Neuroimaging of pain and distress: From blobs to biomarkers to translation

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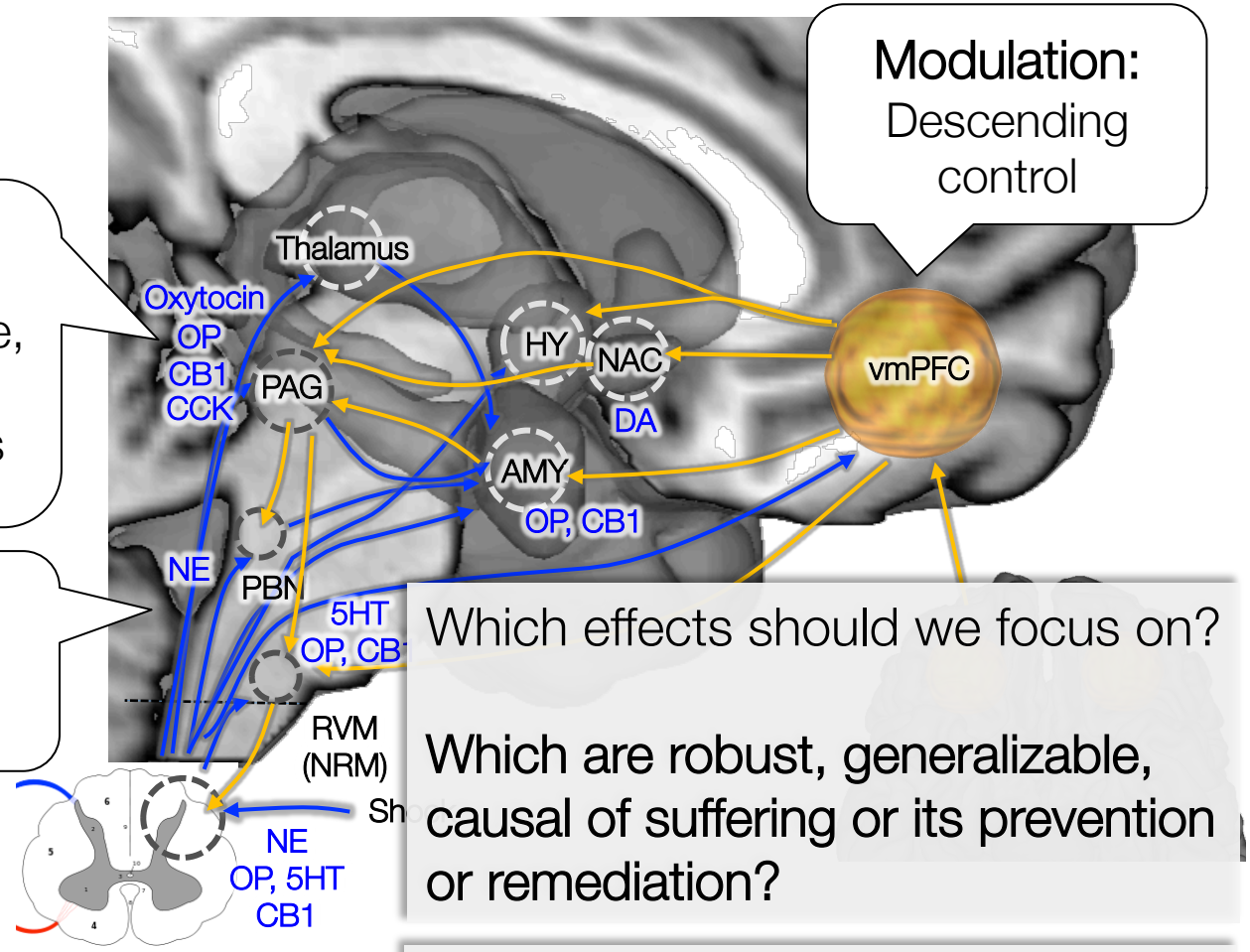
What we know about pain

Pharmacology:
Opioids, dopamine, serotonin, hormones, others

Nociception:
Ascending pathways

Modulation:
Descending control



Which effects should we focus on?

Which are robust, generalizable, causal of suffering or its prevention or remediation?

Where is the *pain*?

Wager & Atlas, submitted; Fields 2004; Heinricher & Fields 2013; Altier & Stewart 1999; Willis & Westlund 1997

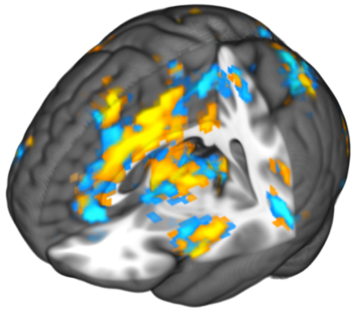
What we'd like to know: Representations and biomarkers

Representation: Causal, obligatory physical basis for a mental experience or information structure

Biomarker: physiological, objectively measured process that indicates a mental experience or process

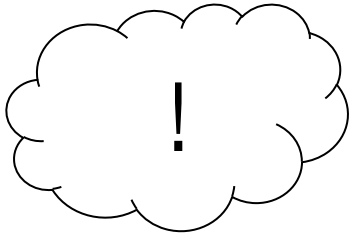
(Biomarker Definitions Working Group, 2001; Borsook et al., 2011)

Noxious event



Global pattern

Biomarker:
Measured pattern



Mental experience

Sensitive
Specific

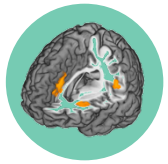
Brain biomarkers are *gateways* to measures of representations

How are pain and emotion represented in the brain?

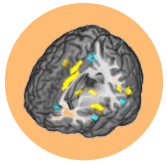
Roadmap

Representations & Biomarkers

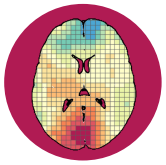
Act I: **Blobs**



Act II: **Biomarkers**



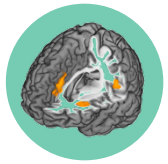
Act III: **Translation**



Roadmap

Representations
& Biomarkers

Act I:
Blobs

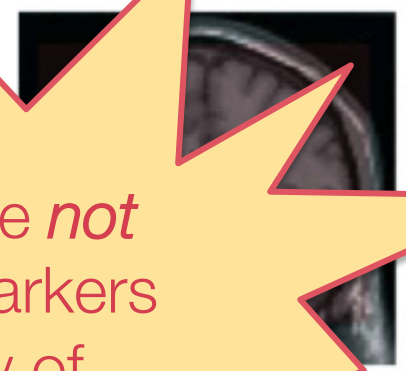


Don't we already have biomarkers for many kinds of mental events?

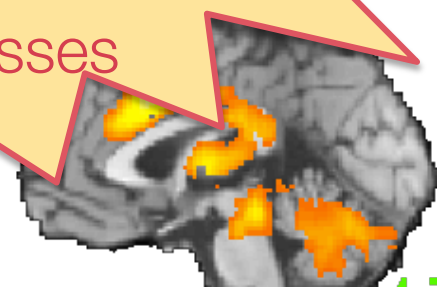
fMRI activity is implicitly used as a biomarker in nearly all studies of psychological phenomena

- Reward
- Value
- Memory
- Pain
- Visual pr
- Social co
- Specific e
- Etc.

There are *not yet* biomarkers for any of these processes



Amygdala response to aversive images



"Pain processing" responses to noxious heat

Anterior cingulate and insula: 'pain affect'

The problem with current approaches

These brain results are not biomarkers.

1. Definition and replication

   We do not agree on precisely what these patterns are (which voxels?)

   Lack of exact replication

2. Application to individual cases

   Neuroimaging results are typically group results, and do not apply to individuals

3. Diagnostic value. P(psych | brain)?

   - Sensitivity

   We do not know how big the effects of our manipulations are.

   P(brain | psychological event)?

   - Specificity

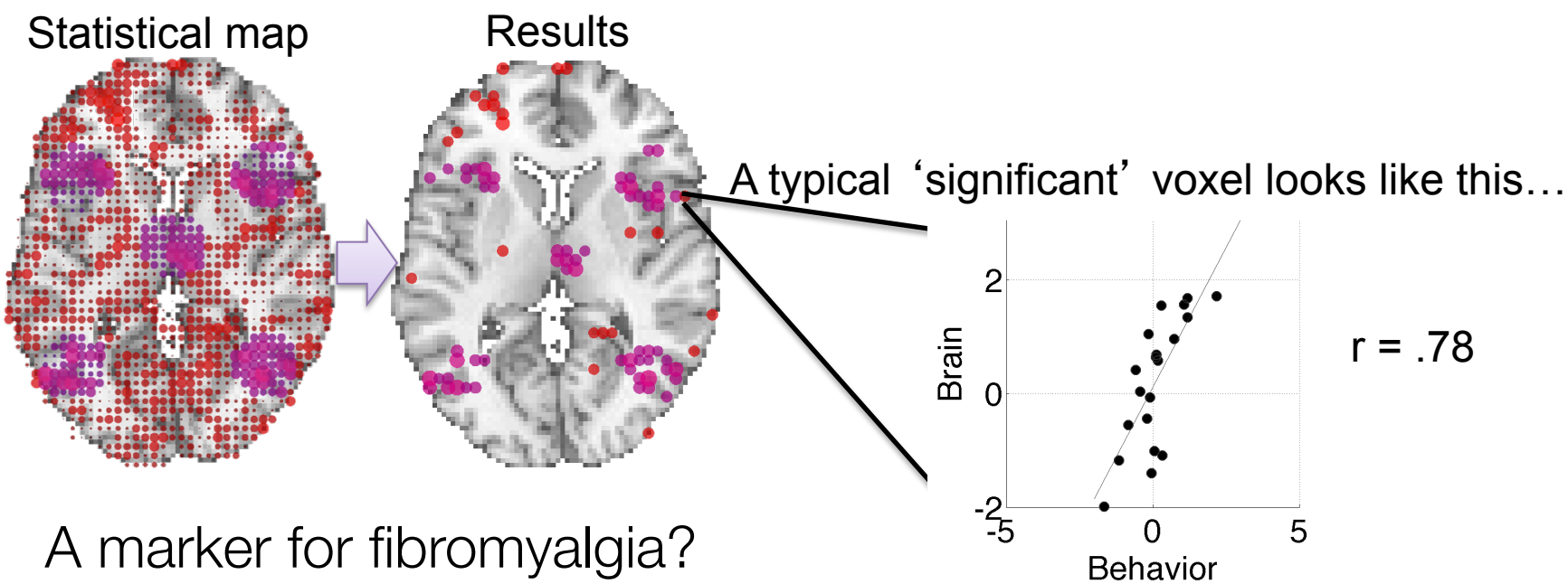
   We do not know if observed patterns are specific enough to be useful as biomarkers

   P(brain | absence of psych)?

e.g., Button et al. 2013 Nat Neurosci; Ioannidis 2005

The problem of replication

Hypothetical correlation
with fibromyalgia



A marker for fibromyalgia?

