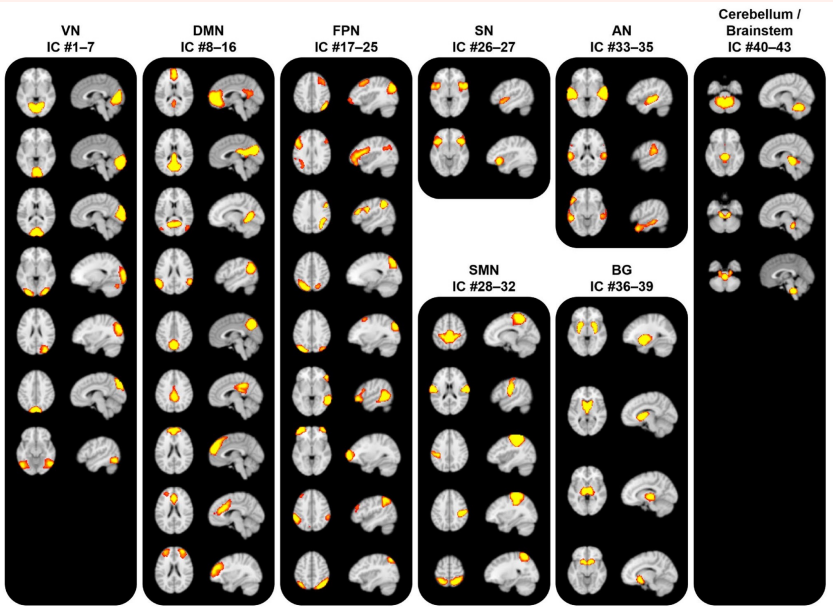
Mediation analysis basics 1 (overview)

Choong-Wan Woo
Director of the Cocoan Lab

Slide credit: Tor Wager

Two basic kinds of connectivity

ICA (Park et al., 2020)



Data reduction approaches

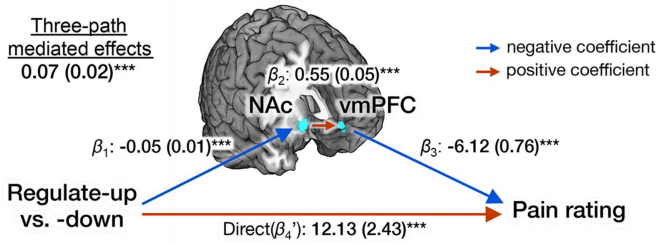
- Identify distributed patterns
- PCA, ICA, PLS, tensor-ICA, CCA, SOMs, Autoencoder, etc.

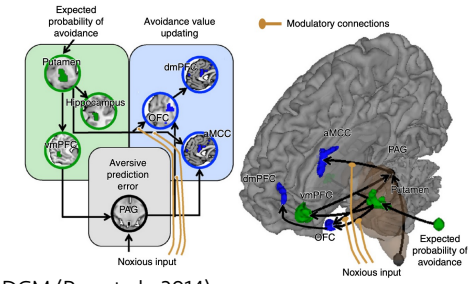
Path modeling family

- Inferences on specific connections
- Path models, PPI, SEM, spectral coherence, Granger causality, DCM, etc.

These can be complementary

Mediation analysis (Woo et al., 2015)





DCM (Roy et al., 2014)

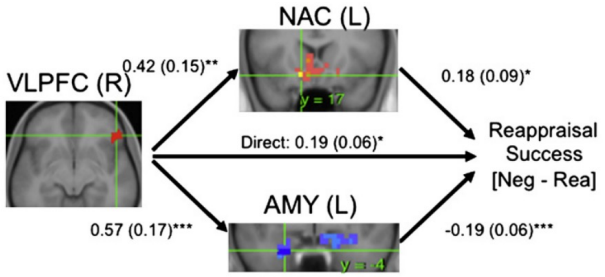
Pathways are a natural organizing principle of brain function

Goal

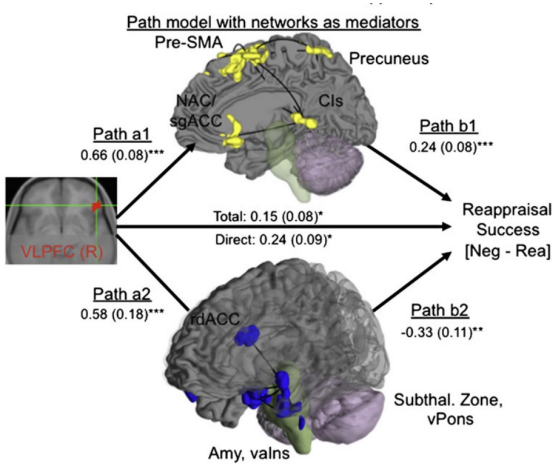
- To build models of functional pathways
- Path models can be used for pathway discovery

Benefits

- Connections with neuroanatomical studies
- "Systems-level" description of brain function
- Stability: More robust and generalizable predictions

