Neuroimaging of pain and distress: A biomarker development approach

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Current pain measurement technology
Pain reports: Complex determinants

- Prior Beliefs
- Nociception
- Emotional Experience
- Reporting Context
- Communication Decisions
Pain reports: Complex determinants

Social influences on thermal pain

In 200 participants, 94% show effect

“Other people rated this as…”  “Low”   “High”

Same stimulus intensity

If patients report pain relief during a clinical trial, does this reflect long-term therapeutic gains, or short-term effects of the clinical trial context?

Do we know the treatment affected the intended mechanism? Are all treatments that reduce pain reports ‘disease modifying’?
Gene therapy for Parkinson’s disease: A randomized, placebo-controlled trial

Olanow et al. 2015

Problems for clinical trials

Placebo responses in pain trials are growing across years

- Specifically in the U.S. (not Europe)
- Drug responses are not growing, causing more trials to fail
- Possibly related to direct-to-consumer marketing, longer/more involved clinical trials, coupled with subjective pain measures

*Tuttle et al. 2015, Pain*
Biomarkers for pain

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

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

Noxious event  $\rightarrow$ Biomarker: Measured pattern  $\rightarrow$ Subjective experience

Brain biomarkers are *gateways* to measures of representations

**Sensitive Specific**
Biomarkers for pain

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

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

- **Augment** pain reports, don’t replace
- Use them to:
  - **Understand** mechanism, define **targets** and **biotypes**, measure physiological **components**
Why **brain** biomarkers?
Neuroplasticity in chronic pain models above the neck

- Multiple pathological mechanisms: Pain-linked **neuroplasticity** in neurons, glia
- Multiple interventions to reverse or prevent pain

Nerve injury → Persistent pain behavior
Neuroplasticity
Inflammation
Why **brain** biomarkers?

Neuroplasticity in chronic pain models above the neck

- Pain-linked **neuroplasticity** in neurons, glia
- Multiple **interventions** to reverse or prevent pain

For 2006 (review)

Bliss 2016 (review); Zhang 2017; Tan 2017


Metz 2010; Lee 2015; Schwartz 2017

Neugebauer 2003; Carrasquillo 2007

Burgess 2002

Kuner & Flor 2017 (review); McMahon, 1993; Luo, 2014
Why **brain** biomarkers?
Neuroplasticity in chronic pain models above the neck

- Pain-linked *neuroplasticity* in neurons, glia
- Multiple *interventions* to reverse or prevent pain

**Which mechanisms from animal studies are relevant in humans?**
- Need human brain studies

**What is the locus of pathology in a given human patient?**
- Essential for matching treatments to disease mechanisms
Why **brain** biomarkers?
Neuroplasticity in chronic pain models above the neck

- Pain-linked **neuroplasticity** in neurons, glia
- **Multiple interventions** to reverse or prevent pain

**Multiple brain targets**
- Nociceptive pain (e.g., spino-thalamo-cortical)
- Fear and avoidance (e.g., PBN-amygdala)
- Motivation, anhedonia (e.g., vmPFC-accumbens)

The vast majority of pain drugs act via these circuits
Use cases

For clinical trialists and treatment design

Penetrance
Pharmacodynamics
Efficacy
Mechanism

For patients and clinicians

“What is wrong with me?”
Risk and prevention
‘Precision’ interventions

Duff et al. 2015, Sci Trans Med
Use cases: “Stop” vs. “Go” decisions in early trials

For clinical trialists and treatment design

Penetrance
Pharmacodynamics
Efficacy
Mechanism

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**Detailed Table**

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug (reference/clinicaltrials.gov ID)</th>
<th>Patient condition</th>
<th>n subjects</th>
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<td>a</td>
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<td>b</td>
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<td>Fibromyalgia</td>
<td>23</td>
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**References**

Duff et al. 2015, Sci Trans Med

See also Borsook, Hargreaves et al. 2006, 2011
Use cases: “Stop” vs. “Go” decisions in early trials

For clinical trialists and treatment design

Pharmacodynamics: Reliable drug vs. placebo discrimination?

