

Point-by-point response to: “The effect of stimulus saliency on the modulation of ongoing neural oscillations related to thermonociception: a Registered Report”

Recommender (Zoltan Dienes):

The two reviewers are largely positive about your Stage 2, though make some excellent points. Reviewer 1 urges structuring more closely based on the Study Design Table; indeed, as I was reading the Results section, I had to have the Study Design Table up in another window to go through step by step to check, and it still needed a fair amount of cognitive effort. You could go through listing each question given in the Table, and then the relevant test. Likewise the Discussion, as suggested by the Reviewer. Reviewer 2 raises some relevant substantive points to consider.

We would like to thank the recommender for his favorable feedback. We believe that by taking into account all the comments below we were able to improve the manuscript and in particular increase the clarity of the discussion section as well as achieve a more structured presentation of our results. Upon re-reading the introduction, we also chose to update a section with relevant papers of our group which directly motivated this experiment and were published since the RR stage I submission.

- *On the subject of the Table, note how non-significance was declared as not indicating no effect. As the literature almost universally rides roughshod over this point, it can be hard to break habits absorbed from the literature! Go through thoroughly making sure you do not claim there are no effects when there was simply non-significance. For example: p 24 "while no difference was found between oddball and baseline cycles in the low oddball condition stimulation ($F(750)=0.0404$, $p=0.841$)"; "no difference" -> "no significant difference"(as you have not established there was no difference.) Same point arises on page 30, 33, 34, 36, 37. There may be other places.*

We agree with the recommender that absence of an effect cannot be stated based on our results and we have adjusted the manuscript accordingly.

- *For all changes to IPA, note them in a footnote at the point they are first mentioned, together with when the change was approved by PCI RR.*

The manuscript was updated as suggested with footnotes corresponding to adaptation to the IPA.

Review by Markus Ploner, 04 Dec 2024 14:59

The stage 2 manuscript mostly follows the outlines of the stage 1 manuscript. Different than initially planned, the stimulation hardly elicited painful sensations. Therefore, the title and the abstract have been changed to account for this lack of pain induction. Beyond that, the main finding is that high oddball stimuli elicited painful sensations and neural responses, which differed from baseline stimuli. In contrast, the low oddball stimuli did not. Thus, no definite conclusion can be drawn regarding the relationship between stimulus saliency, stimulus intensity, pain perception, and ongoing oscillations.

We appreciate the overall positive feedback of the reviewer and hope that we have adequately responded to the thoughtful suggestions, increasing the clarity of the results and relevancy of the discussion section.

The manuscript presents the results mostly clearly and discusses the findings extensively. Some revisions might further improve the manuscript:

1. **Title and abstract.** *Unlike initially planned, the stimulation hardly elicited painful sensations, which changed the title and the abstract from pain perception to thermonociception. I'm wondering whether this tacit focus change is in accordance with the idea of a registered report. The authors might consider presenting and explaining this change in the abstract.*

We agree with the reviewer that this is indeed an important issue to raise. Our rationale was that using "pain perception" in the title of the paper would be misleading, since we were – as you also noted – not able to induce a consistent perception of pain and therefore not able to relate our findings to pain perception. With this we did not mean to change the overall aim / rationale of the hypothesis, but rather to stay true to the sensory experience we elicited and to not claim something in the title that we did not have any evidence for. As per your suggestion, we added a sentence in the abstract to clarify this shift from pain perception to thermonociception. Given this adaptation we would like to argue that the title should not be misleading / infringe on the RR rules.

2. **Results.** *The presentation of the results does not clearly relate them to the hypothesis table. I understand the hypothesis table as a core part of a registered report that should guide the analysis and interpretation. Thus, the authors should explicitly relate the findings to the hypothesis table.*

We would like to thank the reviewer for raising this concern, as we absolutely agree with that the hypothesis table is a fundamental part of the RR, which sets it apart from other pre-registration methods. We apologize for the lack of clarity in the presentation of the results section and have modified it to make the relationship between hypothesis table and results / applied statistics clearer.

