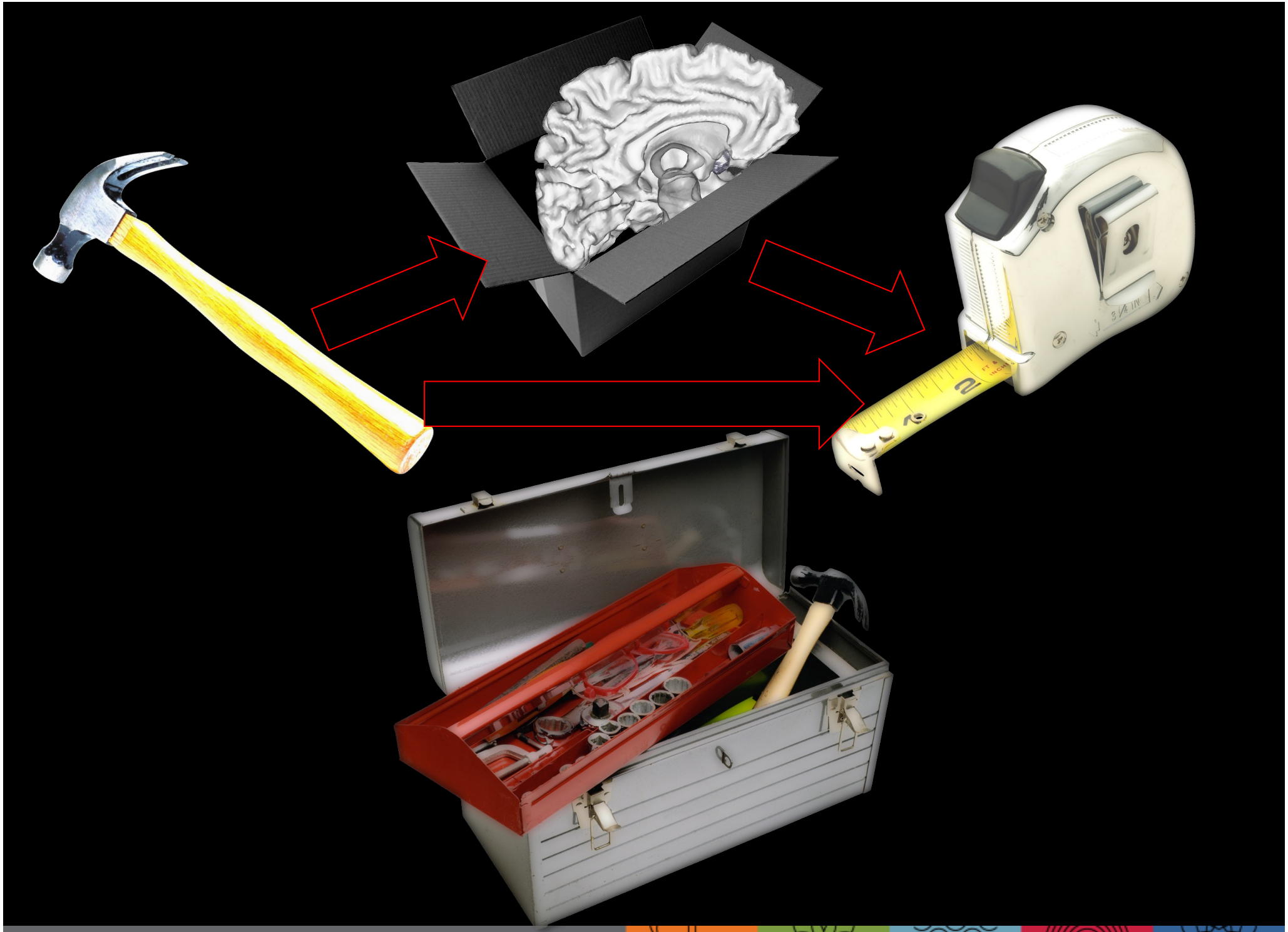
U.S. Department of Health & Human Services • National Institutes of Health

NIH National Center for Complementary and Integrative Health

Mediation analysis for fMRI-based pain assessment

Lauren Atlas

August 9, 2016


National Center for Complementary and Integrative Health

Mediation analysis for fMRI

- ✓ Assess dynamic relationships between experimental manipulation, brain, and behavior
- ✓ Voxelwise mixed effects (multilevel) path analysis
- ✓ Identify candidates for causal inference
- ✓ Effective connectivity analysis
- ✓ Identify sources of individual differences in pathway strength

Roadmap

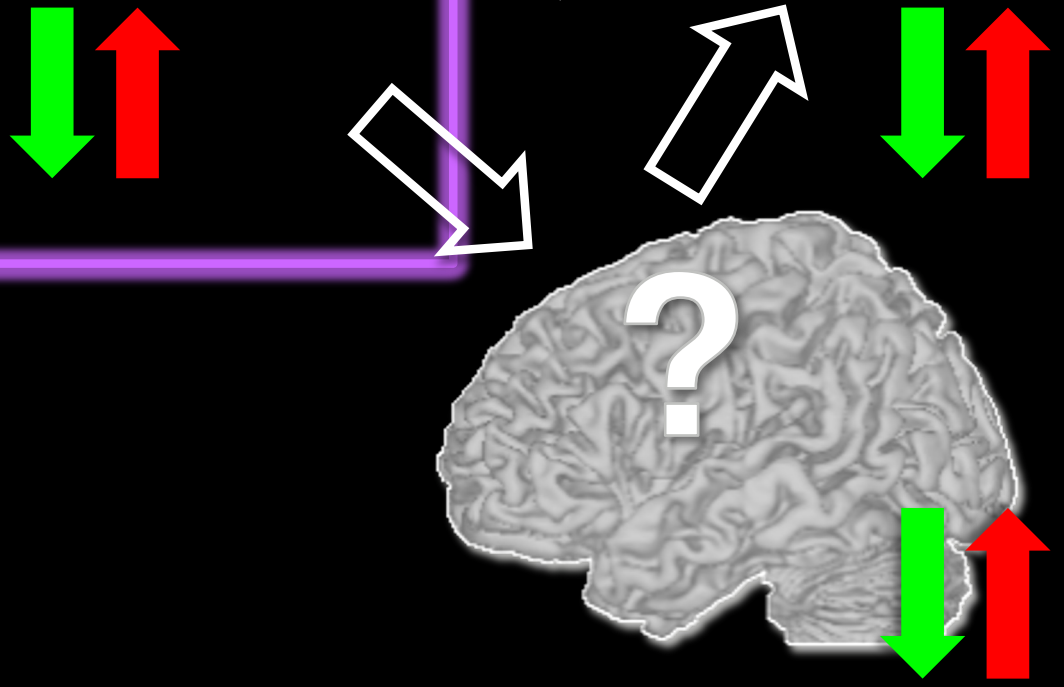
- Introduction (Pain imaging)
- Mediation analysis for fMRI
  - Single level mediation
  - Multi-level mediation
- Brain mediators of the effects of heat on pain
- Brain mediators of expectancy effects on pain

Roadmap

- Introduction (Pain imaging)
- Mediation analysis for fMRI
  - Single level mediation
  - Multi-level mediation
- Brain mediators of the effects of heat on pain
- Brain mediators of expectancy effects on pain

PAIN

Expectations ⇨ Experience

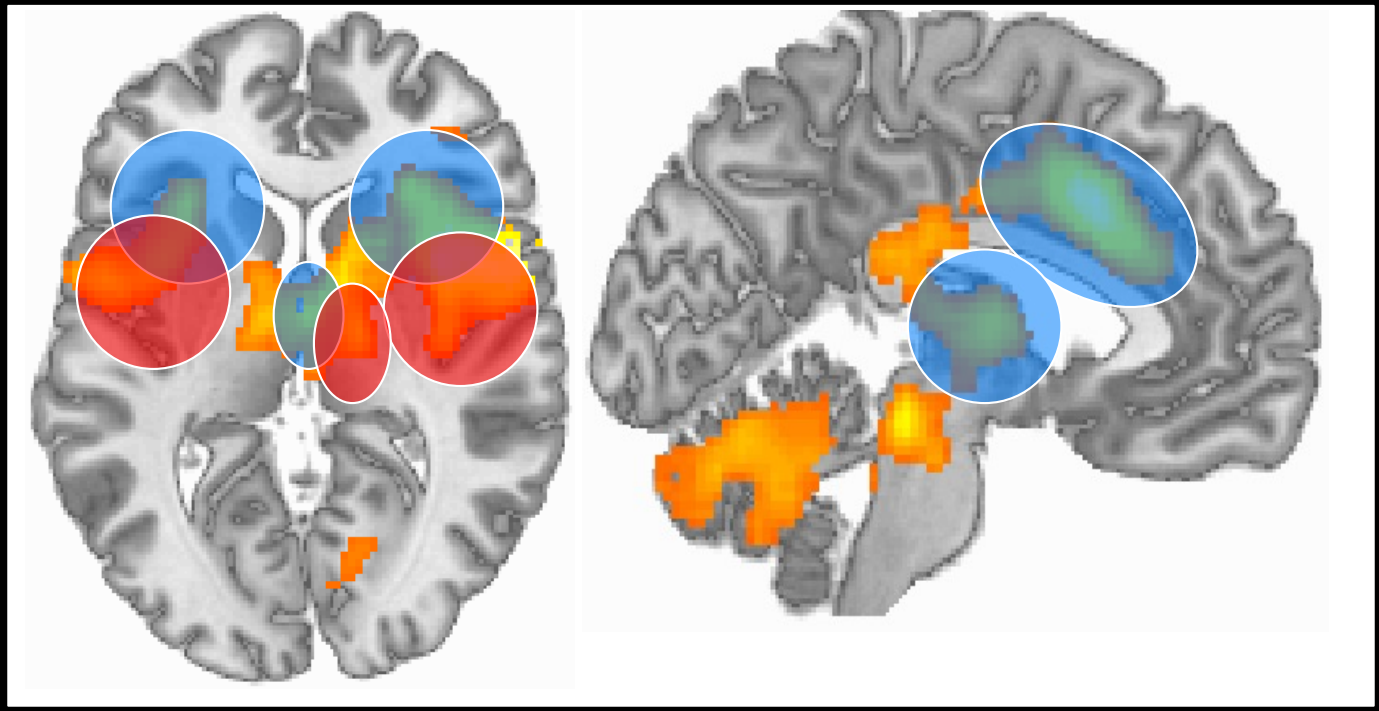


PAIN

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

–IASP Task force on taxonomy, 1994

“The pain matrix”



Sensation

Lateral thalamus
SI
SII
Posterior Insula

Affect

Medial thalamus
Anterior cingulate
Anterior insula

High vs Low intensity stimulation
Five studies, N = 114
FWE, p<.05

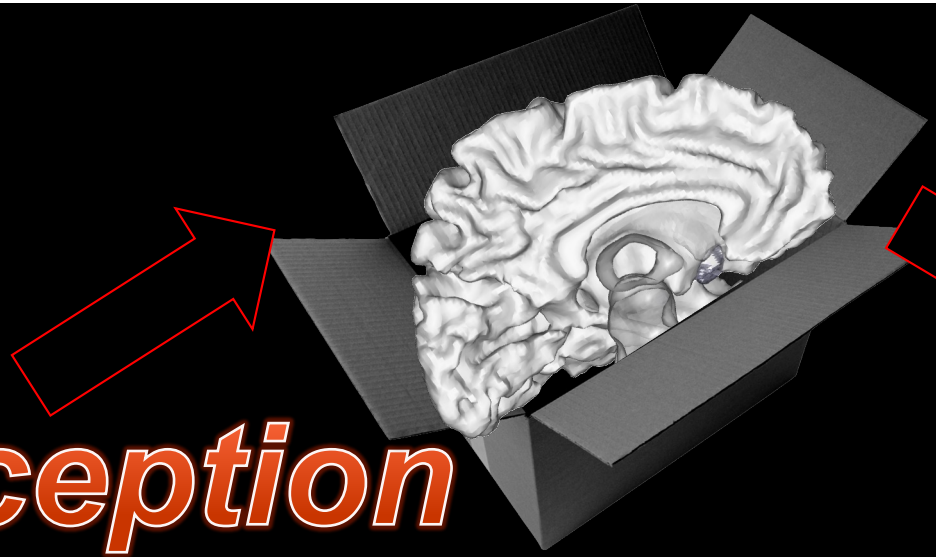
Atlas et al. (2010), *JNeurosci*

PAIN

"Pain is always subjective."

"Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause."

–IASP Task force on taxonomy, 1994



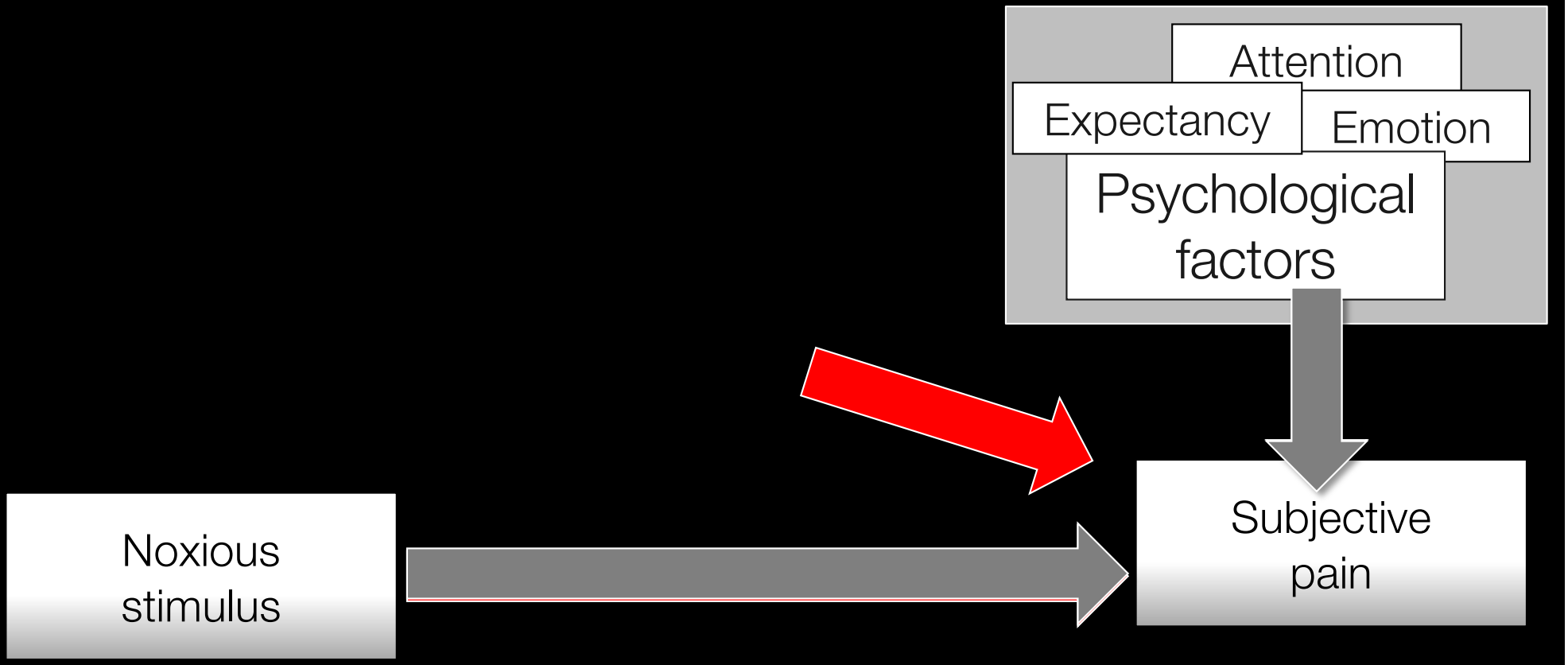
Nociception

PAIN

Noxious stimulus

Subjective pain

I. Which brain pathways mediate the effects of noxious stimuli on subjective pain?



I. Which brain pathways mediate the effects of noxious stimuli on subjective pain?

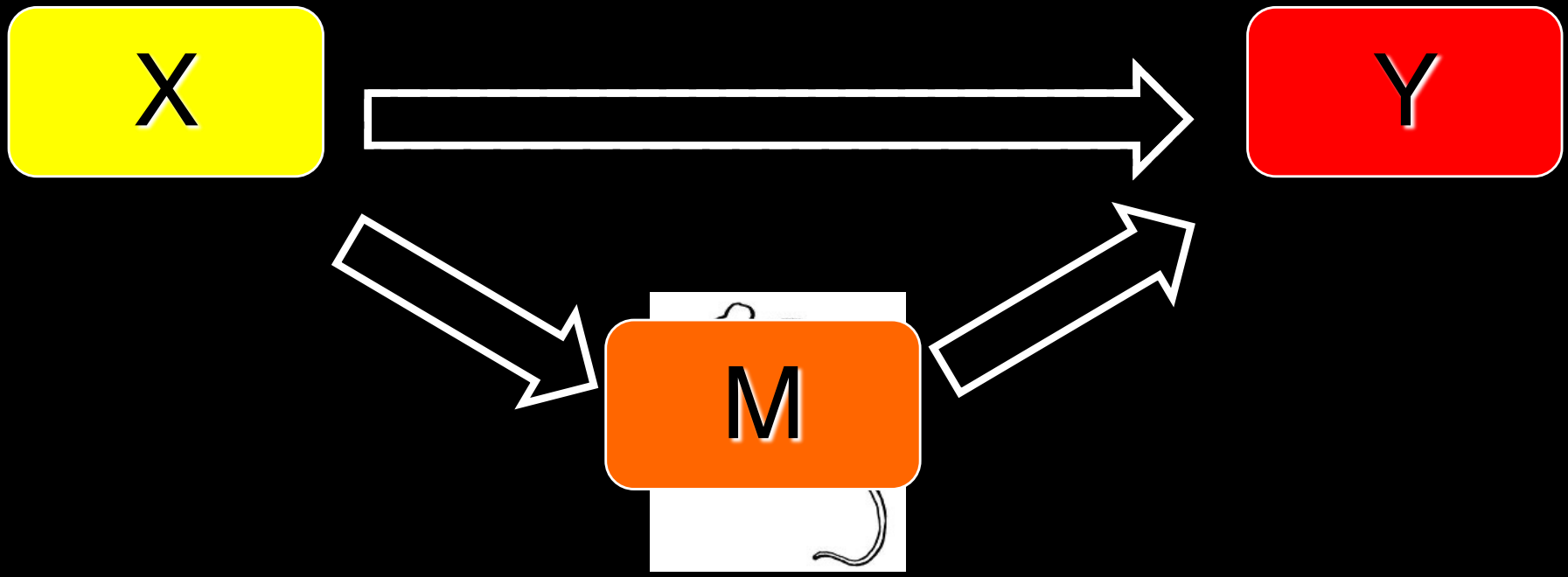
II. Which pathways mediate expectancy effects on pain?

Roadmap

- Introduction (Research questions)
- Mediation analysis for fMRI
  - Single level mediation
  - Multi-level mediation
- Brain mediators of the effects of heat on pain
- Brain mediators of expectancy effects on pain

Mediation

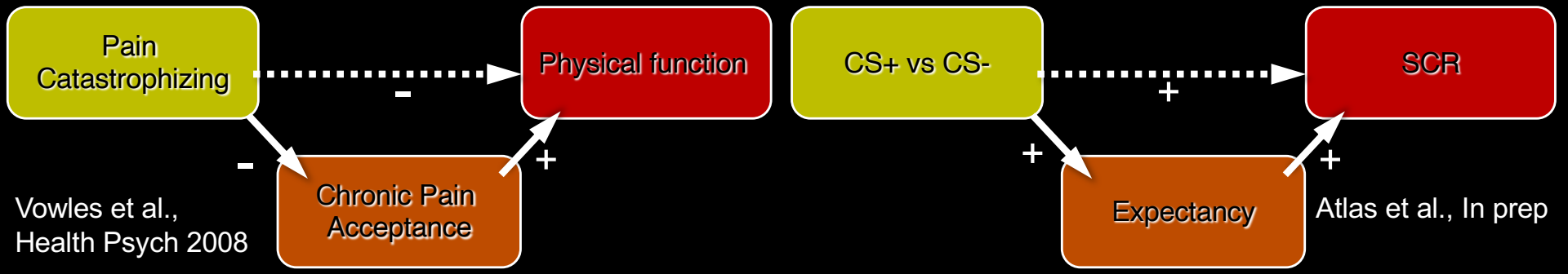
Mediator: The process / intervening variable that explains the relationship between the independent and dependent variables



Woodworth, 1928

Mediation in behavioral experiments

Mediator: The process / intervening variable that explains the relationship between the independent and dependent variables



SINGLE LEVEL MEDIATION

MULTI-LEVEL MEDIATION

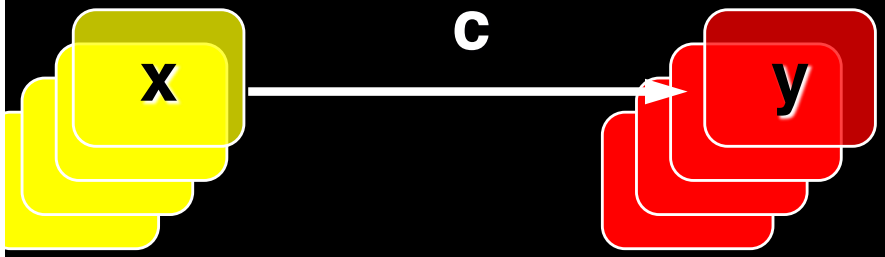
INTERPRETATION: **X** leads to changes in **M** which in turn leads to changes in **Y**

*NOTE: **Causality can only be truly established** by experimentally manipulating X and M.*
Statistics simply evaluate your theorized causal model.

