Neuroscience and Biobehavioral Reviews 34 (2010) 148–159

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

The cutaneous sensory system

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ARTICLE INFO

Keywords:
Somatosensory
Cutaneous
C-fibres
CT-afferents
Touch
Temperature
Itch
Pain
Pleasure

ABSTRACT

The cutaneous senses are traditionally thought to comprise four recognized submodalities that relay tactile, thermal, painful and pruritic (itch) information to the central nervous system, but there is growing evidence for the presence of a fifth modality that conveys positive affective (pleasant) properties of touch. Cutaneous sensory channels can be further classified as serving predominantly either *discriminative* or *affective* functions. The former provides information about the spatial and temporal localisation of events on the body surface, e.g., the presence of an insect or the temperature of a cold wind; and the latter, although widely recognised as providing the afferent neural input driving the negative emotional experience of pain, is here posited to provide the afferent neural input driving the positive emotional experience of affiliative touch as well. A distinction is made between the properties of fast conducting myelinated afferents and those of slowly conducting unmyelinated afferents, with the former subserving a sensory-discriminative role, and the latter an affective-motivational one. Here we review the basic elements of the somatosensory system and outline evidence for the inclusion of the 'fifth' sub-modality, conveyed by low-threshold C-fiber mechanoreceptors as the counterpart of high-threshold C-fiber nociceptors with both C-fiber systems serving opposing aspects of affective touch, yet underpining a common mechanism for the preservation of self and species.

Contents

1. Introduction to the somatosensory system

The primary sensory modality subserving the body senses is collectively described as the somatosensory system. It comprises all those peripheral afferent nerve fibers, and specialised receptors, subserving proprioceptive (joint, muscle) and cutaneous sensitivity. The former processes information about limb position and

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0149-7634/$ – see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.neubiorev.2009.08.004

muscle forces which the central nervous system uses to monitor and control limb movements and to ensure that a planned action or movement is executed fluently via elegant feedback and feedforward mechanisms. This review paper will focus on sensory inputs arising from the skin, namely cutaneous sensibility.

Sensory modalities operate within interconnecting, intermodal and crossmodal networks, ensuring that interactions with the environment are generally multisensory (see Calvert et al., 2004, for review). Vision and hearing are classified as exteroceptive senses and provide information that can be used to guide approach or avoidance behaviours; olfaction is also able to provide such information: think only of the smell of burning, or the aroma of coffee. For many behaviours, a physical and/or chemical contact sense is required in order to extract more information about stimuli in the immediate environment, and the senses of touch and taste provide this information. The cutaneous senses are classically defined as including tactile, thermal, pain and itch sensing submodalities, and there is growing evidence for an additional cutaneous sensory channel that subserves positively affective aspects of touch, such as those generated during grooming and nurturing behaviours. 'Touch' in this context is seen as interoceptive, providing information about the homeostatic state of the body, and even the sense of self (Craig, 2009). The skin is a highly complex organ, innervated by a wide array of specialised sensory neurones sensitive to heat, cold, pressure, irritation, itch and pain. Touch is the first sense to develop *in utero*, Montagu (1978, p. 195) reporting tactile responses to a hair stroking the cheek of a foetus at around 8 weeks gestational age. Cutaneous sensitivity of the embryonic body extends to the genital area by week 10, the palms by week 11, the soles by week 12, the abdomen and buttocks by week 17, and by week 32 every part of the body is responsive to the gentle stroke of a single hair. This developmental hierarchy of tactile sensitivity is reflected anatomically: the sites developing cutaneous sensitivity first possessing the greatest number and variety of sensory receptors in adults. Consequently, they are also represented cortically with larger areas of primary somatosensory cortex. In addition to demonstrating sensitivity to light touch, prenates also respond to tissue harming stimuli. Giannakoulopoulos et al. (1994) have reported that within 10 min of inserting a hypodermic needle into a fetus's intrahepatic vein, for a transfusion, there is a 590% rise in beta-endorphin and a 183% rise in cortisol. This biochemical evidence of a physiological response to nociception, and evidence that cutaneous C-fiber systems are functional at a discriminative level at an early developmental stage, raises the possibility that C-fiber systems are also functional at an affectively positive level. The component of the cutaneous senses that is relayed to the somatosensory cortex includes the entire body from the neck down; sensations from the face are relayed via cranial nerves, with both parts sharing a common central organization. As with other sensory modalities, information is relayed from entry level cortex to higher order neural systems controlling perception, attention and emotion, as well as systems that integrate this information with other sensory modalities. This pattern of connectivity enables neural processing systems to maximize information received from the senses about the conditions in the external world.

2. The peripheral nervous system

The skin is the most extensive and versatile of the body's organs and in a fully grown adult covers a surface area approaching 2 m^2. Apart from its role as a sensory organ the skin contains in excess of 2 million sweat glands and 5 million hairs, that may be either fine vellous types covering all surfaces apart from the soles of the feet and the palms of the hands (glabrous skin). Skin consists of an outer stratified squamous epithelium of ectodermal origin – the epidermis – and an inner, thicker, supporting layer of connective tissue of mesodermal origin—the dermis. The thickness of this densely innervated layer varies from 0.5 mm over the eyelid to >5.0 mm in glabrous skin. Afferent nerve impulses are conveyed by fibers of primary sensory neurons located in trigeminal and dorsal root ganglia, which are comprised of a heterogeneous population comprising of cell bodies of all the peripheral afferents innervating the skin. Efferent axons of dorsal root ganglia neurons terminate in the skin where they innervate a variety of cutaneous structures such sweat glands, hair follicles, Merkel cells, Meissner's corpuscles and blood vessels. The nerve bundles course through the dermis vertically, forming a horizontal sub-epidermal neural plexuses before losing their Schwann cell covering at the dermo-epidermal junction and penetrating the epidermal basement membrane, ascending between the keratinocytes and terminating as free nerve endings. Cutaneous innervation consists mainly of unmyelinated fibers, accounting for around 90% of all dermal nerve fibers (Ebenezer et al., 2007).

2.1. Touch

Most primate research into skin sensory processing has focused on the glabrous surface of the hand, in particular the digits, and a description of this somatic site will provide for a general understanding of somatosensation (Johansson, 1976; Vallbo et al., 1979; Darian-Smith, 1984a,b; Willis and Coggeshall, 1991; Gescheider et al., 1992; Greenspan and Lamotte, 1993). Of the four 'classical' submodalities of the somatosensory system the tactile one subserves the perception of pressure, vibration, and texture, and relies upon four different receptors in the digit skin: (1) Pacinian corpuscles, (2) Meissner's corpuscles, (3) Merkel's disks, and (4) Ruffini endings, collectively known as low-threshold mechanoreceptors (LTMs), a class of cutaneous receptors that are specialised to transduce mechanical forces impinging the skin into nerve impulses (Fig. 1). The first two are classified as fast adapting (FA) as they respond to the initial and final contact of a mechanical stimulus on the skin, and the second two are classified as slowly adapting (SA), continuing to fire during a constant mechanical stimulus. A further classification relates to the LTM's receptive field (RF), i.e., the surface area of skin to which they are sensitive which is determined by the LTM's anatomical location within the skin. Those near the surface, at the dermal/epidermal boundary (Meissner's corpuscles and Merkel's disks) possessing small RFs, and those lying deeper within the dermis, (Pacinian corpuscles and Ruffini endings), having large RFs.

