Pain Biomarkers:
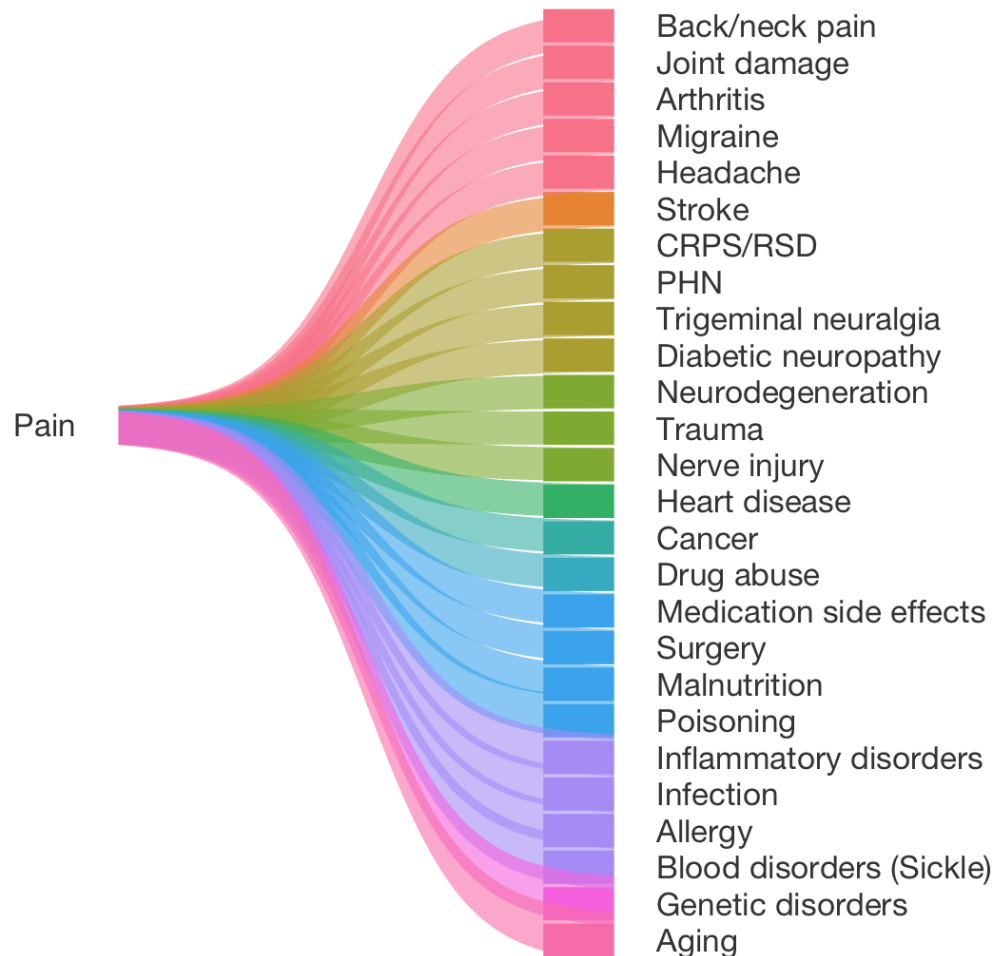## Current progress and challenges for the future

Tor D. Wager

Department of Psychology and Neuroscience
And the Institute for Cognitive Science

The University of Colorado, Boulder

Pain: A root problem

A primary reason people seek medical attention, and primary impact on wellbeing and function

Pain

- Back/neck pain
- Joint damage
- Arthritis
- Migraine
- Headache
- Stroke
- CRPS/RSD
- PHN
- Trigeminal neuralgia
- Diabetic neuropathy
- Neurodegeneration
- Trauma
- Nerve injury
- Heart disease
- Cancer
- Drug abuse
- Medication side effects
- Surgery
- Malnutrition
- Poisoning
- Inflammatory disorders
- Infection
- Allergy
- Blood disorders (Sickle)
- Genetic disorders
- Aging

edicine 2011: Relieving chronic pain in America

Pain: A root problem

100 million adults
suffer from chronic pain in the U.S.

Legal issues:

- Disability status, V.A. benefits
- Workers' compensation
- Tort claims (esp. in the US)
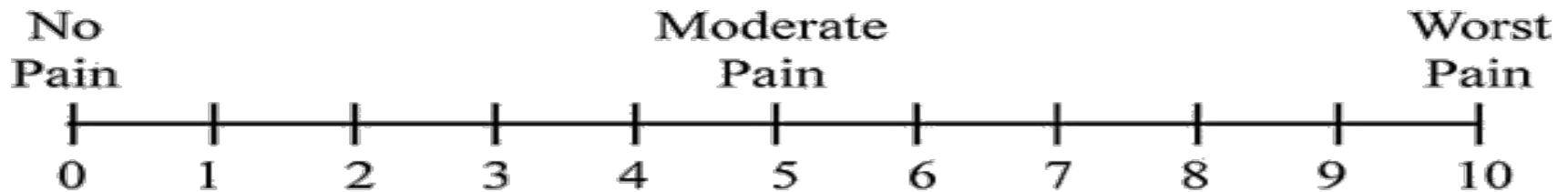- Insurance, Medicare coverage for treatment

Depends on:

- Presence and severity of pain
- Cause of pain in the brain/body
- Personal predispositions ('thin skull')

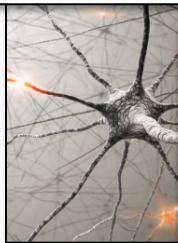# Pain reports: Complex determinants

Pain reports: Complex determinants

No Pain   Moderate Pain   Worst Pain

0   1   2   3   4   5   6   7   8   9   10
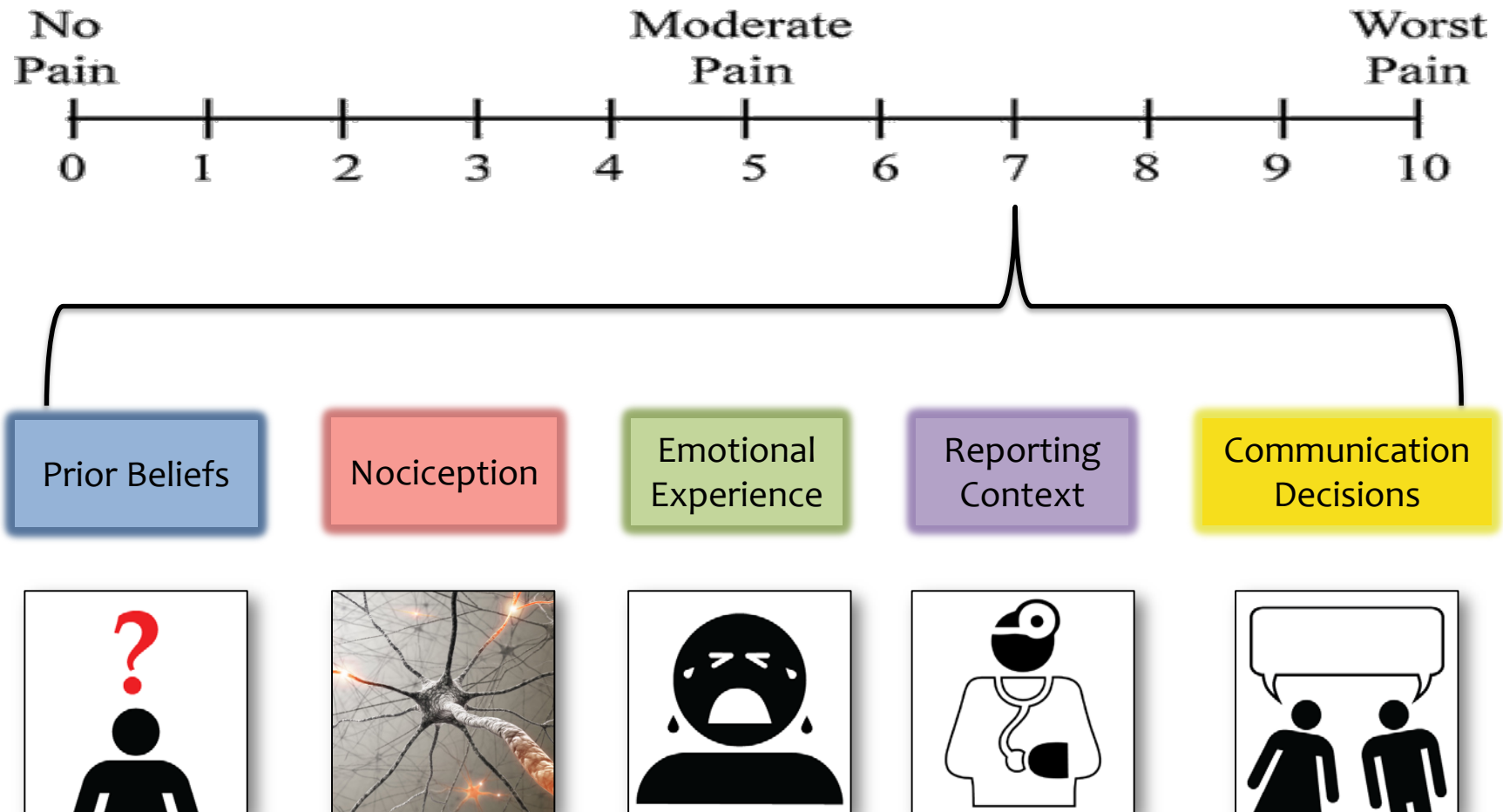
The New York Times

SundayReview | The Opinion Pages

The Gender Gap in Pain

By LAURIE EDWARDS
Published: March 16, 2013
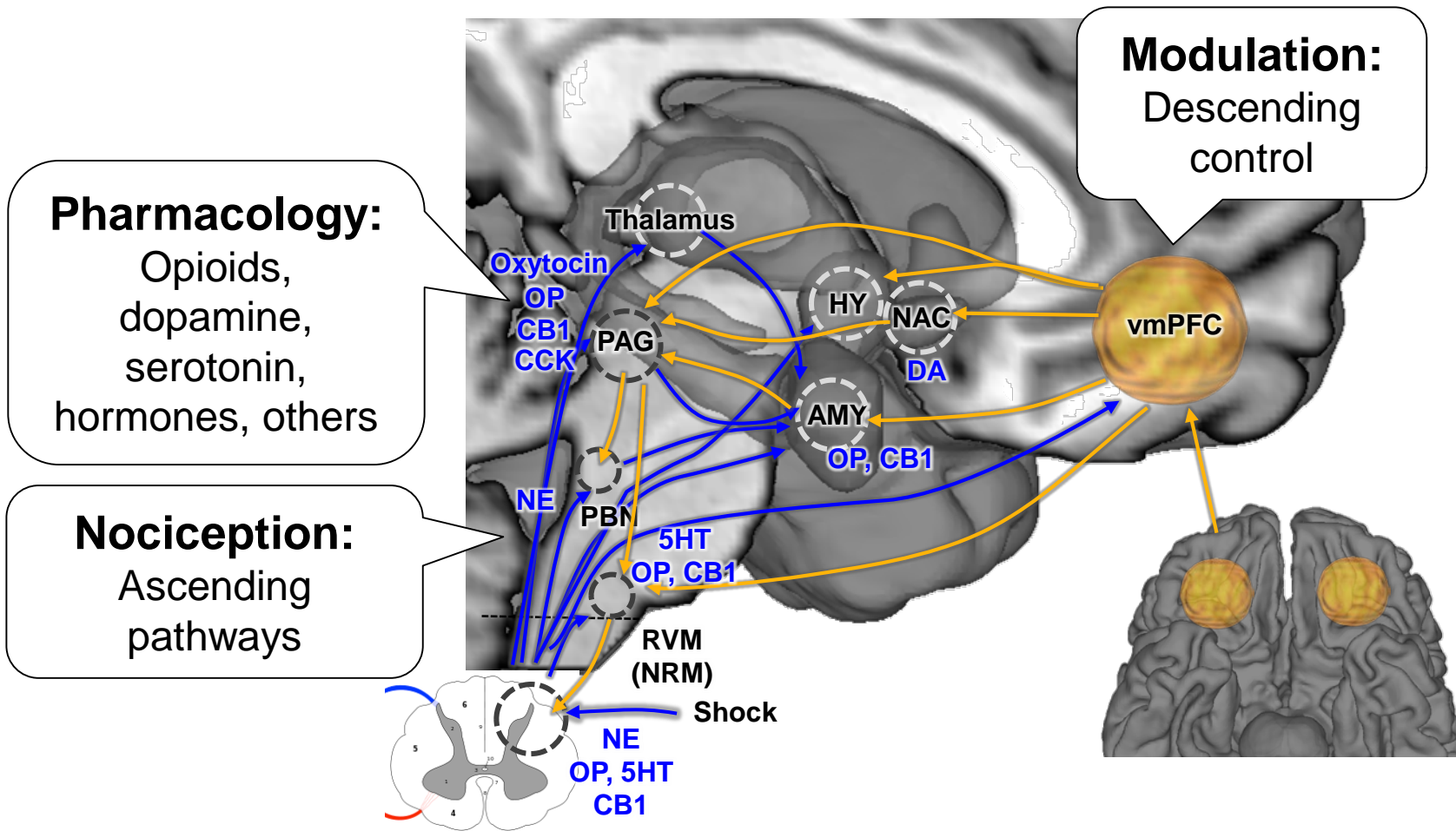
...ting ...ext

Communication Decisions

?

Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites

Kelly M. Hoffman[a,1], Sophie Trawalter[a], Jordan R. Axt[a], and M. Norman Oliver[b,c]

The neurophysiology of pain

Pharmacology:
Opioids, dopamine, serotonin, hormones, others

Nociception:
Ascending pathways

Modulation:
Descending control

Oxytocin
OP
CB1
CCK

Thalamus

PAG

HY   NAC
DA

AMY
OP, CB1

NE

PBN

5HT
OP, CB1

RVM
(NRM)

Shock

NE
OP, 5HT
CB1

vmPFC

"Sensory, Affective, and Evaluative components" (e.g., Casey & Melzack, 1968)

Wager & Atlas, 2015, Nat Rev Neuro; Fields 2004; Heinricher & Fields 2013; Altier & Stewart 1999; Willis & Westlund 1997; Bushnell 2013 Nat Rev Neuro; Tracey 2008

Pain biomarkers

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

Sensitive
Specific
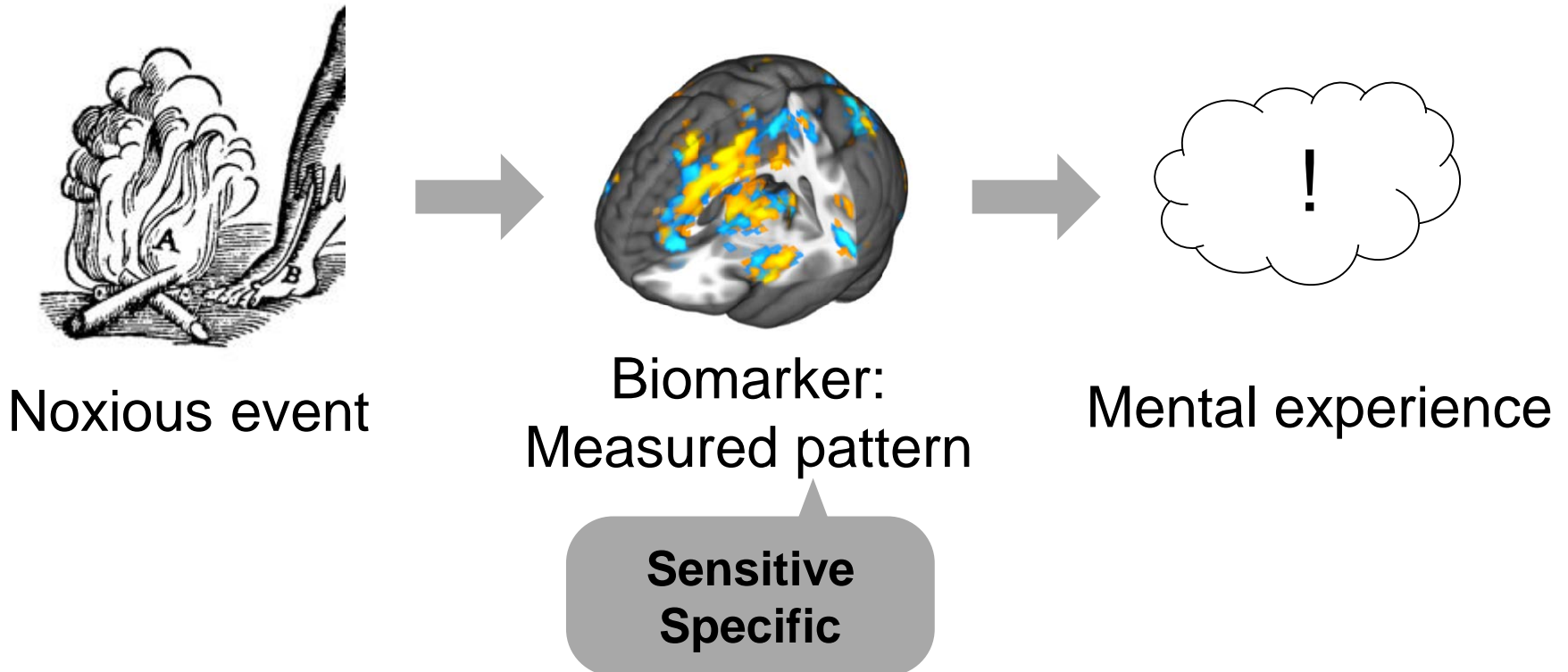
Standards of evidence

Pain in court: A cautionary tale

Carl Koch: Arm burned by a glob of molten asphalt in 2005, reported chronic pain later and sued his former employer, Western Emulsions in Tucson, Arizona, for damages
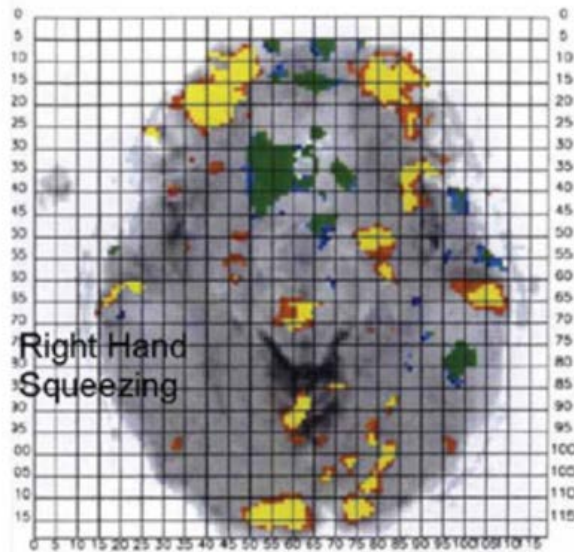
Reardon 2015, Nature; Davis, 2016 ABA Journal

Pain in court: A cautionary tale

Carl Koch: Arm burned by a glob of molten asphalt in 2005, reported chronic pain later and sued his former employer, Western Emulsions in Tucson, Arizona, for damages

Functional magnetic resonance imaging. Carl Koch's brain scan nearly two years after the accident shows that he experienced extreme pain when moving the injured side of his body, according to neuroscience specialist Joy Hirsch.

Hirsch: Brushing and squeeze-ball on affected body site "consistent with" pain claims. Publications not necessary; sensory mapping already validated

Judge Chon-Lopez: Testimony admitted, based on "a combination of generally accepted scientific principles (fMRI) and inductive reasoning from her own research." Frye does not apply.

Case settled for $800,000 without testimony.

Reardon 2015, Nature; Davis, 2016 ABA Journal

Inferring what a brain pattern measures

What does this map *mean*?

Neuros
Acti
from
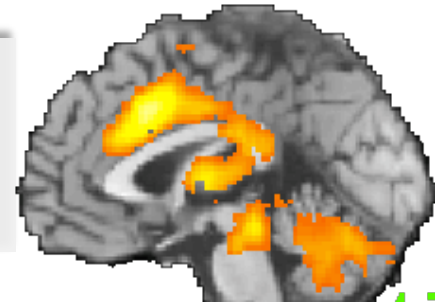
Romantic rejection
Kross et al. 2011, PNAS

or this pattern:
xious, heat, somatosensory, painful, sensation, stimulation, muscle, temperature
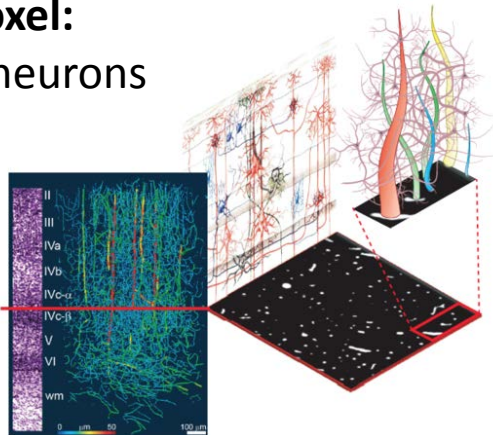
The problem of specificity

Anterior cingulate and insula have often been used as markers for pain – but they are not specific for pain or any type of affect.
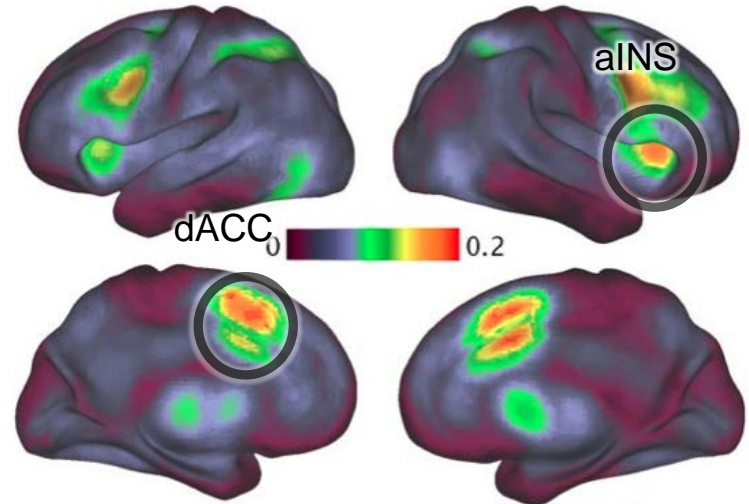
Voxels are mixed measures of multiple neuronal populations
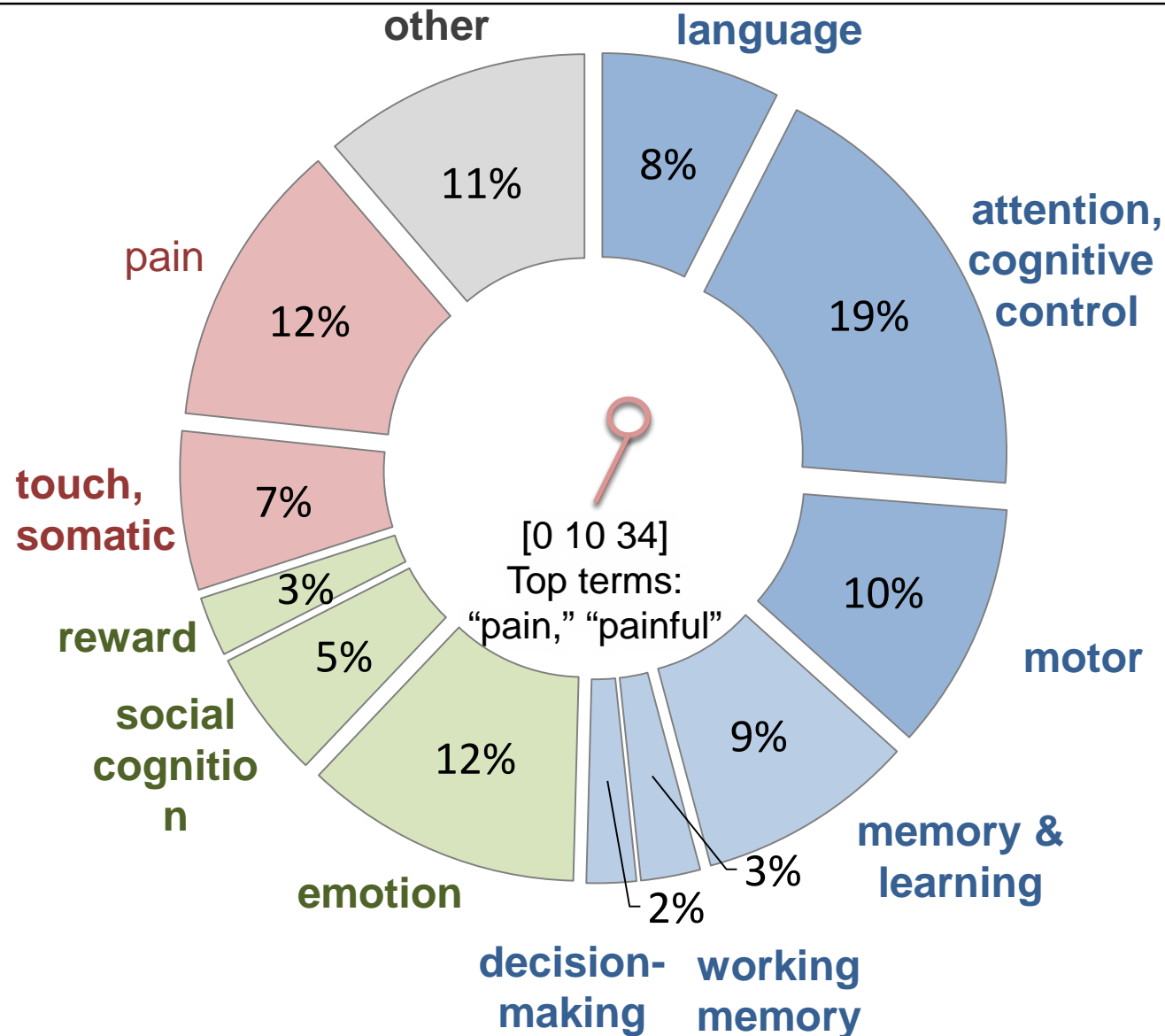
One voxel:
5.5 M neurons

Logothetis, Nature, 2008

Base rate, P(activation) across

3489 neuroimaging studies Yarkoni et al. (2012)

aINS

dACC 0 0.2

Yarkoni, Poldrack, Van Essen, & Wager, 2011, Nature Methods; See Poldrack 2006; Sarter et al. 1996 cf. Lieberman and Eisenberger, 2016; Wager et al. 2016 PNAS
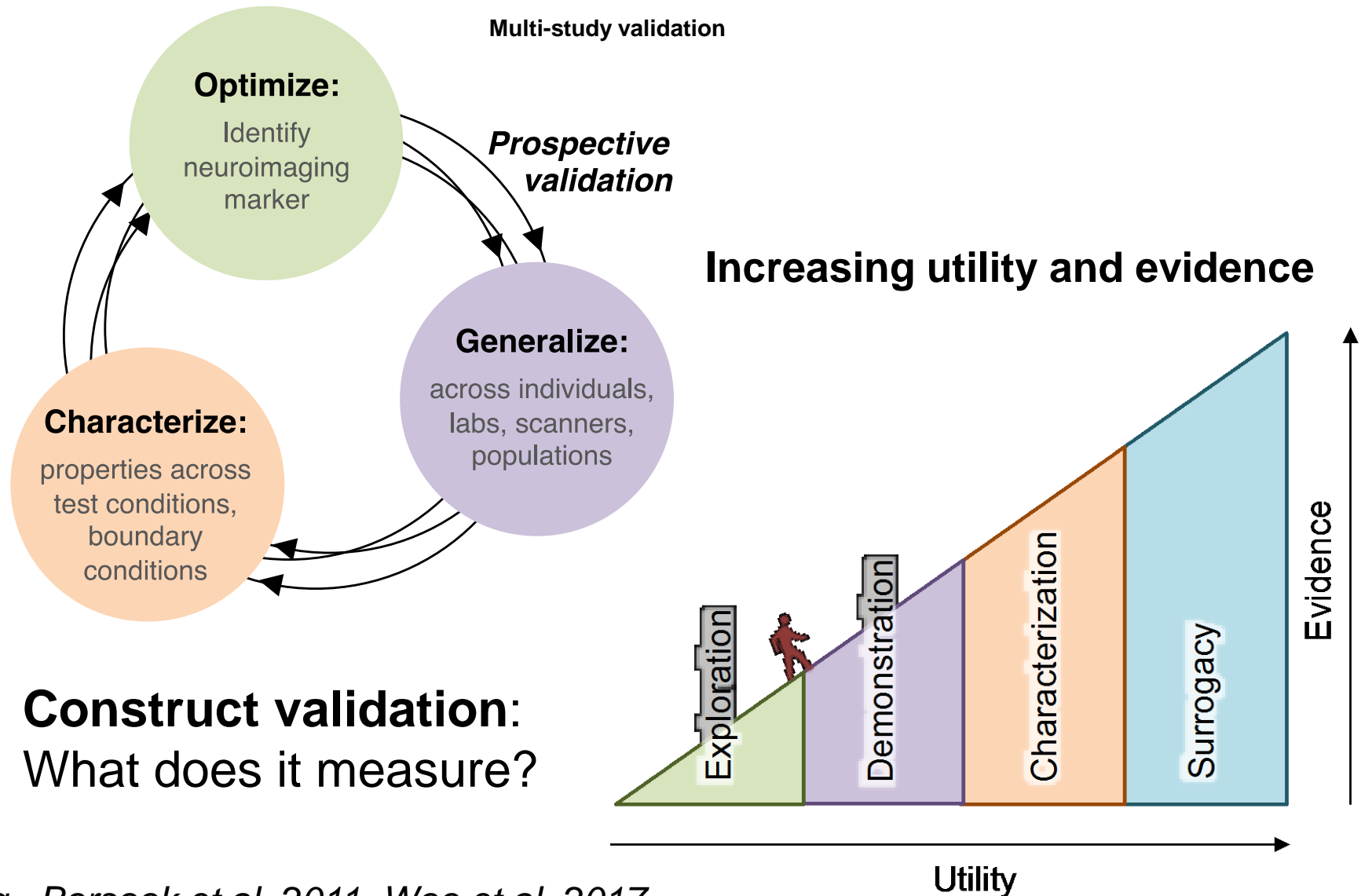
Anterior cingulate activation across 250 studies

other — 11%
language — 8%
attention, cognitive control — 19%
motor — 10%
memory & learning — 9%
working memory — 3%
decision-making — 2%
emotion — 12%
social cognition — 5%
reward — 3%
touch, somatic — 7%
pain — 12%