Moderator: A variable that alters relationship between X and Y

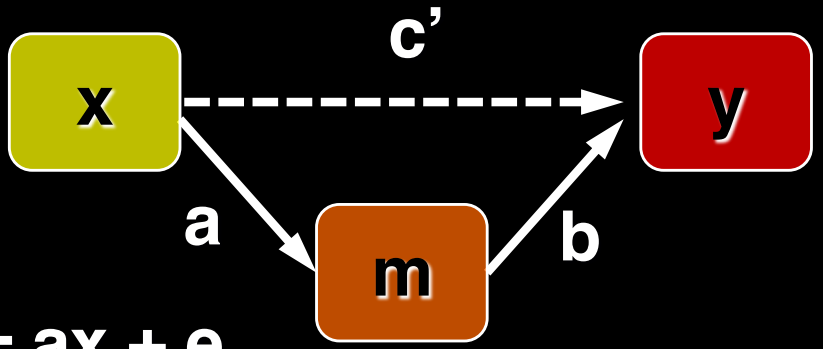
Statistical Mediation

Reduced model, without mediator



$y = cx + e_y$

Full model, with mediator



$m = ax + e_m$

$y = bm + c'x + e'_y$

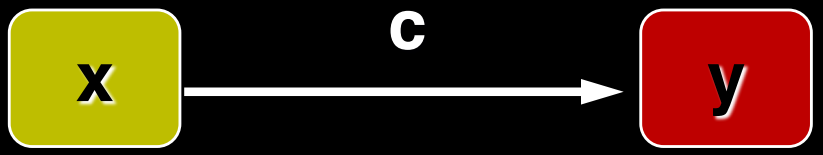
Baron and Kenny (1986) – conjunction of 3 effects:

1) ***c* effect: There is a relationship to be mediated**
2) ***a* effect: initial variable related to mediator**
3) ***b* effect: mediator relates to outcome, controlling for initial variable**

And, if m is a complete mediator, c' = 0

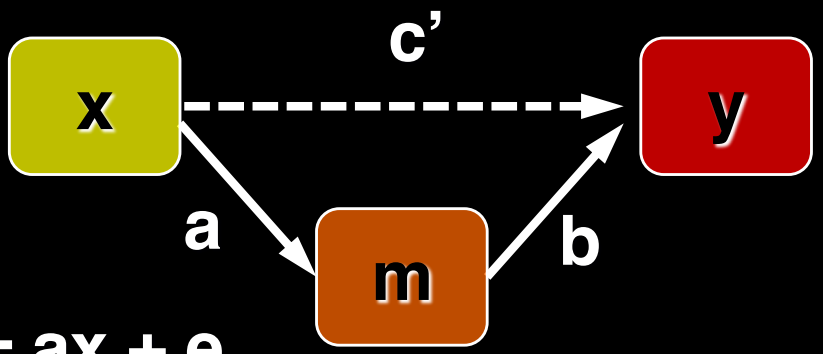
Demonstrating Mediation

Reduced model, without mediator



$y = cx + e_y$

Full model, with mediator



$m = ax + e_m$

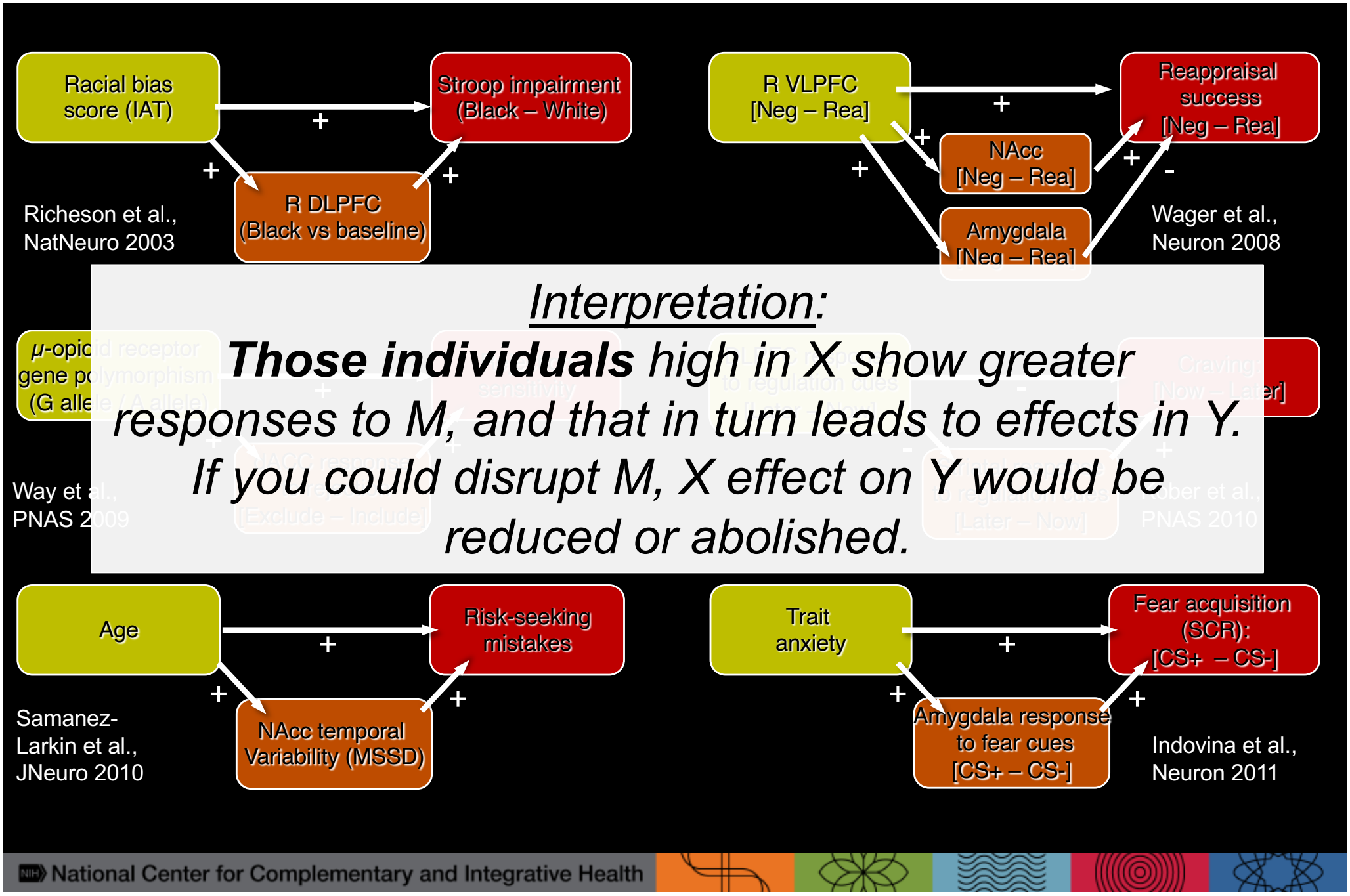
$y = bm + c'x + e'_y$

Does *m* explain some of the x-y relationship (c)?

$$c\text{-}c' = a*b$$

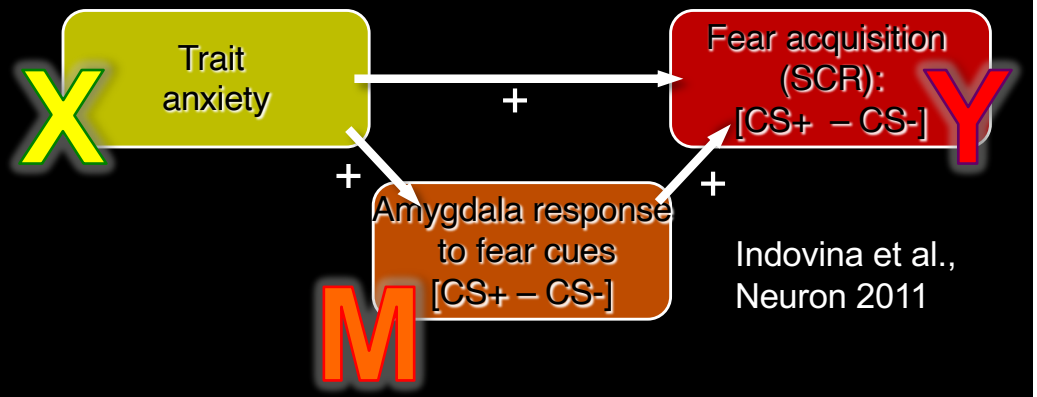
Counterfactual: If we were to prevent m from varying, the effect of *x* on *y* would be reduced or absent.

Single level mediation in neuroimaging



Interpreting mediation

- Individuals higher in [X] show greater [Y] because of changes in [M]
- The effect of [X] on [Y] can be explained by individual differences in [M]
- Group differences in [Y] are due to group differences in [M]



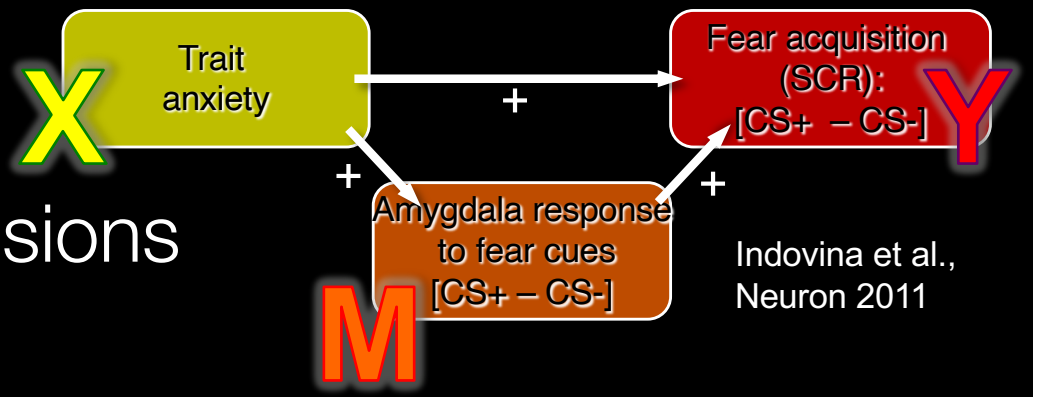
Indovina et al., Neuron 2011

Interpreting mediation

Stronger inferences about directionality if variables are randomly assigned, separated in time

Strongest inference when you can experimentally manipulate X **AND** M (e.g. using TMS)

- Two randomized experiments:
  1) X causes M, X causes Y
  2) M causes Y
- See Holland, Rubin, social psychology discussions

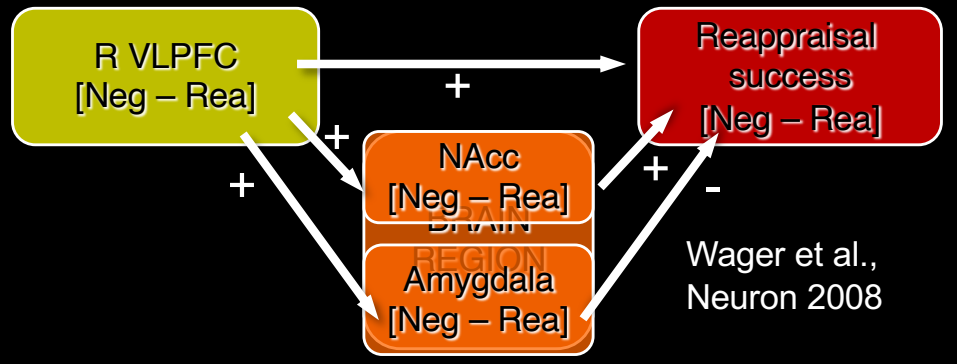


Indovina et al., Neuron 2011

Roadmap

- Introduction (Research questions)
- Mediation analysis for fMRI
  - Single level mediation
  - Multi-level mediation
- Brain mediators of the effects of heat on pain
- Brain mediators of expectancy effects on pain

Single level mediation in neuroimaging



Wager et al., Neuron 2008

Voxel-wise mediation effect parametric mapping (MEPM)

“Mediation Effect Parametric Mapping”

X (initial variable)

X is…
A between-subjects experimental variable:
Healthy controls vs Chronic pain patients

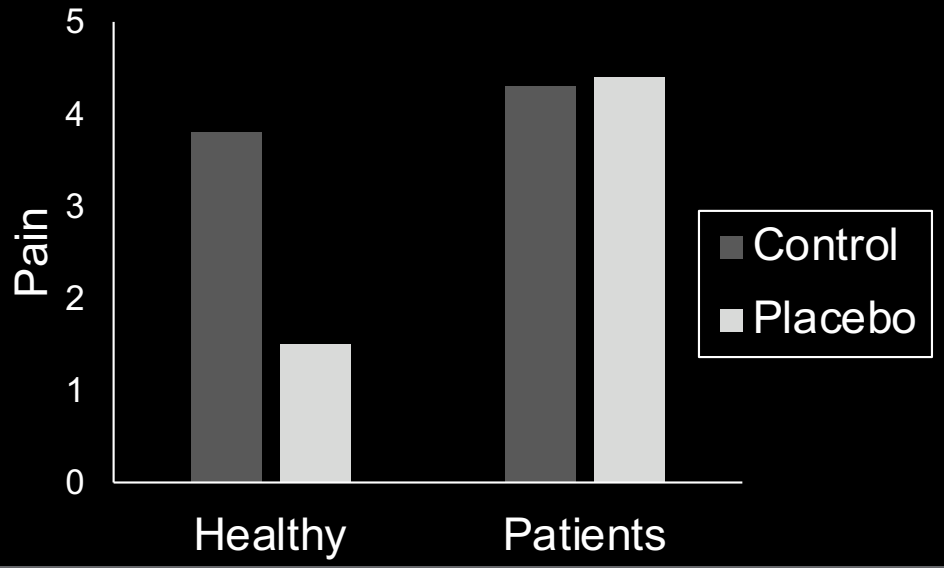
Brain

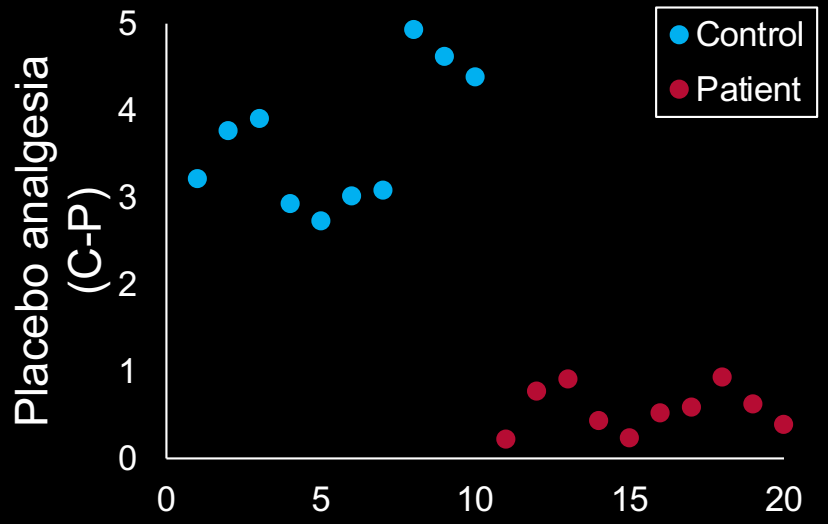
?

M is…
Contrast values from a voxel
[Control – Placebo]

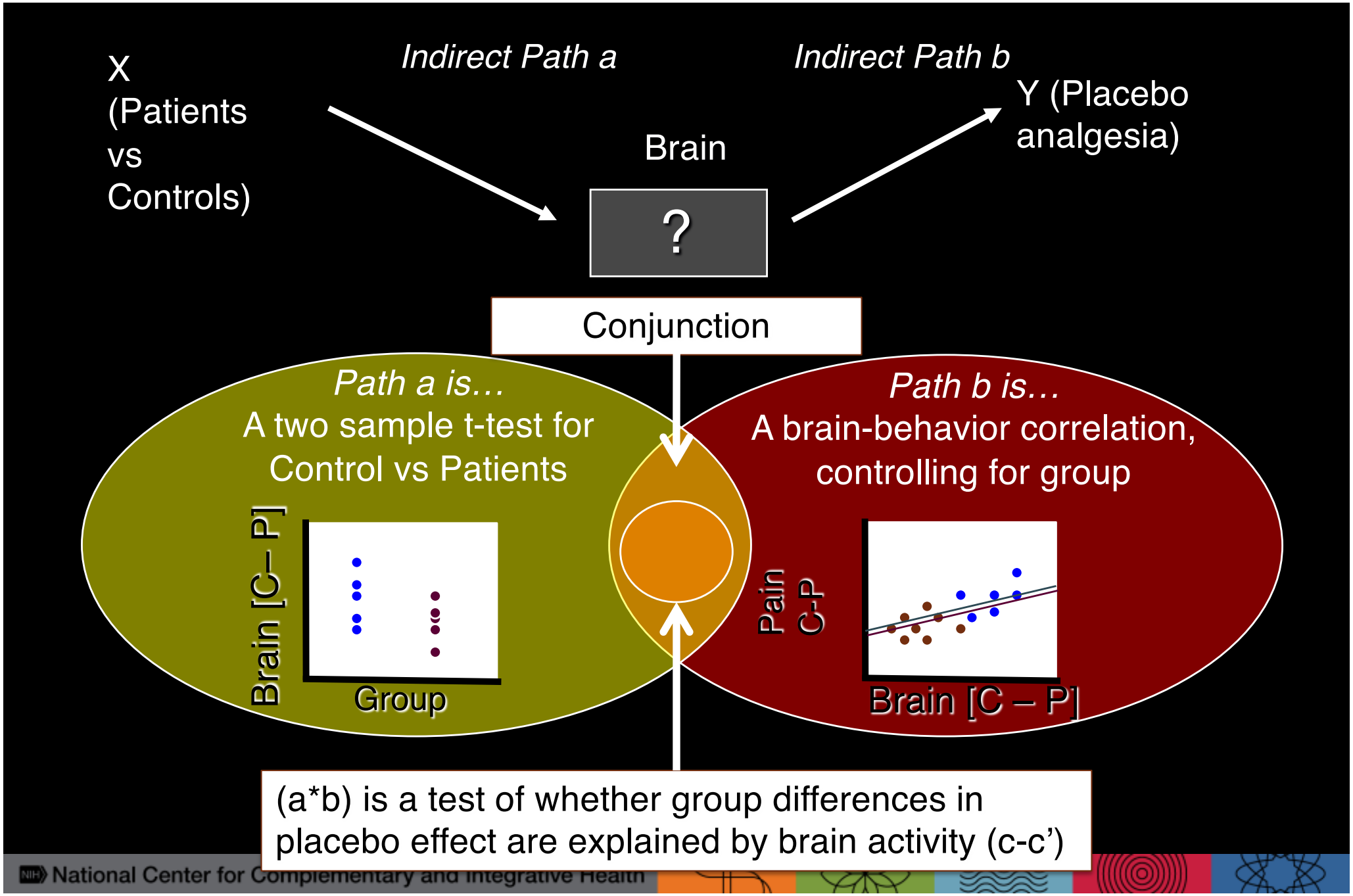
Y (outcome)