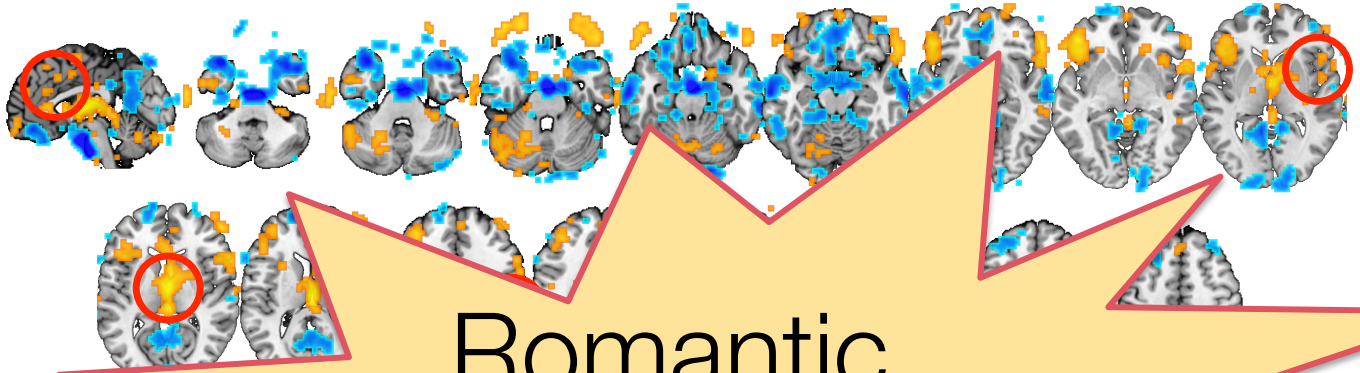
Unfortunately, no: There is no true signal, and this is all noise.

Why? 'File drawer' problem. We have picked the winners.

Vul et al. 2009, Kriegeskorte 2009, Yarkoni 2009

The problem of specificity

What does this map *mean*?



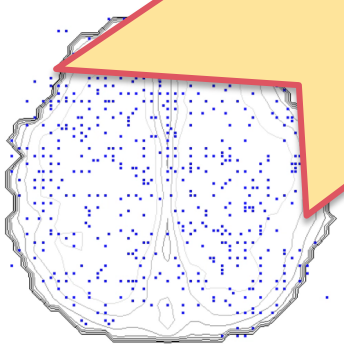
Romantic rejection

Kross et al. 2011, PNAS

Neurosy

Acti

from

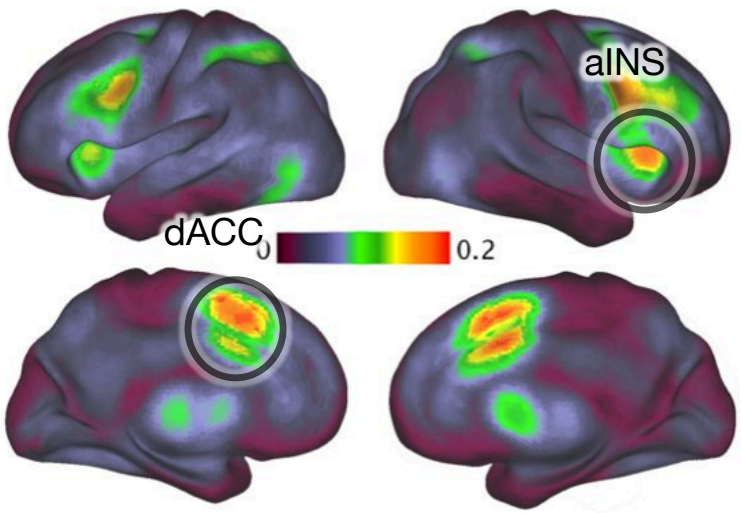


this pattern:

ious, heat, somatosensory, painful, sensation, stimulation, muscle, temperature

The problem of specificity

Base rate of activation across 3489 studies



Anterior cingulate and insula activity are not specific for pain or any type of affect.

Yarkoni, Poldrack, Van Essen, & Wager, 2011, Nature Methods; See Poldrack 2006; Sarter et al. 1996

Roadmap

Representations & Biomarkers

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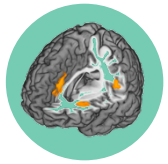

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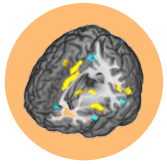
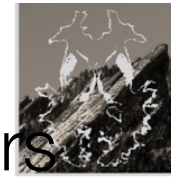


A new approach: Multi-study validation of brain markers



Development and validation

Optimize: Identify marker (brain pattern). Maximize sensitivity/ specificity, interpretability

Replicate: Assess generalizability across individuals, studies

Characterize: properties of marker across test conditions

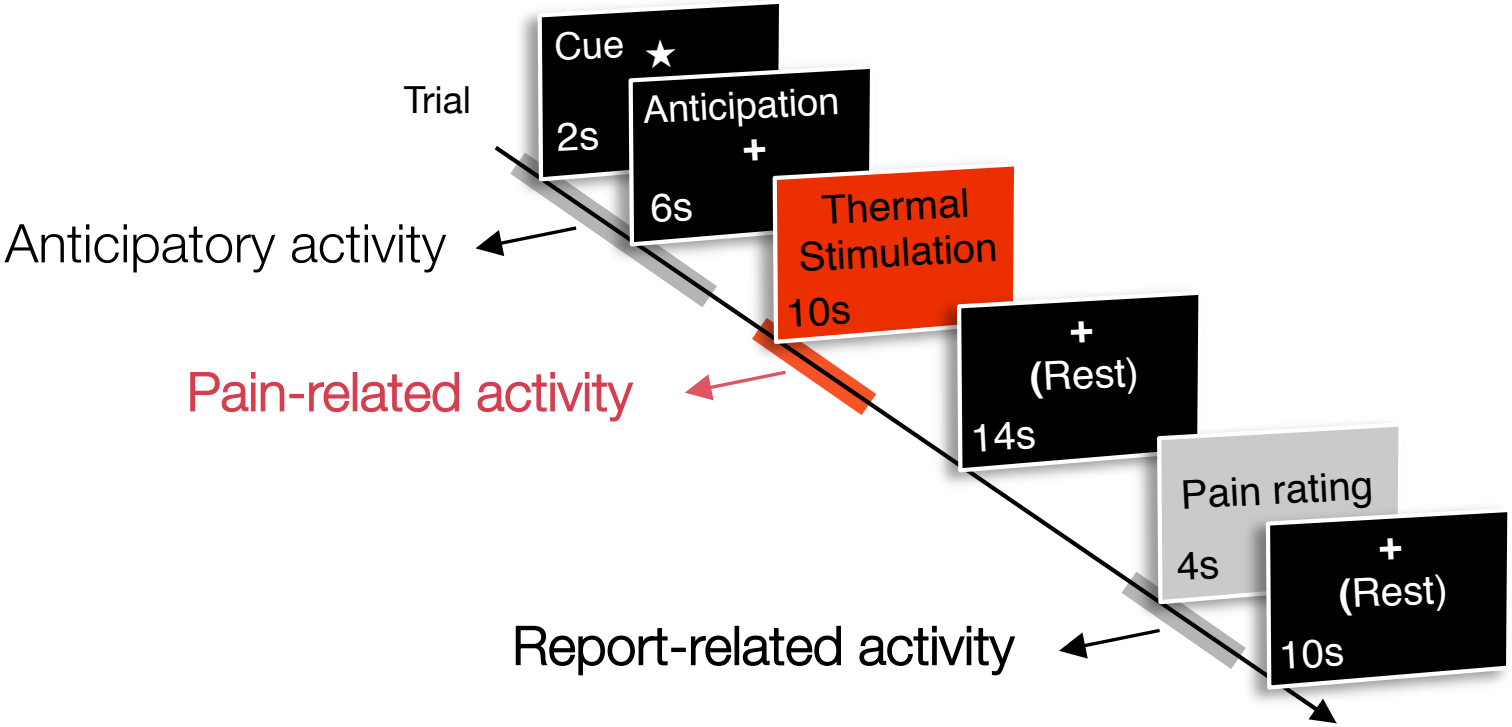
Application

- Test new treatments, uncertain cases
- Patient stratification: Identify subtypes
- Understand representation and mechanism

- *Develop* under conditions where pain ratings are very accurate and reliable
- *Test* in cases where pain reports are unreliable, unavailable

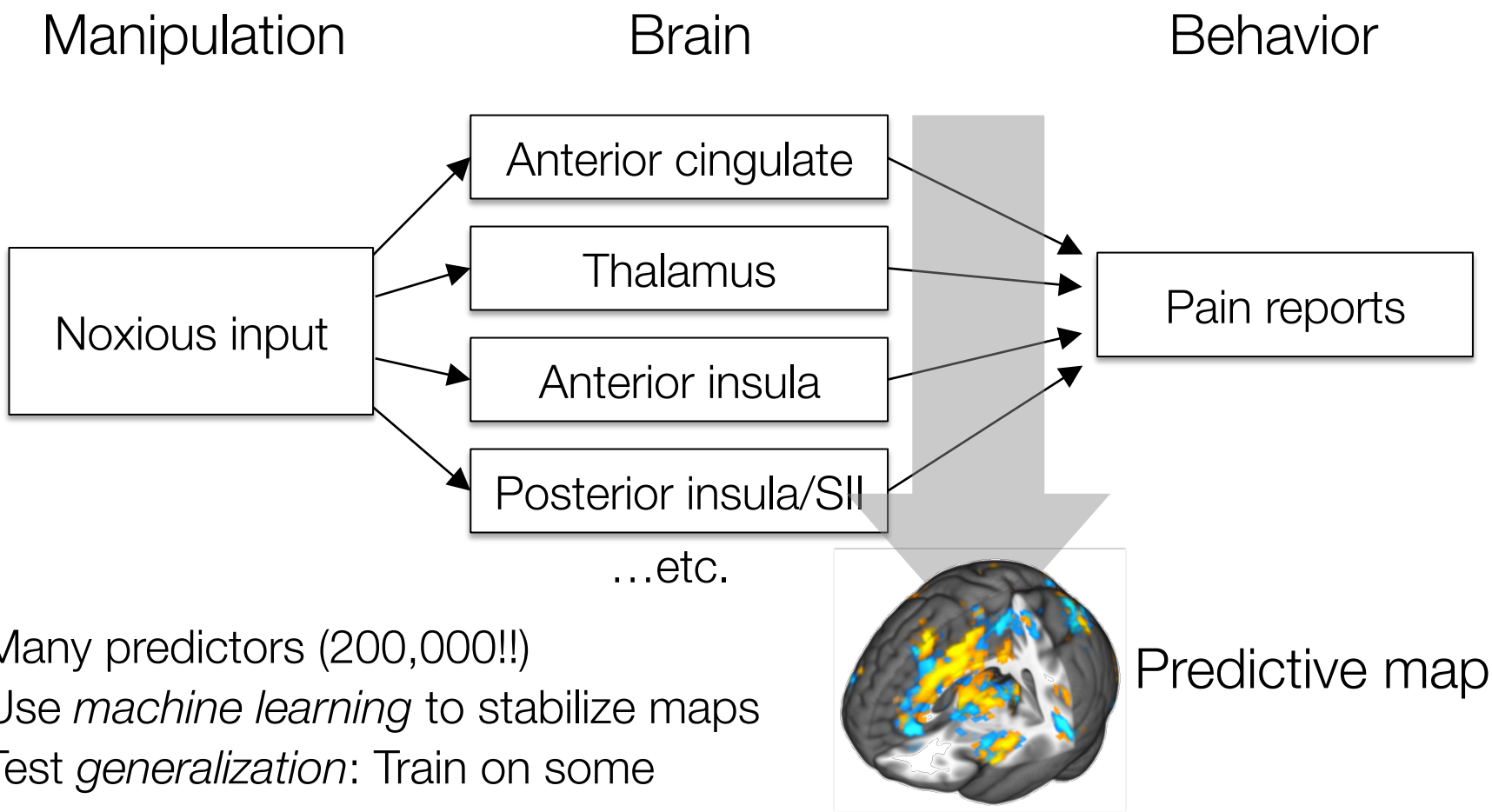
Biomarker development: Predicting pain

- N = 20 healthy individuals
- Thermal pain on left arm
- 12 trials at each of 4 temperatures
- Warm, Low, Medium, High pain
- Standard GLM -> resp. to heat



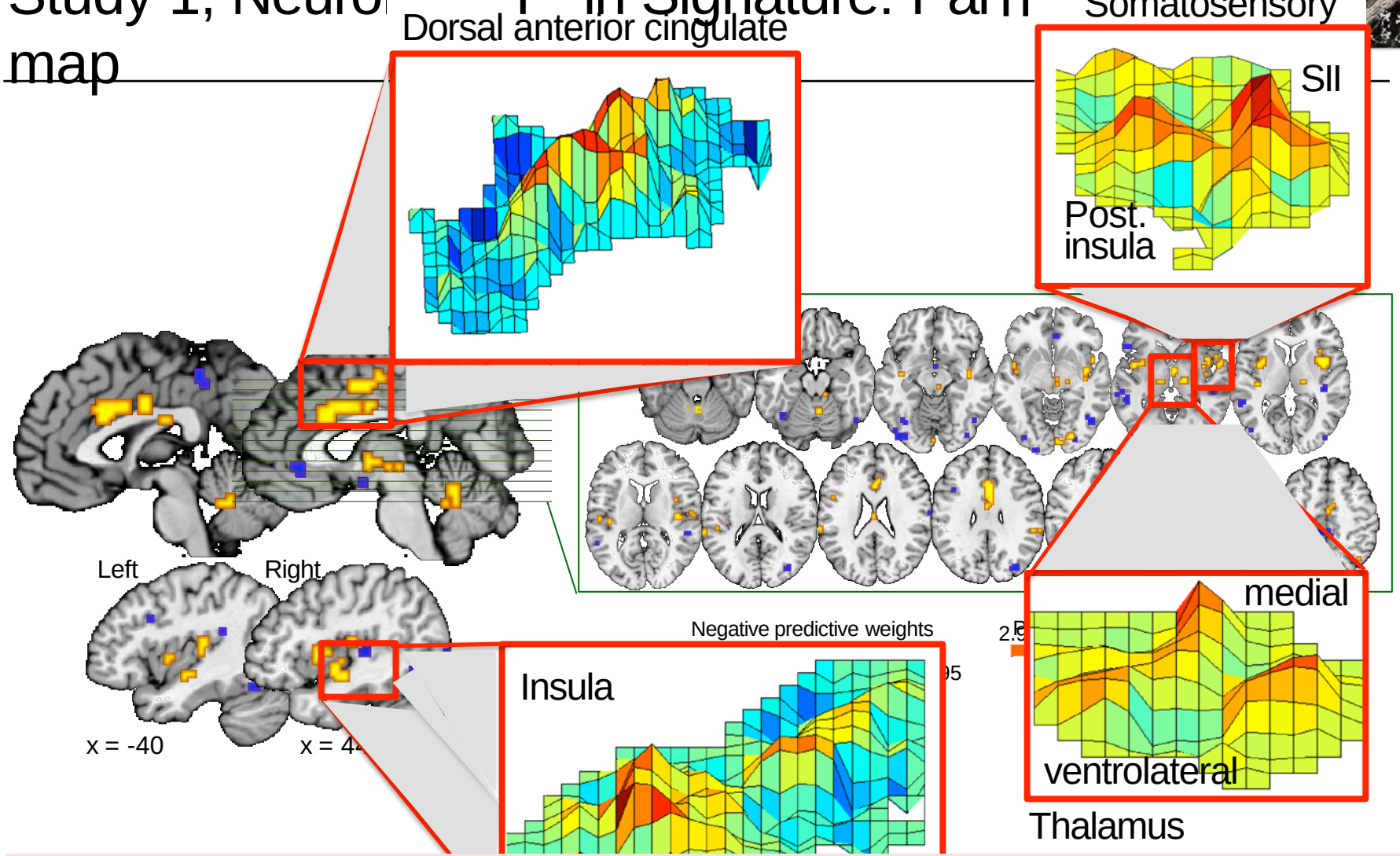
Analysis framework: Machine learning/statistical learning

Multivariate approach: Multiple brain regions predict pain



- Many predictors (200,000!!)
- Use *machine learning* to stabilize maps
- Test *generalization*: Train on some subjects, test on others

Study 1, Neurologic Pain Signature: Pain map



- Can apply to individual-person data to generate a prediction about pain intensity
- Can apply to existing data from many conditions (test sensitivity/specificity)

Threshold for display: q < .05 FDR (bootstrap)

Wager et al. 2013, NEJM

What is the NPS really measuring?

Specific ⟷ General

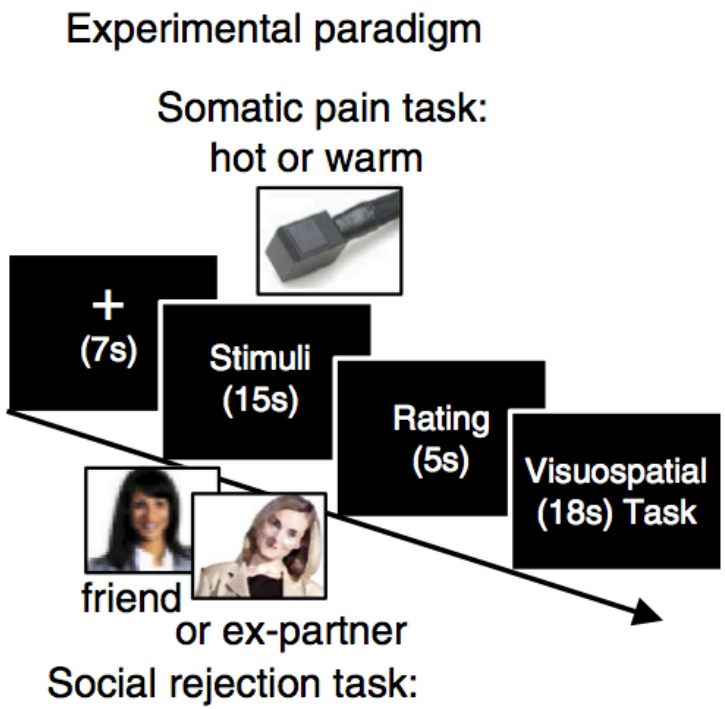
sub-types of pain – somatic pain – negative affect – arousal – salience

Study 3: Social rejection

Choong-Wan Woo Ethan Kross

N = 60 participants, All romantically rejected

Viewed pictures of ex-partners and friends
Painful and non-painful heat

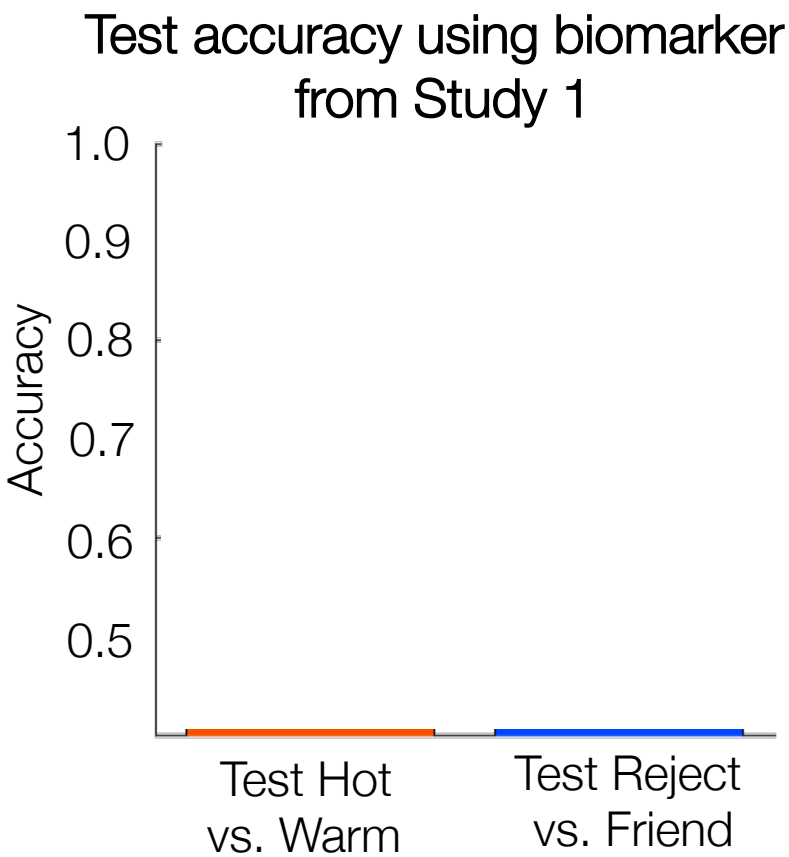


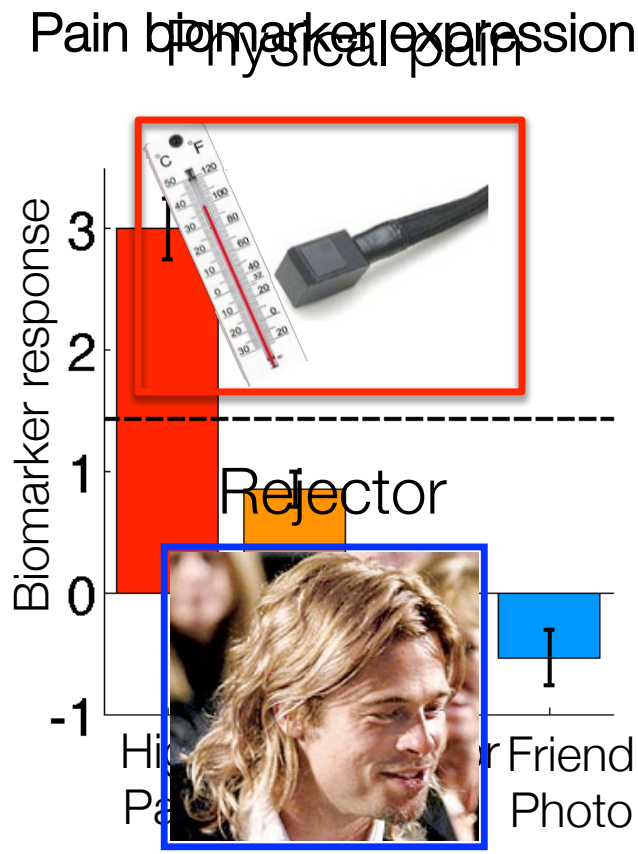
Rejection and pain:
Similar negative ratings
Similar brain activity

Kross et al., 2011, *PNAS*; Woo et al., 2014, *Nature Comms*

NPS application to Study 3

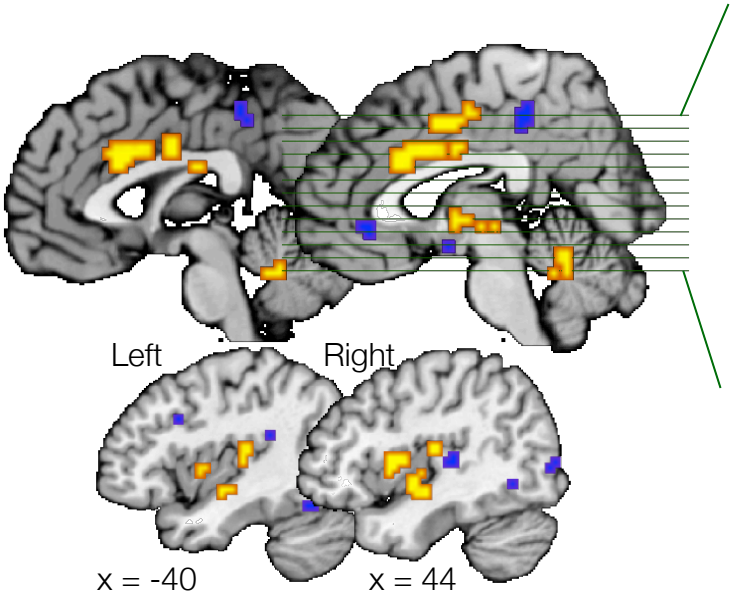
Does the biomarker trained on Study 1 discriminate high vs. low pain the Kross et al. experiment? Is it *specific* to physical pain?

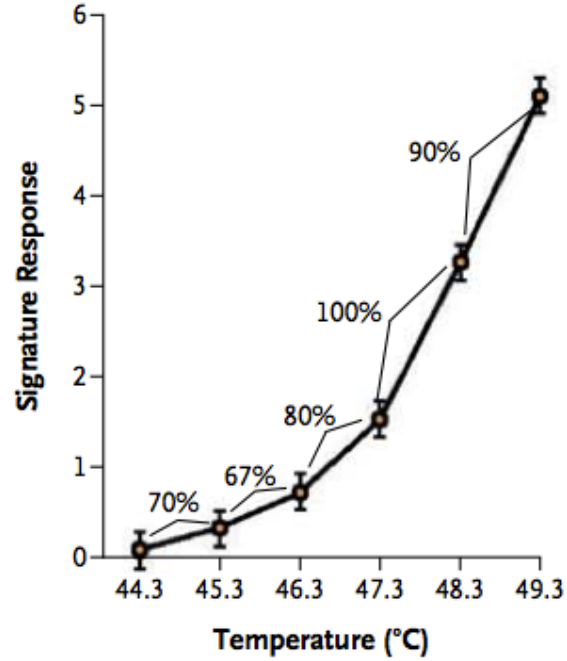




Wager et al. 2013, NEJM

NPS Characteristics Across Studies





Application to a new dataset from a different sample (N = 30, Wager et al. 2013, Study 2)

- 1. 90-100% sensitivity and specificity to pain in individuals
- 2. No response to other salient, affective events
- 3. Tracks pain more closely than temperature
- 4. Shows analgesic treatment response
- 5. Transfers across body sites and some types of *acute* pain
- 6. Sensitive across many datasets from different sites
- 7. Rapid testing on existing data: can test limits

Wager et al. 2013, NEJM

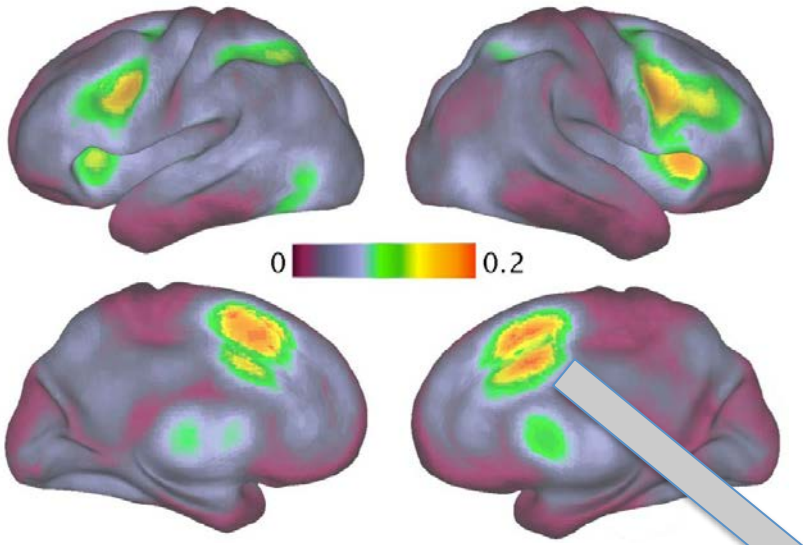
Different brain patterns for different types of affect:

Neuroimaging can identify patterns predictive of **distinct types** of pain- and emotion-related signals

Why does it work?
Common regions, different patterns

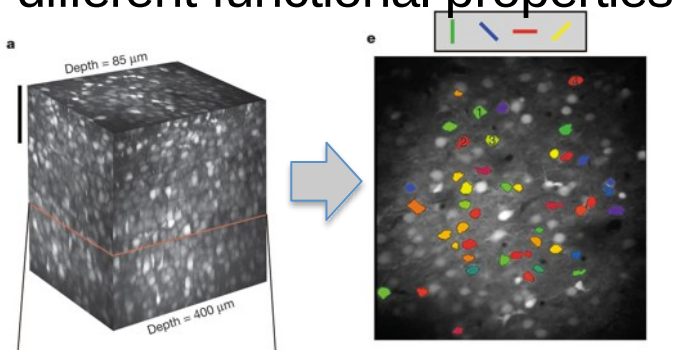
Machine-learning derived patterns provide more fine-grained information

Overall activation of anterior cingulate is non-specific…



Base-rate of activity in Neurosynth Database (~3500 studies)

Brain regions include many neurons with different functional properties



Rat V1

Ohki 2005/2006 Nature, 2-photon imaging

Anterior cingulate:

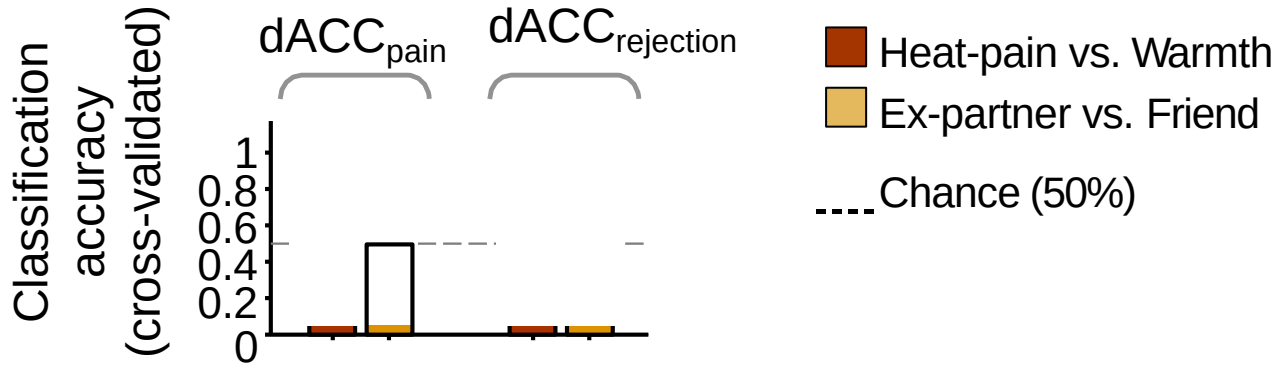
- Separate neurons respond to mechanical and thermal pain (25% overlap); *Sikes and Vogt (1982)*
- Separate circuits for reward onset and offset in foraging; *Kvitsiani et al. (2013), Nature*

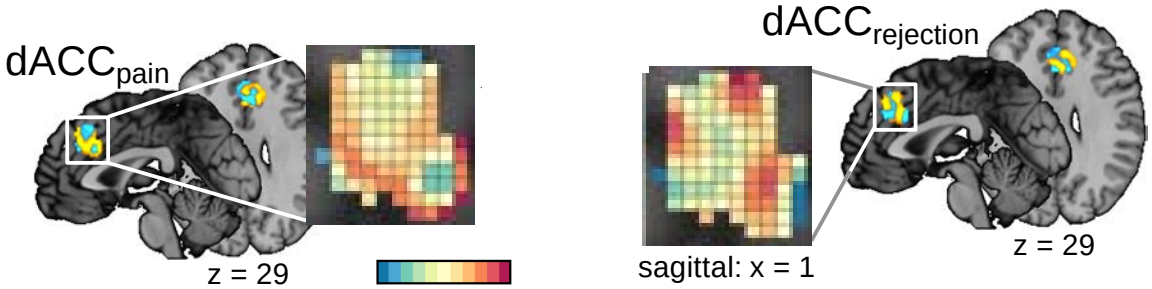
Common regions, different patterns

Separate modifiability of pain and rejection in ‘pain affect’ regions

Choong-Wan Woo

Multivariate pattern classifiers only within dACC





Pattern correlation:
r = -.04

dACC Pain pattern

dACC Rejection pattern

- No evidence for shared representation in ‘pain affect’ regions
- Whole brain patterns are also separately modifiable

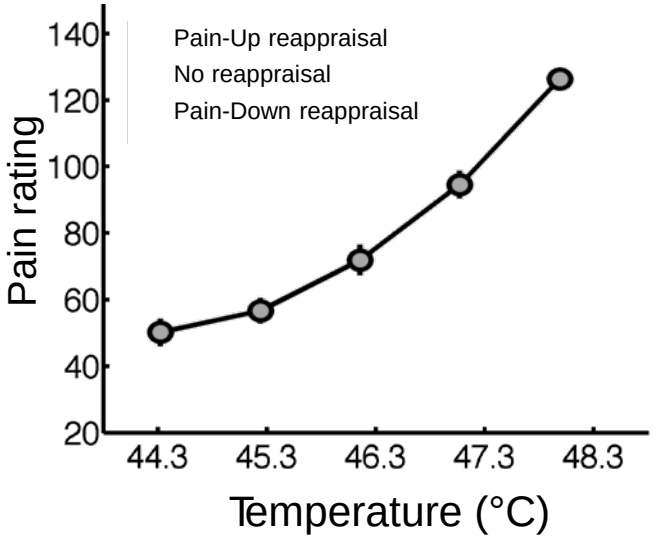
Woo et al. 2014, *Nature Comms*

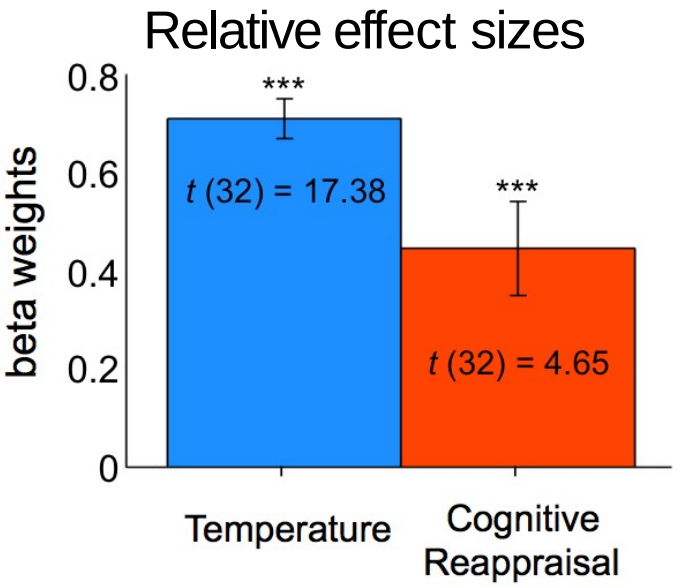
Beyond a single-system view:
Multiple cerebral pathways to pain

- ‘Bottom-up’ nociceptive pain system
- ‘Top-down’ prefrontal-striatal system

Psychological modulation: Cognitive reappraisal (N = 30)

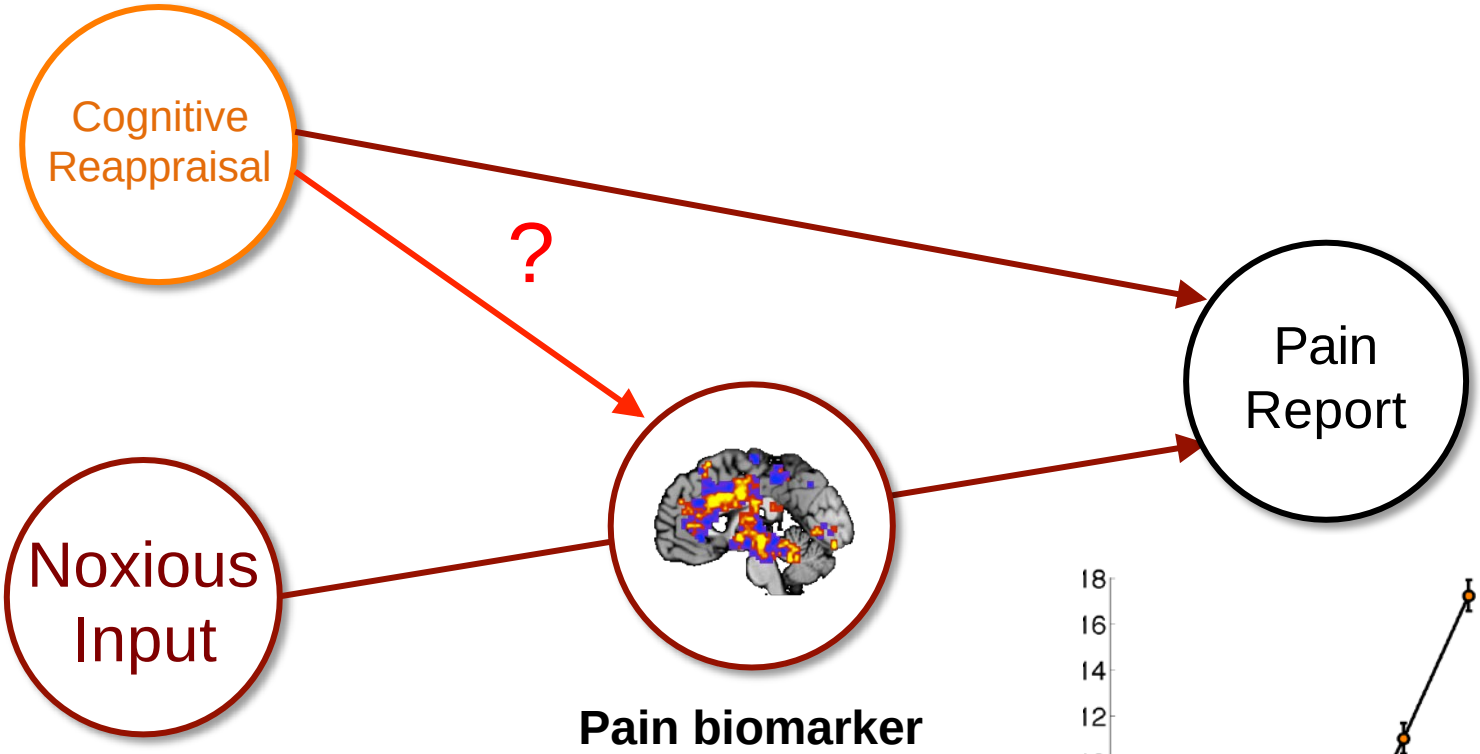
- "Appraise-up:" imagine your skin is *burning*, *sizzling*, *melting*
- "Appraise-down:" imagine *spreading warmth,* like your skin is under a warm blanket on a cold day

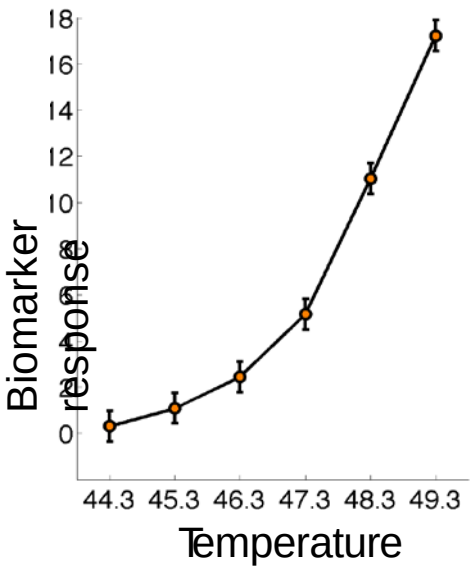




Woo et al., in press, PloS Biology

Cognitive reappraisal of pain



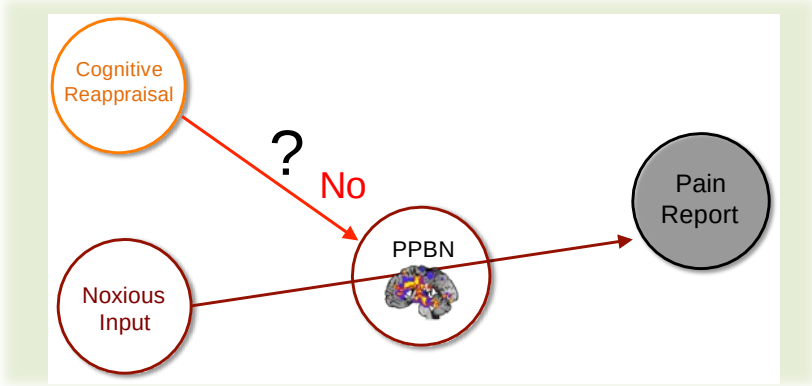


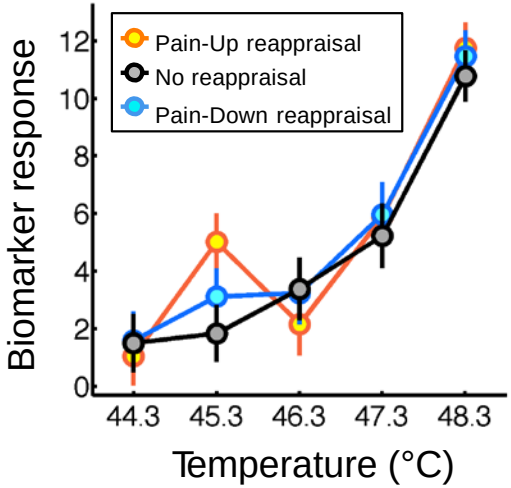
If yes: Appraisal may work at a “deep” level

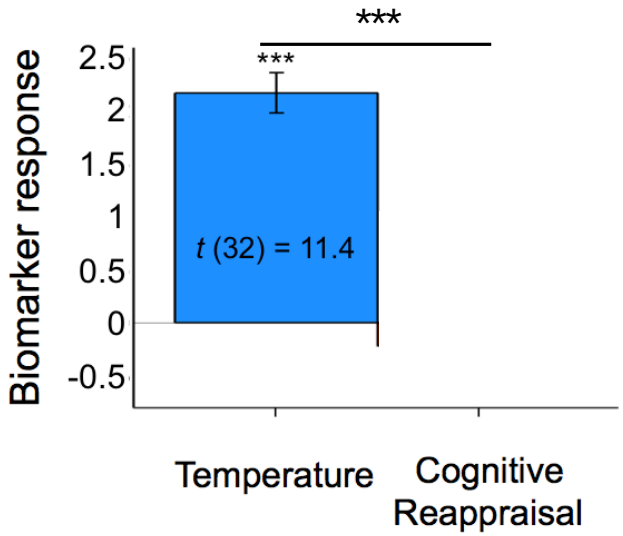
If no: Appraisal mainly influences post-nociception evaluation (may still be important!)

Woo et al., 2015, PloS Biology

Results: Does reappraisal influence the NPS? No.





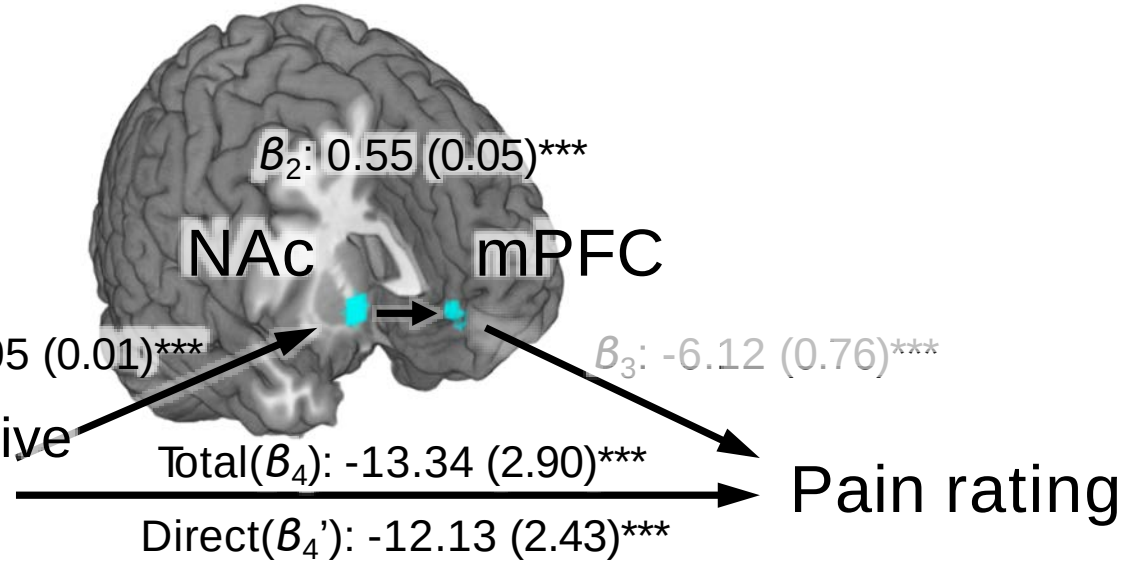


*** $p < .001$

Nucleus Accumbens-Medial PFC:

A second route to pain

<u>Three-path</u>
<u>mediated effects</u>
-0.07 (0.02)***



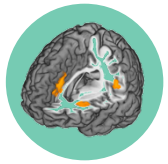
mPFC: Tracks expected value, sensitive to reappraisal
NAc: Involved in behavioral modulation of pain

- Both regions do not encode stimulus intensity (not 'pain' regions)
- Pathway important for ***<u>functional significance</u>***, not nociception

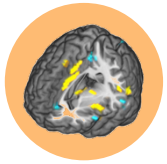
Roadmap

Representations & Biomarkers

Act I: Blobs

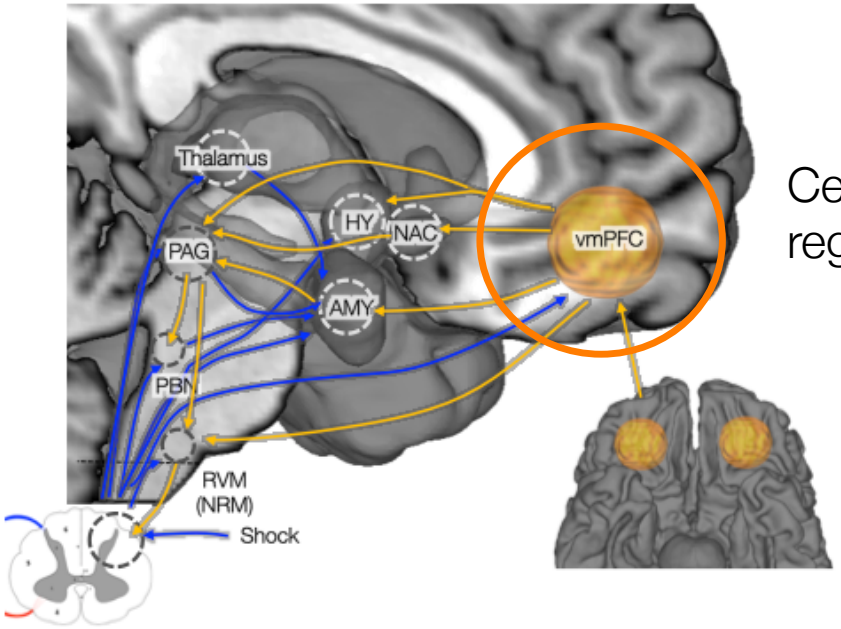


Act II: Biomarkers



Act III: Translation

Why care about the brain, even if you are developing peripheral therapeutics?

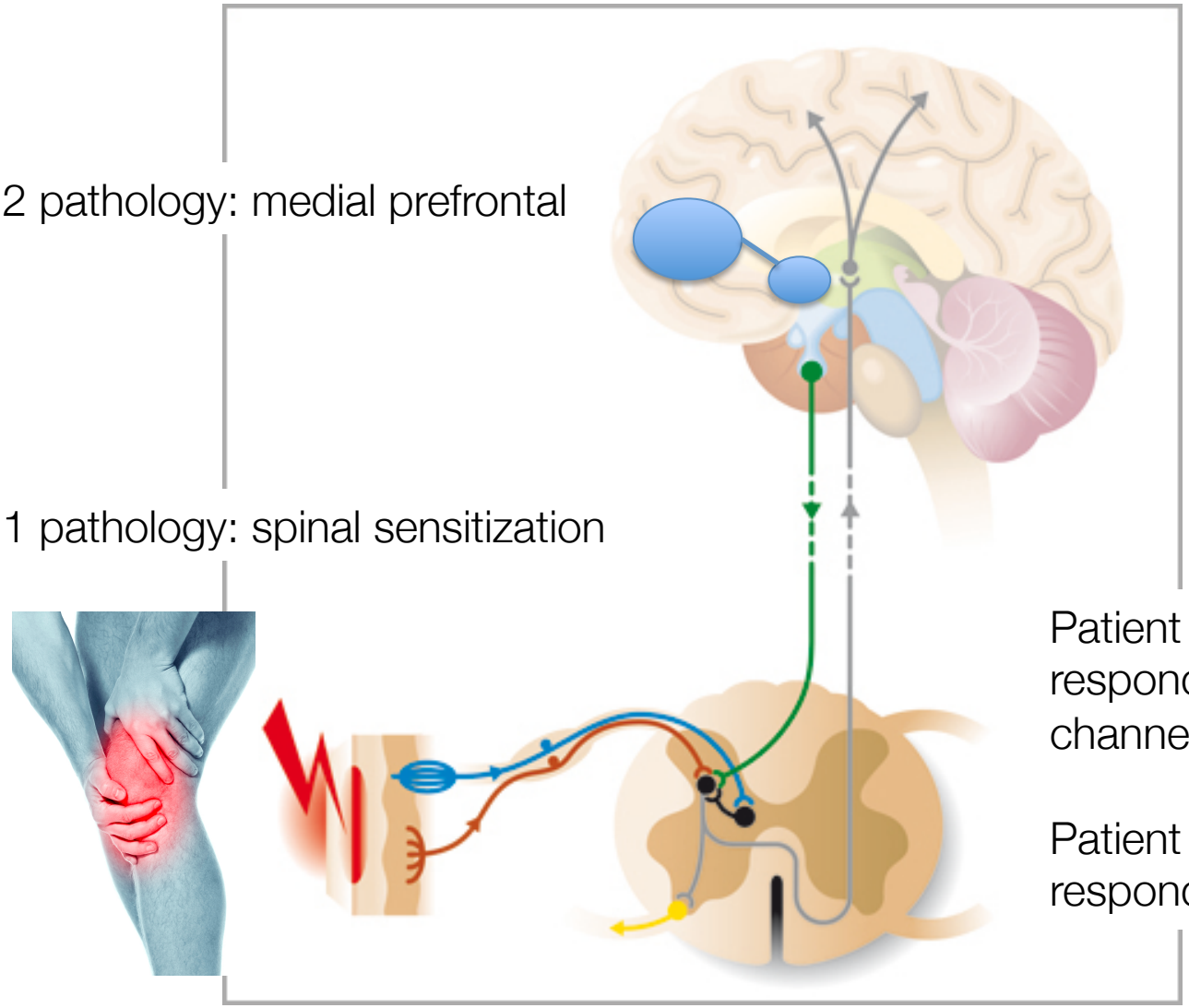


Cerebral generation and regulation of pain

Different treatments for different types of patients

Patient 2 pathology: medial prefrontal

Patient 1 pathology: spinal sensitization



Patient 1
responds to TRP
channel blocker

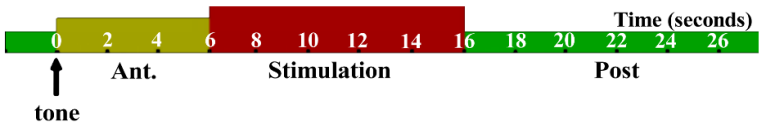
Patient 2
responds to CBT

New brain targets for fibromyalgia

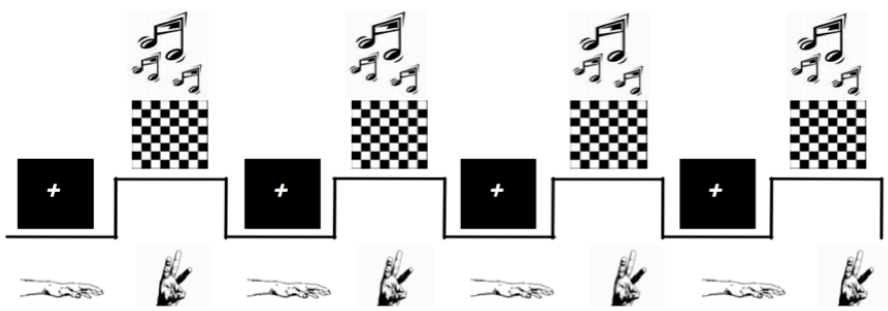
Targets

Marina López-Solà

- Fibromyalgia patients (FM, N = 37)
- Matched healthy controls (N = 35)

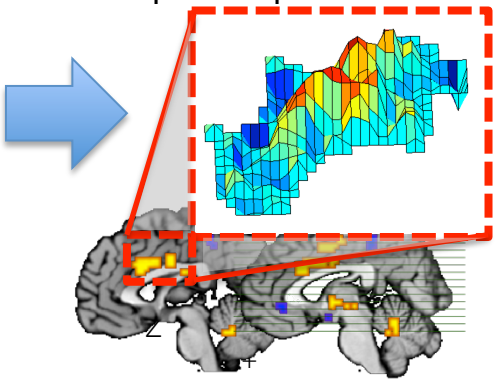


PRESSURE PAIN
(RIGHT THUMB NAIL, 4.5KG/CM^2)
6 trials



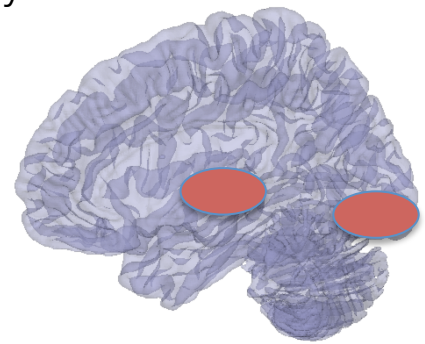
MULTISENSORY-MOTOR PARADIGM

Nociception-positive NPS



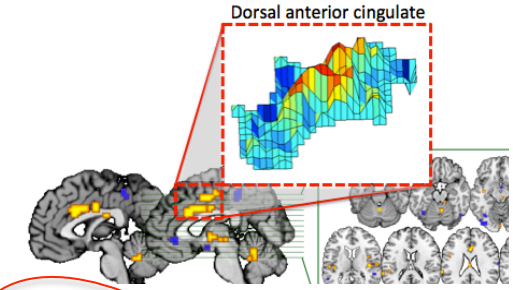
Nociception-negativeNPS

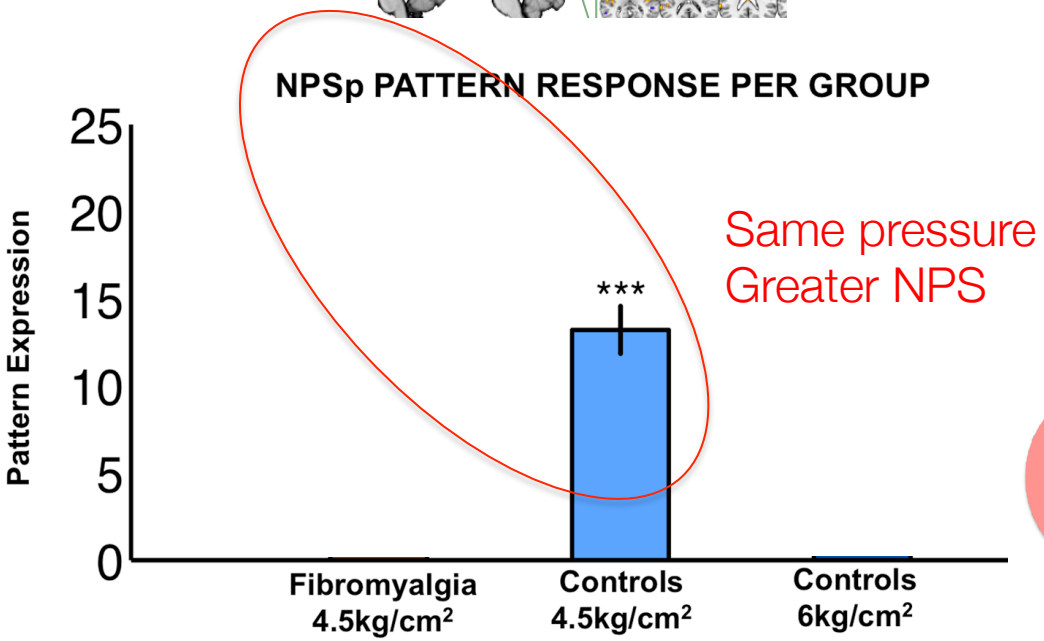
Sensory cortical reductions

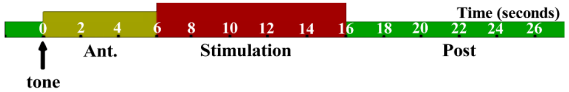


Lopez-Sola et al. 2014 A&R; Lopez-Sola et al. under review

Fibromyalgia:
Enhanced "Neurologic Pain Signature" (NPS) responses

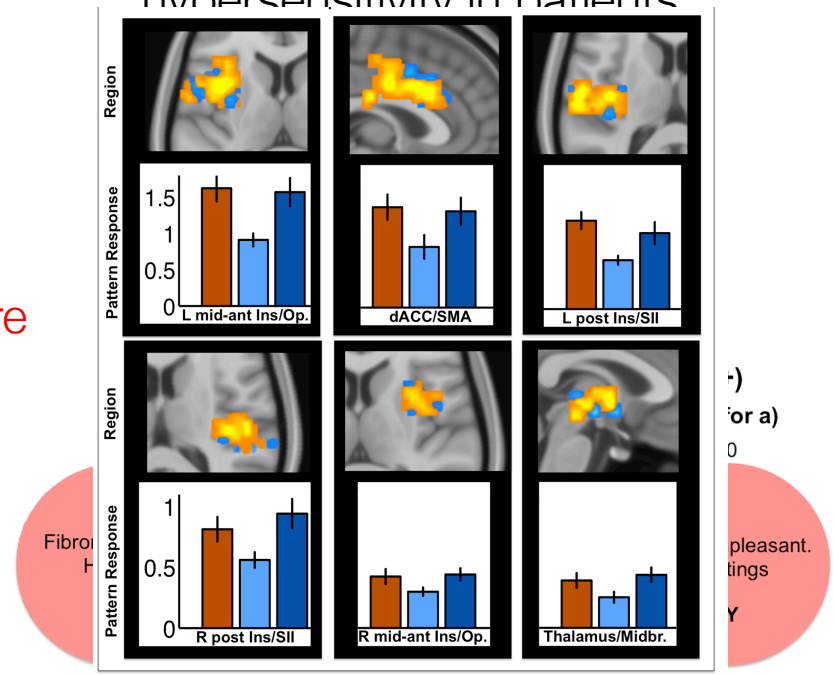






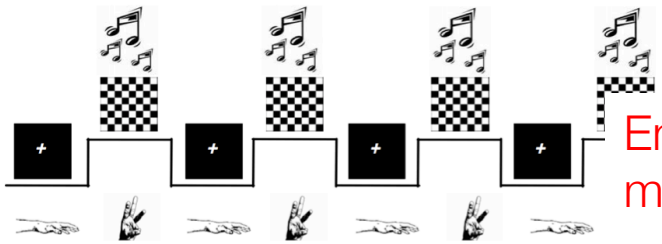
NPS increases expressed in both 'sensory' and 'affective' regions

NPS increases mediate hypersensitivity in patients



Lopez-Sola et al. Under review

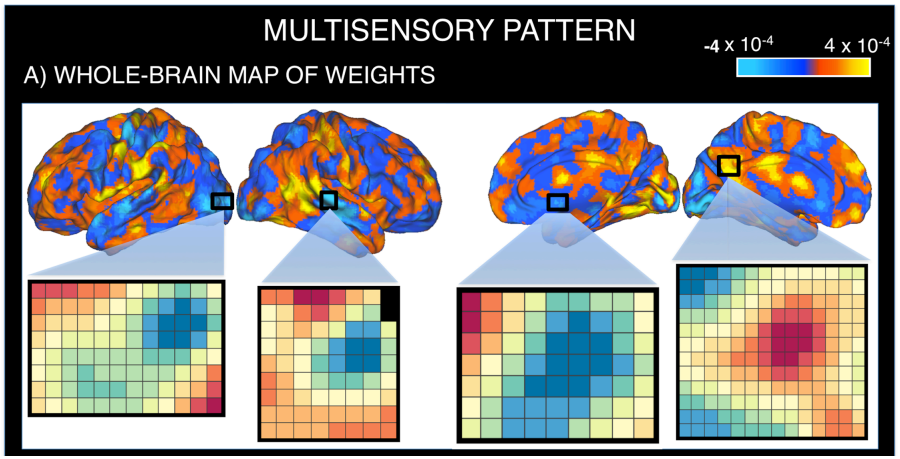
Altered multisensory brain responses predictive of fibromyalgia

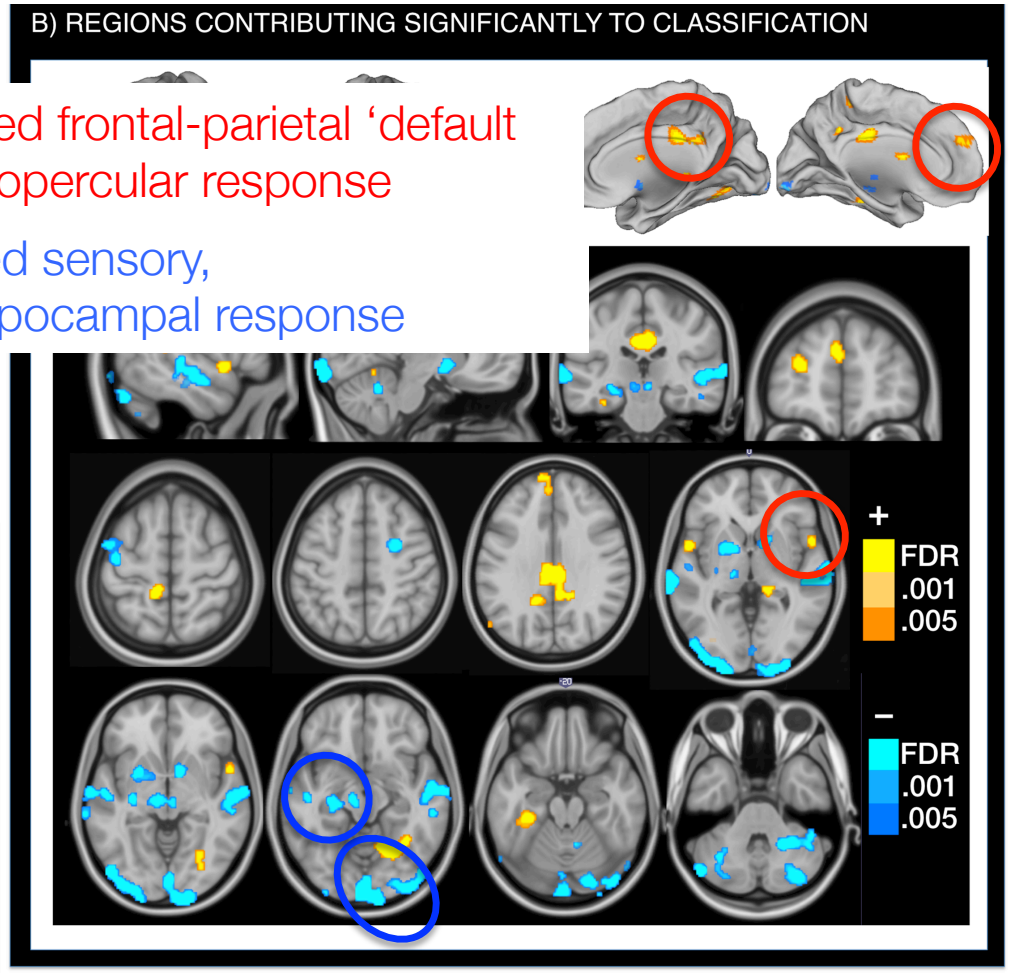


Enhanced frontal-parietal 'default mode', opercular response

Reduced sensory, parahippocampal response

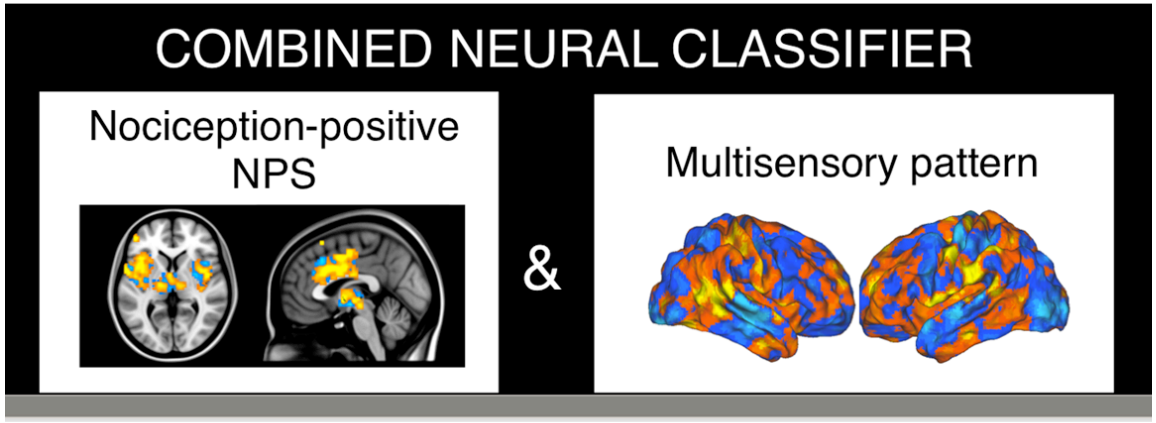
Cross-validated analysis of patterns
Predictive of fibromyalgia status

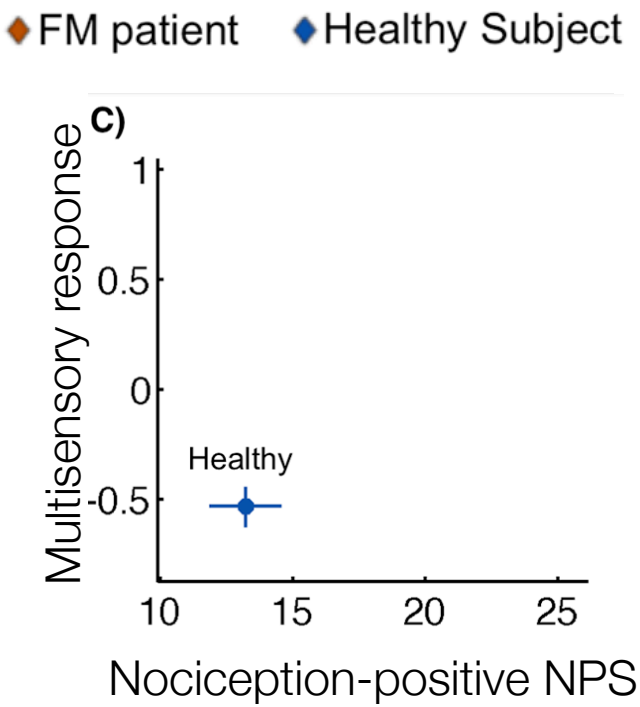


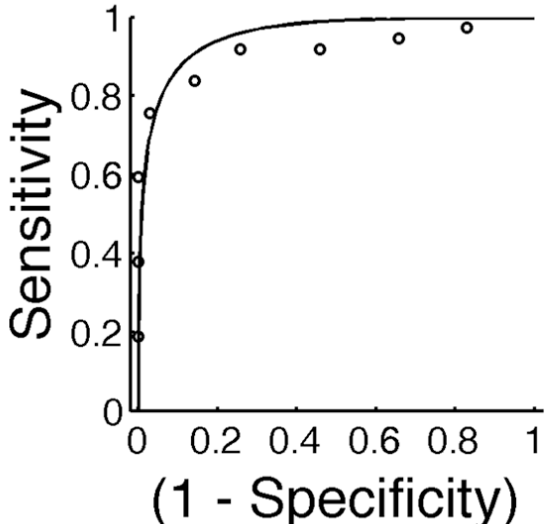


Lopez-Sola et al. Under review

An objective Neural Signature for FM status based on Pain-Specific and Multisensory processing







Fibromyalgia vs. control:
89% accurate

89% sensitivity
86% specificity

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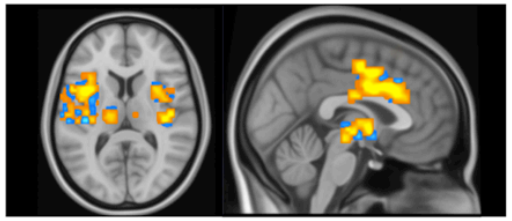
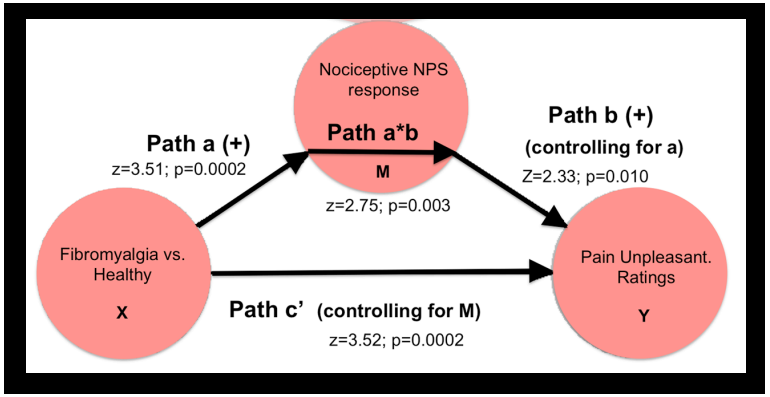
Elements of Fibromyalgia Neural Signature predict different symptoms

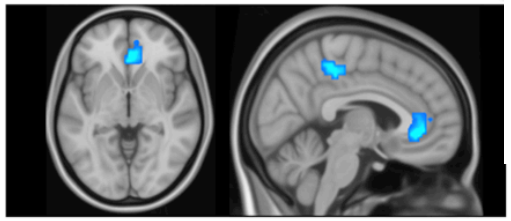
Fibromyalgia

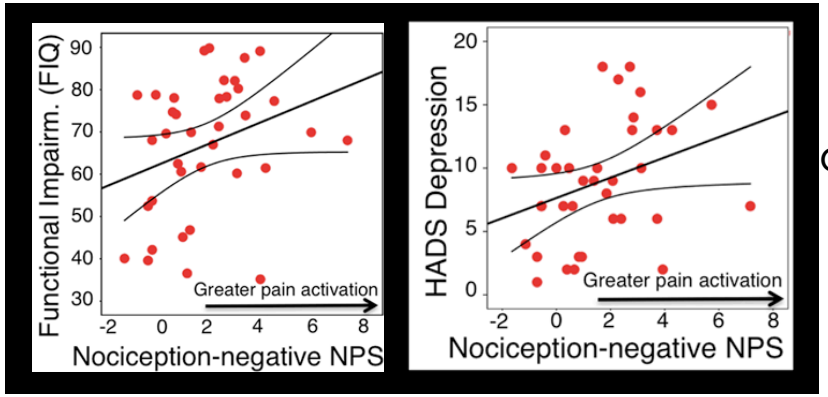
Nociception-positive NPS





Nociception-negative NPS





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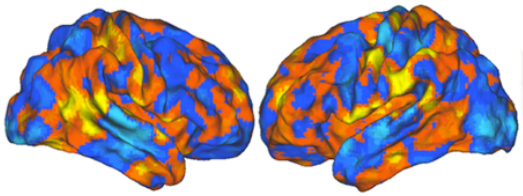
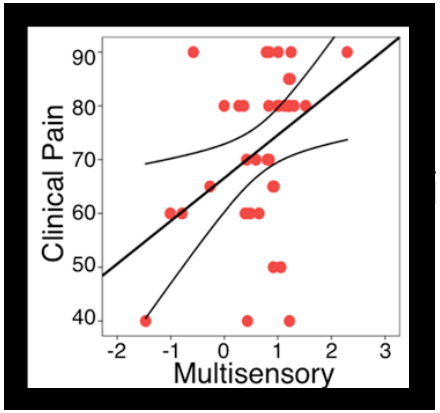
Multisensory





cal Pain

Lopez-Sola et al. under review

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