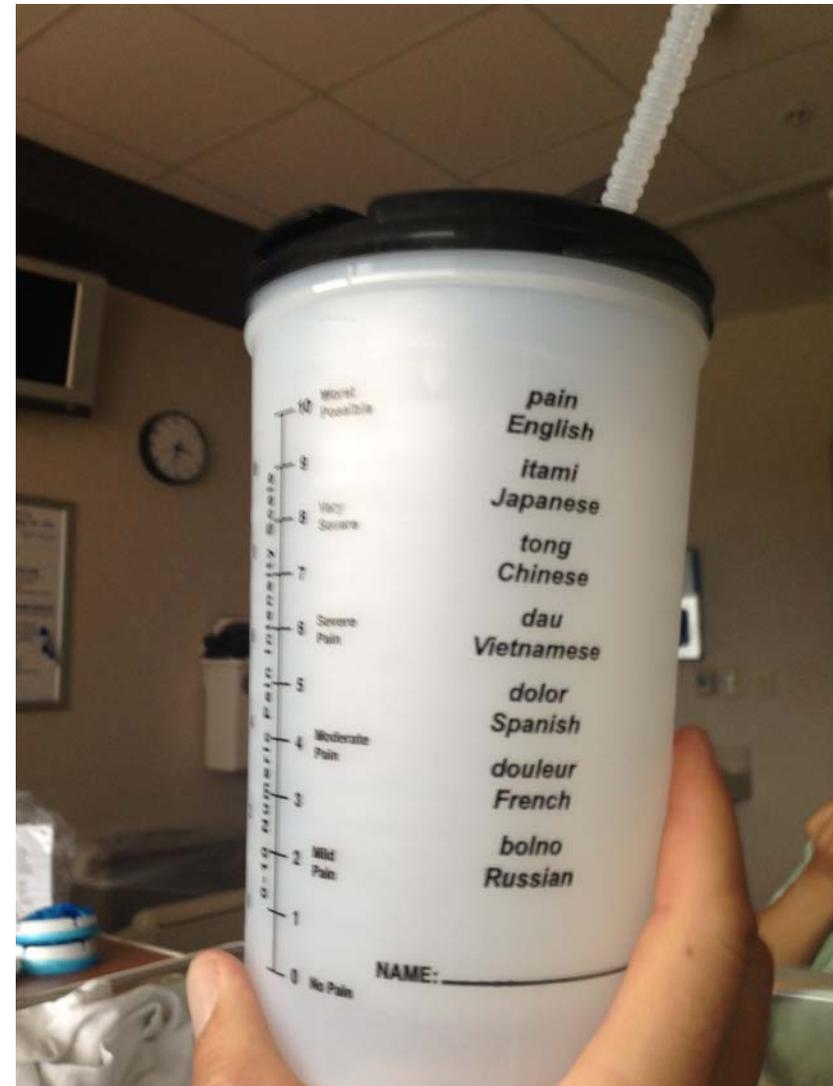
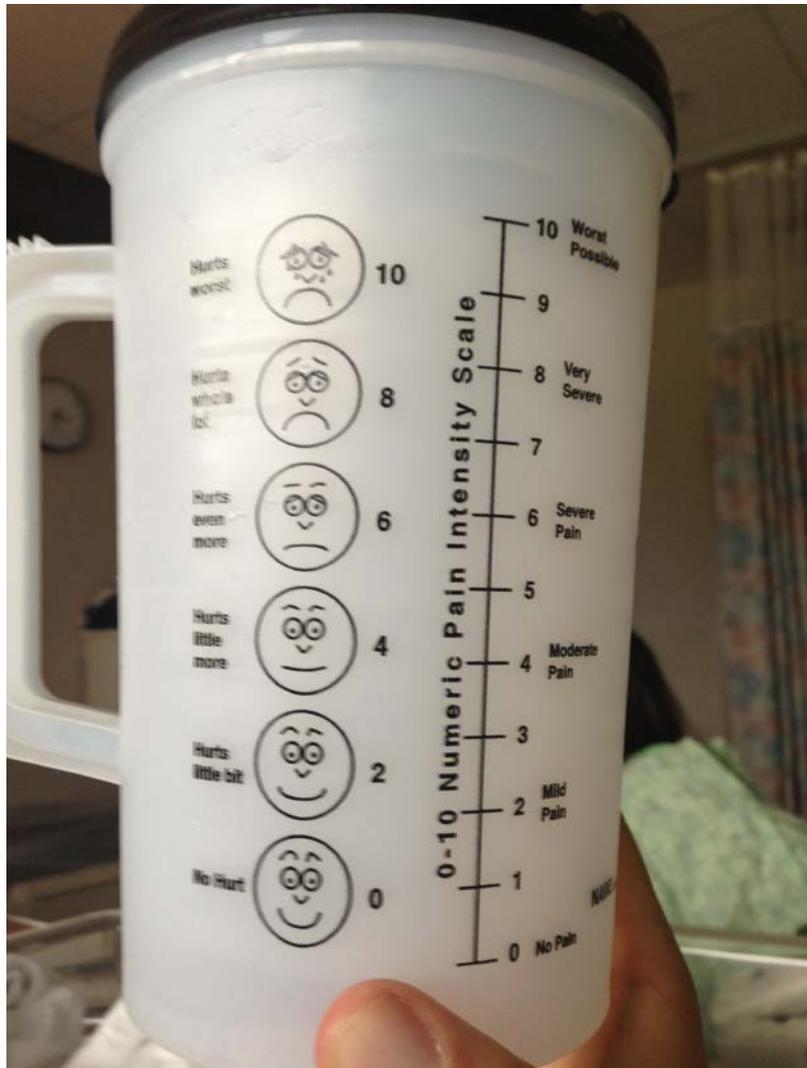