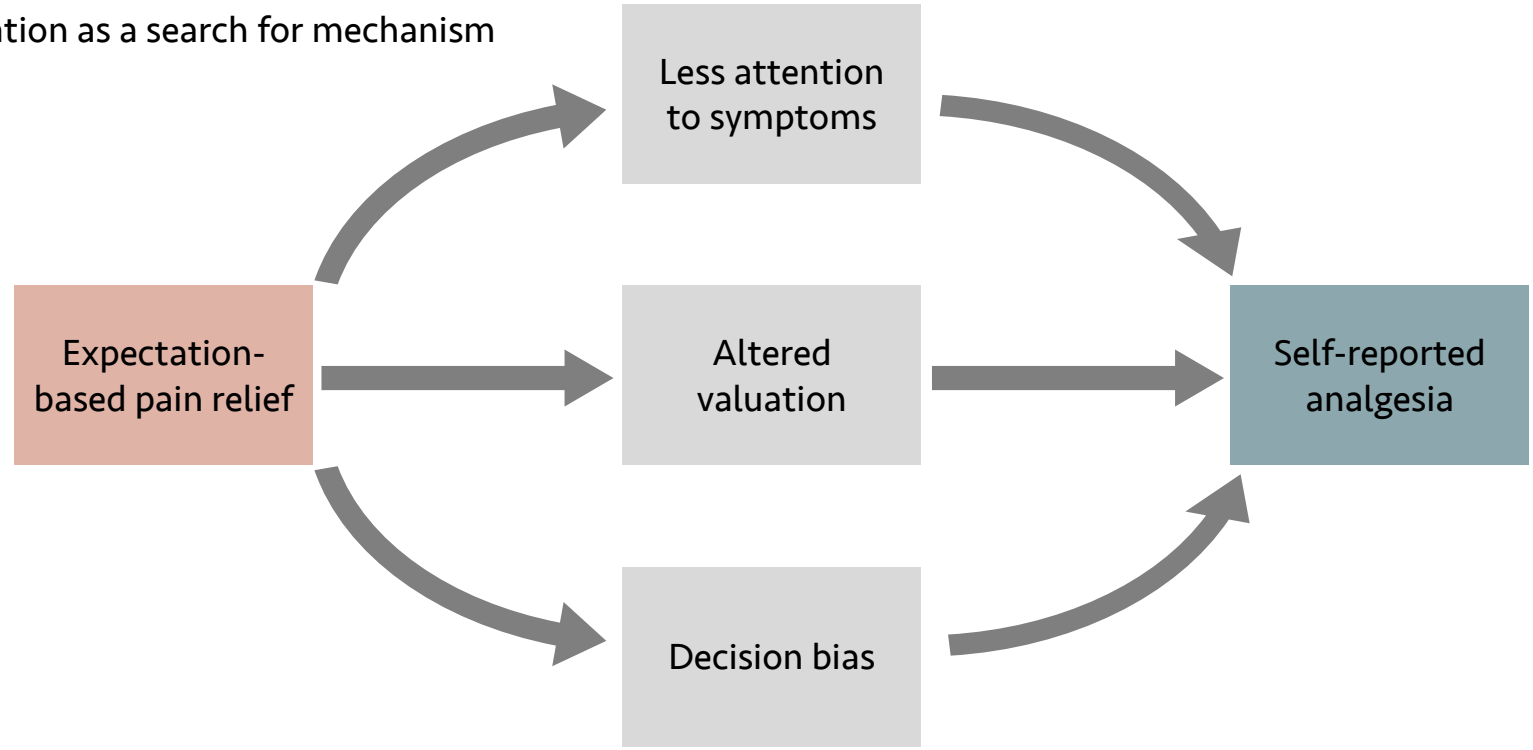


Wager et al., 2008

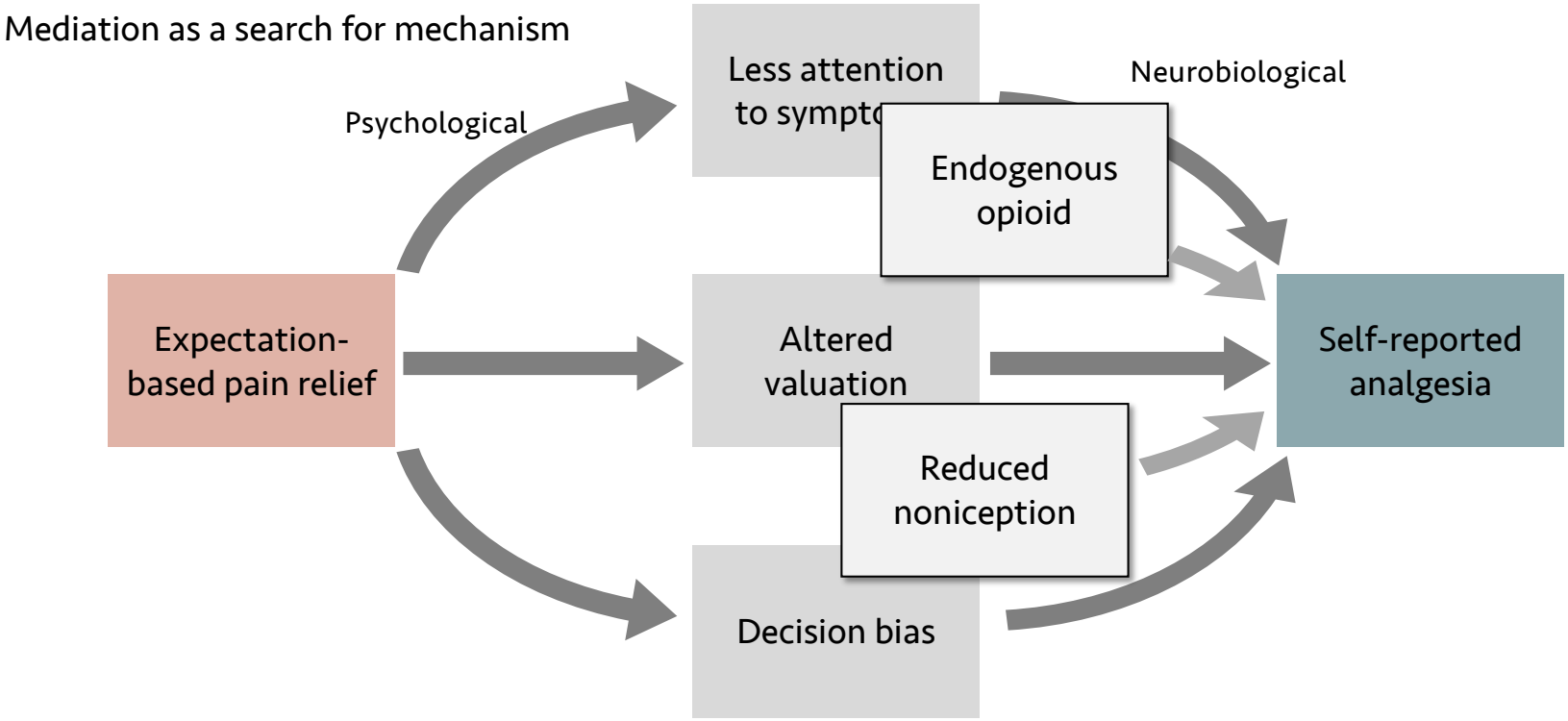


Why path modeling?

Mediation as a search for mechanism



Why path modeling?



Core ideas

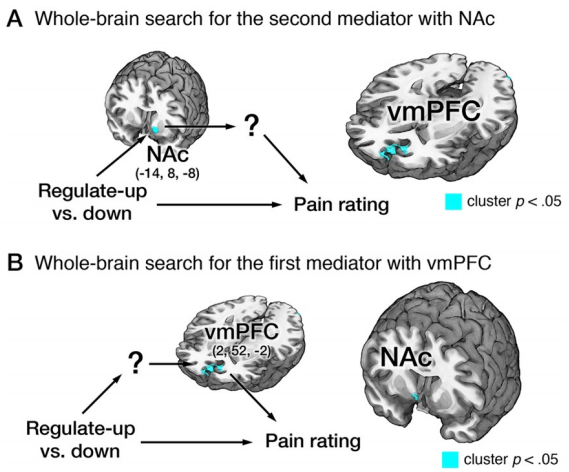
Linking experiment, brain, and behavior: Experimental manipulations, brain measures, and outcomes linked in a single model

Unique advantages: Flexibility, transparency, specified assumptions and limitations

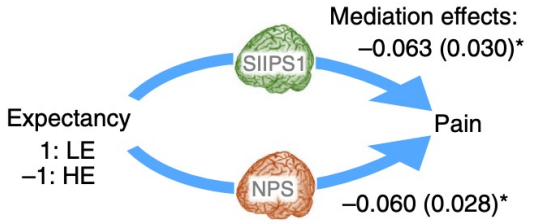
Building models of brain mechanisms: Multiple brain regions simultaneously predict outcomes

Integrating levels of analysis: Multilevel mediation can capitalize on rich within-subject data and address heterogeneity across individuals

Complementary functional tools: Combining mediation with pattern-recognition and component-based approaches



Woo et al., 2015



Woo et al., 2017

Mediation analysis basics 2 (example study)

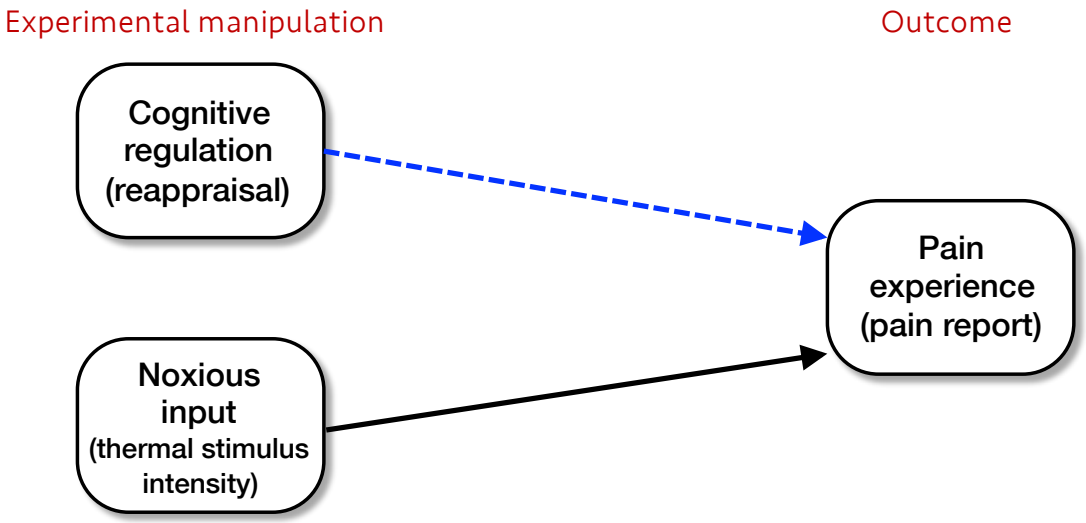
Choong-Wan Woo
Director of the Cocoan Lab

Slide credit: Tor Wager

Example study: Linking experiment, brain, and behavior

Does cognitive reappraisal influence pain perception in ways that matter?

Randomized experimental manipulation is the gold standard for establishing causality:



Woo et al., 2015

Example study: Linking experiment, brain, and behavior

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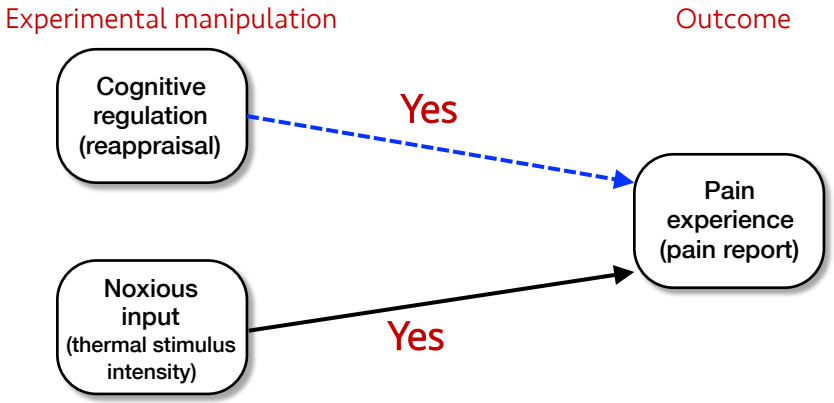
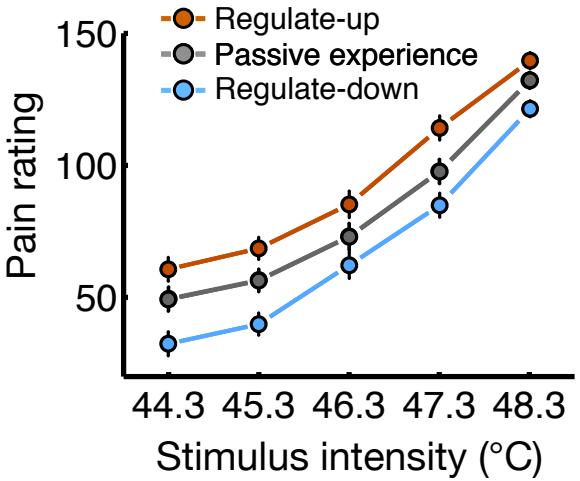
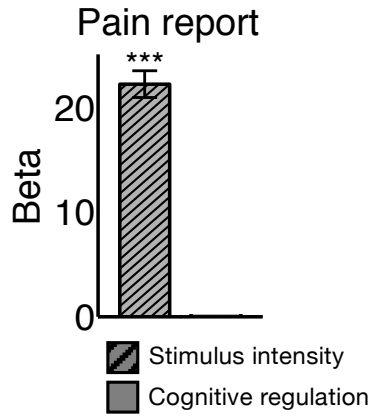




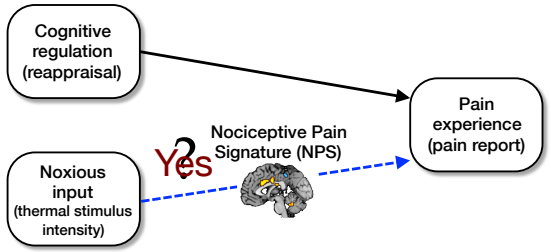


But does cognitive reappraisal affect nociception?

How to investigate its brain mechanisms?

Woo et al., 2015

Does noxious input influence pain report through NPS?



