Reviewer’s report

Title: Low threshold unmyelinated mechanoafferents can modulate pain

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Reviewer: Andrea Truini

Reviewer's report:

In this study the Authors investigated the possible pain modulation effect of C-tactile afferents in healthy subjects and in patients with small fibre neuropathy. Given that the Authors found that C-tactile afferent stimulation reduced the pain perception in healthy subjects but not in patients with small fibre neuropathy (i.e. patients with damaged C-fibres), they conclude that C-tactile afferent input modulates pain.

This is a well-written and interesting study. I have however some major concerns.

I did not see a clear explanation about the synchronization of heat and tactile stimuli with fMRI acquisition.

I think that with this experimental protocol it is impossible to distinguish the contribution of A-beta fibres on the pain modulation. That patients with small fibre neuropathy (with damaged C-fibres and preserved A-beta fibres) have no C-tactile input modulation cannot support the conclusion that the C-fibres produce the modulation of pain, because these patients, though without allodynia, have central sensitization, and thus A-beta fibre input might have unpredictable effects (e.g. the intensity of pain with the light stroking increases). Maybe some experiments in normal subjects could be better organized with a A-beta fibre block in at least a few healthy subjects.

Another serious problem is the risk of bias. I wonder whether healthy subjects were familiar with the experiments and the aim of this study. In particular because the reduction of heat pain is extremely small (less than 4, in the 100-mm VAS).

I have the doubt that the data of healthy subjects showed in the Figure 2, do not correspond to those presented in the Results. Please verify.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.
Yes

**Are the conclusions drawn adequately supported by the data shown?**
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Yes

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I am able to assess the statistics

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