Neuroimaging of pain and distress: A biomarker development approach

Tor D. Wager

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

Current pain measurement technology

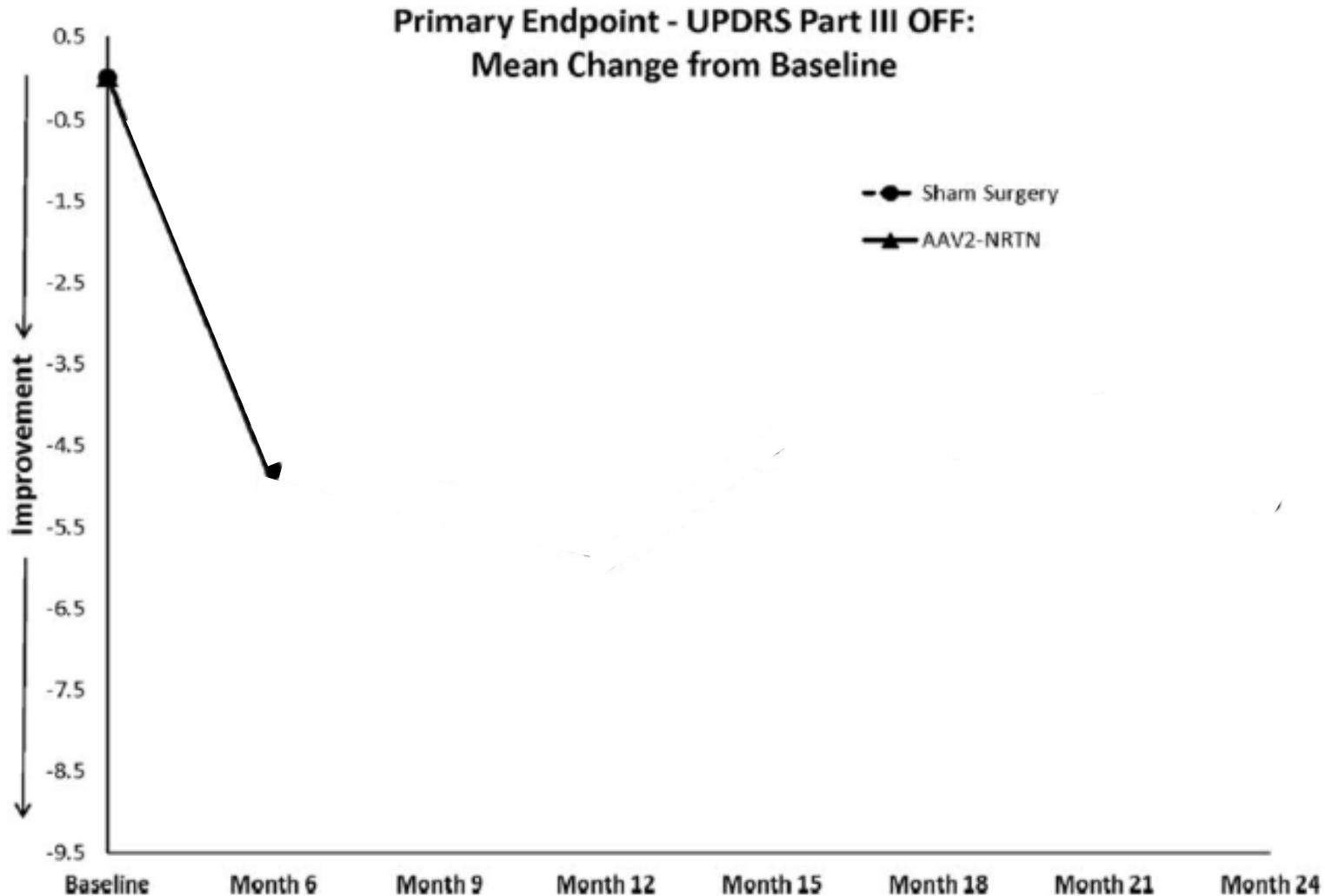




If patients report pain relief during a clinical trial, does this reflect **long-term therapeutic gains**, or **short-term** effects of the clinical trial context?

Do we know the treatment affected the **intended mechanism**? Are all treatments that reduce pain reports 'disease modifying'?

