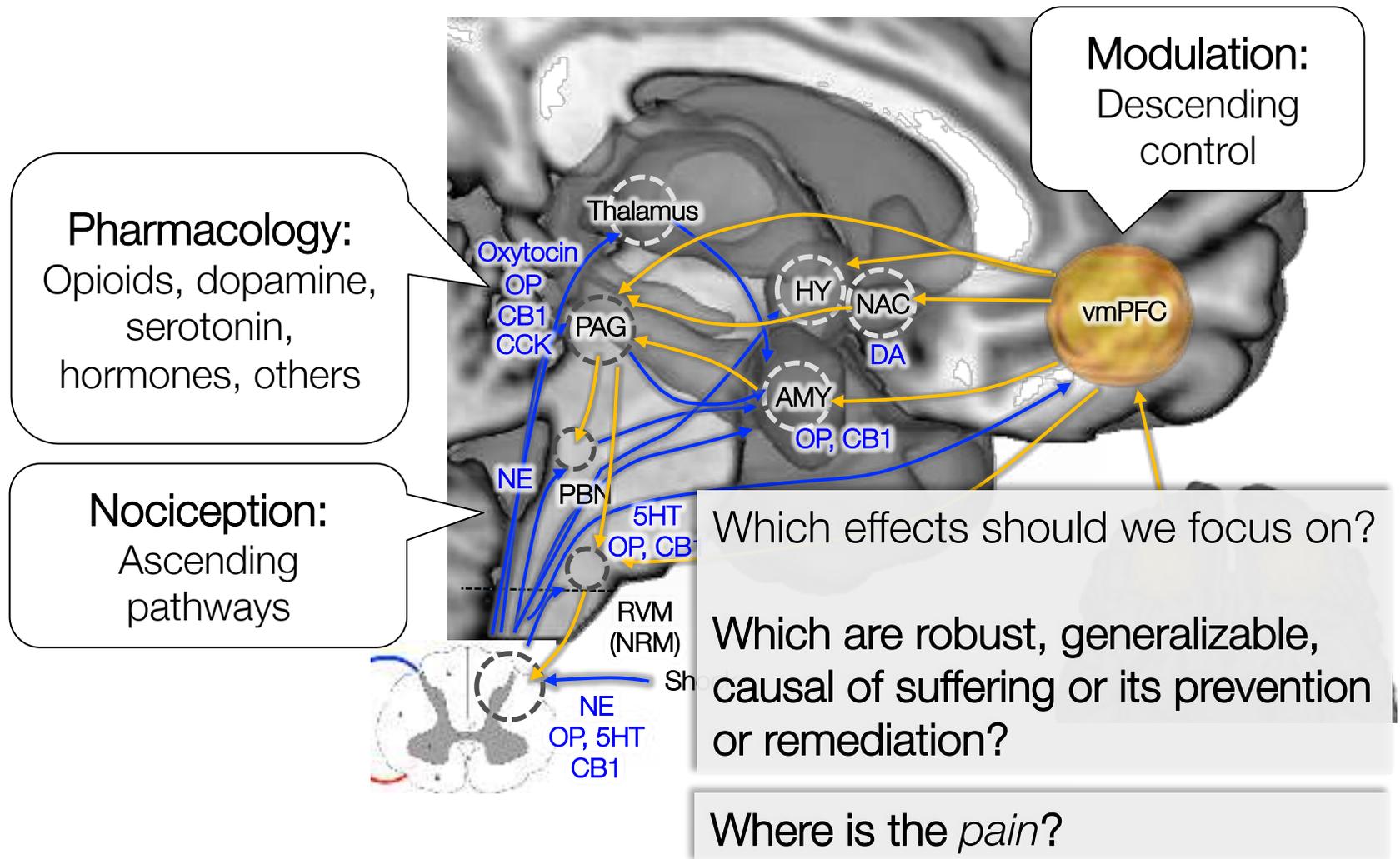


Neuroimaging of pain and distress: From blobs to biomarkers to translation

Tor D. Wager

Department of Psychology and Neuroscience
And the Institute for Cognitive Science
The University of Colorado, Boulder

What we know about pain





What we'd like to know: Representations and biomarkers

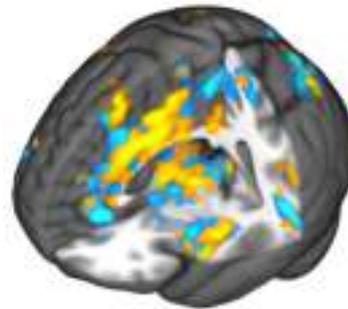
Representation: Causal, obligatory physical basis for a mental experience or information structure

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

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

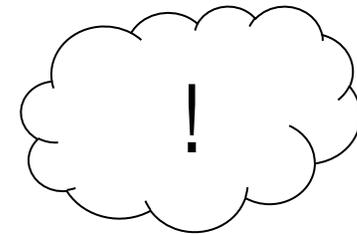


Noxious event



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



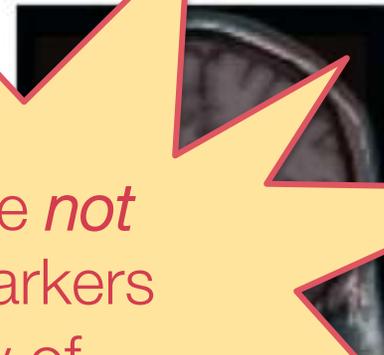
Don't we already have biomarkers for many kinds of mental events?



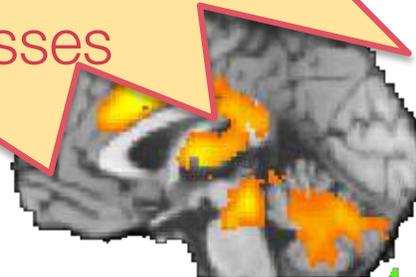
fMRI activity is implicitly used as a biomarker in nearly all studies of psychological phenomena

- Reward
- Value
- Memory
- Pain
- Visual processing
- Social cognition
- Specific emotions
- 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. $P(\text{psych} | \text{brain})$?

■ Sensitivity

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

$P(\text{brain} | \text{psychological event})$?

■ Specificity

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

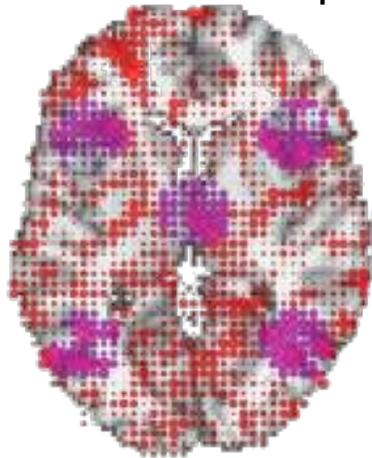
$P(\text{brain} | \text{absence of psych})$?



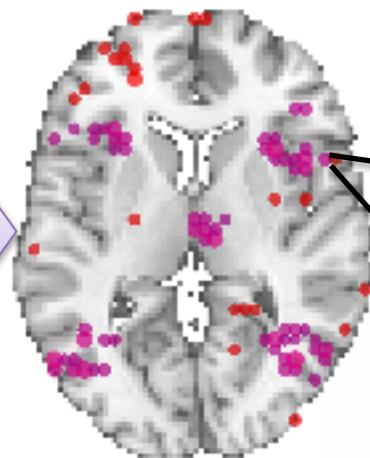
The problem of replication

Hypothetical correlation
with fibromyalgia

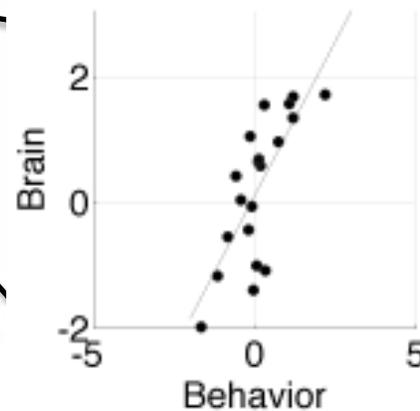
Statistical map



Results



A typical 'significant' voxel looks like this...



$r = .78$

A marker for fibromyalgia?

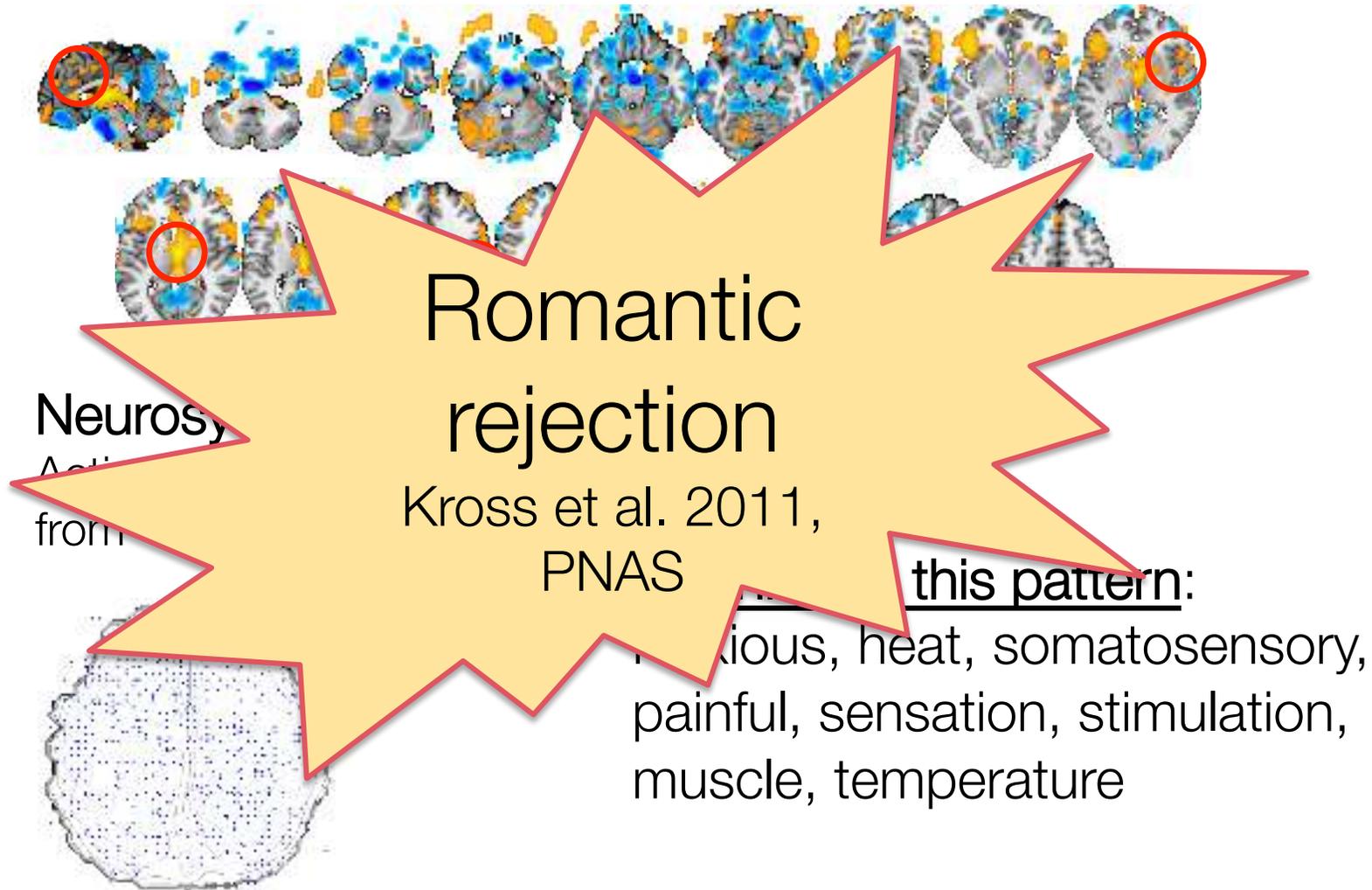
Unfortunately, no: There is no true signal, and this is all noise.

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



The problem of specificity

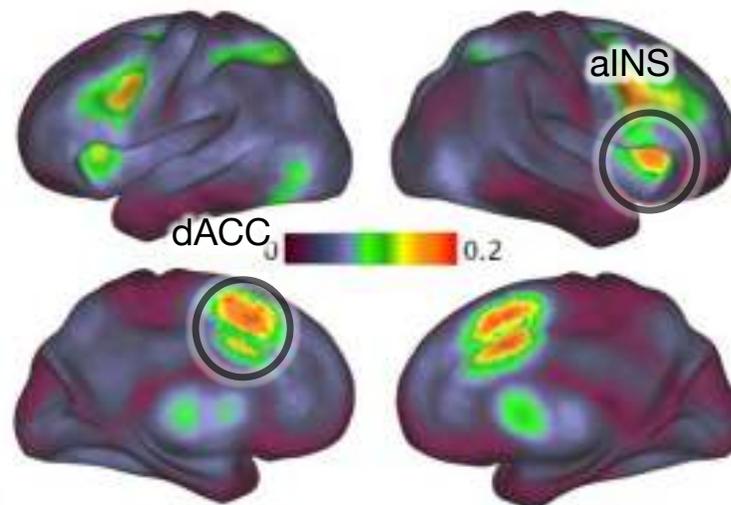
What does this map *mean*?





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.

Roadmap

Representations
& Biomarkers



Act I:
Blobs



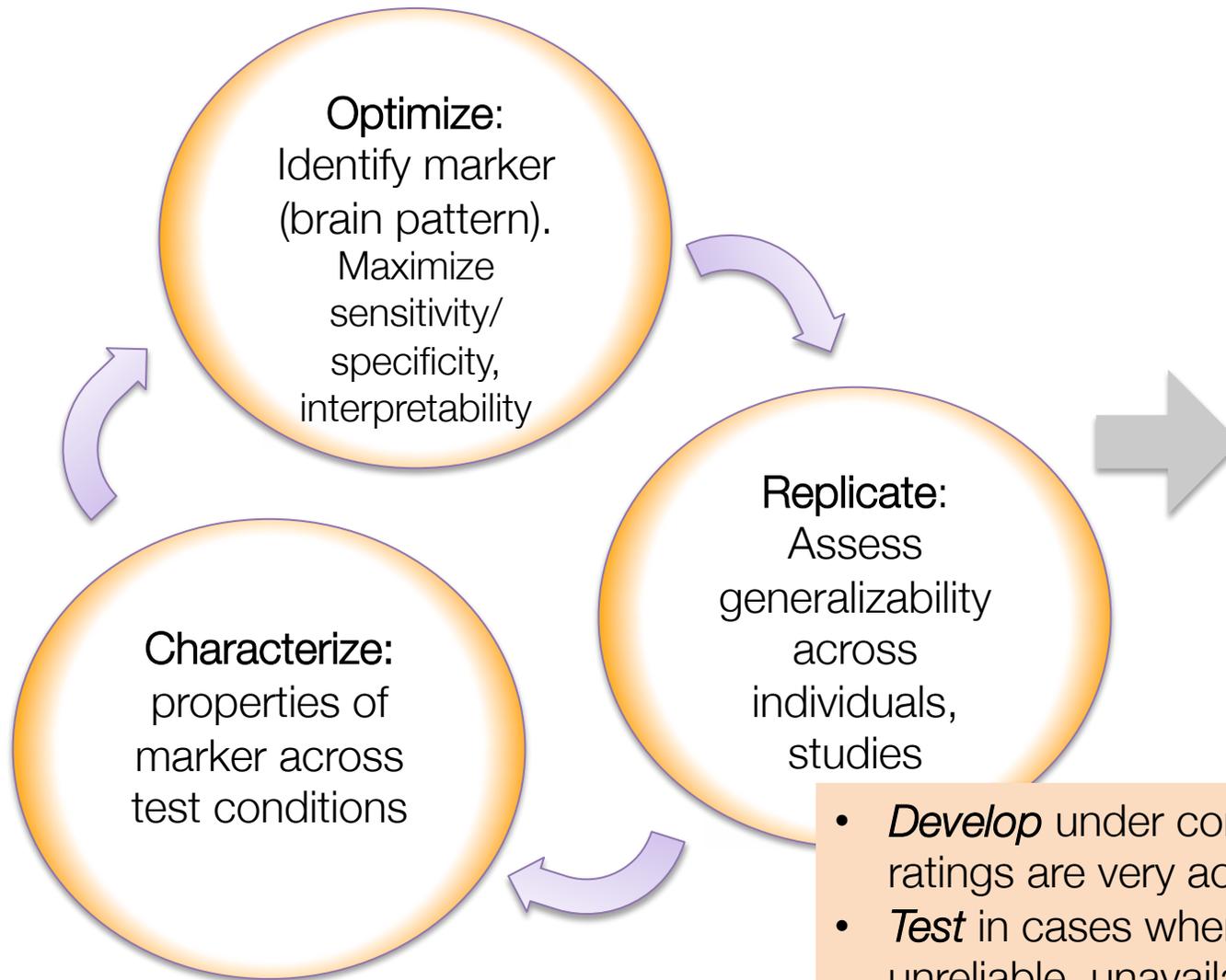
Act II:
Biomarkers





A new approach: Multi-study validation of brain markers

Development and validation



Application

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

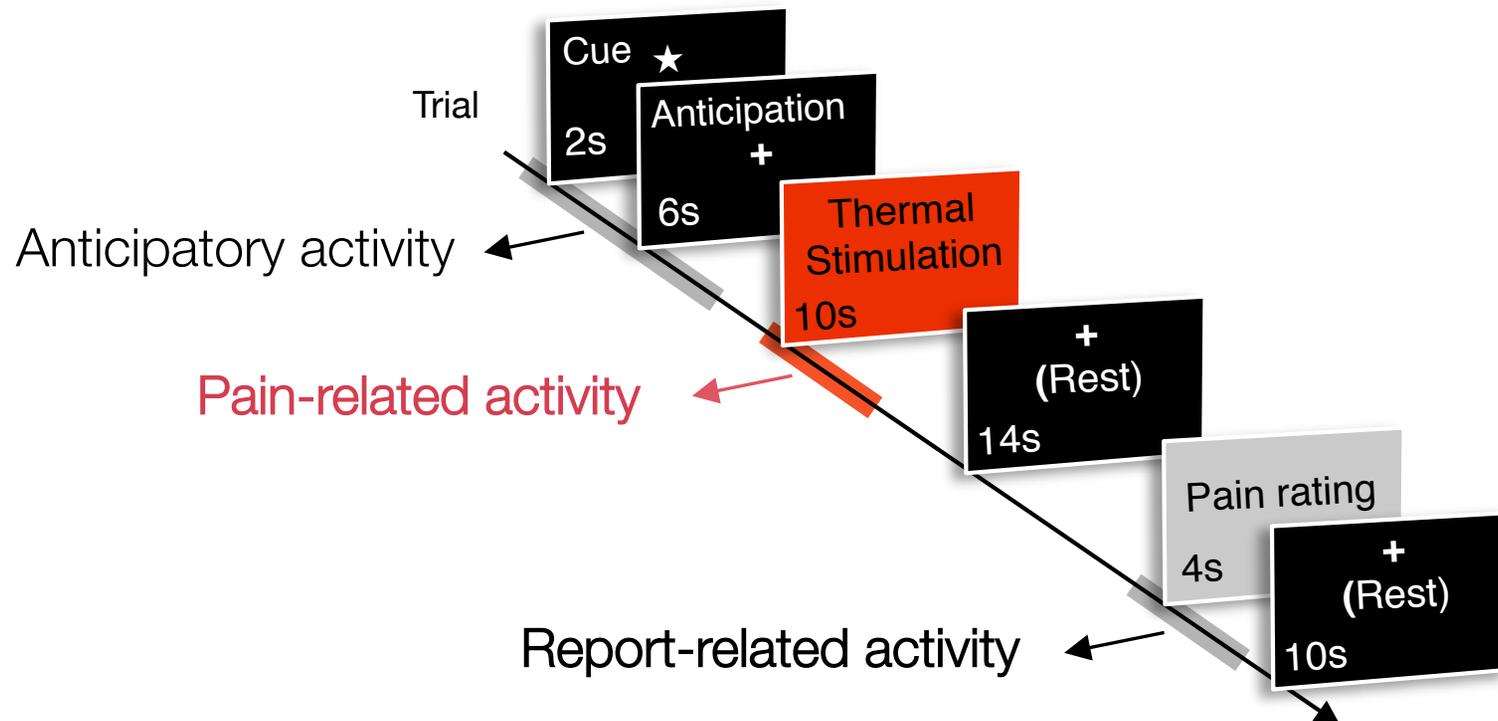
- *Develop* under conditions where pain ratings are very accurate and reliable
- *Test* in cases where pain reports are unreliable, unavailable



Biomarker development: Predicting pain



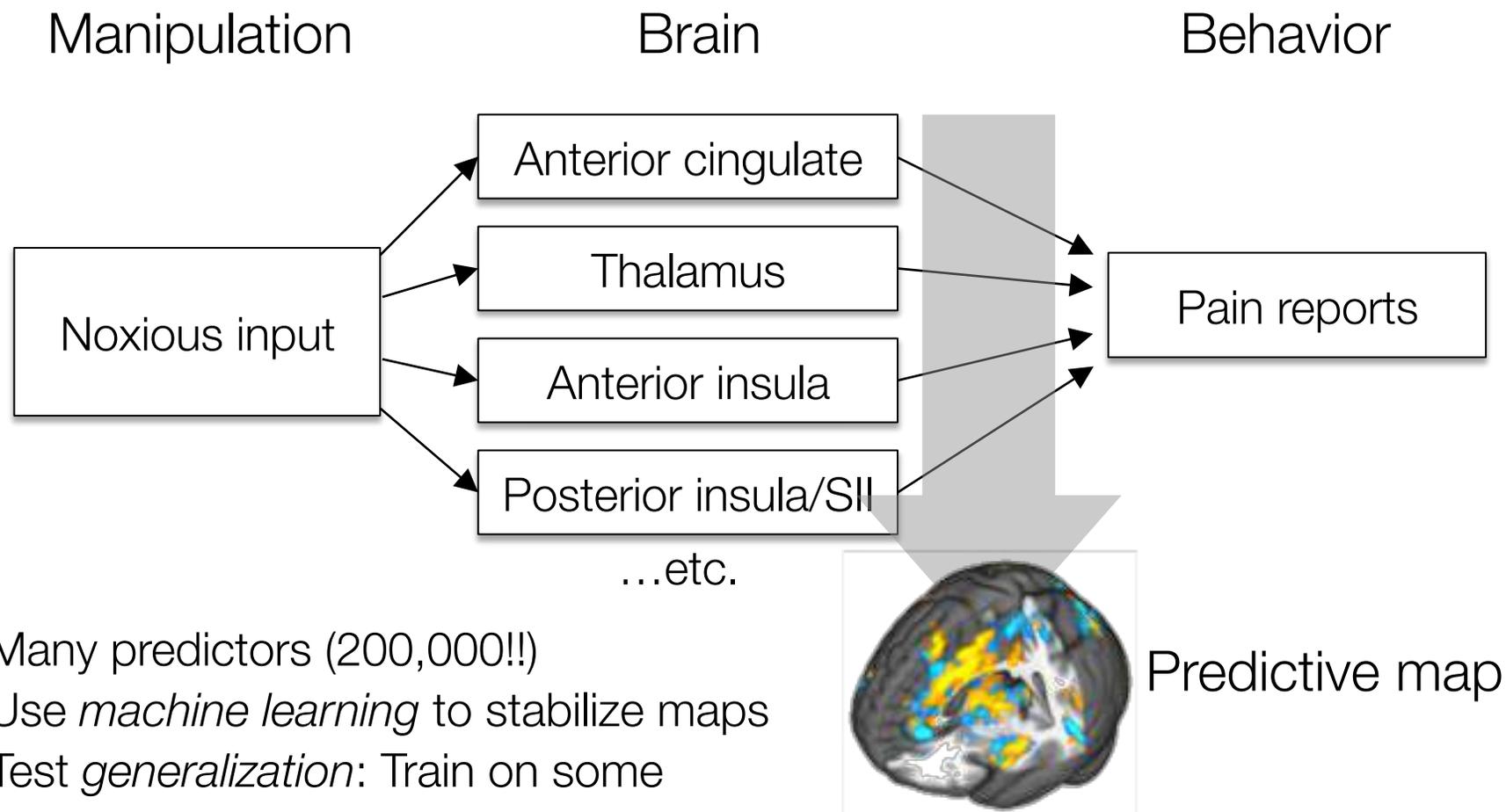
- N = 20 healthy individuals
- Thermal pain on left arm
- 12 trials at each of 4 temperatures
- Warm, Low, Medium, High pain
- Standard GLM -> resp. to heat





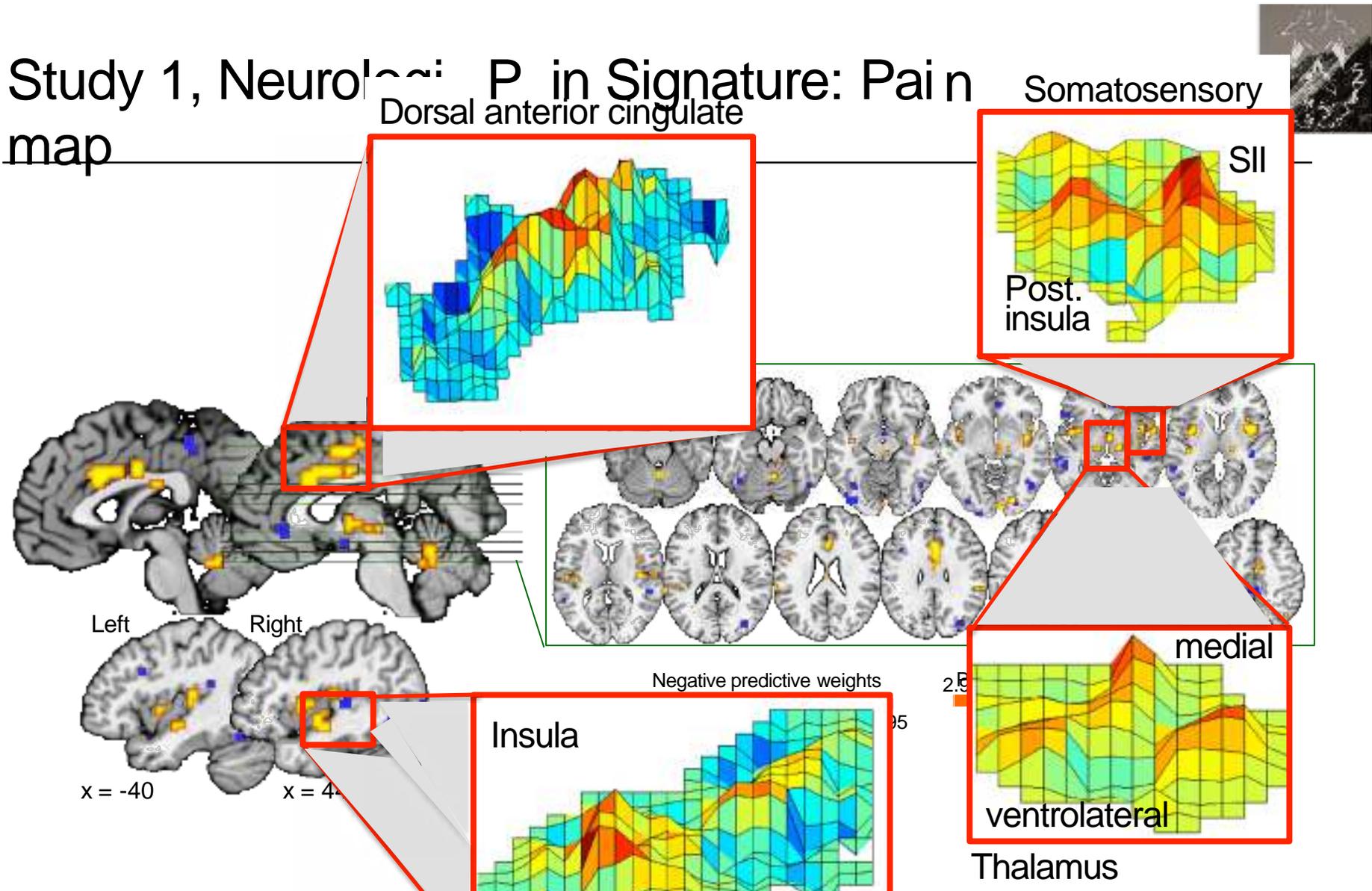
Analysis framework: Machine learning/statistical learning

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, Neuroimaging: P in 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

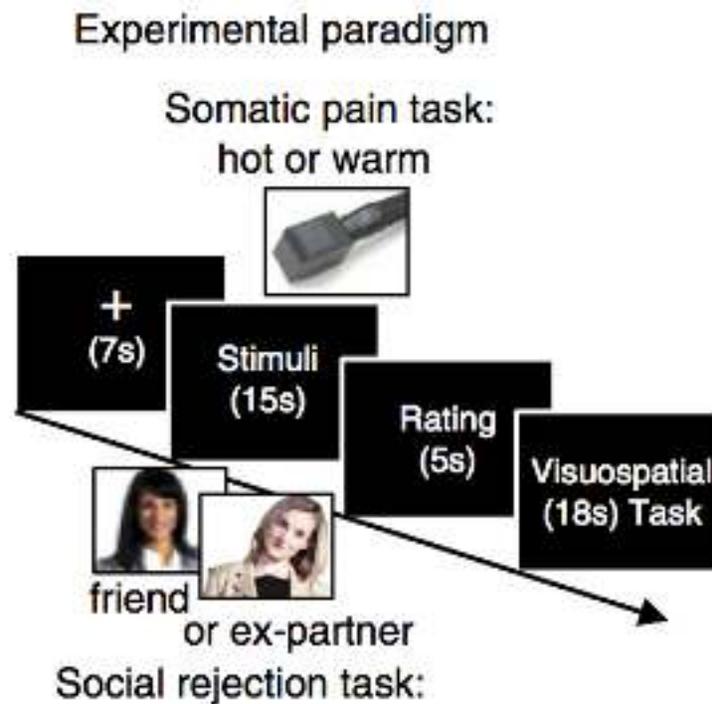


Choong-Wan Woo

Ethan Kross

$N = 60$ participants, All romantically rejected

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

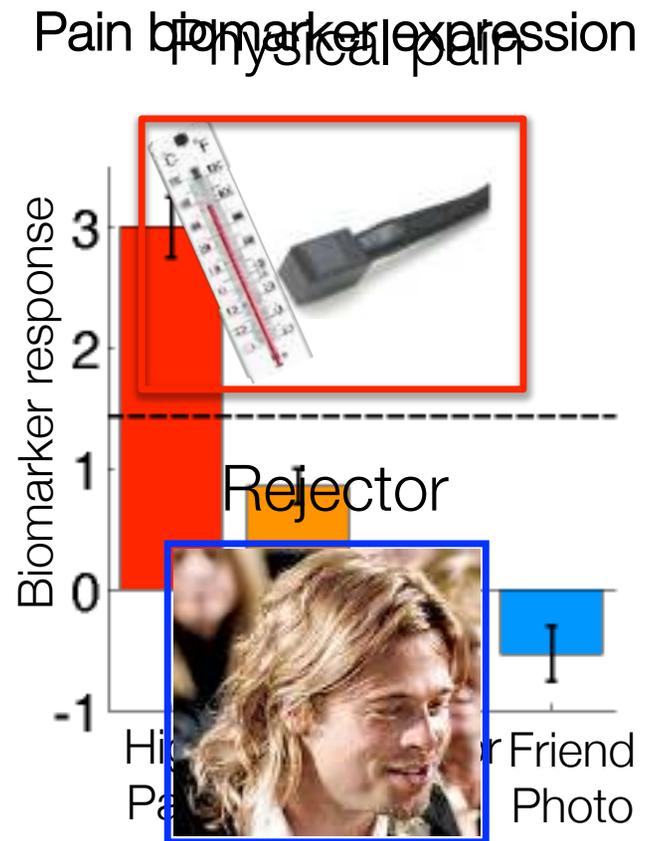
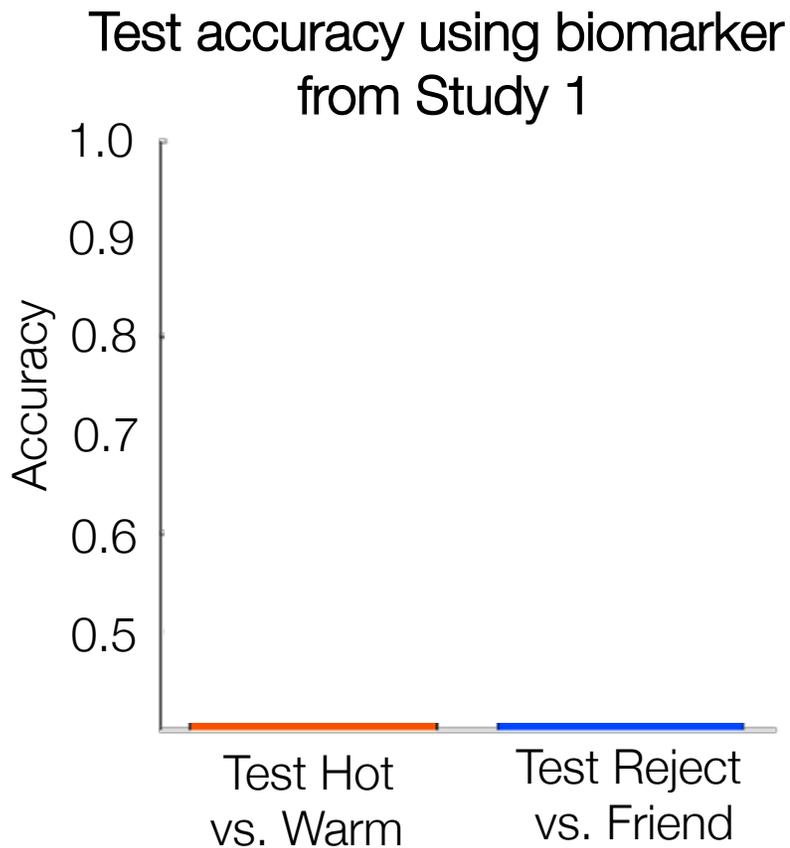


Rejection and pain:
Similar negative ratings
Similar brain activity



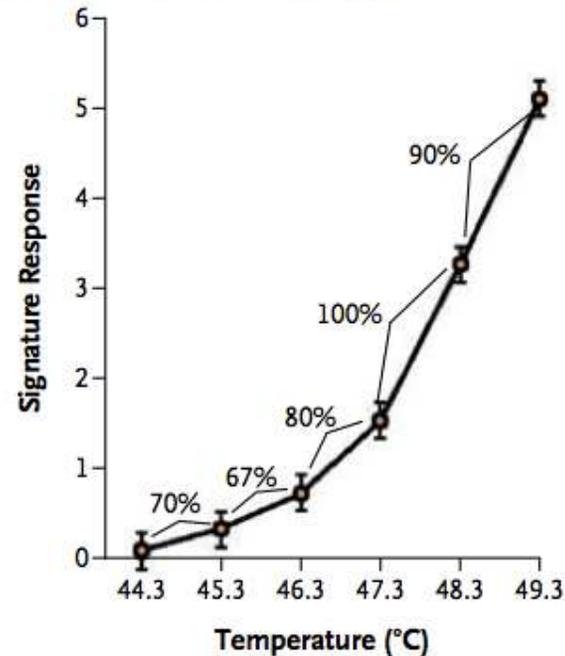
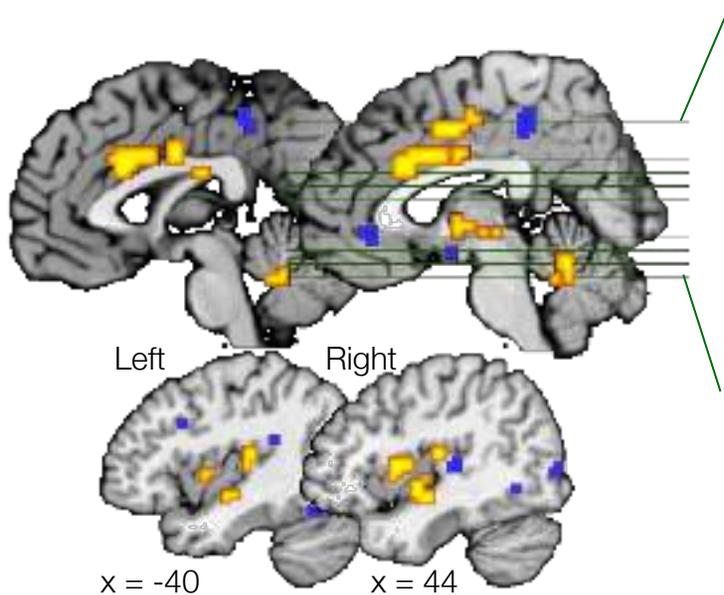
NPS application to Study 3

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





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

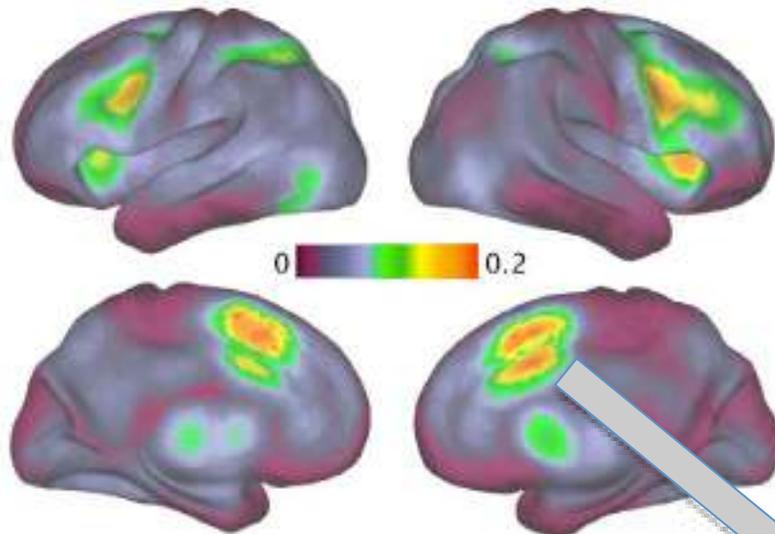
Why does it work?

Common regions, different patterns



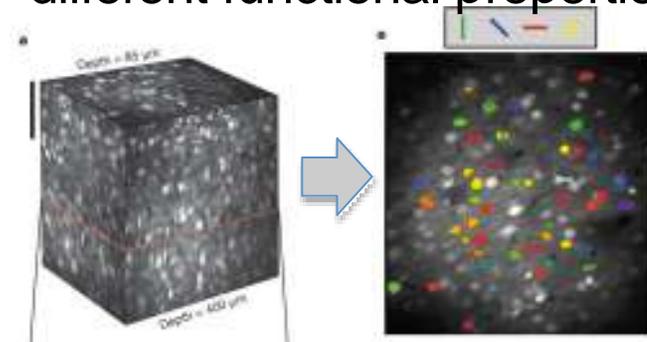
Machine-learning derived patterns provide more fine-grained information

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*

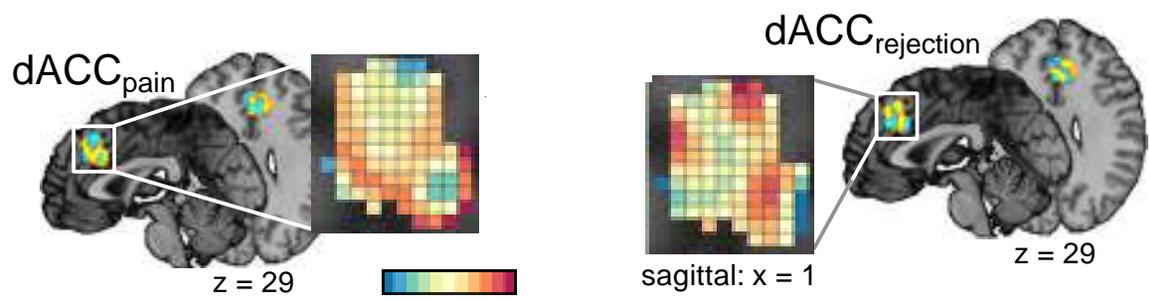
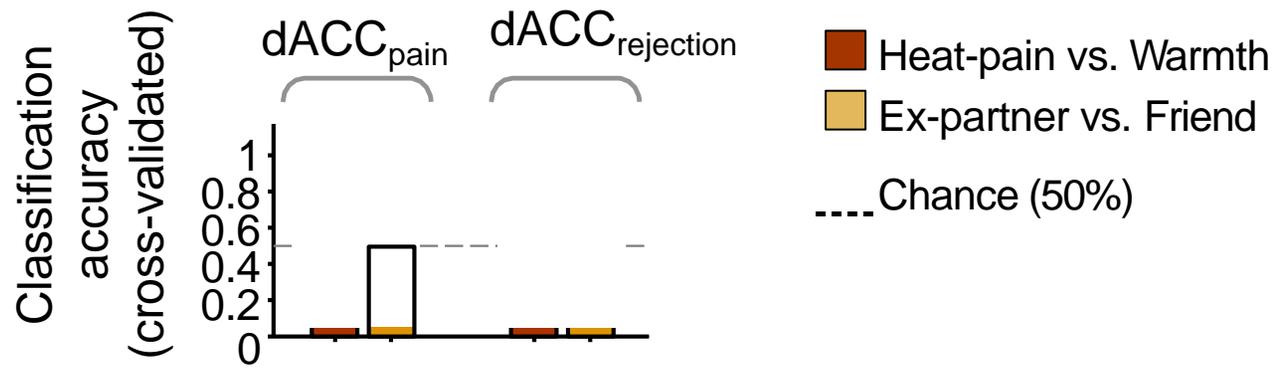


Choong-Wan Woo

Common regions, different patterns

Separate modifiability of pain and rejection in 'pain affect' regions

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

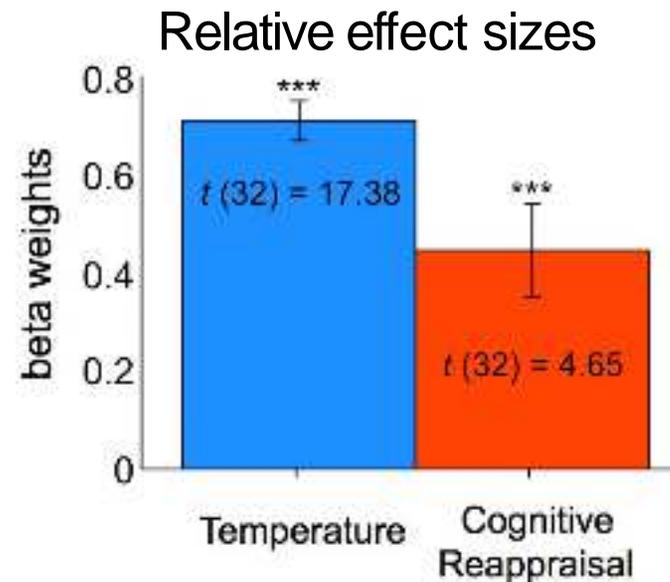
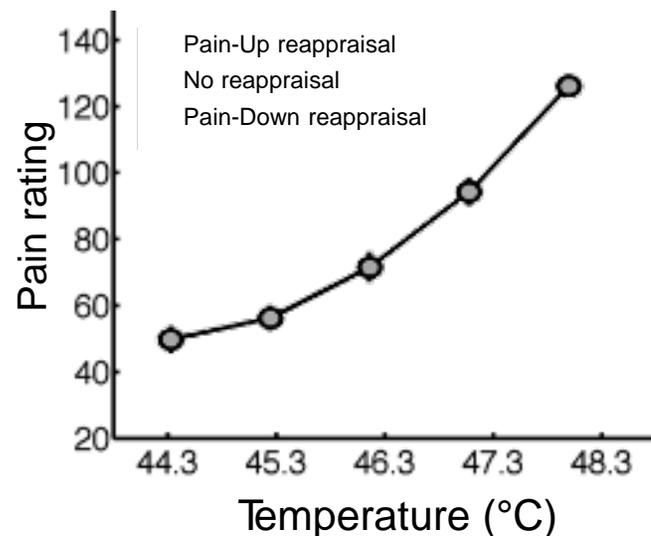
Beyond a single-system view:
Multiple cerebral pathways to pain

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

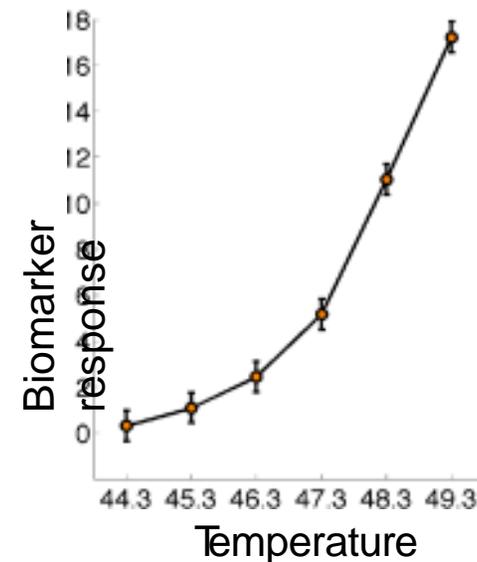
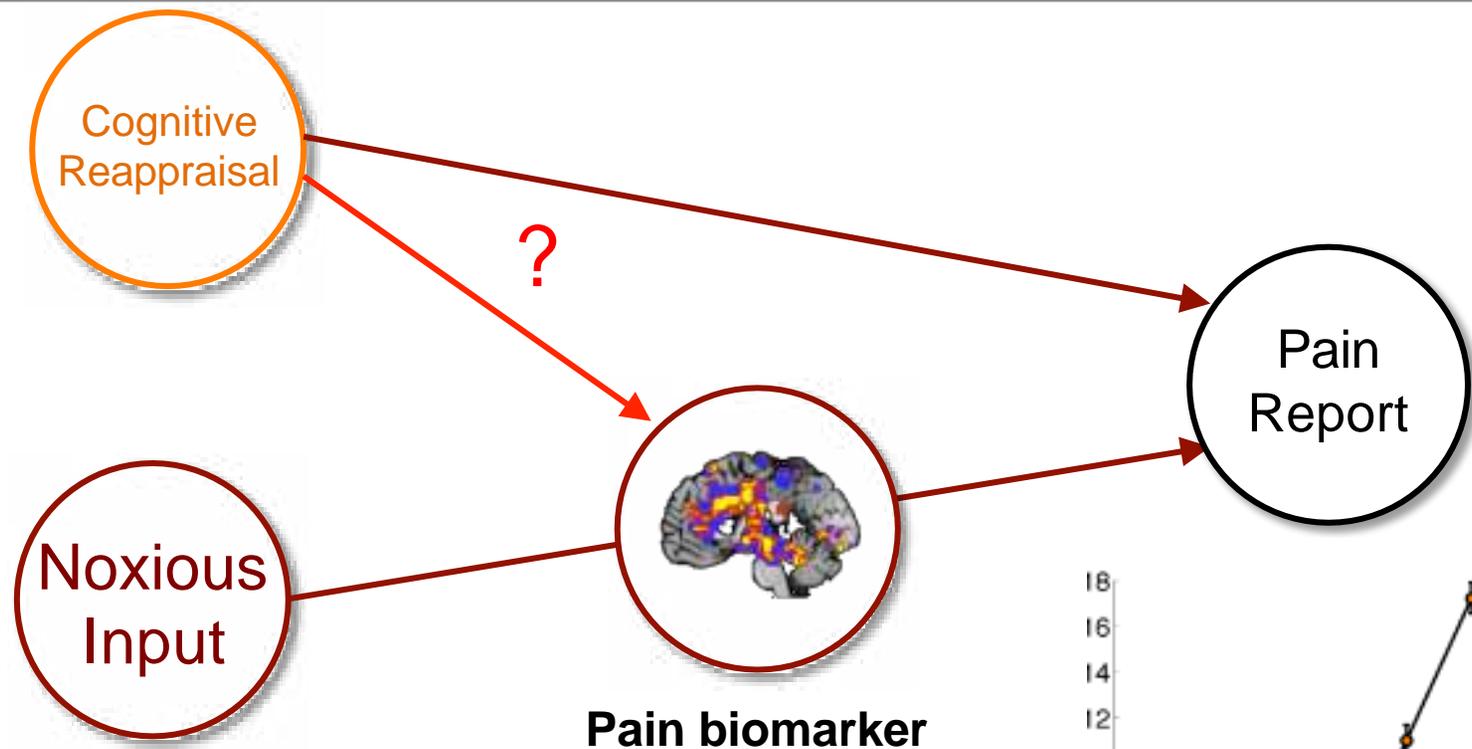


Psychological modulation: Cognitive reappraisal (N = 30)

- “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



Cognitive reappraisal of pain

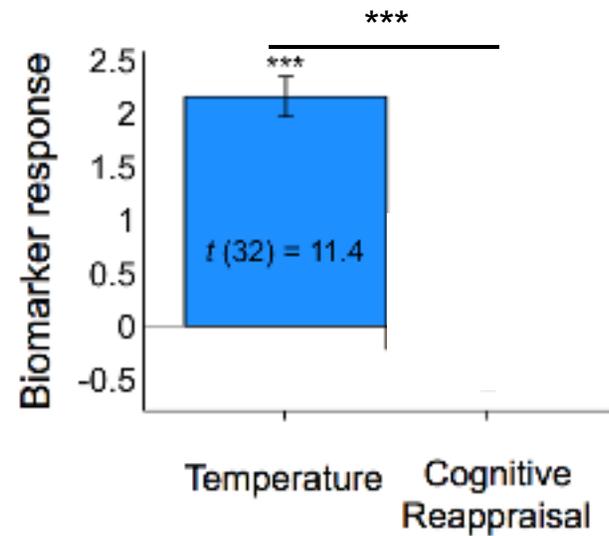
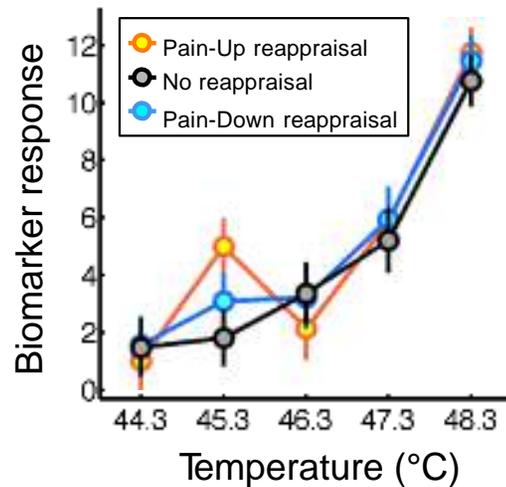
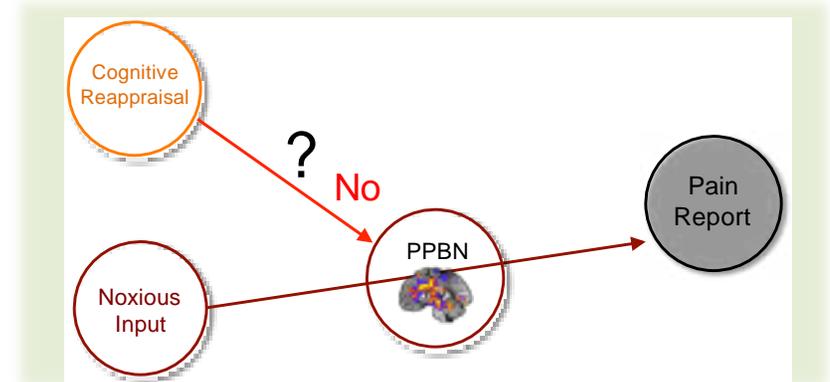


If **yes**: Appraisal may work at a “deep” level

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



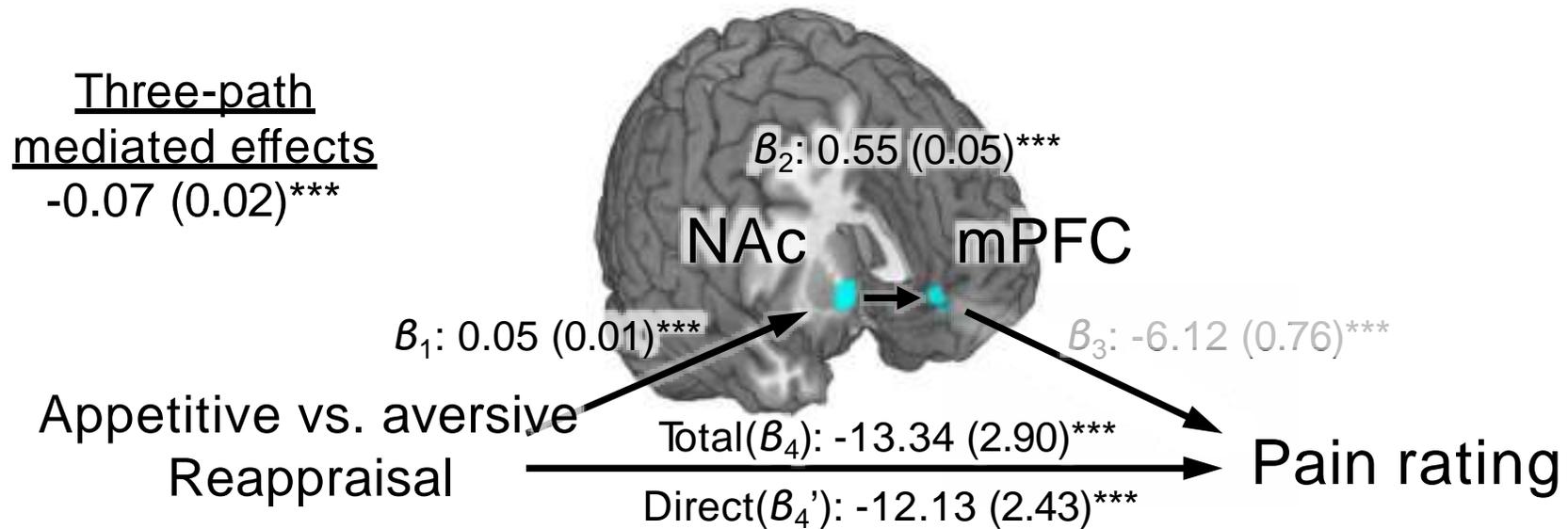
Results: Does **reappraisal** influence the NPS? **No.**



*** $p < .001$

Nucleus Accumbens-Medial PFC:

A second route to pain



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 functional significance, not nociception

Roadmap

Representations
& Biomarkers



Act I:
Blobs



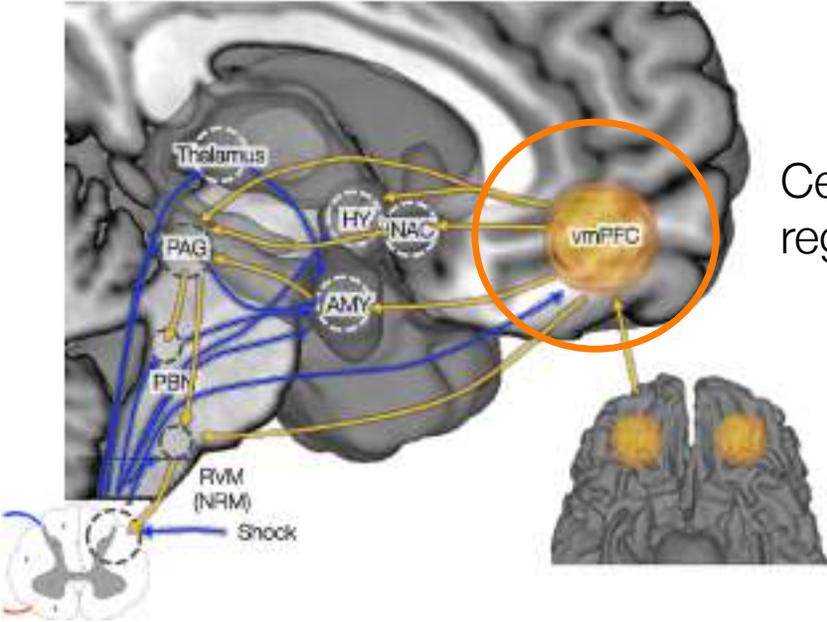
Act II:
Biomarkers



Act III:
Translation



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



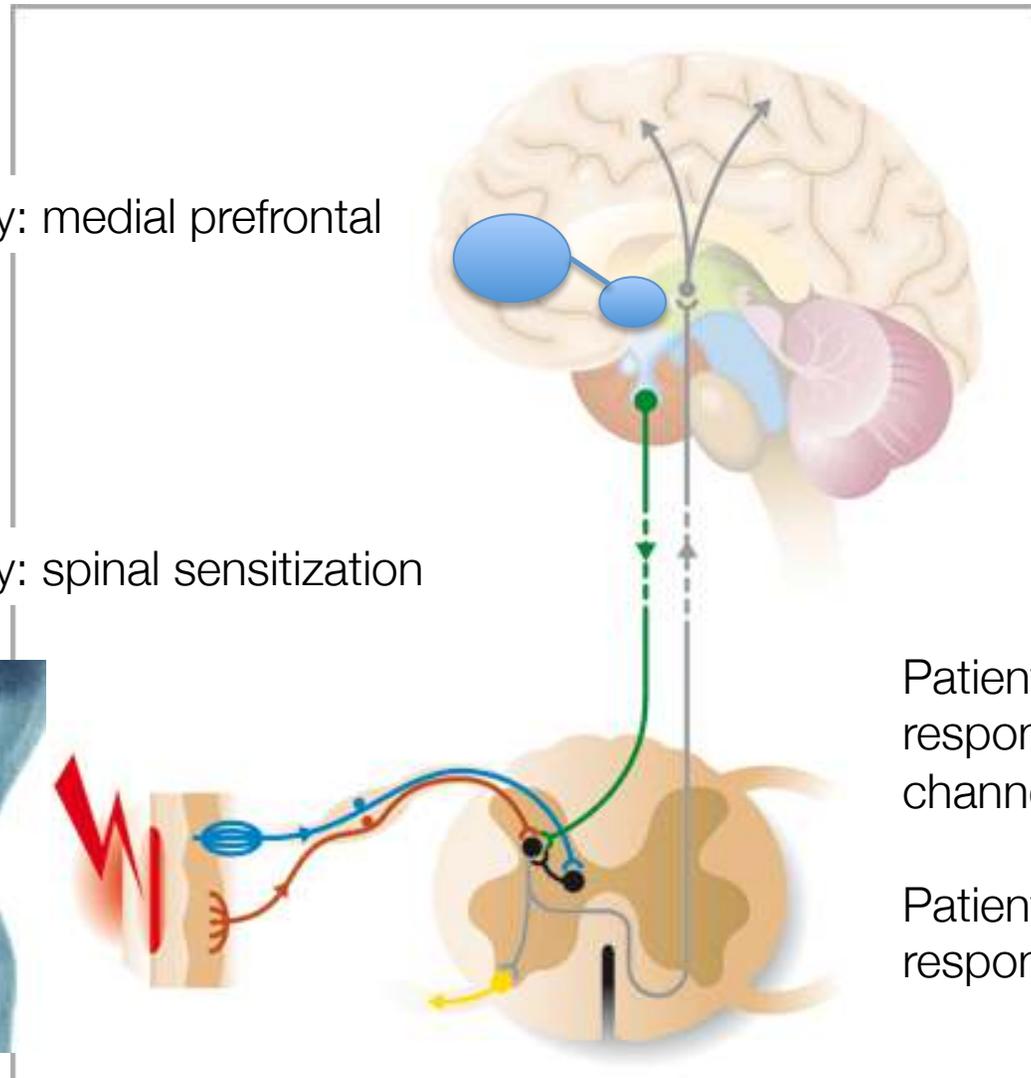
Cerebral generation and regulation of pain



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

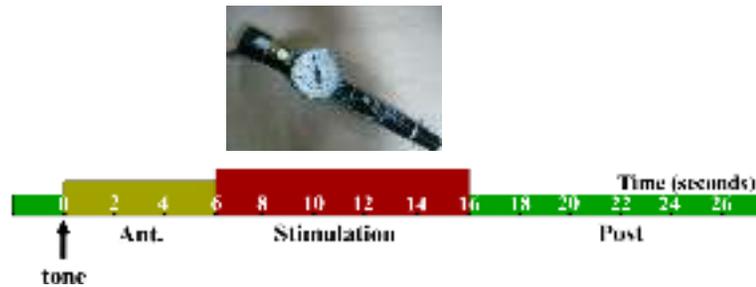
New brain targets for fibromyalgia

Targets

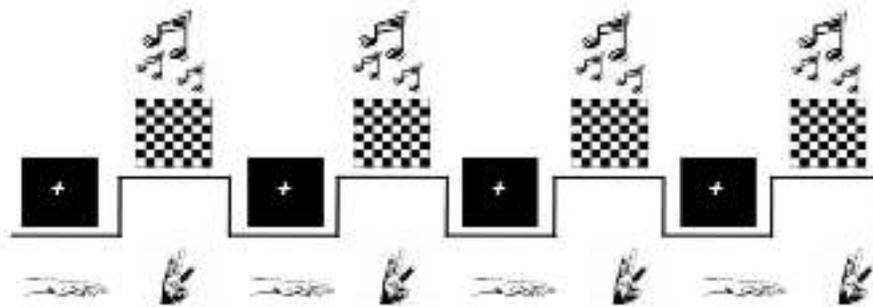


Marina López-Solà

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

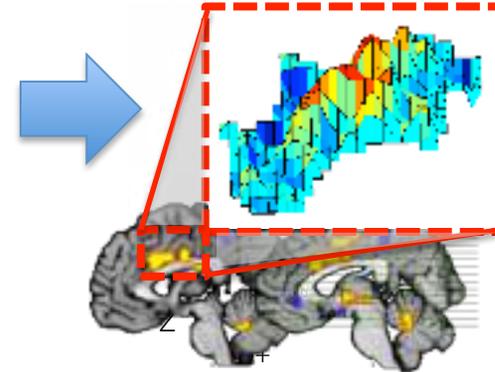


PRESSURE PAIN
(RIGHT THUMB NAIL, 4.5KG/CM²)
6 trials

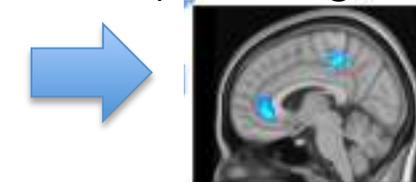


MULTISENSORY-MOTOR PARADIGM

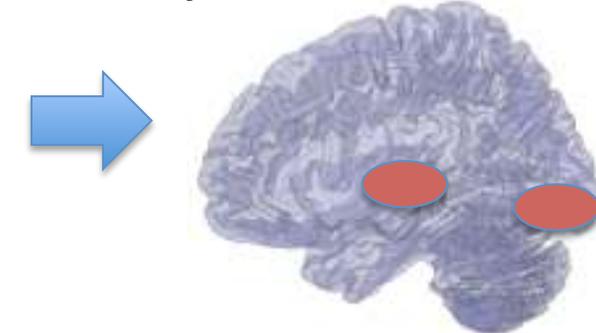
Nociception-positive NPS



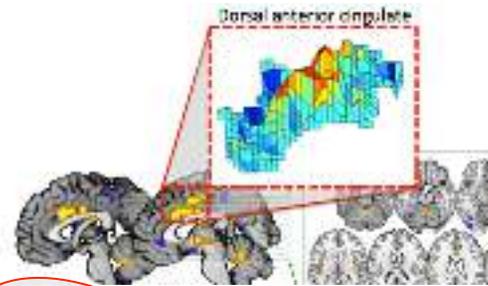
Nociception-negative NPS



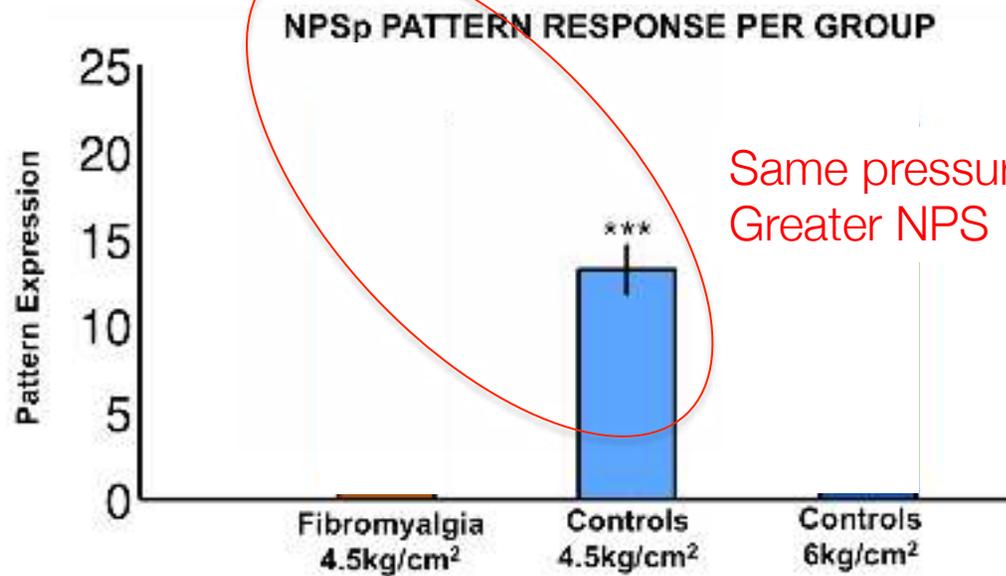
Sensory cortical reductions



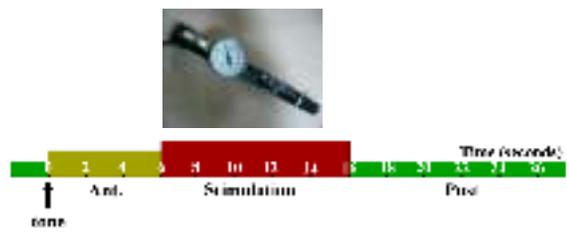
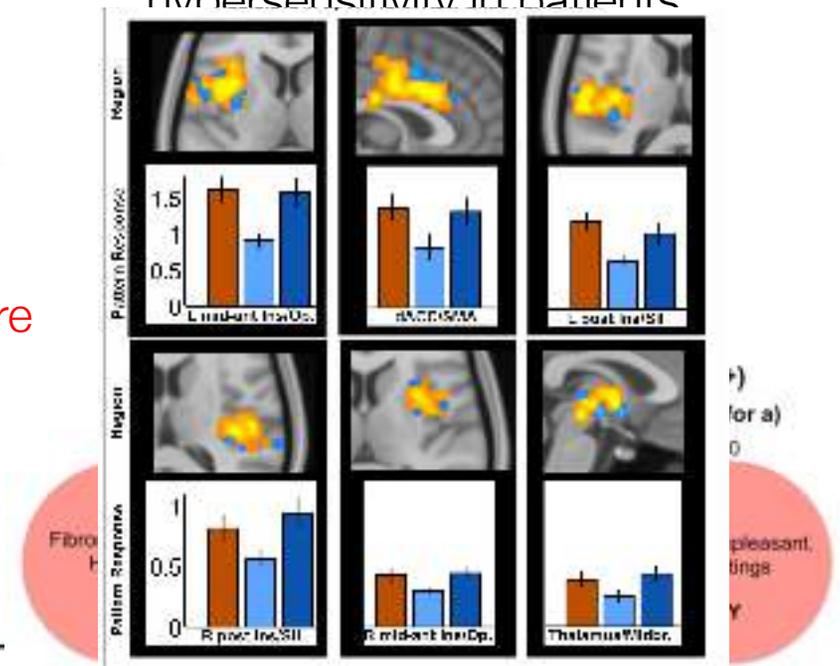
Fibromyalgia: Enhanced "Neurologic Pain Signature" (NPS) responses



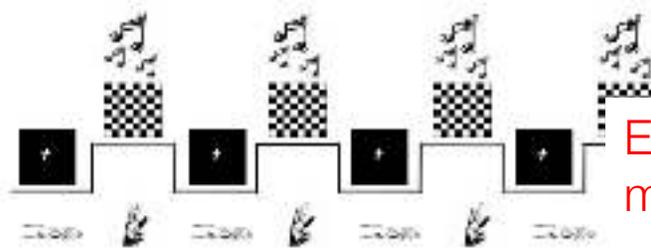
NPS increases expressed in both 'sensory and affective' regions
NPS increases mediate hypersensitivity in patients



