

A Corticospinal Signature for Interindividual Pain Sensitivity

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This manuscript has been previously reviewed at another journal. This document only contains information relating to versions considered at Nature Communications.

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 1:

Reviewer comments:

Reviewer #2

(Remarks to the Author)

I thank the authors for the detailed and thoughtful responses to my previous comments. Overall, I feel that all important concerns have been addressed satisfactorily. Specifically, I appreciate the authors' additional analyses comparing the Elastic Net model with nonlinear approaches such as support vector regression and random forests. I also welcome the inclusion of a sham-controlled rTMS group, which significantly improves the rigor and interpretability of the results.

(Remarks on code availability)

Reviewer #3

(Remarks to the Author)

I had the opportunity to review this manuscript prior to the transfer.

The manuscript provides a study on the construction and testing of an integrated corticospinal model which seems able to reliably predict participant pain sensitivity scores. This is a foundational study which examines several functional data sets from the human brain, brainstem, and spinal cord. The authors have developed and tested several models, and their final model seems able to predict individual pain sensitivity scores from corticospinal functional MR images. The authors were also able to model changes in pain sensitivity in a data set where participants received a TMS session and compared this to a sham session to show the model can reliably predict changes in pain sensitivity.

The original manuscript was overall well written, quite technical but necessarily so, and provided insight into the different methods with which the model was developed and tested. The original manuscript had several areas that I believe required revision. The authors seem to have diligently and carefully addressed reviewer concerns and responded to reviewer questions with enough detail to get a sense of the scientific validity of the study.

I have some remaining comments, suggestions, and concerns, but I do not believe any of them render the manuscript unfit for publication. The authors have put forward a very interesting foundational study, and I believe other research teams should have the opportunity to build on, replicate, and explore this work.

Here is my remaining feedback:

1- Pain is a complex conscious experience and includes many dimensions which are either difficult to measure reliably, or measured with very different methods. Instead of using an operational definition of pain sensitivity which quantifies how much pain a participant perceives from a certain stimulus, the authors use a method where participants are administered a ramped thermal stimulus and report when they first feel pain. The temperature is then recorded and used as a measure of pain sensitivity. This is a good way to provide consistency across the methods and is a reliable operationalization.

I'm not sure 'corticospinal pain sensitivity signature' is an appropriate name for this model. A signature implies something that is closely and -distinctly- identified with pain sensitivity. You certainly seemed to have achieved closeness to pain

sensitivity, especially seeing as you have validated and tested this model over several independent data sets and a data set with manipulation of functional connectivity. A temperature threshold, however, can only measure so much. You have the temperature at which each person reports pain, but the point at which discomfort becomes pain is different between individuals, how distressed an individual is by pain is also variables, how participants choose to attend to pain is variable, etc. etc. There's a conscious interpretive component to pain, and I don't think we can fully capture that with a temperature threshold. Calling it a signature implies this is the only and final way functional connectivity between the brain, brainstem, and spinal cord translates to the experience of pain. I fear you may run into issues similar to other earlier works which attempted to put forward a 'signature of pain' and had considerable criticism. Something like 'corticospinal pain sensitivity model' may have a more open reception, although I do understand the draw of your chosen name.

Ultimately I believe you should be able to call your model whatever you like, regardless of whether I think it's a good name for it or not. I like that you've positioned the Csp as a complementary biomarker to other predictive methods. You also have several good suggestions for future directions in the manuscript which could help refine the model.

2- I like the addition of some brief methods explanations to orient the reader, as the bulk of your detailed methods is at the end of the manuscript. I also like several of your figures, and I think the added supplemental figures are a good support for the study. I still get lost sometimes when trying to evaluate work that was done on different data sets. There is a breakdown of the data sets in Figure 1, but it's organised by research question and doesn't have a lot of detail due to the small space. I think a small supplemental table with details for each data set would be helpful (e.g. final sample size, average pain sensitivity and range of pain sensitivity ratings in the data sets, whether the participants were healthy, and whether there was an manipulation in addition to the heath stimulus).

3-With a large interdisciplinary team it's helpful to list author contributions at some point. I'm not sure how this specific journal prefers the structure of the manuscript, but a section near the end such as after the data availability statement would help.

4-You have shown considerable research integrity as a team with the way in which you responded to authors, added material to the manuscript, and collected additional sham data to compare with the TMS data set results. I think your commitment to making both the data and code available is also commendable. This will be an important step for other teams to be able to build on this work.

(Remarks on code availability)

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Reviewer #2 (Remarks to the Author):

I thank the authors for the detailed and thoughtful responses to my previous comments. Overall, I feel that all important concerns have been addressed satisfactorily. Specifically, I appreciate the authors' additional analyses comparing the Elastic Net model with nonlinear approaches such as support vector regression and random forests. I also welcome the inclusion of a sham-controlled rTMS group, which significantly improves the rigor and interpretability of the results.

Response:

We sincerely thank you for your encouraging evaluation. We appreciate your note that our prior concerns were addressed satisfactorily and your recognition of the added analyses and the sham-controlled rTMS group.

Reviewer #3 (Remarks to the Author):

I had the opportunity to review this manuscript prior to the transfer.

The manuscript provides a study on the construction and testing of an integrated corticospinal model which seems able to reliably predict participant pain sensitivity scores. This is a foundational study which examines several functional data sets from the human brain, brainstem, and spinal cord. The authors have developed and tested several models, and their final model seems able to predict individual pain sensitivity scores from corticospinal functional MR images. The authors were also able to model changes in pain sensitivity in a data set where participants received a TMS session and compared this to a sham session to show the model can reliably predict changes in pain sensitivity.

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I have some remaining comments, suggestions, and concerns, but I do not believe any of them render the manuscript unfit for publication. The authors have put forward a very interesting foundational study, and I believe other research teams should have the opportunity to build on, replicate, and explore this work.