NPS: Wager et al., 2013

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

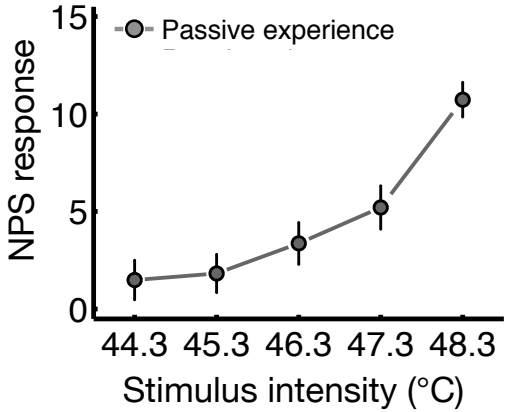
Persistent pain is measured by means of self-report, the sole reliance on which hampers diagnosis and treatment. Functional magnetic resonance imaging (fMRI) holds promise for identifying objective measures of pain, but brain measures that are sensitive and specific to physical pain have not yet been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

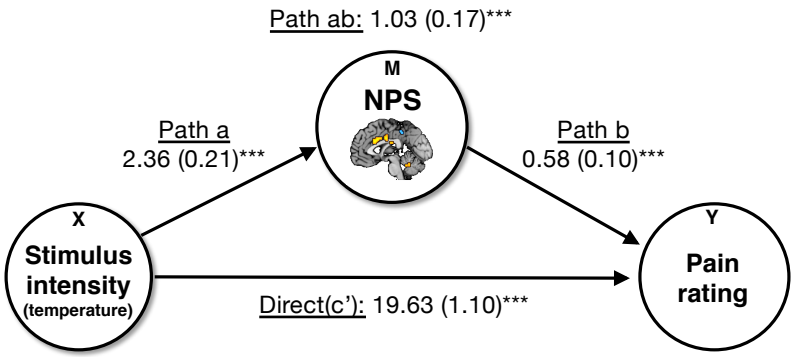
METHODS

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 brain regions — a neurologic signature — that was associated with heat-induced pain. The pattern included the thalamus, the posterior and anterior insulae, the secondary somatosensory cortex, the anterior cingulate cortex, the periaqueductal gray matter, and other regions. In study 2, we tested the sensitivity and specificity of the signature to pain versus warmth in a new sample. In study 3, we assessed specificity relative to social pain, which activates many of the same brain regions as physical pain. In study 4, we assessed the responsiveness of the measure to the analgesic agent remifentanil.

RESULTS

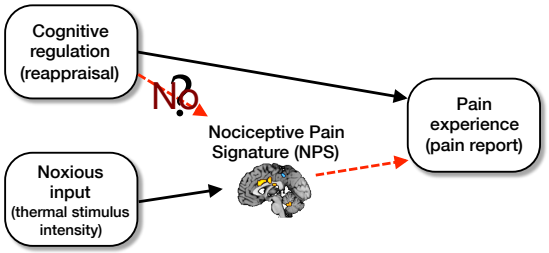
In study 1, the neurologic signature showed sensitivity and specificity of 94% or more (95% confidence interval [CI], 89 to 98) in discriminating painful heat from nonpainful warmth, pain anticipation, and pain recall. In study 2, the signature

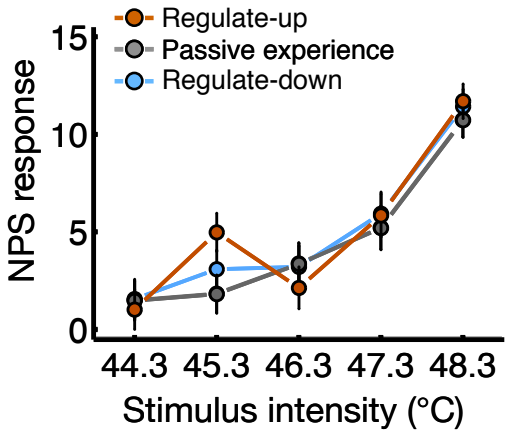


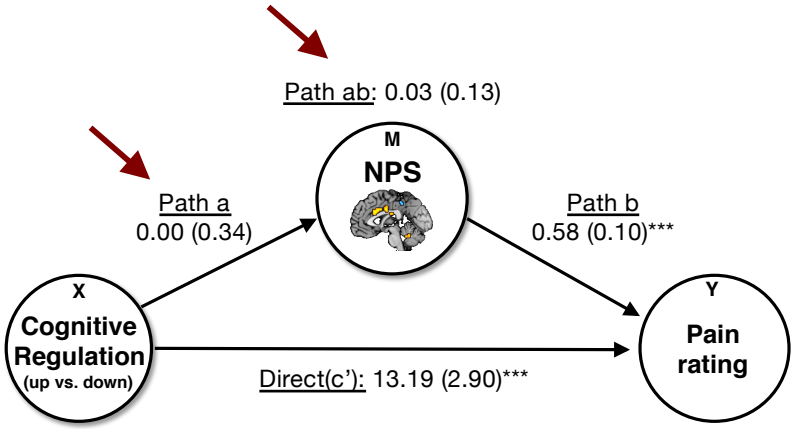


Woo et al., 2015

Does cognitive regulation influence pain report through NPS?

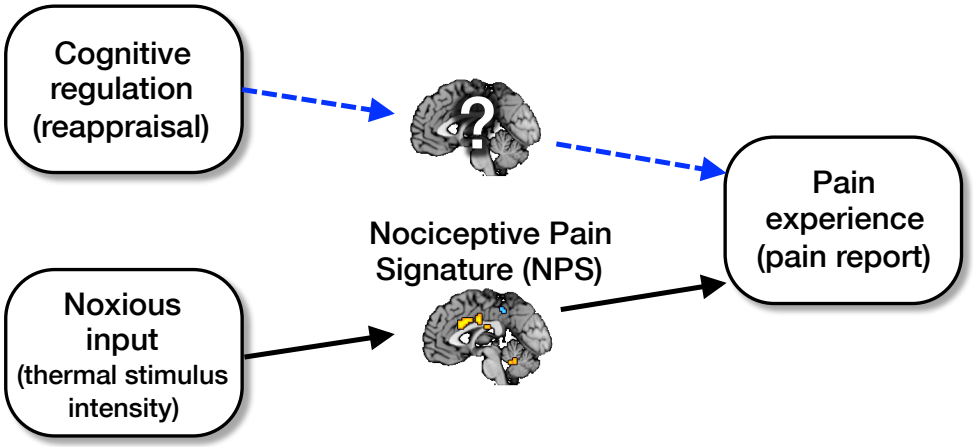






Woo et al., 2015

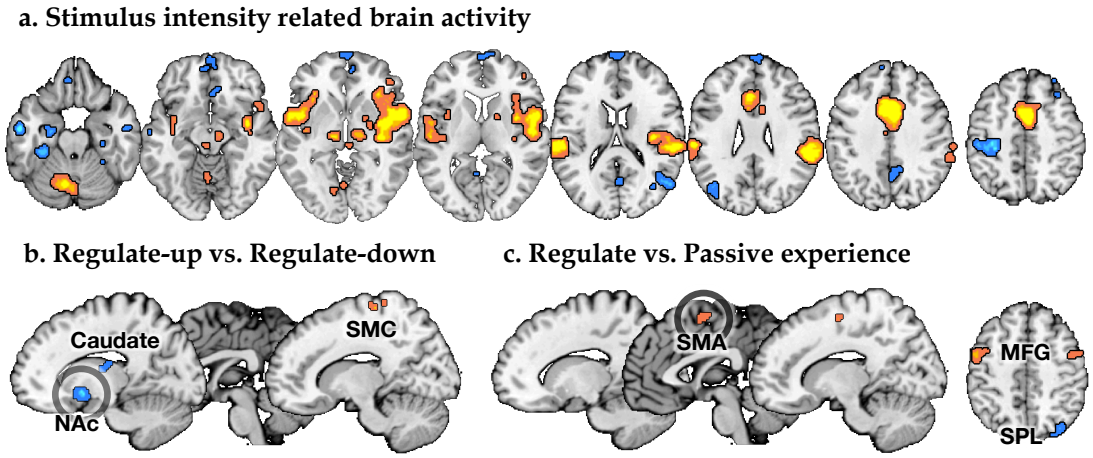
Then, what other systems mediating cognitive regulation effects on pain?



Woo et al., 2015

Voxel-wise mapping of cognitive regulation

Cluster FWER $p < .05$



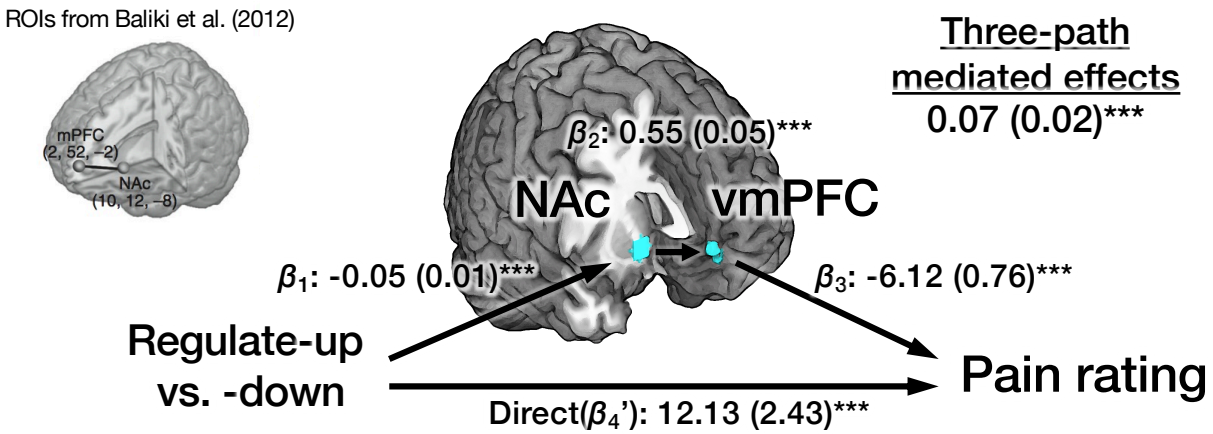
- Tempting to infer that these areas are important for driving cognitive reappraisal-induced changes in pain. But...

  Do all these regions actually predict reported pain?

- We conducted the whole-brain search with one-step mediation framework, but no cluster survived
- This may suggest that there exist additional mediation steps.