Y is…
A behavioral variable
Pain reports for [Control – Placebo]:
Placebo analgesia





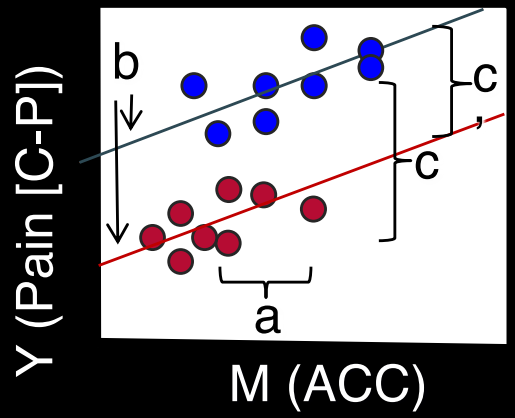
"Mediation Effect Parametric Mapping"



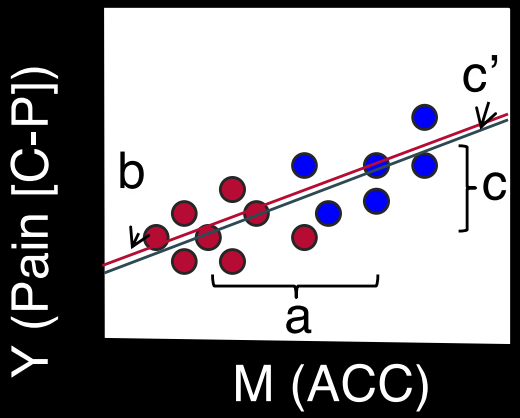
Mediation vs. Conjunction

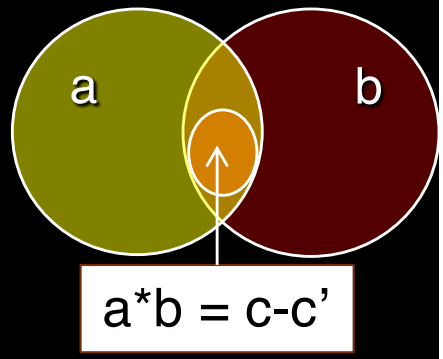
X
- Controls
- Chronic pain patients

Conjunction without mediation



Conjunction and Mediation





Path *c*: Group difference in placebo effects on pain

Path *a*: Group difference in placebo effect on ACC

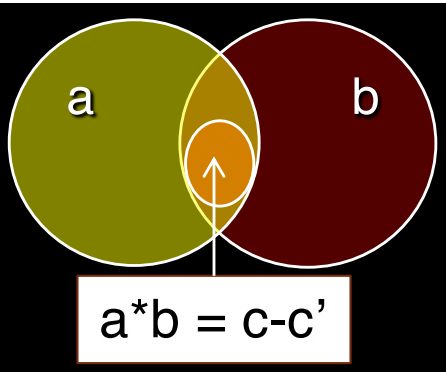
Path *b*: Brain-behavior correlation in ACC, controlling for group

Path *c'*:

Left: Group difference in placebo analgesia even when you account for path *b*: No mediation, c – c' = 0

Right: Group diffs in ACC responses entirely explain group diffs in placebo analgesia; Full mediation, c' = 0

Testing the significance of a*b



- Sobel test

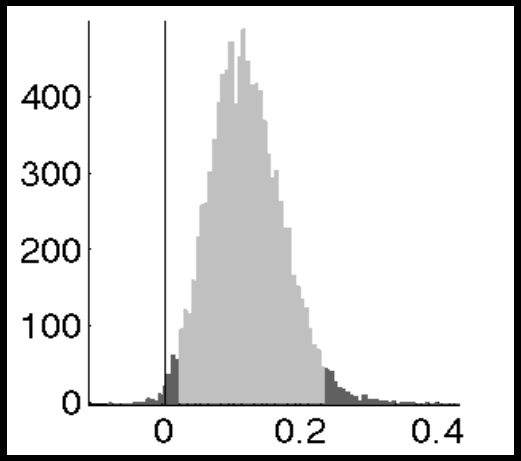
  Aroian, L. A (1944)

$$Z = \frac{ab}{b^2 se(a)^2 + a^2 se(b)^2 + se(a)^2 se(b)^2}$$

  - Assumes a, b are normally distributed
  - Usually conservative (p-values higher than needed)

- Bootstrap test :

  Efron, 1994; Shrout & Bolger, 2002; Preacher & Hayes, 2004



Histogram of bootstrapped Indirect (a*b) effects

Roadmap

- Introduction (Research questions)
- Mediation analysis for fMRI
  - Single level mediation
  - Multi-level mediation
- Brain mediators of the effects of heat on pain
- Brain mediators of expectancy effects on pain

Mediation analysis:

Single vs multilevel mediation

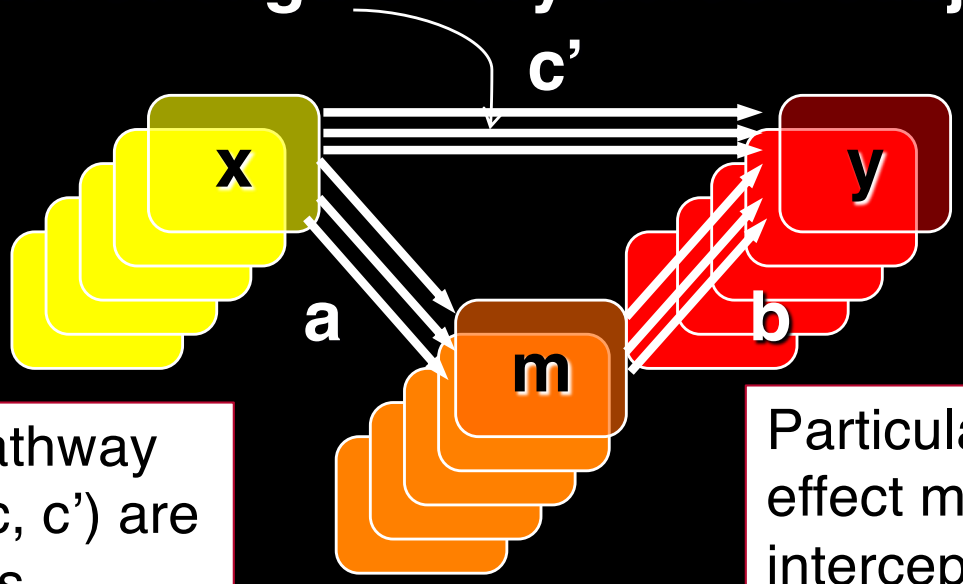
c-c’=a*b + cov(a,b)

Rather than one value per subject

model the entire timeseries, assess within-subjects effects

Kenny, Korchmaros, & Bolger (2003)

Path strengths vary across subjects



Observations on each variable are nested within subjects

Subject-level pathway strengths (a, b, c, c’) are random variables

Particular type of mixed-effect model: Random intercept, random slope model, with subject as random effect

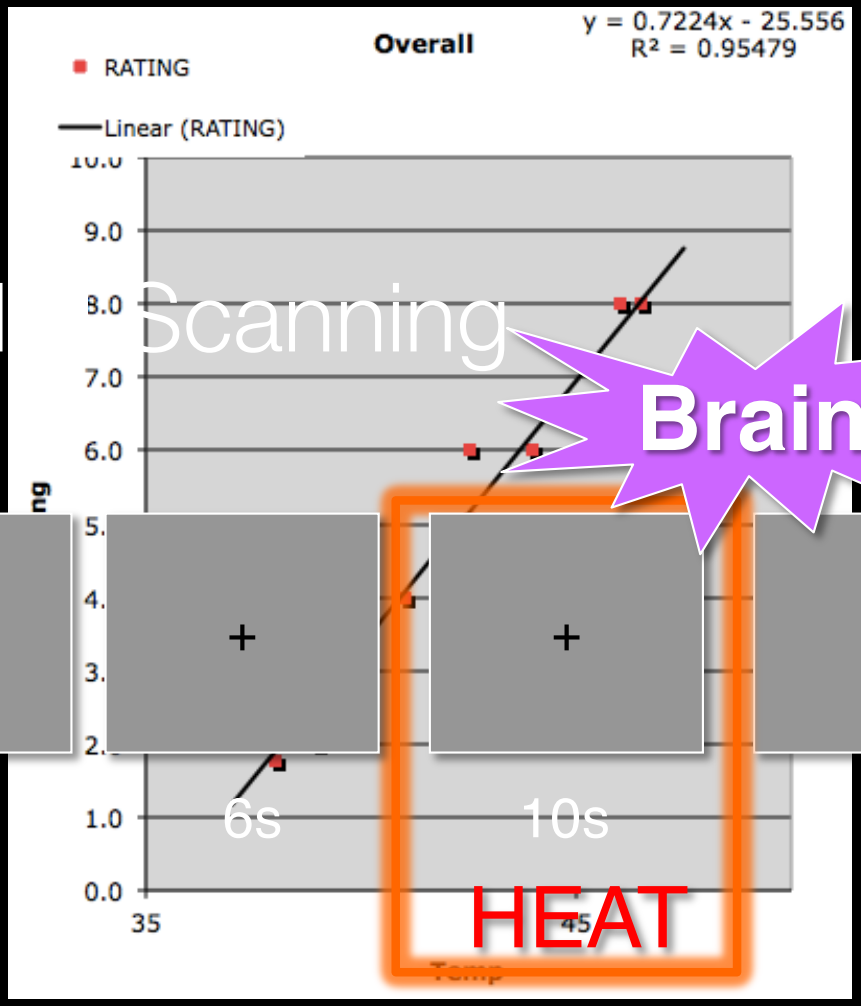
Example: FMRI experiment

Which brain pathways mediate the effects of temperature (noxious heat) on pain?

Atlas et al., 2014, Pain

Design

1. Adaptive calibration:



2. fM Scanning

Warmth (Level 1)
Low Pain (Level 3)
Med Pain (Level 5)
High Pain (Level 7)

IV

Brain

CUE

+

+

+

2s

6s

10s

HEAT

How Painful?

DV

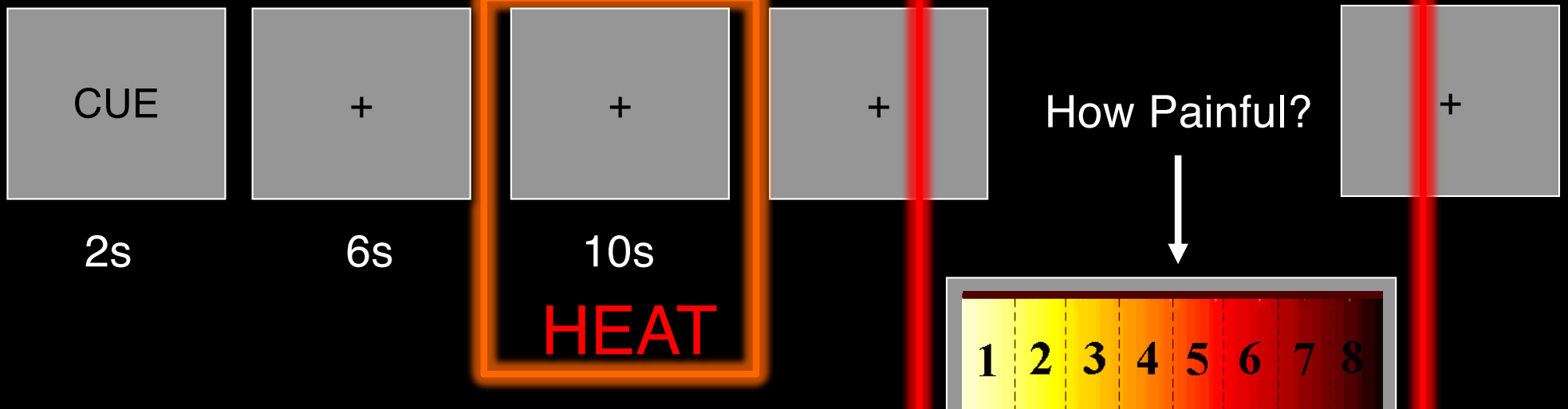
1 2 3 4 5 6 7 8

Design

1. Adaptive calibration:

Warmth (Level 1)
Low Pain (Level 3)
Med Pain (Level 5)
High Pain (Level 7)

2. fMRI Scanning

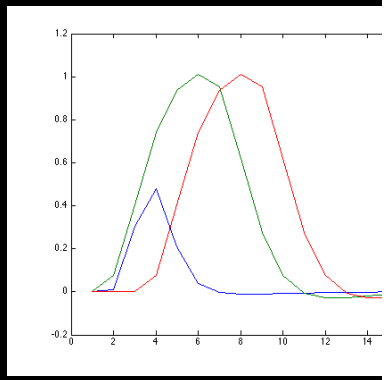


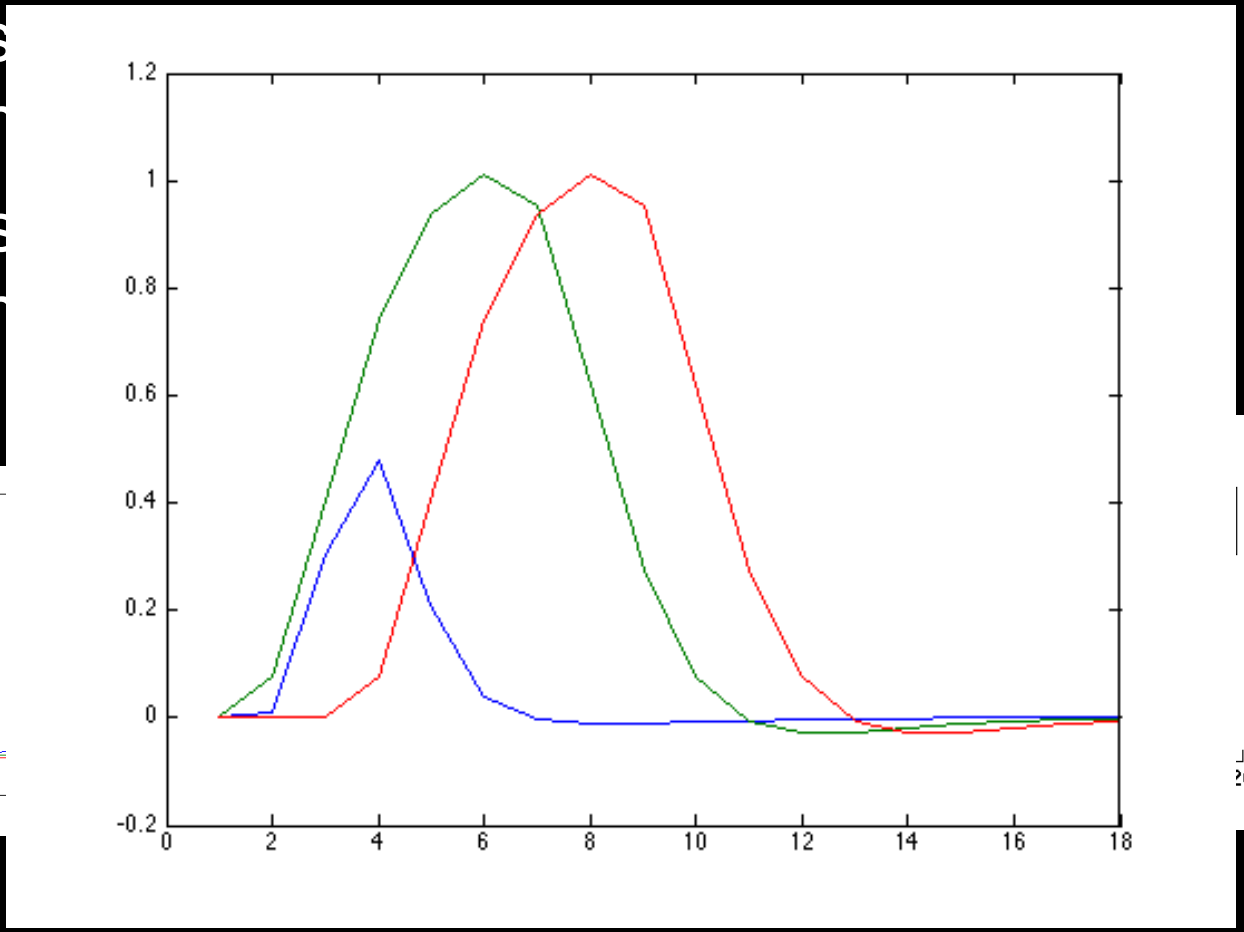
Important! # of observations

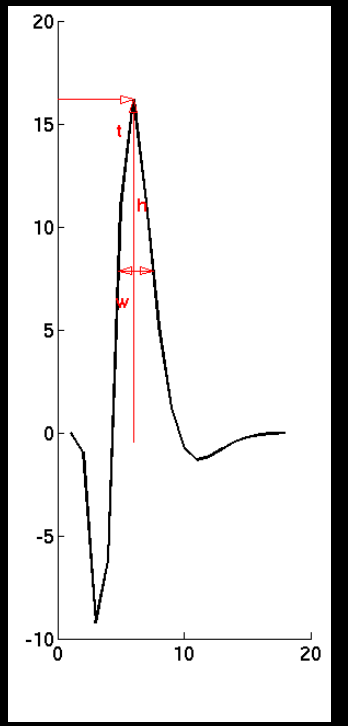
- Within each subject, need **equal observations of X, M, and Y**
- Easy if individual differences or 3 brain regions (connectivity)
- Here, each trial has:
  - 1 temperature (X)
  - 1 rating (Y)
  - ~10 seconds of pain, plus HRF!