3. **Discussion.** *The discussion is quite long and discusses many details of the paradigm, but the results and their interpretation are less discussed along the hypothesis table. The authors might significantly shorten the discussion and change the focus from discussing methodological details to the main topic and the interpretation of the main results.*

We thank the reviewer for his suggestions. As for the results, the discussion section was adapted to relate more closely to the hypothesis table. We agree that – in an effort to explain the discrepancy with our expectations – the methodological consideration might have taken up too much space in the discussion, primarily in section 4.1 which discusses the behavioral results. Thus, we have significantly

shortened this section, making the methodological considerations more concise. Still, given the overall negative results, it still seems important to discuss methodological shortcomings, as they might have substantially contributed to the non-significant results. Especially as we were not able to induce a change in perception at the oddball cycles in the low oddball condition, we could not expect a change at the neural level or attempt to disentangle contributions of saliency, intensity and pain perception. Therefore, the discussion of why we were not able to induce the desired change in perception (despite our expectations) seemed more relevant than potential neural effects that we could not observe due to the limitations in the induced levels of perception.

Review by Bjoern Horing, 22 Dec 2024 08:36

Let me first say that I am excited that the results are in! Thank you for a well thought-out and informative study, it's been a pleasure accompanying this process.

In the following, page numbers refer to the clean PDF. All comments are rather minor, but I would strongly argue for a re-reading of the discussion that seems a bit frayed occasionally.

We would like to thank the reviewer for his supportive comments and suggestions. We believe that the careful consideration of each mentioned point has substantially improved the paper.

GENERAL COMMENTS

- *The abstract does not mention the (final) sample size which seems like a relevant information for me; furthermore, it is not clear from the descriptions in 2.1 versus 3. whether the final sample size is 35 or 33 (for behavioral data) and 31 (for EEG data), respectively - or if the sample was expanded considering the drop-outs*

We thank the reviewer for pointing out this discrepancy in the manuscript. The final sample size was indeed 31 for EEG data and 33 for behavioral data. We added a paragraph explaining this to section 2.1, to avoid any confusion.

- *3.1, paragraph 1: The authors suggest to "see Supplementary Material for single subject average examples"; later it more specifically points to "see Supplementary Materials S.IV for single subject average examples"; however, that section seems not to exist, at least not in the two PDFs provided (RR_Saliency Stage II_clean, RR_Saliency Stage II_marked)*

We would like to apologize for this mistake, which must have happened in between different versions of this document. The supplementary materials section S.IV was added accordingly to this revised manuscript. We additionally homogenized the referencing as to always pointing to "S.IV" for clarity.

- *3.1, paragraph 2: It is quite surprising that the (ostensibly) high temperatures employed did not yield robust pain; it would be an interesting data point exactly what these temperatures were, so could the authors provide at least the descriptives (calibrated mean \pm SD), at best a plot showing perception threshold, pain threshold, and max temperature (possibly akin to Fig 5)? This may seem pedantic at this point, but I feel it's pertinent given that the thermal stimulation seems to have been one of the big issues during actual empiry.*

We thank the reviewer for this suggestion. As reported in the methods section (p. 10) the average temperature at baseline was 50.197 ± 0.984 °C, increased or decreased by 2°C for high and low oddball respectively. A perception threshold would be hard to identify, as participants were instructed to only move the slider of the Visual Analog Scale (VAS) if they perceived something. Thus, any deflection from zero on the VAS scale indicated the passing of the perception threshold. Similarly, the pain threshold should be the baseline stimulation temperature (or slightly lower), since the staircase procedure that we used aimed to find the temperature at which the perception changed to "painful during the entire trial".

- 3.3.2, line 7, “considering the first two harmonics in the high oddball condition” is unfortunately phrased, you mean “including the first two harmonics...” (in addition to the oddball frequency itself), right? So FOSagg is $0.125+0.25+0.375$, not just $0.25+0.375$. This confusion also exists on p. 35, line 2 (it’s activity at the first 2 harmonics AND the oddball frequency).
- 4.1, the high oddball supposedly was “the only stimulation that was consistently perceived as painful” seems to be a stretch: Fig 5 and the top mean \pm SD of 5.5 ± 2.4 VAS (5 being pain threshold) clearly indicate that large portions of the sample did not in fact perceive them as painful. I suggest replacing “consistently” with “on average”.

