SMALL DIAMETER CUTANEOUS AFFERENT STIMULATION AND ITS EFFECT ON BEHAVIOR IN HUMANS

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IRENE PERINI

Faculty opponent:
Professor Martin P. Paulus
Department of Psychiatry
University of California San Diego

This thesis is based on the following studies:

I. Perini I, Bergstrand S, Morrison I. Where pain meets action in the human brain.
In press, Journal of Neuroscience

II. Perini I, Ceko M, Olausson H, Minde J, Morrison I. Effects of a human nerve growth factor beta (NGFB) mutation on cerebral structure and function in pain.
Manuscript

III. Morrison I, Löken L, Minde J, Wessberg J, Perini I, Nennesmo I, Olausson H. Reduced C-afferent fibre density affects perceived pleasantness and empathy for touch.
Brain 2011: 134; 1116–1126.

IV. Perini I, Olausson H, Morrison I. The relationship of pleasant touch pathways to reward processing: an fMRI study.
Manuscript

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Irene Perini
Department of Clinical Neurophysiology, Institute of Neuroscience and Physiology, University of Gothenburg, Sweden.

Abstract
Sensation and behavior are linked dimensions in human lives. Experiencing a gentle caress from a loved one is very different than getting our hand burnt on a hot stove. However both those stimuli are signaled in small diameter cutaneous afferents and have an inherent affective valence that modulates our actions. Pain is transmitted by thinly myelinated A∂ fibers and unmyelinated C fibers, and affective touch is mediated by unmyelinated C-Tactile mechanoreceptors (CT). Both critical for survival, pain and pleasure sit on opposite ends, with pain serving avoidance and pleasure eliciting approach motivation. This thesis investigates the impact of painful and pleasant stimuli on our behavior and the brain mechanisms involved in these processes. Our research population includes healthy subjects and a group of carriers with a rare hereditary sensory and autonomic neuropathy type V (HSAN-V), causing a selective loss of small diameter afferents. In **Paper I** we addressed whether in healthy subjects part of the activation during pain can be accounted for motor processing, supporting the idea of a central multidimensionality of pain. Areas including the cingulate, motor cortex, thalamus and cerebellum serve a motoric role during pain. In **Paper II** we focused our attention on the perception and reaction to thermal pain in a group of HSAN-V patients. Using the same design as in Paper I, we addressed the effects of lower density of small diameter cutaneous fibers on the experience of pain. The patients showed difficulties in recognizing and reacting to pain suggesting that their peripheral fiber loss resulted in unreliable and less adaptive responses to acute pain. In **Paper III** we addressed the patients' ability to appreciate affective touch, conveyed by CT fibers. The critical characteristic of CT fibers is their velocity dependent response pattern for stroking stimuli, with higher firing for intermediate speeds (~3 cm s^{-1}) compared to very fast or very slow ones. This firing pattern matches linearly with the touch pleasantness ratings in healthy subjects. The patients did not show the same pleasantness ratings pattern across velocities suggesting an alternative route for affective touch processing. In **Paper IV** we investigated the relationship of CT fibers to the reward system in the brain by creating a feedback-based task in which healthy subjects could decide to receive the stimulation they preferred the most. CT optimal speeds were the most preferred and elicited activation in reward related areas like the caudate, insula and prefrontal cortex. In conclusion, this thesis provides an understanding of the cerebral and behavioral mechanisms underlying the experience of painful and pleasant somatosensory stimuli in healthy individuals and following thin fiber neuropathy.

Keywords: *pain, cingulate, action, fMRI, touch, hairy skin, reward, NGFB mutation.*

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