[0 10 34]
Top terms: "pain," "painful"

Wager, Pain Research Forum; Wager et al., 2016, PNAS

CONSENSUS
STATEMENT

Criteria for establishing biomarkers:

- Precisely defined measures (biomarkers)
- Replicated and applied without adjustment across across laboratories, pain variants, and populations
- Sensitive and specific to pain
- Generalizable to patient group and test setting

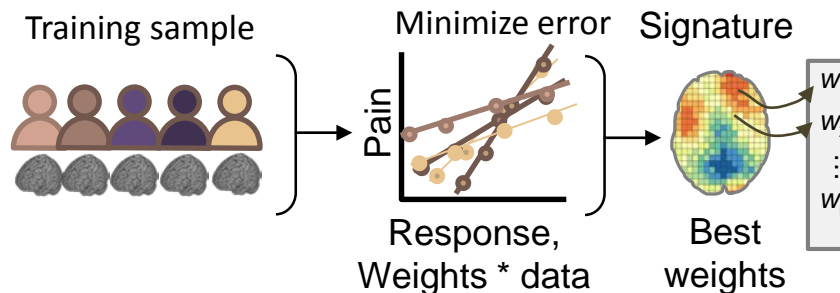*Woo et al. 2017 Nature Neurosci; Davis et al. 2017 Nat. Rev. Neurology*

A biomarker development framework

Multi-study validation

Optimize: Identify neuroimaging marker

Prospective validation

Generalize: across individuals, labs, scanners, populations

Characterize: properties across test conditions, boundary conditions

Increasing utility and evidence

Exploration · Demonstration · Characterization · Surrogacy

Evidence

Utility

Construct validation: What does it measure?

e.g., Borsook et al. 2011, Woo et al. 2017

Identify a 'signature' for pain

Training sample   Minimize error   Signature

Pain

Response,
Weights * data

Best
weights

w_1
w_2
$\vdots$
w_n

The 'Neurologic
Pain Signature'

Wager et al. 2013, NEJM

Dorsal anterior cingulate

Somatosensory
SII

Post. insula

Left   Right

x = -0   x = 44

Insula

medial

ventrolateral

Thalamus
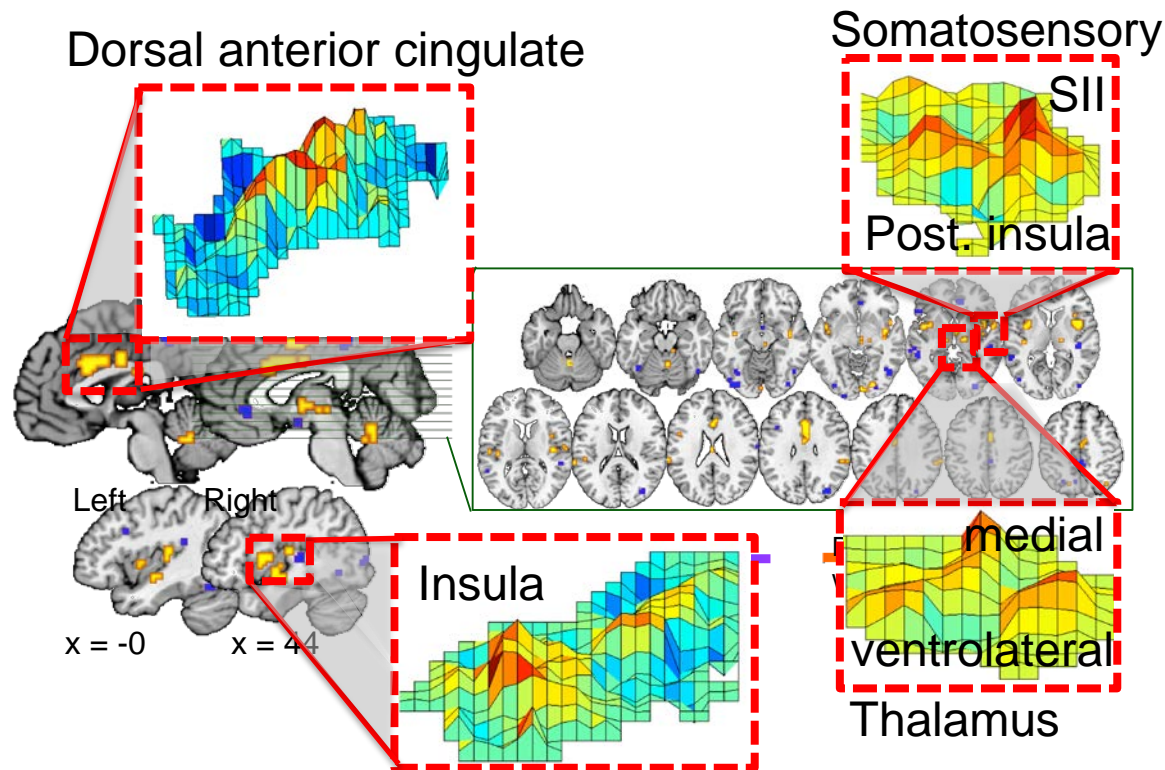
Measures of pain using fMRI

Apply the signature to new test data

New sample   Signature   Data

sum [*] = Response
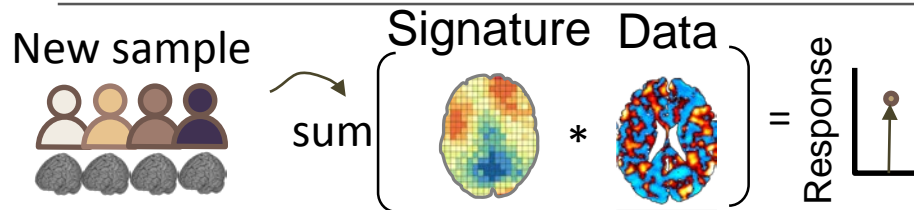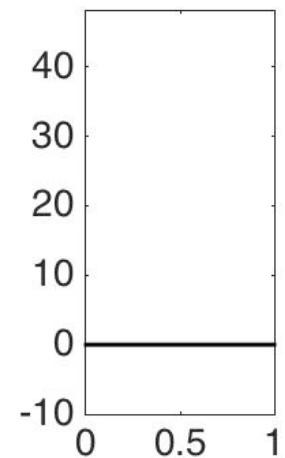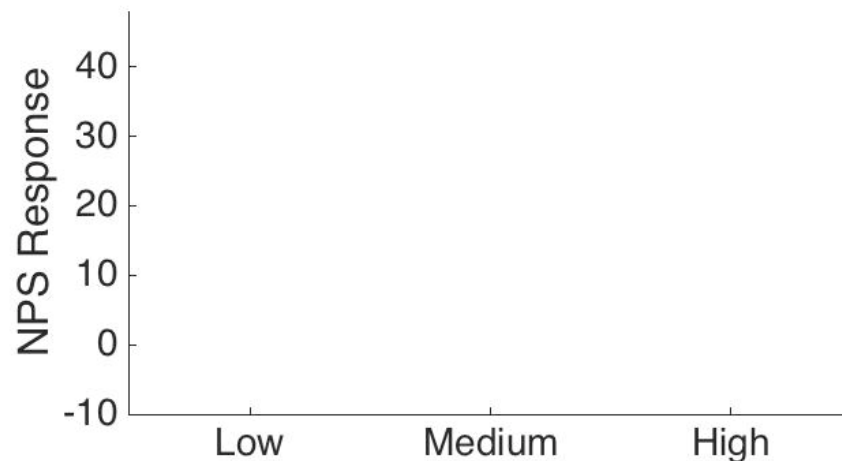
The 'Neurologic Pain Signature'

Chang et al. 2015
Woo et al. 2015
Krishnan et al. 2016
Wager et al. 2013, NEJM
Vachon-Presseau et al. 2016
Becker et al. 2016
Ma et al. 2016
Lopez-Sola et al. 2016
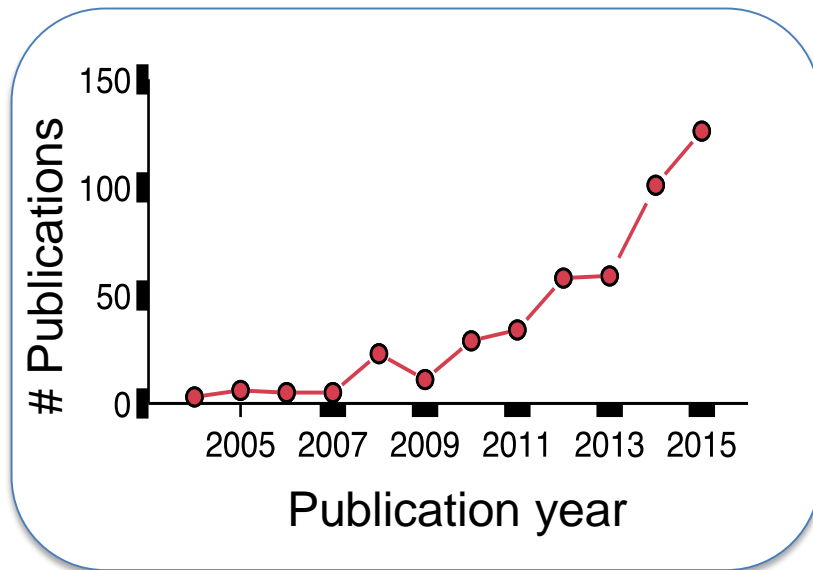*Woo et al. in revision*
van Oudenhove et al. in prep
Kragel et al. in prep
Zunhammer et al. in prep

Noxious heat

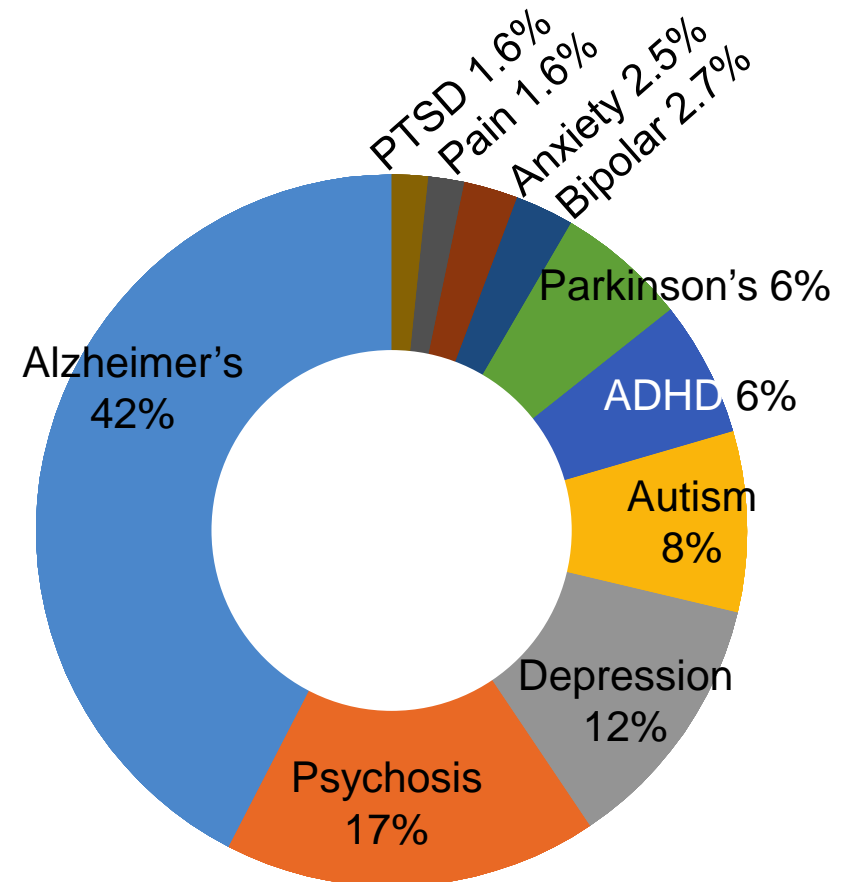
High - Low

Krishnan et al. 2016, eLife

Sensitivity and generalizability

Predictive models across disorders

Translational neuroscience
615 predictive maps, 475 studies

Variable accuracy
Little prospective validation…yet
But this is changing!

Woo et al., under review

Translational neuroscience: A snapshot

615 predictive maps, 475 studies

Choong-Wan Woo

Classification performance: Patient vs. Control

Woo et al., 2017 Nature Neuroscience

Translational neuroscience: A snapshot

Choong-Wan Woo

9%
Perform prospective testing

Prospective testing
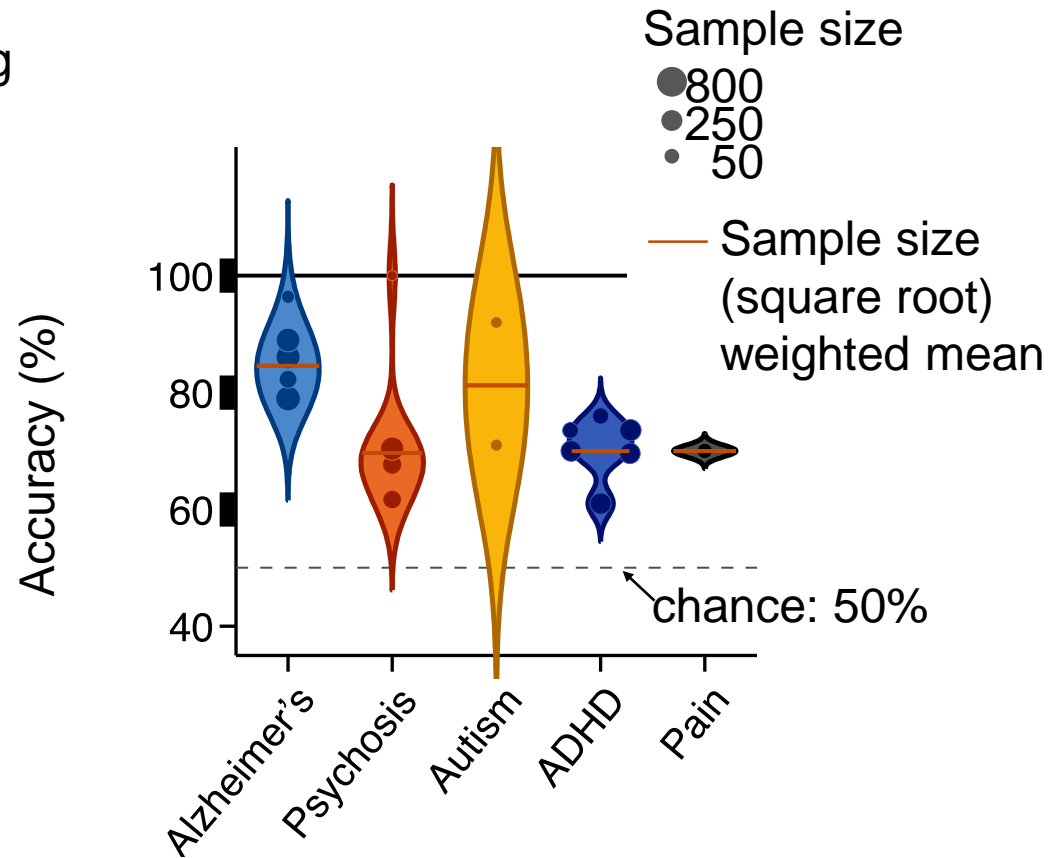
Sample size
- ●800
- ●250
- · 50