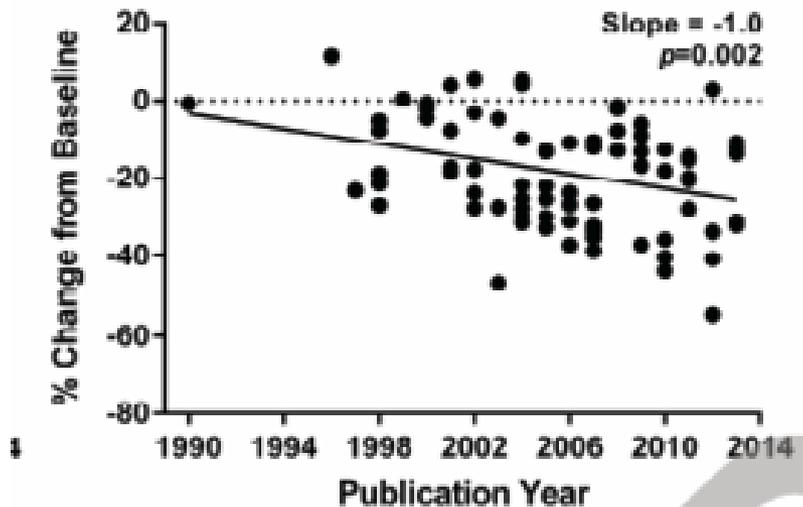
Gene therapy for Parkinson's disease: A randomized, placebo-controlled trial



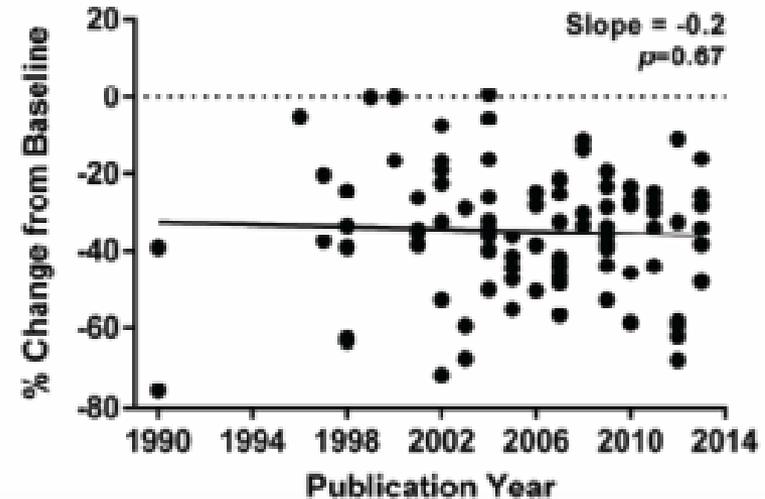
Problems for clinical trials



B. Placebo Response



C. Drug Response



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

Biomarkers for pain

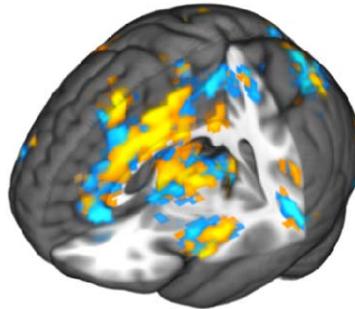
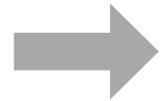


Biomarker: physiological, objectively measured process that indicates a mental experience or process

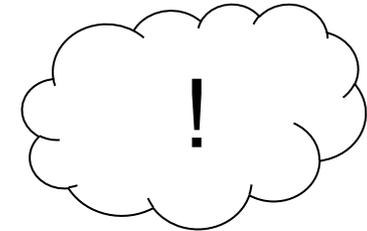
(Biomarker Definitions Working Group, 2001; Borsook et al., 2011)



Noxious event



Biomarker:
Measured pattern



Subjective experience

**Sensitive
Specific**

Brain biomarkers are **gateways** to measures of representations

Biomarkers for pain

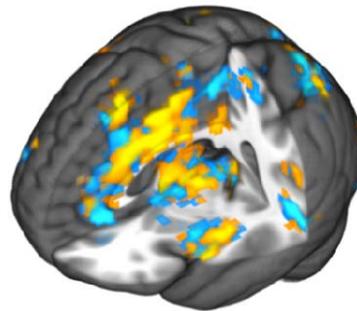
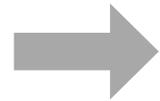


Biomarker: physiological, objectively measured process that indicates a mental experience or process

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Noxious event



Biomarker:
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Subjective experience

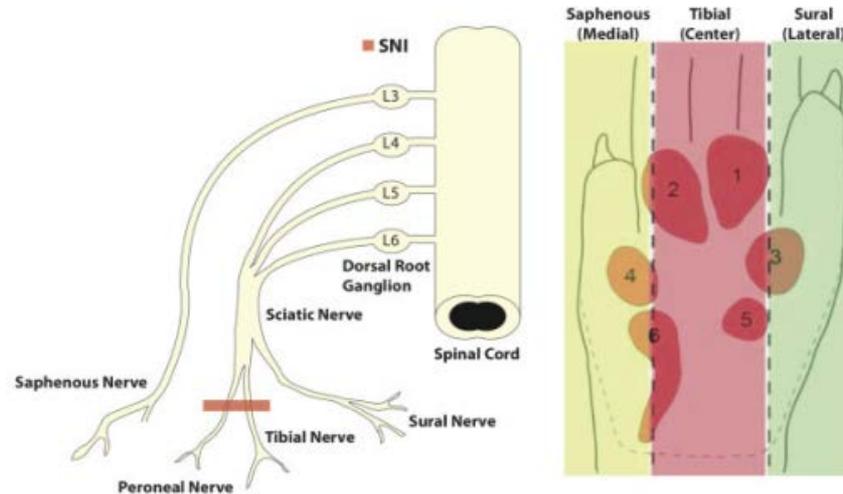
- **Augment** pain reports, don't replace
- Use them to:
- **Understand** mechanism, define **targets** and **biotypes**, measure physiological **components**

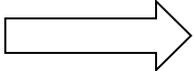
Why **brain** biomarkers?

