Author’s response to reviews

**Title:** A systematic review of experimental methods to manipulate secondary hyperalgesia in humans: protocol

**Authors:**

Victoria Madden (torymadden@gmail.com)

Gillian Bedwell (BDWGIL001@myuct.ac.za)

Prince Chikezie (830725@students.wits.ac.za)

Andrew Rice (a.rice@imperial.ac.uk)

Peter Kamerman (peter.kamerman@wits.ac.za)

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Reviewer comments and authors' responses, with changes shown (where applicable).

Please note that this is also provided, with formatting, in the supplementary material at the bottom of the re-submission PDF.

Reviewer’s comment

Reviewer #1:

1. Authors should refer “Submission Guidelines” carefully provided at the journal homepage, and I recommend following these narrowly.

Thank you. We did think we had followed the guidelines closely, but we have double-checked that that is the case.

2. I am not sure that the authors have the plan of systematic review only or systematic review and meta-analysis. If the authors have the plan about meta-analysis, they should present the planned general approach to synthesis of data. (e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned) Besides, I recommend to describe detailed contents throughout the manuscript.

We were surprised by this comment, because our protocol clearly mentions meta-analysis and a strategy for pooling of data. We have also specified quantitative pooling and narrative synthesis.
However, we had not used the word ‘quantitative’ so we have now added that, as shown in the text excerpt copied to the right, here. We have also specified that this is not a meta-analysis of individual patient data.

"Data from different studies will be quantitatively pooled where possible and sensible, with subgrouping according to modality of induction/manipulation (e.g. negative expectation manipulation will be grouped separately to ketamine manipulation) and outcome (e.g. secondary hyperalgesia to mechanical punctate stimulation will be grouped separately to secondary allodynia to brush stroke), and with consideration given to measures of statistical heterogeneity (e.g. I2 statistic) and sensitivity analyses that exclude studies with particularly high risk of bias and studies in which obvious sources of methodological heterogeneity have been identified. This is not an individual patient data meta-analysis. We plan to use the RevMan software (25) or the R software with the package metafor to pool data and plot pooled data. The most up-to-date version of the relevant software package will be used. The outcome measure will be a standardised mean difference. We will use a random effects model to allow for anticipated heterogeneity between studies.

Where data exist but are unavailable, we plan to discuss the information that is available (e.g. number of participants tested, reasons for data unavailability, methods used) in narrative form, so as to mitigate against publication bias and provide a comprehensive summary of the literature available to answer the review question."

3. Statistical tools, software (R version) and statistical tests of pooled data should be mentioned precisely. And there is no exact plan for sensitivity test, or sub-group analysis by detail categorization.

Thank you for pointing this out. Considering that the release times of software package updates are reasonably unpredictable, we have added text to indicate that we will use the most up-to-date version of the relevant software packages. It is difficult to provide more detail on subgroup analysis than we have already provided before beginning this review process. In publishing a review protocol, our intention is to be transparent and to follow a carefully planned process. However, we do not know the exact features of the studies that will be retrieved during the full search process. Therefore, we have opted to provide as much clear detail as possible, including specifying the criteria according to which a sensitivity analysis will be conducted. Please see text reproduced above.

Reviewer #2

1. I think this protocol has been well written with interesting topic. However, there are some minor concerns.

Thank you!
2. The author is aimed to compare experimental methods to manipulate secondary hyperalgesia which is a common feature of neuropathic pain. However, there are various experimental pain models for secondary hyperalgesia. It would be better to describe several experimental pain models in the introduction section.

Thank you for this suggestion. We have added this as shown to the right, here.

"Methods that have been used to induce this secondary hyperalgesia in the experimental context include application of capsaicin (intradermal or topical), topical mustard oil, topical menthol, repetitive heating, and high-frequency electrical stimulation (6, 9)."

3. Also, there are several tools for evaluating pain scale such as brain imaging. In this protocol, does author plan to compare only mechanical (eg, VFF) secondary hyperalgesia? More description about pain models with evaluation tools might be described in this manuscript.

In this review, we plan to extract data on mechanical secondary hyperalgesia as the main outcome of interest. However, we will also extract data on the procedure used to verify the success of the manipulation applied (manipulation check). In response to your suggestion, we have chosen to include other outcomes (e.g. brain imaging) from only those studies in which the manipulation of secondary hyperalgesia itself was successful. We believe that this may add interest to the discussion of the phenomenon of secondary hyperalgesia.

"Where studies have included other outcomes associated with changes in secondary hyperalgesia (e.g. changes in brain activity shown on imaging), and when the secondary hyperalgesia data for that study indicate that the manipulation successfully influenced secondary hyperalgesia, we will discuss the findings as they pertain to the other outcomes."