— Sample size (square root) weighted mean

Accuracy (%)

100
80
60
40

chance: 50%

Alzheimer's · Psychosis · Autism · ADHD · Pain

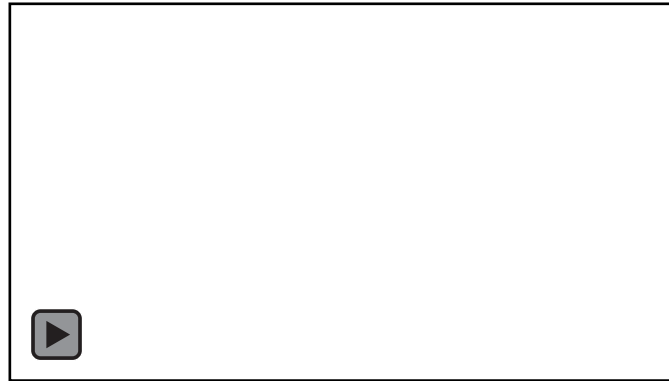*Woo et al., 2017 Nature Neuroscience*

Sharing and prospective testing $\longrightarrow$ specificity, generalizability, construct validation

Wager et al. 2013, NEJM; Chang et al. 2015; Woo et al. 2015; Krishnan et al. 2016; Vachon-Presseau et al. 2016; Becker et al. 2016; Lopez-Sola et al. 2016; Woo et al. 2017; van Oudenhove et al. in prep; Kragel et al.

Generalization: Pain and placebo meta-analysis

Lorenz J, Schoell E, Weiller C, Büchel, C Wanigasekera V, Wiech K, Mhuircheartaigh R, Lee MC, Ploner M, Tracey I, Choi JC, Yi DJ, Han BS, Lee PH, Kim JH, Kim BH, Eippert F, Schoell ED, Yacubian J, Klinger R, Lorenz J, Ellingsen D-M, Wessberg J, Eikemo M, Liljencrantz J, Endestad T, Olausson H, Elsenbruch S, Kotsis V, Benson S, Rosenberger C, Reidick D, Schedlowski M, Theysohn N, Forsting M, Gizewski ER, Freeman S, Yu R, Egorova N, Chen X, Kirsch I, Claggett B, Kaptchuk TJ, Gollub RL, Kong J., Geuter S, Hindi Attar C, Huber A, Lui F, Porro CA, Kessner S, Forkmann K, Ritter C, Wiech K, Ploner M, Rosman IS, Webb JM, Vangel MG, Polich G, Zyloney C, Rosen B, Rütgen M, Seidel EM, Silani G, Riečanský I, Hummer A, Windischberger C, Petrovic P, Lamm C, Theysohn N, Schmid J, Icenhour A, Mewes C, Gizewski ER, Benson S, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD, Watson A, El-Deredy W, Iannetti GD, Lloyd D, Vogt BA, Wrobel N, Zeidan F, Emerson NM, Farris SR, Ray JN, Jung Y, McHaffie JG
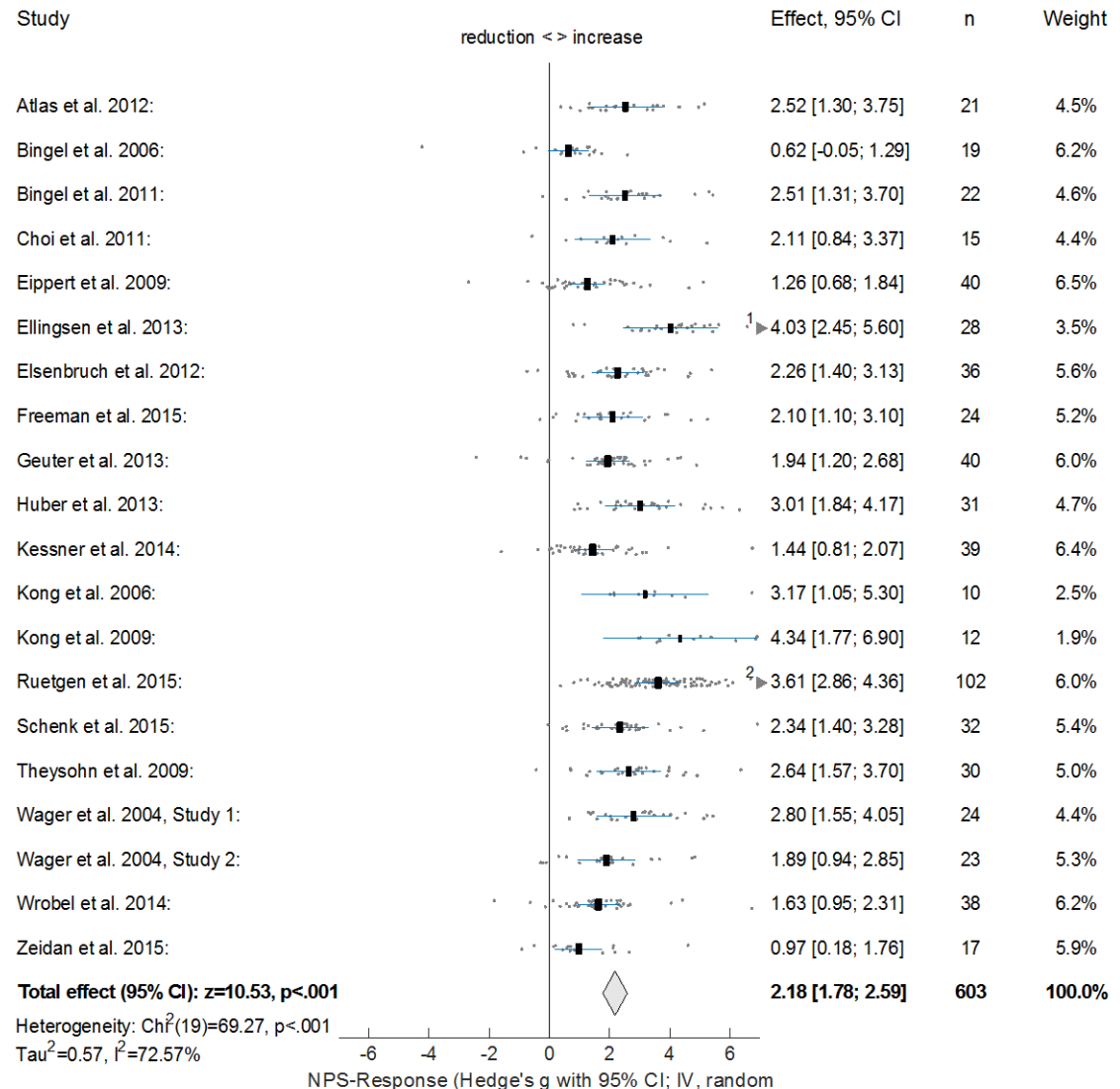
Zunhammer, Bingel et al. under review

Generalization: NPS responds to diverse types of evoked pain

Diverse population:
N = 600 across 20 sites

Multiple pain types:
Electrical, heat, laser, mechanical

Large effects:
Detection in >95% of individuals
Average d = 2.18

Study		Effect, 95% CI	n	Weight
	reduction < > increase			
Atlas et al. 2012:		2.52 [1.30; 3.75]	21	4.5%
Bingel et al. 2006:		0.62 [-0.05; 1.29]	19	6.2%
Bingel et al. 2011:		2.51 [1.31; 3.70]	22	4.6%
Choi et al. 2011:		2.11 [0.84; 3.37]	15	4.4%
Eippert et al. 2009:		1.26 [0.68; 1.84]	40	6.5%
Ellingsen et al. 2013:	[1]	4.03 [2.45; 5.60]	28	3.5%
Elsenbruch et al. 2012:		2.26 [1.40; 3.13]	36	5.6%
Freeman et al. 2015:		2.10 [1.10; 3.10]	24	5.2%
Geuter et al. 2013:		1.94 [1.20; 2.68]	40	6.0%
Huber et al. 2013:		3.01 [1.84; 4.17]	31	4.7%
Kessner et al. 2014:		1.44 [0.81; 2.07]	39	6.4%
Kong et al. 2006:		3.17 [1.05; 5.30]	10	2.5%
Kong et al. 2009:		4.34 [1.77; 6.90]	12	1.9%
Ruetgen et al. 2015:	[2]	3.61 [2.86; 4.36]	102	6.0%
Schenk et al. 2015:		2.34 [1.40; 3.28]	32	5.4%
Theysohn et al. 2009:		2.64 [1.57; 3.70]	30	5.0%
Wager et al. 2004, Study 1:		2.80 [1.55; 4.05]	24	4.4%
Wager et al. 2004, Study 2:		1.89 [0.94; 2.85]	23	5.3%
Wrobel et al. 2014:		1.63 [0.95; 2.31]	38	6.2%
Zeidan et al. 2015:		0.97 [0.18; 1.76]	17	5.9%
Total effect (95% CI): z=10.53, p<.001		**2.18 [1.78; 2.59]**	**603**	**100.0%**

Heterogeneity: $Chi^2(19)=69.27$, p<.001
$Tau^2=0.57$, $I^2=72.57\%$

NPS-Response (Hedge's g with 95% CI; IV, random)

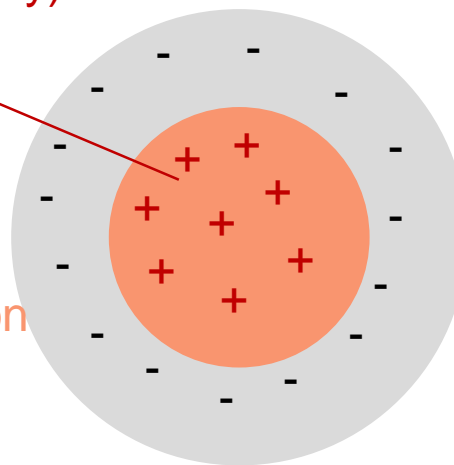Zunhammer, Bingel et al. under review

Sharing and prospective testing $\longrightarrow$ specificity, generalizability, construct validation

Activated by (sensitivity)

- Noxious heat
- Electric shock
- Noxious pressure
- Gastric distention
- Esophageal distention
- Rectal distention
- Vaginal pressure

Sub-threshold:

- Breathlessness
- Aversive taste

Treatments:

Opioids
SSRIs
Conditioned cues
Distraction
Social touch

Dark colors: Published

Light colors: Preliminary

Wager et al. 2013, NEJM; Chang et al. 2015; Woo et al. 2015; Krishnan et al. 2016; Vachon-Presseau et al. 2016; Becker et al. 2016; Lopez-Sola et al. 2016; Woo et al. 2017; van Oudenhove et al. in prep; Kragel et al.

specificity

What is the NPS really measuring?

Specific   General

$\longleftrightarrow$

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

▶

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

Somatic pain task: hot or warm

+
(7s)

Stimuli
(15s)

Rating
(5s)

Visuospatial
(18s) Task

friend
or ex-partner

Social rejection task:
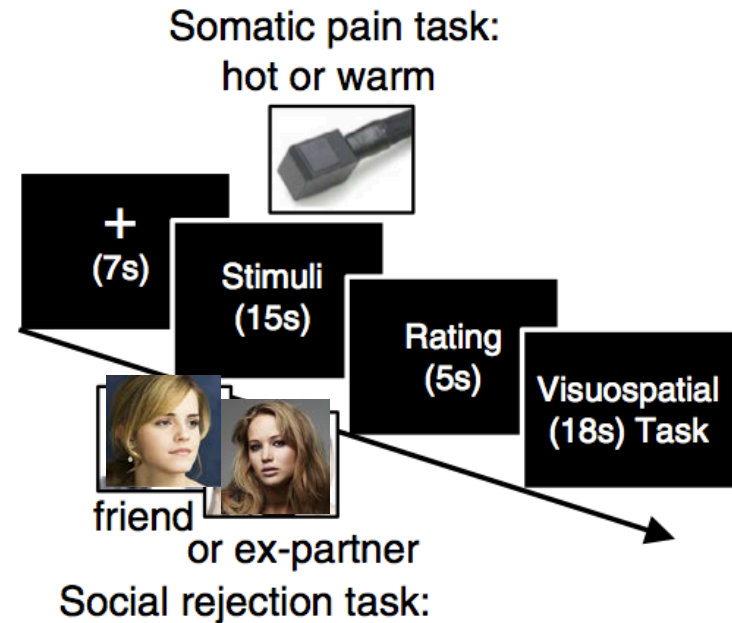
Rejection and pain:
Similar negative ratings, similar brain activity