Psychophysical procedures have traditionally been used to study the sense of touch and, as in hearing research where the sensory receptor is another type of specialised mechanoreceptor, differing frequencies of vibration are used to quantify the response properties of this sensory system. George von Bekesy (1939) was the first to use vibratory stimuli as an extension of his research interests in audition. In a typical experiment participants would be asked to respond with a simple button-press when they were just able to detect the presence of a vibration presented to a digit within one of two time periods. This two alternative forced choice paradigm (2-AFC) generates a threshold-tuning curve, the slopes of which provide information about a particular class of LTM's response properties. As can be seen from Fig. 2, a 'U'-shaped function is generated, with detection thresholds increasing in sensitivity as vibrotactile frequency increases to a 'peak' at around 300 Hz, at which point the curve begins to increase again as sensitivity decreases (Table 1).

By carefully controlling the stimulus parameters of the vibrating probe (spatial configuration, frequency, amplitude, duration and skin surface temperature) as well as the use of various masking techniques, Bolanowski et al. (1988) proposed

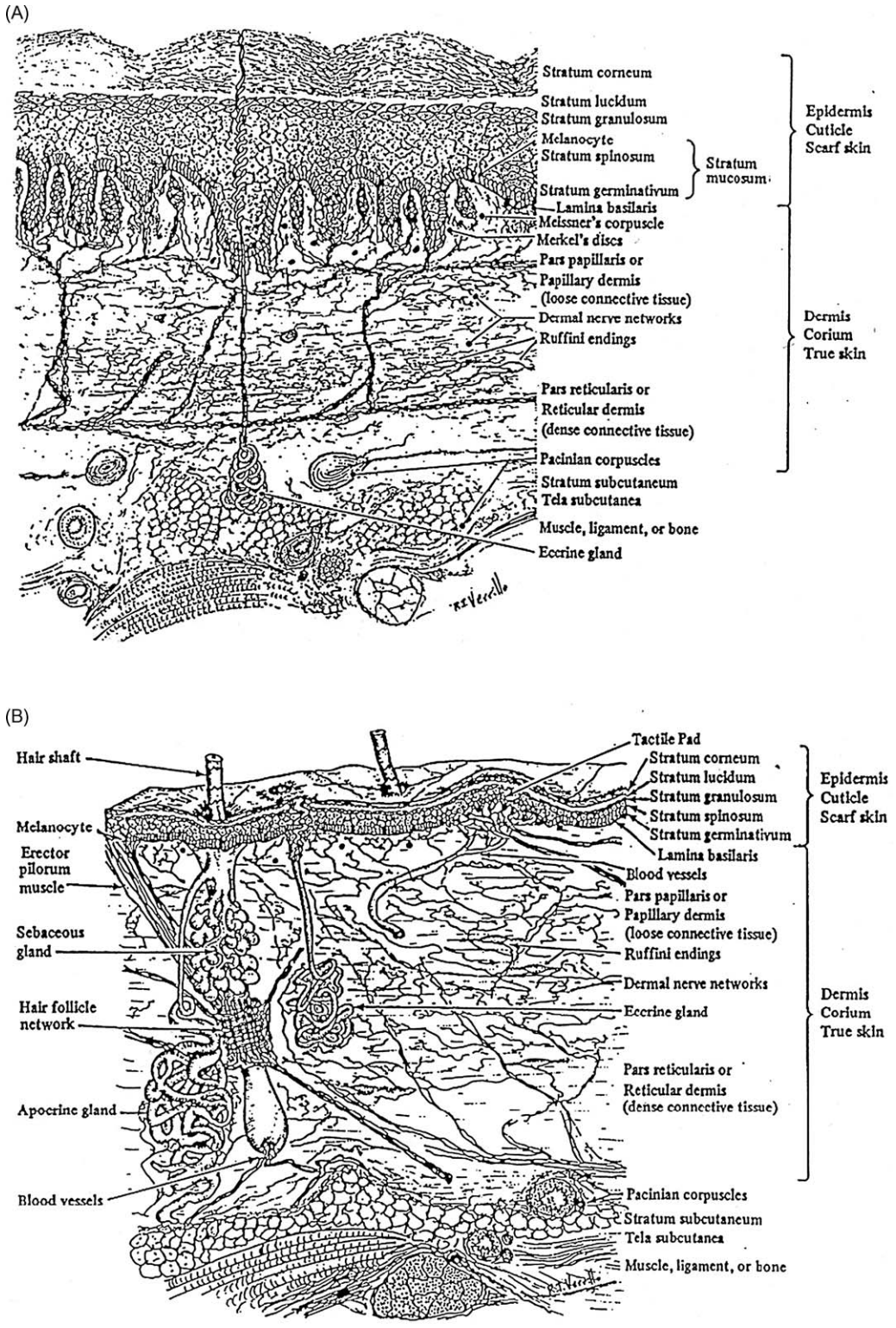

Fig. 1. A cross-sectional perspective of glabrous (A) and hairy (B) skin (with permission of the artist R.T. Verrillo).

that there are four distinct psychophysical channels mediating tactile perception in the glabrous skin of the hand. This model proposes that each psychophysically determined channel is represented by one of the four anatomical end organs and nerve fiber subtypes. Frequencies in the 40–500 Hz range provide a sense of 'vibration', transmitted by Pacinian corpuscles (PC channel or FAII), Meissner corpuscles transmit a sense of 'flutter' in the 2–40 Hz range (NPI channel or FAI), while 'pressure' is mediated by Merkel's disks in the 0.4–2.0 Hz range (NPIII or SAI) and Ruffini end organs produce a 'buzzing' sensation in the 100–500 Hz range (NPII or SAII). Neurophysiological studies have by and large supported this model. See Table 2 for a summary of the properties of these LTMs.

There have been relatively few studies of tactile sensitivity on the hairy skin, the cat being the animal of choice for most of these studies. Mechanoreceptive afferents (Aβ fibers) have been

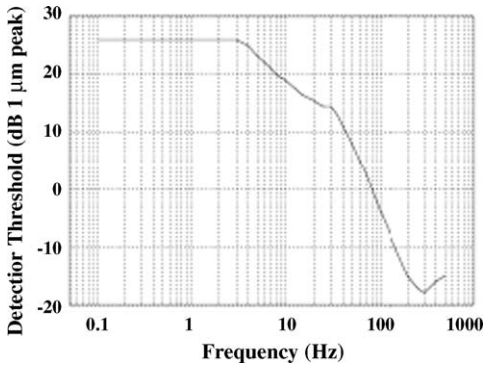

Fig. 2. Absolute detection thresholds for sinusoidal stimuli (from Bolanowski et al., 1988) where it can be seen that as vibration frequency increases detection thresholds decrease (note–log axis).

Table 2
Summarizes the main characteristics of primary sensory afferents innervating human skin.

