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RUNNING TITLE: AFFECTIVE TOUCH

Somatosensory pleasure circuit: from skin to brain and back

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Abstract

The skin senses serve a discriminative function, allowing us to manipulate objects and detect touch and temperature, and an affective/emotional function, manifested as itch or pain when the skin is damaged. Two different classes of nerve fibre mediate these dissociable aspects of cutaneous somatosensation; i) myelinated A-beta and A-delta afferents that provide rapid information about the location and physical characteristics of skin contact, and ii) unmyelinated, slow conducting C-fibre afferents that are typically associated with coding the emotional properties of pain and itch. However, recent research has identified a third class of C-fibre afferents that code for the pleasurable properties of touch – c-tactile afferents or CTs. Clinical application of treatments that target pleasant, CT mediated-touch (such as massage therapy) could, in the future, provide a complementary, non-pharmacological means of treating both the physical and psychological aspects of chronic skin conditions such as itch and eczema.

Key words: c-tactile fibres, itch, massage therapy, pain, pleasant touch

Introduction

Touching the skin can be a powerful means of modulating human emotion. An emotional response to tactile stimulation (so-called 'affective touch') can increase quality of life and form part of social and affiliative behaviours in humans and other mammals. It also plays a critical role in physical and cognitive development (1,2). Pleasant touch decreases stress in pre-operative situations (3) and nursing-home staff have found increases in eating behaviour associated with increased tactile contact (4). Although there is evidence for the benefits of pleasant touch on mood, health and well-being it might also be the case that it plays a neuro-modulatory role in the peripheral nervous system, in particular the transmission of itch and pain signals to the central nervous system. In this

Viewpoint article we will i) outline the neurophysiological mechanisms that mediate affective touch, including its overlap with the c-fibre afferent nerves mediating itch and pain; ii) provide an overview of affective touch, with evidence for the clinical application of treatments, and iii) propose how this new understanding of a c-fibre system, that is distinct from the more well recognised itch and pain c-fibre channels, may play a critical modulatory role on itch and pain channels.

Neurophysiological systems mediating affective touch: the role of CT-afferents

Light touch sensitive c-fibres (also known as c-low threshold mechanosensitive nerves – CLTM) were first discovered in rodents in 1939 by Zotterman (5). The recent discovery of a similar class of unmyelinated mechanosensitive nerve fibres innervating human skin, called c-tactile afferents (CTs), that respond optimally to gentle stroking touch (6,7, 8) raises the intriguing possibility that this, as yet not fully characterised system of nerves, may well interact with the more well-known functional properties of itch and pain nerves (also c-fibres). Recent evidence shows that this is the case, at least for pain (9-11), whilst Seal et al (12) have proposed that inflammation or trauma may change the sensation conveyed by CTs from gentle touch to pain. CTs are a separate class to those sensing pain and itch and are hypothesised to provide the neurobiological substrate for affiliative or affective touch (9,13). Microneurography studies show that the preferred stimulus for CTs is slow and gentle stroking across their receptive field at ~5cm/s and that this same stroking velocity leads to the highest pleasantness ratings during psychophysical studies (7,14). It is of interest here that CTs have not been found in glabrous skin. They project to limbic cortex including orbitofrontal cortex (OFC) and posterior insula (15,16), supporting their function in conveying the affiliative (rewarding) aspects of gentle touch (the 'affective touch hypothesis'; 9,17) and promoting emotional, hormonal and behavioural responses during intra- and interactive tactile behaviour such as nurturing and grooming (18).

Genetic visualisation studies in mice have identified CLTMs that also detect massage-like stroking of hairy skin *in vivo* (19). The functional characterisation of these neurons in humans opens the way to identifying the molecular transduction mechanisms and higher-order circuitry that are engaged to produce a positive affective state (20).

