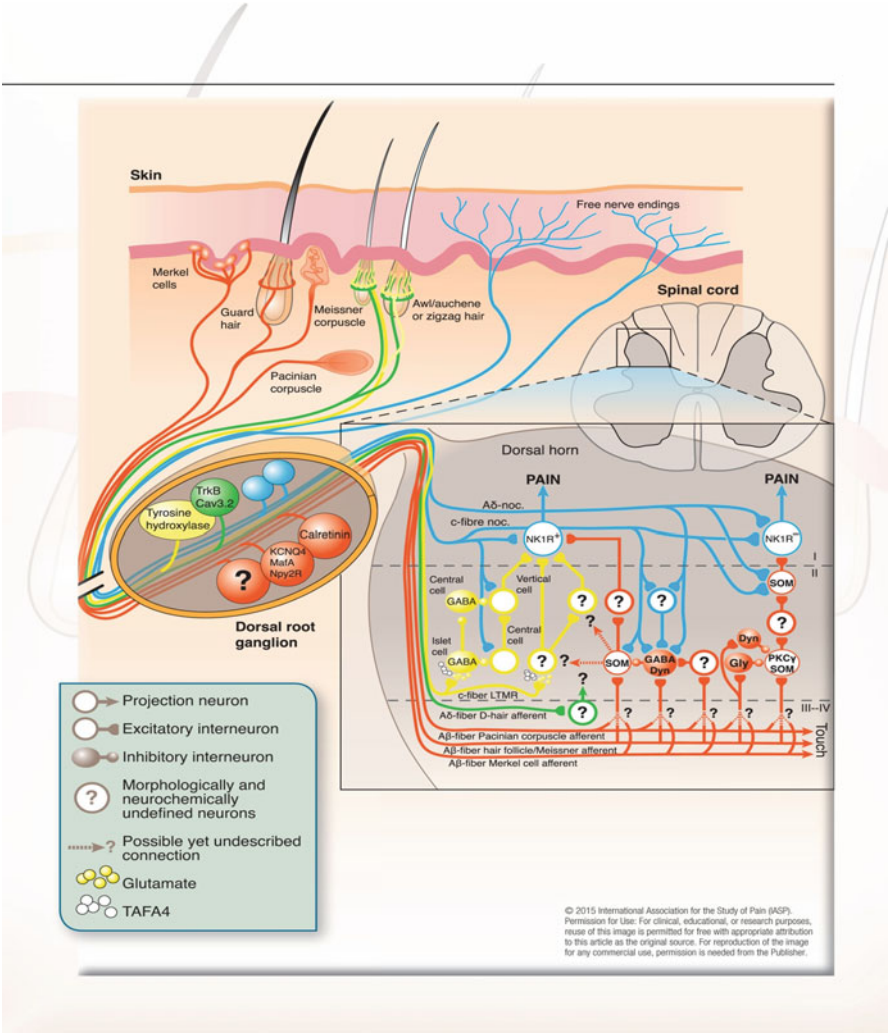

Fig. 24.4 Under physiological conditions nociception and touch are processed separately in the spinal cord. However, under pathophysiological conditions, such as nerve inflammation or trauma, touch can evoke pain, that is, tactile allodynia. Neurokinin-1 receptor (NK1R) expressing projection neurons in lamina I which are activated by somatostatin (SOM) expressing interneurons following nociceptive input can, following nerve injury, be activated by Aβ afferents. Under normal conditions this connection is inhibited by dynorphin-/GAD67-expressing GABAergic interneurons in lamina II controlled by Aβ afferents as well as Aδ- and C-afferent nociceptors. PKCγ$^+$/SOM$^+$ interneurons (in turn controlled by glycinergic and dynorphin-expressing interneurons), central cells, and SOM$^+$ interneurons in the outer lamina II provide other connective links for Aβ afferents with lamina I NK1R projection neurons. C-LTMRs release glutamate and the protein TAFA4 from central synapses. C-LTMRs access NK1R-expressing neurons via projections to lamina IIi and to lamina I spinoparabrachial neurons. C-LTMRs also exert a regulatory role of the nociceptive inflow to NK1R cells from C-nociceptors via central and vertical cells by activation of GABAergic islet cells in lamina II. The existence of a functional connection between C-LTMRs and Aβ afferents remains unknown. Original publication: Arcourt, A. and S.G. Lechner, *Peripheral and spinal circuits involved in mechanical allodynia*. Pain, 2015. **156**(2): p. 220–1

acuity (Flor et al. 1995, 1997; Maihofner et al. 2004; Pleger et al. 2005). Furthermore, tactile acuity increases as pain diminishes (Maihofner et al. 2004; Pleger et al. 2005; Nathan 1960).

In the same study we again, using the heat/capsaicin experimental model, presented further evidence suggesting altered CT processing in experimental allodynia (Liljencrantz et al. 2013). Skin stroking at a CT preferred velocity (3 cm s^{-1}) was found to be, relative to intact skin, the most unpleasant type of touch, suggesting an altered processing of CT information (Liljencrantz et al. 2013). In the allodynic zone, the pleasantness ratings for the CT-targeted stroking dropped to those of the Aβ-targeted stroking suggesting that the CT processing was suppressed (Delfini et al. 2013). A similar finding of reduced pleasantness ratings has been observed in CT-denervated patients (Morrison et al. 2011).

The details of the anatomical and functional reorganization of the dorsal horn during tactile allodynia are controversial (Campbell and Meyer 2006) (Fig 24.4) (Arcourt and Lechner 2015). Although C-LTMRs activate nociceptive (WDR) lamina I projection pathways of the dorsal horn in rats, a C-LTMR-specific spinal pathway has not yet been observed (Andrew 2010). However, noxious stimulation suppresses CT signaling through a postulated C-touch spinal pathway (resulting in the reduced perception of CT-targeted touch in the intended allodynic zone in Aβ-denervated subjects), whereas CT signaling through the WDR pathway may be enhanced. Thus, for CT afferents, there may be a gating that results in a significant decrease in pleasantness perception (Andrew 2010; Craig 2002) which then prioritizes the nociceptive information from the periphery. Hence, suppressed signaling in a postulated C-touch pathway and increased signaling in the WDR pathway may contribute to the allodynic condition.

Novel findings in mice show that C-LTMR signaling releases TAFA4, and that this protein acts to prevent mechanical hypersensitivity (Delfini et al. 2013). Following inflammation and nerve injury TAFA4-null mice show enhanced mechanical and chemical hypersensitivity which is reversed by application of recombinant TAFA4 protein (Delfini et al. 2013). Thus, it is tempting to speculate that restoring normal CT processing could be a novel therapeutic strategy against neuropathic pain.

In summary, under normal conditions, CT afferents have a pain inhibiting role mediated by the release of TAFA4. However, under neuropathic pain conditions, CT afferents change their role from pain inhibition to instead contributing to the pain through changes in dorsal horn connections. Thus, restoring the pain inhibiting function of CT afferents using, for example, drugs that promote TAFA4 release, or blocking pathological CT signaling using specific CT antagonists, could be novel treatment strategies against neuropathic pain.

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