Neuroplasticity in chronic pain models above the neck



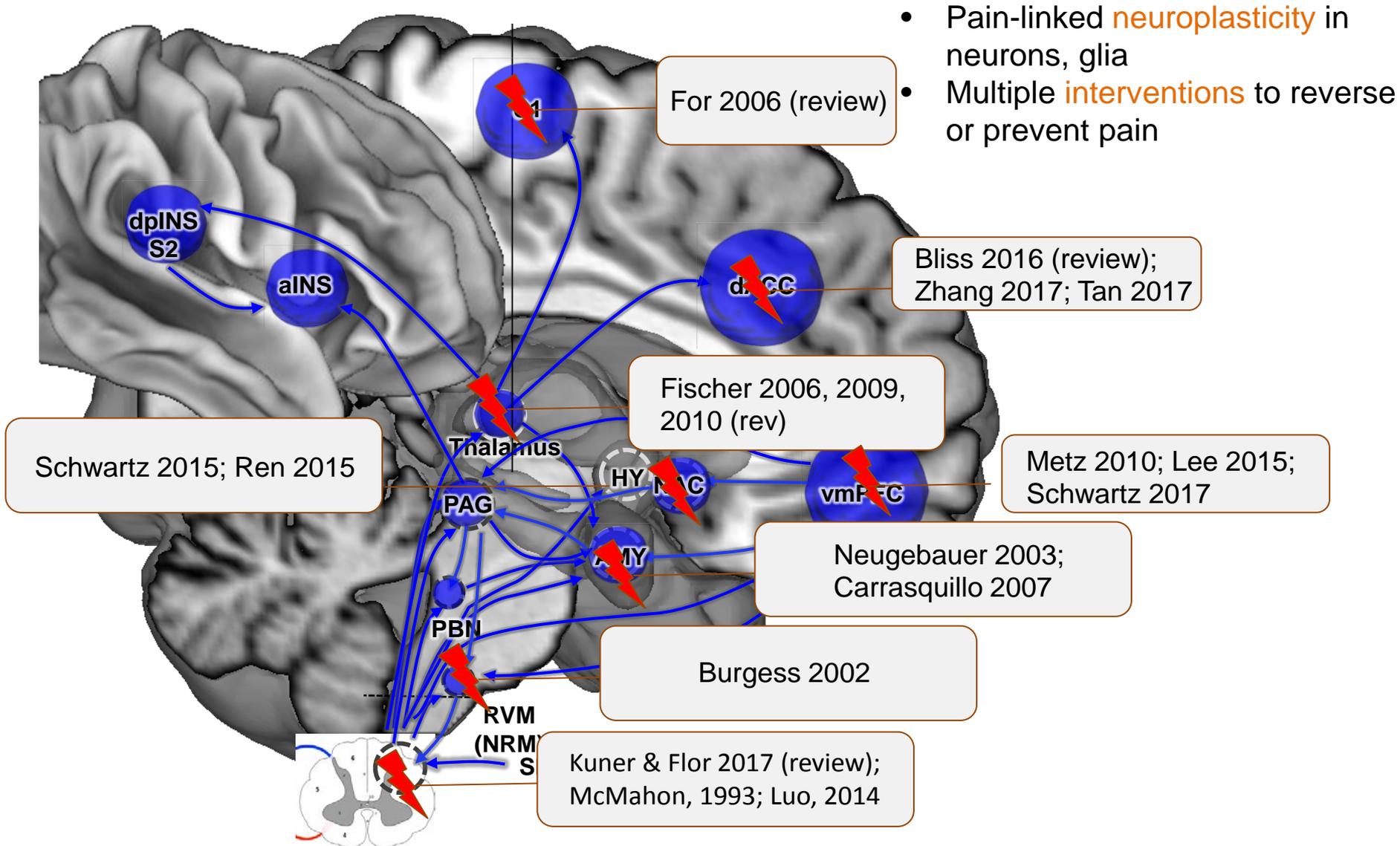
- Multiple pathological mechanisms: Pain-linked **neuroplasticity** in neurons, glia
- Multiple **interventions** to reverse or prevent pain



Nerve injury  Persistent pain behavior
Neuroplasticity
Inflammation

Why **brain** biomarkers?

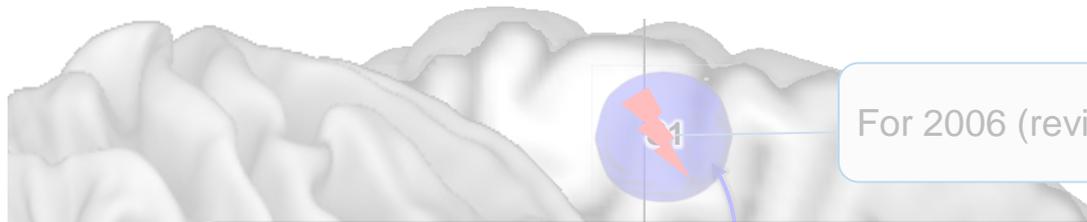
Neuroplasticity in chronic pain models above the neck



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

Why **brain** biomarkers?

