

The role of the human C-tactile system in affective somatosensation and pain

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This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Ackerley R*, Backlund Wasling H*, **Liljencrantz J**, Olausson H, Johnson R D, Wessberg J. Human C-Tactile Afferents Are Tuned to the Temperature of a Skin-Stroking Caress. *R.A. and H.B.W. contributed equally to this work.
Accepted for publication in The Journal of Neuroscience
- II. **Liljencrantz J**, Björnsdotter M, Morrison I, Bergstrand S, Ceko M, Seminowicz D A, Cole J, Bushnell M C, Olausson H. Altered C-tactile processing in human dynamic tactile allodynia. *PAIN. 2013 Feb;154(2):227-34.*
- III. **Liljencrantz J**, Marshall A, Ackerley R, Olausson H. Discriminative and affective touch in human experimental tactile allodynia.
Accepted for publication in Neuroscience Letters
- IV. **Liljencrantz J**, Strigo I, Ellingsen D M, Krämer H H, Lundblad L, Leknes S, Olausson H. Pleasant touch modulates heat pain perception in humans.
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UNIVERSITY OF GOTHENBURG

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ABSTRACT

Affective touch perception in humans is a complex construct of input from mechanoreceptive afferents, current homeostatic state and contextual factors. Previously, a relationship has been identified between the pleasantness perception of soft skin stroking and the firing rate of unmyelinated C-low-threshold mechanoreceptive afferents (C-LTMRs) known as C-tactile (CT) afferents in humans. This relationship is not seen for myelinated A β -LTMRs. The work in this thesis continued the basic characterization of CT response properties to pleasant touch by adding a thermal component to the stimulus. Using the electrophysiological technique of microneurography in combination with psychophysical testing we found a significant relationship between the hedonic evaluation of slow skin stroking stimuli and CT responses only for stimuli of skin-like temperature (i.e. not cooler or warmer temperatures), (**Paper I**). This finding supports the role of CT afferents in pleasant touch, particularly relating to skin-to-skin contact between individuals and thus emphasizes the significance of CTs in signaling affective, interpersonal touch.

In patients with reduced density of thinly myelinated and unmyelinated afferent nerve fibers (hereditary sensory and autonomic neuropathy type V), gentle skin stroking (CT targeted touch) is perceived as less pleasant, even unpleasant. In addition, research in mice suggests a role for CTs in tactile allodynia. Here, in humans, we investigated the role of CTs in A β denervated patients and found no experimental tactile allodynia but a reduced C-touch sensation. These psychophysical findings were confirmed by fMRI data, comparing stroking in the allodynic to a control zone, and showed altered processing in the posterior insular cortex (primary cortical receiving area for CTs) and reduced processing in medial prefrontal cortices (part of the hedonic network encoding C-touch). In neurologically intact subjects we found a greater drop in touch pleasantness for CT optimal compared to suboptimal (A β targeted) stimuli in the allodynic area but we did not find stimulus related differences in touch evoked pain. Thus, we conform to the canonical view of A β afferents mediating allodynic pain. We conclude that CT processing is altered but find no evidence for CTs signaling experimental tactile allodynia, (**Papers II and III**).

Other animal work has suggested that C-LTMRs exert a spinal inhibition on nociceptive signaling. Furthermore, C-LTMRs may release a protein with analgesic effects when activated and pharmacogenetic activation of C-LTMRs has positively reinforcing and anxiolytic behavioral effects. Here, we demonstrated a robust psychophysical reduction in experimental heat pain following CT targeted touch suggesting that activation of the CT system modulates pain perception also in humans (**Paper IV**).

In conclusion, the contribution of CTs to experimental tactile allodynia seems to be a reduced CT mediated hedonic processing and possibly also a loss of their pain inhibitory role. Thus, restoring normal CT function could be considered when investigating novel therapeutic strategies for neuropathic pain.

Keywords: touch, hairy skin, CT-afferents, microneurography, temperature, heat pain, experimental tactile allodynia, psychophysics, functional magnetic resonance imaging

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