Voxelwise single trial analysis

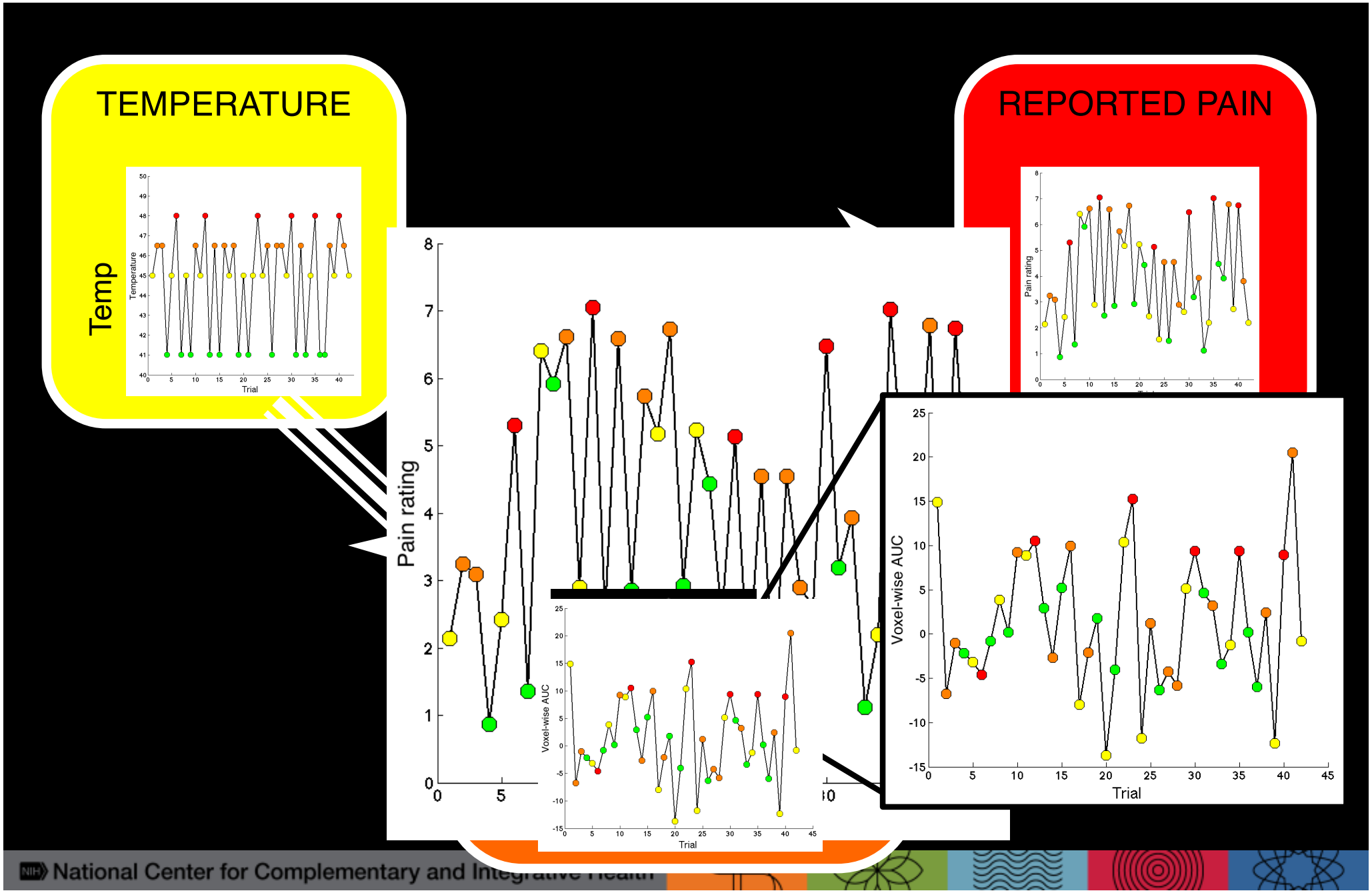
1. Fit basis functions trial-by-trial
2. Es
   ar
3. Us
   ar



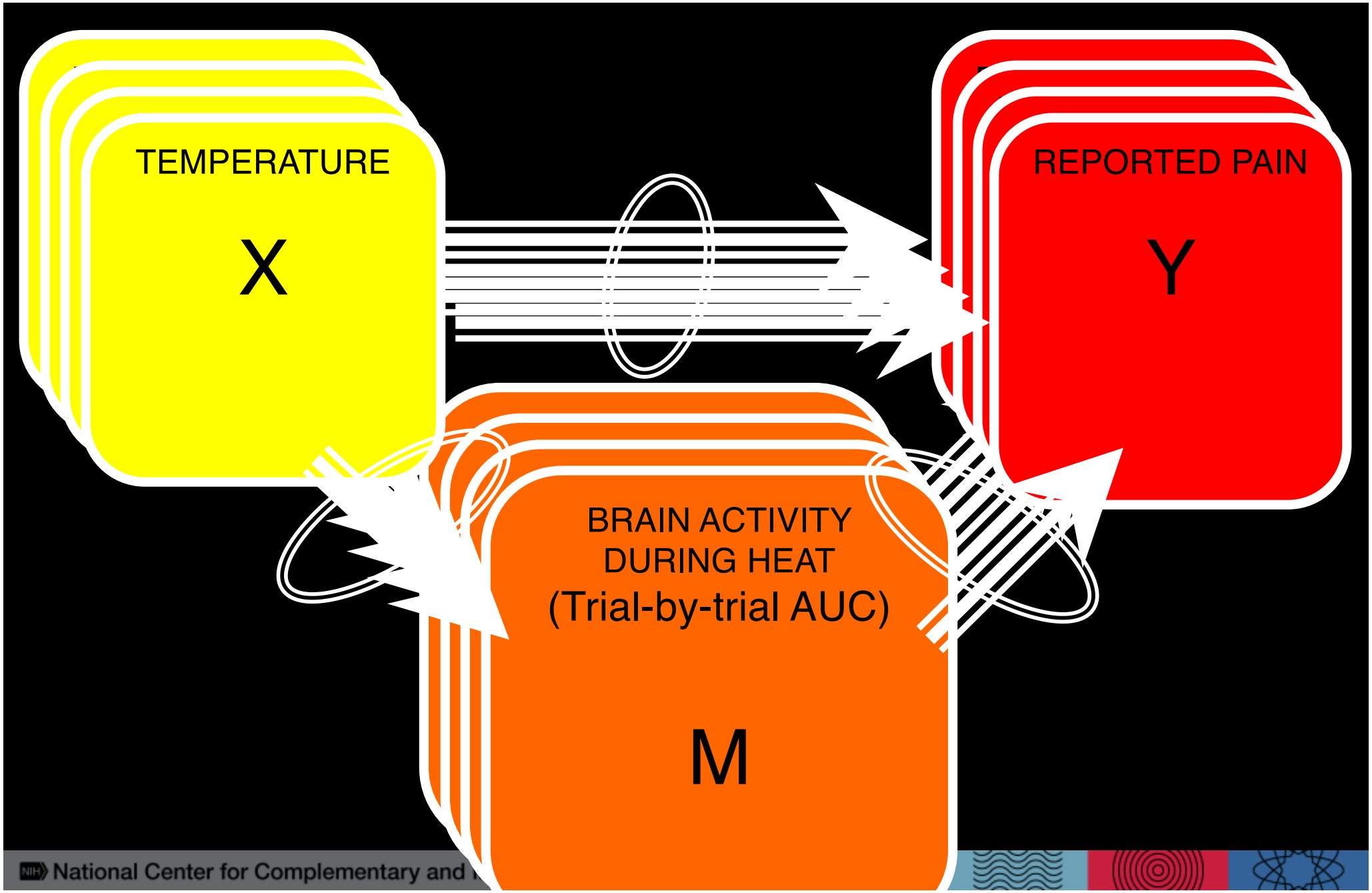




Mediation model



Mediation model

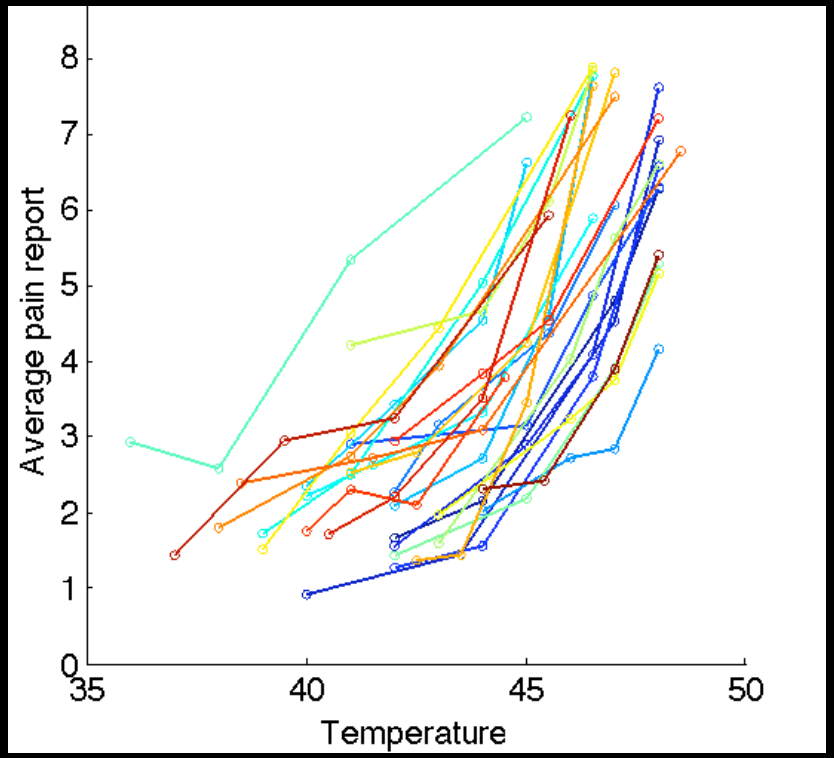


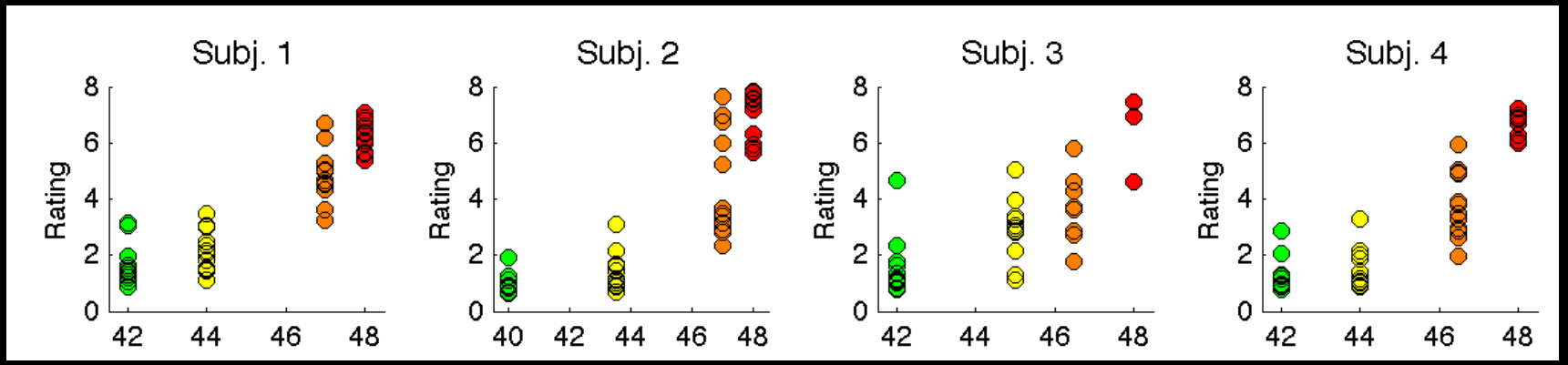
RESULTS

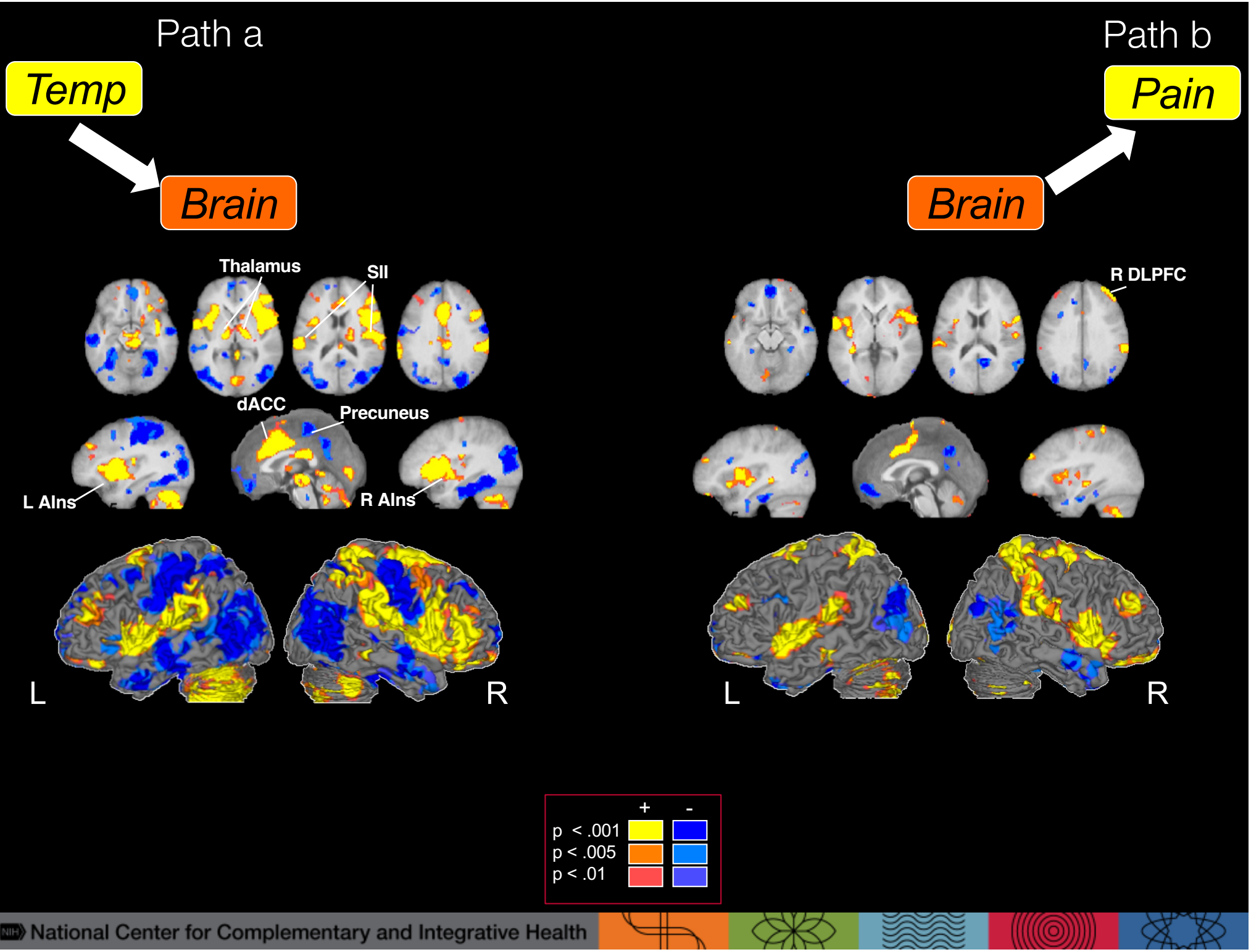
Atlas et al., 2014, Pain

Path c

Temp → *Pain*






Path a
Temp
Brain
Thalamus
SII
dACC
Precuneus
L AIns
R AIns
L
R
Path b
Pain
Brain
R DLPFC
L
R
+
-
p < .001
p < .005
p < .01

Path a

Path b

Temp

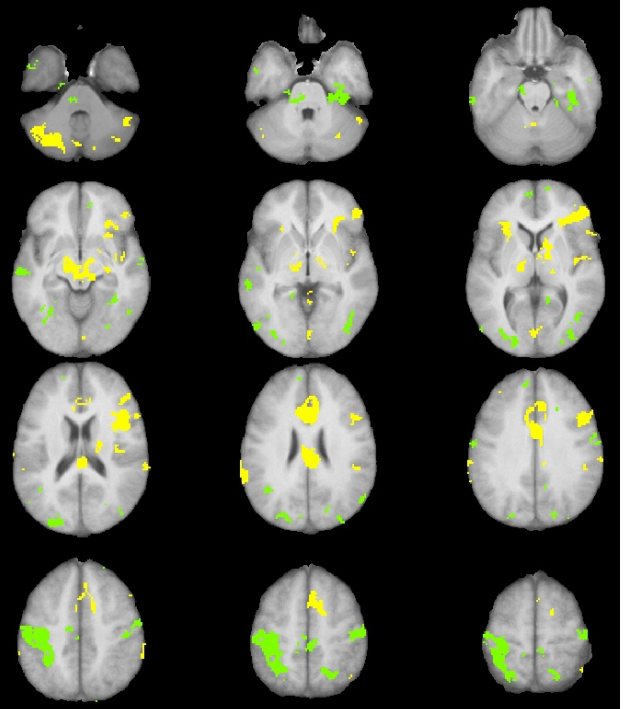
Brain

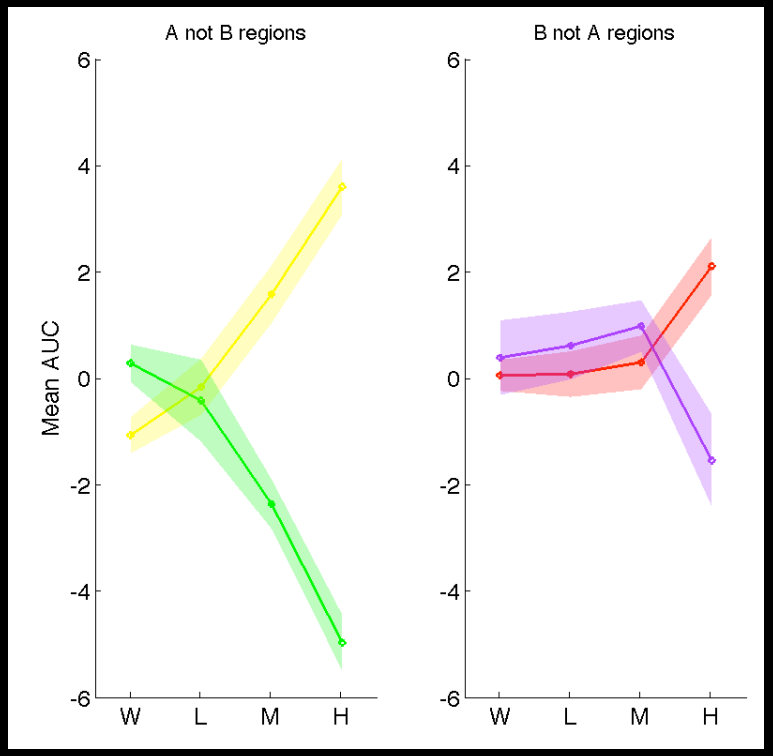
Path *a* (temperature), not *b*

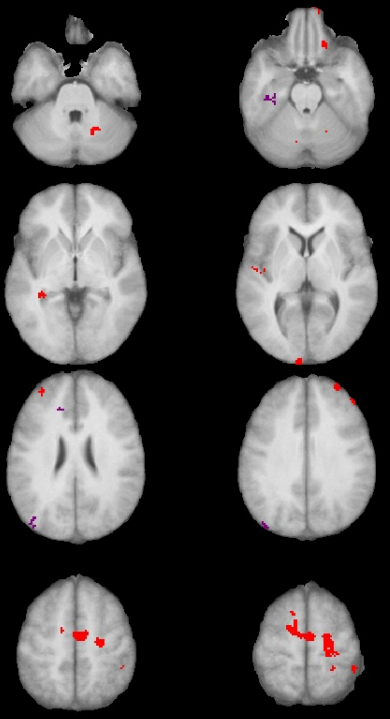
Path *b* (pain report), not *a*

Brain

Pain







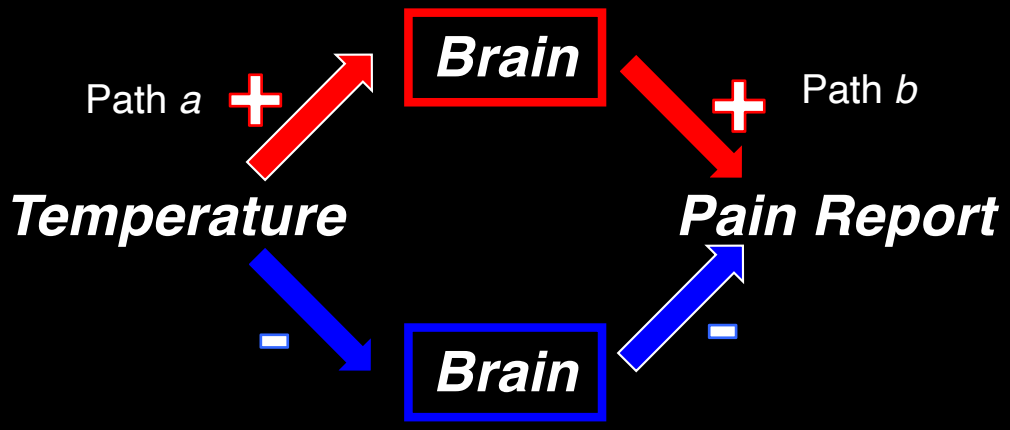
+ -

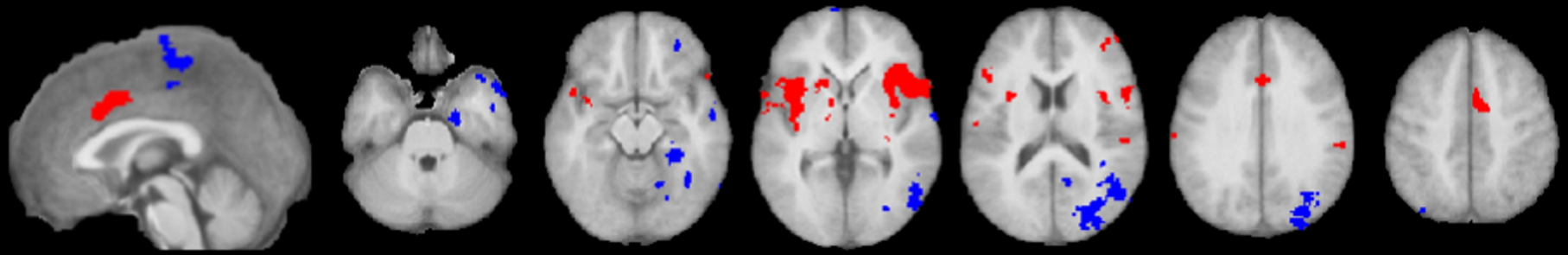
p < .001

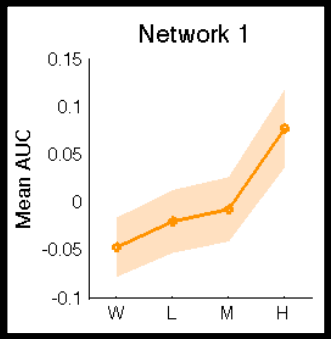
p < .005

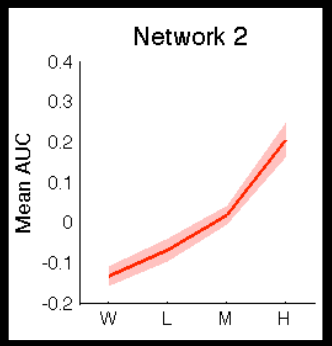
p < .01

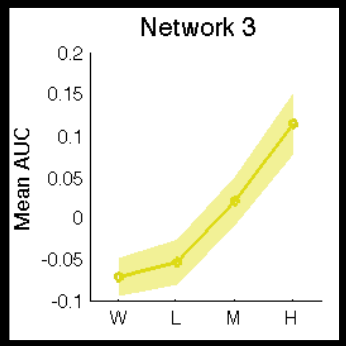
Consistent mediators (significant Path a and Path b effects in group)

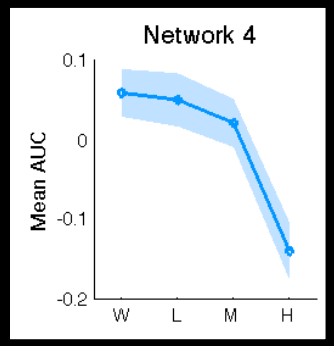












Study 1 Summary

Pain is generated by a combination of independent networks

- Increases with temp + increases predict pain (e.g. SII, “salience network”)
- Decreases with temp + decreases predict pain (e.g. DMN)
- Suppression effects / negative mediators (DMPFC, mOFC)
- Pain-related without responding to temperature (e.g. DLPFC, DMPFC, OFC)

Mediation can help identify regions that link objective stimulus with subjective response

Study 2

Which brain pathways mediate expectancy effects on pain?