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

Physical pain

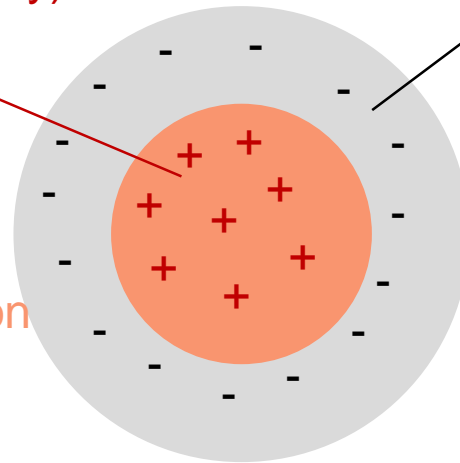**Discrimination performance** **Pain biomarker expression**
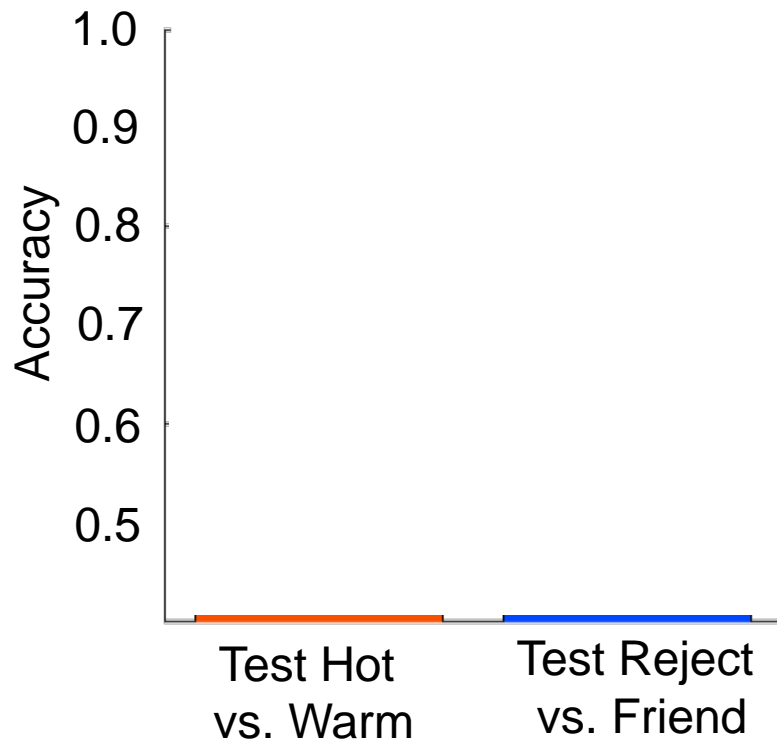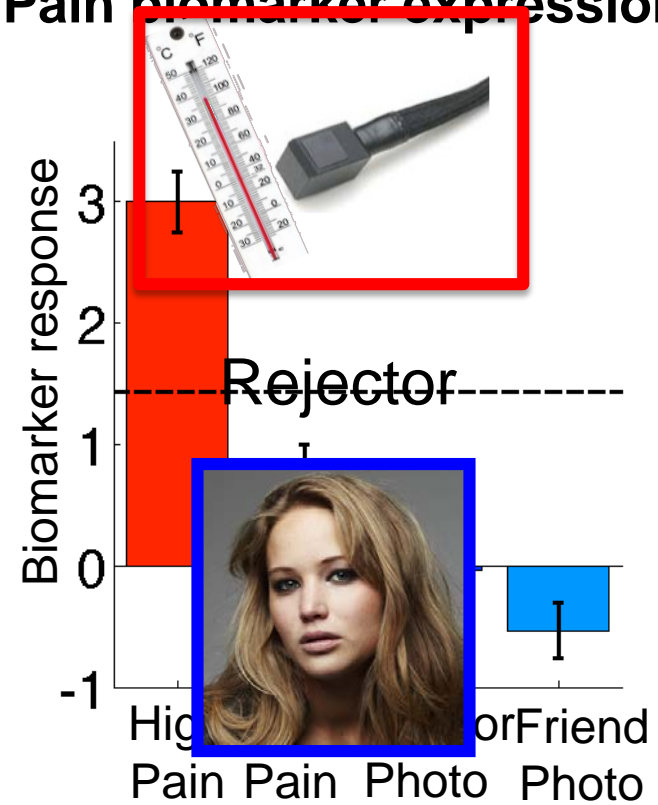
Measures of pain: Sensitivity and specificity of the NPS

Activated by (sensitivity)

- Noxious heat
- Electric shock
- Noxious pressure
- Gastric distention
- Esophageal distention
- Rectal distention
- Vaginal pressure

Sub-threshold:
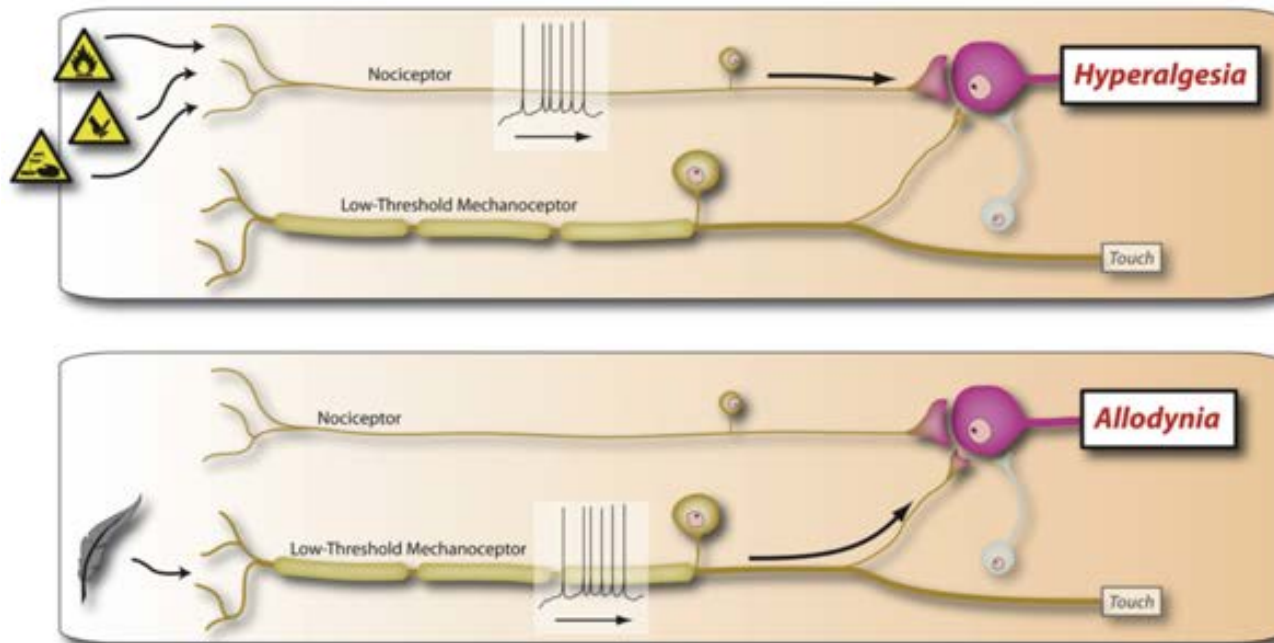
- Breathlessness
- Aversive taste
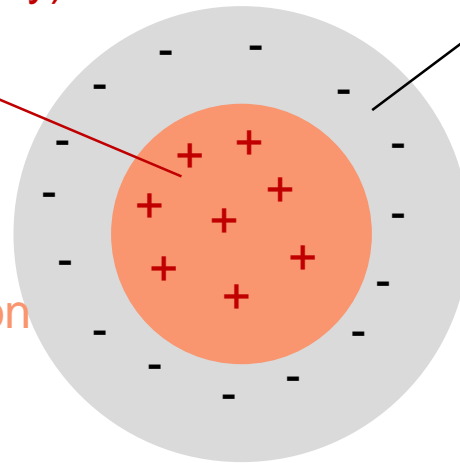
Not activated by (specificity)

- Aversive images
- Social rejection
- Observed pain
- Pain anticipation
- Nausea
- Itch
- Cognitive demand
- Pain recall
- Warmth

Dark colors: Published
Light colors: Preliminary

Wager et al. 2013, NEJM; Chang et al. 2015; Woo et al. 2015; Krishnan et al. 2016; Vachon-Presseau et al. 2016; Becker et al. 2016; Lopez-Sola et al. 2016; Woo et al. 2017; van Oudenhove et al. in prep; Kragel et al.

Counter
measures

Can you "rethink" responses in the NPS?
Sensitivity to cognitive reappraisal (N = 30)

ChoongWan Woo Mathieu Roy

- "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
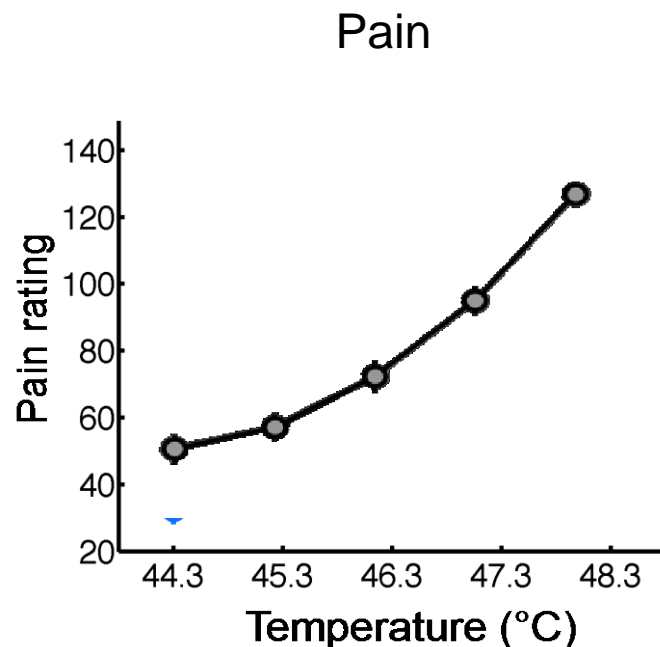
Pain

Neurologic Pain Signature response
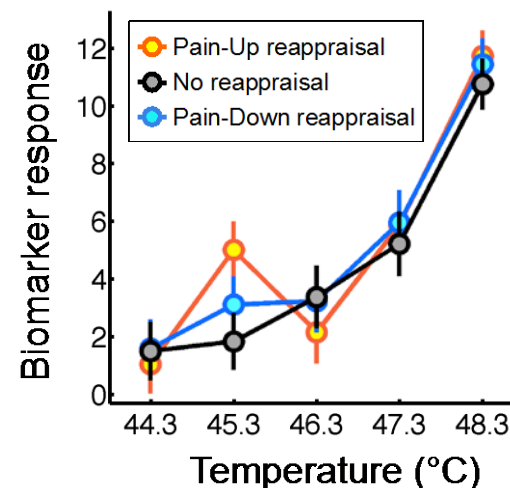
Placebo treatment: Strong effects on pain

Placebo significantly reduces pain in all studies.

Average effect size:
d = -0.65

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. under review

Activated by (sensitivity)

Not activated by (specificity)

- Noxious heat
- Electric shock
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SSRIs
Conditioned cues
Distraction
Social touch

Cognitive regulation
Placebo
Perceived control
Reward
Social cues

Wager et al. 2013, NEJM; Chang et al. 2015; Woo et al. 2015; Krishnan et al. 2016; Vachon-Presseau et al. 2016; Becker et al. 2016; Lopez-Sola et al. 2016; Woo et al. 2017; van Oudenhove et al. in prep; Kragel et al.

Use cases
and limitations

Spinal plasticity: Central sensitization

Nociceptive spinal dorsal horn neurons sensitize to inputs
- Hypersensitivity, allodynia, 'spontaneous' pain

Features of many pain conditions:

Fibromyalgia, osteoarthritis, musculoskeletal disorders, headache, temporomandibular joint disorders, neuropathic pain (e.g., stroke, diabetes), complex regional pain syndrome, irritable bowel syndrome, and post-surgical pain

Woolf, 2011, Pain

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

Fischer 2006, 2009, 2010 (rev)

Schwartz 2015; Ren 2015

Metz 2010; Lee 2015; Schwartz 2017

Neugebauer 2003; Carrasquillo 2007

Burgess 2002

Kuner & Flor 2017 (review); McMahon, 1993; Luo, 2014

dpINS S2
aINS
d.CC
Thalamus
HY NAC
vmPFC
PAG
AMY
PBN
RVM (NRM) S

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

For 2006 (review)

Schw

Multiple mechanisms and pathways

Multiple relationships with pain
Predispositions, consequences, and mediators

Interactions with other processes
- Cognitive appraisal, emotion, attention
  - Different legal implications for these

Kuner & Flor 2017 (review);
McMahon, 1993; Luo, 2014
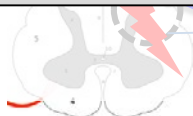
Fibromyalgia

Hypersensitivity

Widespread pain

Fatigue

Multiple
sensitivities

Fibromyalgia:
Enhanced "Neurologic Pain Signature" (NPS) responses
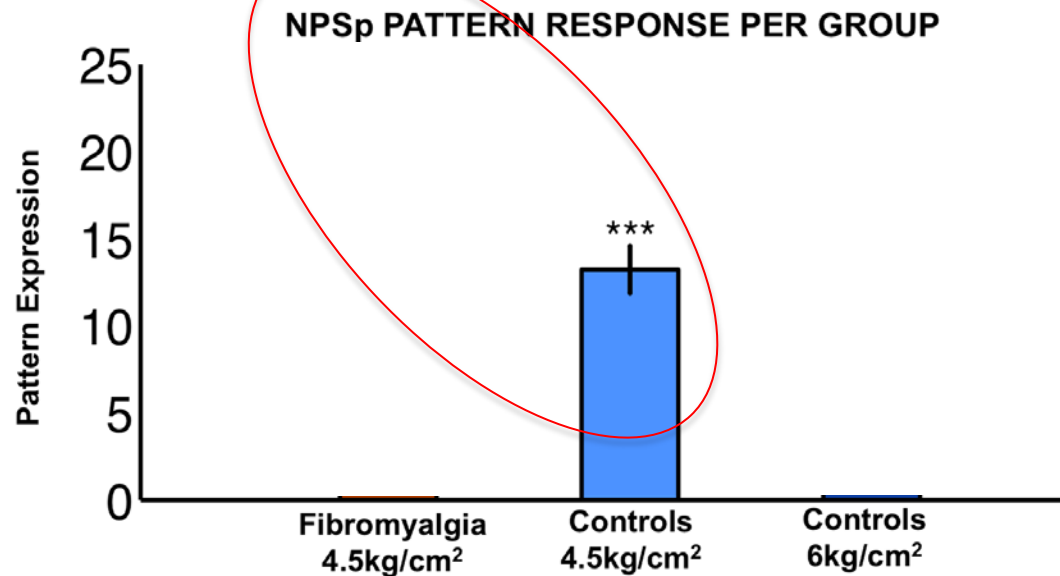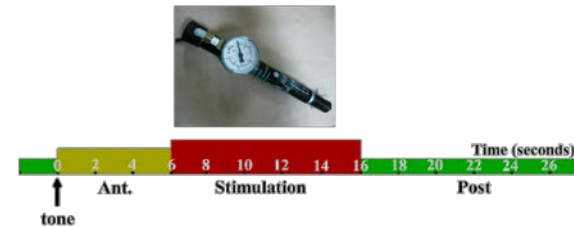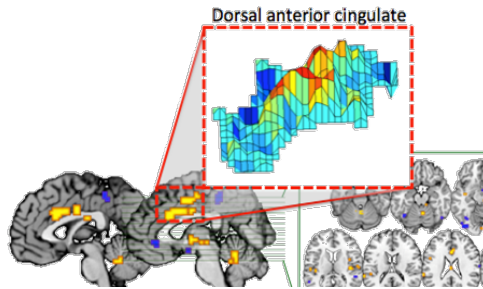
Same pressure
Greater NPS

Lopez-Sola et al. 2016

Fibromyalgia: Multiple systems

NPS: Hypersensitivity
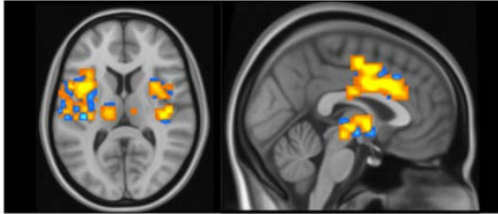
'Regulatory' systems become **pro-pain**
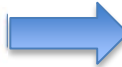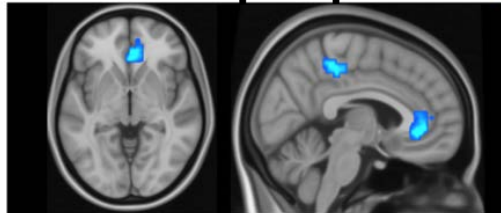
Fibromyalgia