Woo et al., 2015

Then, what other systems mediating cognitive regulation effects on pain?

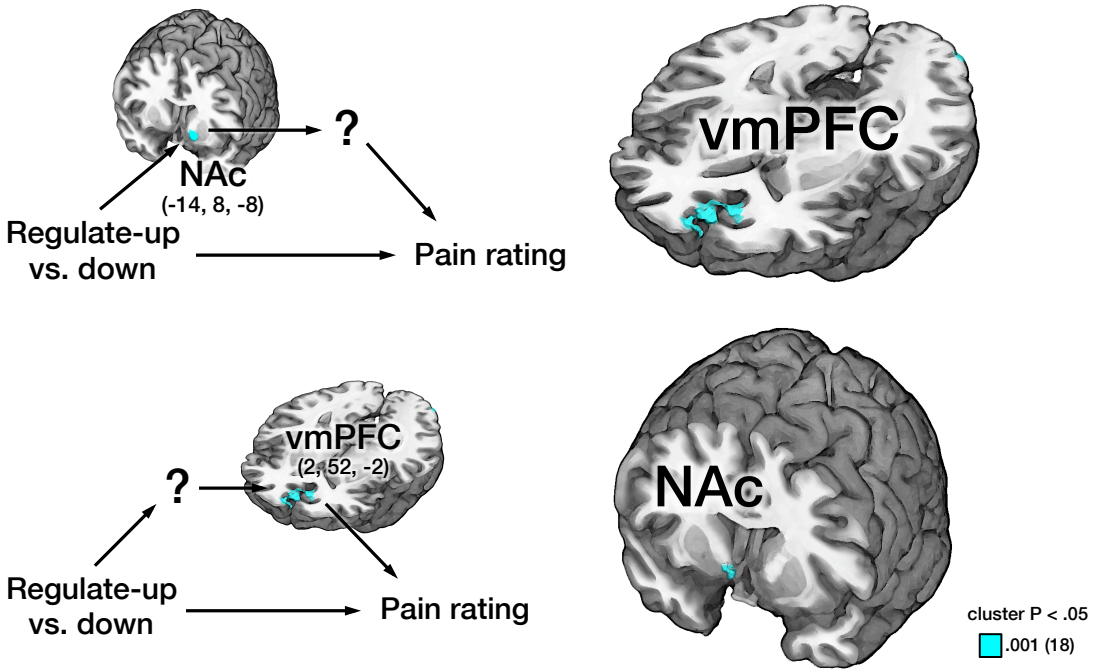


- The **NAc-vmPFC pathway** from Baliki et al. (2012) was **a significant, positive mediator** of the relationship between cognitive regulation and pain ratings (Reversing the direction of the mediation yielded non-significant results).

Woo et al., 2015

Whole brain search for mediators

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



Woo et al., 2015

Summary of Woo et al., 2015

- 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.

Core ideas

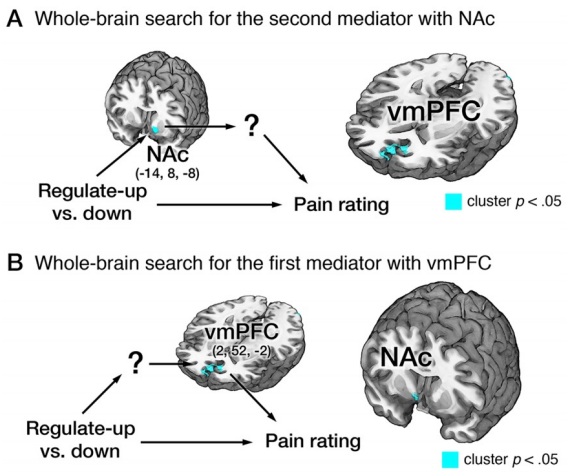
Linking experiment, brain, and behavior: Experimental manipulations, brain measures, and outcomes linked in a single model

Unique advantages: Flexibility, transparency, specified assumptions and limitations

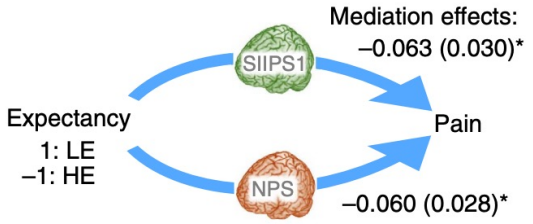
Building models of brain mechanisms: Multiple brain regions simultaneously predict outcomes

Integrating levels of analysis: Multilevel mediation can capitalize on rich within-subject data and address heterogeneity across individuals

Complementary functional tools: Combining mediation with pattern-recognition and component-based approaches



Woo et al., 2015



Woo et al., 2017

Mediation analysis basics 3 (mediation explained)

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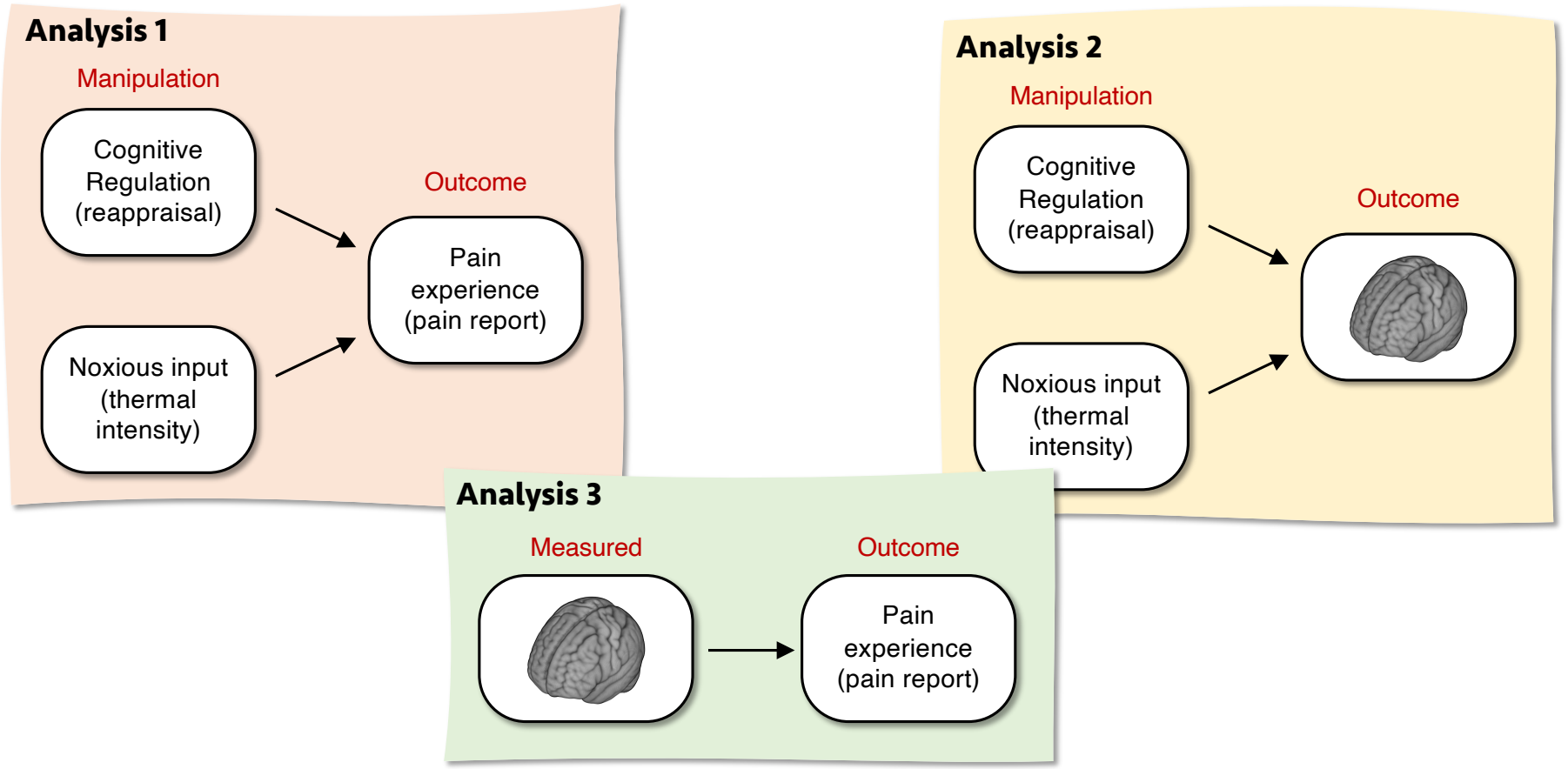
Director of the Cocoan Lab