Atlas et al., 2010, JNeurosci

Working model

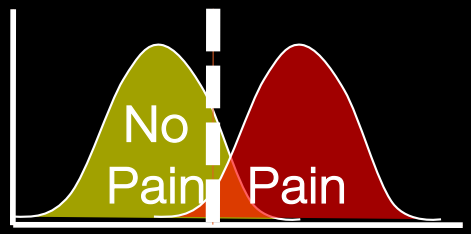
Expectation/ Prior

Sensory processing/ Bodily state

Subjective response

Report biases/ Changes in decision-making?

(Hrobjartsson & Gotzsche 2001/04; Allan & Siegel 2002; Clark 2003)

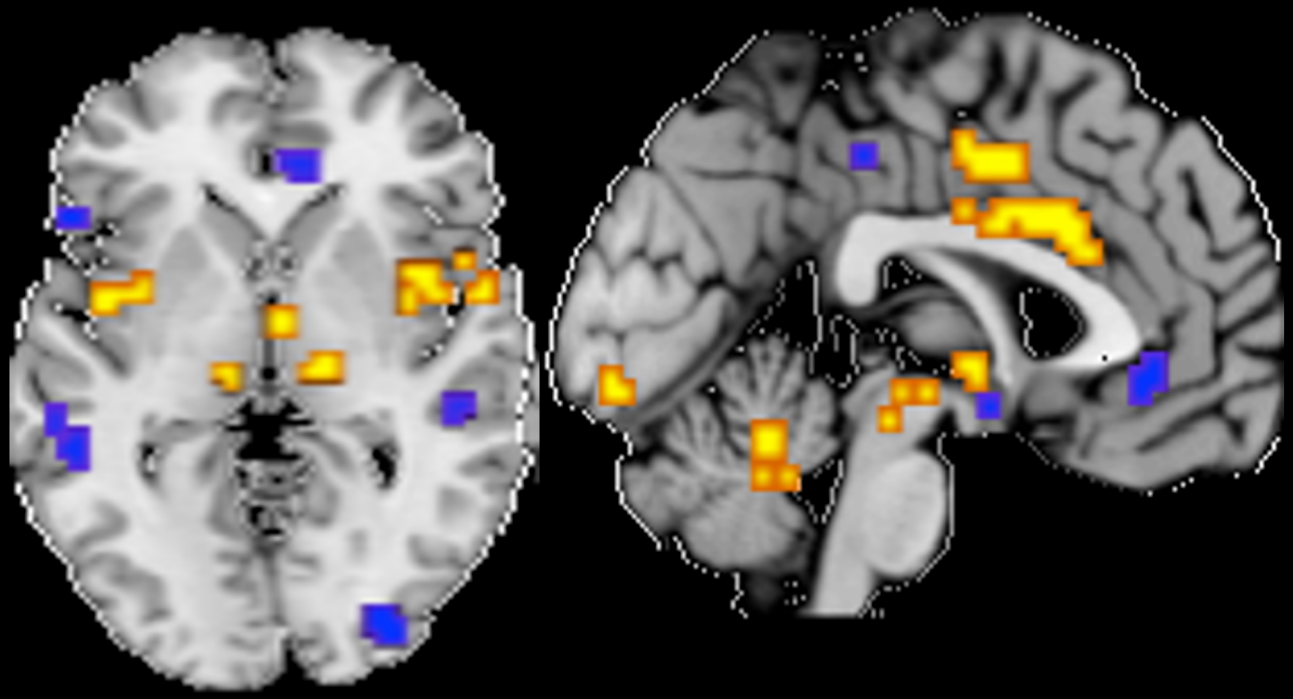


Expectation/ Prior

Sensory processing/ Bodily state

Subjective response

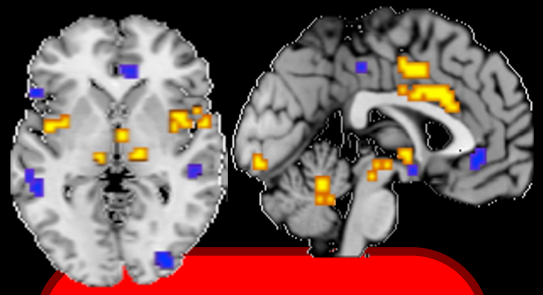
“Neurologic pain signature”



- *Predicts pain in new subjects, in new scanners, in new studies*
- *Highly specific to pain*

Wager, Atlas, et al. (2013), *NEJM*

Do expectations cause changes in pain processing network, and does that give rise to changes in subjective pain?



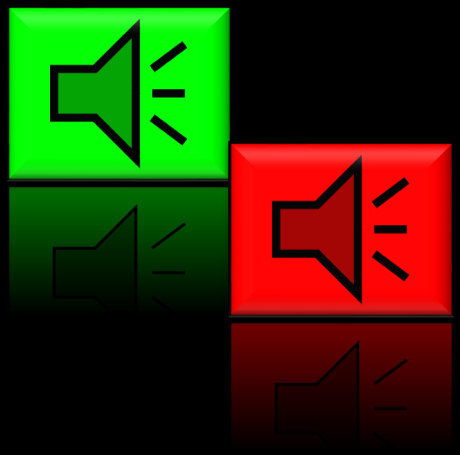
Expectation/ Prior

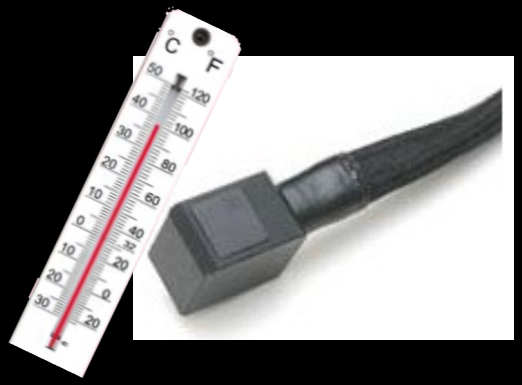
Sensory processing

Subjective response

Study 2

Conditioned cues





Expectation/ Prior → Sensory processing/ Bodily state → Subjective response

Atlas et al., 2010, *JNeurosci*

Expectancy effects on subjective pain

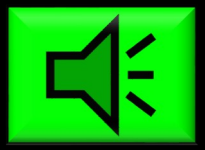
Pain calibration

Level 2
(Slight pain)

Level 5
(Medium pain)

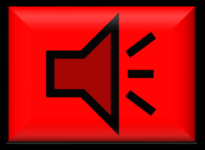
Level 8
(Max pain)

Verbal instructions



"Low Pain"

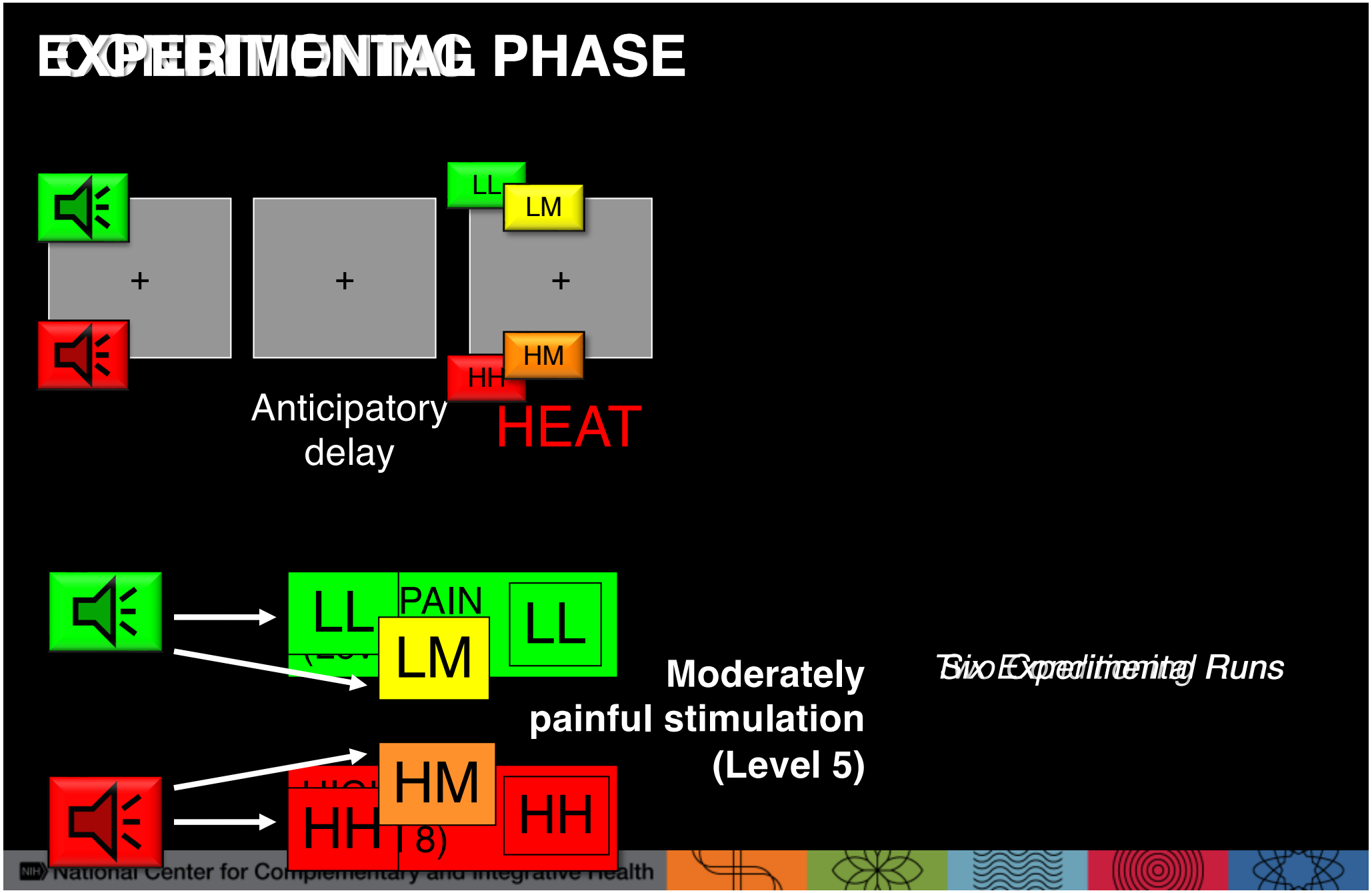
(Counterbalanced)



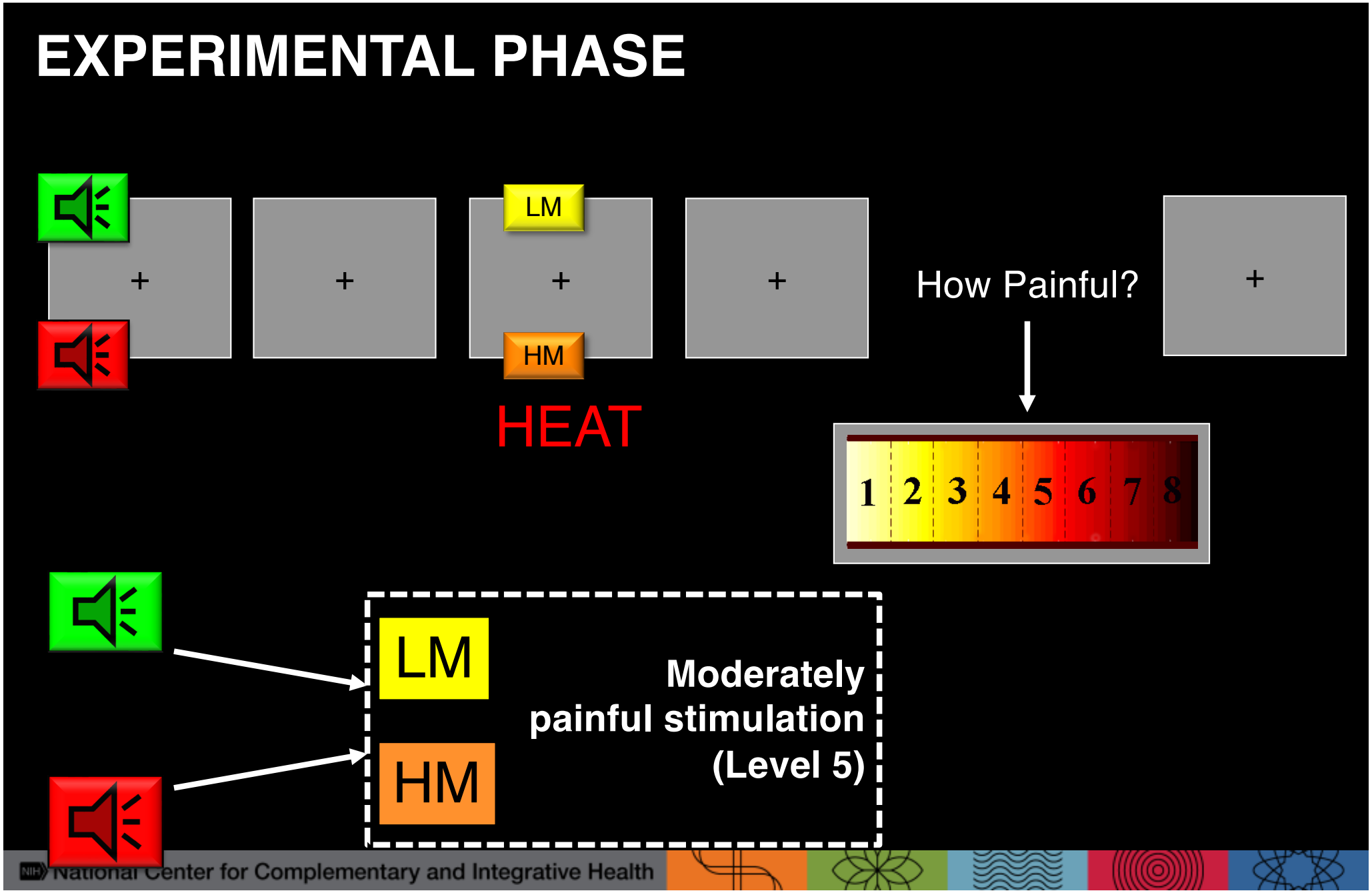
"High Pain"