Multisensory sensitivity
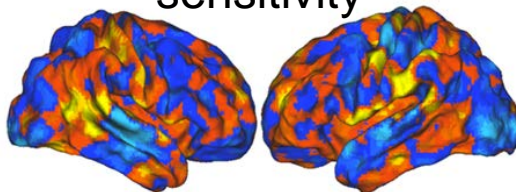
Combined measure:
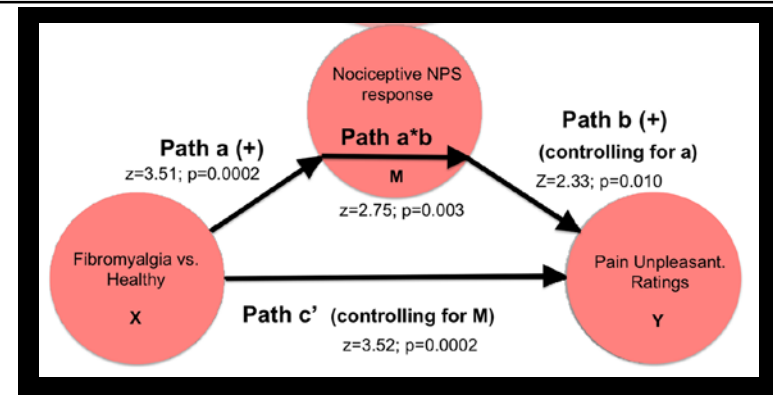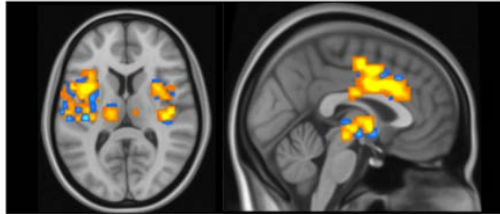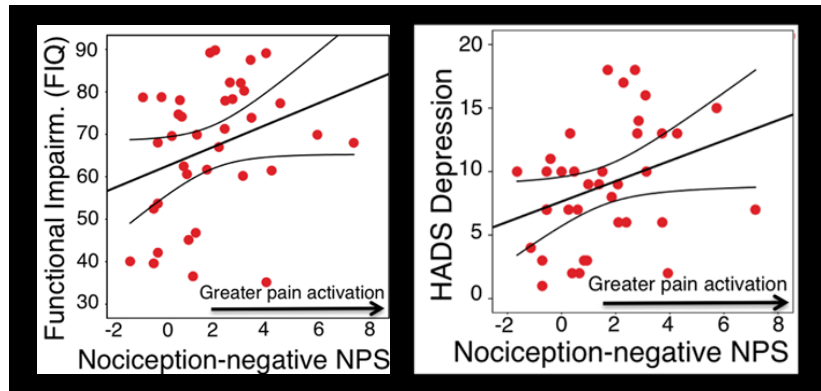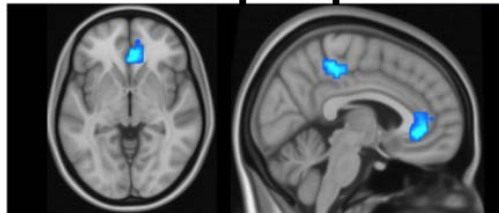
93%

accuracy for fibromyalgia vs. controls

Lopez-Sola et al. 2016

Fibromyalgia: Multiple systems

NPS: Hypersensitivity

'Regulatory' systems become **pro-pain**

Fibromyalgia

Multisensory sensitivity

Lopez-Sola et al. 2016
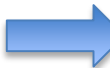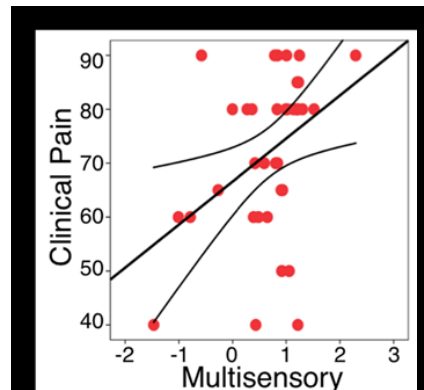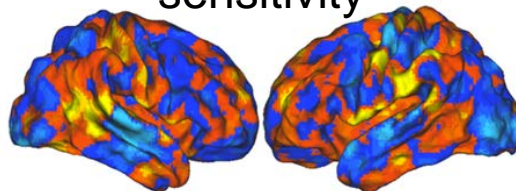
Future directions:

- **Construct validation**: Biomarkers need to be tested for sensitivity, specificity, generalizability to diverse populations

  - Need data resources for testing, e.g., biobank of study data

- **Countermeasures**: Need more extensive tests (distraction, pain induction during control conditions)

  - Brain models specific to body site as well as intensity

- **Applicability to chronic pain**: Need model development/validation with multiple pain disorders, 'spontaneous' pain

  - Multi-systems approach, multiple pain targets
  - Extensions to deal with tonic/sustained pain
  - Separation of risk factors, consequences, and mediators
  - New methods to deal with plasticity/reorganization

Cognitive and Affective Neuroscience Lab
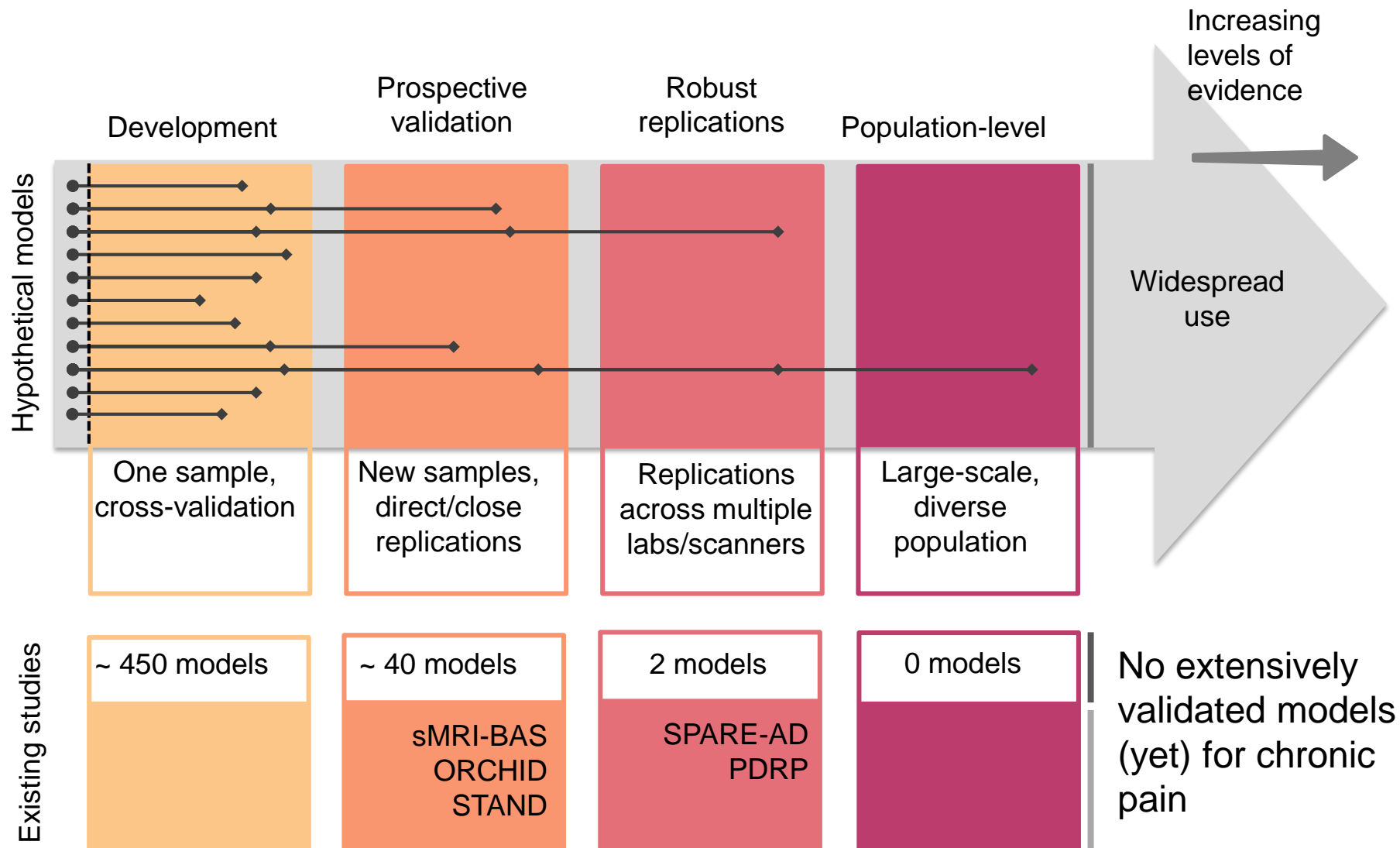University of Colorado at Boulder

Funding Sources

Catalan government
Mind, Brain, Body and Health Network

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

Established neuromarkers for neuro/psychopathology

Increasing levels of evidence

Development — One sample, cross-validation

Prospective validation — New samples, direct/close replications

Robust replications — Replications across multiple labs/scanners

Population-level — Large-scale, diverse population

Widespread use

Hypothetical models

Existing studies:
- ~ 450 models
- ~ 40 models — sMRI-BAS, ORCHID, STAND
- 2 models — SPARE-AD, PDRP
- 0 models

No extensively validated models (yet) for chronic pain

Woo et al. 2017, Nat Neurosci

# Central mechanisms of chronic pain in Fibromyalgia

- Chronic widespread musculoskeletal pain

- No well-established tissue pathology (cf. Serra et al. 2004)

- Diagnosis based on subjective reports. Patients often not believed and appropriately diagnosed.

Study

- 37 female patients, 35 matched controls (age, education)

- fMRI during mechanical pain (pressure) and other multisensory tasks

Next 10 years: Evidentiary Standards for evaluating biomarkers

Right Hand Squeezing
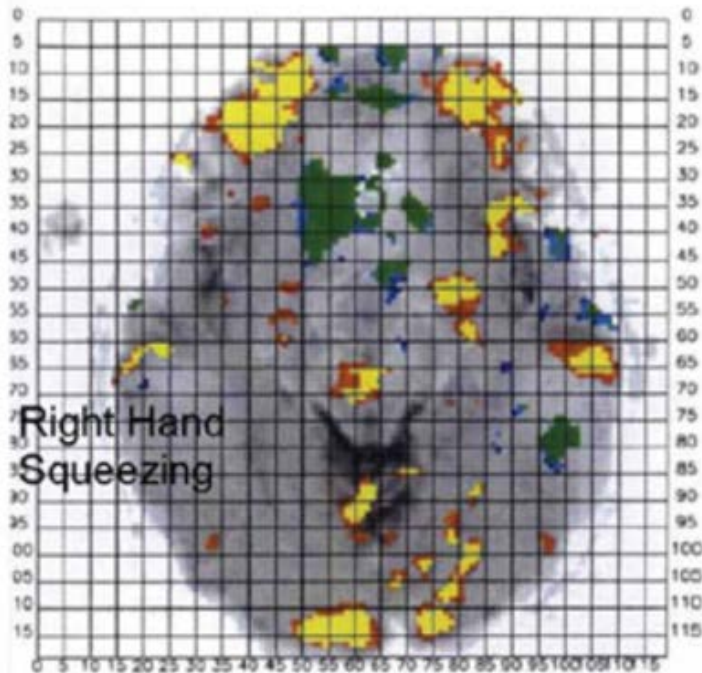
- fMRI scans cannot be "read" the way a neuroradiologist reads a clinical scan for pathology
  - …just as genetic tests cannot be "read" by an expert's subjective impression of what the gene patterns "look like"

- Models must be precisely specified and quantitatively evaluated

- Pain is not just "stronger touch" Somatosensory activity in general does not indicate pain

International Association for the Study of Pain Task Force

- 1. Consider the technical and physiological capabilities of brain imaging to detect whether an individual has chronic pain.

- 2. Place the capability of brain imaging as a diagnostic test of chronic pain in an ethical and legal context.

- 3. Establish guidelines for health care systems, government and legal policymakers on the validity and ethics of adopting a brain imaging-based test of pain.

A "cheat sheet" for lawyers and judges

1. Are all parameters of the "pain test" defined in advance?
- Which 'voxels', and what relative contributions of each voxel?
- What threshold or cutoff values?

2. What is the sensitivity of the test for this type of pain?

- How many individuals with this type of pain have shown positive findings? How many negative findings?
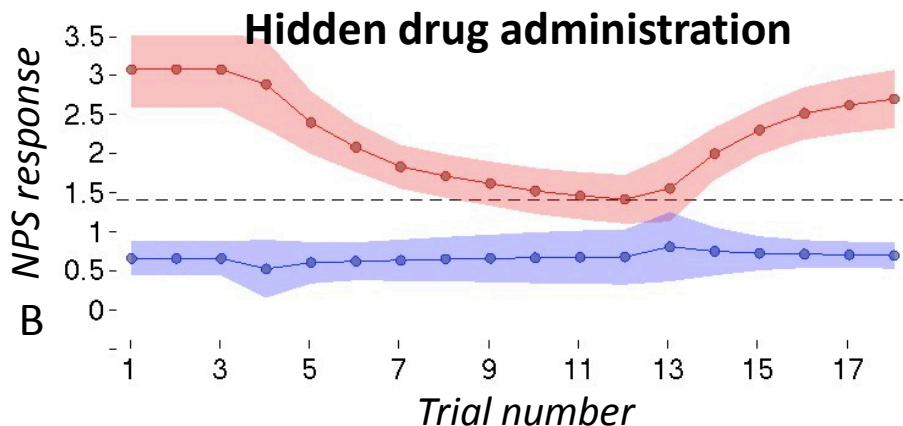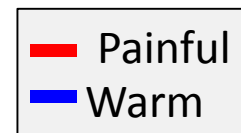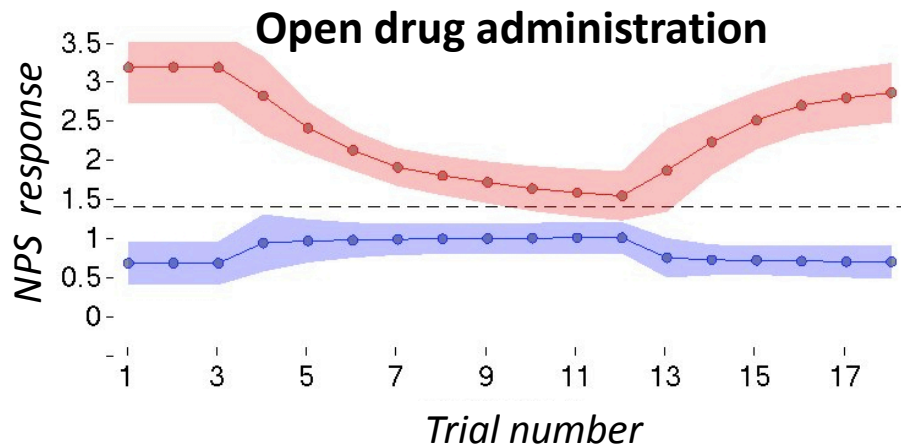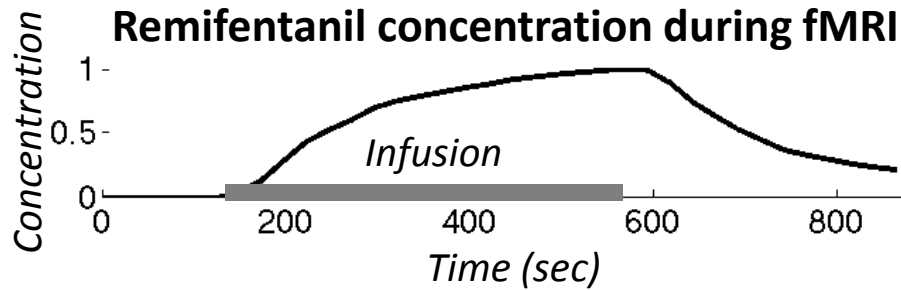
3. What is the specificity of the test for this type of pain?