Neuroplasticity in chronic pain models above the neck



For 2006 (review)

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

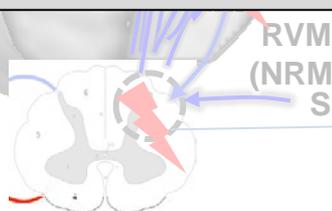
Which mechanisms from animal studies are relevant in humans?

- Need human brain studies

What is the locus of pathology in a given human patient?

- Essential for matching treatments to disease mechanisms

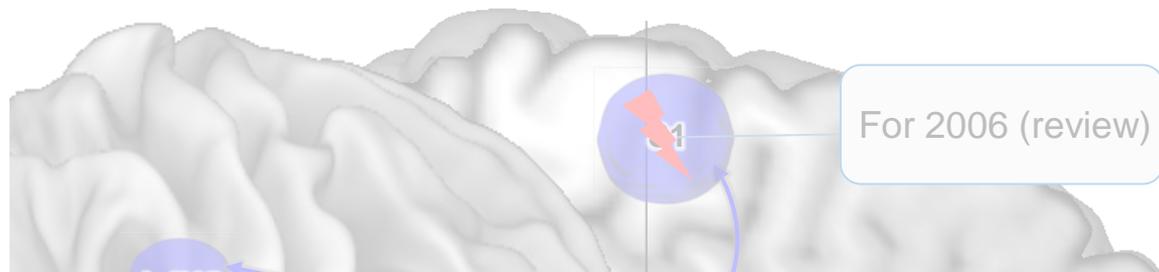
Schw



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

Why **brain** biomarkers?

Neuroplasticity in chronic pain models above the neck



For 2006 (review)

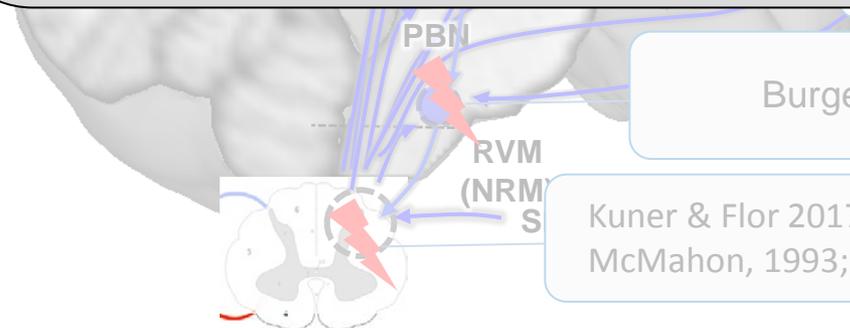
- Pain-linked **neuroplasticity** in neurons, glia
- Multiple **interventions** to reverse or prevent pain

Multiple brain targets

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

Sch

The vast majority of pain drugs act via these circuits



Burgess 2002

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

Use cases



For clinical trialists
and treatment
design



For patients and
clinicians



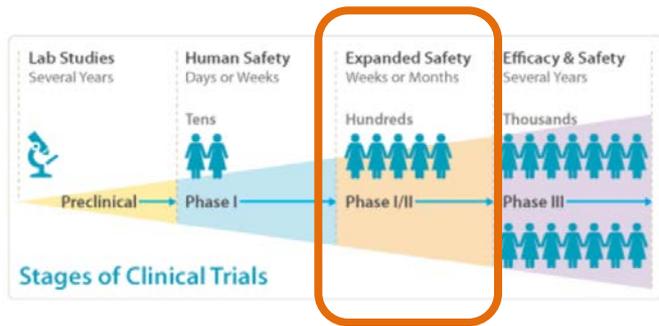
Penetrance
Pharmacodynamics
Efficacy
Mechanism

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



Use cases: “Stop” vs. “Go” decisions in early trials

For clinical trialists
and treatment
design



Phase IIa

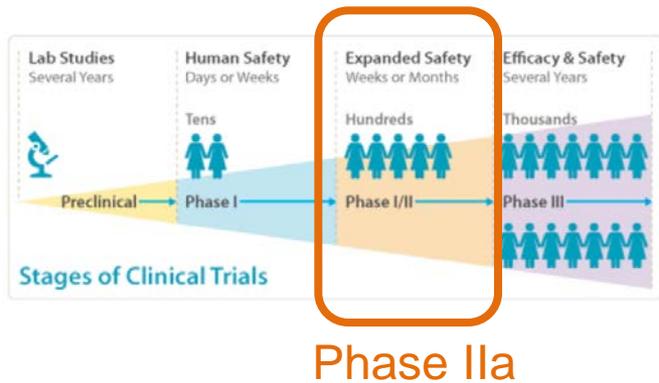
Penetrance
Pharmacodynamics
Efficacy
Mechanism

Study	Drug (reference/ clinicaltrials.gov ID)	Patient condition	n subjects
Analgesic			
a	Gabapentin (9)	Healthy	12
b	Pregabalin (24)	Fibromyalgia	23
c	Pregabalin (25) (NCT00610155)	PTNP	16
d	Tramadol (25) (NCT00610155)	PTNP	16
e	Remifentanil (6, 18)	Healthy	22
f	Remifentanil (21)	Healthy	12
g	THC (23)	Healthy	14
h	Naproxen (22)	Osteoarthritis	19
Control			
i	2nd placebo (study b)	Fibromyalgia	23
j	2nd placebo (study e)	Healthy	22
k	2nd placebo (study f)	Healthy	12
l	Remifentanil (study f)	Healthy	12
m	Remifentanil (study f)	Healthy	12
n	Naproxen (study h)	Osteoarthritis	19

Use cases: “Stop” vs. “Go” decisions in early trials

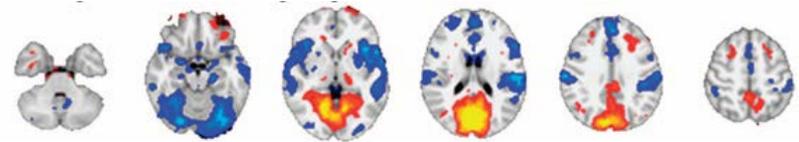


For clinical trialists
and treatment
design



Penetration
Pharmacodynamics
Efficacy
Mechanism

Pharmacodynamics: Reliable drug
vs. placebo discrimination?