Sensory afferent nerves			
Class	Modality	Axonal diameter (um)	Conduction velocity (m/s)
Myelinated			
Aα	Proprioceptors from muscles and tendons	20	120
Aβ	Low-threshold mechanoreceptors	10	80
Aδ	Cold, noxious, thermal	2.5	12
Unmyelinated			
C-pain	Noxious, heat, thermal	1	<1
C-tactile	Light stroking, gentle touch	1	<1
C-autonomic	Autonomic, sweat glands, vasculature	1	<1

described that are analogous to those found in human glabrous skin (FAI, FAII, SAI, SAII). Essick and Edin (1995) have described sensory fibers with these properties in human facial skin, however, the relationship between these sensory fibers and tactile perception is still uncertain, and this is exemplified by the response properties of SAI afferents. Harrington and Merzenich (1970) reported that these afferents are responsive to levels of stimulation that are below perceptual thresholds. Meanwhile, Jarvilehto et al. (1976) describe high levels of activity in human hairy skin SAIs that are not perceivable, in contrast to the responses of this class of afferent in glabrous skin where SAI nerve activity is directly correlated with a sense of pressure.

Sensory axons are classified according to their degree of myelination, the fatty sheath that surrounds the nerve fiber. The degree of myelination determines the speed with which the axon can conduct nerve impulses, and hence the nerve's conduction velocity. The largest and fastest axons are called Aα, and include some of the proprioceptive neurons, such as the muscle stretch receptors. The second largest group, called Aβ, includes all of the discriminative touch receptors being described here. Pain and temperature include the third and fourth groups, A-δ and C-fibers, and will be discussed in Section 2.2 (see Table 2).

Vallbo and Johansson (1978) developed an electrophysiological technique called microneurography to study the function of single peripheral nerve fibers innervating the human hand, which has provided a generally accepted model of touch that relates the four anatomically defined types of cutaneous or subcutaneous sense organs to their neural response patterns. Microneurography involves inserting a fine tungsten microelectrode, tip diameter <5 μm, through the skin of the wrist and into the underlying median nerve, which innervates the thumb and first two digits. A sensitive biological amplifier records and amplifies the spike discharges conveyed by the axons and feeds these to a loudspeaker to enable the experimenter to hear the spike activity and 'hone-in' on a single unit. Skilled manual micromanipulation of the electrode, coupled with stroking across the hand to stimulate LTMs, results first in a population response being recorded, i.e., neural activity in a nerve fascicle containing hundreds of peripheral axons until finally, sometimes after many hours, a single axon is isolated. At this stage the threshold force for activation and receptive field (RF) of the single unit are mapped with thin nylon filaments (Von-Frey hairs') and the unit subtype (i.e. FA or SA) is identified. Once this stage is completed, a small pulsed current of a few microamps (typically <7 μA) is delivered to the nerve to provides additional perceptual confirmation of the unit subtype. If, for example, a FA unit has been isolated, microstimulation is perceived as a 'flutter' or 'vibration', depending on the frequency of the electrical pulses, and is perceptually localised to the previously mapped RF. Fig. 3 depicts the relationships between RF, adaptation rate and unit type from studies carried out on the human hand (Westling, 1986).

2.2. Temperature

The cutaneous somatosensory system detects changes in ambient temperature over an impressively wide range, initiated when thermal stimuli that differ from a homeostatic set-point excite temperature specific sensory nerves in the skin (see Ringkamp, in this issue). Within the innocuous thermal sensing range there are two populations of thermosensory fibers, one responding to warmth and the other to cold, and include fibers from the Aδ and C range. Specific cutaneous cold and warm receptors have been defined as slowly conducting units that exhibit a steady-state discharge at constant skin temperature and a dynamic response to temperature changes (Hensel and Boman, 1960; Hensel, 1973). Cold-specific and warm-specific receptors can be distinguished from nociceptors that respond to noxious low and high temperatures (<20 °C and >45 °C) (Torebjörk and Hallin, 1976; Campero et al., 1996), and also from thermo-sensitive mechanoreceptors (Hensel and Boman, 1960; Konietzny, 1984). Konietzny recorded from 13 cold-specific units in humans using microneurography, and measured conduction velocities (CVs) in the C-fiber range (0.43–2.04 m s^{-1}). Serra et al. (1999) uncovered a number of spontaneously active fibers with microneurography,

Table 1
Summarizes the major findings in Bolanowski et al. (1988) and previous work done by these researchers at the Institute for Sensory Research, Syracuse University (Verrillo, 1963; Gescheider et al., 1982, 1983, 1985).

Channel	Pacinian	NPI	NPII	NPIII
Frequency response	40–80 Hz	3–100 Hz	15–400 Hz	<0.3–>100 Hz
Threshold (re 1 μm)	<−20 dB @ 300 Hz	28 dB @ 3 Hz	10 dB @ 300 Hz	28 dB @ 3 Hz
Sensation	Vibration	Flutter	Not known	Pressure
Temporal summation	Yes	No	Yes	No
Spatial summation	Yes	No	Not known	No
Receptor type	FAI Pacinian corpuscle	FAII Meissner's corpuscle	SAII Ruffini end organ	SAI Merkel's disk

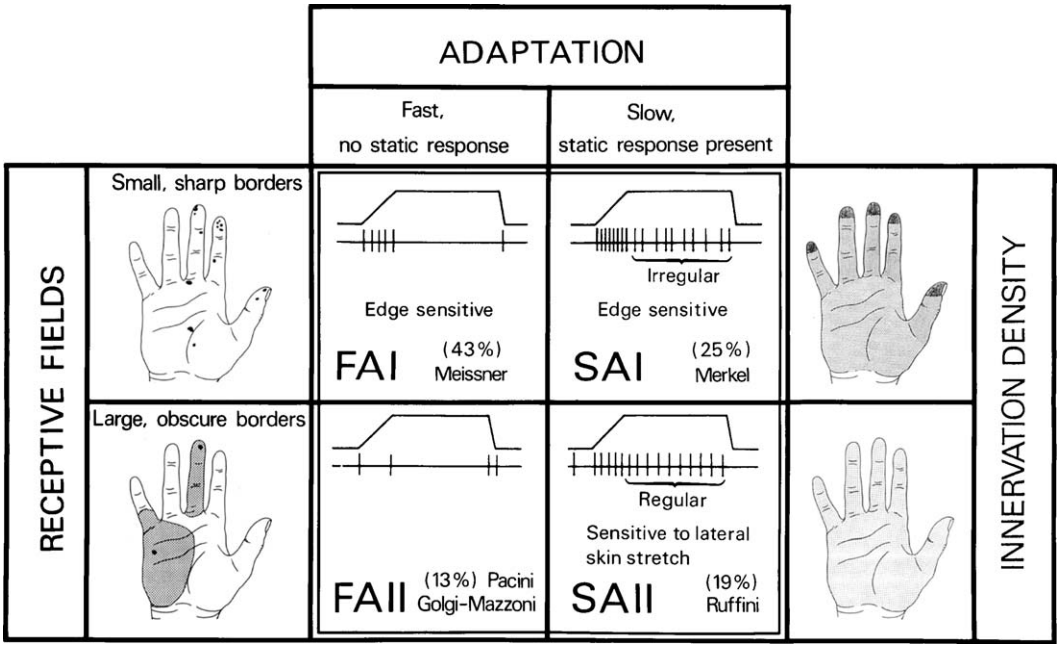

Fig. 3. The four types of low-threshold mechanoreceptors in human glabrous skin are depicted. The four panels in the centre show the nerve firing responses to a ramp and hold indentation and in % the frequency of occurrence and putative morphological correlate. The black dots in the left panel show the RFs of Type I (top) and Type II (bottom) afferents. The right panel shows the average density of Type I (top) and Type II (bottom) afferents with darker areas depicting higher densities (after Westling, 1986).

