

Lecture 03

Target research articles and datasets

Target articles and datasets:

OPEN ACCESS Freely available online

PLOS | **BIOLOGY**

Distinct Brain Systems Mediate the Effects of Nociceptive Input and Self-Regulation on Pain

Choong-Wan Woo^{1,2}, Mathieu Roy^{1,2}, Jason T. Buhle³, Tor D. Wager^{1,2*}

1 Department of Psychology and Neuroscience, University of Colorado, Boulder, Colorado, United States of America, **2** Institute of Cognitive Science, University of Colorado, Boulder, Colorado, United States of America, **3** Department of Psychology, Columbia University, New York, New York, United States of America

Abstract
 Cognitive self-regulation can strongly modulate pain and emotion. However, it is unclear whether self-regulation primarily influences primary nociceptive and affective processes or evaluative ones. In this study, participants engaged in self-regulation to increase or decrease pain while experiencing multiple levels of painful heat during functional magnetic resonance imaging (fMRI) imaging. Both heat intensity and self-regulation strongly influenced reported pain, but they did so via two distinct brain pathways. The effects of stimulus intensity were mediated by the neurologic pain signature (NPS), an *a priori* distributed brain network shown to predict physical pain with over 90% sensitivity and specificity across four studies. Self-regulation did not influence NPS responses; instead, its effects were mediated through functional connections between the nucleus accumbens and ventromedial prefrontal cortex. This pathway was unresponsive to noxious input, and has been broadly implicated in valuation, emotional appraisal, and functional outcomes in pain and other types of affective processes. These findings provide evidence that pain reports are associated with two dissociable functional systems: nociceptive/affective aspects mediated by the NPS, and evaluative/functional aspects mediated by a fronto-striatal system.

Citation: Woo C-W, Roy M, Buhle JT, Wager TD (2015) Distinct Brain Systems Mediate the Effects of Nociceptive Input and Self-Regulation on Pain. PLoS Biol 13(1): e1002036. doi:10.1371/journal.pbio.1002036

Academic Editor: Michael Posner, University of Oregon, United States of America

Received July 10, 2014; Accepted November 21, 2014; Published January 6, 2015

Copyright: © 2015 Woo et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All fMRI data are available from the OpenfMRI portal (accession number ds000140) at <https://openfmri.org/dataset/ds000140>. Other relevant data are within the paper and its Supporting Information files.

Funding: This work was funded by R01 DA027794 and R01 MH076136 (TDW), by a Fulbright Graduate Study Fellowship to CW, and by a post-doctoral scholarship from the Canadian Institutes of Health Research grant (CIHR) to MR. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* Tor.Wager@Colorado.Edu

Abbreviations: aINS, anterior insula; dACC, dorsal anterior cingulate cortex; dPIIS, dorsal-posterior insula; fMRI, functional magnetic resonance imaging; FWER, family-wise error rate; NAc, nucleus accumbens; NPS, neurologic pain signature; ROI, region-of-interest; S2, secondary somatosensory cortices; vmPFC, ventromedial prefrontal cortex.

Research Paper

PAIN

Cognitive self-regulation influences pain-related physiology

Gordon M. Matthewson^{a,b}, Choong-Wan Woo^{c,d}, Marianne C. Reddan^{a,b}, Tor D. Wager^{a,b,e,*}

Abstract
 Cognitive self-regulation can shape pain experience, but its effects on autonomic responses to painful events are unclear. In this study, participants (N = 41) deployed a cognitive strategy based on reappraisal and imagination to regulate pain up or down on different trials while skin conductance responses (SCRs) and electrocardiogram activity were recorded. Using a machine learning approach, we first developed stimulus-locked SCR and electrocardiogram physiological markers predictive of pain ratings. The physiological markers demonstrated high sensitivity and moderate specificity in predicting pain across 2 data sets, including an independent test data set (N = 84). When we tested the markers on the cognitive self-regulation data, we found that cognitive self-regulation had significant impacts on both pain ratings and pain-related physiology in accordance with regulatory goals. These findings suggest that self-regulation can impact autonomic nervous system responses to painful stimuli and provide pain-related autonomic profiles for future studies.

Keywords: Pain, Self-regulation, Autonomic nervous system, SCR, ECG

1. Introduction
 Cognitive self-regulation is a way of modulating pain and emotion by consciously changing one's thoughts and appraisals of sensations and the context in which they occur.^{1,10,19,26,27,36} Psychological interventions such as hypnosis and placebo have long been documented as effective methods of pain control,³¹ and several cognitive self-regulation techniques have also been documented for their ability to reduce pain (for a review, see Ref. 15). Some of the most prominent include mental imagery^{6,11} and *reappraisal*, which involves contextual reinterpretation of painful sensations.^{39,42} Beliefs and conditioning are known to have strong physiological impacts, such as in the case of placebo effects^{24,33,47} but the relationship between conscious self-

Painful events induce dramatic changes in the autonomic nervous system. These changes, including increases in blood pressure, heart rate, skin conductance, and pupil dilation,^{4,8,9,18,34} are consistent with sympathetic activation and parasympathetic withdrawal and believed to be mediated by interactions with parabrachial nociceptive pathways in the brainstem.^{5,7,40} However, quantifying pain-related autonomic responses in the context of cognitive pain modulation is challenging because autonomic changes are not specific to pain. During cognitive pain modulation, for example, the autonomic nervous system responds to noxious stimulation, but also to orientation to a stimulus,¹⁶ cognitive load,^{32,35} and stress.²² As a result, it is difficult to isolate cognitive effects on pain-related physiology from those related to other processes, including cognitive

Target articles and datasets:

OPEN ACCESS Freely available online

PLOS | BIOLOGY

Distinct Brain Systems Mediate the Effects of Nociceptive Input and Self-Regulation on Pain

Choong-Wan Woo^{1,2}, Mathieu Roy^{1,2}, Jason T. Buhle³, Tor D. Wager^{1,2*}

1 Department of Psychology and Neuroscience, University of Colorado, Boulder, Colorado, United States of America, **2** Institute of Cognitive Science, University of Colorado, Boulder, Colorado, United States of America, **3** Department of Psychology, Columbia University, New York, New York, United States of America

Abstract
 Cognitive self-regulation can strongly modulate pain and emotion. However, it is unclear whether self-regulation primarily influences primary nociceptive and affective processes or evaluative ones. In this study, participants engaged in self-regulation to increase or decrease pain while experiencing multiple levels of painful heat during functional magnetic resonance imaging (fMRI) imaging. Both heat intensity and self-regulation strongly influenced reported pain, but they did so via two distinct brain pathways. The effects of stimulus intensity were mediated by the neurologic pain signature (NPS), an *a priori* distributed brain network shown to predict physical pain with over 90% sensitivity and specificity across four studies. Self-regulation did not influence NPS responses; instead, its effects were mediated through functional connections between the nucleus accumbens and ventromedial prefrontal cortex. This pathway was unresponsive to noxious input, and has been broadly implicated in valuation, emotional appraisal, and functional outcomes in pain and other types of affective processes. These findings provide evidence that pain reports are associated with two dissociable functional systems: nociceptive/affective aspects mediated by the NPS, and evaluative/functional aspects mediated by a fronto-striatal system.

Citation: Woo C-W, Roy M, Buhle JT, Wager TD (2015) Distinct Brain Systems Mediate the Effects of Nociceptive Input and Self-Regulation on Pain. PLoS Biol 13(1): e1002036. doi:10.1371/journal.pbio.1002036

Academic Editor: Michael Posner, University of Oregon, United States of America

Received July 10, 2014; Accepted November 21, 2014; Published January 6, 2015

Copyright: © 2015 Woo et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All fMRI data are available from the OpenfMRI portal (accession number ds000140) at <https://openfmri.org/dataset/ds000140>. Other relevant data are within the paper and its Supporting Information files.

Funding: This work was funded by R01 DA027794 and R01 MH076136 (TDW), by a Fulbright Graduate Study Fellowship to CW, and by a post-doctoral scholarship from the Canadian Institutes of Health Research grant (CIHR) to MR. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* Tor.Wager@Colorado.Edu

Abbreviations: aINS, anterior insula; dACC, dorsal anterior cingulate cortex; dPINS, dorsal-posterior insula; fMRI, functional magnetic resonance imaging; FWER, family-wise error rate; NAc, nucleus accumbens; NPS, neurologic pain signature; ROI, region-of-interest; S2, secondary somatosensory cortices; vmPFC, ventromedial prefrontal cortex.

- The first dataset that Wani analyzed for his PhD
 - Main point: "Cognitive self-regulation can change pain"
 - We identified the brain mediation path for the effects of cognitive self-regulation on pain
 - The raw dataset (fMRI + behavior) has been publicly shared
- <https://openneuro.org/datasets/ds000140/versions/00001>

OpenNEURO

Versions

00001 2018-07-18

Distinct brain systems mediate the effects of nociceptive input and self-regulation on pain

uploaded by Chris Gorgolewski on 2018-05-02 - over 2 years ago
last modified on 2018-07-18 - about 2 years ago
authorized by Choong-Wan Woo, Mathieu Roy, Jason T. Buhle, Tor D. Wager
126 12035

Download Analyze on brainlife.io

OpenNeuro Accession Number: ds000140
Files: 4198, Size: 5.48GB, Subjects: 33, Session: 1
Available Tasks: heat pain with regulation and ratings
Available Modalities: T1w, bold

1st paper:
Woo et al. (2015) PLoS Biology

09/16/2013
Master's Thesis Defense

Deconstructing pain: Sensory and cognitive manipulations of pain are mediated by distinct systems

Choong-Wan Woo, Mathieu Roy, Jason, T. Buhle, and Tor D. Wager

Cognitive and Affective Neuroscience Lab
Department of Psychology and Neuroscience
The University of Colorado Boulder



Mathieu Roy



Jason T. Buhle



Tor D. Wager

Cognitive regulation of pain and emotion

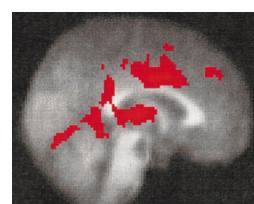
- Cognitive strategies (such as reappraisal) can effectively regulate pain (Tracey, 2010) and emotion (Gross & Thompson, 2007).
- The neural mechanisms underlying cognitive reappraisal (self-regulation) of emotion have been intensely studied (for reviews, see Ochsner et al., 2012).
- However, there are few studies on cognitive reappraisal of pain.
- Many current therapies for chronic pain rely on cognitive reappraisal (e.g., Cognitive Behavioral Therapy and Acceptance Commitment Therapy; Kerns et al., 2011), making the study of cognitive reappraisal crucial.

Cognitive regulation of pain and emotion

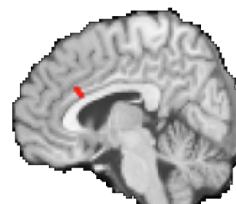
- Does cognitive pain regulation influence core sensory and affective processes or later-stage valuation and decision-making processes?
- The answer remains **unclear** because...

1. Results are mixed.

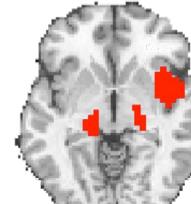
- a. Distraction/Placebo-induced decreases in pain processing regions during painful events



Bantick et al. (2002) *Brain*

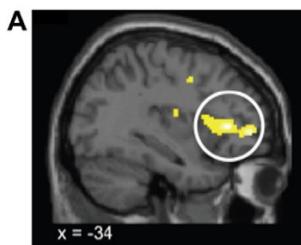


Wager et al. (2004) *Science*

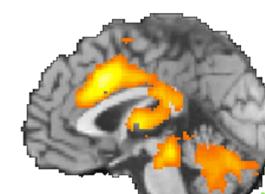


Pain-processing regions

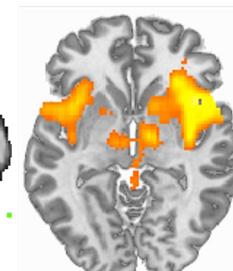
- b. No effect of cognitive therapy on pain-processing regions



Jensen et al. (2012) *Pain*



Wager lab, N=115
Thermal pain on left arm
 $p < .05$ FWE corrected



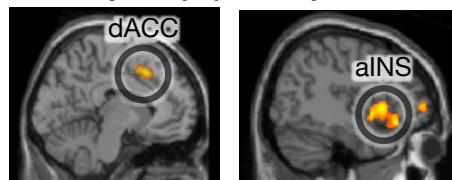
Cognitive regulation of pain and emotion

- Does cognitive pain regulation influence core sensory and affective processes or later-stage valuation and decision-making processes?
- The answer still remains **unclear** because...

2. Brain markers with high sensitivity and specificity for pain and emotion has not been identified.

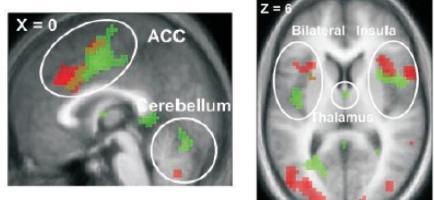
- Averaged fMRI signal across voxels within certain regions cannot be **specific** to somatic pain...

Social pain (rejection)



Eisenberger et al. (2003)

Pain empathy (observed pain)



Green = self, red = other

Singer et al. (2004)

Somatic pain



Wager lab, N=115
Thermal pain on left arm
 $p < .05$ FWE corrected

Evidence for **shared processes?**

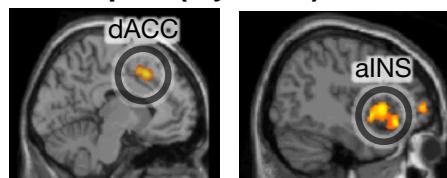
Cognitive regulation of pain and emotion

- Does cognitive pain regulation influence core sensory and affective processes or later-stage valuation and decision-making processes?
- The answer still remains **unclear** because...

2. Brain markers with high sensitivity and specificity for pain and emotion has not been identified.

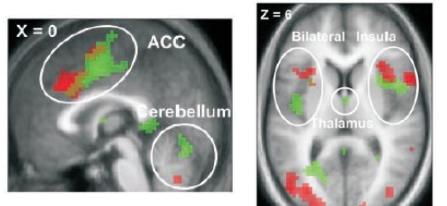
- Averaged fMRI signal across voxels within certain regions cannot be **specific** to somatic pain...

Social pain (rejection)



Eisenberger et al. (2003)

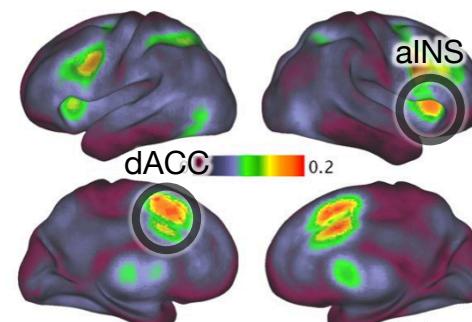
Pain empathy (observed pain)



Green = self, red = other
Singer et al. (2004)

Base rate, P(activation) across

3489 neuroimaging studies Yarkoni et al. (2012)



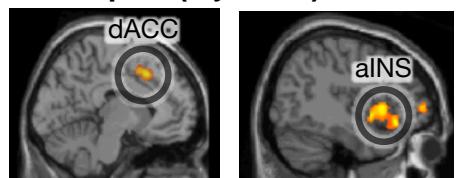
Cognitive regulation of pain and emotion

- Does cognitive pain regulation influence core sensory and affective processes or later-stage valuation and decision-making processes?
- The answer still remains **unclear** because...

2. Brain markers with high sensitivity and specificity for pain and emotion has not been identified.

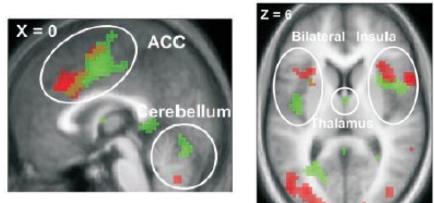
- Averaged fMRI signal across voxels within certain regions cannot be **specific** to somatic pain...

Social pain (rejection)

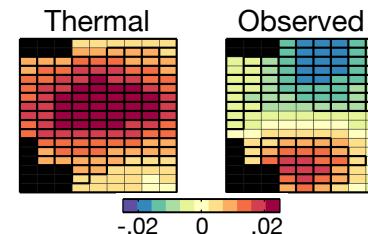
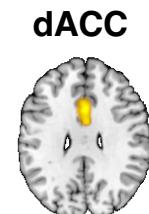


Eisenberger et al. (2003)

Pain empathy (observed pain)



Green = self, red = other
Singer et al. (2004)



Anjali Krishnan



Neurologic signature of physical pain (Nociceptive pain signature, **NPS**)

- Recently, using machine learning, we derived a neural signature, which we term the ‘nociceptive pain signature (NPS)’, that predicts the intensity of physical pain.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An fMRI-Based Neurologic Signature of Physical Pain

Tor D. Wager, Ph.D., Lauren Y. Atlas, Ph.D., Martin A. Lindquist, Ph.D.,
Mathieu Roy, Ph.D., Choong-Wan Woo, M.A., and Ethan Kross, Ph.D.

ABSTRACT

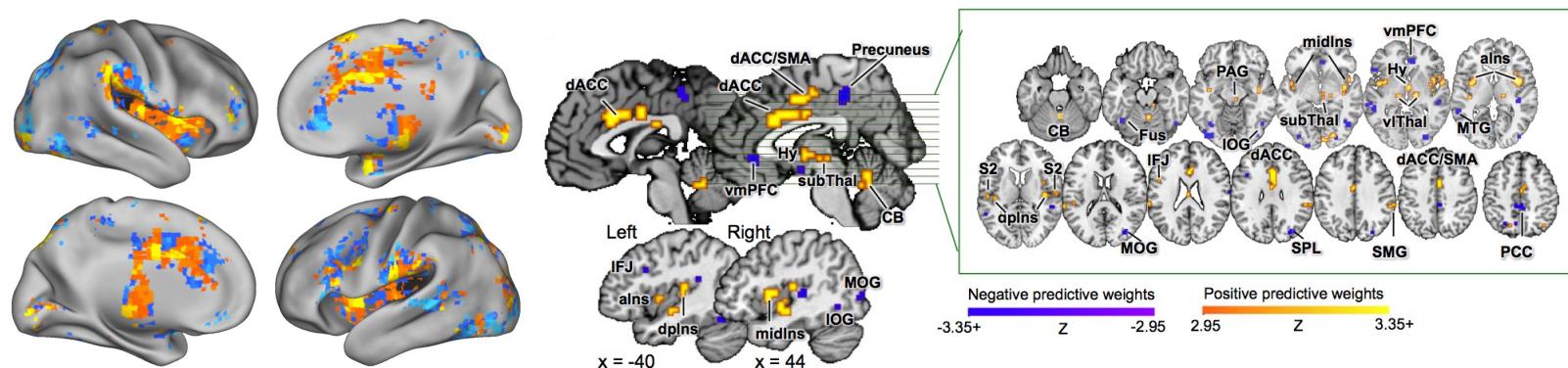
BACKGROUND
Persistent pain is measured by means of self-report, the sole reliance on which hampers diagnosis and treatment. Functional magnetic resonance imaging (fMRI) holds promise for identifying objective measures of pain, but brain measures that are sensitive and specific to physical pain have not yet been identified.

METHODS
In four studies involving a total of 114 participants, we developed an fMRI-based measure that predicts pain intensity at the level of the individual person. In study 1, we used machine-learning analyses to identify a pattern of fMRI activity across

From the Department of Psychology and Neuroscience, University of Colorado, Boulder (T.D.W., M.R., C.-W.W.); the Department of Psychology, New York University, New York (L.Y.A.); the Department of Biostatistics, Johns Hopkins University, Baltimore (M.A.L.); and the Department of Psychology, University of Michigan, Ann Arbor (E.K.). Address reprint requests to Dr. Wager at the Department of Psychology and Neuroscience, ...

Neurologic signature of physical pain (Nociceptive pain signature, **NPS**)

- Recently, using machine learning, we derived a neural signature, which we term the ‘nociceptive pain signature (NPS)’, that predicts the intensity of physical pain.
- Across four fMRI studies, the NPS response (pattern expression) discriminated physical pain from non-painful warmth, pain anticipation, emotional pain, and pain recall with over 90% sensitivity and specificity and was responsive to the reduced pain by analgesic treatment.
- Using this brain marker for physical pain, we can ask the question again: Whether cognitive regulation modulates pain experience via core pain-processing or other value-related brain systems.

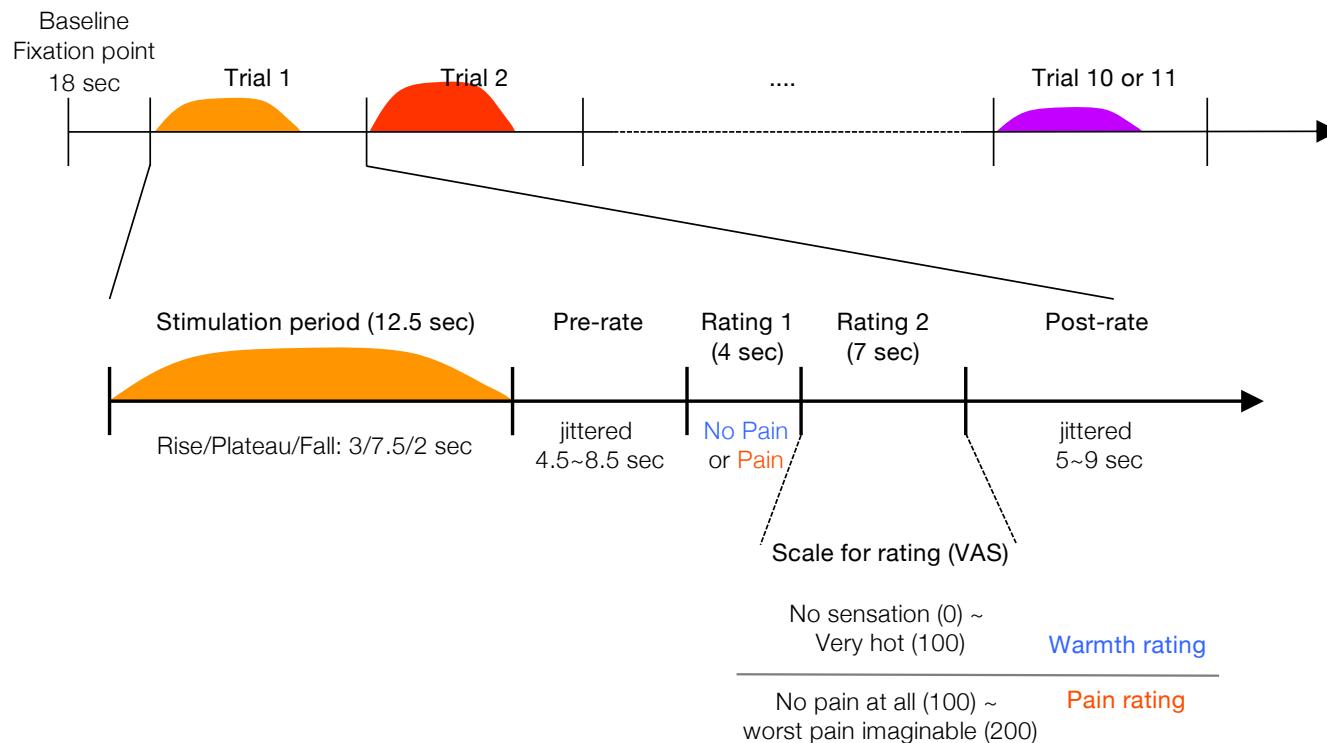


Wager et al., (2013) NEJM

Methods

- We combined fMRI imaging with an experimental pain paradigm, and concurrently manipulated both the intensity of noxious input and a cognitive reappraisal strategy for regulating pain.
- **Participants (N = 33)** experienced thermal stimulation at six distinct temperatures during fMRI scanning (44.3-49.3°C in 1-°C increments on the left forearm, with 15~20 repetitions of each stimulus).
- After each trial, participants judged whether the stimulus was painful or not, followed by a judgment of pain or warmth intensity on a 100-point visual analog scale.

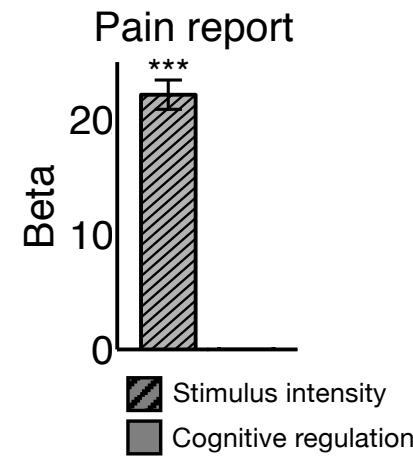
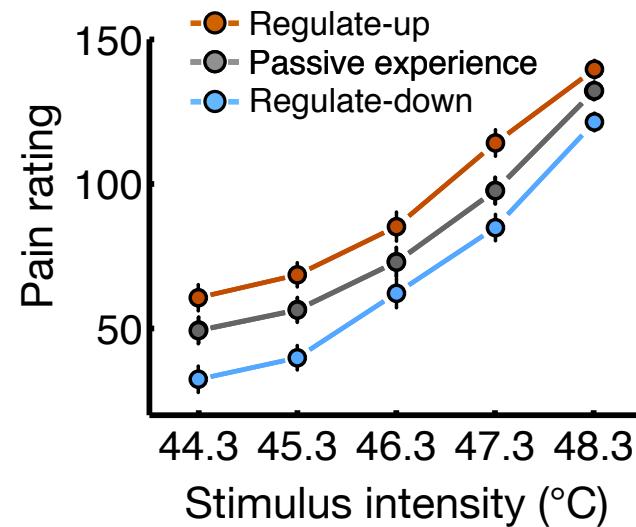
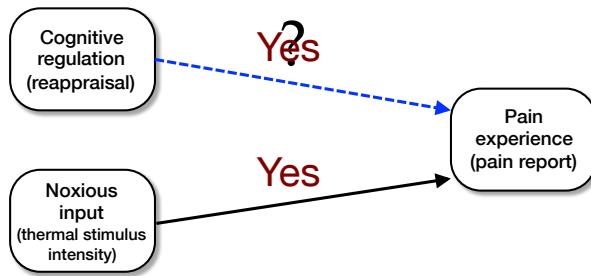
Methods



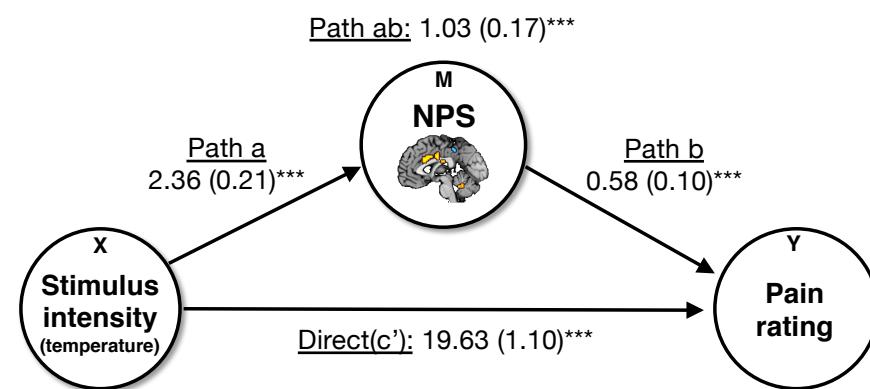
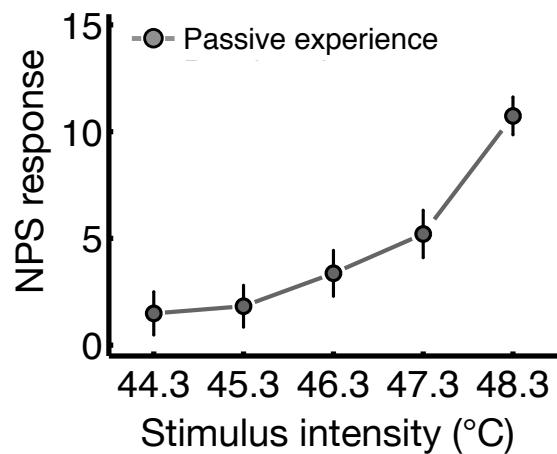
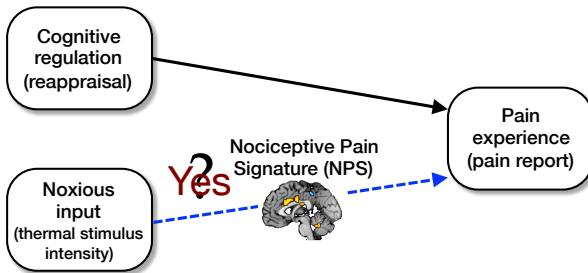
Methods

- We combined fMRI imaging with an experimental pain paradigm, and concurrently manipulated both the intensity of noxious input and a cognitive reappraisal strategy for regulating pain.
- Participants ($N = 33$, 22 females) experienced thermal stimulation at six distinct temperatures during fMRI scanning (44.3-49.3°C in 1-°C increments on the left forearm, with 15~20 repetitions of each stimulus).
- After each trial, participants judged whether the stimulus was painful or not, followed by a judgment of pain or warmth intensity on a 100-point visual analog scale.
- On **seven** of the nine experimental runs, participants passively experienced and rated the stimuli ("Passive experience" condition).
- On **two** "Regulation" runs (the 3rd and 7th), we asked participants to cognitively increase or decrease pain intensity (the order of regulate-up and -down was counterbalanced).
- In the **Regulate-up** run, participants increased pain by imagining their skin to be burning, sizzling, and melting. In the **Regulate-down** run, they imagined that the heat was pleasant and diffuse, like "a warm blanket on a cold day".

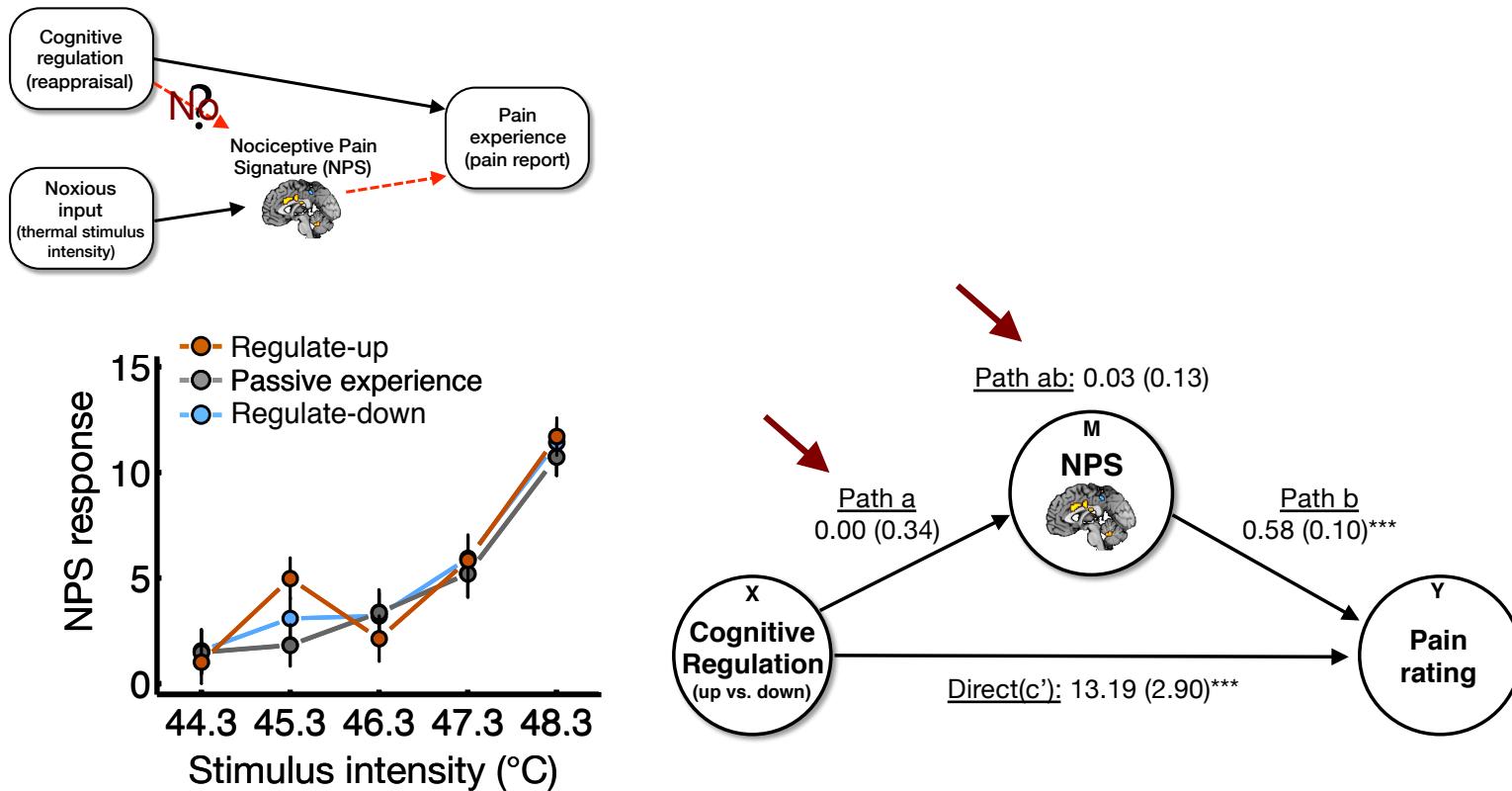
Results(1): Does cognitive regulation work? **Yes.**



Results(2): Does noxious input influence pain report through NPS? **Yes.**



Results(3): Does cognitive regulation influence pain report through NPS? **No.**



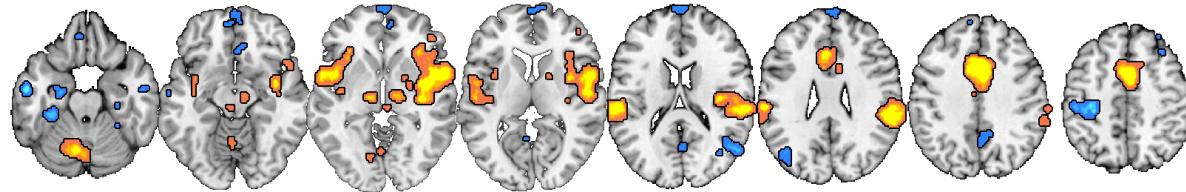
Interim summary

- As expected, both heat intensity and cognitive regulation substantially influenced pain ratings.
- Heat intensity had a significant effect on NPS, but cognitive regulation had no effect on NPS.
- Mediation analyses showed NPS mediated the relationship between stimulus intensity and pain ratings, but not between cognitive regulation and pain ratings.

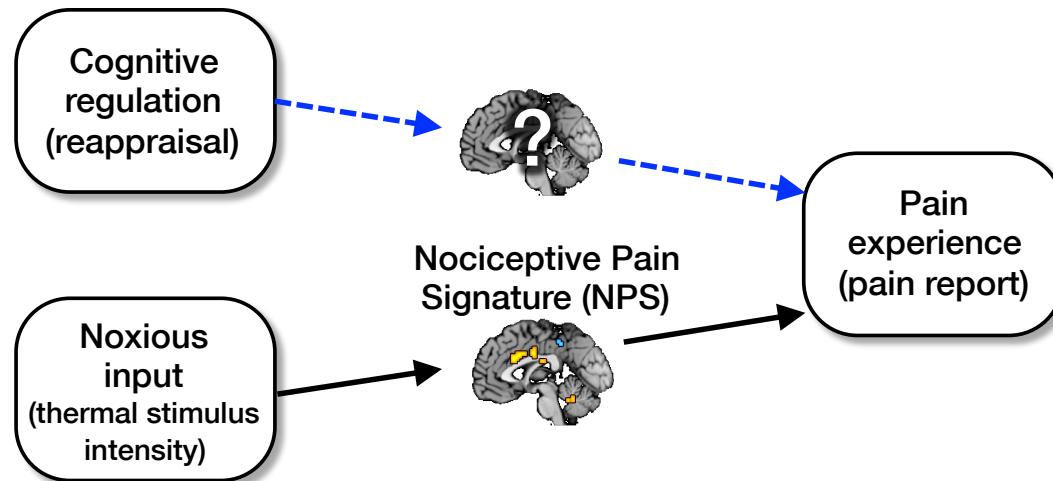
Results(4): Voxel-wise mapping

- Voxel-wise mapping of the effects of stimulus intensity and cognitive regulation showed two manipulations yielded very different patterns of brain activity.

a. Stimulus intensity related brain activity



Results(5): Other systems mediating cognitive regulation effects on pain

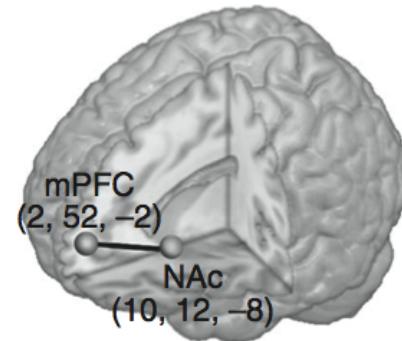


Results(5): Other systems mediating cognitive regulation effects on pain

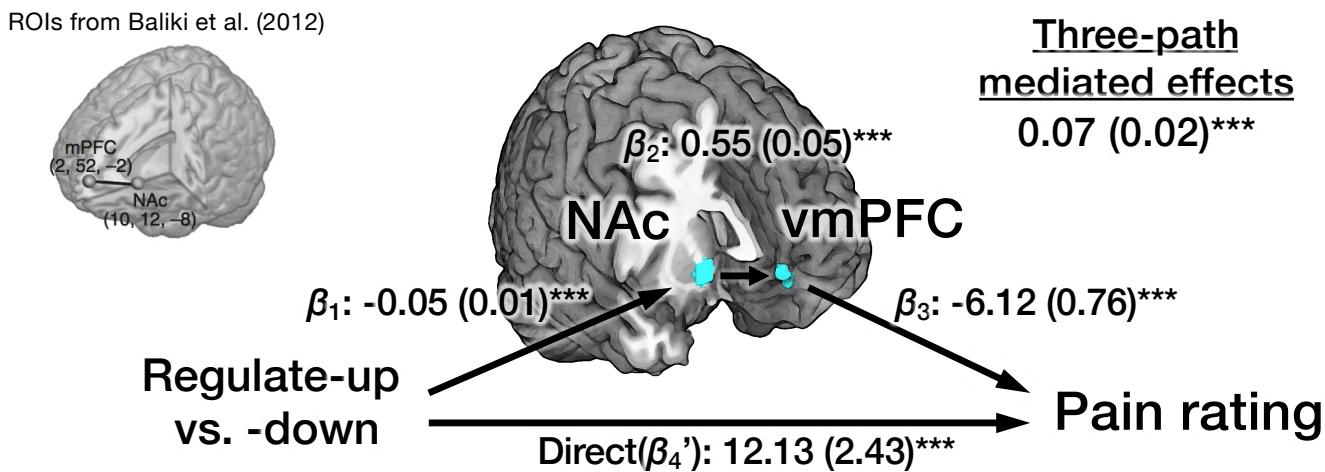
- We conducted the whole-brain search with one-step mediation framework, but no cluster survived, suggesting the existence of additional mediation steps.
- Then, we took *a priori* approach based on recent findings that a pathway connecting the nucleus accumbens (NAc) and ventromedial prefrontal cortex (vmPFC) is implicated in pain valuation and the transition to chronic pain.

Corticostriatal functional connectivity predicts transition to chronic back pain

Baliki et al. (2012) *Nature Neurosci*



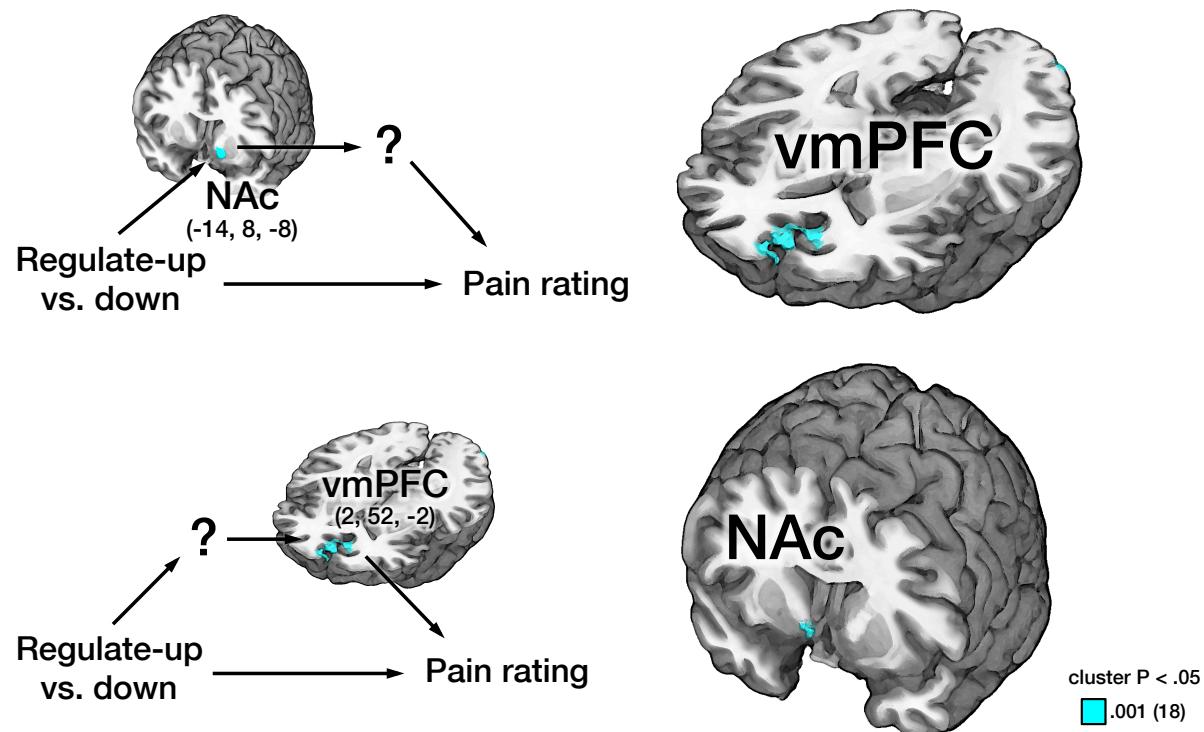
Results(5): Other systems mediating cognitive regulation effects on pain



- The **NAc-vmPFC pathway** from Baliki et al. (2012) was a significant, positive mediator of the relationship between cognitive regulation and pain ratings (Reversing the direction of the mediation yielded non-significant results).

