Reviewer’s report

Title: Evoked Potentials after Painful Cutaneous Electrical Stimulation Depict Pain Relief during a New Conditioned Pain Modulation model

Version: 0 Date: 06 Feb 2017

Reviewer: Gwyn Lewis

Reviewer’s report:

This study evaluated a new method to examine conditioned pain modulation using cutaneous electrical stimulation. In a cross-over study, the authors demonstrated reversible pain inhibition during exposure to a painful cold conditioning stimulus. This was accompanied by a reduction in the amplitude of associated cortical evoked potentials. The change in pain rating and change in evoked potential were correlated. The authors propose use of the technique to further evaluate pain modulation pathways.

The study is reasonably well designed, rigorously conducted, and succinctly described. I guess one of my main concerns though is the rationale for the study and what it adds to the literature. As the authors point out, there are lots of methods for assessing CPM already, so why do we need to develop another one? The authors should describe in more detail that perceived benefits of the technique over what is currently published. In particular, comparison to lower limb electrical stimulation to elicit a flexion reflex would be beneficial. In this protocol, subjective pain ratings and physiological measures of both spinal and cortical level processing can be obtained. I also think it would have been useful to report on the reliability of the technique, both in terms of the test stimulus and using it to assess CPM. The reliability of other protocols to assess CPM has been established already and it would be useful to compare these.

I was a bit confused by some of the analyses undertaken and results presented. It appears that both raw values and change values of pain and EP data are described? I am not sure that both are needed. The description of the statistical analyses and results need clarifying in general and it would help if consistent terminology is used throughout the different sections. In the results, it would be useful if the results were described, rather simply stating the significant findings. In the initial analysis, I would have thought the interaction between temperature and time period was the key result, yet I can't seem to see it described?

I am also a little concerned about the NRS values for the 24 deg stimulus. The fact that participants were reporting pain with this temperature suggests to me that they were not interpreting the scale appropriately, as I find it hard to believe that a healthy person would find this temperature painful.

Abstract, lines 14-15. It is difficult to determine what the pain and EP values presented represent, given that there are two values presented yet the text refers to three time periods. In the following sentence, does "changes of electrical pain” mean subjective pain ratings?
Page 3, lines 20-26. This is a particularly long and confusing sentence. It needs simplifying. In relation to this, the point of these fMRI findings needs to be clarified. What do these findings mean in relation to the current study and its rationale?

Page 5, 1st paragraph. Was the stage of the menstrual cycle of female participants documented or controlled in any way?

Page 5, line 20. Should this be an "air" conditioned room?

Page 5, line 26. "or" sequence B?

Page 6, line 8. The abbreviation NRS needs to be expanded. I found the explanation of the pulses and trains here and on page 7 to be quite confusing. Is there a way to show this protocol pictorially that may be easier to understand? Is there a reference for the stimulation protocol?

Page 6, line 17. I find it hard to believe that participants (or even examiner) were blinded to the conditioning stimulus. As soon as they put their hand in the water it would be obvious to the participants, and I am fairly sure the examiner as well, what the temperature of the water was.

Page 6, lines 23-24. Given that the effects of conditioning may last 15 mins and recommended protocol is for at least 10 mins between stimuli (Yarnitsky 2015), the authors should justify the relatively short 5 min gap between testing. This is potentially a limitation of the study protocol.

Page 7, final sentence. This statement needs a reference. Is the startle response likely to influence pain ratings too?

Page 8, line 11. Ref [2] is not Granot et al. I also think this is a fairly liberal interpretation of the recommendation. It would be more sensible that a change beyond a certain value (e.g. 10%) would better reflect an "efficient" pain inhibition.

Page 8, line 16. A reference is required.

Page 9, line 21. Should "electrically-induced pain" be PCES-pain?

Page 11, line 3. The actual P value should be presented.

Page 12, lines 5-6. Are these values CPM-effect pain and CPM-effect amplitude?

Page 12, line 7. I do not understand where the 24 datasets are from. For a Pearson correlation, these need to be independent values.

Page 13, line 10. Given the NRS values, I would hesitate to call the two conditions "painful" and "control".

Page 13, line 26. The abbreviation CHEP needs expansion.
Page 14, final paragraph. It would be useful to have some explanation of what it means physiologically that pain ratings and EP amplitudes are correlated.

Page 16, lines 1-2. I do not understand what this sentence means. It would be useful to have further discussion/explanation as to why the amount of inhibition was correlated with CS pain in this study but has not been in others.

Page 16, lines 13-14. If the study was powered appropriately, I find it unusual to describe it as quite small.

Page 16, lines 15-16. I thought both change scores and ratios were determined?

Page 17, line 16. The reliability of the technique was not assessed in the study.

Page 17, line 22. The technique is not that easy compared to, for example, mechanical pressure pain thresholds.

Figure 1. Some explanation of sequence A and B is required.

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

No

**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.

Yes

**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 recommend additional statistical review

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

Needs some language corrections before being published
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.

I declare that I have 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