Slide credit: Tor Wager

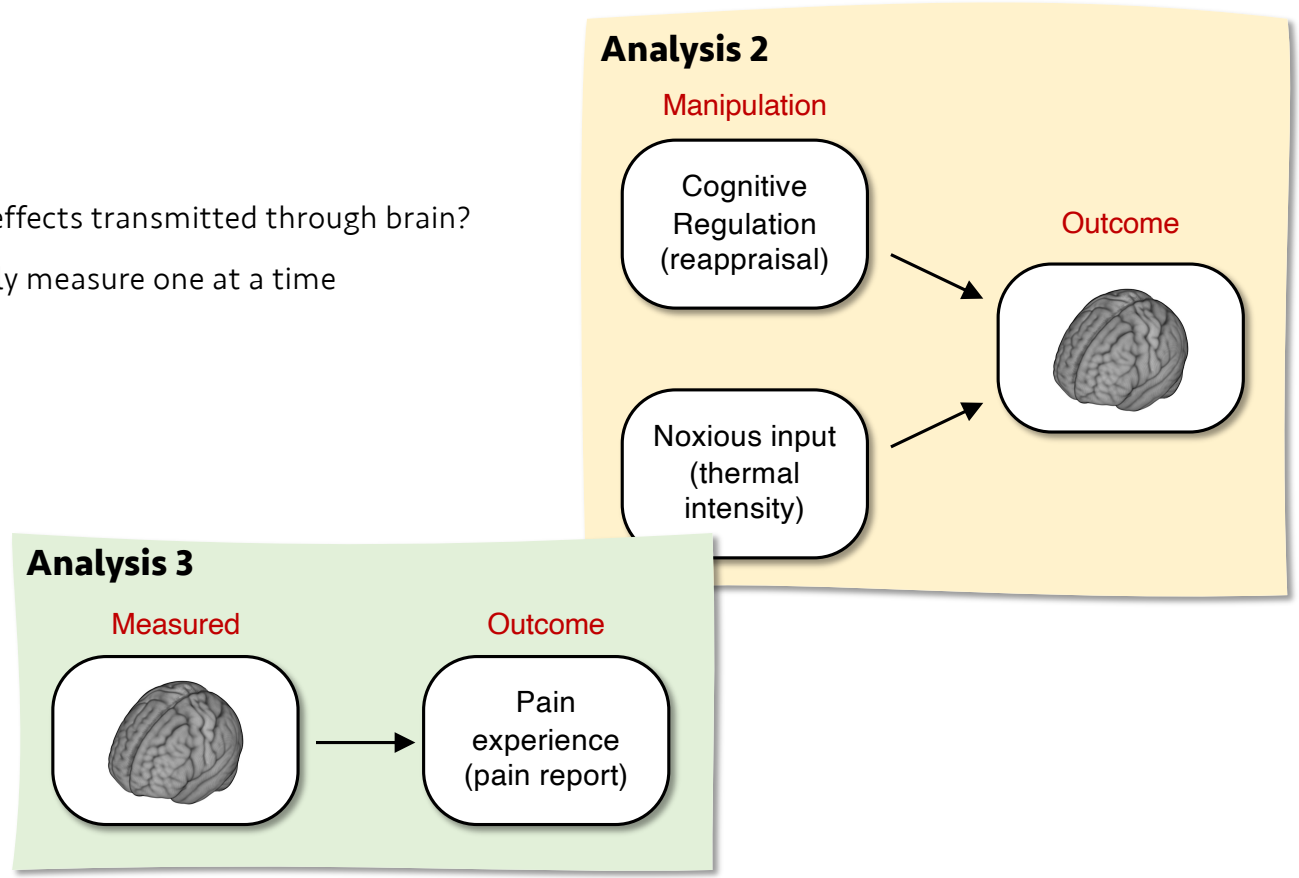
We need to combine three analyses to link experiment, brain, and behavior



We need to combine three analyses to link experiment, brain, and behavior

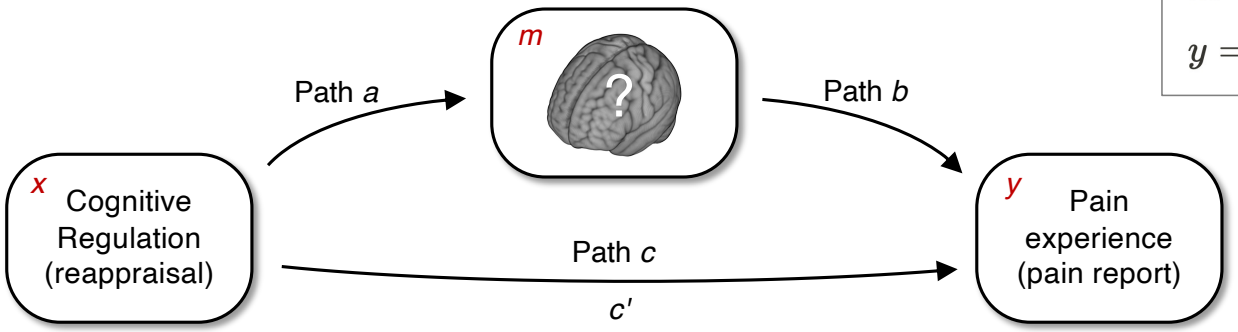
Issues:

- Are the voxels the same?
- Are effect sizes consistent with effects transmitted through brain?
- Typical analysis packages can only measure one at a time



Baron and Kenny's mediation framework

$$y = i_y + cx + e_y$$
$$m = i_m + ax + e_m$$
$$y = i_y + bm + c'x + e'_y$$



Baron and Kenny (1986): mediation effects = conjunction of 3 effects

1) *c* effect: There is a relationship to be mediated

*but not always: see Kenny, Kashy, and Bolger (1998)

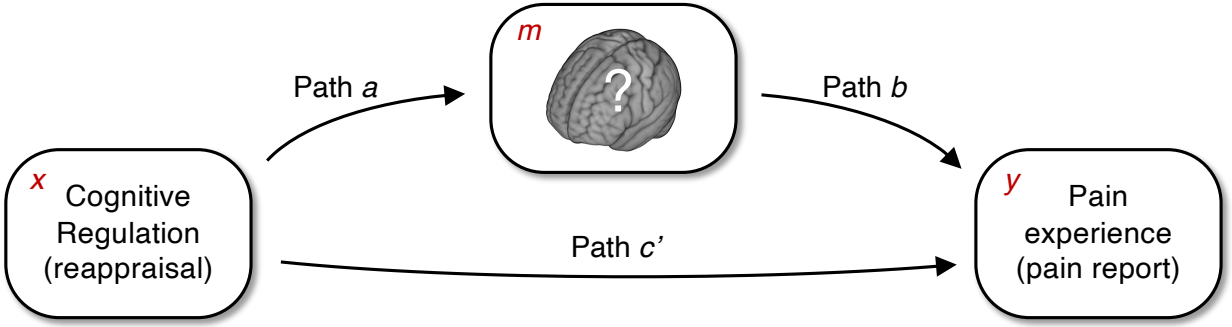
2) *a* effect: initial variable (*x*) related to mediator (*m*)

3) *b* effect: mediator (*m*) relates to outcome (if *m* is a complete mediator, *c'* = 0)

Single tests of mediation

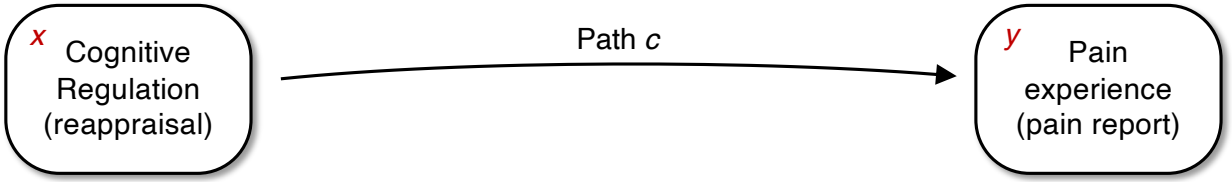
Full model, with mediator

$$m = i_m + ax + e_m$$
$$y = i_y + bm + c'x + e'_y$$



Reduced model, without mediator

$$y = i_y + cx + e_y$$



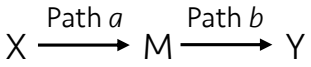
Counterfactual: If we were to prevent *m* from varying, the effect of *x* on *y* would be reduced or absent

- Does *m* explain some of the *x*-*y* relationship, Path *c*?
- Test *c*–*c'*, same as significance of Path *a*·*b* product

Mediation effects

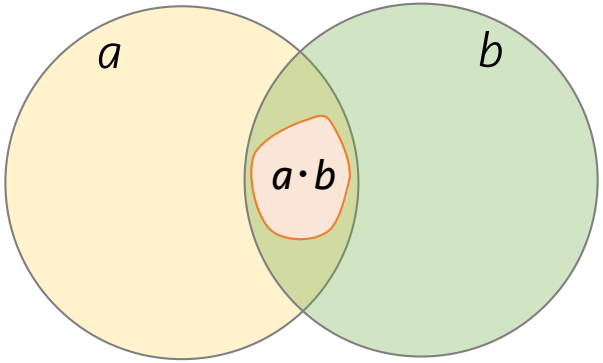
- The statistical test of $a \cdot b$
- Sobel test: Aroian version (Aroian, 1944) $Z = \frac{ab}{b^2 se(a)^2 + a^2 se(b)^2 + se(a)^2 se(b)^2}$
  - Overconservative

- Now replaced with bootstrap test (Efron, 2002; Shrout & Bolger, 2002; Preacher & Hayes, 2004; Wager et al., 2009)



Venn Diagram
(Significant tests)

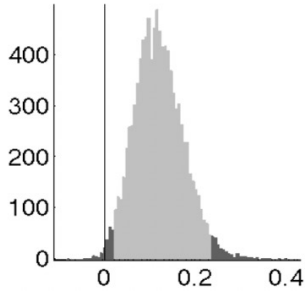
$a \cdot b$ is a subset of the "conjunction"



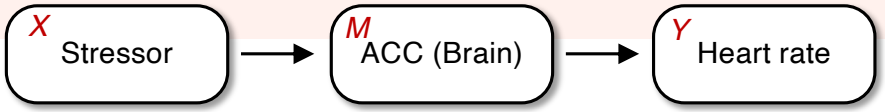
Testing the significance of $a \cdot b$

- **Bootstrap test** (Efron, 2002; Shrout & Bolger, 2002; Preacher & Hayes, 2004; Wager et al., 2009)
  - Sample rows of matrix [*x m y*] with replacement to fill sample of *N* subjects
  - Calculate mediation effect $a \cdot b$
  - Repeat many times (e.g., 10,000 for inference at tails)
  - Confidence interval/*p*-values based on bootstrapped distribution

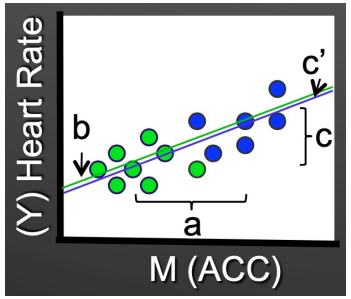
Histogram of bootstrapped indirect $a \cdot b$ effects