- Against what other conditions has specificity been evaluated?
- What is the specificity relative to aversive, but not painful, touch? Relative to emotional 'pain'? Relative to cognition about pain?

4. If this test involves comparing an individual to a reference sample, was that sample matched on age, sex, handedness, SES/education, fMRI scanner?

5. Has a normative neuroanatomical organization been demonstrated in this individual, so that the reference sample applies?

Testing treatment response (pharmacodynamics)

Remifentanil concentration during fMRI

Infusion

Open drug administration

Strong reduction with remifentanil

Painful
Warm

Hidden drug administration

No response to placebo
(open vs. hidden administration)

Wager et al. 2013, NEJM;
Ma et ai. 2016: citalopram effects

A "cheat sheet" for lawyers and judges (2)

- Has this individual's hemodynamic (blood flow) response been shown to match assumptions made in the test?

- Have tests of non-pain-related conditions demonstrated positive findings, to validate image quality?

- Is the test adequately powered in this individual?

- Have countermeasures and deception (e.g., self-induced pain during scanning) been ruled out?

A "cheat sheet" for lawyers and judges (3)

1. Are all parameters of the "pain test" defined?
- Which 'voxels'?
- What relative contributions of each voxel?
- What threshold or cutoff values?

2. Does the test provide a meaningful conclusion about an individual person?

3. How have methodological procedures of the test been validated?
- Have they been validated for this exact test, or for more general cases (e.g., fMRI)?
- Are the specific processing steps peer-reviewed and accepted in the scientific literature?
- Have the procedures been shown to be robust to head movement and physiological artifacts, and in what percentage of individual patients?

4. What positive and negative controls established image quality in the particular individual tested?

If pain test is negative:
- Has this individual's hemodynamic (blood flow) response been shown to match assumptions made in the test?
- Have tests of non-pain-related conditions demonstrated positive findings, to validate image quality?
- Is the test adequately powered in this individual?
- Have countermeasures been ruled out?
- Has a normative functional neuroanatomical organization been demonstrated in this individual?
- Has a normative physiological basis for pain been established in this individual?

If pain test is positive:
- Have confounds such as head movement and physiological artifacts been ruled out?

5. What is the sensitivity of the test for this type of pain?
- What types of pain has the test been shown to respond to?
- What is the sensitivity for patients with comparable pain conditions and demographics (age, sex, ethnicity/race)?
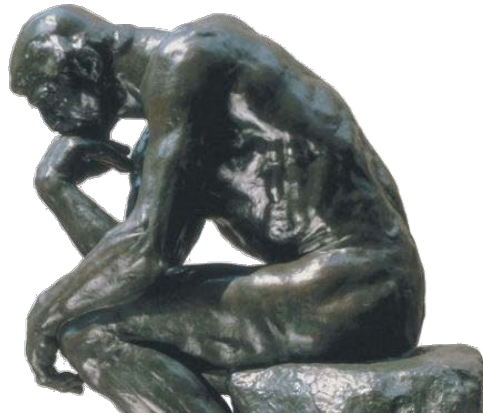
6. What is the specificity of the test for this type of pain?
- Against what other conditions has specificity been evaluated?
- What is the specificity relative to aversive, but not painful, touch?
- What is the specificity relative to emotional 'pain'?
- What is the specificity for patients with comparable pain conditions and demographics (age, sex, ethnicity/race)?
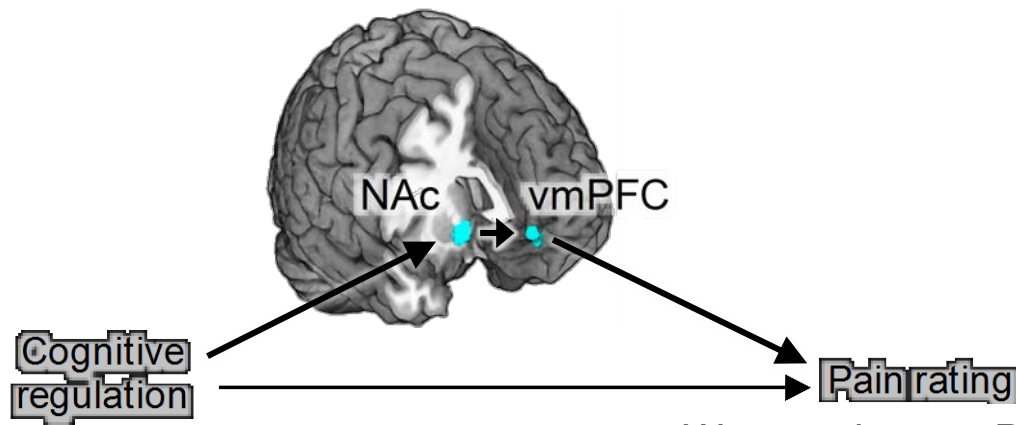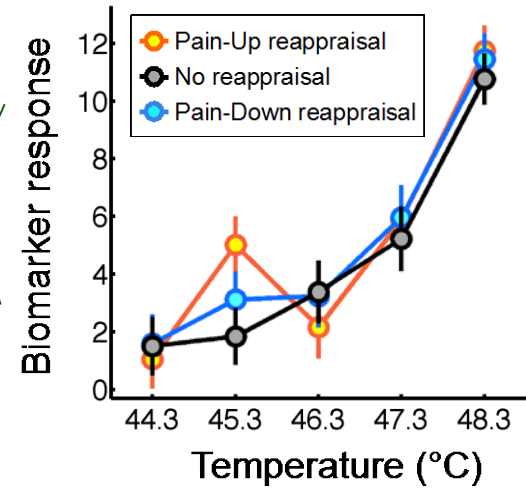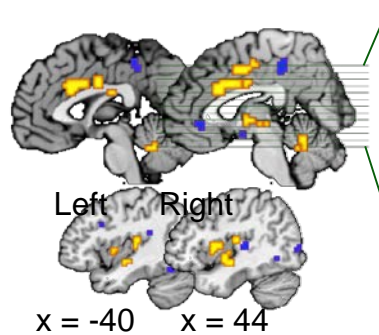
Rethinking pain

NPS

Left   Right

x = -40   x = 44

- Pain-Up reappraisal
- No reappraisal
- Pain-Down reappraisal

Biomarker response

Temperature (°C)

NAc   vmPFC

Cognitive regulation
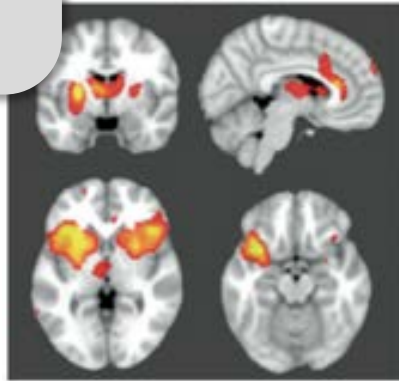
Pain rating

Woo et al. 2015 PLoS Biol

Human evidence on pain chronification:
Shift from classic nociceptive systems to 'emotional' ones

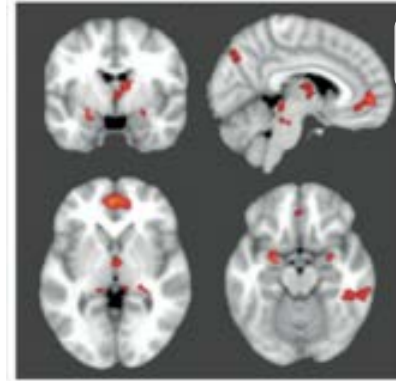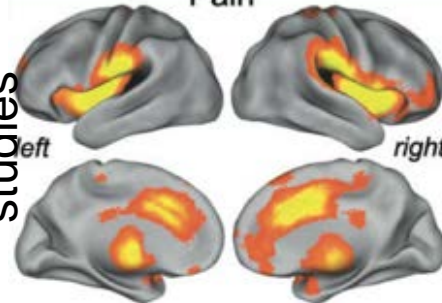Nociceptive targets: Cingulate, insula, thalamus

One year later

vmPFC

Back pain persists

Visit 1

Visit 4

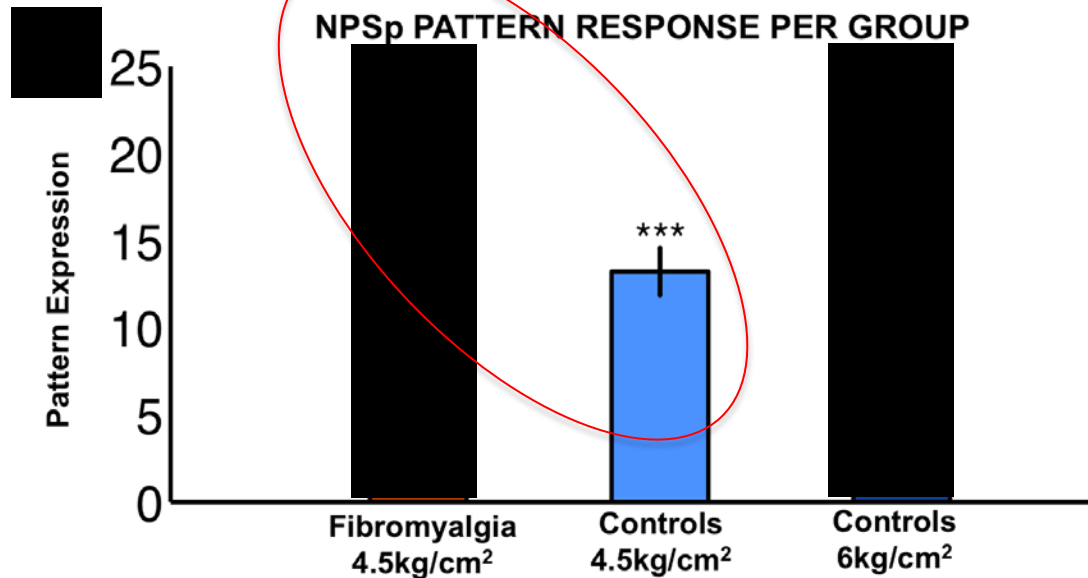Meta-analysis of basic studies

Pain

Emotion

left
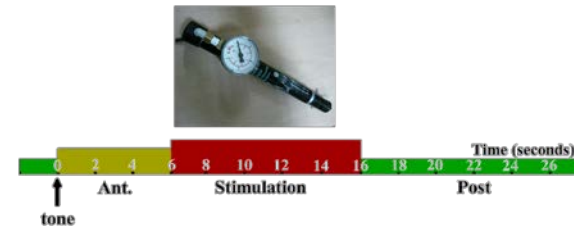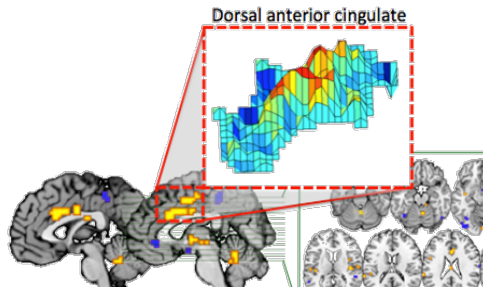
right

2.3 | 9.0

Yarkoni et al. 2011, Neurosynth.org

Apkarian et al. 2011; Baliki et al. 2012; Geha et al. 2008; Hashmi et al. 2013

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

Same pressure
Greater NPS

Lopez-Sola et al. 2016
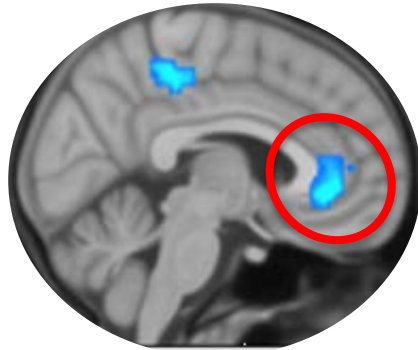
Fibromyalgia:
Alterations in other pathways beyond pain transmission

Alterations in pain-regulatory systems

Medial frontal cortex becomes **pro**-pain

Multisensory responses beyond pain

93% accuracy for fibromyalgia vs. controls

Lopez-Sola et al. 2016
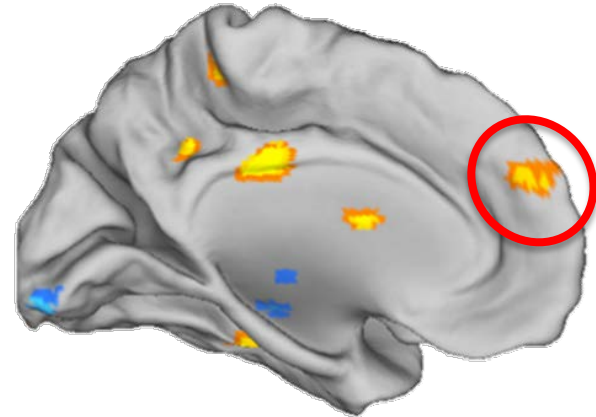
Biomarkers for pain – **scalable**, cost-effective **measures**

Behavior (QST)

