THIN-FIBRE SIGNALLING IN HUMANS
CORTICAL PROCESSING OF SENSORY AFFERENCE AND AUTONOMIC EFFERENCE

Dissertation for degree Doctor of Philosophy (Medicine) at the Sahlgrenska Academy, the University of Gothenburg, to be publicly examined in lecture hall Arvid Carlsson, Friday, December 11, 2009 at 13.00

by

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This thesis is based on the following papers, which are referred to in the text by their roman numerals:

I **Unmyelinated tactile afferents have opposite effects on insular and somatosensory cortical processing.**
Olausson HW, Cole J, Vallbo A, McGlone F, ElamM, Krämer HH, Rylander K, Wessberg J, Bushnell MC.
Neuroscience Letters 2008 May 9;436(2):128-32.

II **Cortical processing of tactile C-fibre stimulation**
Rylander K, Elam M, Olausson H
Manuscript

III **Functional role of unmyelinated tactile afferents in human hairy skin: sympathetic response and perceptual localization.**
Olausson H, Cole J, Rylander K, McGlone F, Lamarre Y, Wallin BG, Krämer H, Wessberg J, Elam M, Bushnell MC, Vallbo A.
Experimental Brain Research 2008 Jan;184(1):135-40.

IV **Central nervous control of cutaneous sympathetic responses: disentangling afferent and efferent processing of mild rectal distension.**
Rylander K, Posserud I, Simrén M, Olausson H, Elam M
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Cortical processing of sensory afference and autonomic efference

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Abstract
Thin nerve fibres innervate the entire human body and mediate sensations such as pain, temperature and visceral sensory input. Moreover, a special class of unmyelinated afferents responsive to light touch has recently been found in humans: C-tactile (CT) fibres. In the efferent side, C-fibres are the path for signalling in the autonomic nervous system, controlling the internal milieu of the body. There is growing evidence that C-fibres form the basis for monitoring and regulating the physical status of the body. This thesis focuses on central projections of mild thin-fibre input and their integration with autonomic reactions. Brain activity was studied with functional magnetic resonance imaging (fMRI).
The first paper examined cortical activation of selective CT-stimulation by soft tactile stimulation in two rare patients lacking Aβ fibres. The results confirmed previous findings based on one of these patients, showing that CT stimulation activates the insular cortex. In addition, CT stimulation deactivated somatosensory cortices.
The second paper further investigated cortical effects of CT stimulation in healthy controls by comparing rapid vibration (predominantly activating Aβ fibres) and soft brush stroking (combined Aβ and CT activation) on the skin. The ventromedial prefrontal cortex was significantly more activated by brushing than by vibration, an area previously implied in coding for the expected emotional value of an event.
The third paper focused on the role of CT fibres and autonomic function. We again studied the two Aβ deafferented patients to examine whether CT stimulation could evoke an autonomic response. We also examined their ability to localise the CT stimulations to the correct limb. Capacity for localisation of the stimulus was poor but above chance. Despite producing only a vague percept in the patients, the CT stimulus gave rise to a skin sympathetic reaction which was indexed by a galvanic skin response.
The fourth paper studied the cortical mechanisms behind a restricted autonomic response elicited by a perceptually weak C-fibre input in healthy subjects. We used low-intensity rectal distension while recording autonomic variables and cortical responses. Rectal distension activated insular cortex. Central activation specifically related to the skin sympathetic response was, in addition to the brainstem, limited to the right inferior frontal gyrus (IFG).

The CT evoked insular activation and the Aβ-denervated patients' poor ability to localise a CT stimulation support the concept that these fibres underpin affective rather than discriminative aspects of touch. The rectal distension study indicated that insular activation via low-threshold mechanovisceral thin fibres predominantly reflects afferent processing whereas IFG and the brainstem may be important in the generation of autonomic responses. Further, the studies suggest that stimulus perception is a prerequisite for cutaneous autonomic responses to both CT and visceral thin fibre stimuli. These findings set the stage for future studies of thin nerve fibre function, including neural mechanisms of hedonic processing as well as pathophysiological studies of conditions such as irritable bowel syndrome, which may tease out putative contributions from afferent input, cognitive processing and autonomic consequences.
Keywords: *CT afferent, thin fibre, autonomic, insula, fMRI*
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