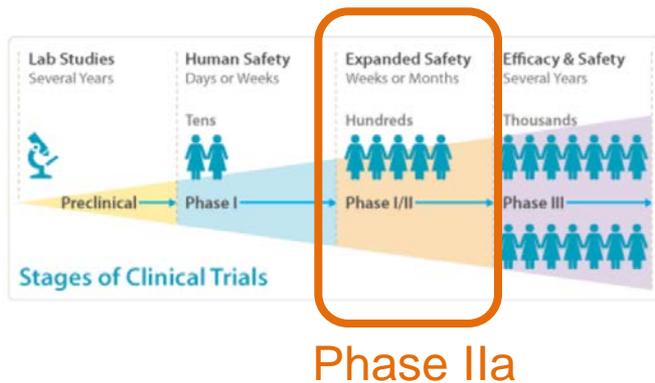
Brain classifier: Yellow = more
activity with drug, blue less

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

Use cases: “Stop” vs. “Go” decisions in early trials

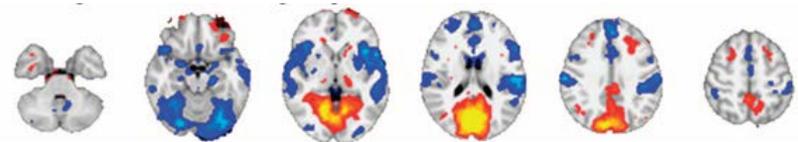


For clinical trialists
and treatment
design



Penetrance
Pharmacodynamics
Efficacy
Mechanism

Discovery and repurposing



- Drug effects are complex
- Multiple systems
- Possible to assess brain similarity across drugs, infer new uses?

Gabapentin	0.92		0.62		0.95	0.58	0.57	0.63
Pregabalin (I)	0.75	0.70	0.75		0.73	0.58		0.74
Pregabalin (II)	0.58	0.74	0.81	0.62	0.77			0.68
Tramadol			0.62	0.56				0.74
Remifentanil (I)	0.75	0.57	0.62	0.56	0.86	0.75	0.57	0.68
Remifentanil (II)	0.58		0.62		0.82	0.83	0.54	0.58
THC							0.71	
Naproxen	0.75	0.65	0.69	0.62	0.86		0.64	0.74
All	0.83	0.61	0.69	0.75	0.82	0.75	0.57	0.74
	Gabapentin	Pregabalin (I)	Pregabalin (II)	Tramadol	Remifentanil (I)	Remifentanil (II)	THC	Naproxen

Testing data set

Training data set

Criteria for brain-based measures



CONSENSUS STATEMENT

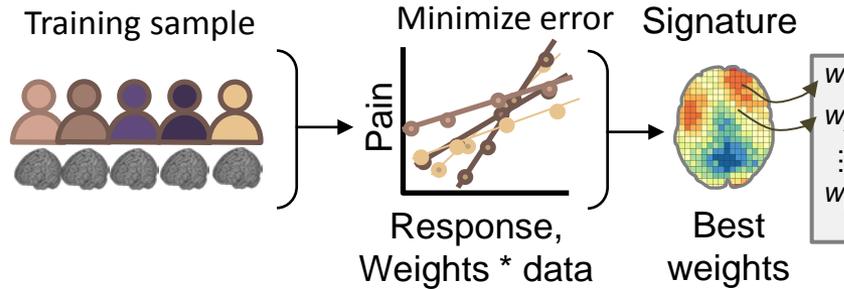
Criteria for establishing biomarkers:

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

Measures of pain using fMRI

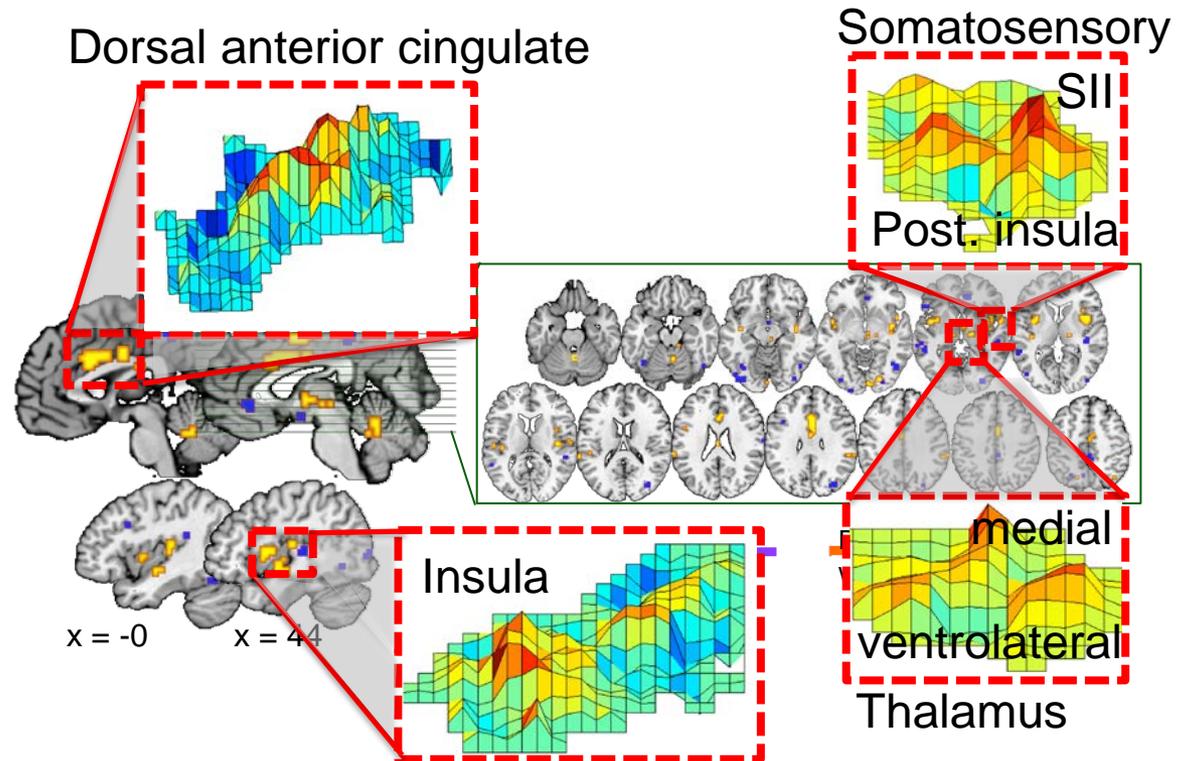


Identify a 'signature' for pain



The 'Neurologic Pain Signature'

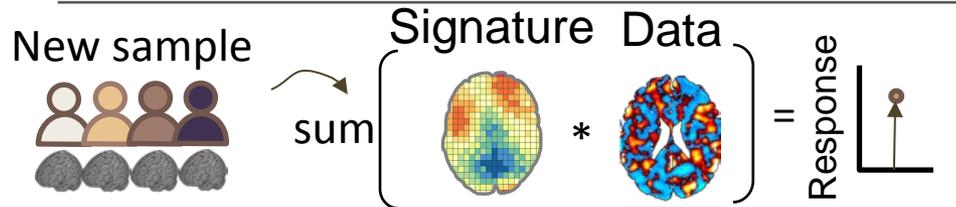
Wager et al. 2013, NEJM





Measures of pain using fMRI

Apply the signature to new test data



The 'Neurologic Pain Signature'