Results(5): Other systems mediating cognitive regulation effects on pain

- Whole-brain searches using multilevel three-path mediation analyses
- Three variables were specified *a priori*.



Summary

- Both sensory and cognitive manipulations of pain strongly influenced reported pain, but they did so via two distinct brain pathways.
- The effects of stimulus intensity were mediated by NPS, but cognitive regulation was mediated via a NAc-vmPFC pathway.
- The NAc-vmPFC pathway was unresponsive to noxious input and has been broadly implicated in valuation and emotional appraisal and in the transition from acute to chronic pain.
- These findings suggest that sensory and cognitive manipulations of pain are mediated by two distinct systems associated with different stages of processing.

2nd paper:
Matthewson et al. (2019) PAIN

Video abstract: <https://youtu.be/R1QtvyAt-F8>



Cognitive self-regulation influences pain-related physiology

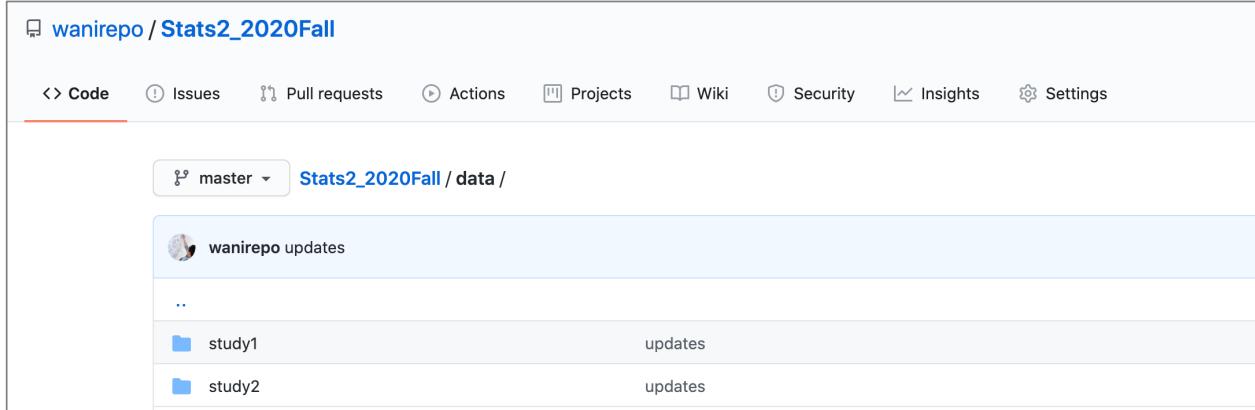
Gordon Matthewson*, Choong-Wan Woo*, Marianne C. Reddan, Tor D. Wager

Thanks for watching!!



Datasets

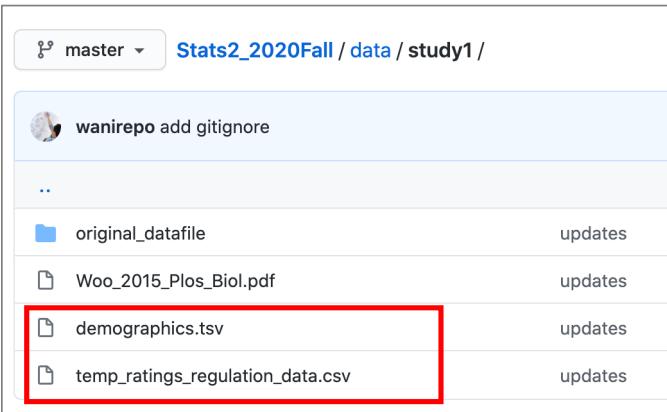
https://github.com/wanirepo/Stats2_2021Fall/tree/master/data



The screenshot shows the GitHub repository `wanirepo / Stats2_2020Fall`. The `Code` tab is selected. The repository has one branch, `master`, which contains a folder named `data`. Inside `data`, there are two subfolders: `study1` and `study2`, both of which have the status `updates`.

Stats2_2020Fall / data /

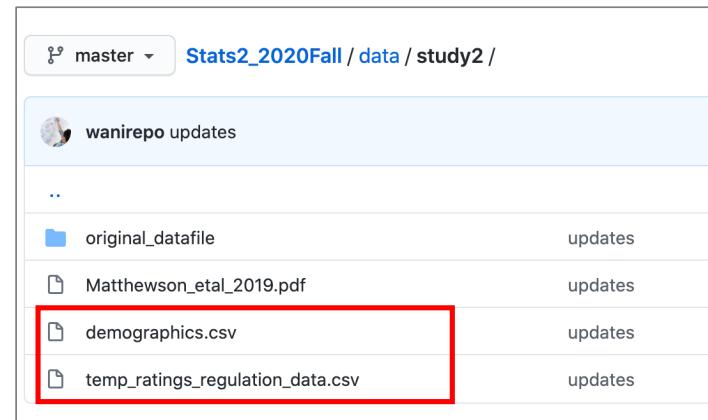
- wanirepo updates
- ..
- study1 updates
- study2 updates



The screenshot shows the contents of the `study1` folder within the `data` folder. It includes a file named `original_datafile`, a PDF file named `Woo_2015_Plos_Biol.pdf`, and two CSV files: `demographics.tsv` and `temp_ratings_regression_data.csv`. The `demographics.tsv` and `temp_ratings_regression_data.csv` files are highlighted with a red border.

Stats2_2020Fall / data / study1 /

- wanirepo add gitignore
- ..
- original_datafile updates
- Woo_2015_Plos_Biol.pdf updates
- demographics.tsv** updates
- temp_ratings_regression_data.csv** updates



The screenshot shows the contents of the `study2` folder within the `data` folder. It includes a file named `original_datafile`, a PDF file named `Matthewson_et.al_2019.pdf`, and two CSV files: `demographics.csv` and `temp_ratings_regression_data.csv`. The `demographics.csv` and `temp_ratings_regression_data.csv` files are highlighted with a red border.

Stats2_2020Fall / data / study2 /

- wanirepo updates
- ..
- original_datafile updates
- Matthewson_et.al_2019.pdf updates
- demographics.csv** updates
- temp_ratings_regression_data.csv** updates