which were sensitive to small temperature changes and that were described as cold-specific units, but all had CVs in the C-fiber range (0.43–1.27 m s^{-1}). Textbooks describe the cutaneous cold sense in man as being mediated by myelinated A-fibers with CVs in the range 12–30 m s^{-1} (Darian-Smith, 1984a,b). However, Campero et al. (2001) have found that either human cold-specific afferent fibers are incompletely myelinated 'BC' fibers, or are C as well as A-cold fibers, with the C-fiber group contributing little to sensation. Duclaux et al. (1976) described 'BC' fibers as having electrophysiological and morphological properties of C-fibers in their distal part of the axon process, and B fibers at their proximal end. An example of a feature of these units can be seen in Fig. 4 where the resting activity at room temperature (21 °C), which is characterized by a low frequency discharge (~1 Hz), is suppressed by the sudden warming of the RF and is increased by cooling.

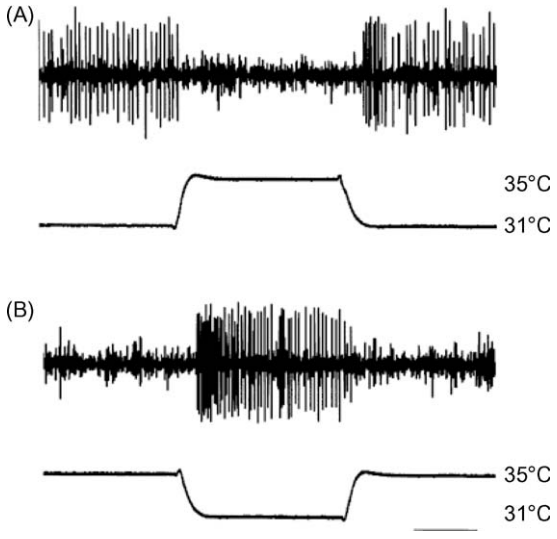

Fig. 4. Resting discharge of a C cold fiber at room temperature. (A) The resting discharge is suppressed by warming of the receptive field (RF) from 31 °C to 35 °C. (B) From a holding temperature of 35 °C, at which the unit is silent, activity is initiated by cooling the RF to 31 °C. (Time bar: 5 s) (see Campero et al., 2001 for single unit responses to a range of temperatures).

Free nerve endings for cold-sensitive or warm-sensitive nerve fibers are located just beneath the skin surface, and the terminals of an individual temperature-sensitive fiber do not branch profusely or widely. Rather, the endings of each fiber form a small, discretely sensitive point, separated from the sensitive points of neighboring fibers. The total area of skin occupied by the receptor endings of a single temperature-sensitive nerve fiber is relatively small (~1 mm in diameter) with the density of these thermo-sensitive points varying in different body regions. For example, there are approximately 20 cold points per square centimeter in the lips, 4 in the finger, and less than 1 cold point per square centimeter in trunk areas. There is also a differential innervation of cold and warm neurons with at least 5 times as many cold-sensitive points as warm-sensitive points. It is well established from physiological and psychophysical testing that warm- and cold-sensitive nerve fibers differ in both structure and function.

2.3. Pain

Here we consider a system of peripheral sensory nerves that innervate all cutaneous structures and whose sole purpose is to protect the skin against potential or actual damage. These primary afferents comprise Aδ and C-fibers that respond selectively and linearly to levels of thermal, mechanical and chemical intensity/strength that are tissue threatening or damaging. This encoding mechanism is termed nociception and describes the sensory process detecting any overt, or impending, tissue damage (see Auvray et al., in this issue). Pain is described in terms of an 'experience' rather than just a simple sensation. Within the nociceptive system there are submodalities which are evident at the peripheral anatomical level are evident with respect to the degree of nerve fiber myelination (see Table 1). Aδ fibers are thin (1–5 um), myelinated axons of mechanical and thermal nociceptors, with average CVs of 12 m/s. C-fibers are thin (<1 um), unmyelinated, slowly conducting axons (<1 m/s). Mechanical

nociceptors in the Aδ range and possess RFs distributed as 5–20 small sensitive spots over an area approximately 2–3 mm in diameter. In many cases activation of these spots depends upon stimuli intense enough to produce tissue damage, such as a pinprick. Aδ units with a short latency response to intense thermal stimulation in the range 40–50 °C have been described as well as other units excited by heat after a long latency—usually with thresholds in excess of 50 °C.

Over 50% of the unmyelinated axons of a peripheral nerve respond not only to intense mechanical stimulation, but also to heat and noxious chemicals, and are therefore classified as polymodal nociceptors (Bessou and Perl, 1969) or C-mechano-heat (CMH) nociceptors (Campbell et al., 1989). A subgroup of polymodal nociceptors have been reported to respond to extreme cold, however, many of these units develop an excitatory response to cooling after prior exposure to noxious heat. A small number of C-fibers have mechanical thresholds in the nociceptor range with no response to heat while others have been found that respond preferentially to noxious heating. RFs of these C-fiber units consist of single zones with distinct borders and in this respect they differ from Aδ nociceptors that have multipoint fields. Innervation densities are high and responses have been reported to a number of irritant chemicals such as dilute acids, histamine, bradykinin and capsaicin. Schmidt et al. (1995) described not only CMH responsive units, but a novel class of C-fiber nociceptors responding only to mechanical stimuli (CM), units responding only to heating (CH), and units that were insensitive to mechanical and heating stimuli and also to sympathetic provocation tests (CMiCHi). Some CM, CH, and CMiCHi units can be sensitised to thermal and/or mechanical stimuli after topical application of skin irritants such as mustard oil or capsaicin—these units then acquire responsiveness to stimuli to which they were previously unresponsive. Recruitment of these 'silent' nociceptors implies spatial summation to the nociceptive afferent barrage at central levels, and may therefore contribute to primary hyperalgesia after chemical irritation and to secondary hyperalgesia as a consequence of central sensitisation (see below).

The axon terminals of nociceptive axons do not possess specialised end organ structures and for that reason are referred to as free nerve endings. This absence of any encapsulation renders them sensitive to chemical agents, both intrinsic and extrinsic. Inflammatory mediators released at a site of injury can initiate or modulate activity in surrounding nociceptors over an area of several millimetres leading to two types of hyperalgesia responses—the phenomenon of increased sensitivity of damaged areas to painful stimuli. Primary hyperalgesia occurs within the damaged area while secondary hyperalgesia occurs in undamaged tissues surrounding this area.

2.4. Itch

The sensation of itch has, in the past, been thought to be generated by the weak activation of pain nerves, but with the recent finding of primary afferent neurons in humans (Schmelz et al., 1997; Schmelz, in this issue), and spinal projection neurons in cats (Andrew and Craig, 2001), that have response properties matching those subjectively experienced after histamine application to the skin, it is now recognised that separate sets of neurons mediate itch and pain, and that the afferent neurons responsible for histamine-induced itch in humans are unmyelinated C-fibers. Until relatively recently is was though that histamine was the final common mediator of itch, but clinical observations in which itch can be induced mechanically or is observed without an accompanying flare reaction, cannot be explained as being mediated by histamine sensitive pruriceptors. These observations support the existence of histamine-independent types of itch nerves (Ikoma et al., 2005) in which itch is generated, without a flare reaction, by cowhage spicules. As with the existence of multiple types of pain afferents, different classes of itch nerves are also likely to account for the various experiences of itch reported by patients (Yosipovitch et al., 2002).

2.5. Pleasure

It is generally accepted that human tactile sensibility is solely mediated by LTMs with fast conducting large myelinated afferents (as described above). However, in recent years a growing body of evidence has been accumulating, from anatomical, psychophysical, electrophysiological and neuroimaging studies, for the presence of a population of C-fibers, found only hairy skin, that are neither nociceptive nor pruritic, but that respond preferentially to low force, slowly moving mechanical stimuli traversing their RFs. These nerve fibers have been classified as C-tactile afferents (CT-afferents), and were first described by Johansson et al. (1988) using microneurography. Evidence of a more general distribution of CT-afferents has subsequently been found in the arm and the leg, but they have never been found in glabrous skin sites (Vallbo et al., 1979). It is well-known that mechanoreceptive innervation of the skin of many mammals is subserved by A-fiber and C-fiber afferents (Zottermann, 1939; Bessou and Perl, 1969; Iggo and Korhuber, 1977), but until the observations made by Nordin (1990), C-fiber mechanoreceptive afferents in human skin appeared to be lacking entirely.

The functional role of CT-afferents is not fully understood (Mackenzie et al., 1975), but their neurophysiological response properties, fiber class, and slow conduction velocities preclude their role in any form of rapid mechanical discriminative or cognitive tasks, and point to a more limbic function, particularly the emotional aspects of tactile perception (Vallbo et al., 1993; Essick et al., 1999). However, the classification of a population of afferent low-threshold C-fiber mechanoreceptors responding preferentially to low velocity and low force mechanical stimulation, and the assignment of a functional role in human skin, has only recently been achieved as described by Olausson et al., in this special issue, and in Loken et al. (2009).

The recognition that cutaneous sensitivity can serve both discriminative and affective functions is best exemplified in the case of pain, in which two independent systems of cutaneous nerves serve two very different qualitative perceptual and emotional states, known as 1st and 2nd pain (Cross, 1994). The former is experienced as sharp or pricking sensation and is conveyed to the central nervous system by fast conducting myelinated Aδ afferents. 1st pain is responsible for controlling withdrawal reflexes such as when a potentially tissue threatening stimulus contacts the body surface. The sensations evoked by transitory stimulation are experienced immediately and are qualitatively devoid of any lasting emotional distress, serving a primary discriminative function—something is damaging the skin. The latter, 2nd pain, is conveyed to the central nervous system by C-fibers and generates far more qualitatively complex and, importantly, temporally delayed sensations and emotions, comprising qualities such as dull, throbbing, radiating and burning (Melzack, 1975). Stimulation of fast conducting A-fibers provides information for discriminative purposes, whereas stimulation of the C-fibers evokes emotional responses. Pain is defined as 'an unpleasant *sensory* and *emotional* experience associated with actual or potential tissue damage, or described in terms of such damage'. Use of the terms 'sensory' and 'emotional' refers to the dual nature of pain, with descriptions like "throbbing, prickly, hot, dull" referring to the sensory component of pain, and descriptions like "torturing, annoying, frightful, sickening" referring to the emotional qualities of pain. Pain is always a subjective psychological state – see Auvray et al., this issue – and it is an accepted fact

that cutaneous 'pain' has both sensory/discriminative and affective/motivational properties – qualities that are critically dependent upon two classes of peripheral afferents – myelinated A-fibers and unmyelinated C-fibers. We propose that 'touch' is also characterised by sensory/discriminative and affective/motivational components, and that there are two touch systems parallel to the two pain systems. 1st touch is subserved by fast conducting Aβ afferents responsible for rapid identification of the physical properties of a tactile stimulus. The sensory information is primarily discriminative and non-emotional, conveying qualitative states such as "wet, hard, rough, etc." and is essentially 'immediate' in terms of conscious awareness. By contrast, 2nd touch, mediated by slowly conducting mechanosensitive C-fibers (CTs), conveys information related to tactile inputs associated with affiliative and affective touch, such as those gentle and slow stroking touches experienced during grooming or nurturing behaviours. Importantly, as these inputs are conveyed via C-fibers, they do not reach immediate conscious awareness, generating the temporally delayed positive emotional attributes of touch in a similar manner to the delayed onset and qualitative properties of 2nd pain.

Work is in progress to identify this class of C-fibers histologically, with a study using the pan-neuronal marker PGP9.5 and confocal laser microscopy to identify a population of free nerve endings located solely within the epidermis that may represent the putative anatomical substrate for this sub-modality (Reilly et al., 1997). Recent evidence from Anderson's group has shown, in a mouse model, a molecular genetic visualization of a rare subset of unmyelinated sensory neurons that they suggested may detect gentle touch (Liu et al., 2007). Using a genetically encoded tracer, they found that Mas-related G protein-coupled receptor B4 (MrgprB4) marks a subpopulation of unmyelinated, non-peptidergic sensory fibers that exclusively, and importantly in terms of the human microneurographic data, only innervate hairy skin. These fibers terminate in large arborisations similar in size and distribution to human C-fiber tactile afferent's RFs, suggesting that MrgprB4 may provide genetic access to these elusive neurons in mice and enable the elucidation of their receptor molecular neurobiology.

2.6. Sensory transduction

Signalling of stimuli such as touch, temperature, pain and pleasure requires molecular recognition of stimulus and mobilization of a response in the form of an electrical signal. However, the relationship between stimulus and transduction pathway is anything but simple, and it is clear that perception of a single stimulus often requires several transduction mechanisms. Conversely, a given protein can contribute to several senses, e.g., heat and touch (Lumpkin and Caterina, 2007). The sensitivity of sensory circuits is further influenced and tonally regulated by extrinsic (e.g. UV radiation) and intrinsic (e.g. nerve growth factor) mediators.

Touch and tactile sensitivity require rapid and direct signalling that is provided by ion channels via interaction with both intracellular cytoskeletal and extracellular matrix proteins (Gillespie and Walker, 2001). The key mammalian ion channel candidates studied to date are the epithelial sodium channels and the acid-sensing ion channels (ASICs), both of which belong to the Degenerin/epithelial amiloride sensitive Na+ channel (DEG/ENaC) superfamily of ion channels, reviewed recently by Bonsch and Lewin (2006).

Although the fundamental role of ion channels as the molecular basis of mechanotransduction was first established in the nematode worm *Caenorhabditis Elegans*, and the fruitfly *Drosophila melanogaster*, a related vertebrate channel from mammalian tissue was later identified by Canessa et al. (1993). The first neural channel identified was the brain sodium channel (BNC1, also known as ASIC2), and it is one of several mammalian DEG/ENaC channels known to form homo- and hetero-multimers and is the basis of voltage-insensitive sodium channels which are expressed in both small and large dorsal root ganglia sensory neurons (Price et al., 2000). These amiloride sensitive sodium channels also respond to protons, although when expressed in low-threshold mechanoreceptors, the ASIC2 channels are not gated by low pH, possibly due to the requirement for activation of intact cytoskeletal support structures to allow gating. Likewise, in ASIC2 knockout mice, phenotypic testing shows that only LTMs are affected (Price et al., 2000; Driscoll and Tavernarakis, 2000; McIlwrath et al., 2005).

Protons can activate members of the ASIC family, generating a perception of sting and pain. However, other candidates have also been identified in recent years. Stimuli such as temperature, pain or chemical challenges acting on nociceptors are controlled peripherally via a complex regulation of activity in another series of ion channels, the thermoTRPs (Transient Receptor Potentials). One of the earliest proteins associated with heat pain was the vanilloid receptor subtype-1 (VR1, also referred to as TRPV1), identified as the molecular target for the pungent irritant, capsaicin (Caterina et al., 1997). TRPV1 is a classical cation channel and is expressed in cutaneous sensory nerve fibers, mast cells and epithelial cells of appendage structures (Stander et al., 2004). Interestingly, activity for temperature (hot and cold), pain and chemesthetic activity can all be explained in terms of the plasticity of a family of thermoTRP cation channels (Montell et al., 2002) which consist of 6-transmembrane polypeptide units that assemble as tetramers to form cation-permeable pores (Clapham, 2003). The presence of multiple TRP channels, with distinct localisation on sub-sets of C- and Aδ-sensory neurons allows for a wide spectrum of physiological activities to be regulated by these channels and accounts, at least in part, for the complexity of these transducer systems (Minke and Cooke, 2002). The gating mechanism for stimuli such as radiant heat remains to be elucidated, but again cytoskeletal components are believed to be crucial for activation of these cation channels.

Development of transgenic mouse models lacking expression of the VR1 gene shows that phenotypic characteristics in VR1 null (−/−) mice support a functional role for VR1 in sensory transduction of nociceptive stimuli, although it was apparent that other receptors could partially compensate for the loss of VR1 function (Caterina et al., 2000; Davis et al., 2000). As an understanding of the process involved in sensing temperature and chemical stimulation of nociceptors has evolved, it has become apparent that there are additional non-TRP proteins and receptors which also play a role in nociception, e.g., ASICs and the P2-X3 ATP receptor (Askwith et al., 2001; Souslova et al., 2000).

A key question in recent years has been whether the sensory neurons are the primary transduction element, or whether non-neuronal cells can act as the key signalling pathway, with subsequent activation of adjacent nerve terminals or neuronal structures resulting in a perception of touch, temperature, pain, or pleasure. Specialised epithelia structures such as hair cells, Merkel cells, and receptors on taste buds are known to play a role in sensory transduction, but recent evidence suggests that other candidates such as keratinocytes may also be primary transducers of mechanical stimuli (Lumpkin and Caterina, 2007). This emerging hypothesis stems from the observation, typically by immunohistochemical visualization, of mechano-, thermo- and chemo-sensitive receptors such as TRPV1 on epidermal keratinocytes (Inoue et al., 2002; Chung et al., 2004) and other non-neuronal cell types. The presence of sensory receptors on epidermal keratinocytes suggested a functional role in terms of permeability barrier homeostasis and it has been shown that TRPV1 agonists delay barrier recovery, whereas TRPV4 accelerates

barrier recovery (Denda et al., 2007a). However, Denda et al. (2007b) further suggested that keratinocytes could be the primary transduction pathway, using signal transduction cascade mechanisms such as intracellular Ca^{2+} fluxes to evoke a response in adjacent C-fibers. Putative keratinocyte–neuron interactions, intermediate molecules and 2nd messenger cascades have been proposed and await validation (Lumpkin and Caterina, 2007).

A tonal balance in terms of mechanotransduction is achieved via several interconnected mechanisms, e.g., modulation of growth factors and receptors; 2nd messenger signalling pathways; interaction with cytoskeletal elements; alteration of nerve firing thresholds following presentation of the stimulus and consequent perceptual processing (e.g. the increase in touch sensitivity and hyperalgesia following inflammation reactions such as sunburn). Without this intricate level of control the sensory system would be swamped with redundant signals, or worse, would fail to recognise noxious and threatening stimuli and would thus fail to act to remove, neutralise or repair the threat. This ensures that at all times an appropriate response is mounted by the organism, whether it be in response to touch, temperature, pain or pleasure.

3. The central projections

The submodalties of skin sensory receptors and nerves that convey information to the brain about mechanical, thermal, and painful/pruritic stimulation of the skin are grouped into three different pathways in the spinal cord and project to different target areas in the brain. They differ in their receptors, pathways, and targets, and also in the level of decussation (crossing over) within the CNS. Most sensory systems *en route* to the cerebral cortex decussate at some point, as projections are mapped contralaterally, e.g., the discriminative touch system crosses in the medulla, where the spinal cord joins the brain, while the affective pain system crosses at the point of entry into the spinal cord.

3.1. Spinal cord

All the primary sensory neurons described above have their cell bodies situated outside the spinal cord in the dorsal root ganglion, with there being one ganglion for every spinal nerve. Unlike most neurons the nerve signal does not pass through the cell body of a sensory neuron: with the cell body sitting off to one side the signal passes directly from the distal axon process to the proximal process, which enters the dorsal half of the spinal cord.

Tactile primary afferents, or first order neurons, immediately turn up the spinal cord towards the brain, ascending in the dorsal white matter and forming the dorsal columns. In a cross-section of the spinal cord, at cervical levels, two separate tracts can be seen: the midline tracts comprise the gracile fasciculus conveying information from the lower half of the body (legs and trunk), and the outer tracts comprise the cuneate fasciculus conveying information from the upper half of the body (arms and trunk). Primary tactile afferents make their first synapse with second order neurons at the medulla where fibers from each tract synapse in a nucleus of the same name: the gracile fasciculus axons synapse in the gracile nucleus, and the cuneate axons synapse in the cuneate nucleus. The neurons receiving the synapse provide the secondary afferents and cross the midline immediately to form a tract on the contralateral side of the brainstem – the medial lemniscus – which ascends through the brainstem to the next relay station in the midbrain, specifically, in the thalamus.