Behavioural and neuroimaging studies investigating affective touch

Myelinated A-beta and A-delta afferents provide rapid information about the location of skin contact and a variety of stimulus parameters have been investigated for the discriminative property of touch (including velocity, indenting force, texture, and threshold detection of light touch and vibration; 21). However, the quantitative assessment of affective touch has been relatively understudied (14). It has been known for well over 100 years that materials that are soft/smooth are rated as pleasant and those that are stiff/rough as unpleasant (22). More recently, Essick et al (23) demonstrated that valid and reliable un/pleasantness ratings could be made of different textures (velvet, cotton, plastic mesh) using a computer-controlled tactile stimulation device (the Rotary Tactile Stimulator or RTS; see Fig. 1).

Unsurprisingly, velvet and cotton produced higher pleasantness ratings than mesh, with light force velocities at ~5cm/sec perceived as more pleasant than faster or slower ones (24). Furthermore, pleasant stimuli moved over hairy skin had higher ratings than the same stimulus moved over glabrous skin (consistent with CTs only being present in hairy skin). The affective response to the same stimulus also varied for different body sites, with facial sites having the strongest affective response. Further studies confirmed the heterogeneity of ratings of pleasant touch, which is inferred to correlate with the innervation density of CTs to these body sites.

To gain better insight into the phenomenological perceptual experiences of pleasant touch Guest et al (25) used a qualitative approach to develop a touch lexicon i.e., a comprehensive language to describe the experience of touch (based on the same method used for the McGill Pain Questionnaire; 26). The results showed that the tactile emotional response was made up of 'pleasure, arousal and dominance' and that these traits have also been identified in other literature and seem to be universal terms relating generally to 'comfort'. They also found increased intensities of sensory and emotional responses were reported when participants passively vs. actively received stimuli, consistent with sensory attenuation (as suggested by the forward-modelling hypothesis; 27), with increased emotional (comfort and arousal) scores reported at the forearm vs. the finger pad (again, consistent with activation of CTs).

Other studies (28) have shown activation of pregenual ACC (pgACC; rostral division) in addition to OFC to pleasant touch, and this region has also been shown to be modulated by the cognitive component of a stimulus by using word labels to indicate pleasantness/richness of a cream applied to the skin (29). Outside of prefrontal cortex, posterior insula activity (driven by CT input) has been shown to respond preferentially to affective touch related to nurturing and grooming (15,30), providing further evidence for a pleasant touch brain matrix.

Types of pleasurable touch: Interpersonal touch

The beneficial effects of interpersonal touch on health and well-being have been known for thousands of years (see Hippocrates 460-377 B.C; 31). Skin-to-skin contact between individuals is often highly pleasurable, conveying important social and affiliative signals in humans and other primates (18,32-34). Interpersonal touch is also critical in physical and cognitive development (1) as demonstrated by the controversial studies of Harlow (35) where an infant monkey reared in captivity

chose the warm/soft surrogate that did not deliver food over the cold/wire framed surrogate that did.

At the receptor level during 'self-touch' the touching and touched body site both convey sensory information to the toucher's brain where an efference copy mechanism (an internal copy of the sensation of movement) predicts the outcome of self-touch and attenuates its sensory consequences – hence, why we cannot tickle ourselves (36). This is in contrast to 'other touch' where only a single body site conveys sensory information. Therefore, the magnitude of sensation should decrease for self-touch, but does pleasantness? Guest et al (33) measured the sensory and affective judgements of skin during inter- (i.e., skin of another individual) vs. intra- (i.e., one's own skin) personal touch. Participants rated their own skin (palm and volar forearm) and another's on four perceptual dimensions: smoothness, softness, stickiness and affectiveness. Ratings of 'own skin' were less pleasant than 'other skin' suggesting that individuals are likely to rate another person's skin as more pleasant than their own during brief interpersonal encounters (e.g., hand shake/caress), not based on the physical structure of the skin. Affective touch is therefore more important for the recipient of another's touch and a mechanism of learned/innate preference to touch. Affective touch perception can also differ between cultures. A large study in different populations demonstrated that Germans and Italians scored significantly higher on the subscale pleasure in parental touching than Syrian and French subjects (37).