Genetics

EEG

Face and voice

Physiology

Inflammation

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

Neuroimaging can be useful for understanding and validating other measures

See work by: M. Bartlett, Picard, Treede/DFNS, Saab, Geuter et al., Dworkin (IMMPACT)
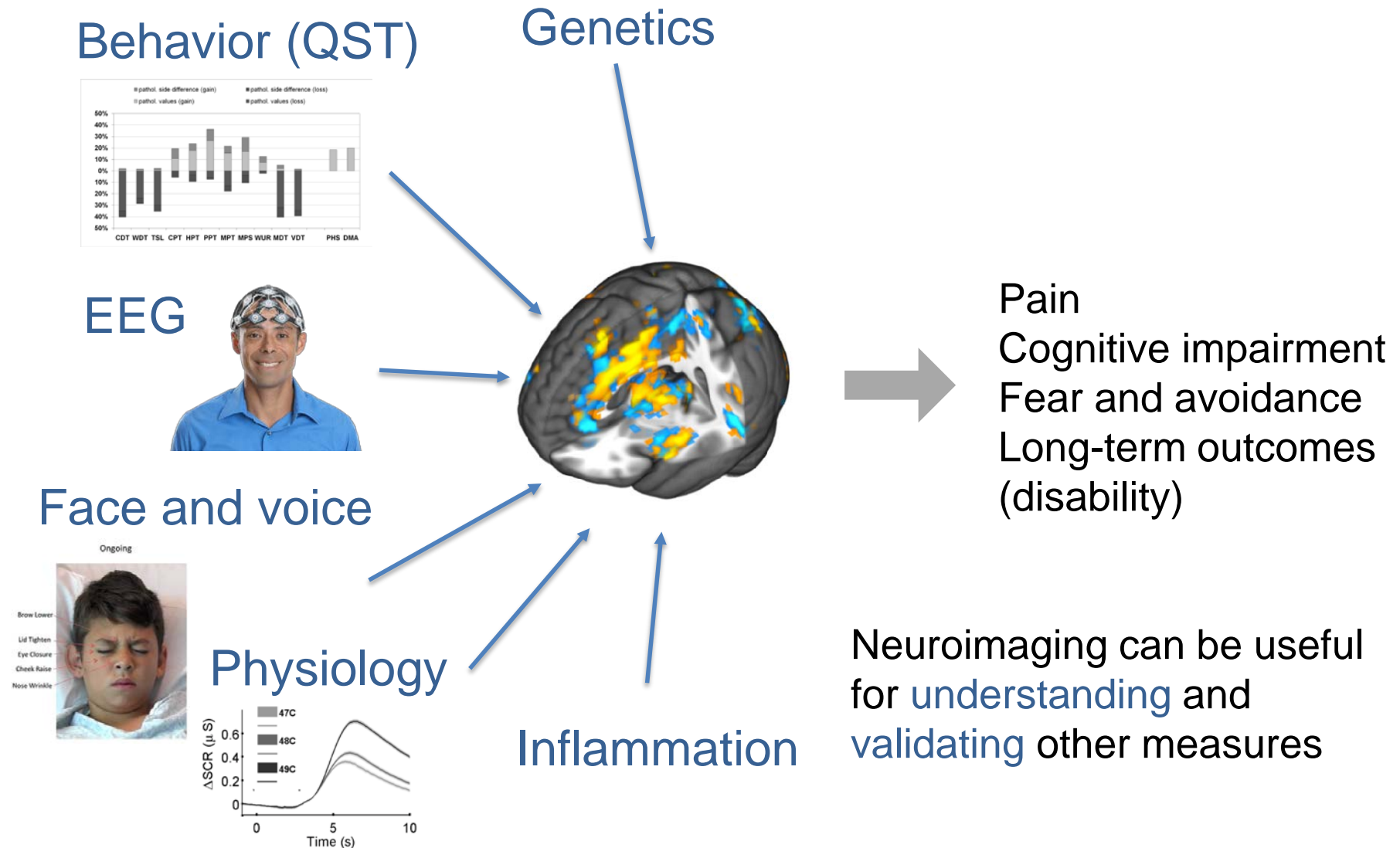
Multivariate _patterns_ afford greater sensitivity and specificity

Local field potential

Voxel pattern

Event type 1

Event type 2

Homogeneous Poisson process

🟡 Neuron type 1
🔵 Neuron type 2
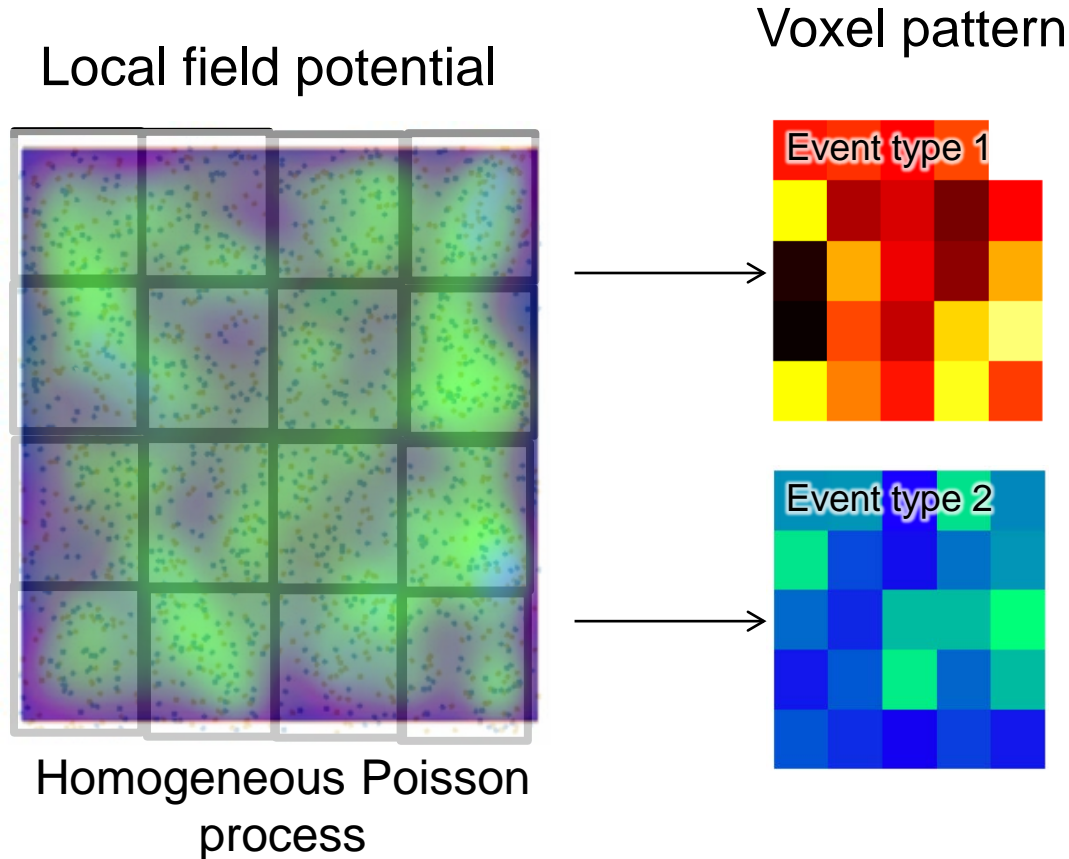
Each pattern reflects different information

Haxby 2001, 2011; Kamitani 2005, 2012; Kriegeskorte 2006; Chaimow 2011; many others

Sensitivity to information at multiple spatial scales
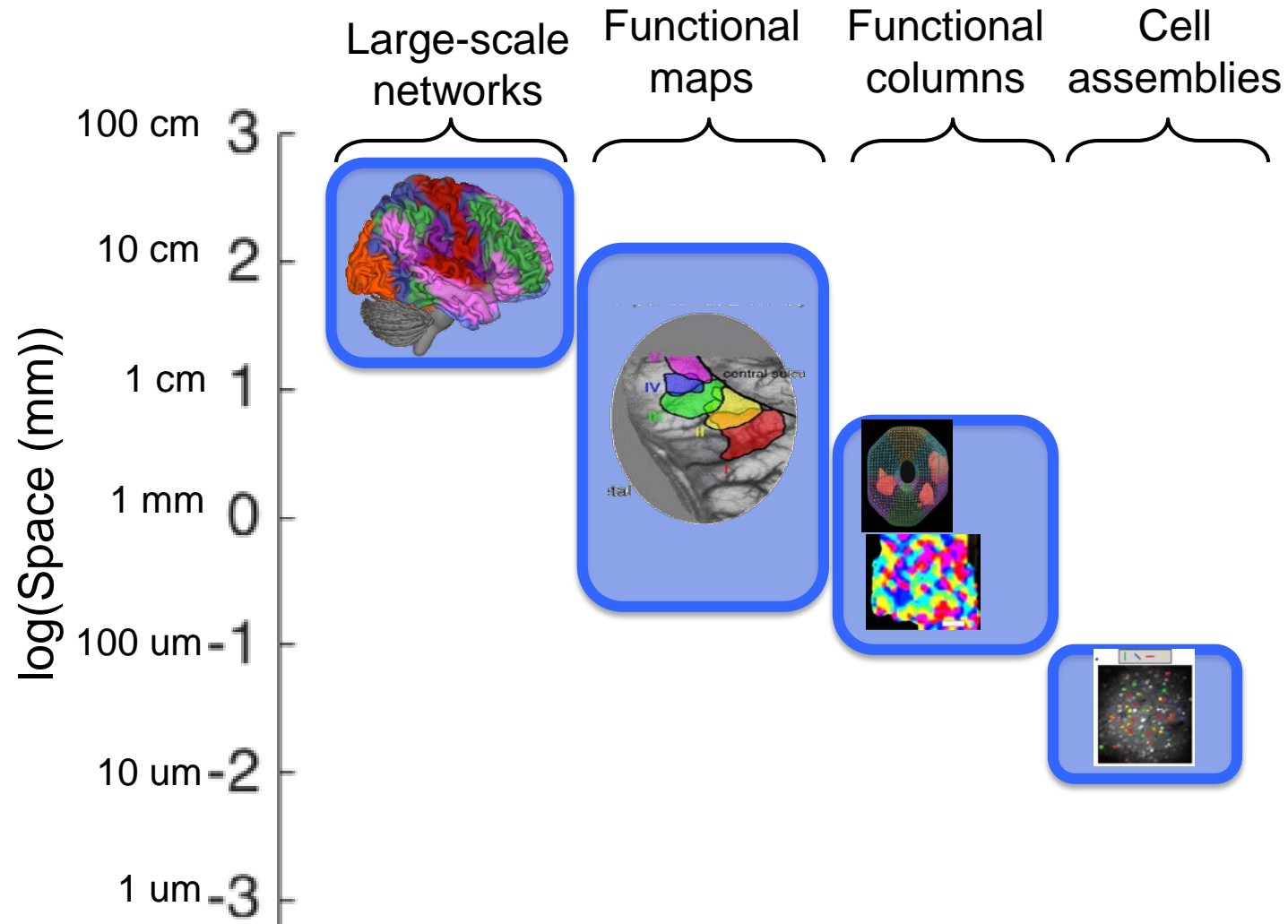
Replication: Single-trial associations with pain

11 studies
378 participants
23,493 single-trial images

Changing views of pain

Symptoms: Inferences about adaptive experience and behavior

Context-based *priors*

P(pain)

⬇

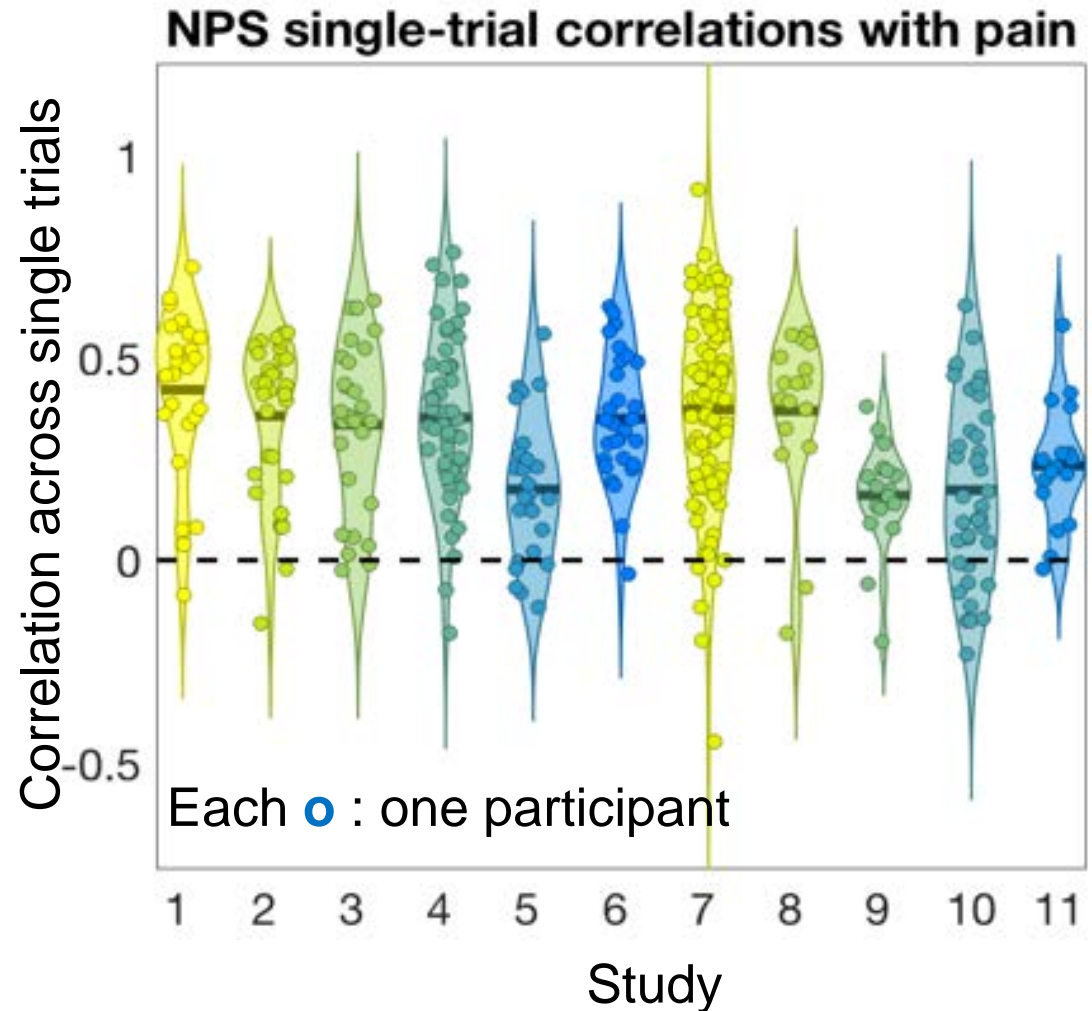Inferred experience
Adaptive responses

→ Experience (symptoms)

→ Autonomic physiology

→ Learning

⬆

Sensory *evidence*

input

Legal issues:

- Who is responsible?
- Is there 'primary pain' for which an injured person bears no responsibility?

Geuter, Koban, & Wager, 2017 Ann Rev Neurosci; Fields 2004, 2007; Bushnell 2014; Tracey, Geuter et al 2017, eLife

Evidentiary Standards
for evaluating biomarkers

- **Criterion 1:** Precise definition

- **Criterion 2:** Applicability to individual persons

- **Criterion 3:** Validation of methodological procedures used during test

- **Criterion 4:** Internal consistency and validation of imaging quality in individuals using positive and negative controls

- **Criterion 5:** Diagnosticity for pain

- **Criterion 6:** Validation of neurophysiology with converging methods

- **Criterion 7:** Generalizability to patient group tested and to test conditions

Standards of evidence for an application (e.g., tort law) decided by the field; these are dimensions helpful for evaluating claims.

Davis et al. 2017, Nat Rev Neurol.; Woo 2017

Specificity
pathways