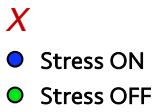


A graphical example of $a \cdot b$



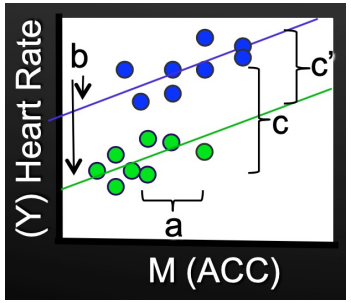
Mediation





- Anterior cingulate (ACC, *M*) mediates Stress (*X*) effects on Heart Rate (*Y*)
  - Effect sizes of *a* and *b* together large enough to explain *c*
  - $c - c' \neq 0$

No mediation



- Significant a and b effects, but little/no mediation
  - $c' = c$

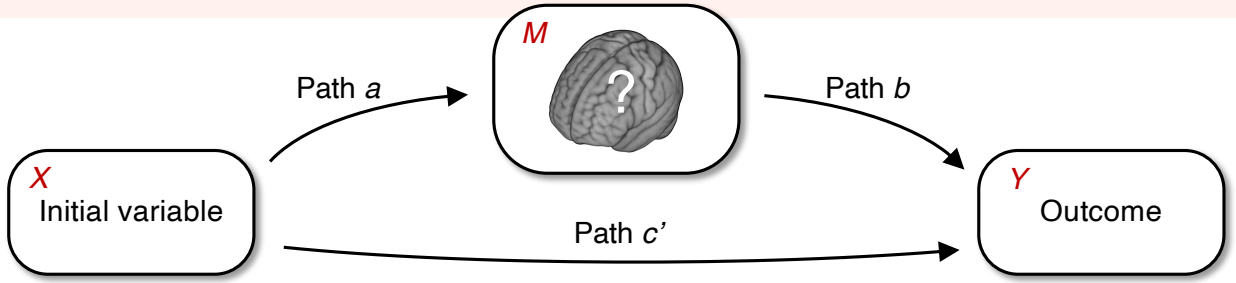
Mediation Effect Parametric Mapping

- Search for brain voxels/regions that are mediators
- Two basic options: single level and multi-level

- Single level:
  - No repeated measures
  - One observation on each variable (*X, M, Y*) per person
  - *M* is usually a contrast image (i.e., Task vs. Control) for each person (but it could be anything, e.g., structural brain features)

- Multi-level:
  - Multiple (repeated) observations of *X, M, Y* for each person
  - *M* is a series of brain maps (for ordered conditions, single-trials or single-volumes)

Mediation Effect Parametric Mapping, Single level

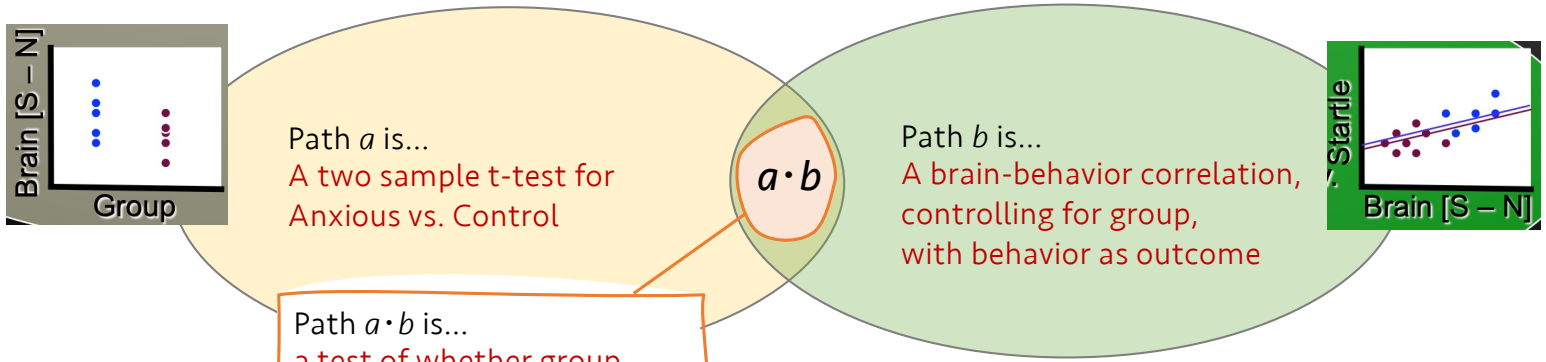


Example:

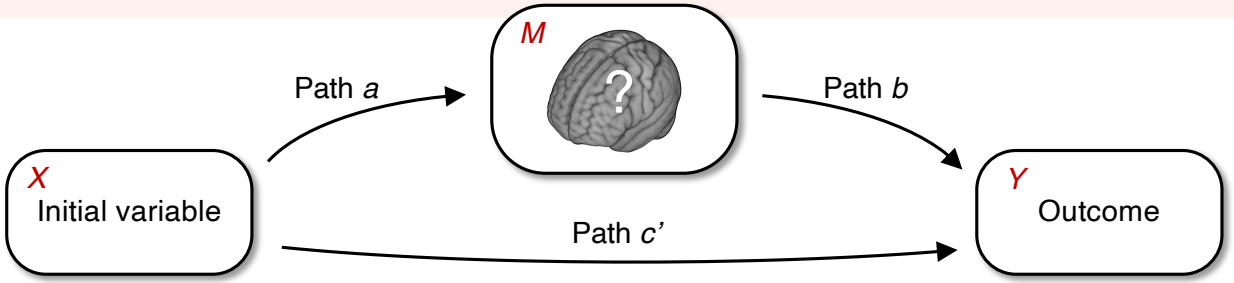
X is...
A grouping variable:
Anxious vs. Control

M is...
Contrast values from a voxel
Spider vs. Neutral

Y is...
A behavioral variable
Startle eyeblink for [Spider vs. Neutral]



Mediation Effect Parametric Mapping, Multi-level

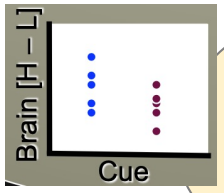


Example:

X is...
Expectancy cue:
High vs. Low

M is...
Trial-by-trial fMRI activity
during pain

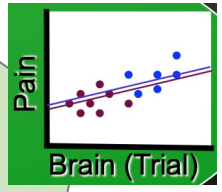
Y is...
A behavioral variable
Reported pain



Path *a* is...
A paired t-test for High
vs. Low Pain Cues

a·*b*

Path *b* is...
A "parametric modulation,"
Reported pain, but controlling
for cue and with pain as
outcome



Path *a*·*b* is...
a test of whether cue
effects on pain are
explained by brain activity

Advantages and limitations of mediation

- Advantages
  - Focus on explaining behavior / other outcomes
  - Transparent: Relying on simple, widely used linear model
  - Works with any kind of data
- Limitations:
  - Inferences about causality and directedness are limited
  - Many assumptions are hard/impossible to check, often violated

Focus on pathway discovery/description rather than causal inference

Mediation analysis basics 4
(additional notes on mediation analysis)

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Slide credit: Tor Wager

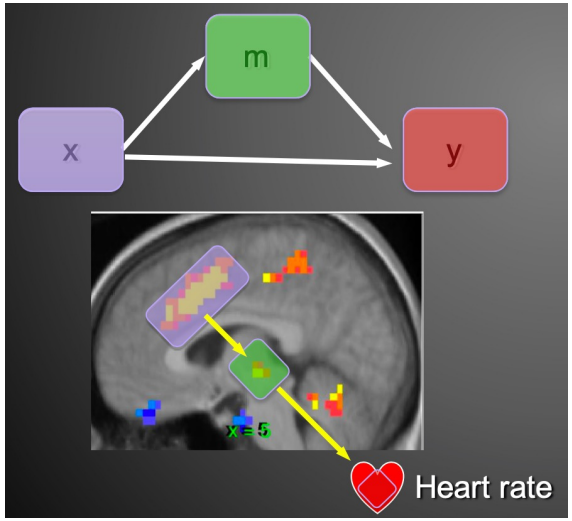
Mediation and moderation

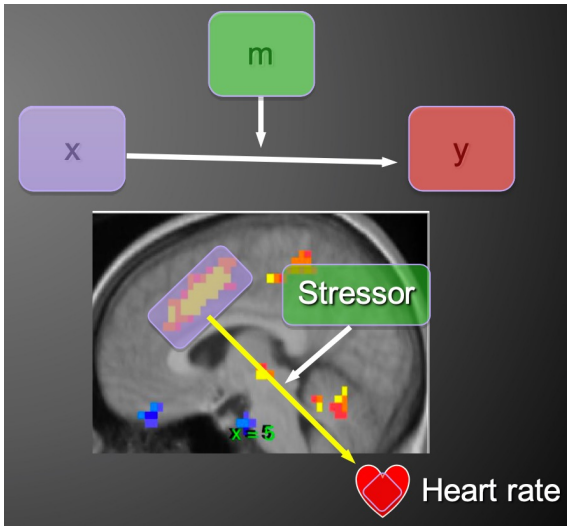
Mediation

- Does *m* explain some or all of the relationship between *x* and *y*?
- Establish pathway

Moderation

- Does the level of *m* influence the relationship between *x* and *y*?
- Establish "regulation of" a pathway