Brain classifier: Yellow = more activity with drug, blue less

56 – 92% hit rate for known drugs; 7/8 “Go” decisions for drugs, 2/6 “Go” for non-drug controls

Penetrance
Pharmacodynamics
Efficacy
Mechanism

Duff et al. 2015, Sci Trans Med

See also Borsook, Hargreaves et al. 2006, 2011
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For clinical trialists and treatment design

Penetrance
Pharmacodynamics
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Duff et al. 2015, Sci Trans Med

Discovery and repurposing

• Drug effects are complex
• Multiple systems
• Possible to assess brain similarity across drugs, infer new uses?
Criteria for brain-based measures

Criteria for establishing biomarkers:

- Precisely defined ‘signatures’
- Replicated and applied without adjustment across laboratories, pain variants, and populations
- Sensitive and specific to pain

Measures of pain using fMRI

Identify a ‘signature’ for pain

- Training sample
- Pain Response, Weights * data
- Minimize error
- Signature
- Best weights

The ‘Neurologic Pain Signature’

Wager et al. 2013, NEJM
Measures of pain using fMRI

Apply the signature to new test data

New sample → Signature * Data = Response

The ‘Neurologic Pain Signature’

Chang et al. 2015
Woo et al. 2015
Krishnan et al. 2016
Vachon-Presseau et al. 2016
Becker et al. 2016
Ma et al. 2016
Lopez-Sola et al. 2016
Woo et al. in revision
van Oudenhove et al. in prep
Kragel et al. in prep
Zunhammer et al. in prep

Noxious heat

Krishnan et al. 2016, eLife
Measures of pain: Sensitivity and specificity of the NPS

Sharing and prospective testing → specificity, generalizability, construct validation

Not activated by (specificity)
- Aversive images
- Social rejection
- Observed pain
- Pain anticipation
- Nausea
- Itch
- Cognitive demand
- Pain recall
- Warmth

Activated by (sensitivity)
- Noxious heat
- Electric shock
- Noxious pressure
- Gastric distention
- Esophageal distention
- Rectal distention
- Vaginal pressure

Sub-threshold:
- Breathlessness
- Aversive taste

Light colors: Preliminary results
Dark colors: Published results

Generalization: Pain and placebo meta-analysis


Zunhammer, Bingel et al. in prep
Placebo treatment: Strong effects on pain

Placebo significantly reduces pain in all studies.

Average effect size: \( d = -0.65 \)
Generalization: NPS responds to diverse types of evoked pain

Zunhammer, Bingel et al. in prep

Generalization: N = 600 across diverse population

Electrical, heat, laser, mechanical

Average effect size: $d = 2.18$
Placebo treatment: No (or little) effect on the NPS

The “Neurologic Pain Signature” is insensitive to placebo

Average effect size $d = -0.07$

Points to contributions from other systems

Zunhammer, Bingel et al. in prep

<table>
<thead>
<tr>
<th>Effect, 95% CI</th>
<th>n</th>
<th>Weight</th>
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</table>

Total effect (95% CI): $z=-1.96$, $p=0.050$

Heterogeneity: $Chi^2(19)=16.89$, $p=0.597$

$\tau^2=0.00$; $I^2=0.00\%$
Use cases

For clinical trialists and treatment design

Penetration
Pharmacodynamics
Efficacy
Mechanism

Intermediate outcomes that are sensitive to pain, but not placebo

Duff et al. 2015, Sci Trans Med
Multiple systems

- Brain measures do not “measure pain”, because pain is subjective
- They measure **neurophysiological systems**, linked to pain
- There are **multiple brain targets** for different facets of pain experience and behavior

1. **Nociceptive pain system(s)**
2. **Emotion, pain avoidance systems**

See Woo et al. 2017, Nature Comms
Human evidence on pain chronification: Shift from classic nociceptive systems to ‘emotional’ ones.