We would like to thank the reviewer for the careful reading of our manuscript, and we have adjusted the wording accordingly for both suggestions.

- Parts of the discussion have a rushed feel and should be revisited, e.g.
 - p. 32 line 7f., “known to be the primarily” => do you mean primary contributors/afferents/some such notion?
 - p. 32 I would think it’s a “heat sink-effect”, not a “heat sink”? Also use “larger” instead of “worse”?
 - p. 32 remove the “, which” after “Wang et al. (2022)”
 - p. 34 “... following the oddball stimulation in the low oddball condition”, the wording here and in the following is a bit ambiguous and you shift from referencing high oddball/low oddball/unspecified oddball results; can you revisit this?

We would like to thank the reviewer for the careful consideration of the discussion section. We have improved the mentioned issues, and hope that together with the larger revisions requested by reviewer 1, the discussion is now clearer and more concise.

- All heat sink-related or neuronal temporal filtering aside (enjoyable as the discussion is), it seems to me that another explanation of high oddball-salience and the absence of low oddball-salience is simply that only the high oddball recruited nociceptors to begin with. Hypothetically, assuming an absence of pain perception for the baseline stimulus (VAS 4.6/VAS 5.0 depending on calculation) chiefly due to an absence of nociceptive drive, the high oddball-related temperature increase might have pushed the stimulus above the pain threshold, leading to a discrete and very salient percept (as in, a new sensory modality arises), whereas baseline/low oddball fluctuations all remain within the non-noxious heat range. This interpretation is tempered, of course, by the fact that roughly half the sample would have actually perceived the baseline peaks as painful (>5.0), as well, without modality-related salience of the high oddball.

We are grateful to the reviewer for these interesting considerations. Yet, we are not sure whether we could claim an absence of C-fiber nociceptor response given the fact that we used exclusively temperatures (min.: 46°C, max.: 53°C) that are above the activation threshold of these nociceptors (Treede et al., 1990). In particular, activation of (thermo-)nociceptors can be present without the sensation of pain (Torebjörk et al., 1985). This is also the reason why we changed the title from “relationship to pain perception” to “relationship to thermonociception”, since our stimuli should have (from a physical / physiological point of view) elicited activity in C-fiber nociceptors even in the absence of pain perception. Nevertheless, the argument that only the high oddball stimulation cycles were perceived as painful and were thus much more salient than the rest of the stimulation is still valid and

indeed supported by our data (Figure 4). Thus, it seems that only the high oddball temperatures were able to cross a certain “threshold” to pain perception. Given the early literature on C-fiber responses to heat stimulation, it seems that spatial and temporal summation play a crucial role in the transition from the perception of warmth/heat to pain, the latter likely being an influential factor in our study design.

- *Another alternative interpretation the authors may or may not want to explore is an accumulating offset effects from the downward slopes, maybe fostering a larger antinociceptive tone of the descending modulation (they already point to the comparatively short time spent "at peak", by nature of the stimulation).*

We thank the reviewer for this input and have added a brief paragraph discussing potential offset analgesia effects to the discussion section of the manuscript.

MINOR FORMAL ISSUES

- p. 23 has at least 2 FOSoddball subscript issues
- p. 29 line 5 subscript period [sub].[/sub]
- p. 31 probably => probable

All typos have been rectified.

References

- Torebjörk, E., Iggo, A., Iversen, L. L., & Cervero, F. (1985). Nociceptor activation and pain. *Philosophical Transactions of the Royal Society of London. B, Biological Sciences*, 308(1136), 227-234. <https://doi.org/doi:10.1098/rstb.1985.0023>
- Treede, R. D., Meyer, R. A., & Campbell, J. N. (1990). Comparison of heat and mechanical receptive fields of cutaneous C-fiber nociceptors in monkey. *Journal of Neurophysiology*, 64(5), 1502-1513. <https://doi.org/10.1152/jn.1990.64.5.1502>