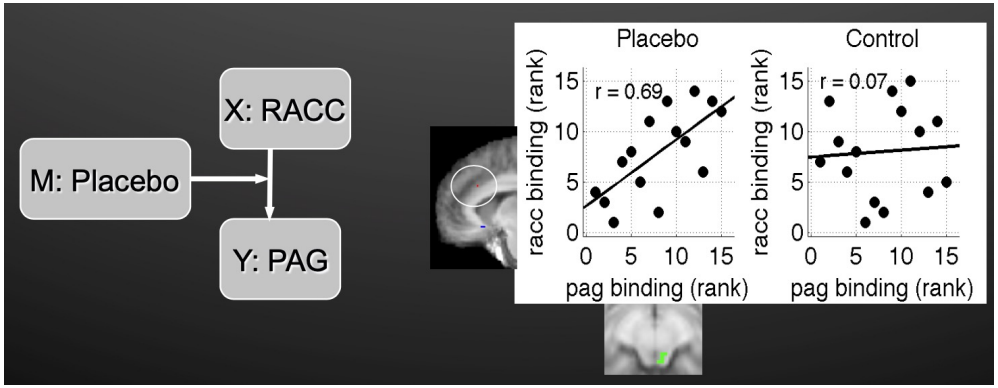




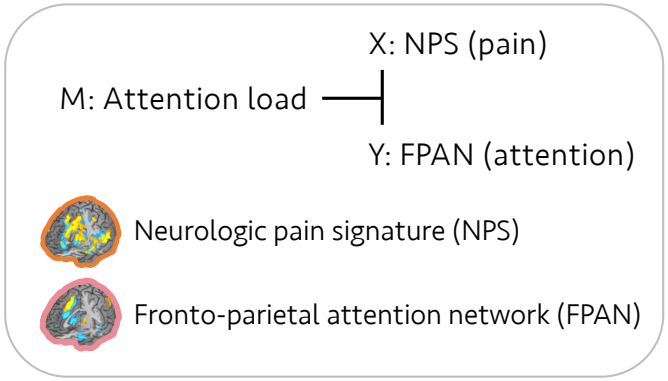
Wager et al., 2009

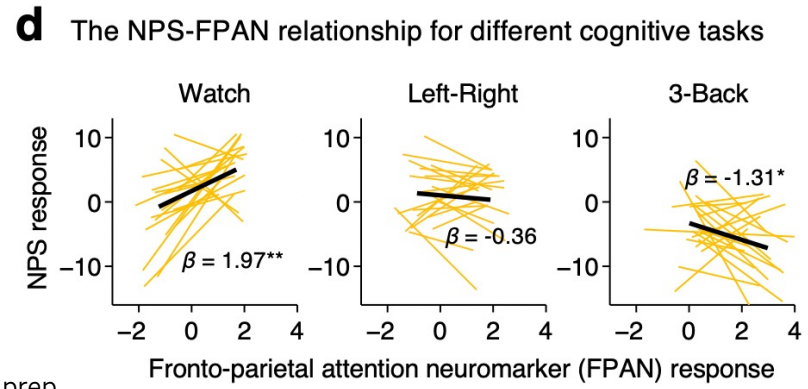
Moderation

- Moderation (Baron & Kenny, 1986)
  - The relationship between region A and B is predicted by the value of *M*
  - Interaction between *X* and *M* on *Y*, e.g., $Y = b(X \times M)$



Wager et al., 2007



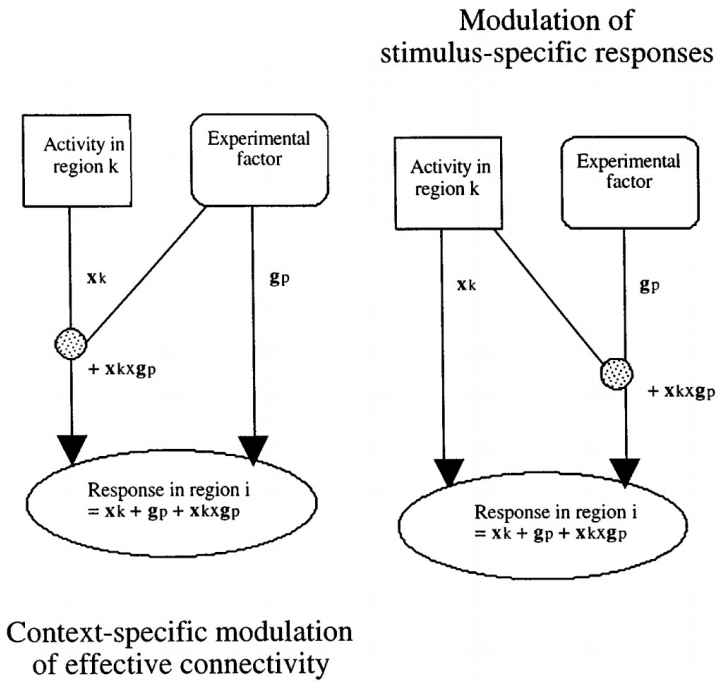


Woo et al., in prep

Relevant technique: PPI

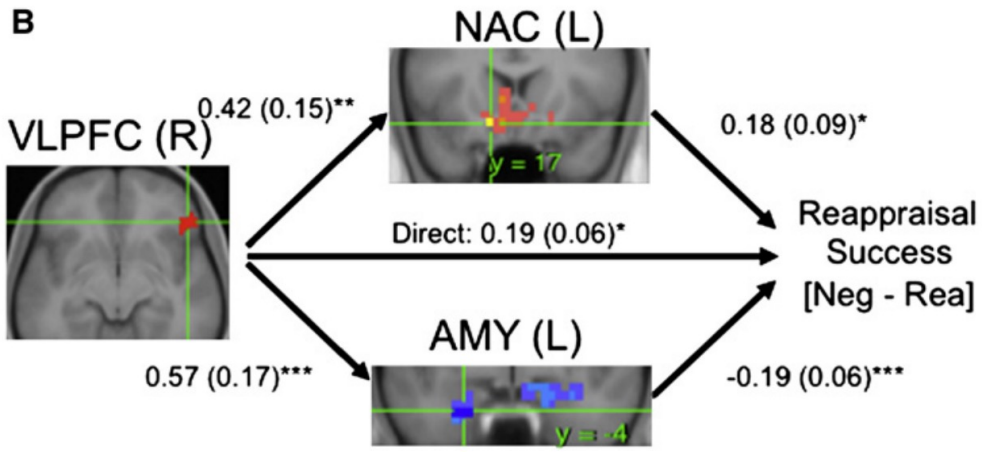
- Two-level search for moderators

- In SPM, on time series data,
  - "Psychophysiological interaction" (PPI): Moderator is a psychological (experimental) variable, and examining the relationship between fMRI activity and each voxel in a brain map (as the outcome)



Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. NeuroImage, 6(3), 218–229.

Two-pathway mediation

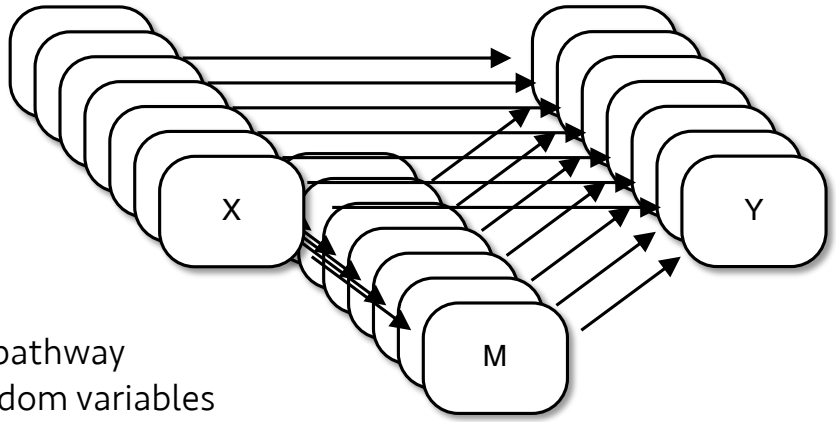


Wager et al., 2008

Path covariance in multi-level mediation

- Different from single level, $c - c' = a \times b$, in multi-level, $c - c' = a \times b + \boxed{cov(a, b)}$

Path strengths vary across subjects

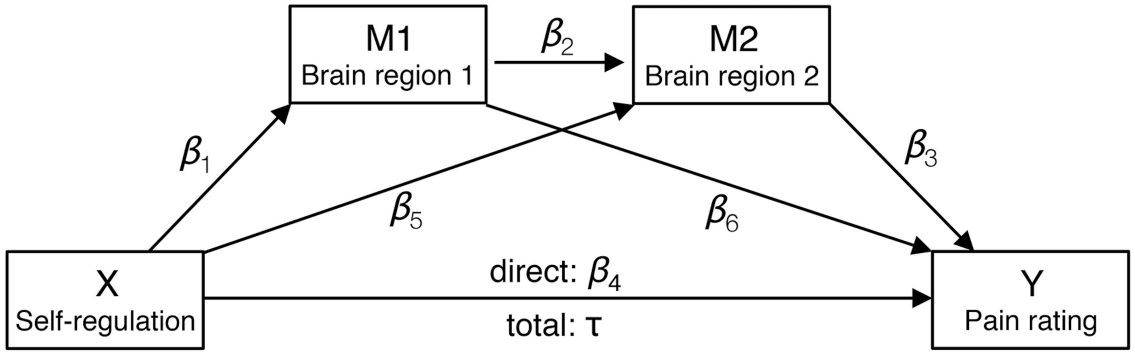


In multilevel, subject-level pathway strengths (*a, b, c, c'*) are random variables

Possible situation:
Non-significant Path *a* and *b*, but significant Path *ab*

Three-path mediation

- **Three-path mediation analysis:** can assess relationships among stimulus intensity or self-regulation (X), two different brain mediators (M1 and M2), and pain report (Y).
  - The analysis is based on a three-path mediation model suggested by Taylor et al. (2007)
  - First implemented (for the brain analysis) and used in Woo et al. 2015



$$y = \tau x + e_y$$

$$m_1 = \beta_1 x + e_{m_1}$$

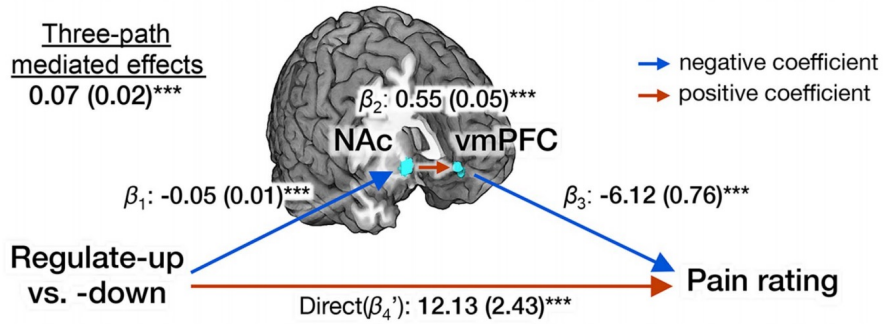
$$m_2 = \beta_2 m_1 + \beta_5 x + e_{m_2}$$

$$y = \beta_4 x + \beta_3 m_2 + \beta_6 m_1 + e'_y$$

$$\sigma^2_{b_1 b_2 b_3} = b_1^2 b_2^2 \sigma^2_{b_3} + b_1^2 b_3^2 \sigma^2_{b_2} + b_2^2 b_3^2 \sigma^2_{b_1}$$

