Reviewer’s report

Title: Low threshold unmyelinated mechanoafferents can modulate pain

Version: 0 Date: 26 Jun 2017

Reviewer: Martin Schmelz

Reviewer's report:

Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

This is an interesting study trying to substantiate a functional loss of C-touch fiber function in patients with small fiber neuropathy. As direct assessment of C-touch fibers is problematic the authors used an indirect effect, i.e. the reduction of heat-induced pain by concomitant touch. Functional fMRI was used to provide objective data on differential effects of touch stimuli on heat pain.

The authors found that concomitant touch reduced heat pain in the healthy volunteers, but not in the SFN patients. However, the heating stimulus (heat pain threshold + 1.5°C; 10 s) provoked pain of about twice the intensity in the patients as compared to the controls. Therefore another control group (of younger volunteers from the lab?) was investigated to induce heat pain at the level of about 50/100 and touch-evoked reduction of pain by stroking was confirmed also at this higher level of pain. No significant differences in the fMRI analysis were found. The authors conclude that their results indicate a reduced function of C-touch fibers in patients with SFN.

Major concerns:

It is important to note that a heat stimulus 1.5°C above the heat pain threshold was much more painful in the SFN patients as compared to the controls (even though the patients had heat hypoalgesia based on heat pain thresholds). This finding indicates that the superthreshold heat stimuli differentially activate nociceptors in the patients - the mechanism of this heat hypersensitivity at higher temperatures is unclear, but it may not be simply mimicked by higher stimulation temperatures as tried in the additional experiment in controls. Thus, the lack of analgesia by touching might be linked to lower C-touch function or to a different mechanism of heat pain in the SFN patients.
The authors conclude that based on normal vibration threshold and conduction velocity there is no evidence for a large fiber affection in the neuropathy patients. On the other hand, higher discharge frequency in the low threshold A-fibers is induced by the stroking stimuli and it is unclear to which extent conduction velocity (based on compound action potential to single stimuli) excludes that the ability of the A-fibers to perfectly encode a stroking stimulus might be limited. Thus, when considering the analgesic effect of vibrotactile stimulation on heat pain (vibration 100 Hz; Staud et al, Eur J Pain. 2011 Sep; 15(8): 836-842) that is mediated most probably via activation of low threshold A-fibers it is less clear whether the clinical measures (normal vibration threshold) and normal conduction velocity really exclude significant reduction of superthreshold A fiber function.

In summary, the authors provide indirect evidence for a C-touch fiber impairment in small fiber neuropathy. Reduced stroke-induced heat analgesia might be due to differences in superthreshold heat pain, subclinical A-fiber impairment or impairment of C-touch fibers. The results would be much stronger if the indirect measure of touch evoked heat analgesia would correlate to a direct C-touch measure such as velocity dependent pleasantness.

**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?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable
Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

No competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal