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

NIH National Center for Complementary and Integrative Health

FMRI of Pain

Lauren Atlas

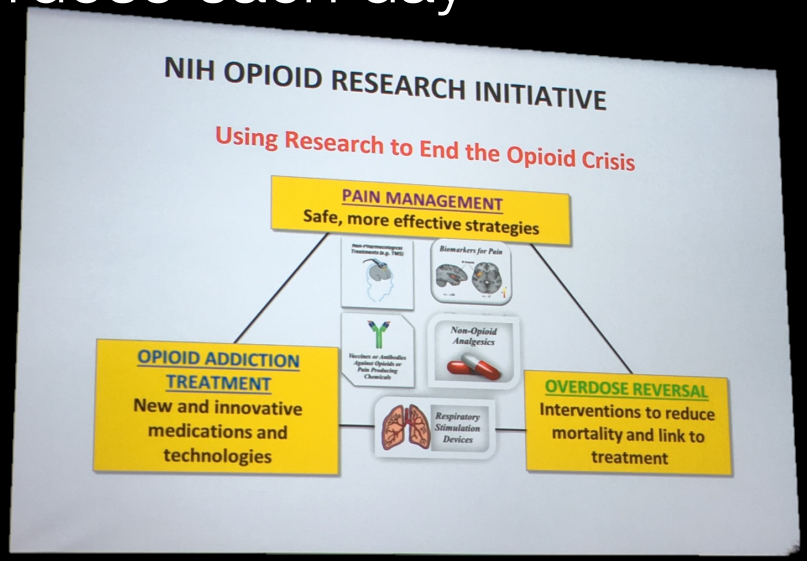
July 20, 2018

Why pain?

~116 million American adults affected by chronic pain (IOM, 2011)

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

Urgent opioid epidemic: >115 Americans die from overdose each day



Why pain?

Clinical significance

- Largest placebo effects in pain
- >100M US adults affected by chronic pain
- “Opioid epidemic” – need better treatments, non-pharmacological interventions
- Comorbid with MDD, anxiety

Experimental model

- Subjective perception
- Sensory & affective components
- Pathways conserved across species
- Can objectively manipulate noxious stimulus
- Coordinated response across levels of NS

ROADMAP

I. Background, definitions, philosophical issues

II. FMRI of pain

   a) Overview

   b) Brain mechanisms of pain perception

   c) Psychological pain modulation

III. Controversies

   a) Social pain / cingulategate

   b) Specificity & Pain biomarkers

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PAIN

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

vs NOCICEPTION: "The neural process of encoding noxious stimuli" (e.g. autonomic, behavioral responses)

IASP Task force on taxonomy, 1994

Types of pain

Transient

"activation of nociceptive transducers in skin or other tissues of the body in the absence of any tissue damage" – ubiquitous, no need to seek health care




Acute

"substantial injury of body tissue and activation of nociceptive transducers at the site of local tissue damage"; pain ends before healing occurs; can seek treatment to reduce pain or expedite healing

- Trauma
- Surgery
- Diseases

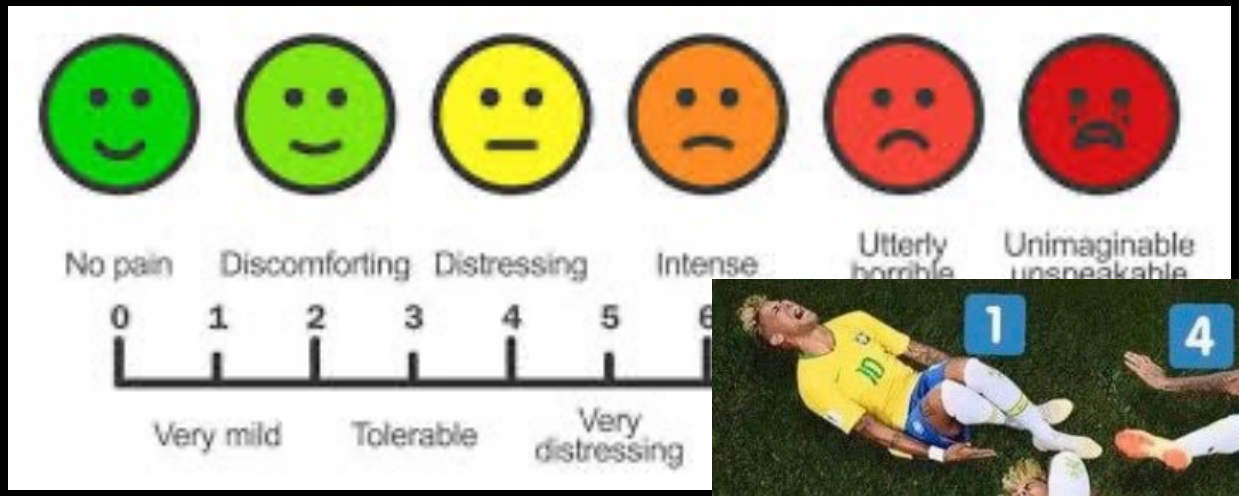
Chronic

"intensity of the pain is out of proportion to the original injury or tissue damage"; "commonly triggered by an injury or disease, but may be perpetuated by factors other than the cause of the pain"

- Low back pain
- Neuropathy
- Fibromyalgia
- Phantom Limb pain

Loeser & Melzack, 1999

Pain measurement



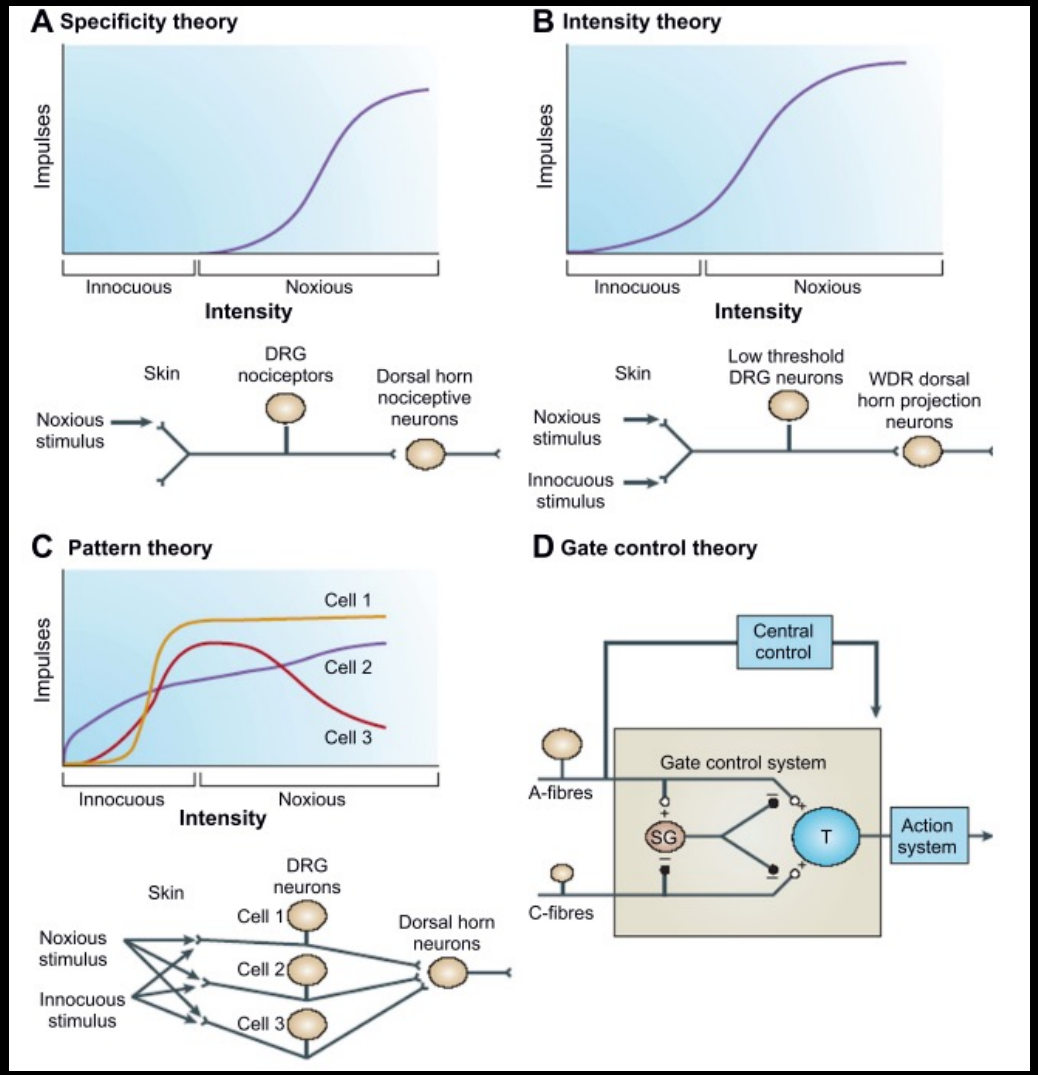
Sensory / Discriminative

Affective / Unpleasantness

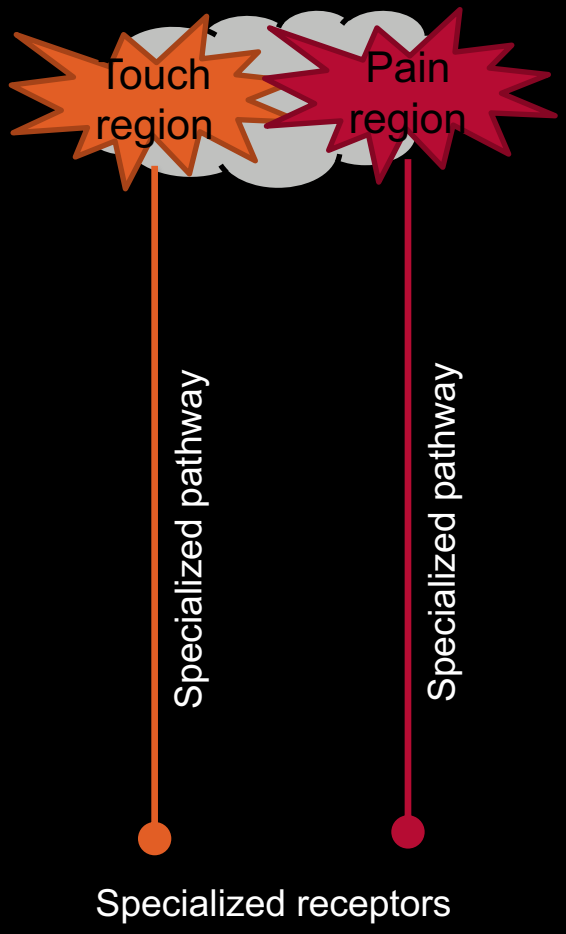
Pain theories

Descartes, 1664
(drawing by La Forge)

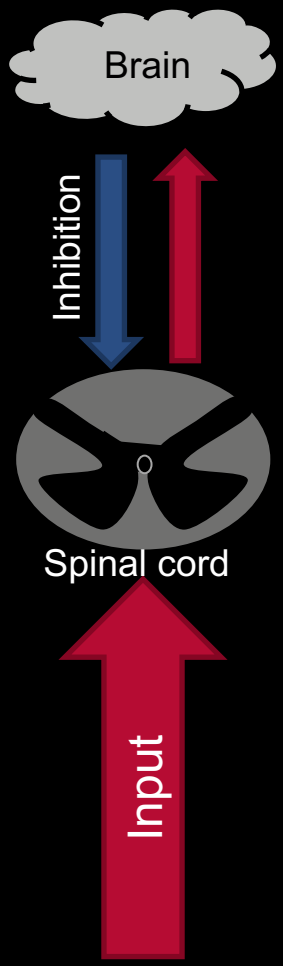
See Moayedi & Davis 2013



Pain theories

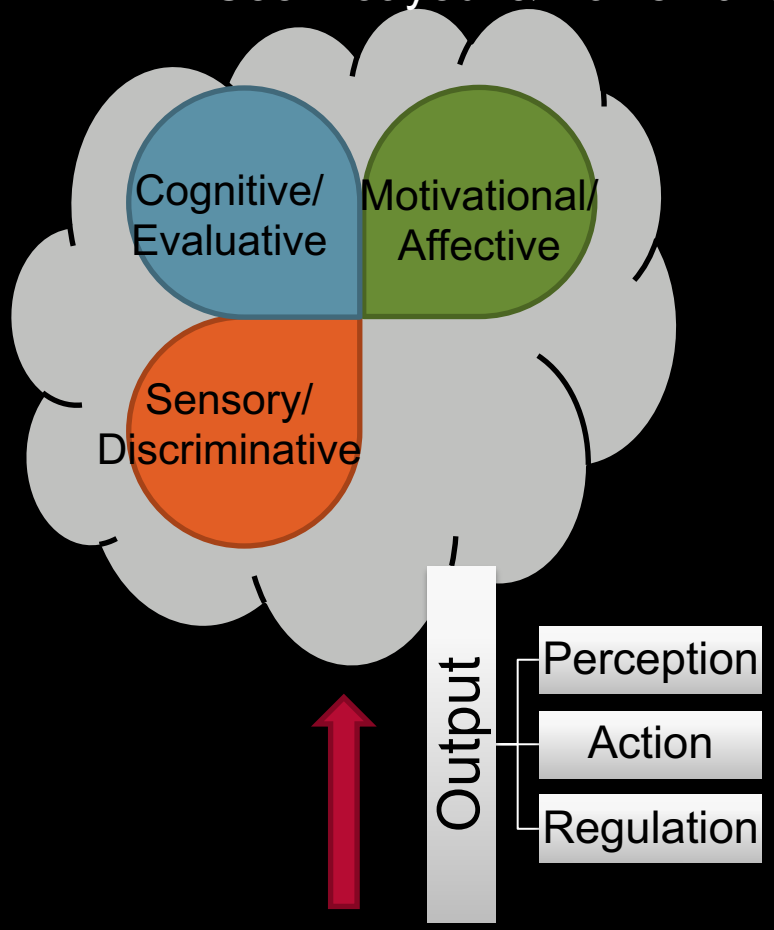


Specificity theory
(Labeled Lines)
Von Frey



Gate Control Theory
Melzack & Wall, 1965

See Moayedi & Davis 2013



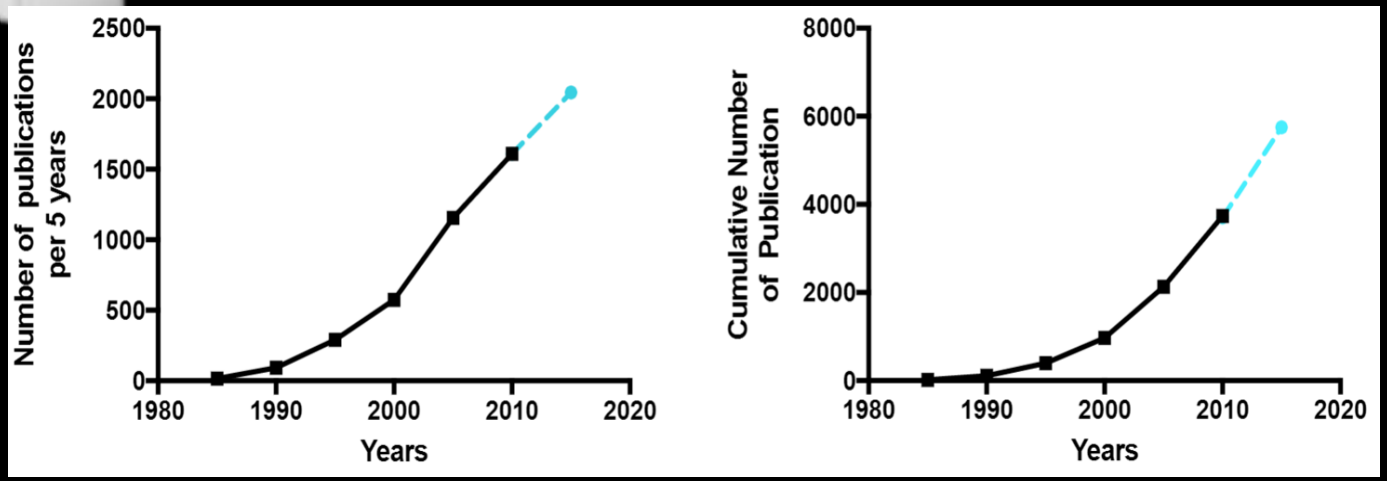
Pain neuromatrix
Melzack, 1990

Pain in the brain (before imaging)

	The brain doesn't contribute to pain	*The brain creates pain*
Lesions	Parietal lesions (Head & Holtz,1911)	Pain reduction with cingulotamy, S1, SII lesions; lesions to SII create pain
Brain stimulation	S1 stim rarely elicits pain (11/800 stims) (Penfield & Boldrev, 1937)	S1 stim elicits pain (Horrax, 1946); PAG & thalamus stim relieves pain (Hosobuchi, 1986)
Primate electrophysiology		Nociceptive neurons in thalamus, S1, area 7b (SII)

Brain imaging to the rescue!

Pain MRI/fMRI papers over time



Moayedi, Salomons, & Atlas 2018

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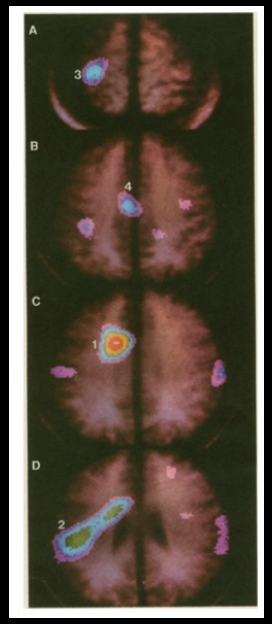
Pain in the human brain: PET rCBF

Multiple Representations of Pain in Human Cerebral Cortex
Talbot et al., Science, 1991

SI

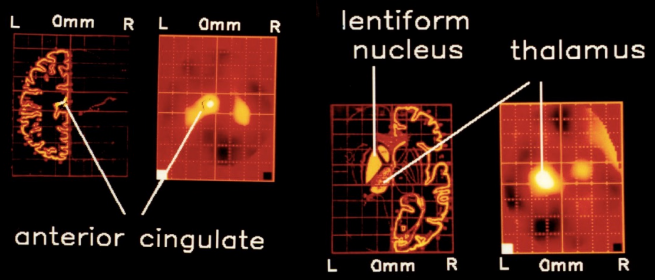
ACC

SII



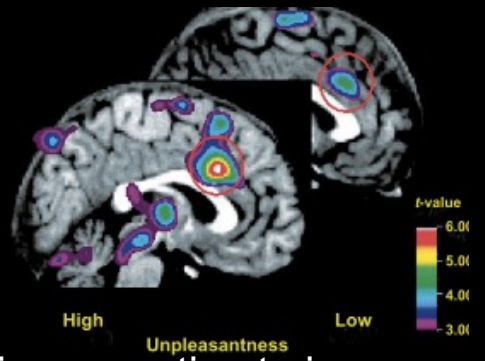
Painful heat vs Warmth

Cortical and subcortical localization of response to pain in man using positron emission tomography
Jones et al., Proc Royal Soc B, 1991



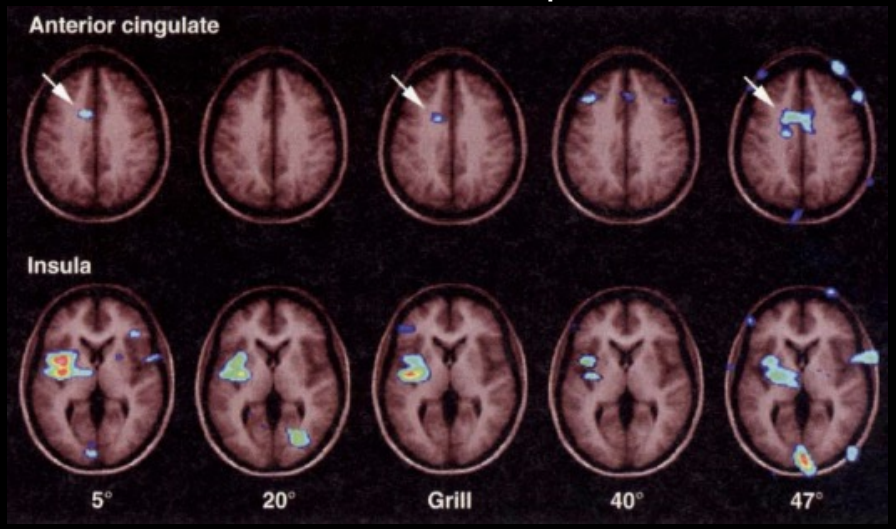
Painful heat vs Warmth

Pain Affect Encoded in Human Anterior Cingulate But Not Somatosensory Cortex
Rainville et al., Science, 1997