Atlas, Bolger, Lindquist, and Wager, 2010, JNeurosci

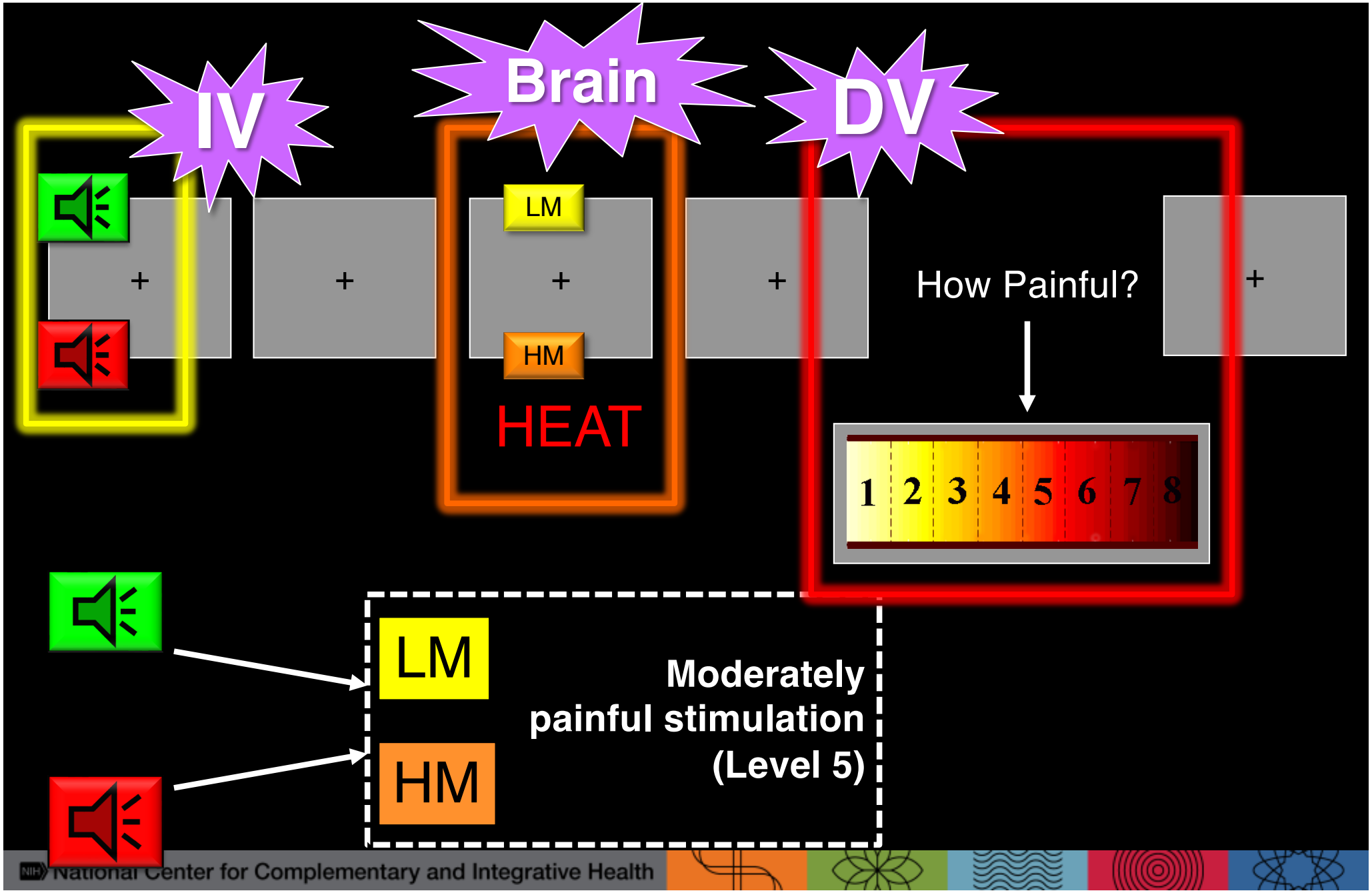
Expectancy paradigm



Expectancy paradigm



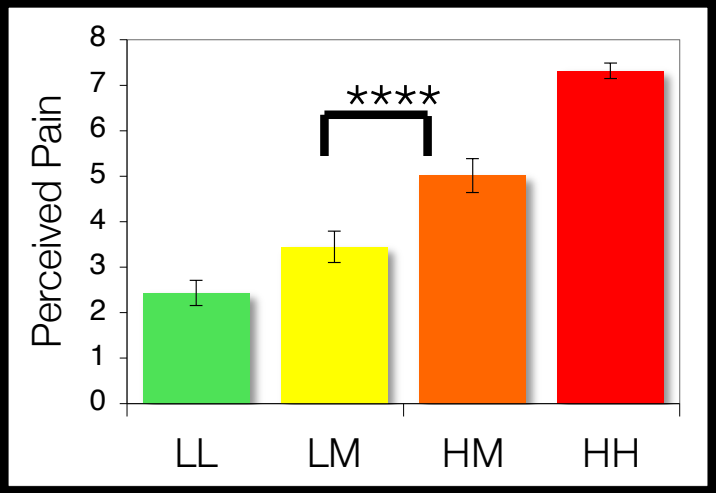
Expectancy paradigm



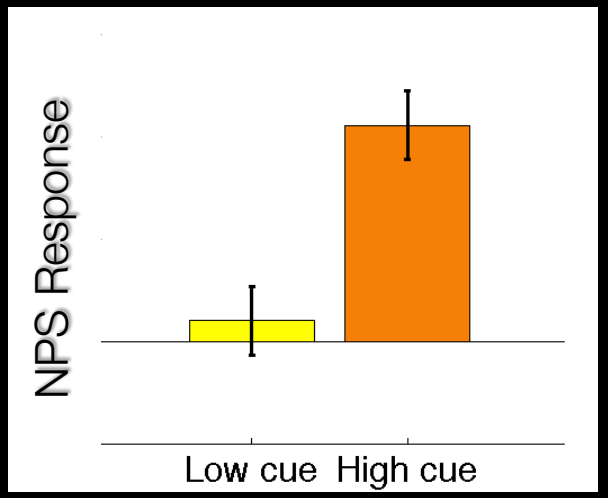
RESULTS

Atlas et al., 2010, *JNeurosci*

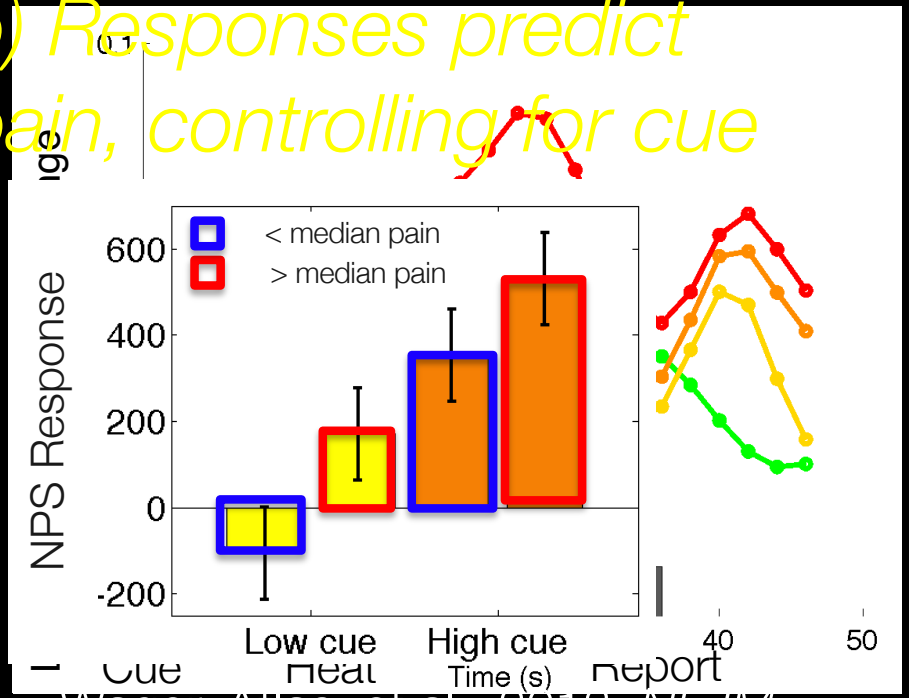
c) Cue-based expectations shape pain



a) Expectations shape responses to heat (HM > LM)

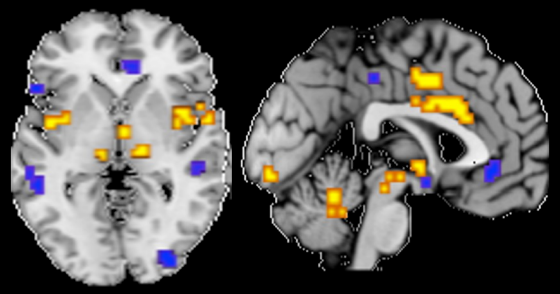


b) Responses predict pain, controlling for cue



Wager, Atlas, et al., 2013, *NEJM*

c-c') Pain network responses mediate cue effects on pain.



Neurologic Pain Signature (NPS)

Atlas et al., 2010, *JNeurosci*

Study 2 summary

Cue-based expectancy effects on pain are mediated by pain-related regions

- Voxelwise analyses (Atlas et al., 2010) reveal other mediating networks as well

Mediation analysis can identify mediators of IV effects on DV

Mediation for effective connectivity

- Cues -> VS and OFC -> Pain-related mediators

Summary

Why use multilevel mediation:

1. Relate independent and dependent variables
2. Test hypothesized pathways
3. Relate individual differences to within-subjects pathway strength

Summary

Consider inferences:

Stronger inferences about directionality if variables are separated in time

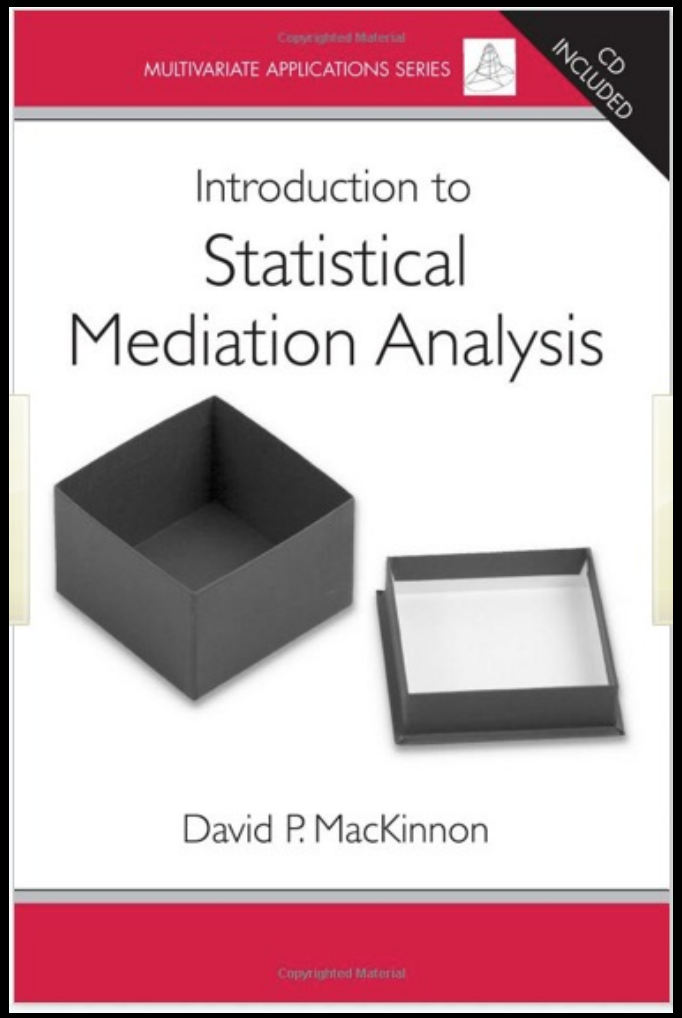
- E.g. Cue -> Anticipation -> Pain -> Report

*Strongest inference when you can experimentally manipulate X **AND** M (e.g. using TMS)*

- see Holland, Rubin

Resources

http://wagerlab.colorado.edu/tools



Mediation analysis:

Baron & Kenny, 1986, JPSP
Shrout & Bolger, 2002, Psychological Methods
Kenny, Korchmaros & Bolger 2003, Psychological Methods

MEPM:

Wager et al., 2008, Neuron
Wager et al., 2009, Neuroimage
Atlas et al., 2010, JNeuro

Thank you.

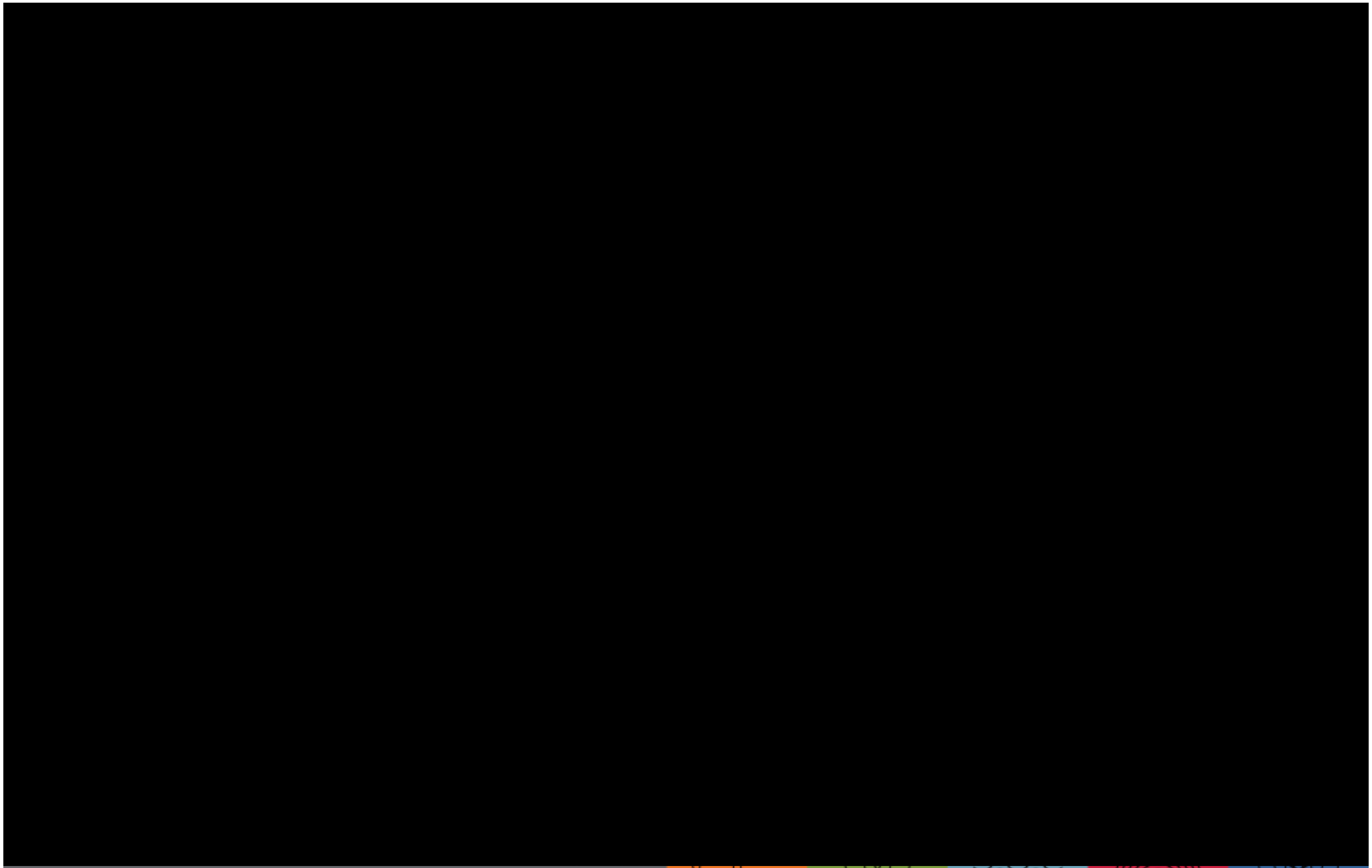
Tor Wager
Univ of Colorado, Boulder
Psychology & Neuroscience

Niall Bolger
Columbia
Psychology

Martin Lindquist
Johns Hopkins
Biostatistics

Affective Neuroscience & Pain Lab

NIH National Center for Complementary and Integrative Health



Attention

Expectancy

Emotion

Psychological factors

Noxious stimulus

Subjective pain

How Painful?

Attention

Expectancy

Emotion

Psychological factors

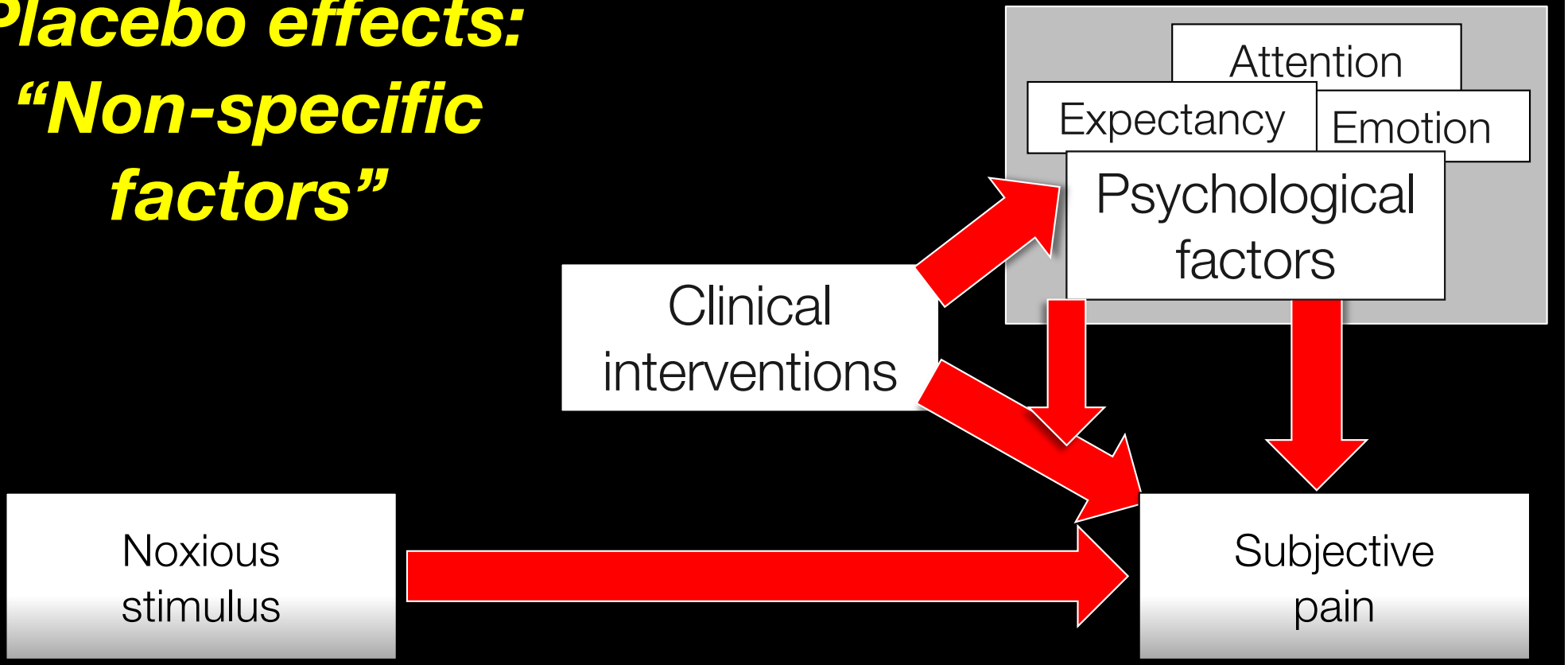
Noxious stimulus

Subjective pain

How Painful?

1 2 3 4 5 6 7 8

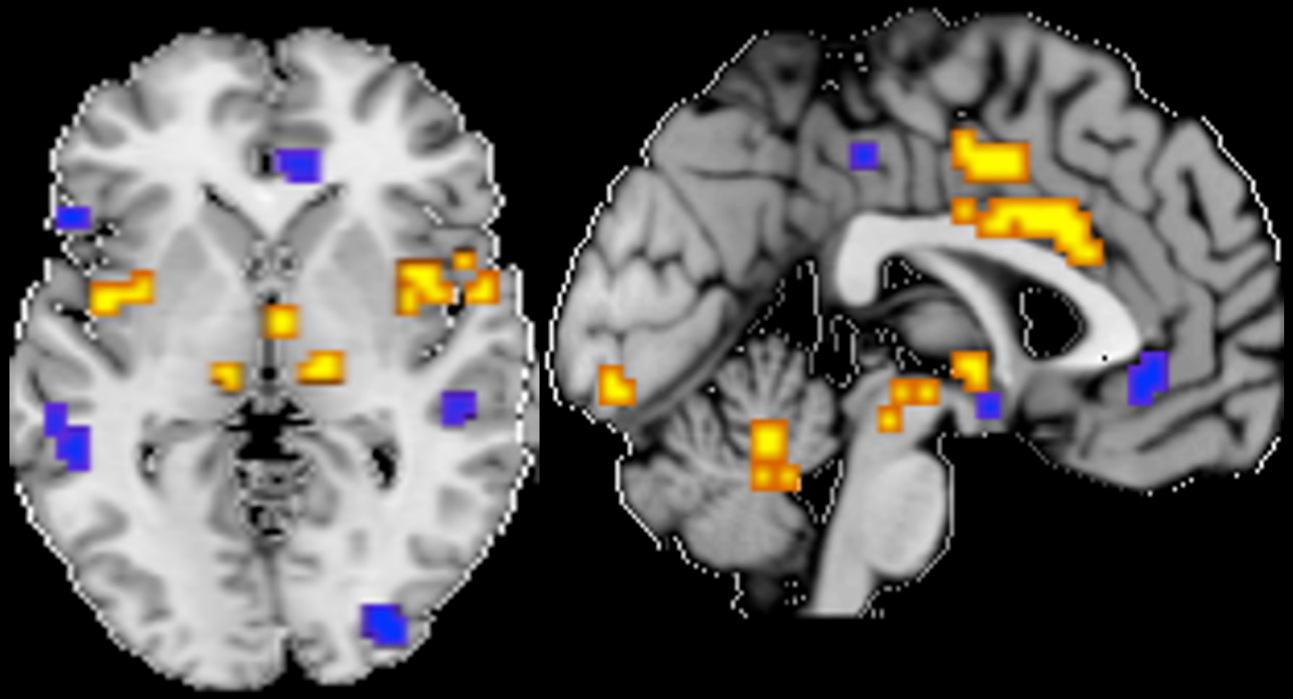
Placebo effects: "Non-specific factors"



~116 million American adults affected by chronic pain
(Institute of medicine of the National Academies, 2011)