As with the tactile system, pain and thermal primary afferents synapse ipsilaterally and the secondary afferents cross, but the crossings occur at different levels. Pain and temperature afferents enter the dorsal horn of the spine and synapse within one or two segments, forming Lissauer's tract. The dorsal horn is a radially laminar structure, the thin outermost layer is the posterior marginalis layer, the second layer the substantia gelatinosa, and the layer medial to that, the nucleus proprius. The two types of pain fibers, C and Aδ, enter different layers of the dorsal horn. Aδ fibers enter the posterior marginalis and the nucleus proprius, and synapse on a second set of neurons which are the secondary afferents which relay the signal to the thalamus. The secondary afferents from both layers cross to the opposite side of the spinal cord and ascend in the spinothalamic tract. C-fibers enter the substantia gelatinosa and synapse on interneurons—neurons which do not project out of the immediate area, but relay to secondary afferents in either the posterior marginalis, or the nucleus proprius. The spinothalamic tract ascends the entire length of the spinal cord and the entire brainstem, and on reaching the midbrain is continuous with the medial lemniscus. These tracts enter the thalamus together.

It is important to note that although the bulk of afferent input adheres to the plan outlined above a degree of mixing occurs between the tracts, for example, with some light touch information traveling in the spinothalamic tract, with the result that damage to the dorsal columns does not completely remove touch and pressure sensation. Some proprioceptive information also travels in the dorsal columns, and follows the medial lemniscus to the cortex providing conscious awareness of body position and movement. The pain and temperature system also has multiple targets in the brainstem and other areas.

Having now covered the basic anatomy of the part of the somatosensory system that serves the trunk and limbs, the peripheral and central anatomy/neurophysiology of facial skin will be briefly summarised here, as there are gross similarities in its innervation. The trigeminal (Vth) nerve innervates all facial skin structures (including the oral mucosa) and, as with the spinal afferents, these neurones have their cell bodies outside of the CNS in the trigeminal ganglion, with their proximal processes entering the brainstem. As in the spinal cord, the four modalities of touch, temperature, pain and itch have different receptors in the facial skin, travel along different tracts, and have different targets in the brainstem—the trigeminal nuclei extending from the midbrain to the medulla. The large diameter (Aβ) fibers enter directly into the main sensory nucleus of the trigeminal nuclei and as with the somatosensory neurons of the body, synapse and then decussate, with the secondary afferents joining the medial lemniscus as it projects to the thalamus. The small diameter fibers conveying pain and temperature enter the midbrain with the main Vth cranial nerve, but then descend through the brainstem to the caudal medulla where they synapse and cross the midline. These descending axons form a tract, the spinal tract of V, and synapse in the spinal nucleus of V, so-called because it reaches as far down as the upper cervical spinal cord, comprising three regions along its length: the subnucleus oralis, the subnucleus interpolaris, and the subnucleus caudalis. The secondary afferents from the subnucleus caudalis cross to the opposite side and join the spinothalamic tract where somatosensory information from the face joins that from the body, entering the thalamus in a separate nucleus, the ventroposterior medial nucleus (VPM).

In summary of this section, somatosensory paths are located in the dorsal columns and spinothalamic tracts, with axons in the former transmitting tactile, pressure, vibration and proprioception impulses, and in the latter pain and temperature. Which pathway CT-afferents travel in is not yet known, but low-threshold tactile inputs to spinothalamic projection cells have been documented (Applebaum et al., 1975), lending credence to reports of subtle, contralateral deficits of touch detection in human patients following destruction of these pathways after chordotomy procedures (White and Sweet, 1969). As will be seen in the next section, we have better knowledge of the cortical projections of CT-afferents.

3.2. Brain

Although we are only considering the peripheral to central pathways of the somatosensory system, the thalamus, often called the 'gateway' to the cerebral cortex, also acts as a relay structure for all other senses—even those from the archaic sense of smell pass through this structure (Herrrero et al., 2002). It should be noted, however, that the thalamus is not simply a 'relay' structure: it plays a major integrative role prior to projecting to the overlying primary sensory cortices. Its sensory inputs are both discriminative and affective, and, the thalamus is critical in adjusting affective scale, as is evidenced by lesions of this structure causing chronic pain for example (Jones, 2002).

The third order thalamocortical afferents (from thalamus to cortex) travel up through the internal capsule to reach the primary somatosensory cortex, located in the post-central gyrus, a fold of cortex just posterior to the central sulcus (Fig. 5A).

The thalamocortical afferents convey all of the signals, whether from VPL or VPM, to primary somatosensory cortex where sensory information from all contralateral body surfaces is mapped in a somatotopic (body-mapped) manner (Penfield and Rasmussen, 1952; Maldjian et al., 1999), with the legs represented medially, at the top of the head, and the face represented laterally (Fig. 5B). Within the cortex there are up to eight separate areas primarily subserving somatosensation. Primary somatosensory cortex. SI, comprising four sub-regions (2, 1, 3a and 3b), secondary somatosensory cortex, SII, located along the superior bank of the lateral sulcus (Woolsey, 1946; Maeda et al., 1999; Coghill et al., 1994; Francis et al., 2000; McGlone et al., 2002), the insular cortex (Schneider et al., 1993), and the posterior parietal cortex, areas 5 and 7b (Fig. 6). The secondary somatosensory cortex receives input primarily from SI and in turn projects to the somatic sensory fields in the insular region. Olausson et al. (2002) have also shown that CT-afferents project to the dorsal posterior part of the insular, presumably bypassing SI, since patients with no Aβ afferents demonstrate a lack of activation to brush stroking of hairy skin in this region (see Olausson et al., in this special issue). In addition to the primary and secondary somatosensory cortices, the posterior parietal lobe also receives somatic inputs. This region is a higher order sensory cortex, similar in function to an association cortex, it relates sensory and motor processing and is concerned with integrating the different somatic sensory modalities necessary for perception.

As with studies of the peripheral nervous system, outlined above, the technique of microneurography has again been used in somatosensory research, in this case to study the relationship between skin sensory nerves and their central projections, as evidenced by the use of concurrent functional magnetic resonance imaging (fMRI). Microstimulation of individual LTM afferents, projecting to RFs on the digit, produces robust, focal and orderly (somatotopic) haemodynamic (BOLD) responses in both primary and secondary somatosensory cortices (Trulsson et al., 2000)—in accordance with the findings of Penfield and Boldrey (1937). It is expected that this technique will permit the study of many different topics in somatosensory neurophysiology, such as sampling from FA and SA mechanoreceptors and C-fibers with neighboring or overlapping RFs on the skin, and quantifying their spatial and temporal profiles in response to electrical chemical and/or mechanical stimulation of the skin areas they innervate, as well as perceptual responses to microstimulation.