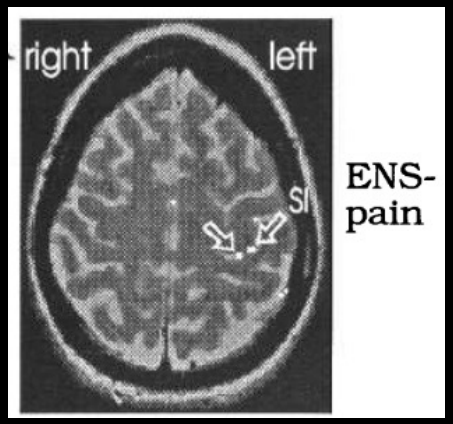
Hypnotic suggestion to increase or decrease unpleasantness

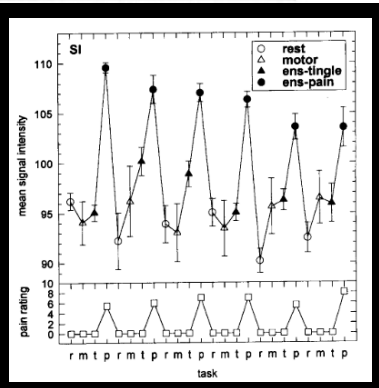
Functional imaging of an illusion of pain
Craig et al., Nature, 1996



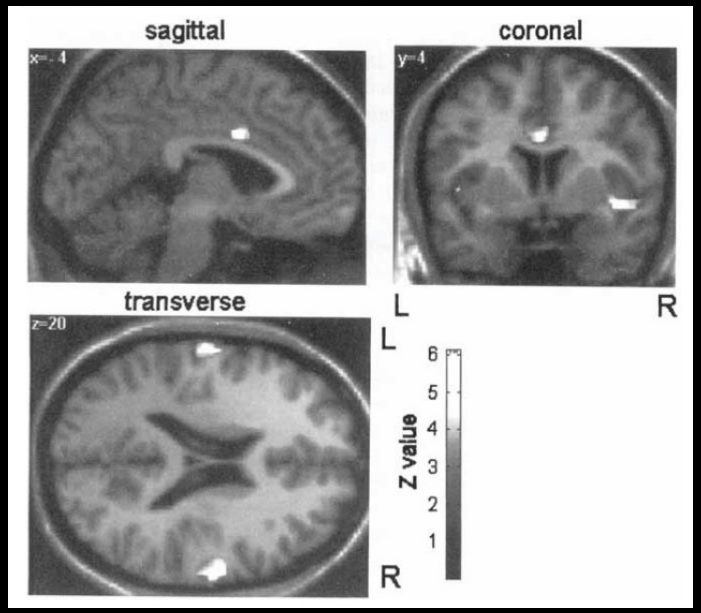
Pain in the human brain: FMRI

fMRI of human somatosensory and cingulate cortex during painful electrical nerve stimulation
Davis et al., Neuroreport, 1995

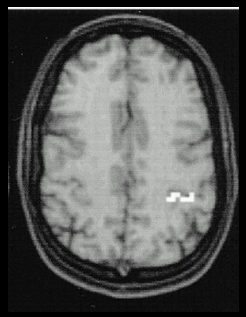


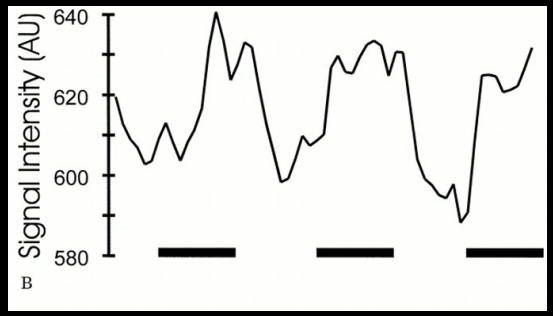


Somatic and Limbic Cortex Activation in Esophageal Distention: A Functional Magnetic Resonance Imaging Study
Binkofski et al., Annals of neurology, 1998



Brain processing of capsaicin-induced secondary hyperalgesia: A functional MRI study
Baron et al., Neurology, 1999

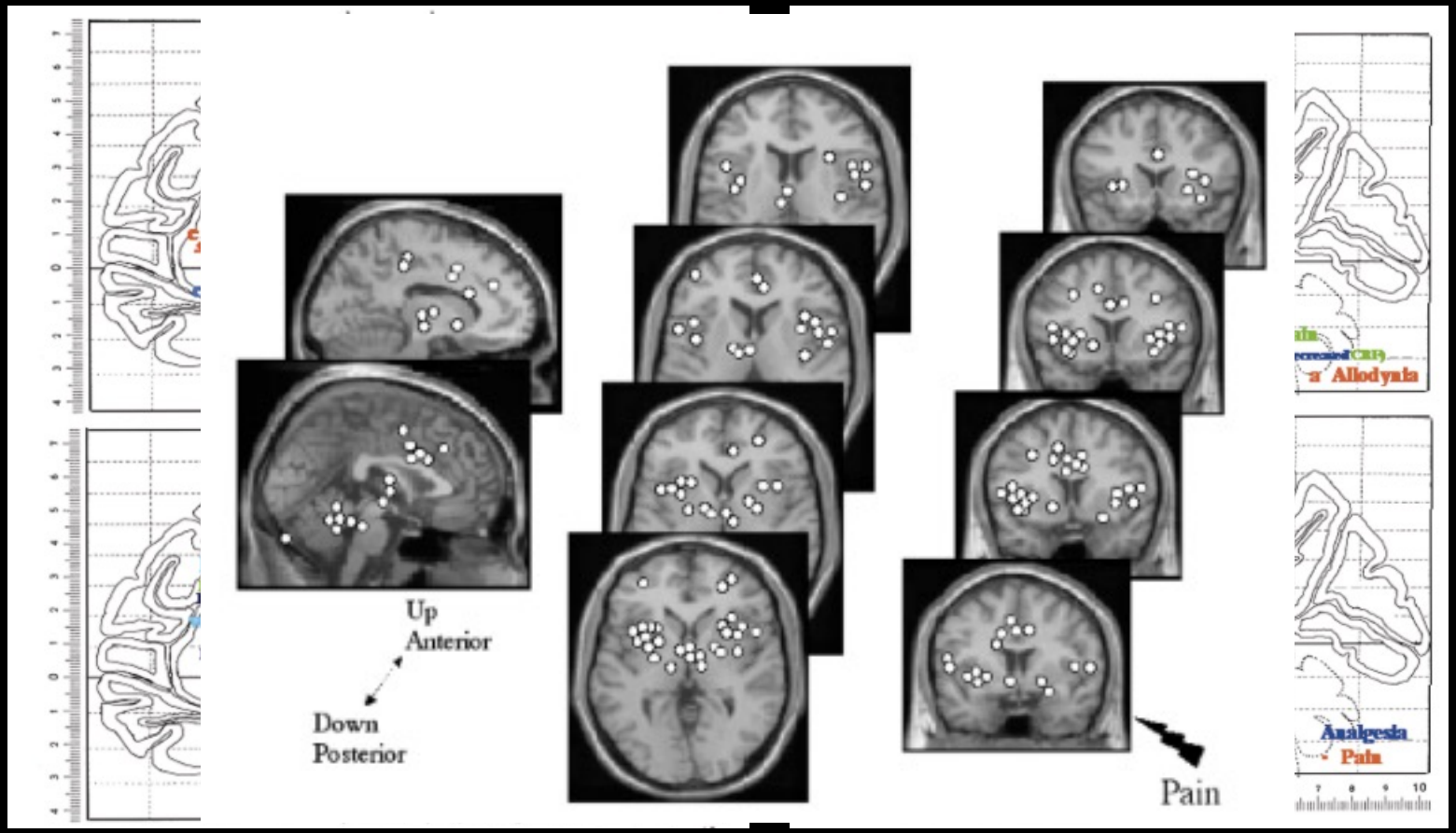




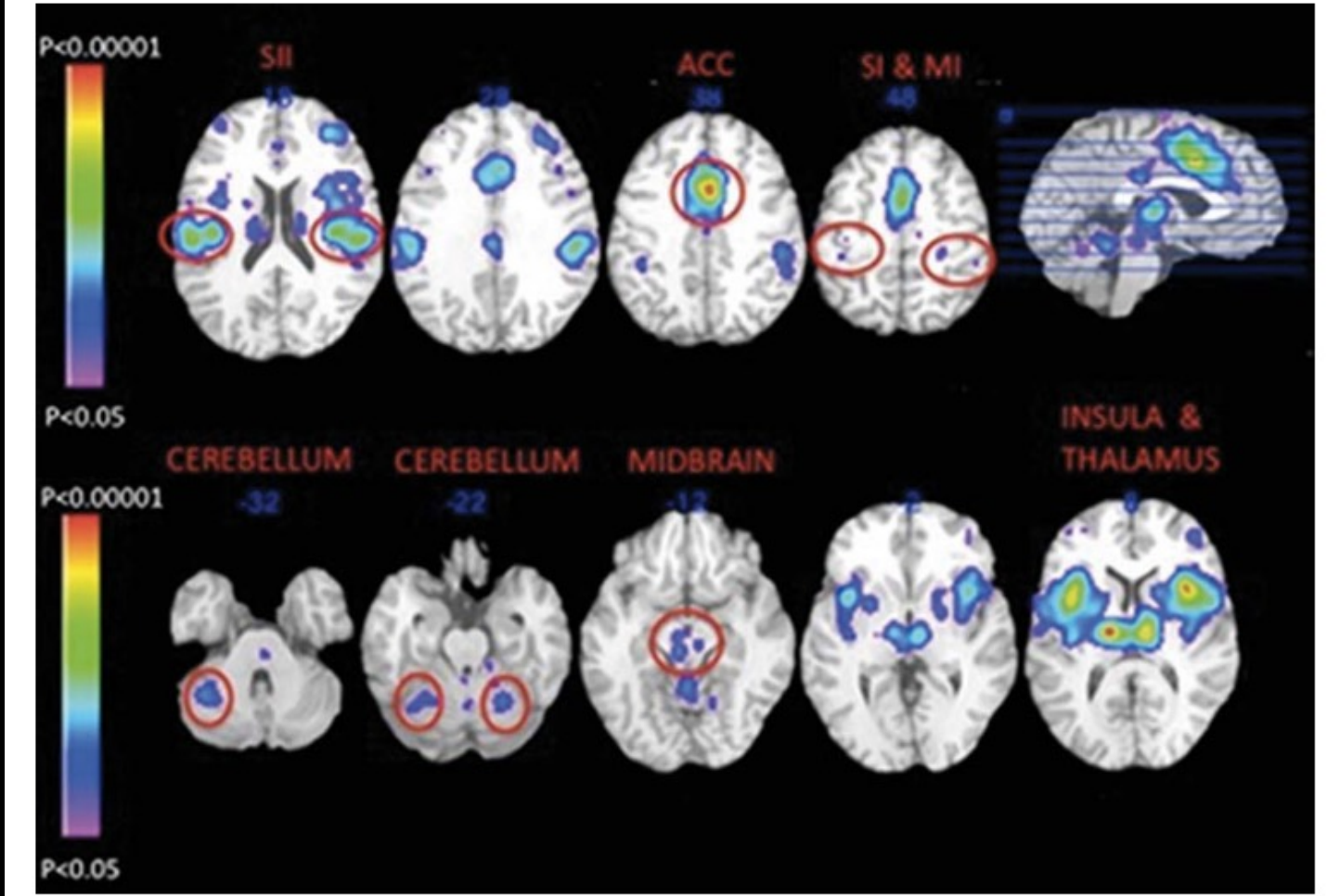
Painful stim vs Rest

Pain in the human brain (2000)

Functional imaging of brain responses to pain. A review and meta-analysis
Peyron et al., 2000

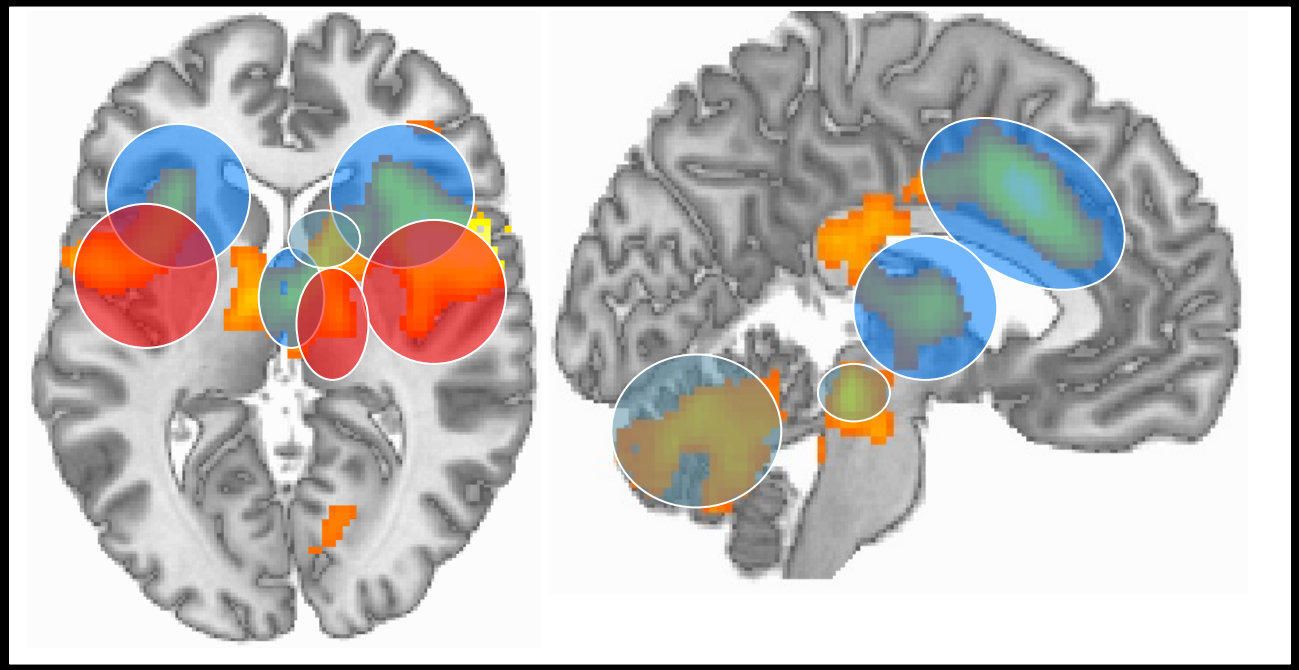


Pain in the human brain (2013)



Duerden et al., HBM, 2013

“The pain [neuro]matrix”



Sensation

Lateral thalamus
SI
SII
Posterior Insula

Affect

Medial thalamus
Anterior cingulate
Anterior insula

PAG
Cerebellum
Striatum

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

Considerations in pain neuroimaging

- No metal
- No movement
- Withdrawals
- Representative sample?
- Salience / specificity (later)

ELSEVIER

The Journal of Pain

Available online 30 March 2018

In Press, Accepted Manuscript

Focus Article

Pain Neuroimaging in Humans: a Primer for Beginners and Non-Imagers

Massieh Moayedi [1, 2, 3], Tim V. Salomons [4, 5], Lauren Y. Atlas [6, 7]

ROADMAP

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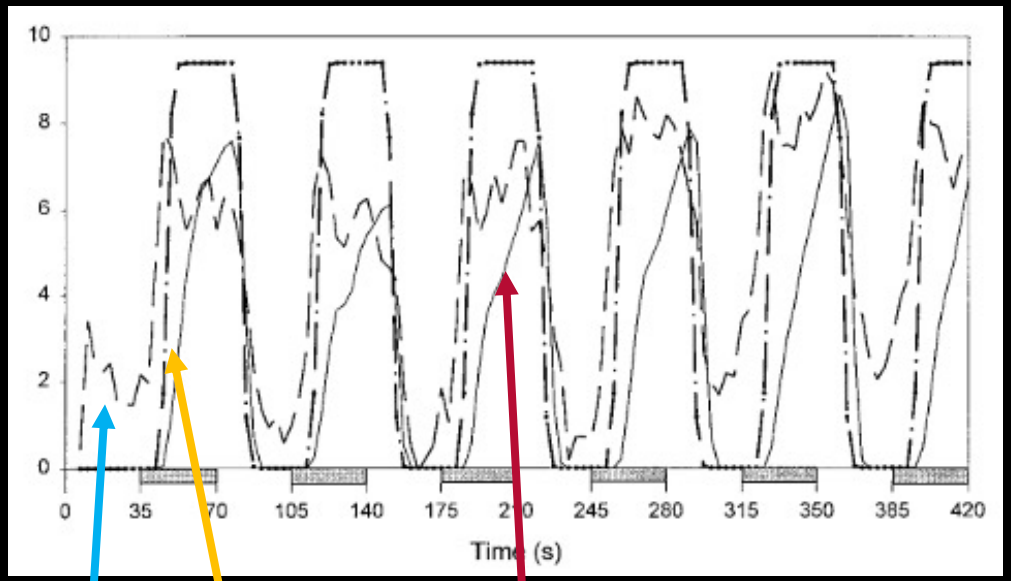
Response to stim intensity & pain

Differentiating Cortical Areas Related to Pain Perception From Stimulus Identification: Temporal Analysis of fMRI Activity

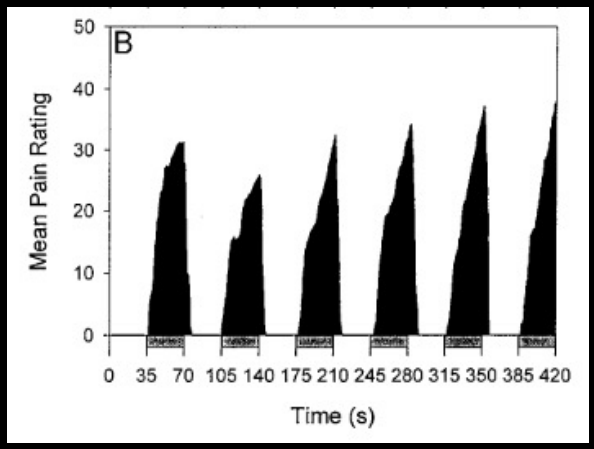
Apkarian et al., 1999



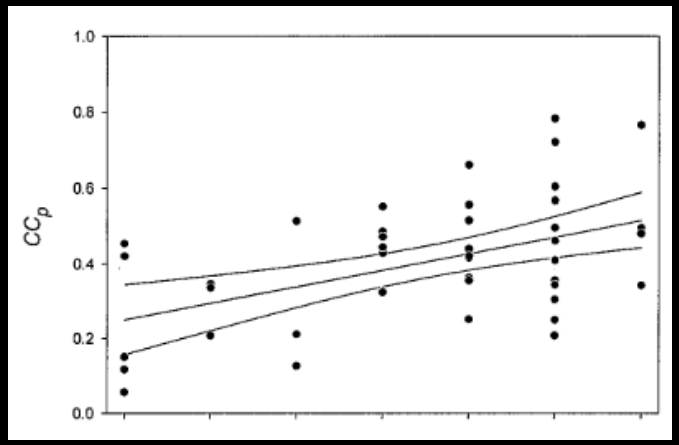
Stim timecourse convolved with HRF

Mean ROI timecourse

Pain timecourse convolved with HRF



Correlation with pain



Anterior

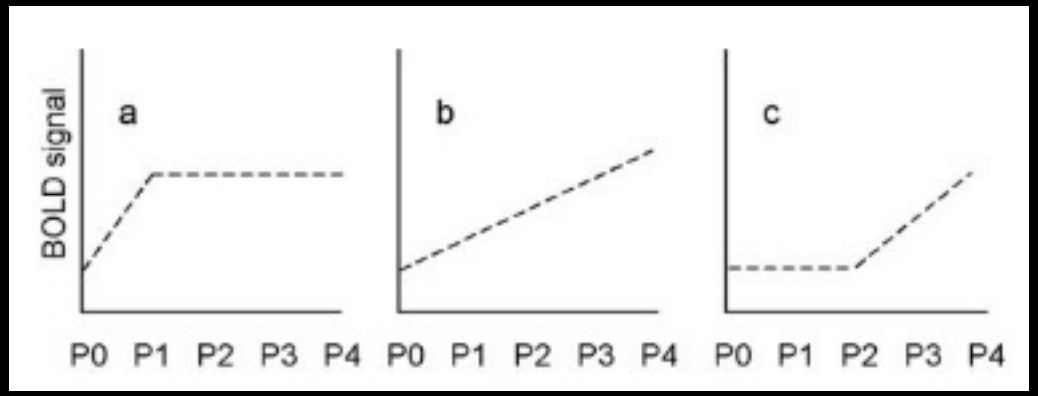
Posterior

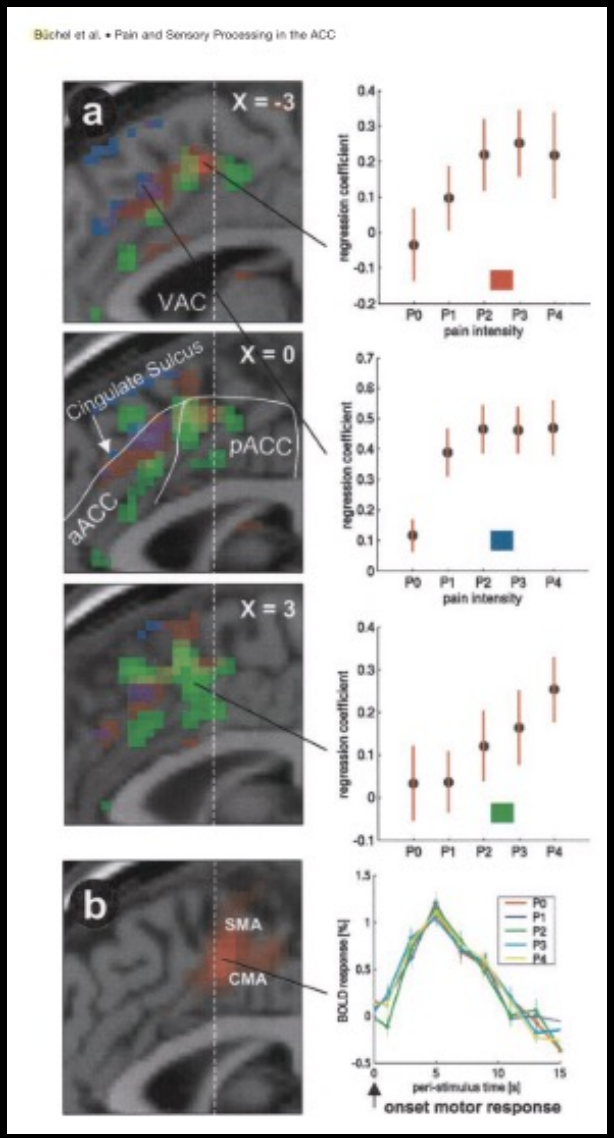
Response to stim intensity & pain

Dissociable neural responses related to pain intensity, stimulus intensity, and stimulus awareness within the anterior cingulate cortex: a parametric single-trial laser functional magnetic resonance imaging study.

Büchel et al., 2002

Cognitive/ awareness | Stim intensity | Pain intensity

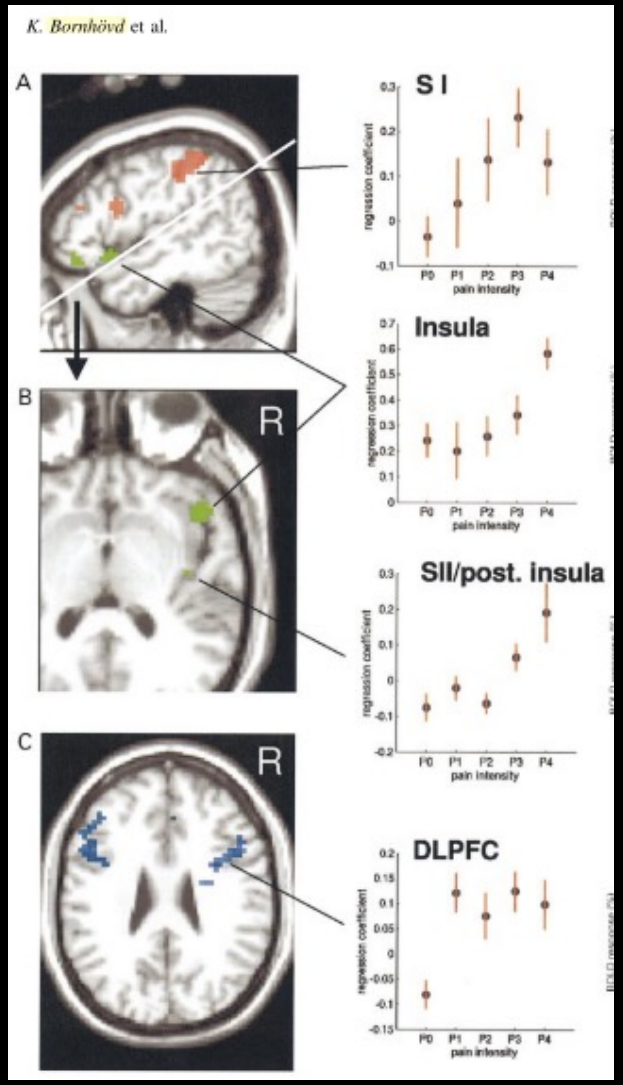


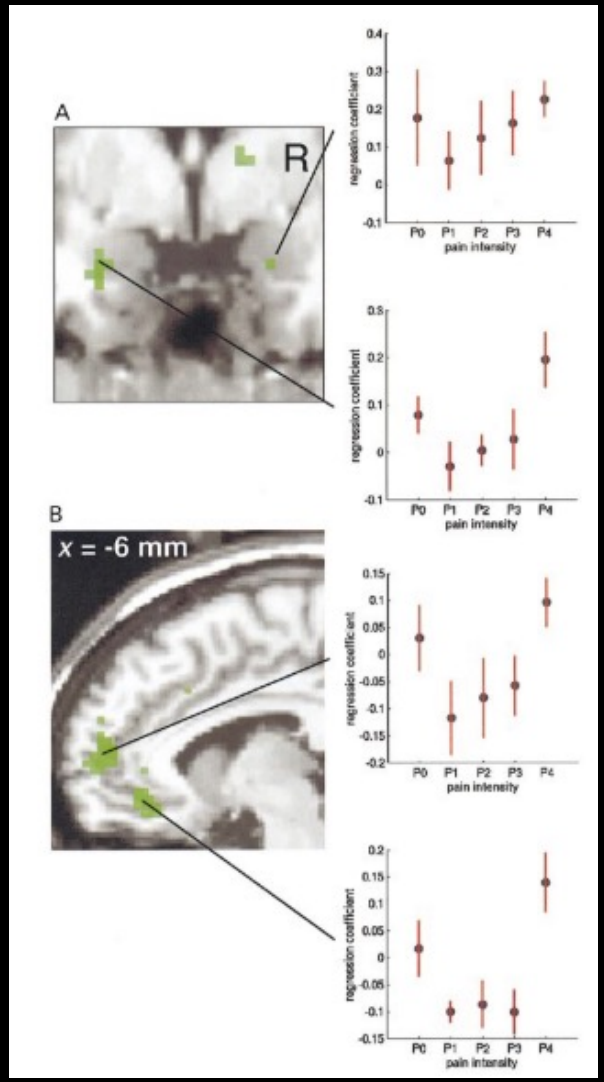


Response to stim intensity & pain

Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study.

Bornhövd et al., 2002



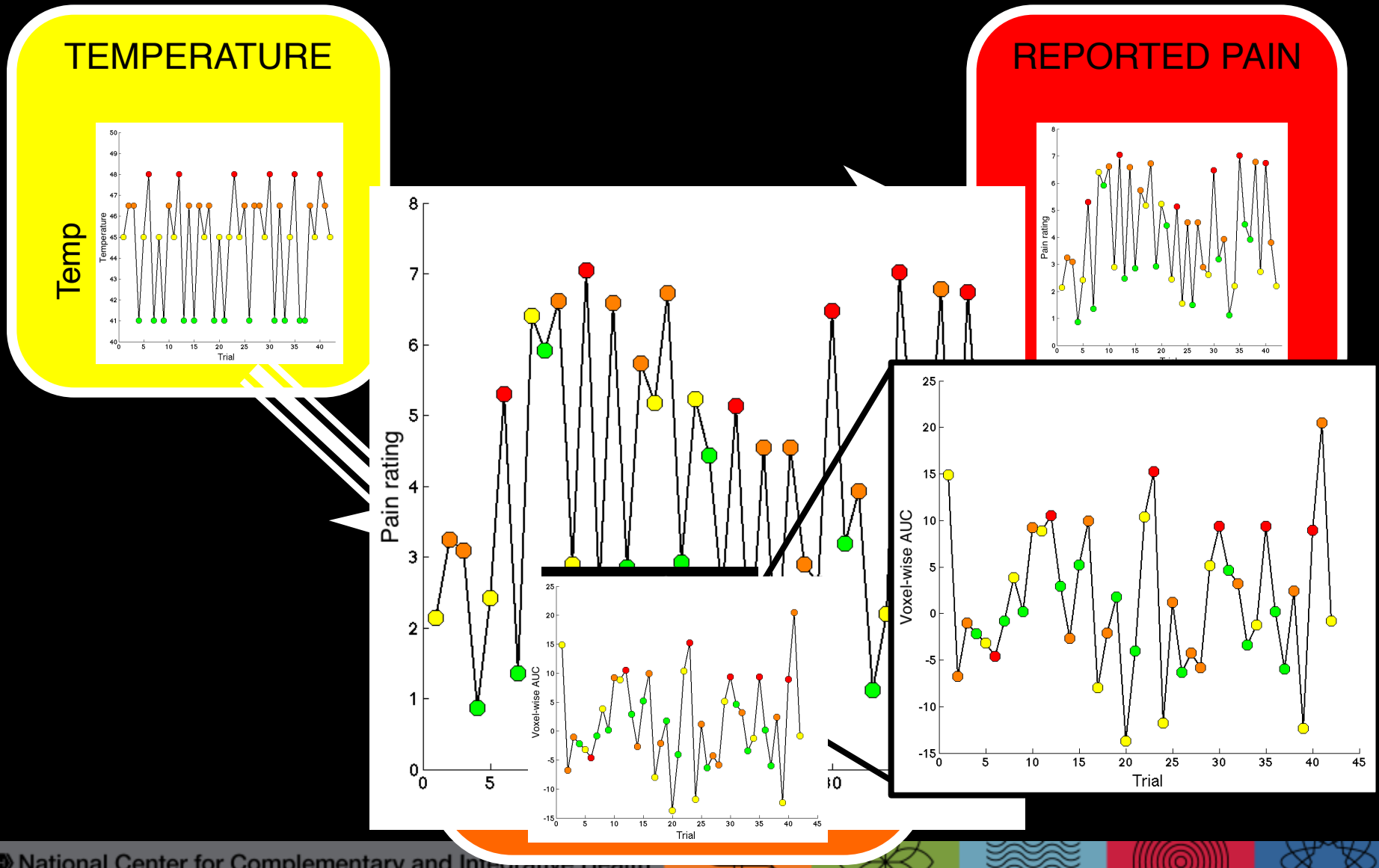


Response to stim intensity & pain

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

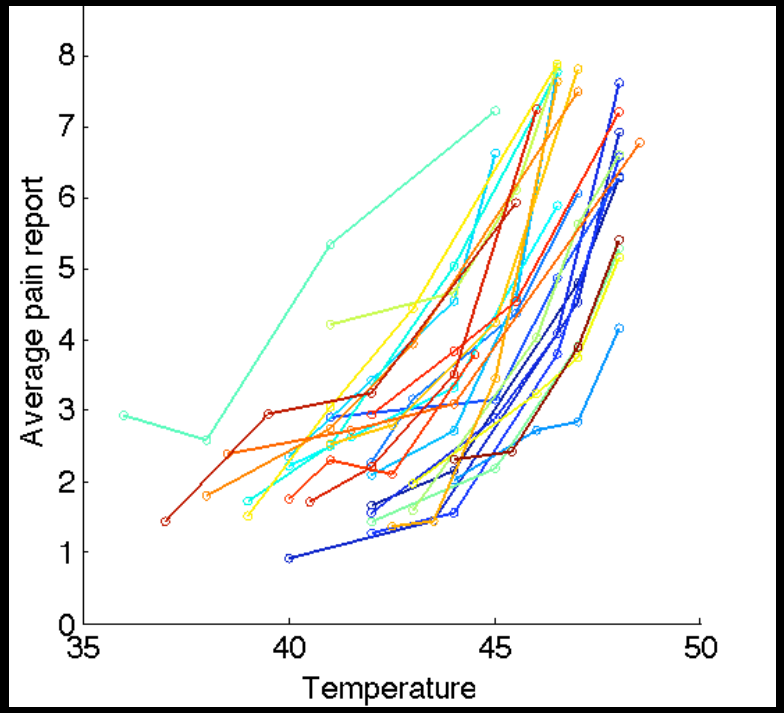
Atlas et al., 2014, Pain

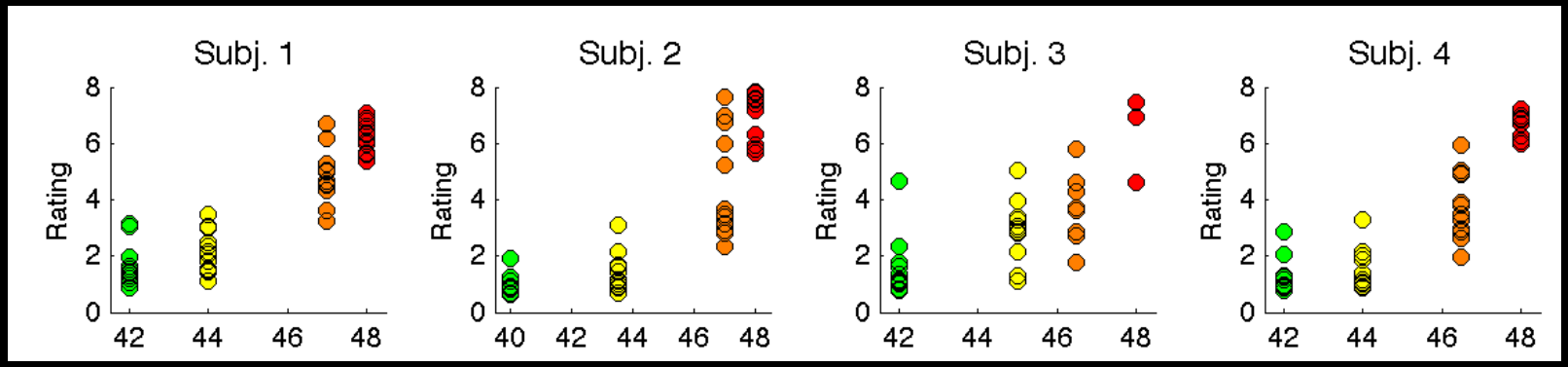
Mediation model



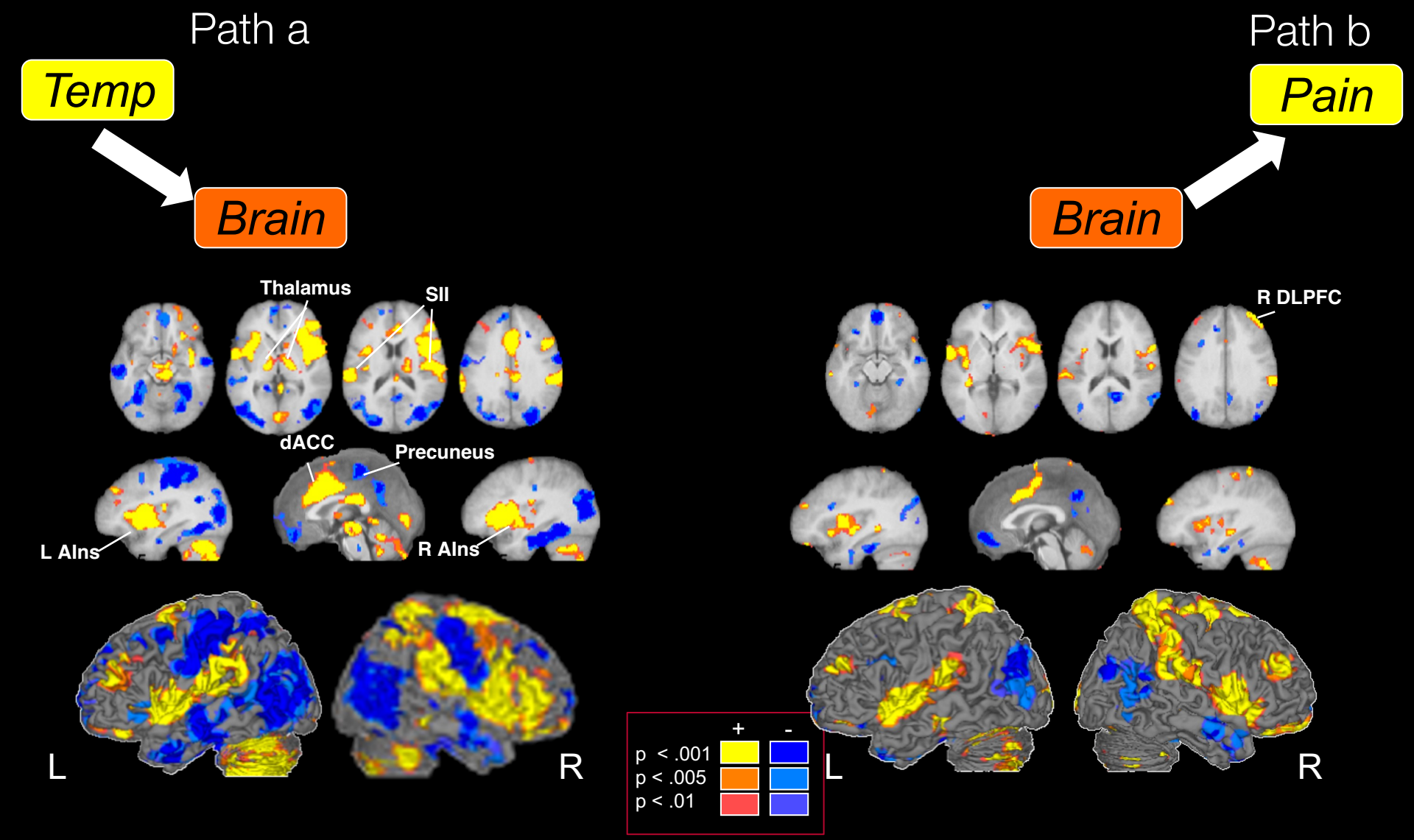
Path c

Temp → *Pain*



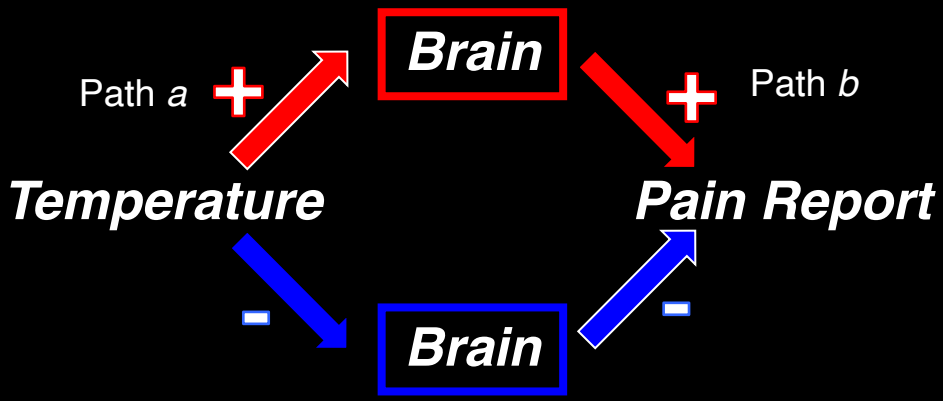


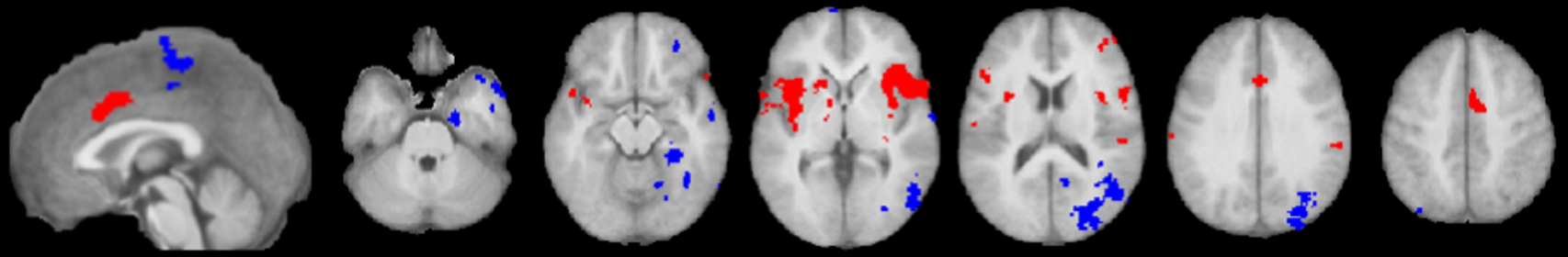
Response to stim intensity & pain

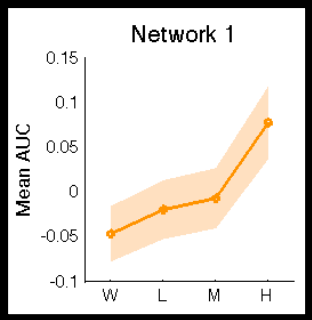


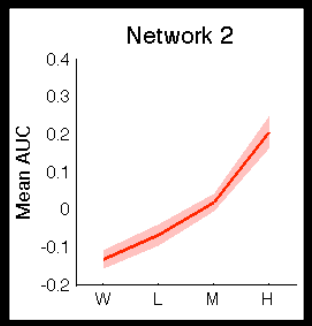
Response to stim intensity & pain

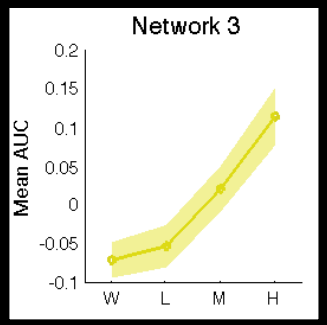
Consistent mediators (significant Path a and Path b effects in group)

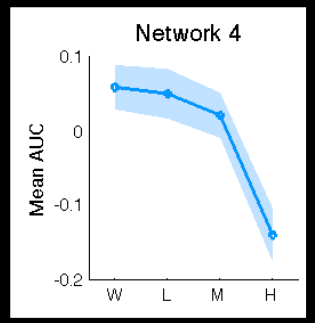


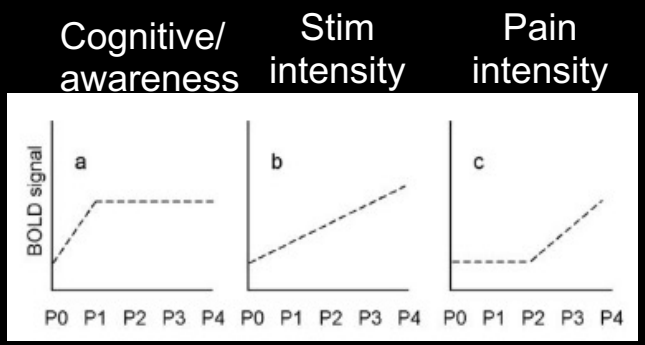






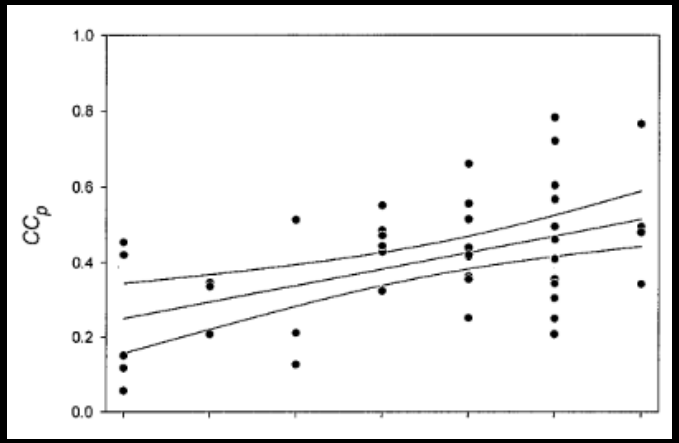






Response to stim intensity & pain

Correlation with pain

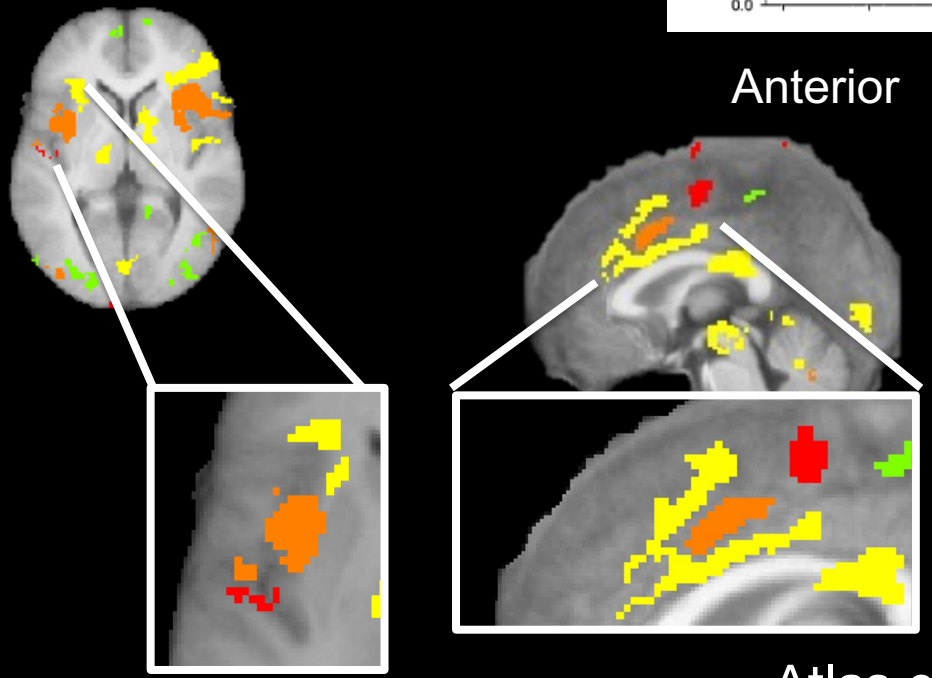


Apkarian et al., 1999

Anterior

Posterior

- Temperature, not pain
- Mediator, Temp + Pain
- Pain report, not temperature



Atlas et al., *Pain* (2014)

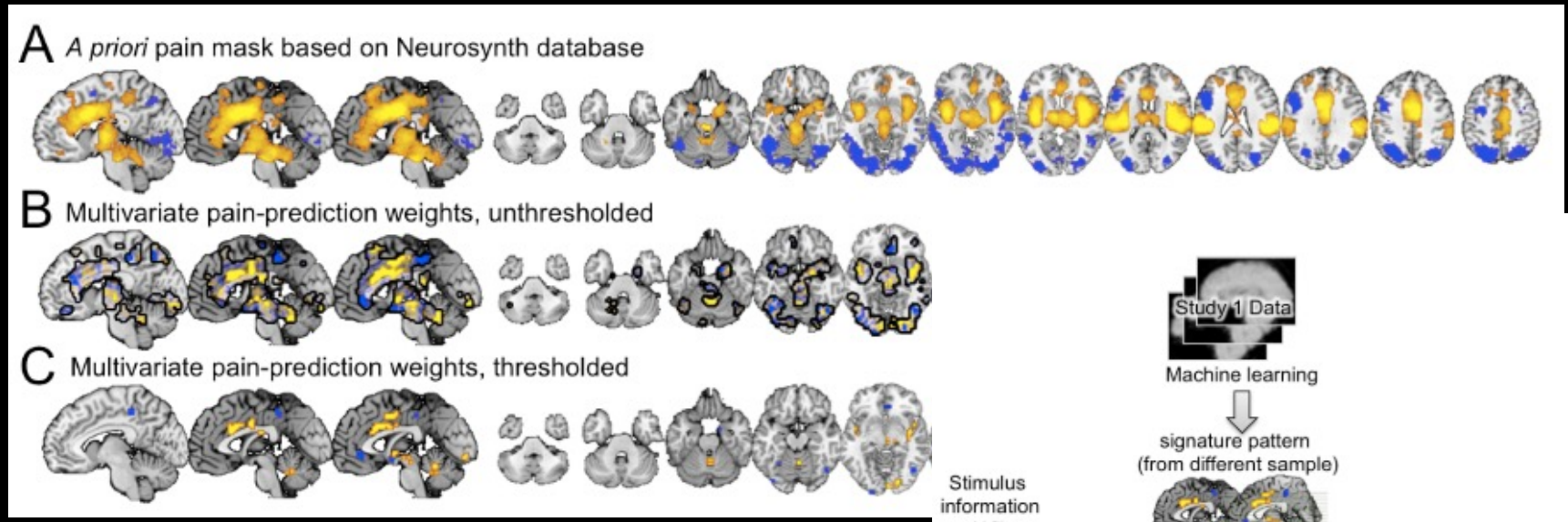
Study 1 Summary

Pain is generated by a combination of independent networks

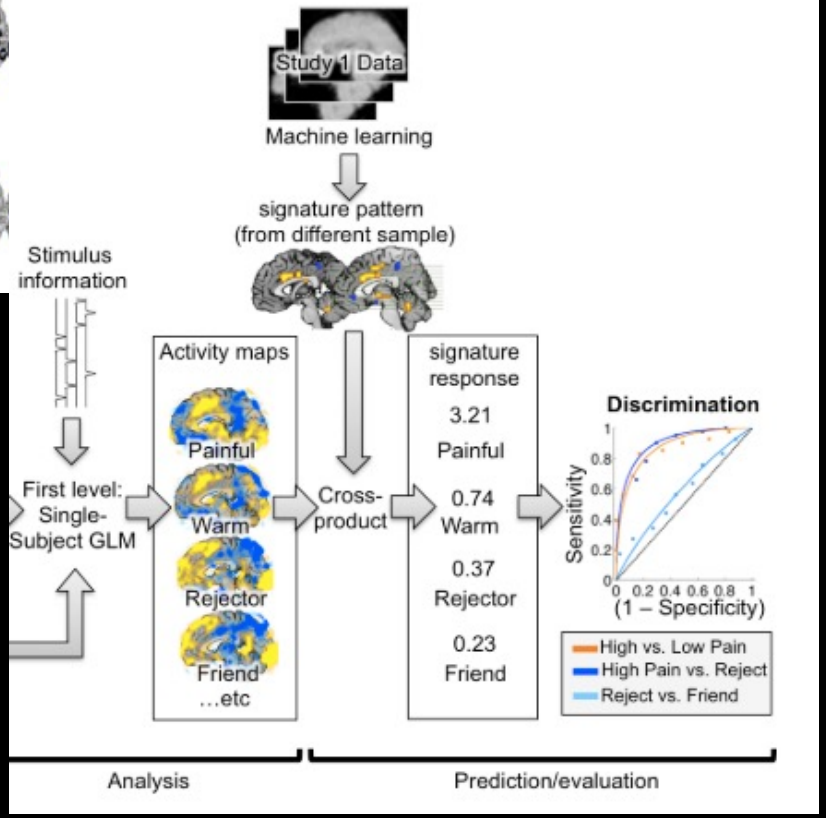
- Increases with temp + increases predict pain (e.g. SII, “salience network”)
- Decreases with temp + decreases predict pain (e.g. DMN)
- Suppression effects / negative mediators (DMPFC, mOFC)
- Pain-related without responding to temperature (e.g. DLPFC, DMPFC, OFC)

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

Neurologic pain signature (NPS)

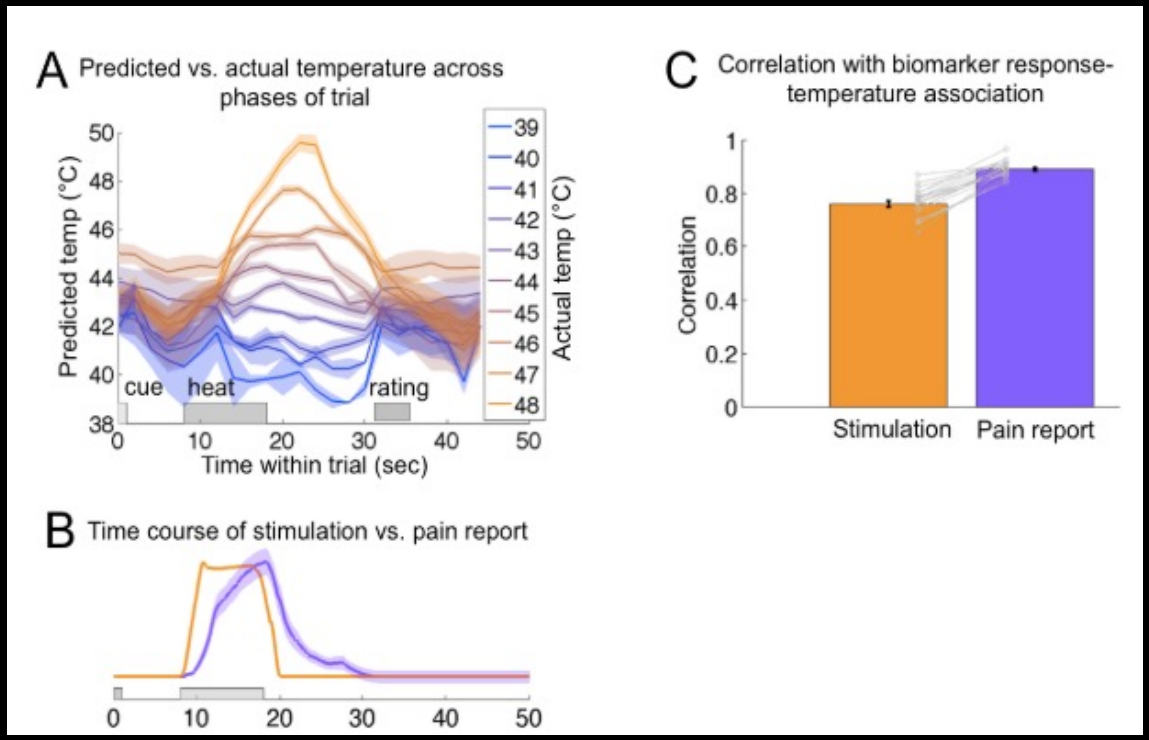


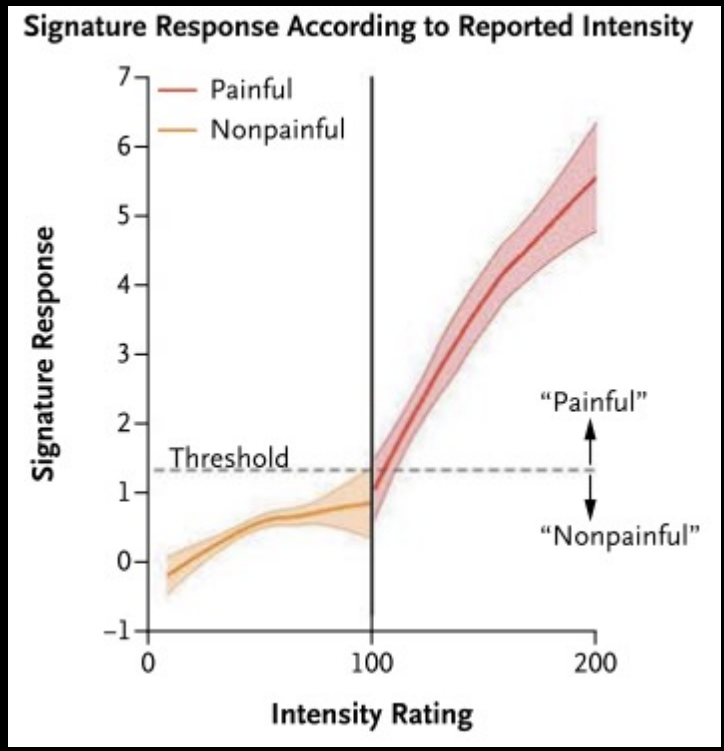
- *LASSO-PCR to generate NPS*
- *Predicts pain in new subjects, in new scanners, in new studies*
- *Highly specific to pain*



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

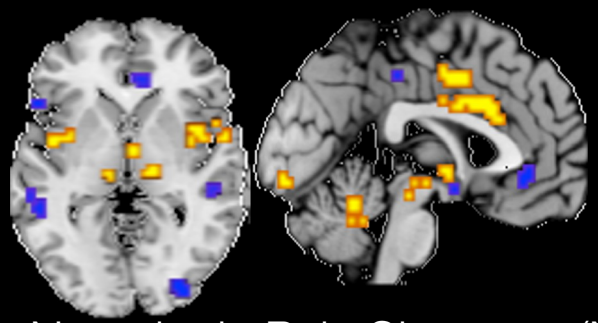
Neurologic pain signature (NPS)





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

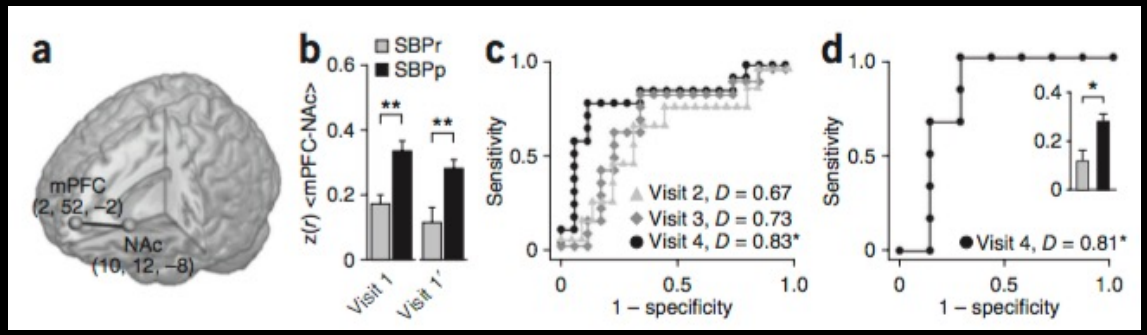
Pain signatures



Neurologic Pain Signature (NPS)

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

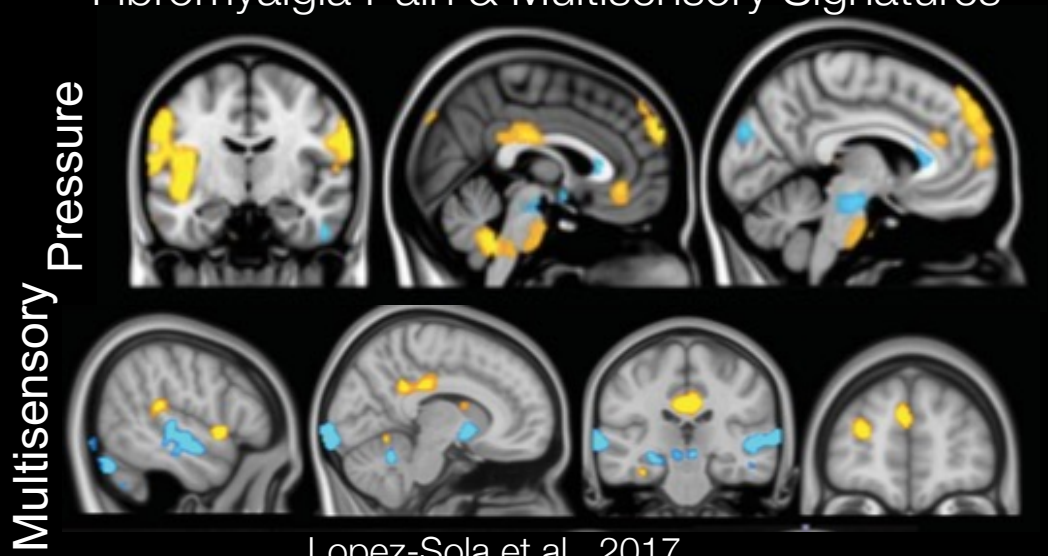
MPFC-NAc connectivity predicts acute to chronic pain



Baliki et al., 2012

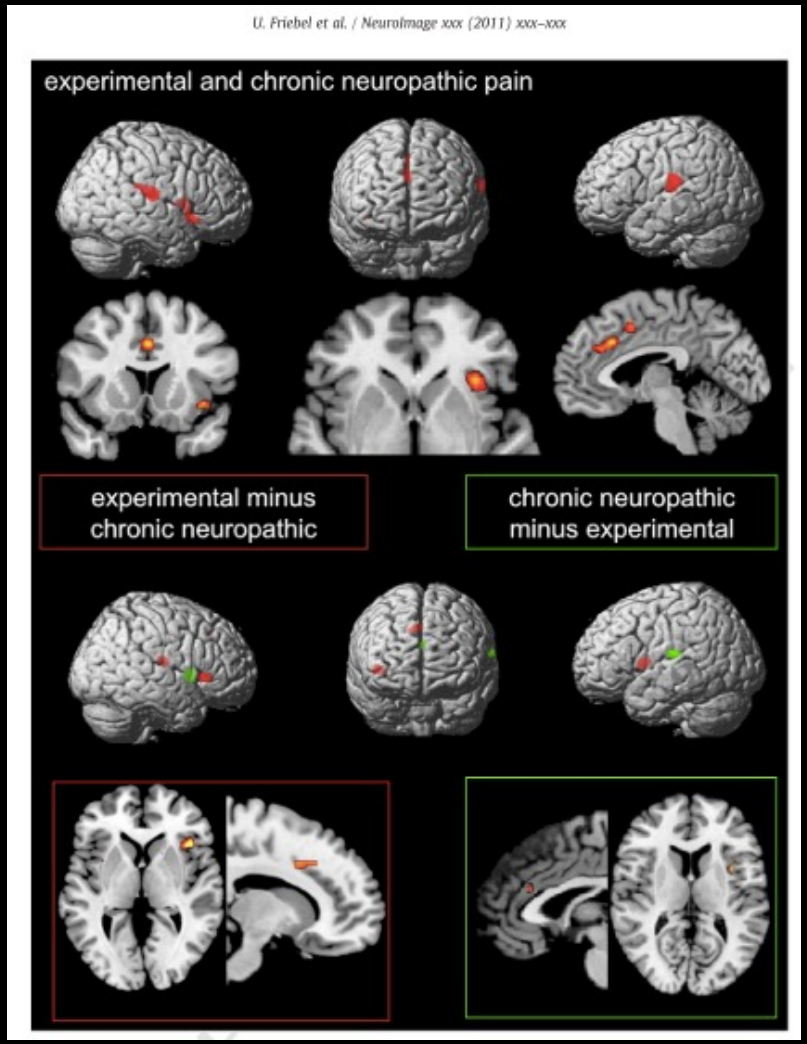
- Vicarious pain signature (Krishnan et al., 2016)
- Stimulus-Intensity Independent Pain Signature (Woo et al., 2017)
- Group-regularized Individual Prediction (Lindquist et al., 2017)
- Principal directions of mediation (Geuter et al., 2018)

Fibromyalgia Pain & Multisensory Signatures



Lopez-Sola et al., 2017

Experimental vs Chronic pain



Friebel et al., 2011

ROADMAP

I. Background, definitions, philosophical issues

II. FMRI of pain

   a) Overview

   b) Brain mechanisms of pain perception

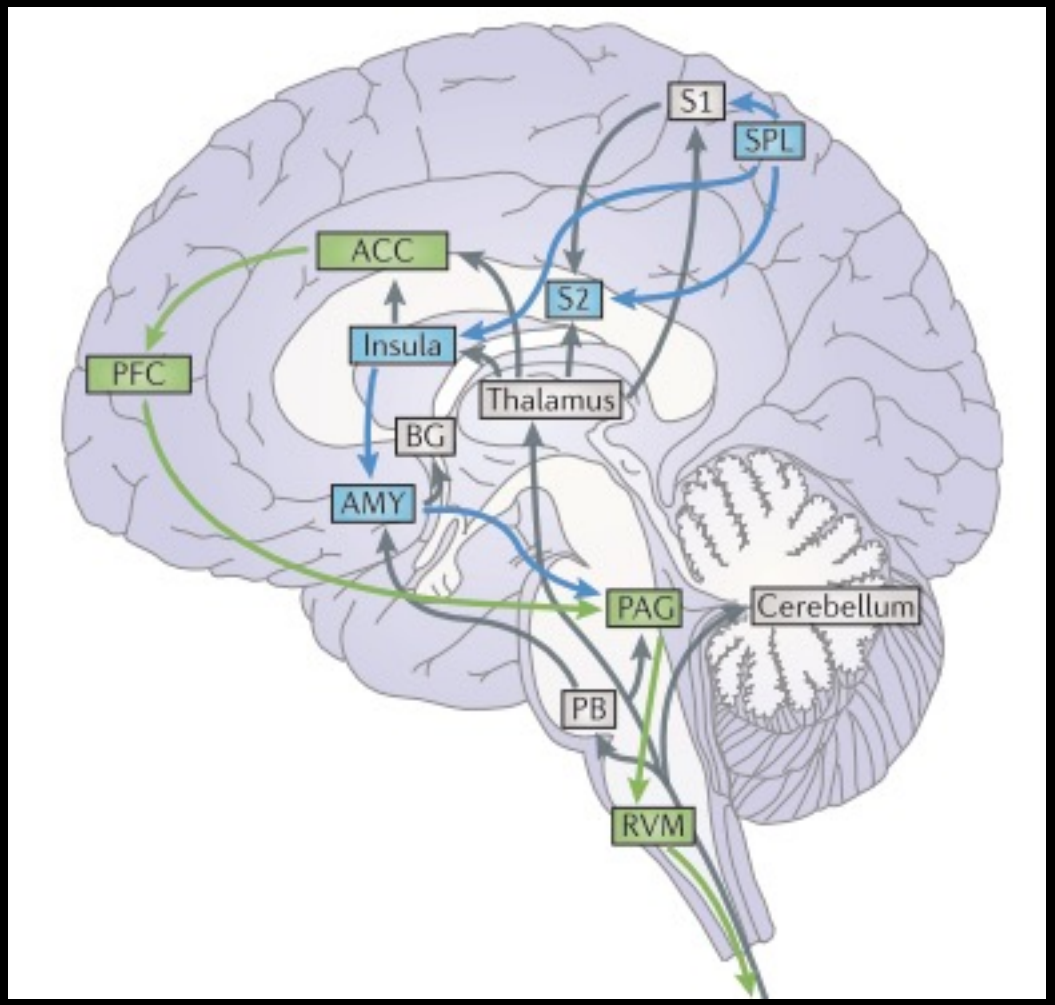
   c) Psychological pain modulation

III. Controversies

   a) Social pain / cingulategate

   b) Specificity & Pain biomarkers

Psychological pain modulation



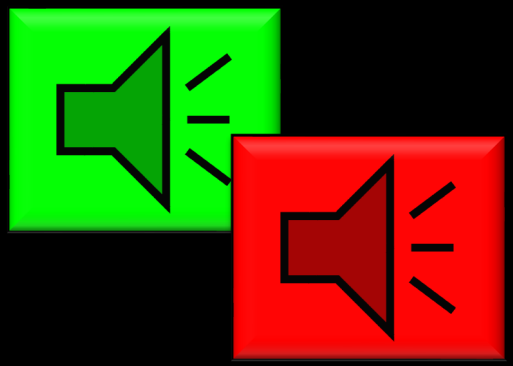
Ascending pathways

Descending pathways:
Emotion & Placebo
Attention

Bushnell, Ceko, Low, 2013, Nature reviews

How do expectancies shape pain?

Pain-predictive cues



STIMULUS EXPECTANCIES

Placebo analgesia

Analgesic treatments

TREATMENT EXPECTANCIES

Expectancies shape brain responses and subjective experience

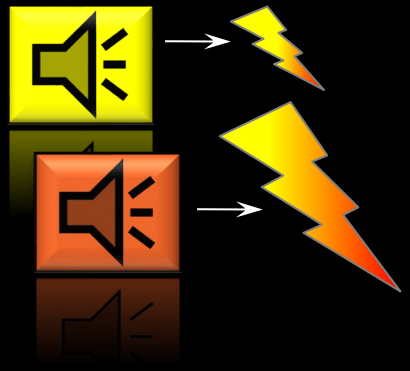
Stimulus expectancy manipulation

Instructions

"Low pain"

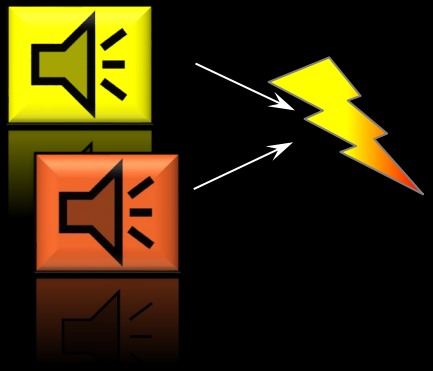
"High pain"

Conditioning



Test:

High vs Low expectancy

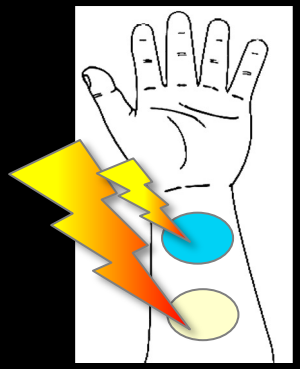


PAIN

Placebo/ Treatment expectancy manipulation

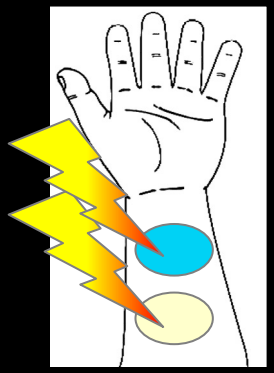
Instructions

Conditioning



Test:

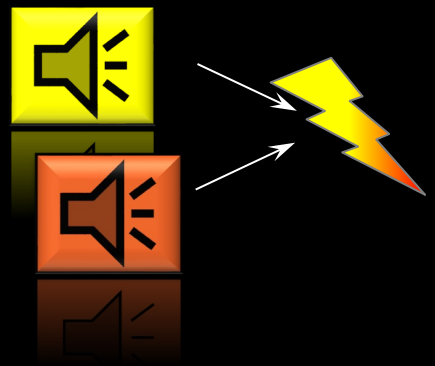
Control vs Placebo



Expectancies shape brain responses and subjective experience

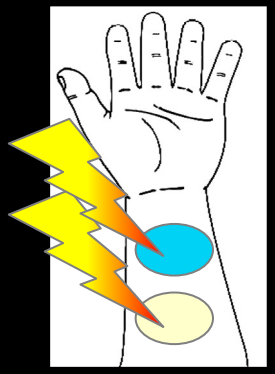
Stimulus expectancy manipulation

High vs Low expectancy

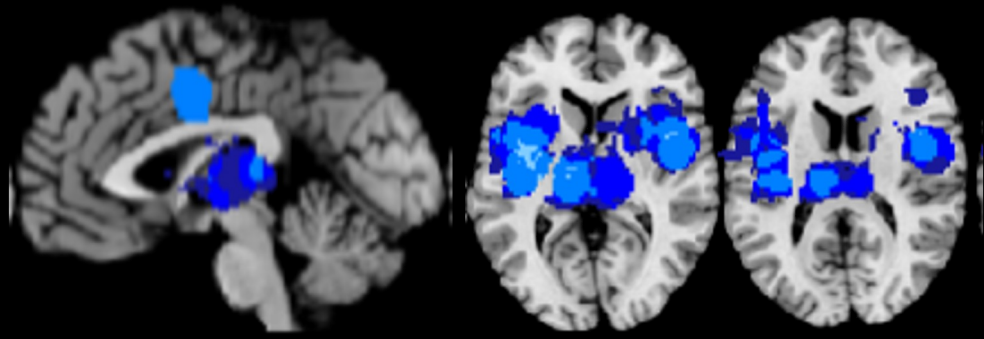


Placebo/ Treatment expectancy manipulation

Control vs Placebo

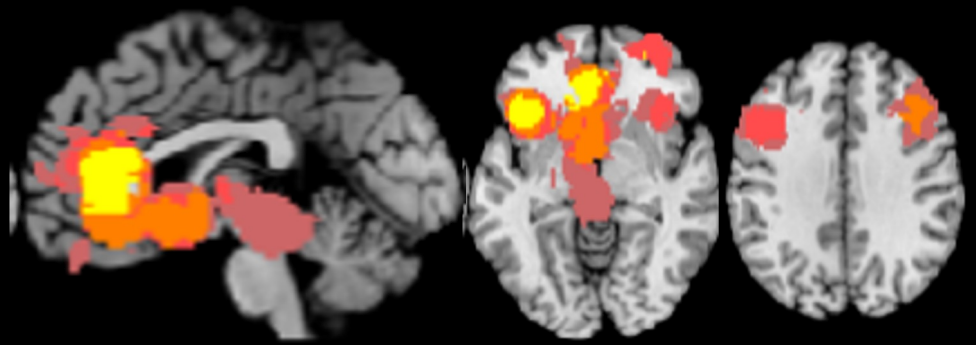


Decreases during pain:



Insula, thalamus, dACC

Modulatory increases



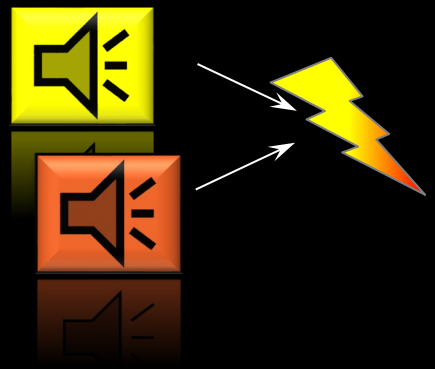
VMPFC, DLPFC, striatum

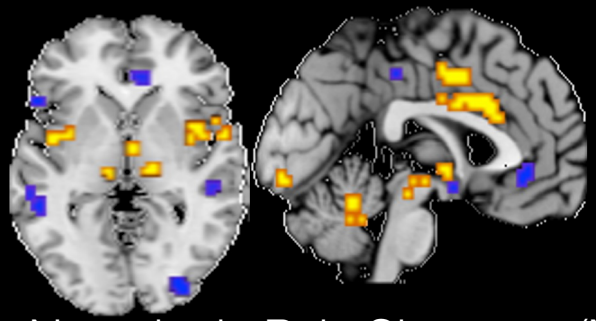
Atlas & Wager, 2014

Expectancies shape brain responses and subjective experience

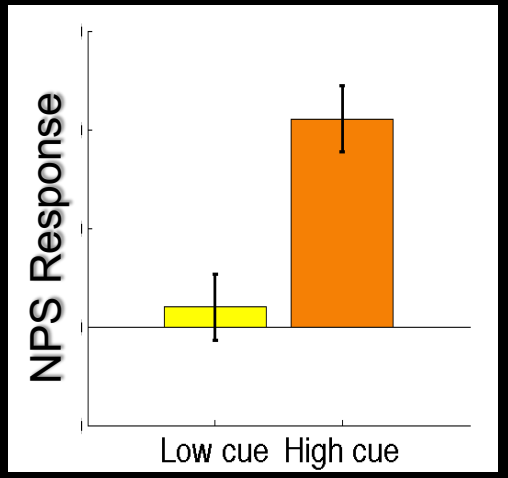
Stimulus expectancy manipulation

High vs Low expectancy





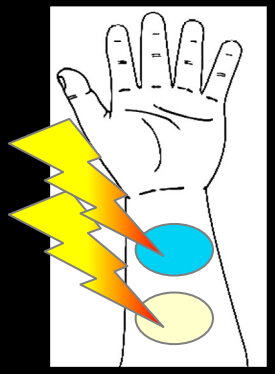
Neurologic Pain Signature (NPS)



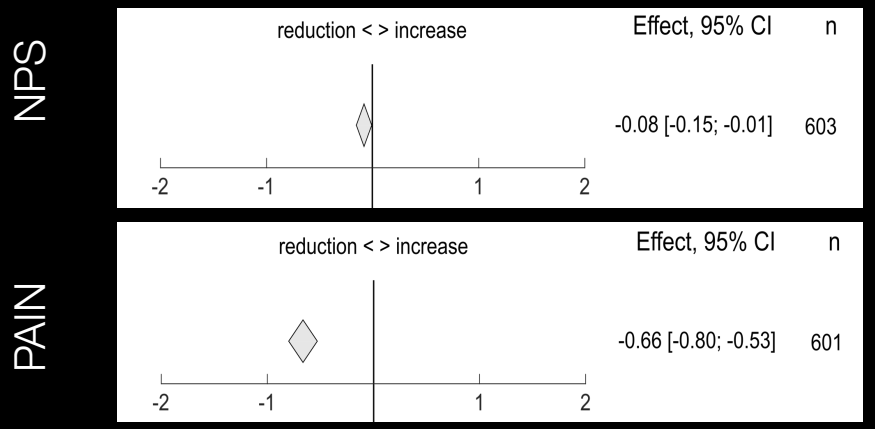
Wager, Atlas, et al., 2013, *NEJM*

Placebo/ Treatment expectancy manipulation

Control vs Placebo



No placebo effect on NPS!



Zunnheimer et al., *In press, JAMA Neurol*

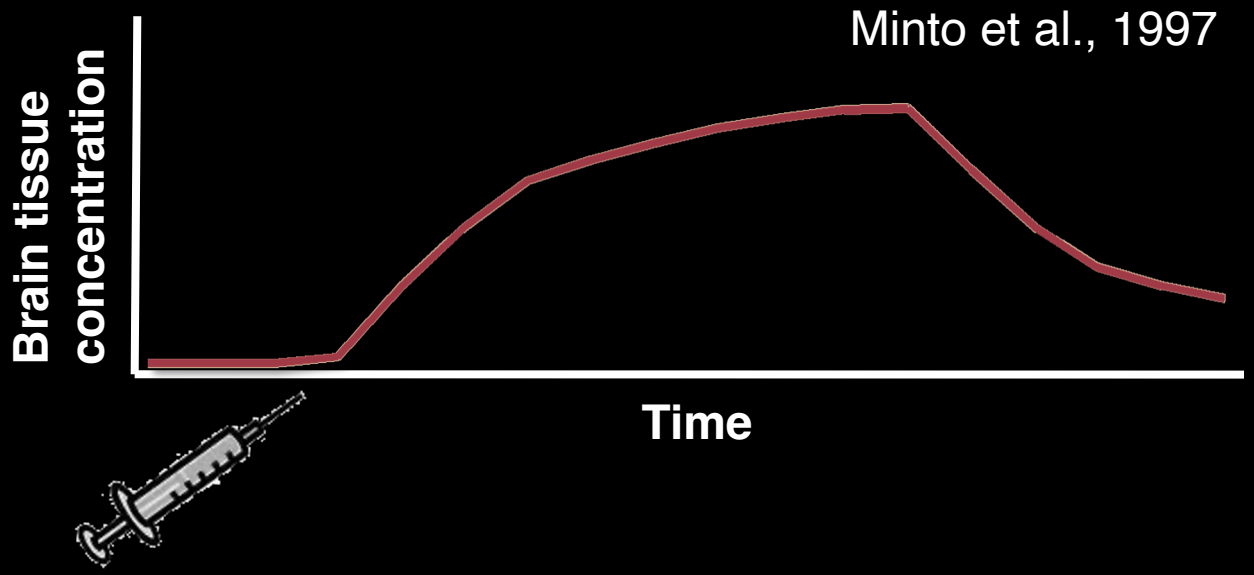
II. Expectancy effects during opioid analgesia

AIM: To isolate the role of expectancy during opioid analgesia

We fully crossed opioid analgesic treatment with expectancy and measured drug effects and expectancy effects on pain and brain responses.

Remifentanil

- μ opioid receptor agonist
- analgesic at low doses
- fast-acting, known pharmacodynamics

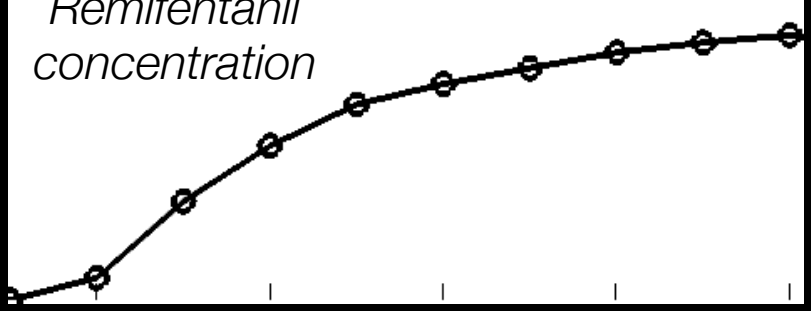
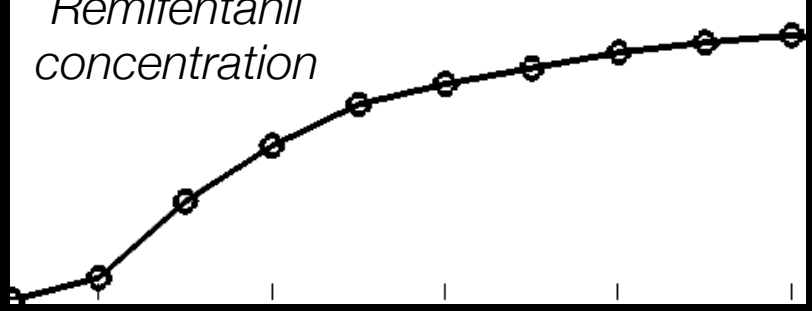
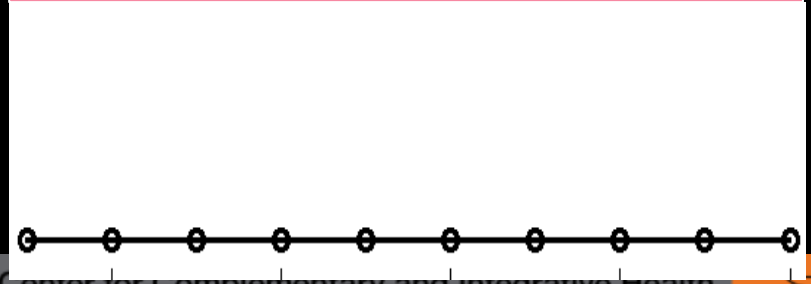
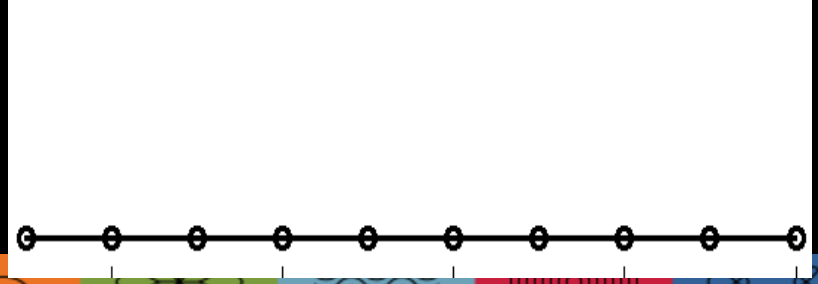


Balanced placebo design

Marlatt & Rohsenow, 1980

Behavioral study: N=14; Imaging study: N=20

Within-subjects design; Runs counterbalanced across subjects

	"On this run, you will receive remifentanil."	*"On this run, you will not receive any drug."*
DRUG	**OPEN** *Remifentanil concentration* 	**HIDDEN** *Remifentanil concentration* 
NO DRUG	**PLACEBO** 	**CONTROL** 

Drug effect

"On this run, you will receive remifentanil."