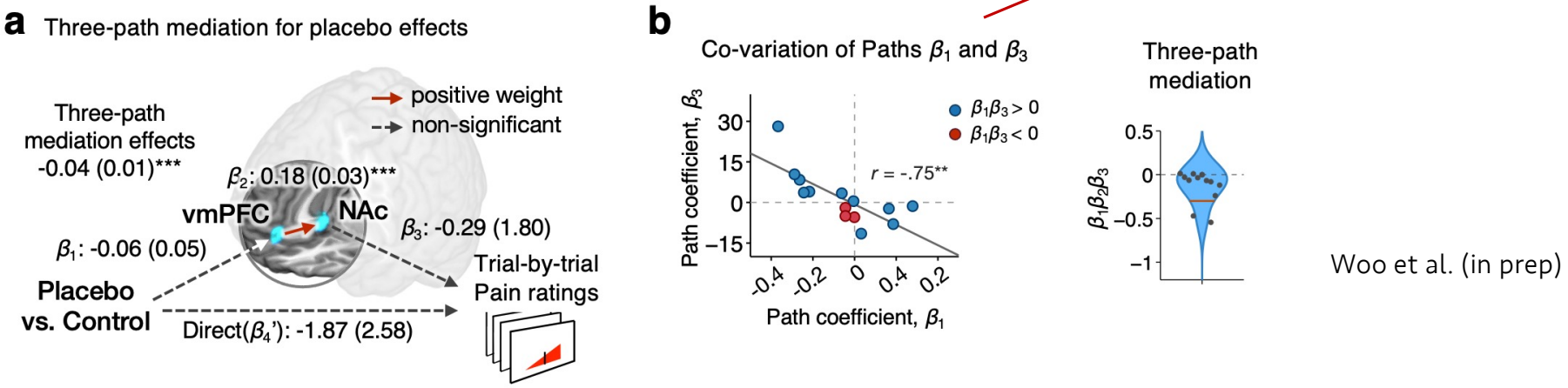
Taylor, a. B., MacKinnon, D. P., & Tein, J.-Y. (2007). Tests of the Three-Path Mediated Effect. Organizational Research Methods, 11(2), 241–269.

Three-path mediation (example results)



Woo et al. (2015)

Significant mediation driven by
the covariance between Paths β_1 and β_3



Woo et al. (in prep)

Mediation analysis basics 5
(CANlab mediation toolbox)

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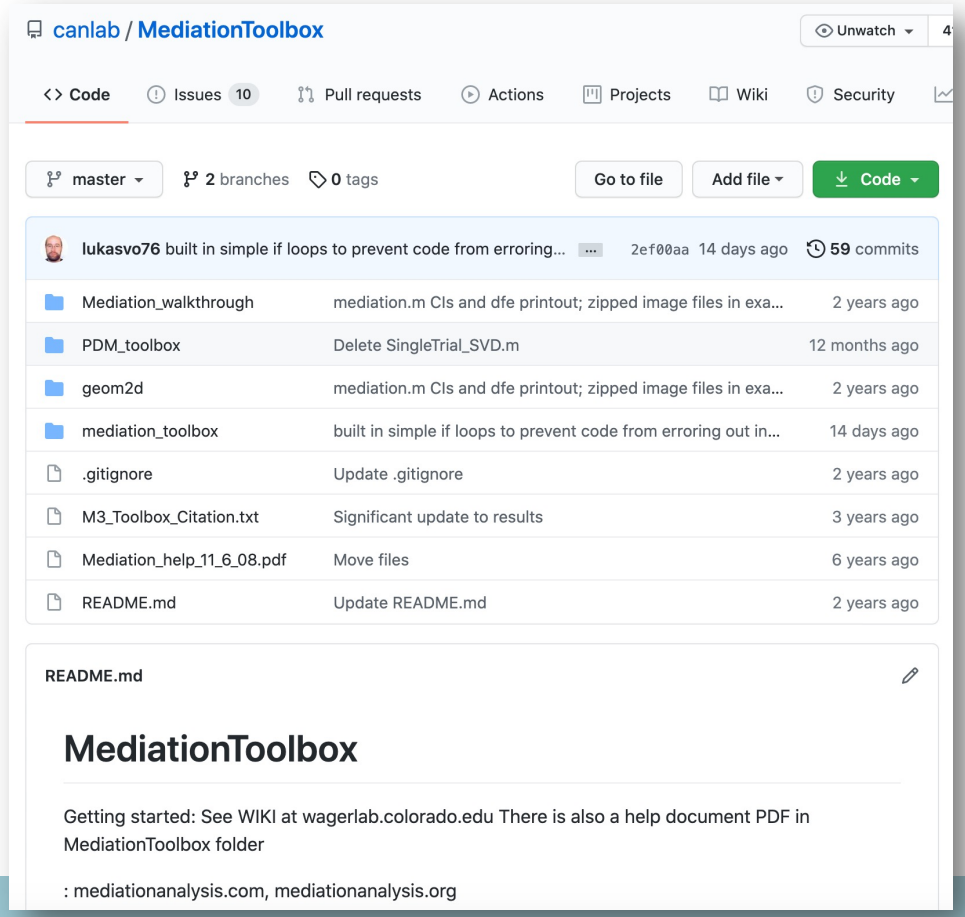
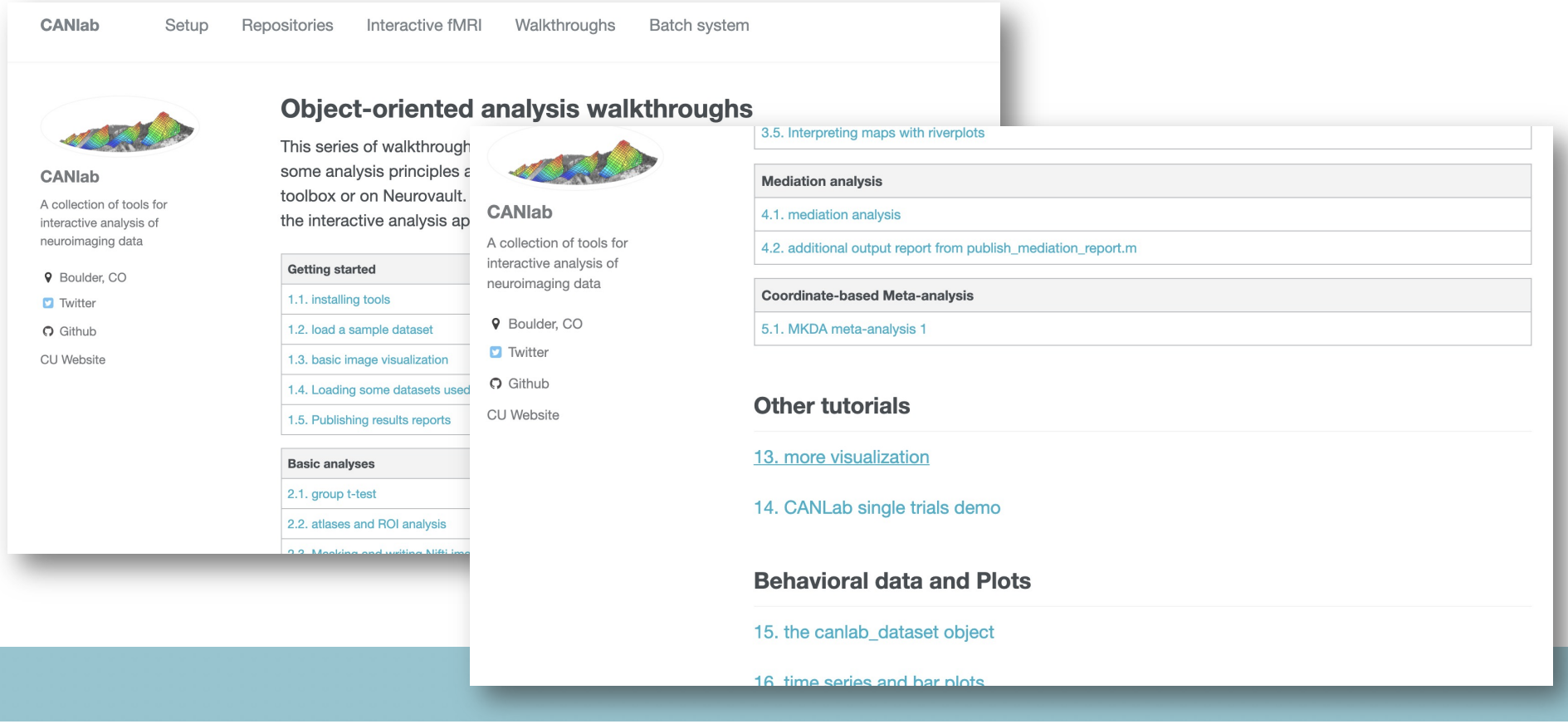
Mediation toolbox

https://github.com/canlab/MediationToolbox



Mediation toolbox walkthroughs

https://canlab.github.io/walkthroughs/



Mediation example codes

https://www.dropbox.com/sh/nlxt9j1ddhdij2r/AADhcokPwY7Bbc1EJ-aIxF0Ya?dl=0