Types of pleasurable touch: Grooming

Grooming is hugely important to humans and primates. Self-grooming is mainly for hygienic reasons, whilst social grooming (allogrooming) leads to social bonding in primates (38). Although humans allogroom much less (de-emphasising the role of touch in favour of language-based communication; 39) social touch still plays an important role in everyday affective human

relationships (i.e., patting, petting and cuddling), which help to form intimate relationships. In primates, social grooming, which is more like traditional Swedish massage, can become so affective and relaxing that it leads to sleep, reduced stress and heart rate (40). The exact neurological processes are unknown, although it is known that grooming releases β-endorphins, which have a role in pain control and itch (41). Similarly, oxytocin is released during non-sexual physical affection i.e., back-rubbing and hugs (42), and massage-like stroking (43), lowering blood pressure and relieving stress and may play a similar role to β-endorphins, but with a shorter effect.

Types of pleasurable touch: Massage

Massage is a general term for pressing, rubbing and manipulating the skin, muscles, tendons and ligaments. Hippocrates (cited in 44) was a renowned advocate of massage and wrote about the use of friction in the treatment of many ailments. Today, massage therapy is a billion dollar industry in North America with 8% (> 4 million) of the population using this on a yearly basis (45). Studies of the benefits of massage demonstrate that it is an effective adjunct treatment for chronic pain and distress, including depression and anxiety (46-50). However, reported benefits on immune system function in cancer pain are mixed (51). Touch massage (also called tactile, gentle or soft massage) consists of long stroking movements over the skin (not stimulating the muscles like Swedish massage) - precisely the preferred stimulus for CTs.

Previous studies using EEG have shown that depressed adolescents who received 15 minutes of massage had a reduction in right frontal activation – an area associated with negative affect and withdrawal tendencies (52). Using fMRI, Lindgren et al (53) scanned participants under 4 conditions – human touch with/without movement and touch with a rubber glove (with or without movement). Human touch with movement was perceived as most affective, activating the pgACC –a sensory reward processing area. This brain region is also activated in response to opioid analgesia and,

interestingly, to placebo interventions (54,55). Stroking movements of the forearm with the human hand or the rubber glove also strongly engaged bilateral insula (consistent with this being a target area for CTs). Observations such as these may well have implications for understanding the role of human touch in clinical settings such as touch-massage treatment of pain, pruritus, stress and anxiety (56-58) and although the underlying mechanisms of action are unknown, CTs may be involved in driving these effects.

Types of pleasurable touch: the relief of itch by scratching?

The relief that is felt by scratching a troublesome itch can be a rewarding and deeply pleasurable experience, yet in chronic skin conditions it can also cause significant pain and distress. Scratching activates mechanically sensitive polymodal C and Aδ fibres, which likely inhibit itch through a central mechanism (59), with recent evidence showing that scratching inhibits histamine-induced primate spinothalamic tract activity (60). The spinothalamic tract conveys itch, pain and temperature information (61), and in all probability CT input as well, implicating the dorsal horn/spinal cord as a critical site for scratch-evoked suppression of itch (see Fig 2). However, the relationship between scratch-evoked suppression of itch and the pleasurable relief felt is highly context-dependent and mediated by where on the body itch is felt. In a recent study (62), the forearm, ankle and back were treated with cowhage spicules, which were then passively scratched by an investigator using a cytology brush. The intensity of itch (with or without scratching) was measured every 30 seconds using visual analogue scales. The results showed that itch intensity and scratching pleasure both increased on the ankle and back more than the forearm, but scratching attenuated itch most effectively on the back, an area where pleasant touch is highly rated.