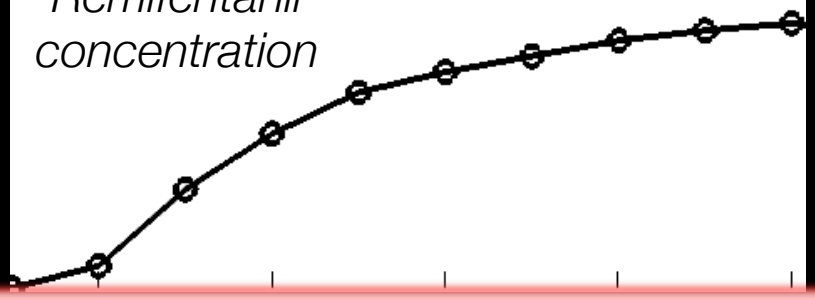
"On this run, you will not receive any drug."

DRUG

NO DRUG

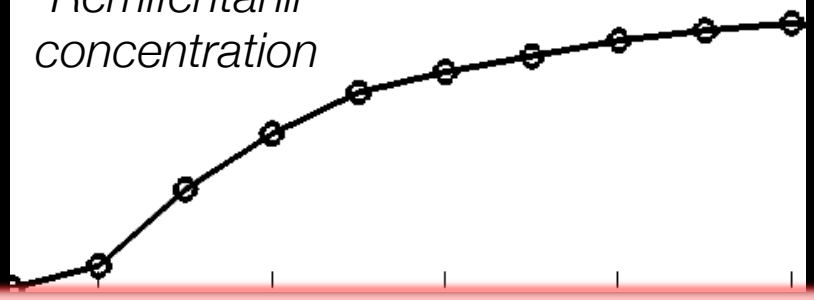
OPEN

Remifentanil concentration

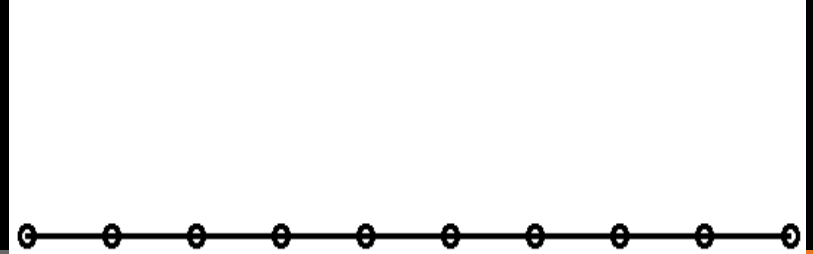


HIDDEN

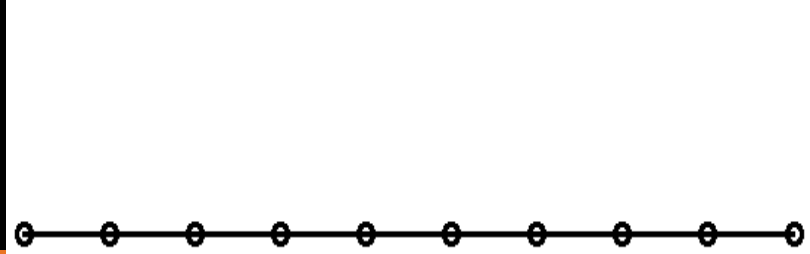
Remifentanil concentration



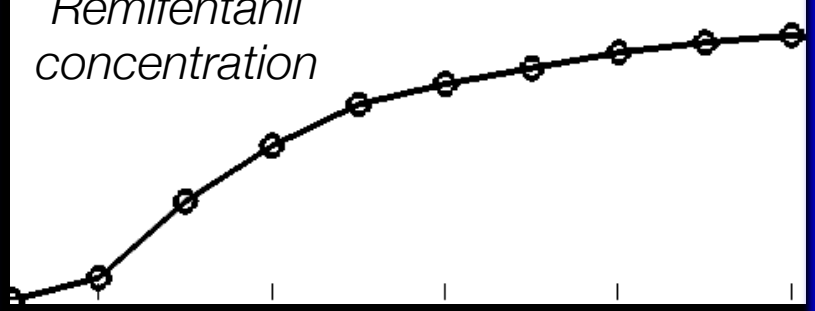
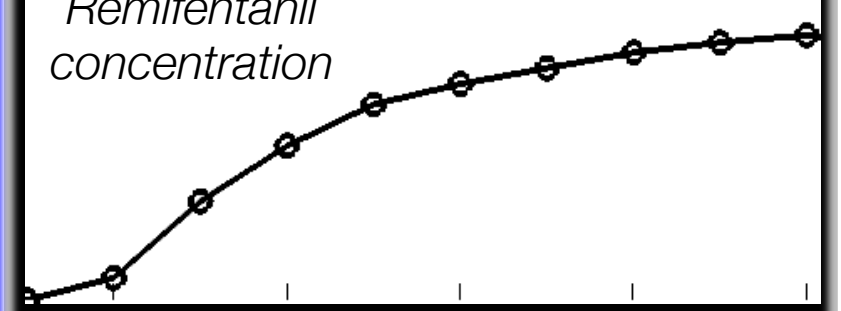
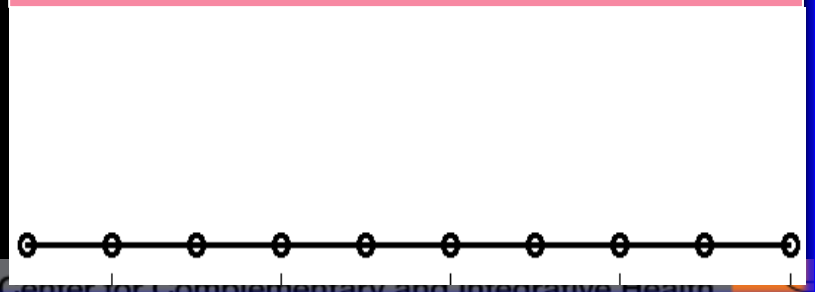
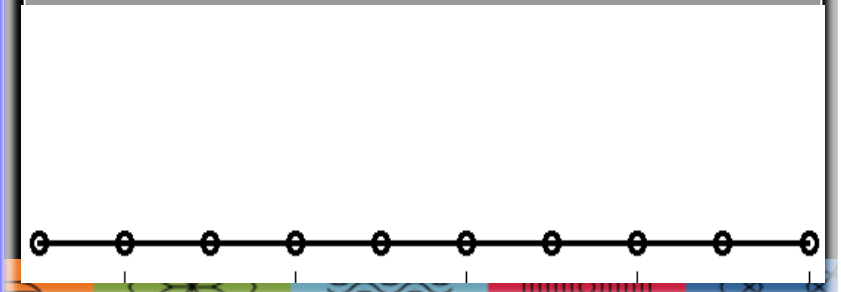
PLACEBO



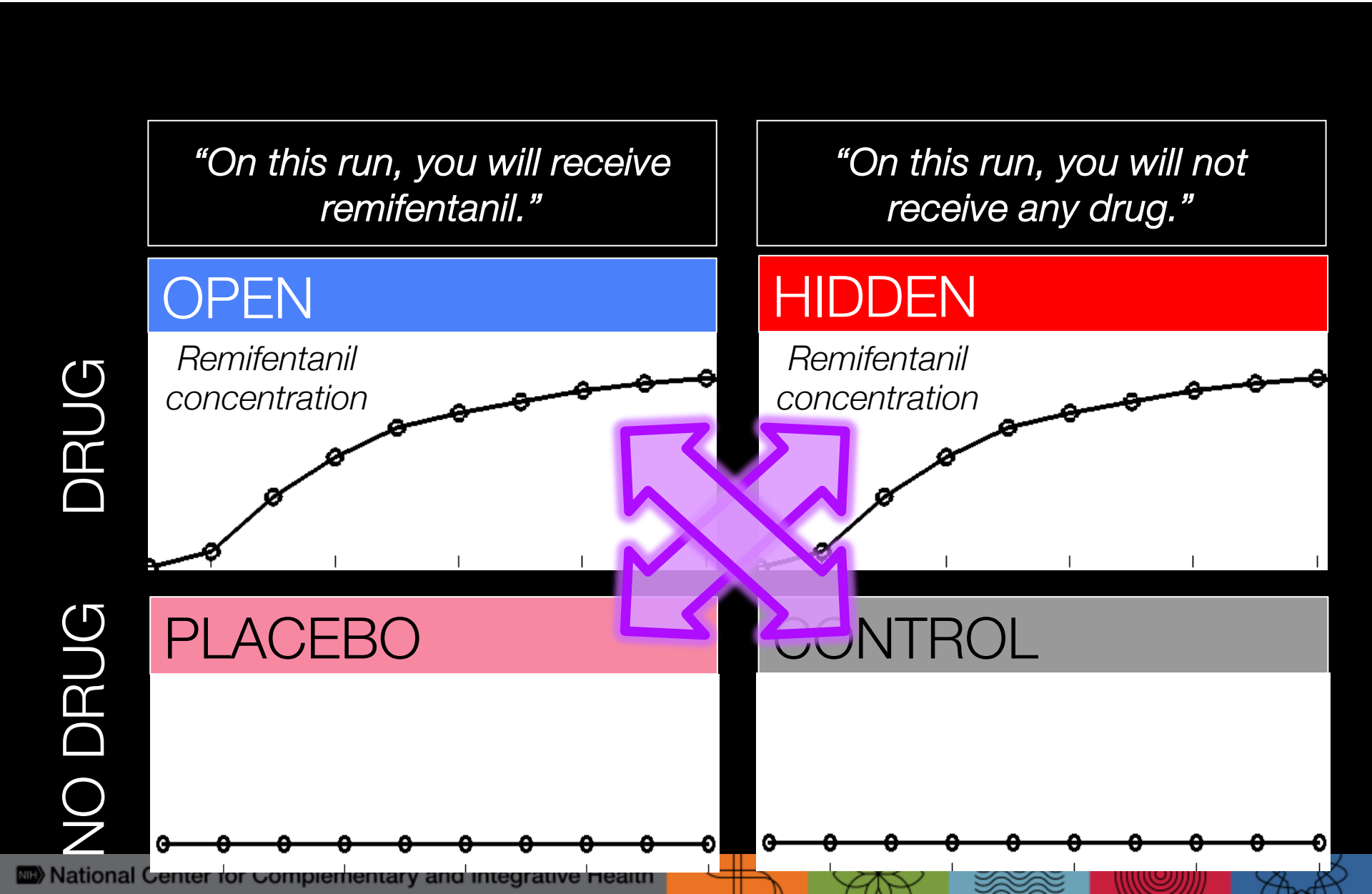
CONTROL



Expectancy effect

	EXPECT RELIEF	EXPECT NO RELIEF
	"On this run, you will receive remifentanil."	*"On this run, you will not receive any drug."*
DRUG	**OPEN** *Remifentanil concentration* 	**HIDDEN** *Remifentanil concentration* 
NO DRUG	**PLACEBO** 	**CONTROL** 