Estimated cost of medical treatment + lost work due to pain
= $635 billion/yr

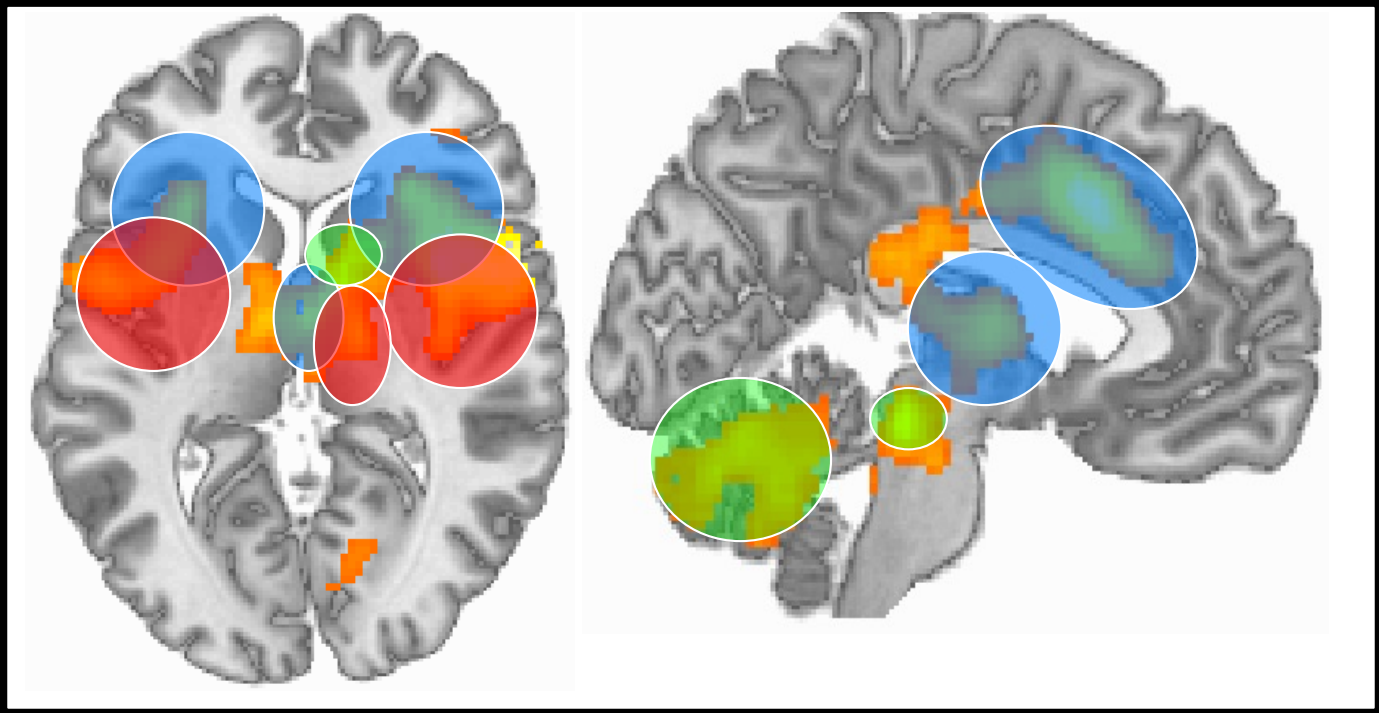
“Neurologic pain signature”



- *Predicts pain in new subjects, in new scanners, in new studies*
- *Highly specific to pain*

Wager, Atlas, et al. (2013), *NEJM*

“The pain matrix”



Sensation

Lateral thalamus
SI
SII
Posterior Insula

Affect

Medial thalamus
Anterior cingulate
Anterior insula

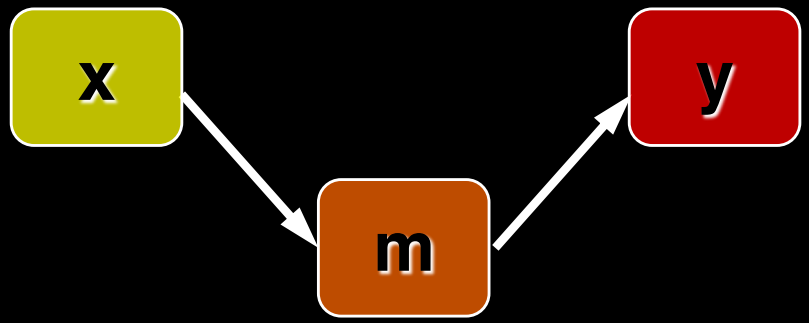
PAG
Cerebellum
Striatum

High vs Low intensity stimulation
Five studies, N = 114
FWE, p<.05

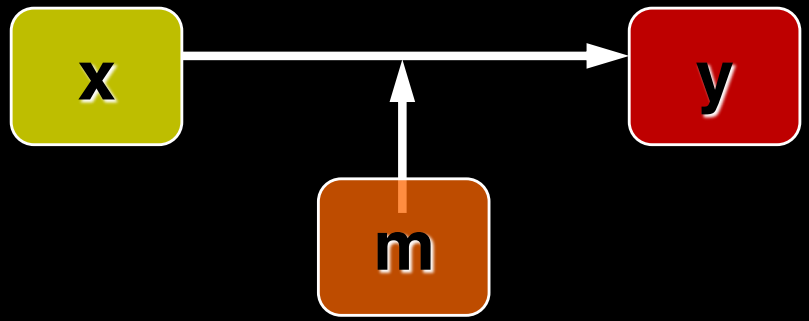
Atlas et al. (2010), *JNeurosci*

Moderation

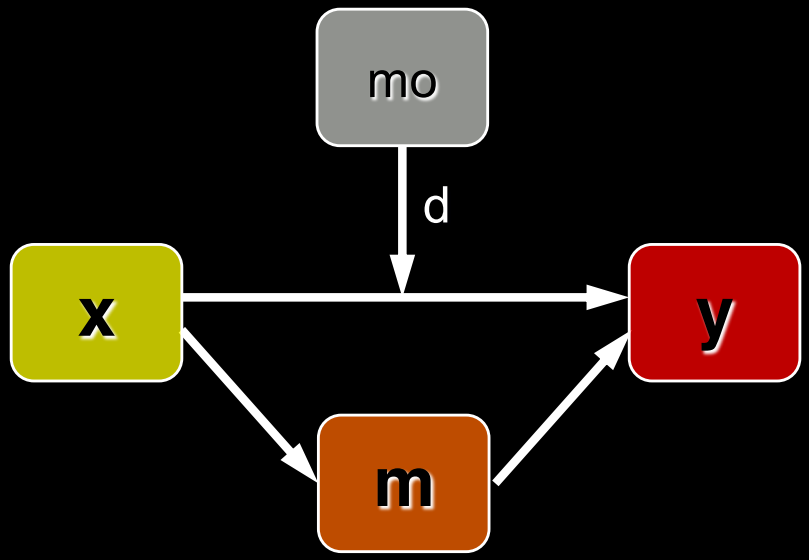
Mediation: does [M] explain some or all of the relationship btwn [X] and [Y]?



Moderation: does the level of [M] influence the relationship btwn [X] and [Y]?



Full model, with mediator and moderator



$m = i_m + ax + e_m$

$y = i_y + bm + c'x + d(mo*x) + e'_y$

Moderator: Level of mo predicts x-y covariance
Mo*x interaction
Should center *x* and *y* to reduce correlation between moderation and *x* effects

Path a

Temp

Brain

Path *a* (temperature), not *b*

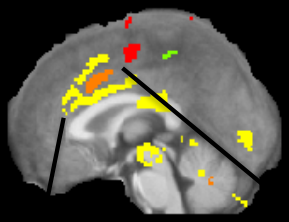
Mediator, *a* and *b*

Path *b* (pain report), not *a*

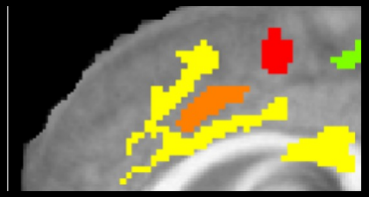
Path b

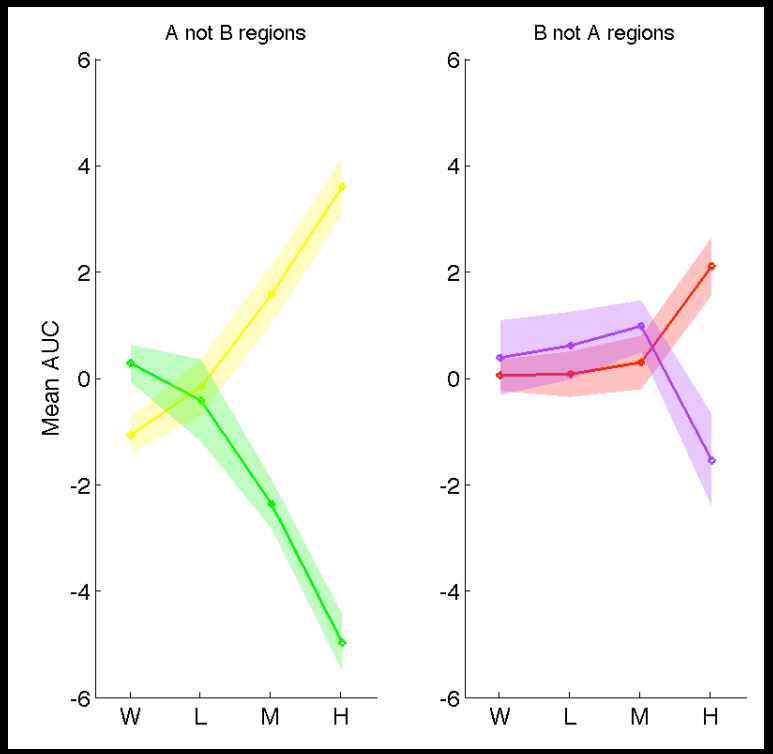
Pain

Brain

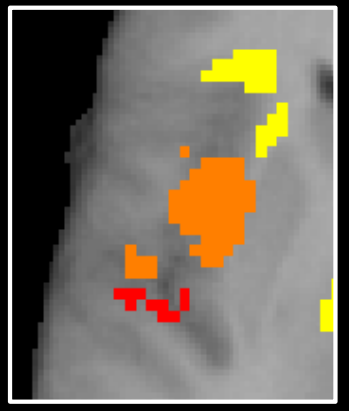


ACC



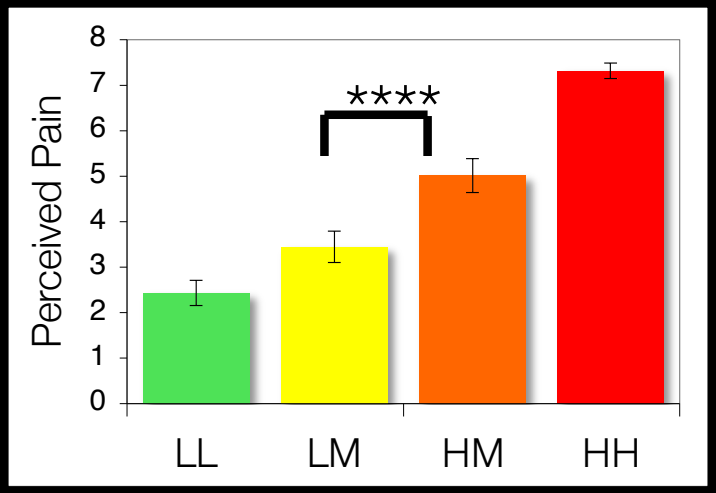


L. Insula



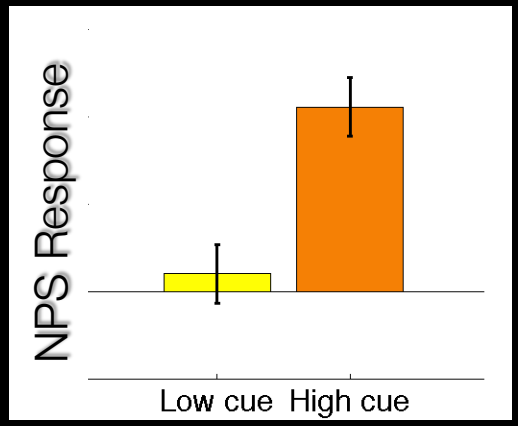
	+	-
p < .001		
p < .005		
p < .01		

c) Cue-based expectations shape pain

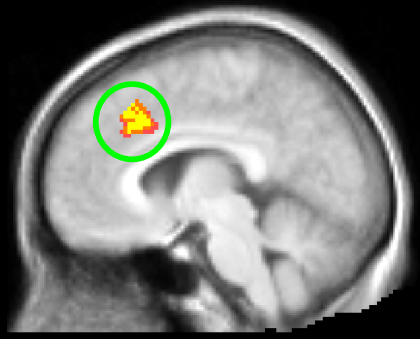


a) Expectations shape responses to heat (HM > LM)

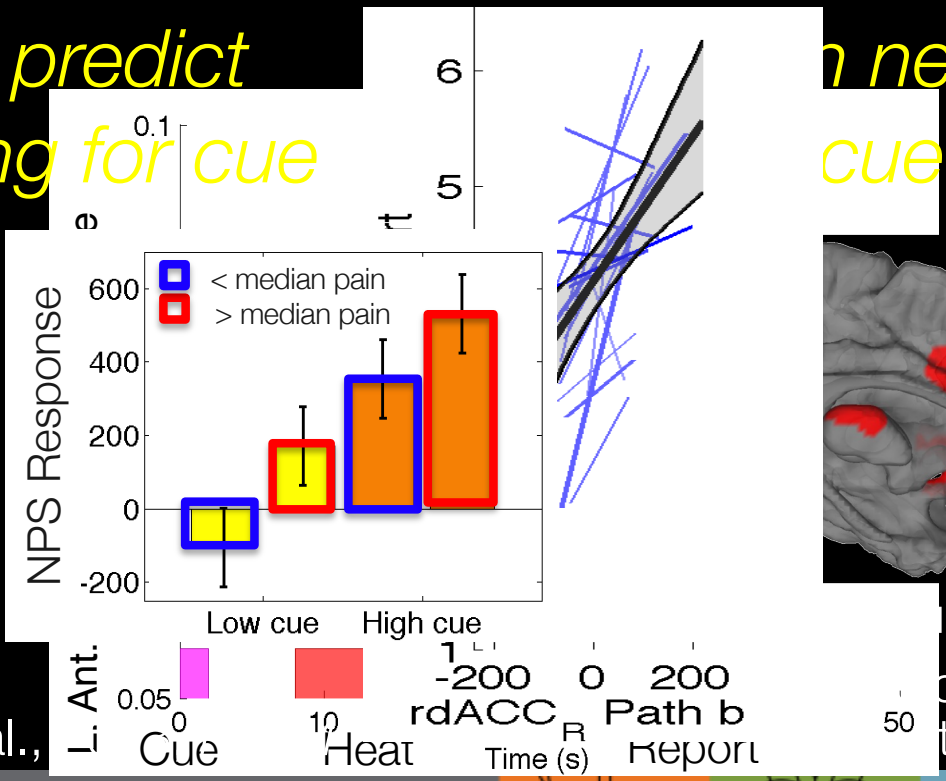
SII, insula, thalamus, dACC, Pre-SMA



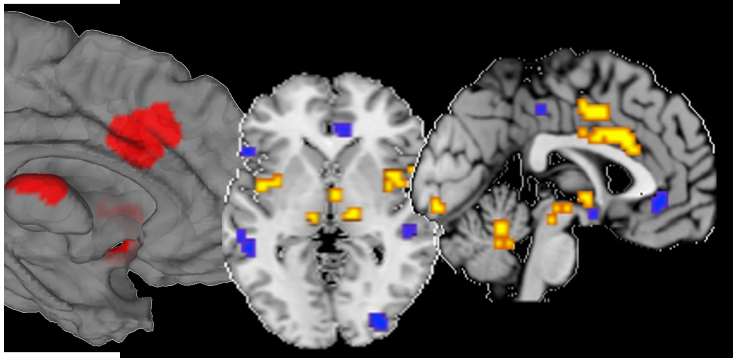
b) Responses predict pain, controlling for cue



rdACC, insula, SMA, cerebellum



n network responses cue effects on pain.

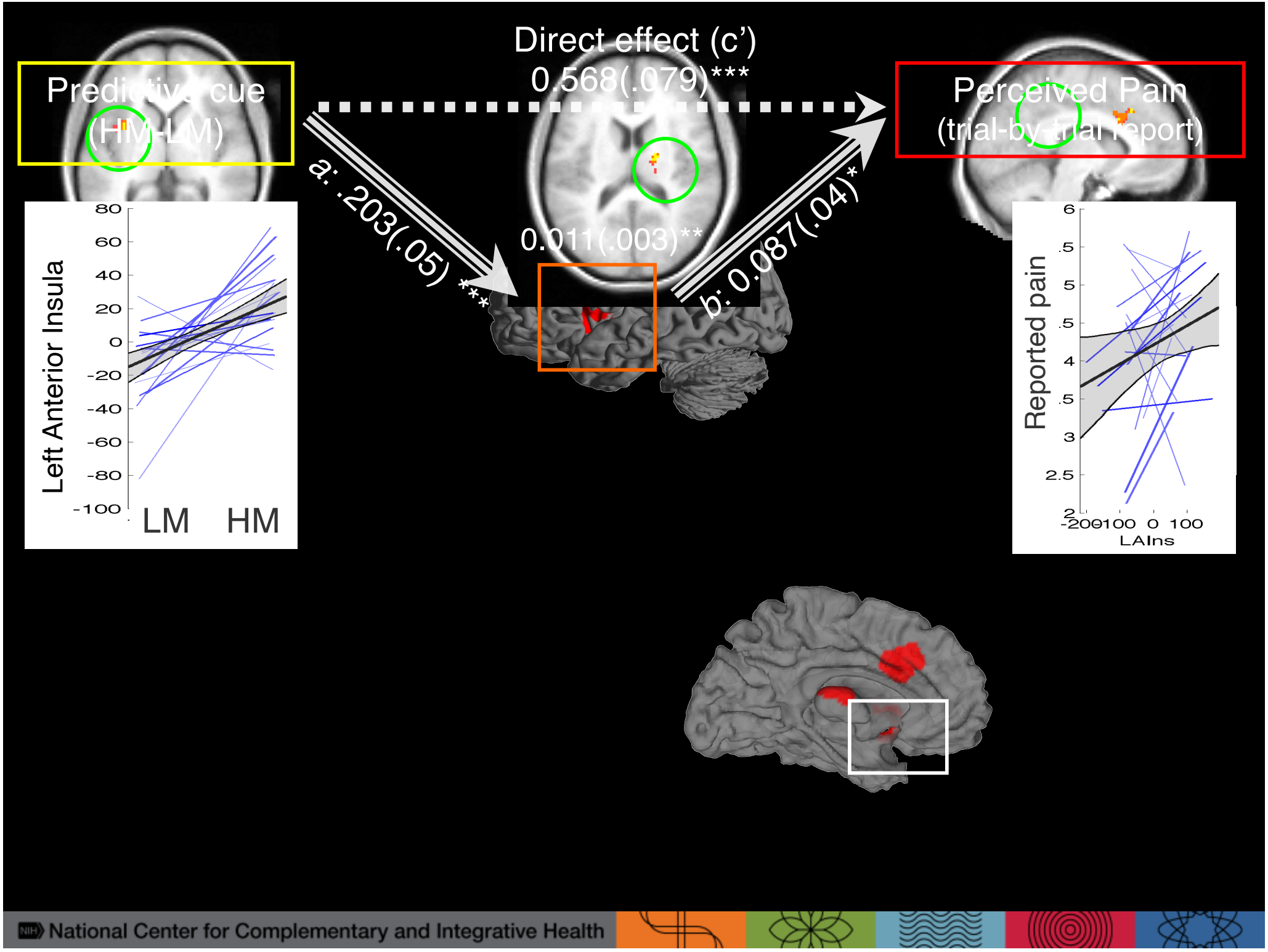


s,

ogic Pain Signature (NPS)

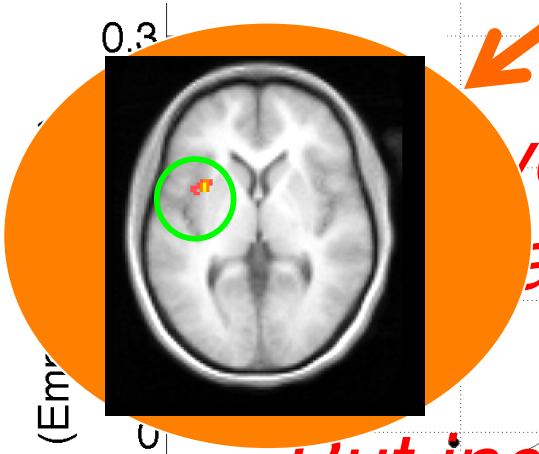
tlas et al., 2010, *JNeurosci*

Wager, Atlas, et al.,


Predictive cue
(HM-LM)
Direct effect (c')
0.568(.079)***
Perceived Pain
(trial-by-trial report)
a: .203(.05) ***
0.011(.003)**
b: 0.087(.04)*
Left Anterior Insula
80
60
40
20
0
-20
-40
-60
-80
-100
LM
HM
Reported pain
6
5.5
5
4.5
4
3.5
3
2.5
2
-200
-100
0
100
LAIns