Response:

We sincerely thank you for reviewing our work both before and after transfer and for the constructive, balanced feedback. We address each point below and have implemented the corresponding clarifications or additions in the revised text.

Here is my remaining feedback:

1- Pain is a complex conscious experience and includes many dimensions which are either difficult to measure reliably, or measured with very different methods. Instead of using an operational definition of pain sensitivity which quantifies how much pain a participant perceives from a certain stimulus, the authors use a method where participants are administered a ramped thermal stimulus and report when they first feel pain. The temperature is then recorded and used as a measure of pain sensitivity. This is a good way to provide consistency across the methods and is a reliable operationalization.

Response:

We agree completely that pain is multidimensional and that our behavioral target is an operational index of nociceptive sensitivity, thermal pain threshold, rather than the full conscious experience of pain. To avoid over-reach, we now emphasize throughout that CSps is a pattern-based MRI biomarker of nociceptive sensitivity as operationalized by thermal thresholds, not a definitive “signature of pain” writ large. We explicitly note this limitation in the Introduction, Methods (operational definition), and Discussion.

I'm not sure 'corticospinal pain sensitivity signature' is an appropriate name for this model. A signature implies something that is closely and -distinctly- identified with pain sensitivity. You certainly seemed to have achieved closeness to pain sensitivity, especially seeing as you have validated and tested this model over several independent data sets and a data set with manipulation of functional connectivity. A temperature threshold, however, can only measure so much. You have the temperature at which each person reports pain, but the point at which discomfort becomes pain is different between individuals, how distressed an individual is by pain is also variable, how participants choose to attend to pain is variable, etc. etc. There's a

conscious interpretive component to pain, and I don't think we can fully capture that with a temperature threshold. Calling it a signature implies this is the only and final way functional connectivity between the brain, brainstem, and spinal cord translates to the experience of pain. I fear you may run into issues similar to other earlier works which attempted to put forward a 'signature of pain' and had considerable criticism. Something like 'corticospinal pain sensitivity model' may have a more open reception, although I do understand the draw of your chosen name.

Ultimately I believe you should be able to call your model whatever you like, regardless of whether I think it's a good name for it or not. I like that you've positioned the Csp as a complementary biomarker to other predictive methods. You also have several good suggestions for future directions in the manuscript which could help refine the model.

Response:

We are grateful for the reviewer's thoughtful concerns about scope. To my knowledge, signature is a technical term for a pre-specified multivariate pattern with fixed weights trained to predict a well-defined target and validated out-of-sample—as in the Neurologic Pain Signature (Wager et al., 2013), the Tonic Pain Signature (Lee et al., 2021) and other validated pain signatures. In this accepted usage, signature does not imply that the pattern is exclusive or exhaustive of the entire pain experience; rather, it denotes that the weights are fixed, prospectively applicable, and linked to a specific operational outcome. In line with this convention, we use corticospinal pain sensitivity signature (CSps) to denote a fixed pattern of corticospinal functional connectivity that predicts nociceptive sensitivity as operationalized by thermal pain thresholds, not the full multidimensional construct of pain.

Nevertheless, we appreciate the concern that “signature” can be read more broadly. To avoid any misunderstanding, we now state explicitly that CSps is a candidate corticospinal signature for pain sensitivity (line 543; line 979)—complementary to other approaches (line 454)—and that its behavioral target is thermal pain threshold in healthy participants, with demonstrated portability to clinical pain ratings. We hope this resolves the concern while preserving the field-standard term signature for a fixed, validated multivariate pattern.

2- I like the addition of some brief methods explanations to orient the reader, as the bulk of your detailed methods is at the end of the manuscript. I also like several of your figures, and I think the added supplemental figures are a good support for the study. I still get lost sometimes when trying to evaluate work that was done on different data sets. There is a breakdown of the data sets in Figure 1, but it's organised by research question and doesn't

have a lot of detail due to the small space. I think a small supplemental table with details for each data set would be helpful (e.g. final sample size, average pain sensitivity and range of pain sensitivity ratings in the data sets, whether the participants were healthy, and whether there was an manipulation in addition to the heath stimulus).

Response:

We thank the reviewer for the encouraging feedback on the orienting methods notes and figures. We agree that navigating analyses across multiple datasets can be challenging. To improve clarity, we have added Supplementary Table S1, which for each dataset reports: final sample size; participant status (healthy vs. clinical); the pain readout and units; mean \pm SD and range of pain sensitivity; heat-stimulus parameters; and any additional manipulation beyond the heat stimulus (e.g., M1 rTMS vs. sham; cold task). We also added in-text callouts to S1 at first mention of each analysis. We hope this compact table and cross-referencing address the reviewer's concern.

3-With a large interdisciplinary team it's helpful to list author contributions at some point. I'm not sure how this specific journal prefers the structure of the manuscript, but a section near the end such as after the data availability statement would help.

Response:

We appreciate this helpful suggestion. We added an Author contributions section near the end of the manuscript that specifies roles in design, acquisition, analysis, visualization, drafting, and review for each co-author.

4-You have shown considerable research integrity as a team with the way in which you responded to authors, added material to the manuscript, and collected additional sham data to compare with the TMS data set results. I think your commitment to making both the data and code available is also commendable. This will be an important step for other teams to be able to build on this work.

Reviewer #3 (Remarks on code availability):

Files are accessible and well organised.

Response:

Thank you for your generous remarks.

We are grateful for the time, care, and expertise both reviewers invested. We believe the revisions have improved clarity, strengthened methodological transparency, and sharpened how we position CSps—as a corticospinal biomarker of nociceptive sensitivity that complements, rather than replaces, other approaches.