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

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What we know about pain

Nociception: Ascending pathways

Pharmacology: Opioids, dopamine, serotonin, hormones, others

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?

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 → Biomarker: Measured pattern → Mental experience

Brain biomarkers are gateways to measures of representations

Sensitive Specific
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
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

Anterior cingulate and insula: ‘pain affect’

Amygdala response to aversive images

“Pain processing” responses to noxious heat
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.** \( P(\text{psych} \mid \text{brain})? \)
   - **Sensitivity**
     We do not know how big the effects of our manipulations are.
     \( P(\text{brain} \mid \text{psychological event})? \)
   - **Specificity**
     We do not know if observed patterns are specific enough to be useful as biomarkers
     \( P(\text{brain} \mid \text{absence of psych})? \)

  e.g., Button et al. 2013 Nat Neurosci; Ioannidis 2005
The problem of replication

Hypothetical correlation with fibromyalgia

Statistical map

Results

A typical ‘significant’ voxel looks like this...

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?

Neurosynth.org
Activation coordinates from ~10,000 studies

Top hits for this pattern:
Noxious, heat, somatosensory, painful, sensation, stimulation, muscle, temperature

Romantic rejection
Kross et al. 2011, PNAS
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

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Act I: Blobs

Act II: Biomarkers
A new approach: Multi-study validation of brain markers

**Development and validation**

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

**Characterize:**
Properties of marker across test conditions

**Replicate:**
Assess generalizability across individuals, studies

**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, Neurologi

**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

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

General
Study 3: Social rejection

$N = 60$ 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?

Test accuracy using biomarker from Study 1

Accuracy

0.5 0.6 0.7 0.8 0.9 1.0

Test Hot vs. Warm Test Reject vs. Friend

Pain biomarker expression

Physical pain

Biomarker response

Wager et al. 2013, NEJM
NPS Characteristics Across Studies

- 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

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

Brain regions include many neurons with different functional properties

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

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

Multivariate pattern classifiers only within dACC

Classification accuracy (cross-validated)

\[ r = -0.04 \]

Pattern correlation:

- 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.

**Graph:**
- **Y-axis:** Biomarker response
- **X-axis:** Temperature (°C)
- **Legend:**
  - Orange: Pain-Up reappraisal
  - Black: No reappraisal
  - Blue: Pain-Down reappraisal

**Statistical Analysis:**
- *p < .001
- t (32) = 11.4

**Diagram:**
- Cognitive reappraisal
- Noxious input
- PPBN
- Pain report
- Question mark: No
Nucleus Accumbens-Medial PFC: A second route to pain

Three-path mediated effects
-0.07 (0.02)***

Appetitive vs. aversive
Reappraisal

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
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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 1 pathology: spinal sensitization

Patient 2 pathology: medial prefrontal

Patient 1 responds to TRP channel blocker

Patient 2 responds to CBT
New brain targets for fibromyalgia

- 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

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

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

Lopez-Sola et al. Under review
Elements of Fibromyalgia Neural Signature predict different symptoms

Nociception-positive NPS

Nociception-negative NPS

Fibromyalgia

Multisensory

Lopez-Sola et al. under review