Finally, the forward projections from these primary somatosensory areas to limbic and prefrontal structures have been studied with fMRI and PET in order to understand the affective representations of skin stimulation for both pain and pleasure. Evidence for the representation of pleasant touch in the brain has been provided by Francis et al. (1999). They showed that the

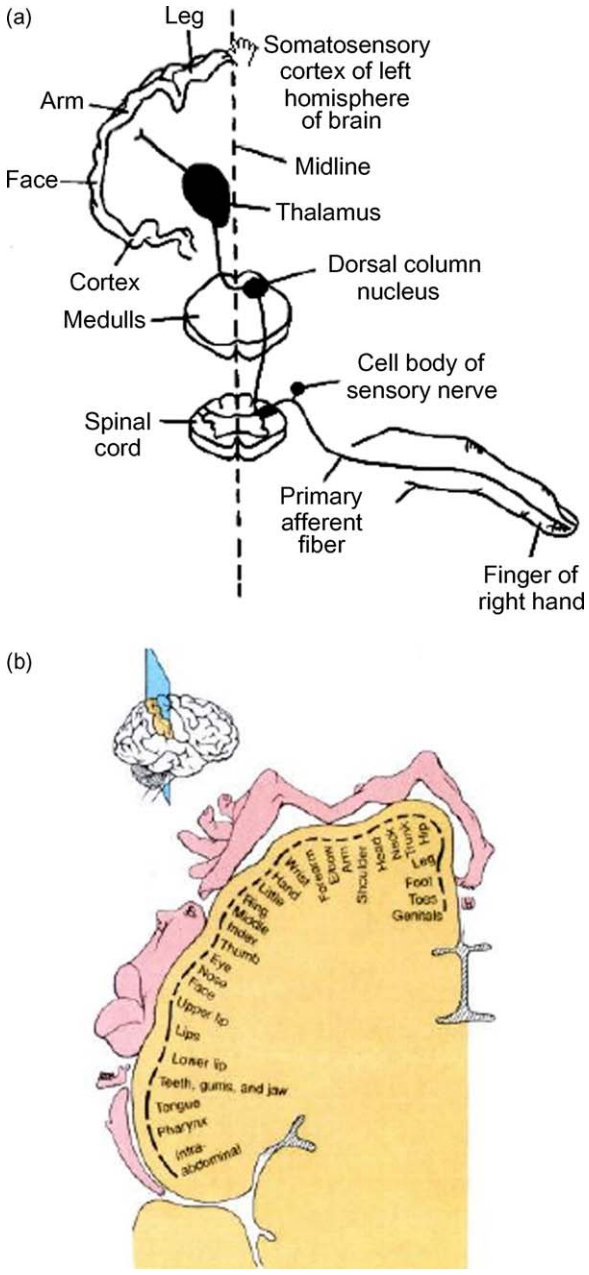

Fig. 5. (A) Outline of the somatosensory pathways from the digit tip to primary somatosensory cortex, via the dorsal column nuclei and the thalamus. (B) Penfield's (Jasper and Penfield, 1954) somatosensory homunculus. Note the relative overrepresentation of the hands and lips, and the relative under-representation of the trunk and arms.

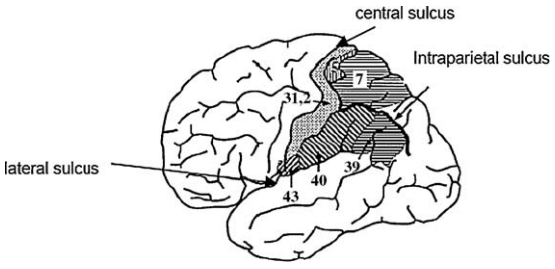

Fig. 6. Cortical areas subserving somatosensation. Primary somatosensory cortex (SI) is located in the posterior bank of the central sulcus and the posterior gyrus and comprises Brodmann Areas 2, 1, 3a and 3b. Secondary somatosensory cortex (SII) is located in the upper bank of the lateral sulcus and comprises Brodmann Areas 43 with two further somatosensory regions in the posterior parietal cortex, Brodmann Areas 5 and 7b.

discriminative and affective aspects of touch are processed in different brain areas, by stroking the body with either a wooden dowel or a piece of velvet. Activation of primary somatosensory cortex was found to be greater to the wood stimulus, whereas the orbitofrontal cortex (an area of the frontal lobes involved in emotion) was activated more by the velvet stimulus. This area has also been shown to represent painful as well as pleasant touch, demonstrating the relevance of this brain region for representing the emotional dimensions of skin sensitivity—the positive and the negative (Rolls et al., 2003).

4. Conclusion

This overview of the cutaneous senses provides a landscape view of the system's structure and function, with the following review papers in this Special Issue highlighting specific aspects and properties of the skin senses and their roles in sensation, affect and cognition. Cutaneous sensitivity is central to human functional, emotional and social life, as is evidenced by it being the most developed sensory modality at birth, contributing to brain and cognitive development throughout infancy and childhood (Stack, 2001; Hertenstein, 2002), and continuing to play a vital role into old age. That the skin senses can serve both a discriminative as well as affective role is well known from our understanding of pain. The different conduction speeds with which tissue-damaging cutaneous sensations are conveyed to the CNS, by myelinated (Aδ) and unmyleninated (C) fibers, leads to the distinction of 1st and 2nd pain, with the former having a discriminative quality and the latter an emotional one. Here we have suggested a similar dualism for touch with discriminative touch being conveyed by myelinated Aβ afferents, and emotional touch by CT-afferents leading to the description of 1st and 2nd touch.

The results of anatomical, psychophysical, behavioural, neurophysiological and neuroimaging studies have shown that separate information processing channels, each with its own neurobiological mechanism exist for the perception of tactile, thermal, pruritic and painful stimuli. Evidence is also presented here (and elsewhere in this Special Issue) for a specific 'fifth' channel, coding for the perception of the rewarding aspects of touch. However, fundamental questions remain concerning the nature of how these channels, with their individual properties, operate together in the perception of the various stimuli naturally encountered by the skin. Co-activation of channels is the norm: mechanical stimuli also activate thermal channels, scratching reduces itch while rubbing reduces pain, and with all forms of affective and affiliative touch there is co-activation of mechanosensitive A-fibers as well as, in hairy skin, mechanosensitive CT fibers. An adequate test of the hypothesis that the perception of any complex cutaneous stimulus involves the interaction of individual channels requires that we fully understand the characteristics of each channel, and determine the mechanisms by which they interact. Evidence for such interactions driving the perception of complex skin sensations comes from the early work of Bentley (1900), who showed that the "touch blend" of pressure and coldness leads to an emergent perceptual experience of wetness. The more recent discovery of linear summation of perceived magnitudes from different mechanosenstive channels provides further partial confirmation of the hypothesis (Gescheider et al., 2003), but there are many other possible ways in which these and the other channels outlined in this paper could interact that must be investigated before the hypothesis becomes a general principle of cutaneous sensory information processing.

The musical analogy of a piano keyboard can best describe the distinctions between activation of single channels, and co-activation of a number of channels. Stimulation of a single SAI channel (note on the keyboard) for example, such as occurs with intra-neural microstimulation, leads to a distinct sensation of pressure emanating from the RF of the unit. We know from the work of Bentley (1900) that if a cold sensing unit were also able to be co-activated (playing a second note on the keyboard), then a 'chord' is struck, perceptually, that relates to neither of the specific channel's coding properties (pressure and temperature), but generates the percept of wetness. The richness of perceived bodily sensations (far more than a channel specific view would serve) is dependent upon the diversity of the many channels of cutaneous sensory input to the CNS, as well as to the integrative properties of the various stages at which these inputs are processed, from the dorsal horn to the sensory awareness stages in SI/SII, to the affective representation in insula and orbitofrontal cortices. It has been recognised for some time that the mind can affect the skin (O'Donovan, 1927; Stokes and Beerman, 1940; Arck et al., 2006), we are now recognising that the skin can affect the mind ….

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