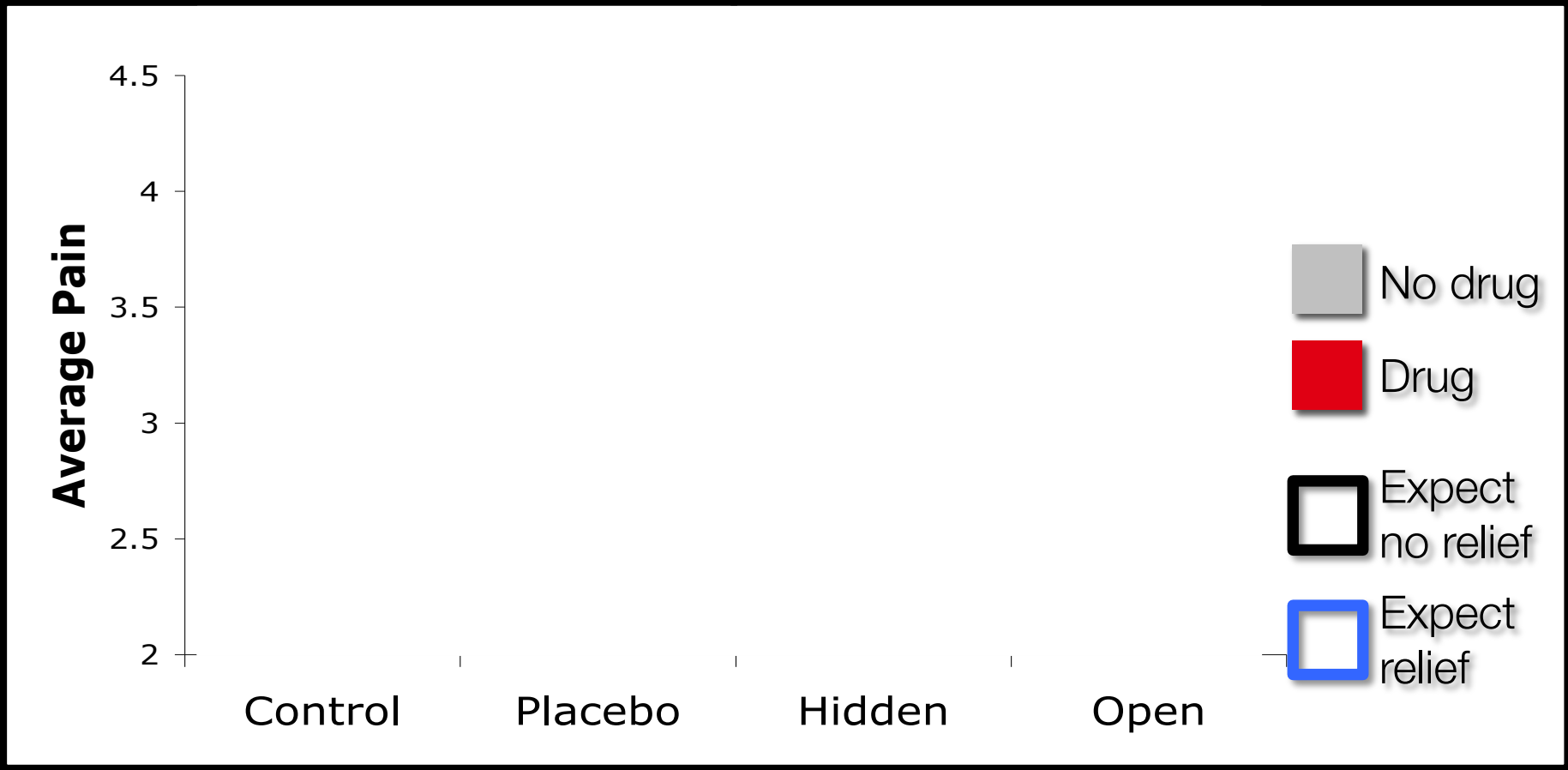
Expectancy x Drug interactions



Expectancy effects during opioid analgesia

Atlas et al., 2012, *JNeurosci*

Drug and treatment expectancy effects on pain are additive



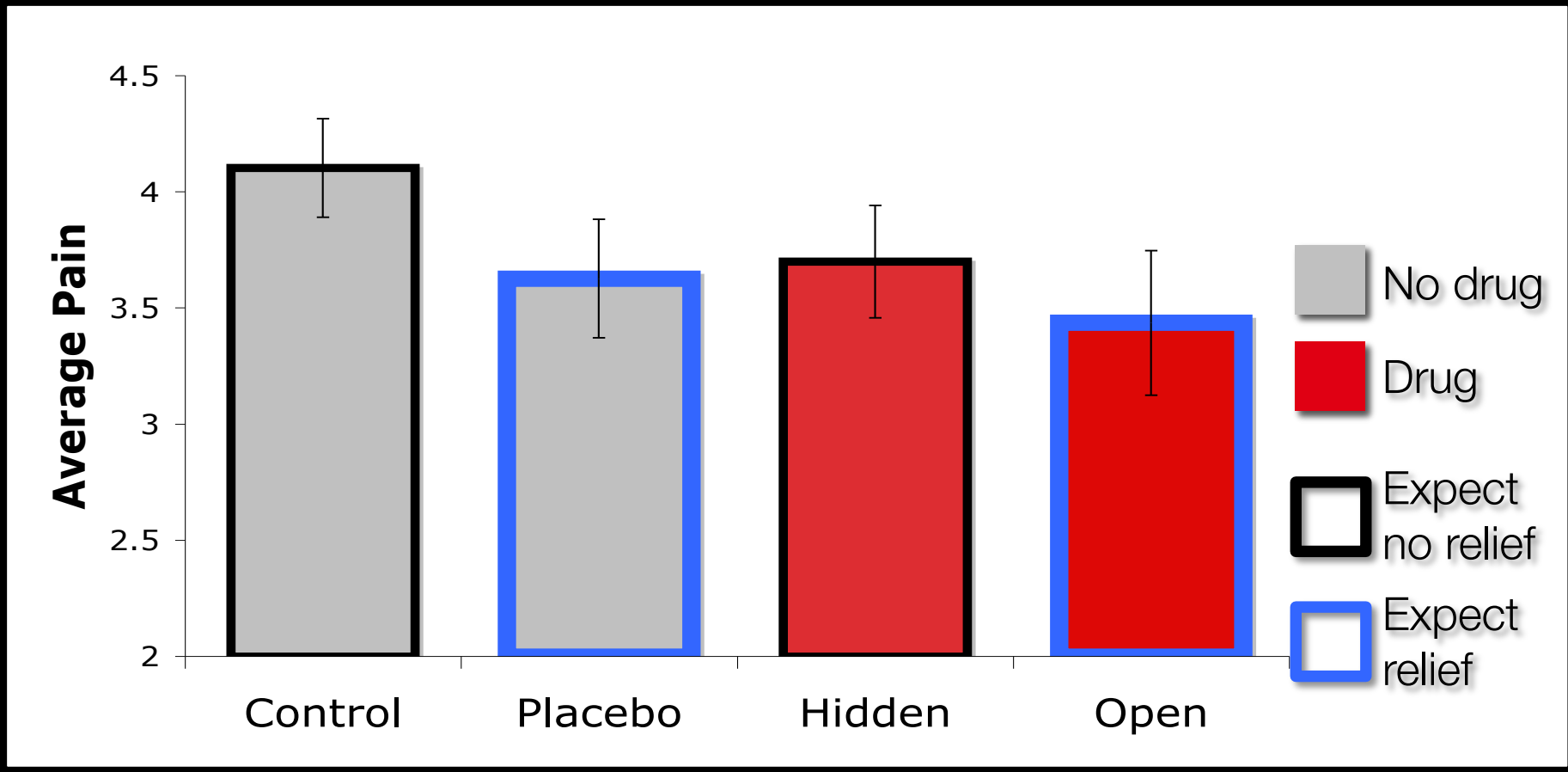
M.E. of Drug:
t(13) = -2.82, p<.05

M.E. of Treatment expectancy:
t(13) = -2.54, p<.05

N=14

Atlas et al., 2012, *JNeurosci*

Drug and treatment expectancy effects on pain are additive



No evidence for placebo-drug interactions

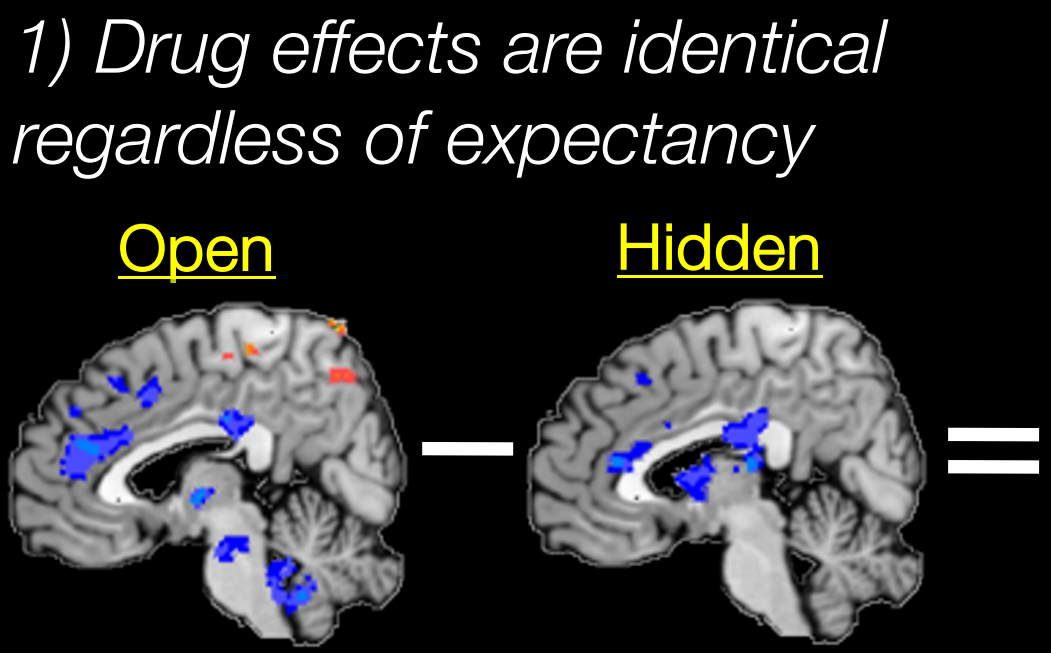
t(13) = -.47, p>.7

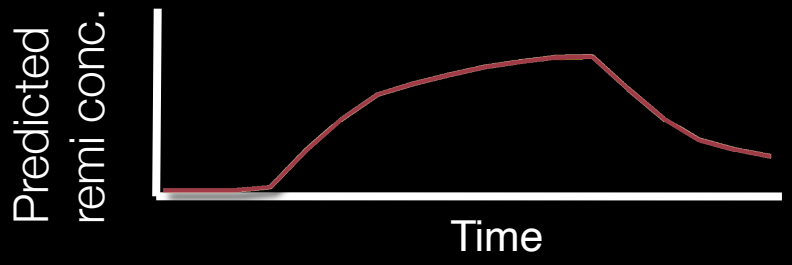
N=14

Atlas et al., 2012, *JNeurosci*

Pharmacological fMRI

1) Drug effects are identical regardless of expectancy



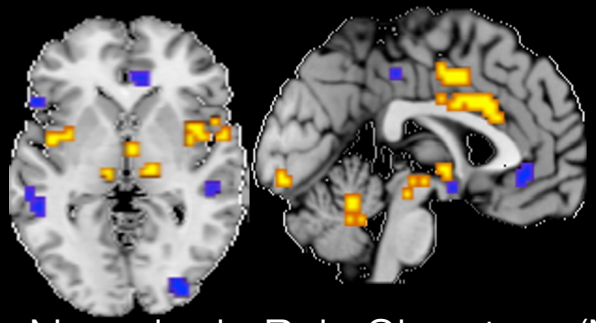


Test for interactions

No differences in drug effects on nociceptive network

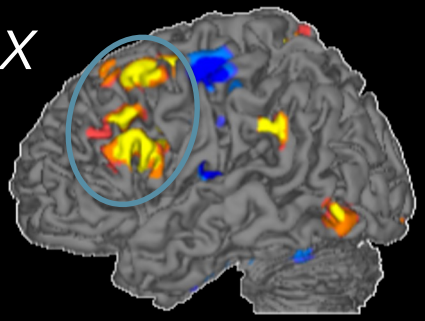
Drug and treatment expectancy effects on brain are additive

1) Drug effects are identical regardless of expectancy



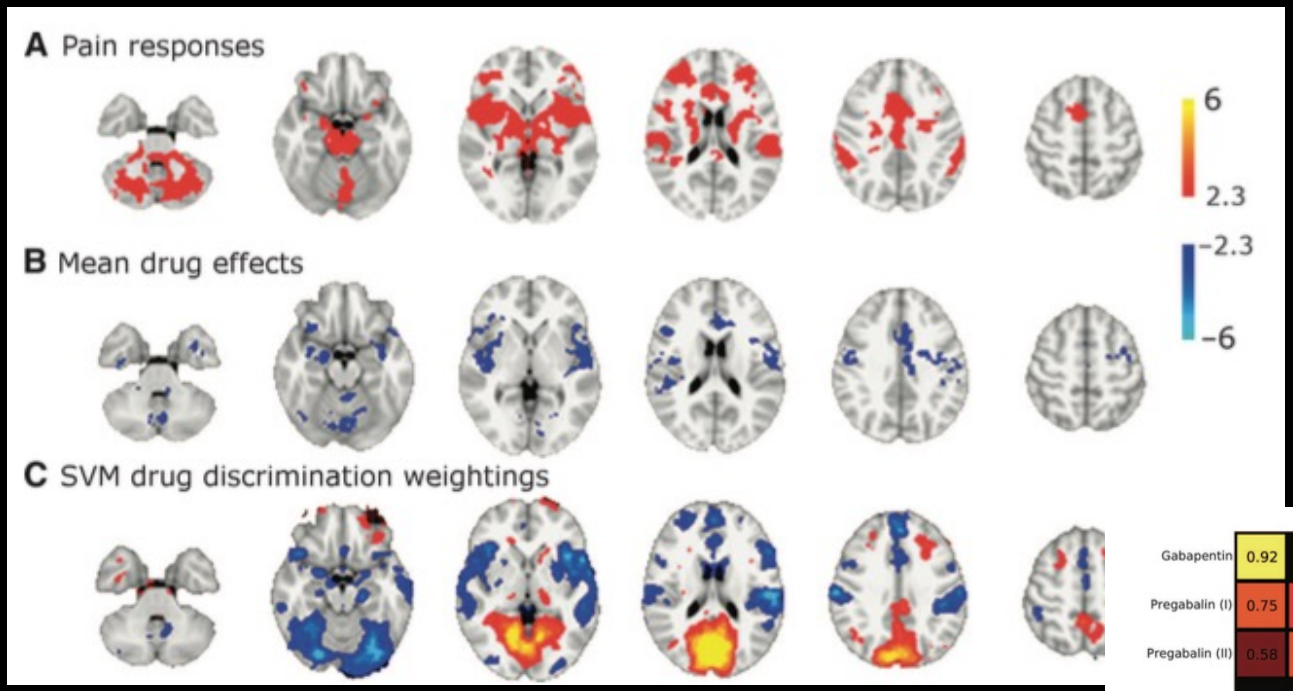
Neurologic Pain Signature (NPS)
Wager, Atlas, et al., 2013, *NEJM*

2) Instructions cause increases in dorsolateral prefrontal cortex



3) Additive expectancy effect on pain correlated with nociceptive network responses: Both earlier than drug effects

Brain classifiers for analgesic efficacy?



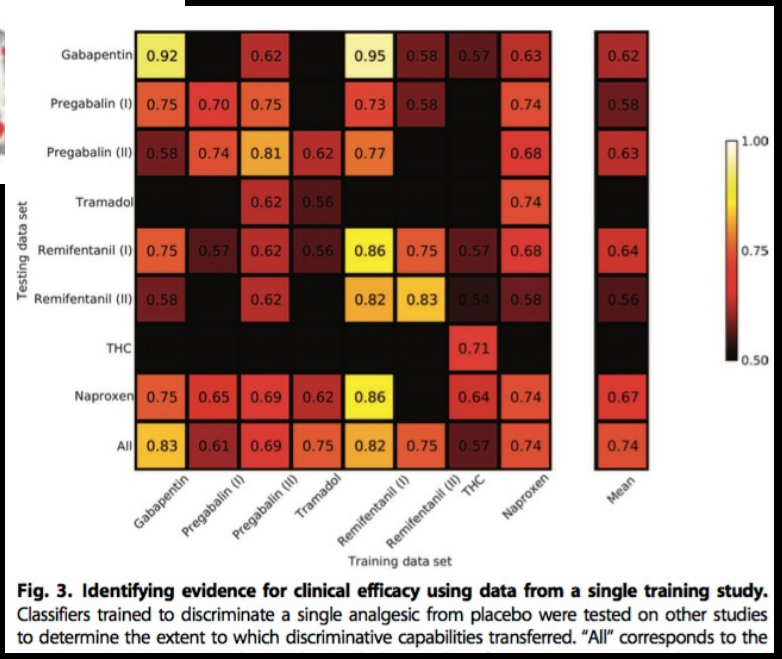


Fig. 3. Identifying evidence for clinical efficacy using data from a single training study. Classifiers trained to discriminate a single analgesic from placebo were tested on other studies to determine the extent to which discriminative capabilities transferred. "All" corresponds to the

Duff et al., 2015, *Sci Trans Med*

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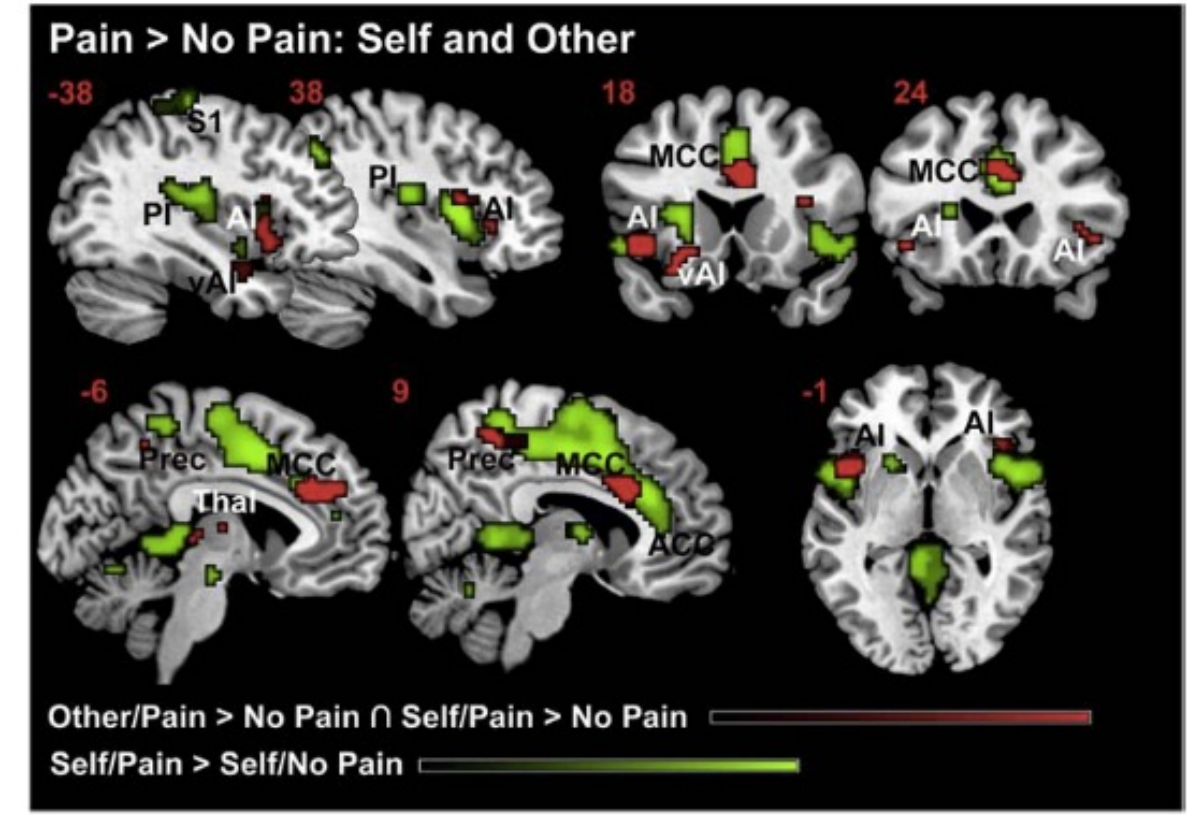
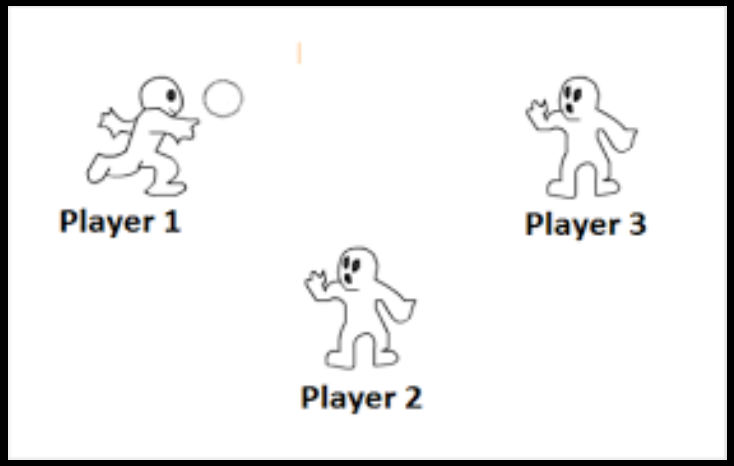
“Social pain”

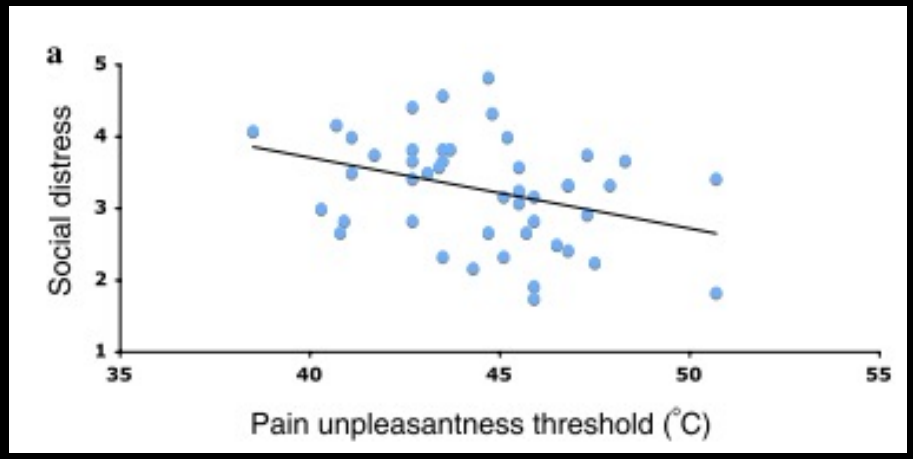


Lamm et al., Neuroimage, 2011

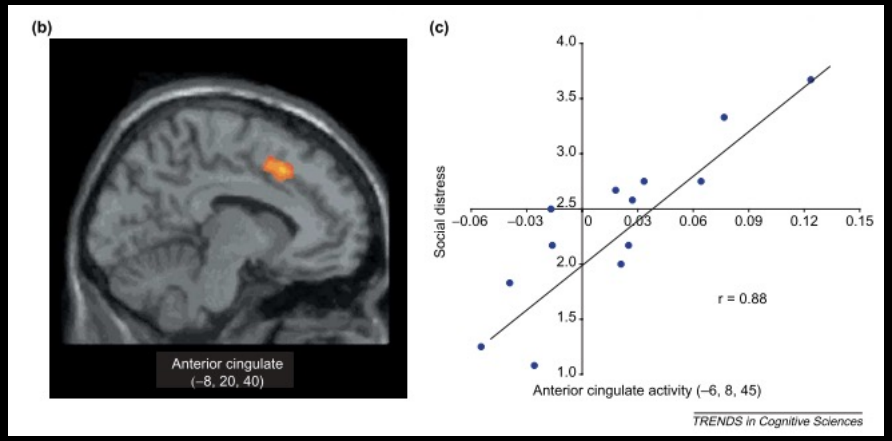
Is rejection painful?



Eisenberger, Science, 2003



Eisenberger, Pain, 2006



Social pain: The reaction

Nature Neuroscience **9**, 1007 - 1008 (2006)
Published online: 2 July 2006 | doi:10.1038/nn1728

Anterior cingulate cortex responds differentially to expectancy violation and social rejection

Leah H Somerville[1], Todd F Heatherton[1] & William M Kelley[1]

This study investigated human anterior cingulate cortex (ACC) involvement during from social rejectio functional magneti and receiving fictiti and consistent or i demonstrate that t whereas the ventra

Conflict monitoring and decision making: Reconciling two perspectives on anterior cingulate function

ARTICLE

Received 8 May 2014 | Accepted 25 Sep 2014 | Published 17 Nov 2014

DOI: 10.1038/ncomms6380

Separate neural representations for physical pain and social rejection

Choong-Wan Woo[1,2], Leonie Koban[1,2], Ethan Kross[3], Martin A. Lindquist[4], Marie T. Banich[1,2], Luka Ruzic[1,2], Jessica R. Andrews-Hanna[2] & Tor D. Wager[1,2]

#Cingulategate

The dorsal anterior cingulate cortex is selective for pain: Results from large-scale reverse inference

Ma

Yarkoni/Neurosynth, 12/05/15:

"No, the dorsal anterior cingulate is not selective for pain: comment on Lieberman and

Lieberman Psychology Today blog, 12/10/2015

Yarkoni/Neurosynth, 12/14/15:

"Still not selective: comment on comment on comment on Lieberman & Eisenberger (2015)"

Pain in the ACC?

Tor D. Wager,
Karen Deboral
Tal Yarkoni

PNAS April 19, 20

Reply to Wager et al.: Pain and the dACC: The importance of hit rate-adjusted effects and posterior probabilities with fair priors

Matthew D. Lieberman, Shannon M. Burns, Jared B. Torre, and Naomi I. Eisenberger

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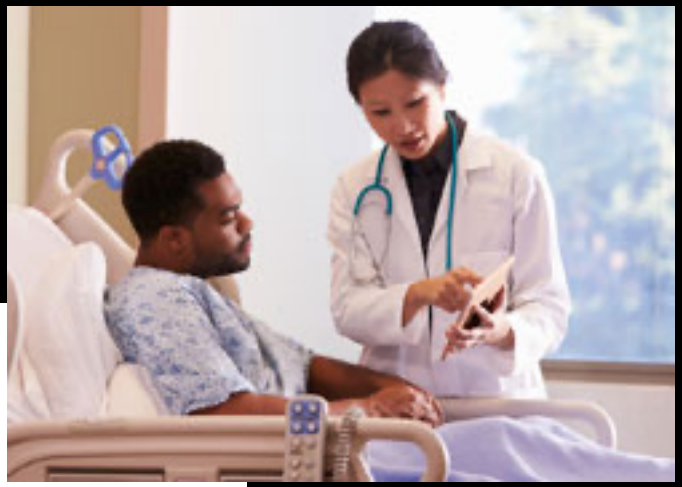
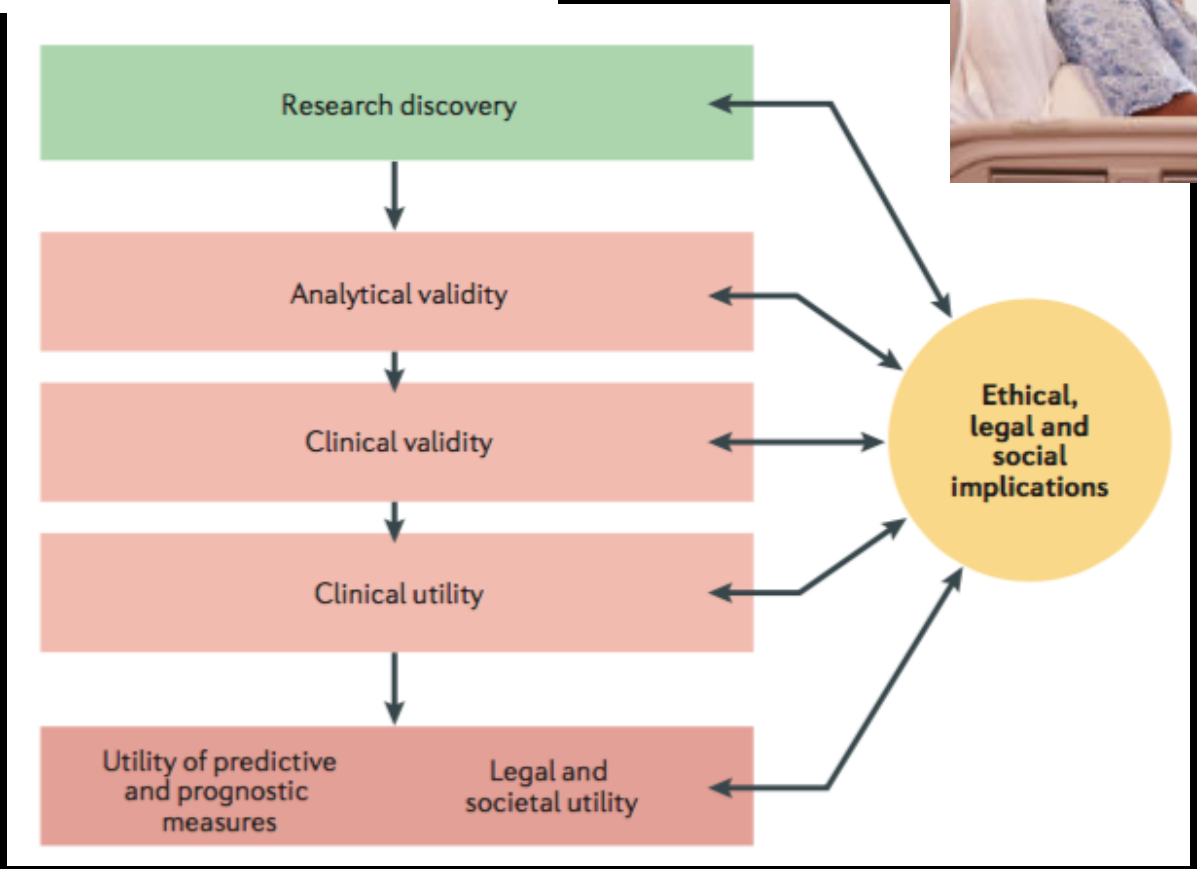
Reading pain from the brain?

Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations

Karen D. Davis, Herta Flor, Henry T. Greely, Gian Domenico Iannetti, Sean Mackey, Markus Ploner, Amanda Pustilnik, Irene Tracey, Rolf-Detlef Treede & Tor D. Wager

Nature Reviews Neurology **13**, 624–638 (2017) | Download Citation





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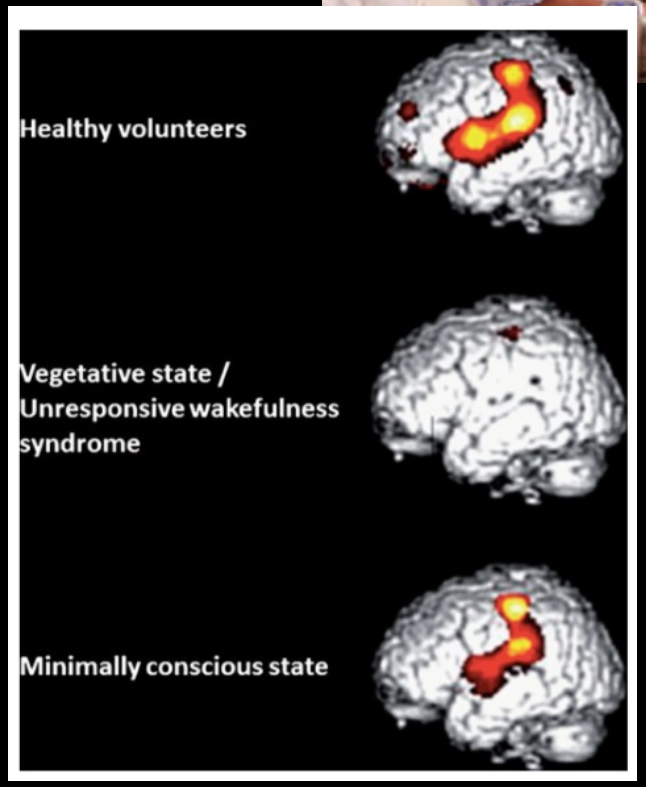
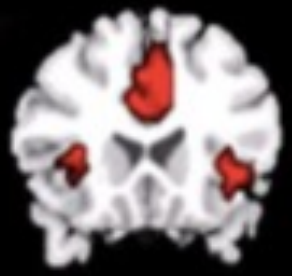
Nature Reviews Neurology **13**, 624–638 (2017) | Download Citation ⭳

What about Pain in Disorders of Consciousness?

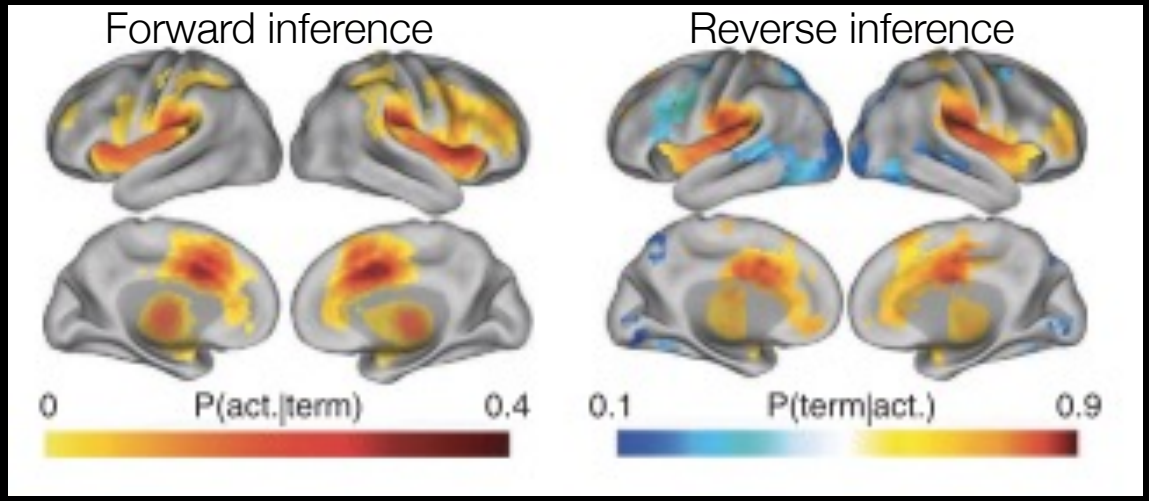
C. Schnakers,[1,2,3,4,5] C. Chatelle,[1,3] A. Demertzi,[1,3] S. Majerus,[2,4] and S. Laureys[1,3,4]



Pain vs salience



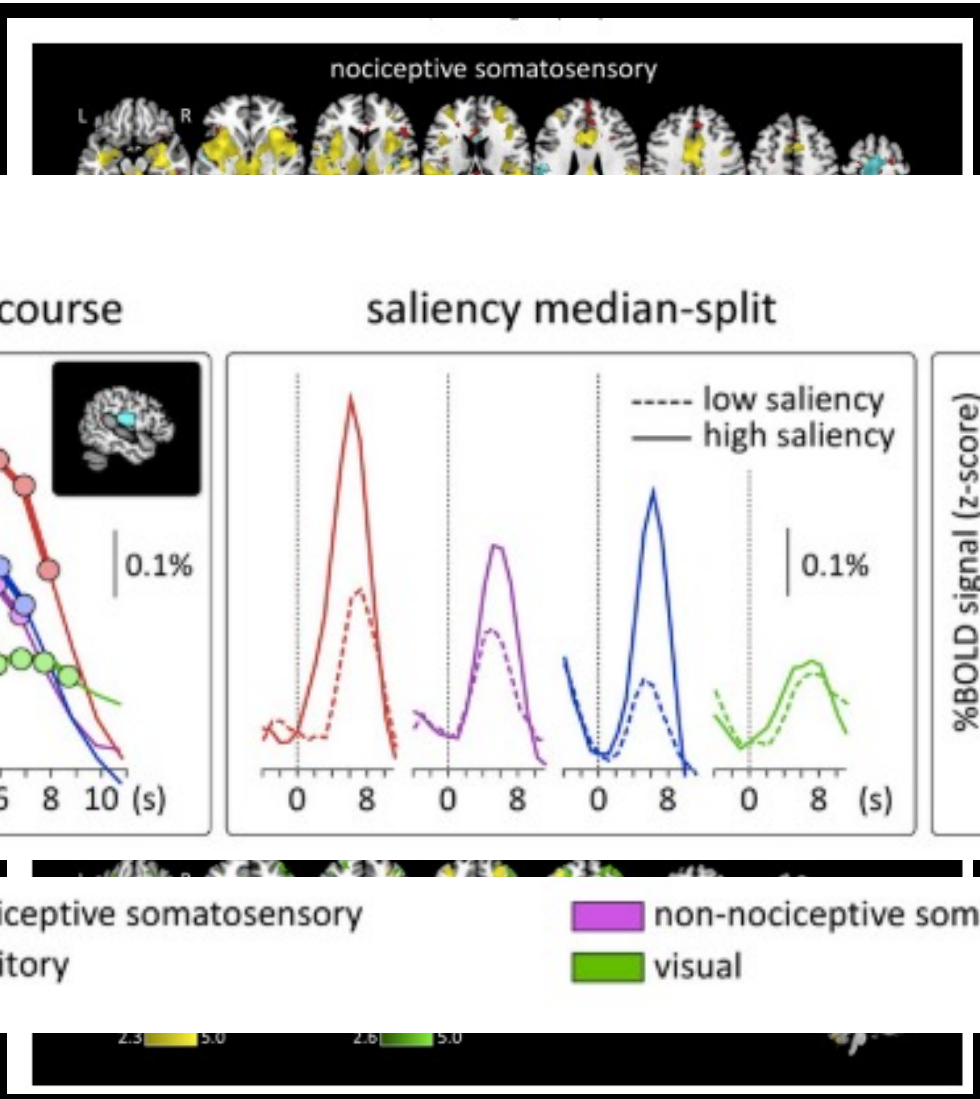
Menon & Uddin, 2010



Yarkoni et al., 2011

Can we even measure pain without varying salience??

Pain vs salience



Mouraux et al., 2011

Summary

- Transient / Acute pain
  - In the brain
  - Dynamically modulated by psychological factors
- Pain neuromatrix
  - Network and pattern analyses are getting us closer
- Lots left to understand!
  - CHRONIC PAIN
  - Leveraging animal models
  - Specificity
  - Multimodal integration (timescale, phfMRI, moderating factors)

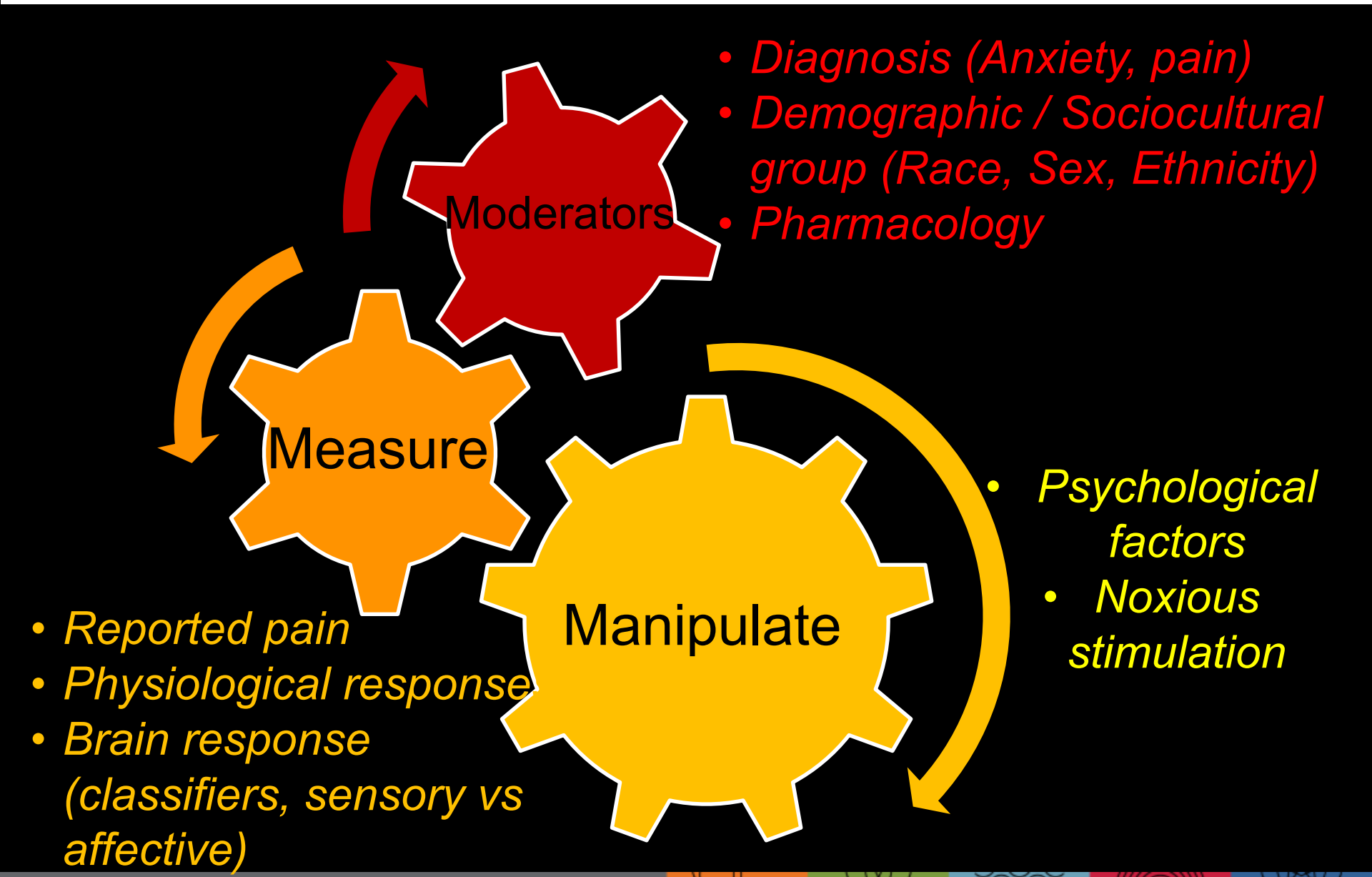
Thank you! Questions?

National Center for Complementary and Integrative Health

National Institute on Drug Abuse

Additional slides

Approach


Moderators
Measure
Manipulate
• Diagnosis (Anxiety, pain)
• Demographic / Sociocultural group (Race, Sex, Ethnicity)
• Pharmacology
• Psychological factors
• Noxious stimulation
• Reported pain
• Physiological response
• Brain response (classifiers, sensory vs affective)

Pain neuromatrix

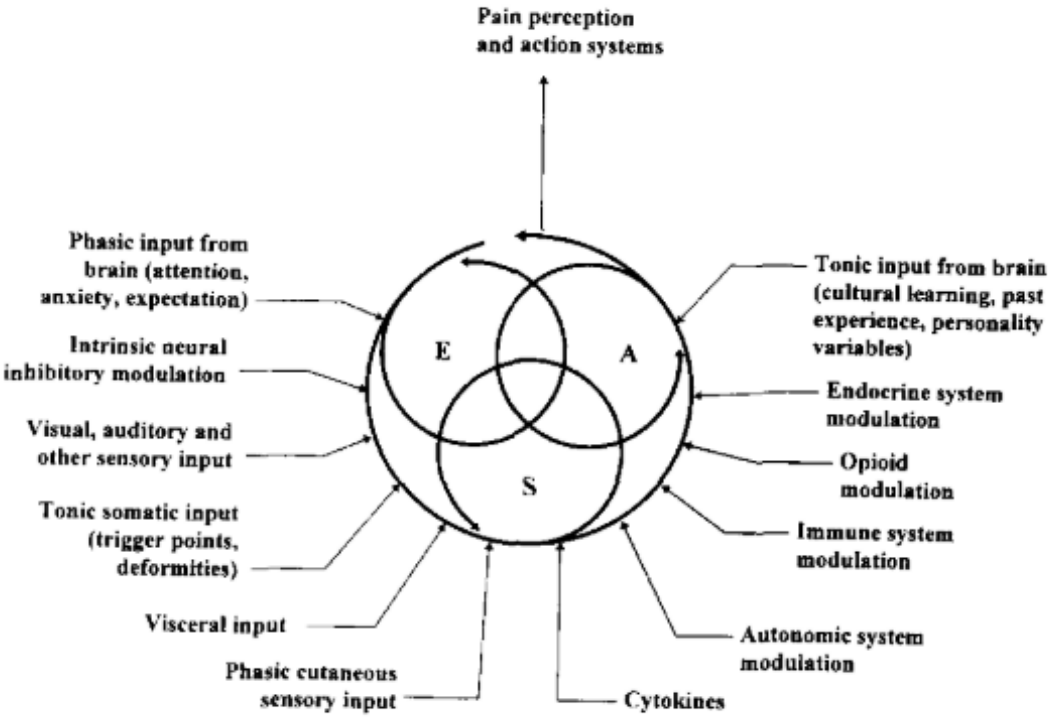


Fig. 2. The body-self neuromatrix. The body-self neuromatrix, which comprises a widely distributed neural network that includes somatosensory, limbic, and thalamocortical components, is schematically depicted as a circle containing smaller parallel networks that contribute to the sensory-discriminative (S), affective-motivational (A), and evaluative-cognitive (E) dimensions of pain experience. The synaptic architecture of the neuroma-

Melzack, 1999

Physiological measurements

Eye tracking / Pupil dilation

Skin conductance

Also HR, Resp, Pulse, BP
NEW: Facial responses (EMG, video)

Cognitive factors shape pain

Pain Affect Encoded in Human Anterior Cingulate But Not Somatosensory Cortex
Rainville et al., Science, 1997

Hypnotic suggestion to increase or decrease pain unpleasantness

Path a

Path b

Temp

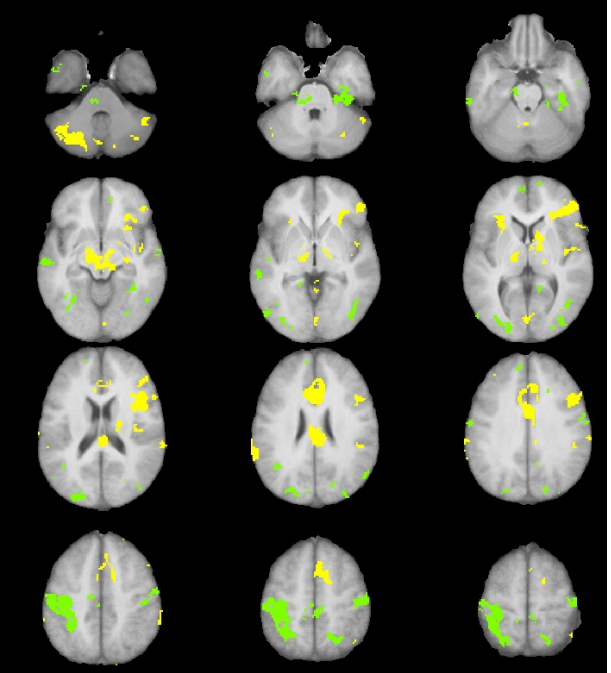
Brain

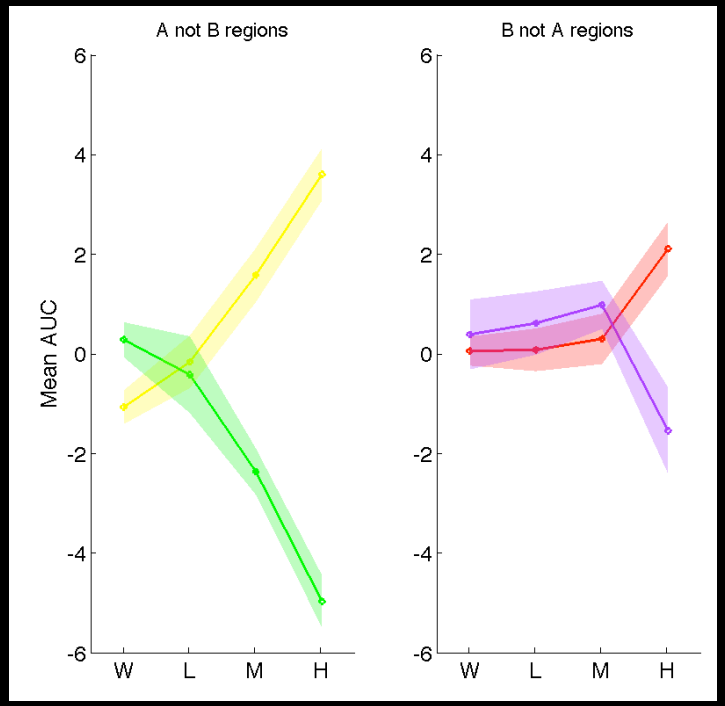
Path *a* (temperature), not *b*

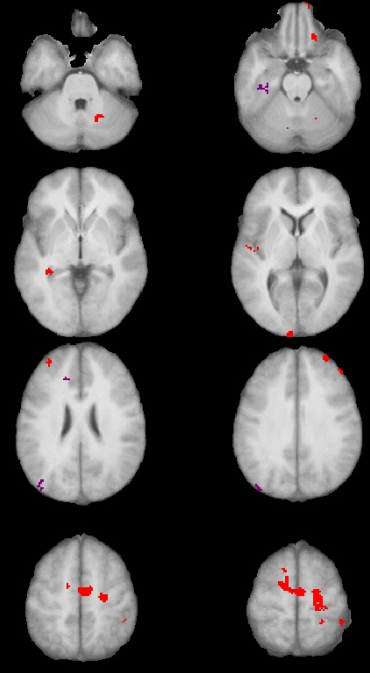
Path *b* (pain report), not *a*

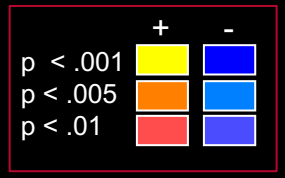
Brain

Pain









Ascending nociceptive pathways