Back pain persists

One year later

Meta-analysis of basic studies

Yarkoni et al. 2011, Neurosynth.org

Apkarian et al. 2011; Baliki et al. 2012; Geha et al. 2008; Hashmi et al. 2013
Human evidence on pain chronification: Shift from classic nociceptive systems to ‘emotional’ ones

Optogenetic activation of vmPFC (prelimbic)-accumbens pathway reduces allodynia and depression-like behavior after spared nerve injury

vmPFC-accumbens connectivity predicts development of chronic back pain 1 year later

Baliki et al. 2012 Nat Neuro; Lee et al. 2015 J Neurosci
A system for valuation, motivated action, and value-driven learning

vmPFC: a circuit for suffering:
- **Learned avoidance**
- **Valuation** of pain
- **Drug craving**
- Relationship of pain with ‘self’
- independent of nociception

**Cognitive interventions**

168 study-level maps, 3513 participants
*Kober, MacLean, & Wager, in prep*

Roy et al. 2014, Nat Neurosci

Woo et al. 2015, Plos Biol
Future treatment decisions? Brain measures for multiple potential causes of pain

1. Nociceptive pain system(s)
2. Pain avoidance systems

Patient stratification: Which treatment is best?

Pathology
Peripheral/spinal
Neuroplasticity in avoidance systems

Measure
Nociceptive pain systems (NPS)
Frontostriatal connectivity

Treatment
Peripheral/spinal Surgery, novel drugs
Central Biobehavioral, CNS drugs
Use cases

For clinical trialists and treatment design

Penetrance
Pharmacodynamics

Efficacy
Mechanism

Stratification

Intermediate outcomes that are sensitive to pain, but not placebo
Select patients likely to benefit

Duff et al. 2015, Sci Trans Med
Use cases

For clinical trialists and treatment design:
- Penetrance
- Pharmacodynamics
- Efficacy
- Mechanism
- Stratification

For patients and clinicians:
- “What is wrong with me?”
- Risk and prevention
- ‘Precision’ interventions
A case study

- ~65 yr old male
- Back strain while loading a suitcase onto an airport conveyor belt

- Two weeks later, lower back pain and spasm, left mid-buttock area.
- Disk herniation suspected, but normal MRIs of spine, pelvis, hip

- 5 months of twice-daily physical therapy, acupuncture, deep tissue massage, posture. No pain relief.

- At 7 mos, pain migrates to left ischial tuberosity. Loss of left hamstring strength. Radiating pain in the left leg.
- Nerve entrapment suspected, but injections of steroids and anesthetics ineffective.

“As time went on and my symptoms and limitations worsened, various clinicians offered suggestions...some wondered whether the pain was becoming “functional.” Others strongly believed that it was probably neuropathic in origin, but without a defined trigger... I began having symptoms of clinical depression...”
A case study

Philip Pizzo, M.D.
Former Dean and David and Susan Heckerman Professor of Pediatrics and of Microbiology and Immunology
Stanford University School of Medicine

Biomarkers for pain – multiple outcomes

**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 → Cognitive impairment

Fear and avoidance

Long-term outcomes (disability)
Biomarkers for pain – scalable, cost-effective measures

See work by: M. Bartlett, Picard, Treede/DFNS, Saab, Geuter et al., Dworkin (IMMPACT)
Biomarkers for pain – **interventions** for prevention and treatment

Pain
Cognitive impairment
Fear and avoidance
Long-term outcomes (disability)

Neuroimaging can provide **neurophysiological targets** for assessing and comparing interventions

Behavioral health (sleep, exercise)
Pharmacotherapy
Physiotherapy
Psychotherapy
Neurofeedback
Neuromodulation
Catalan government
Mind, Brain, Body and Health Network

Code: shared on https://github.com/canlab . Papers, etc. : wagerlab.colorado.edu