Same pressure
Greater NPS

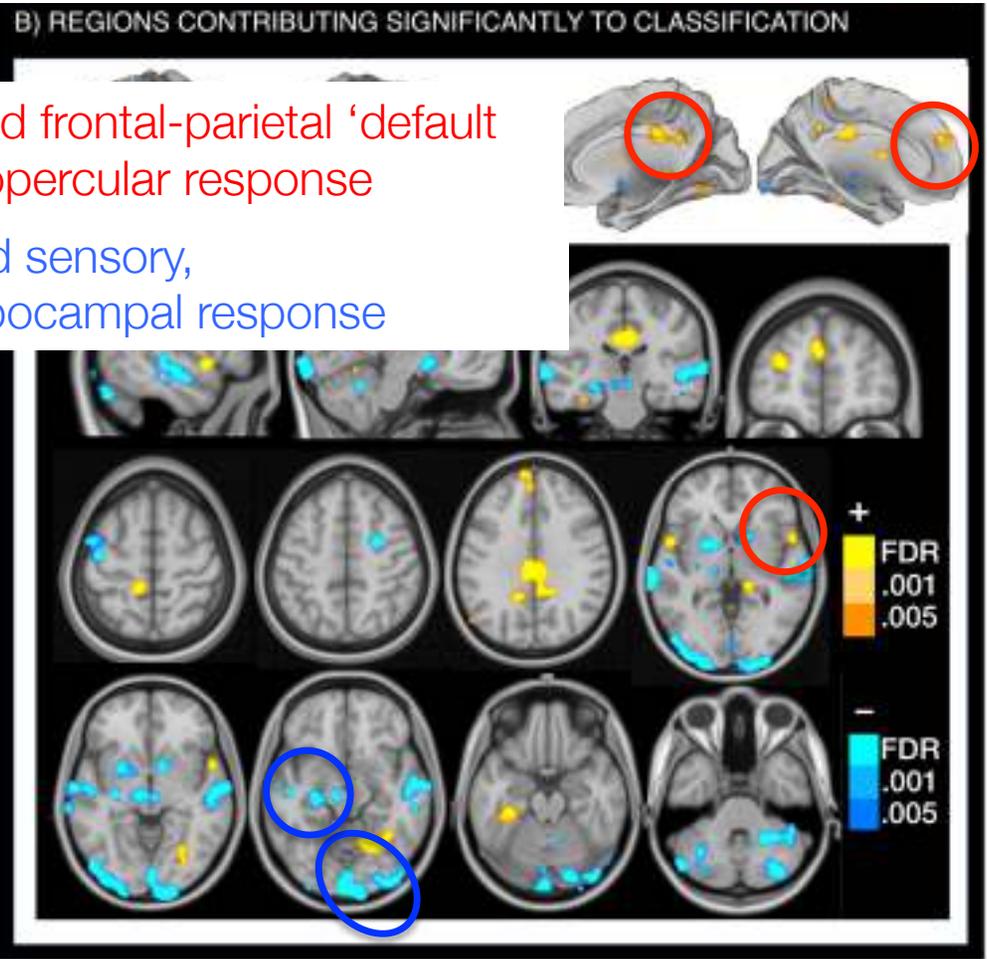


Altered multisensory brain responses predictive of fibromyalgia

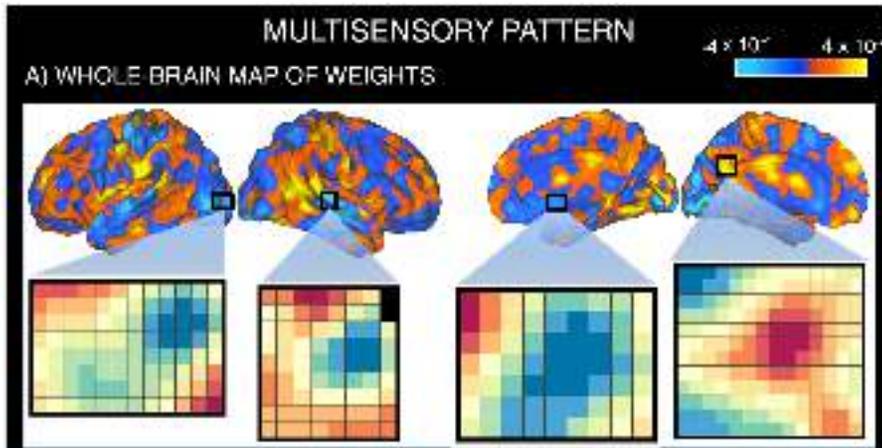


Enhanced frontal-parietal 'default mode', opercular response

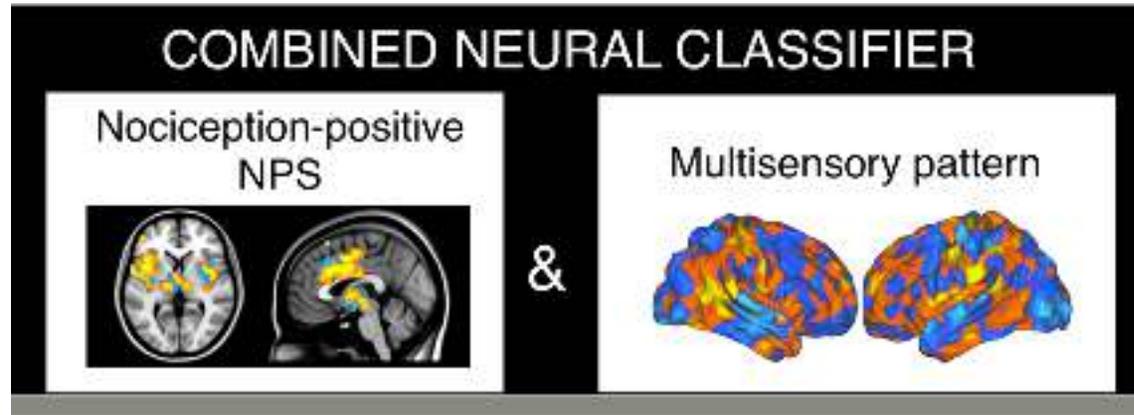
Reduced sensory, parahippocampal response



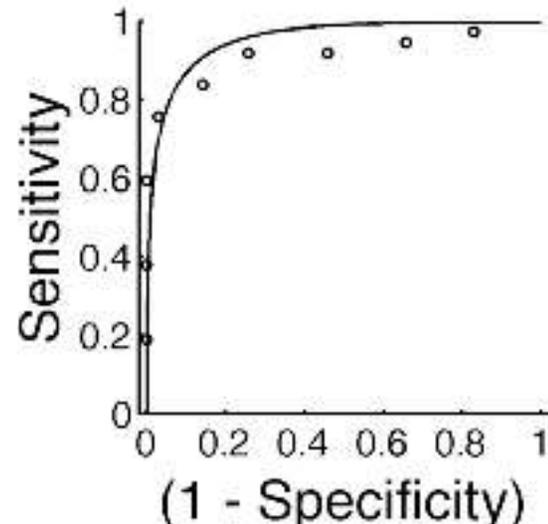
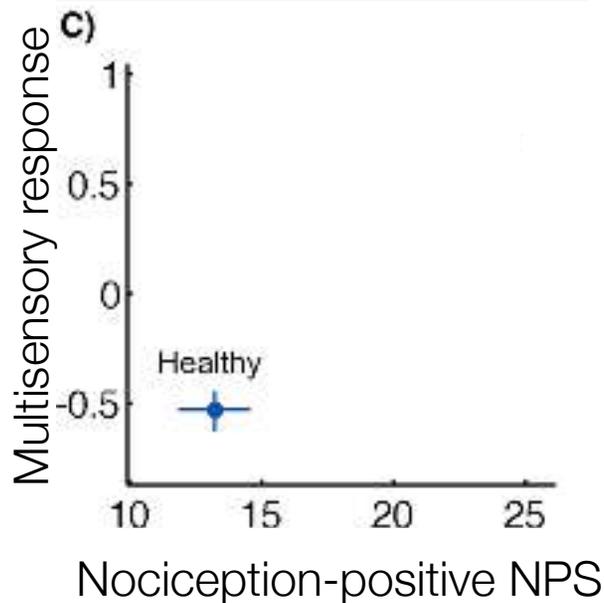
Cross-validated analysis of patterns
Predictive of fibromyalgia status



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



◆ FM patient ◆ Healthy Subject



Fibromyalgia vs. control:
89% accurate

89% sensitivity
86% specificity

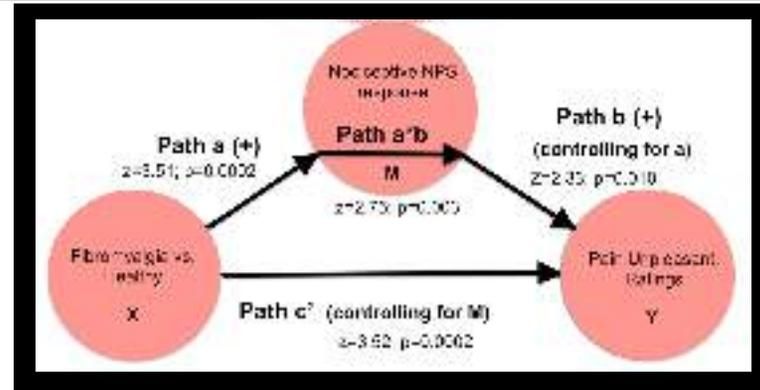
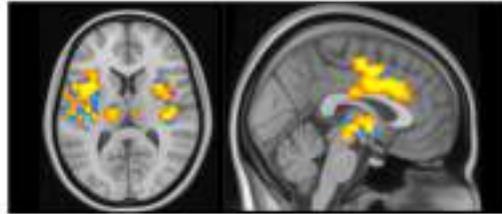
Lopez-Sola et al. Under review

Elements of Fibromyalgia Neural Signature predict different symptoms

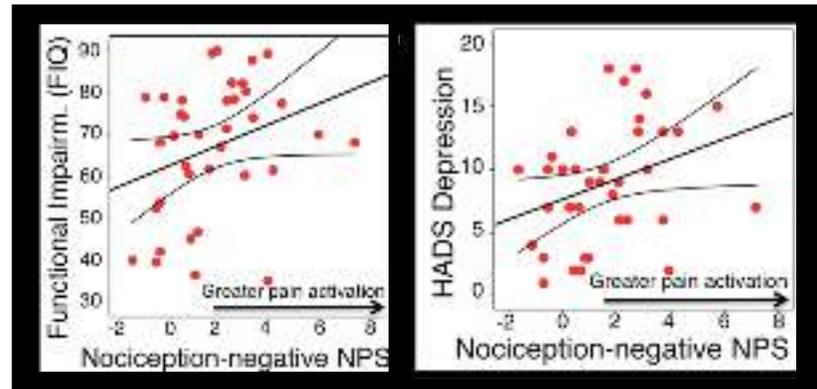
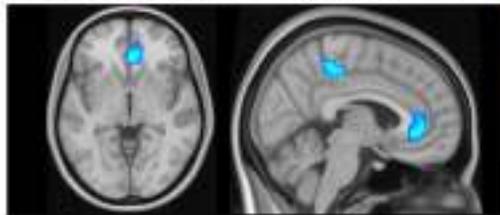


Fibromyalgia

Nociception-positive NPS

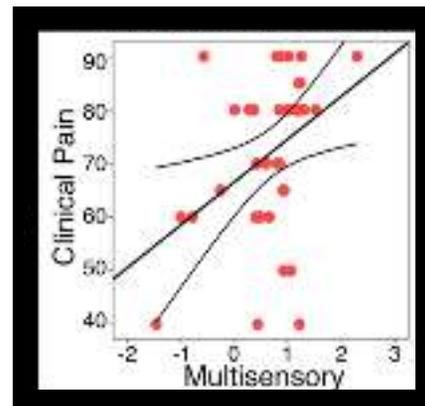
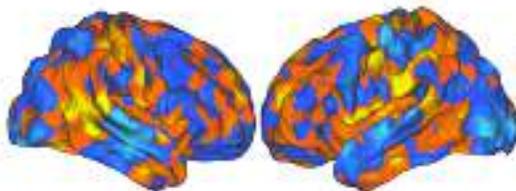


Nociception-negative NPS



d

Multisensory



cal Pain

Cognitive and Affective Neuroscience Lab

University of Colorado at Boulder

Postdocs



Matheiu Roy



Marina López-Solà



Luke Chang



Anjali Krishnan



Leonie Koban



Liz Losin



Marieke Jepma



Hedwig Eisenbarth



Liane Schmidt



Jessica Andrews-Hanna

Graduate Students



Scott Schafer



Jenna Reinin



ChoongWan Woo



Helena Yardley



Yoni Ashar

Staff



Luka Ruzic



Jenifer Sills