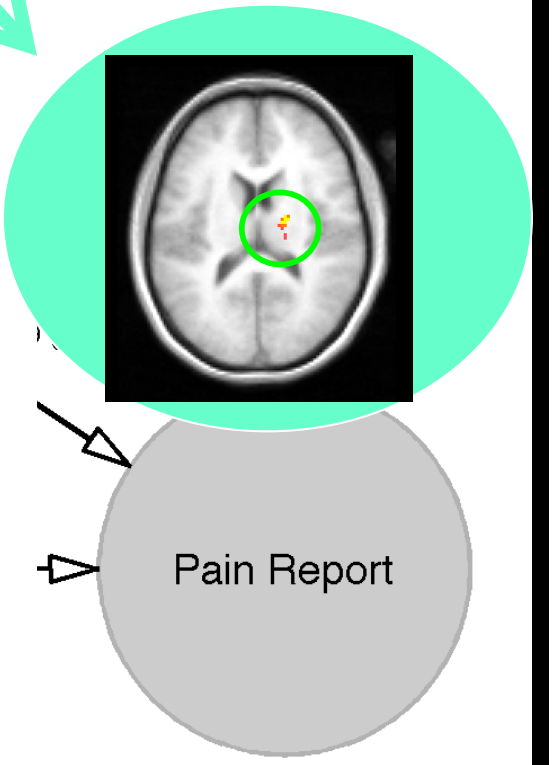
Covariance and multi-level mediation

$$c\text{-}c' = a*b + cov(a,b)$$



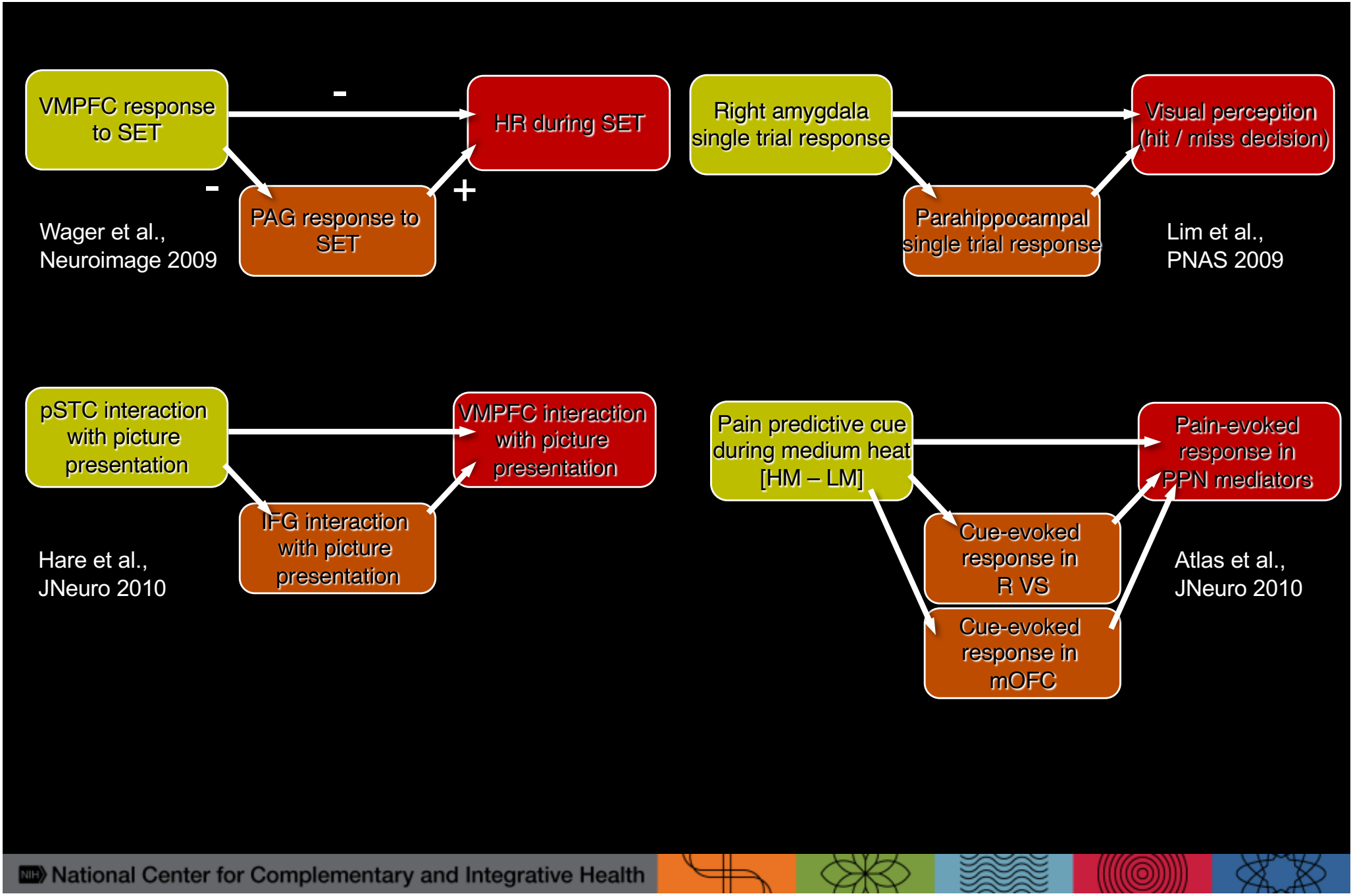
ve functional
ay from X to Y…

But individual differences within paths!



Pain Report

Multilevel mediation and functional connectivity



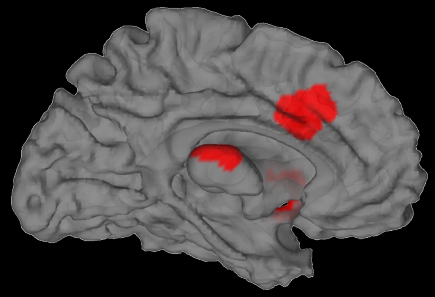
How do expectancy effects on the PPN emerge?

Predictive cue

Anticipation

mOFC
VS
Amyg.

Heat

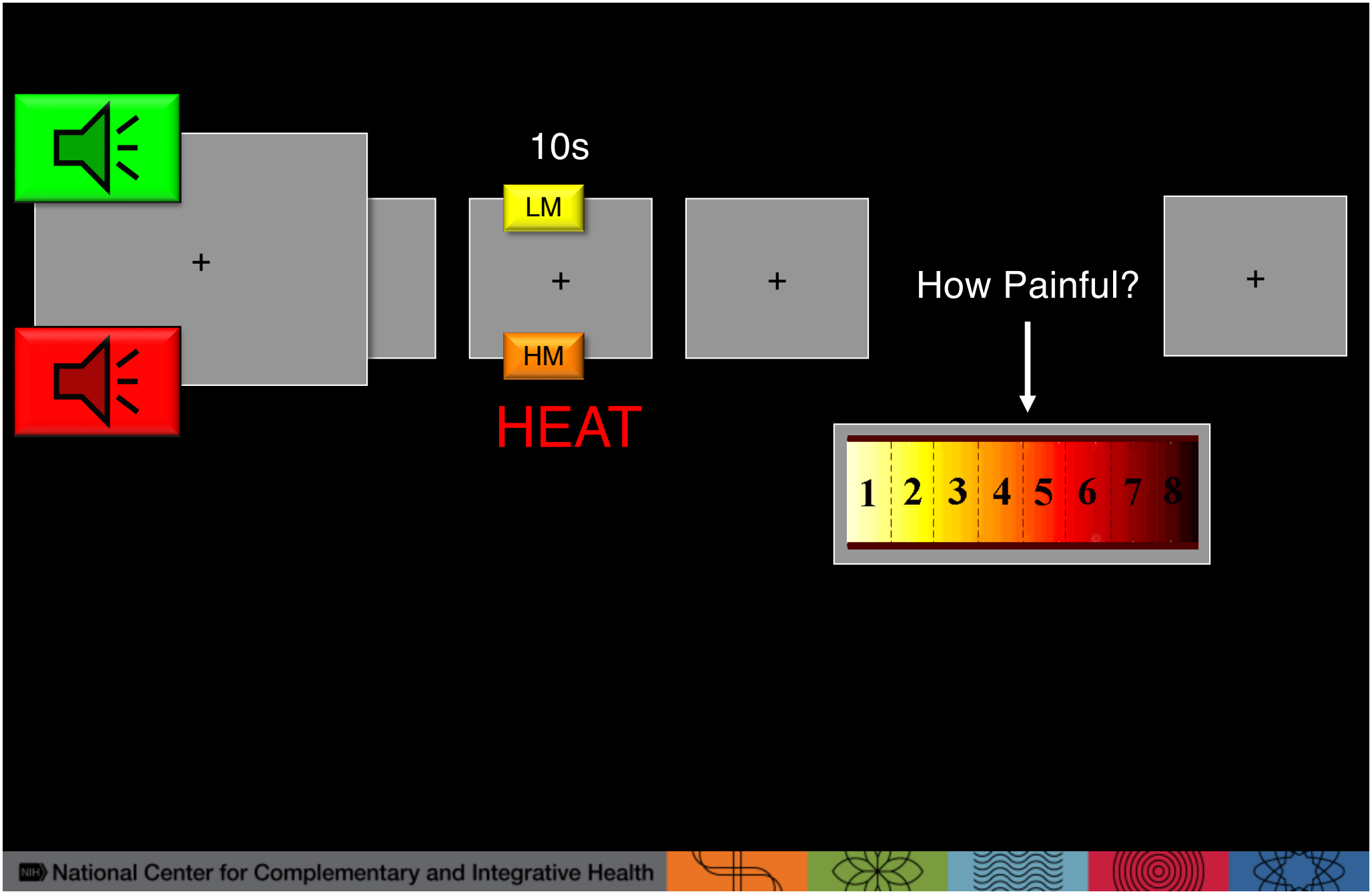


Reported pain

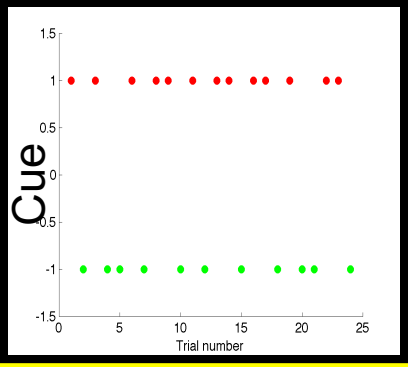
1. Expectations change pain value
(Affective value model)
Fields 2007,
Leknes & Tracey 2008

2. Expectations inhibit responses
(Regulation model)
Lieberman 2004,
Wager 2005,
Wiech Ploner & Tracey 2008

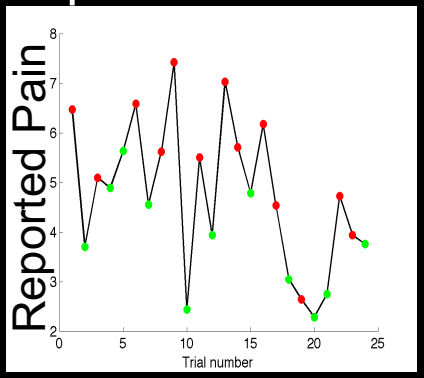
Analysis 2: Cue-evoked responses



Independent variable



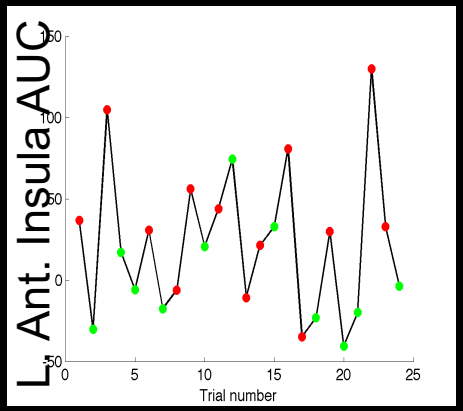
Dependent variable



Expectancy (HM-LM)

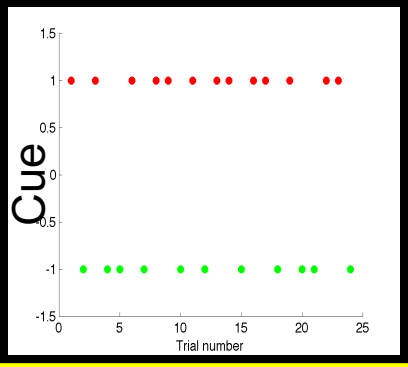
Perceived pain

Brain activity during pain



Pain period Mediator

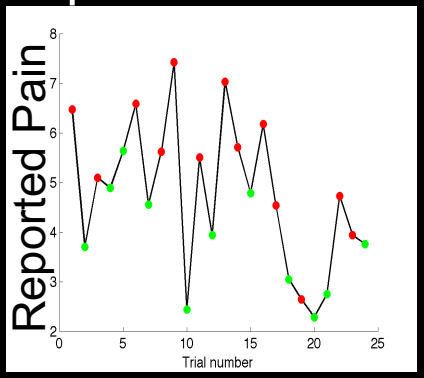
Independent variable



X

Expectancy (HM-LM)

Dependent variable



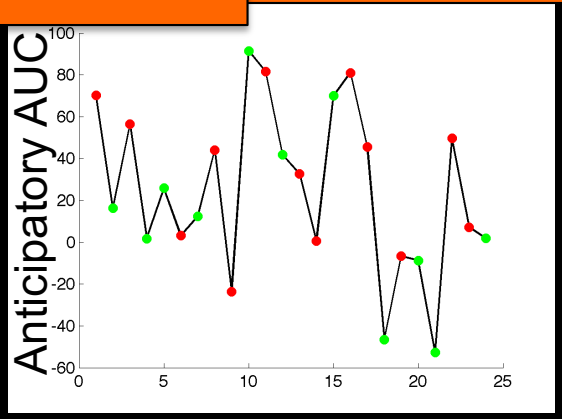
Perceived pain

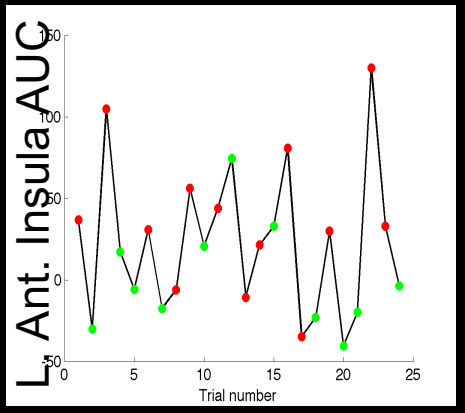
M, voxelwise search

Cue-evoked response

Brain activity during pain

Y

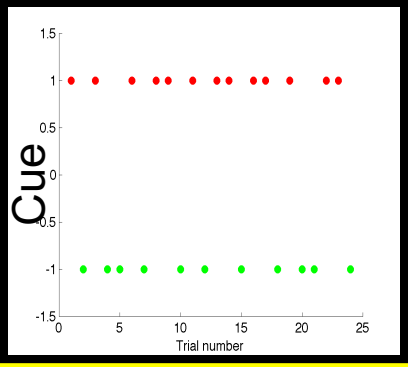




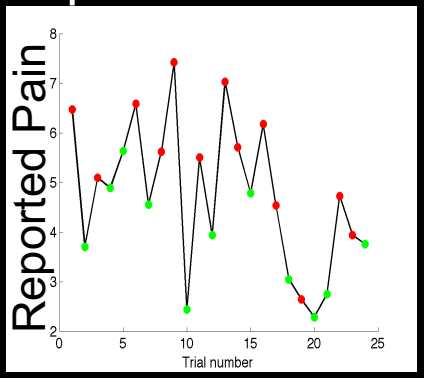
Additional region

Pain period Mediator

Independent variable



Dependent variable

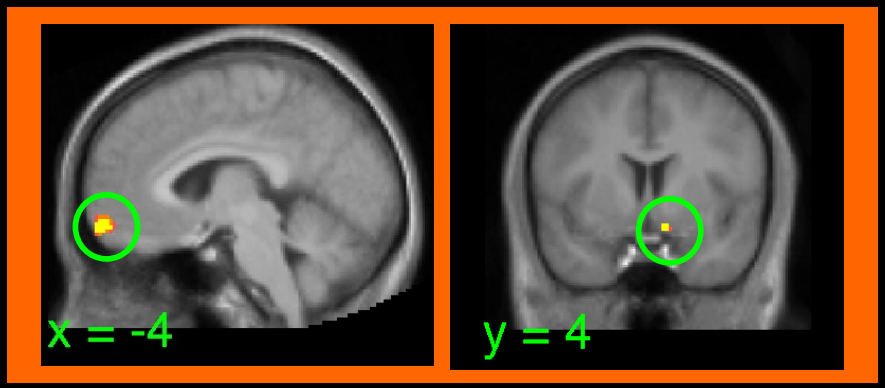


Expectancy (HM-LM)

Perceived pain

Cue-evoked response

Brain activity during pain

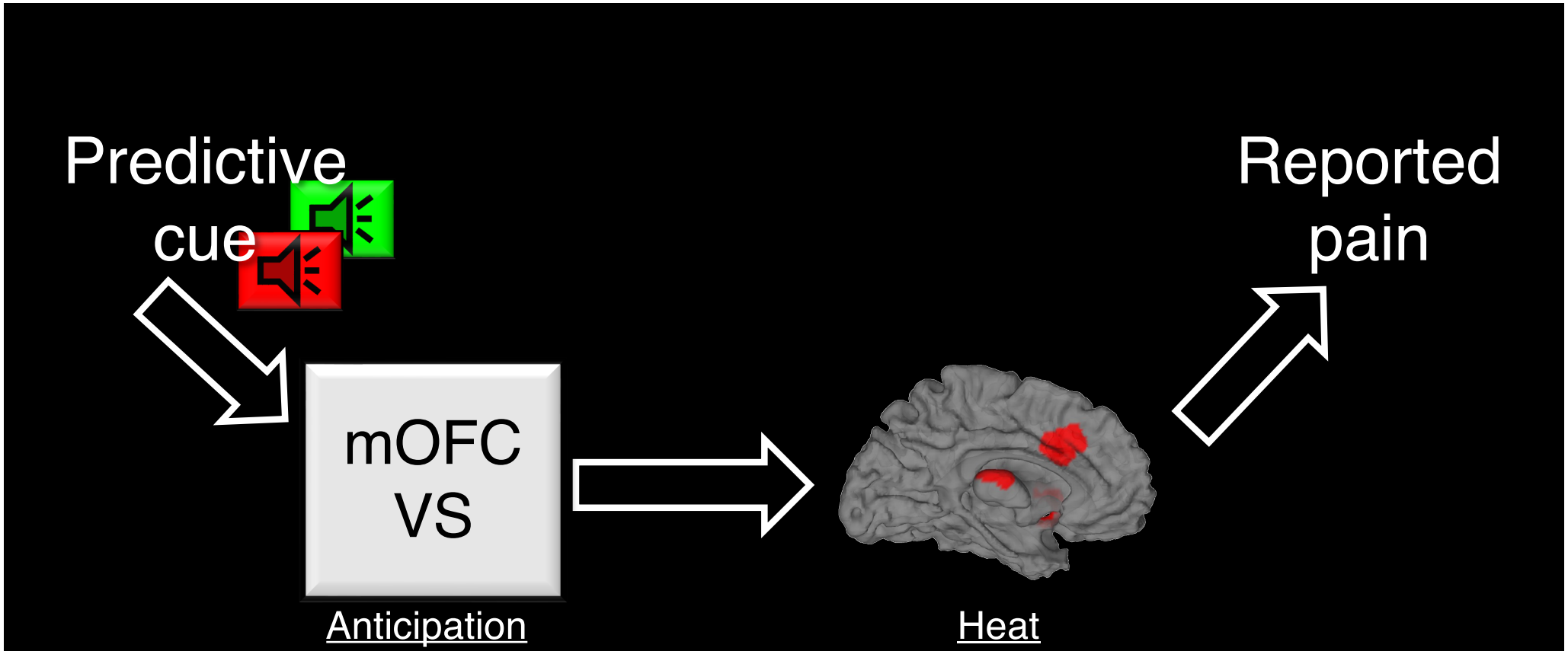


rdACC

L. Ant. Ins

R. Thalamus

Summary



This suggests that regions involved in evaluating predictive cues and generating value shape PPN responses, which in turn shape subjective experience.

Overview

- Introduction, Single level mediation
- Multi-level mediation:
  - Identifying brain regions that link independent and dependent variables
  - Connectivity analysis
  - Level 2 moderators
- Practical aspects
  - Matlab code, M3 toolbox