The observation that scratching is painful and scratching an itch is rewarding is likely also to be a context sensitive phenomenon with a key role of nociceptive input being processed

differentially in each case [59,60]. For example, there is evidence from fMRI studies that repetitive scratching in the *absence* of a pruritic stimulus induces robust bilateral activation of the secondary somatosensory cortex, insula cortex, prefrontal cortex, inferior parietal lobe, and cerebellum [63,64], whilst scratching in the *presence* of a pruritic stimulus activated the putamen, part of the brain's reward system [64]. A further fMRI study has since explicitly measured the degree of pleasantness evoked by scratching, which activated not only the reward system but also key regions of perception (i.e., the primary somatosensory cortex) and awareness of subjective feelings (i.e., the insular cortex), indicating a broad network involved in scratching-induced pleasantness [65]. Moreover, although itch was suppressed by scratching, motor-related regions showed significant activation when pleasantness was evoked and could explain why scratching-induced pleasantness potentially reinforces scratching behaviours.

Interestingly, several studies have shown that the head and face may be most susceptible to contagious scratching (i.e., scratching oneself when viewing another scratching) regardless of which body part is actually being viewed (66-69). Furthermore, patients with chronic itch are more susceptible to these visual cues. This suggests that central top-down mechanisms are involved in the control of acute as well as chronic itch, as well as the bottom-up mechanisms described above (70). For example, a recent fMRI study that imaged self-scratching of an itch vs. other-scratching found that brain responses evoked by self-scratching activated multiple structures known to process 'reward' (71). The responses in most of these areas were correlated with the pleasure of scratching, while other areas were associated with itch relief. In contrast, only limited parts of these circuits were stimulated by other-scratching, suggesting that itch relief and pleasure are not identical processes. The activation in brain areas with abundant dopaminergic activity suggests a role for central dopaminergic pathways in the rewarding, addictive behaviour of the itch-scratch cycle.

Conclusions and clinical perspectives

The evidence reviewed here shows that affective touch is a powerful means of modulating peripheral body sensations. The overlap with c-fibre systems mediating itch and pain means it could one day be used as counter-stimulation therapy for chronic pain or itch-related disorders (72). Indeed, massage therapy has already been used for skin conditions in young children (73), and was shown to decrease stress and improve clinical condition for burns and atopic dermatitis. Self-touch has also been used in other clinical conditions to reinstate body representation after stroke (74). In the future it will be useful to explore whether massage therapy or other forms of affective self-touch (using the hands or soft, pleasant feeling materials) can improve the symptoms or acceptance of a range of chronic skin conditions.

Open questions

- Could rewarding self-grooming be used to alleviate the symptoms of itch or skin disease mediated via CT pathways?
- Could self/social grooming be used to decrease the stress of skin disease (with positive effects on physiological and psychological well-being) through release of β-endorphins or oxytocin?
- Could affective touch therapy be used to regulate itch and modulate prefrontal-insula connectivity of the brain?
- Is pleasant touch, sensed by low-threshold C-fibre mechanoreceptors, not realised or gated when one touches his/her own skin?
- What neurobiological mechanism turns an unpleasant scratch to non-itching skin into sublime pleasure when that same skin site itches?

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FIGURE LEGENDS

Fig 1. In the experiment, a rotary tactile stimulator (RTS) was used to control how the materials brush across the skin while a participant entered in their “pleasantness rating” of that material on a scale of 100% unpleasant to 100% pleasant. “Pleasantness” of contact was noted as affective touch, or touch that evoked a positive emotional response to tactile stimulation. A curtain (not shown) is positioned between the RTS and participant to block sight of the stimulation.

Fig 2. Model depicting the 3 types of C-nerve fibres and the cross talk between them. Massage activates hedonoceptive (CT) nerve fibres. Scratching excites ascending nociceptive and possibly also hedonoceptive neurons projecting to supra-spinal structures that directly or indirectly connect with descending modulatory pathways that are proposed to excite spinal glycinergic/GABAergic inhibitory interneurons that inhibit itch C-fibres. Identifying the supra-spinal structures involved in descending inhibition of itch-signalling spinal neurons is of major interest.