Chang et al. 2015

Woo et al. 2016

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

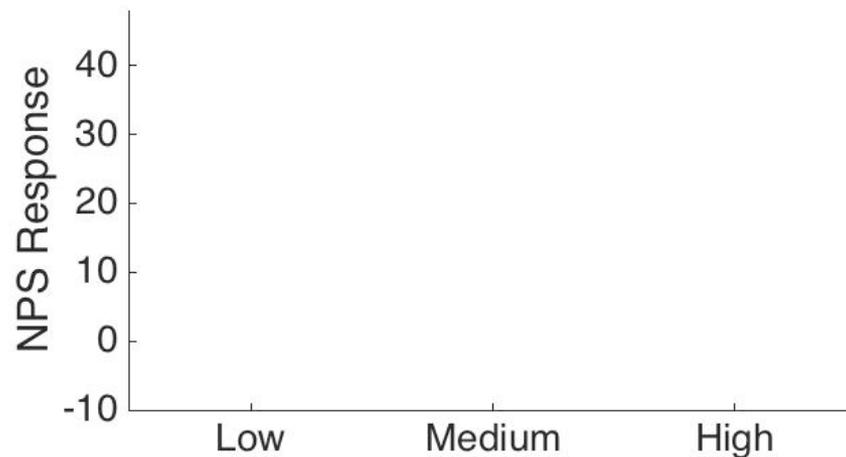
Woo et al. in revision

van Oudenhove et al. in prep

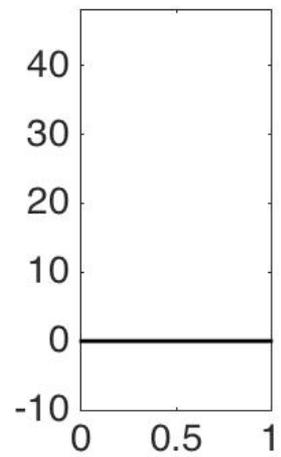
Kragel et al. in prep

Zunhammer et al. in prep

Noxious heat



High - Low



Krishnan et al. 2016, eLife

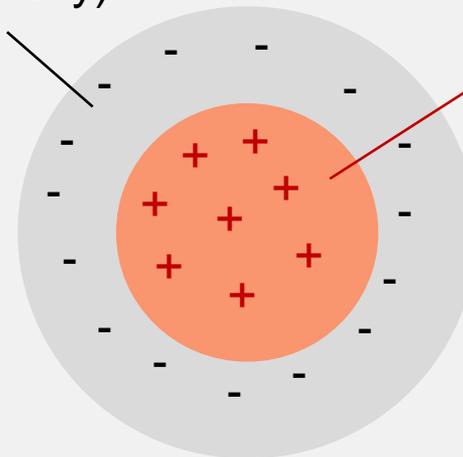


Measures of pain: Sensitivity and specificity of the NPS

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



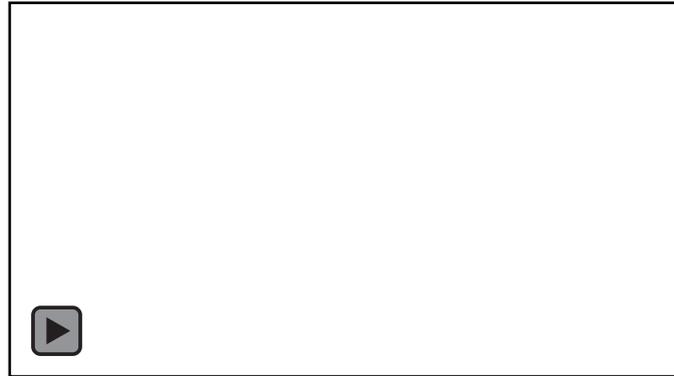
Activated by (sensitivity)

- 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



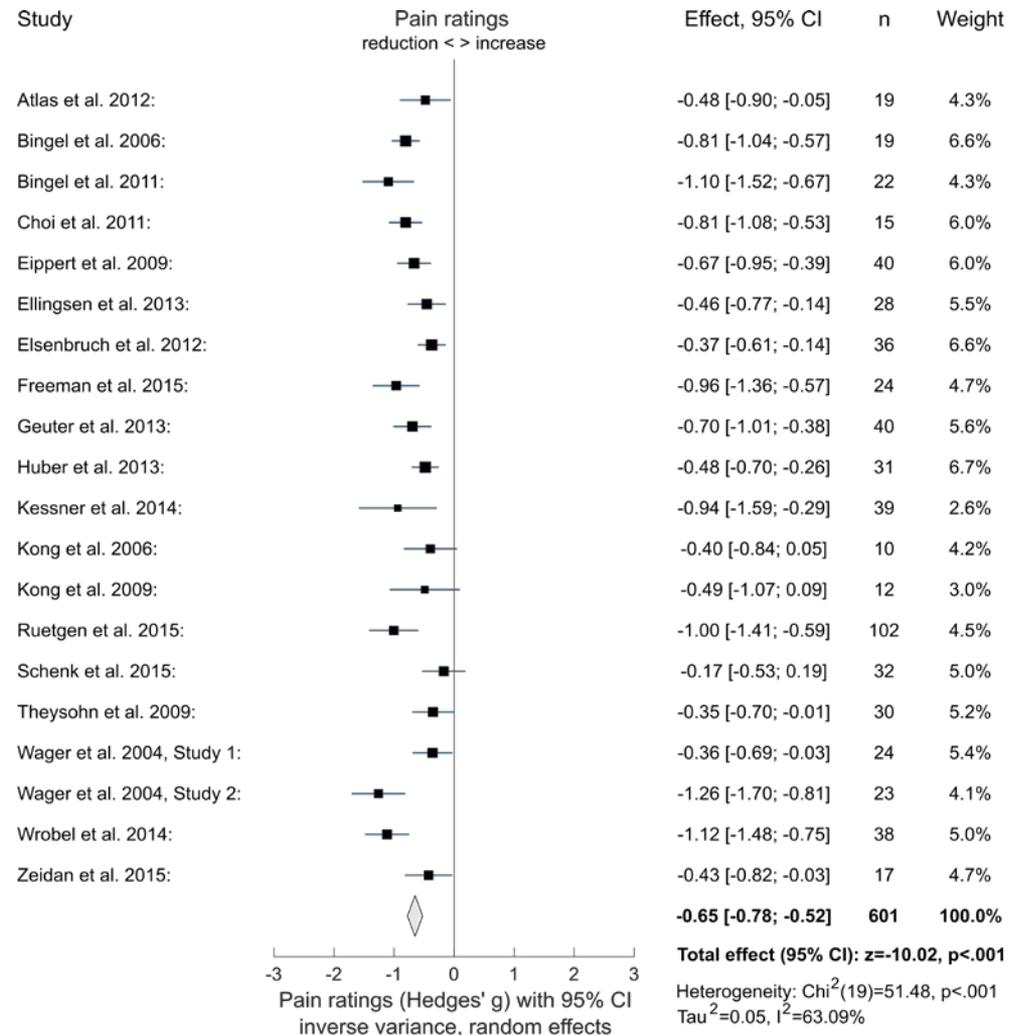
Lorenz J, Schoell E, Weiller C, Büchel, C Wanigasekera V, Wiech K, Mhuircheartaigh R, Lee MC, Ploner M, Tracey I, Choi JC, Yi DJ, Han BS, Lee PH, Kim JH, Kim BH, Eippert F, Schoell ED, Yacubian J, Klinger R, Lorenz J, Ellingsen D-M, Wessberg J, Eikemo M, Liljencrantz J, Endestad T, Olausson H, Elsenbruch 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

Placebo treatment: Strong effects on pain



Placebo significantly reduces pain in all studies.

Average effect size:
 $d = -0.65$



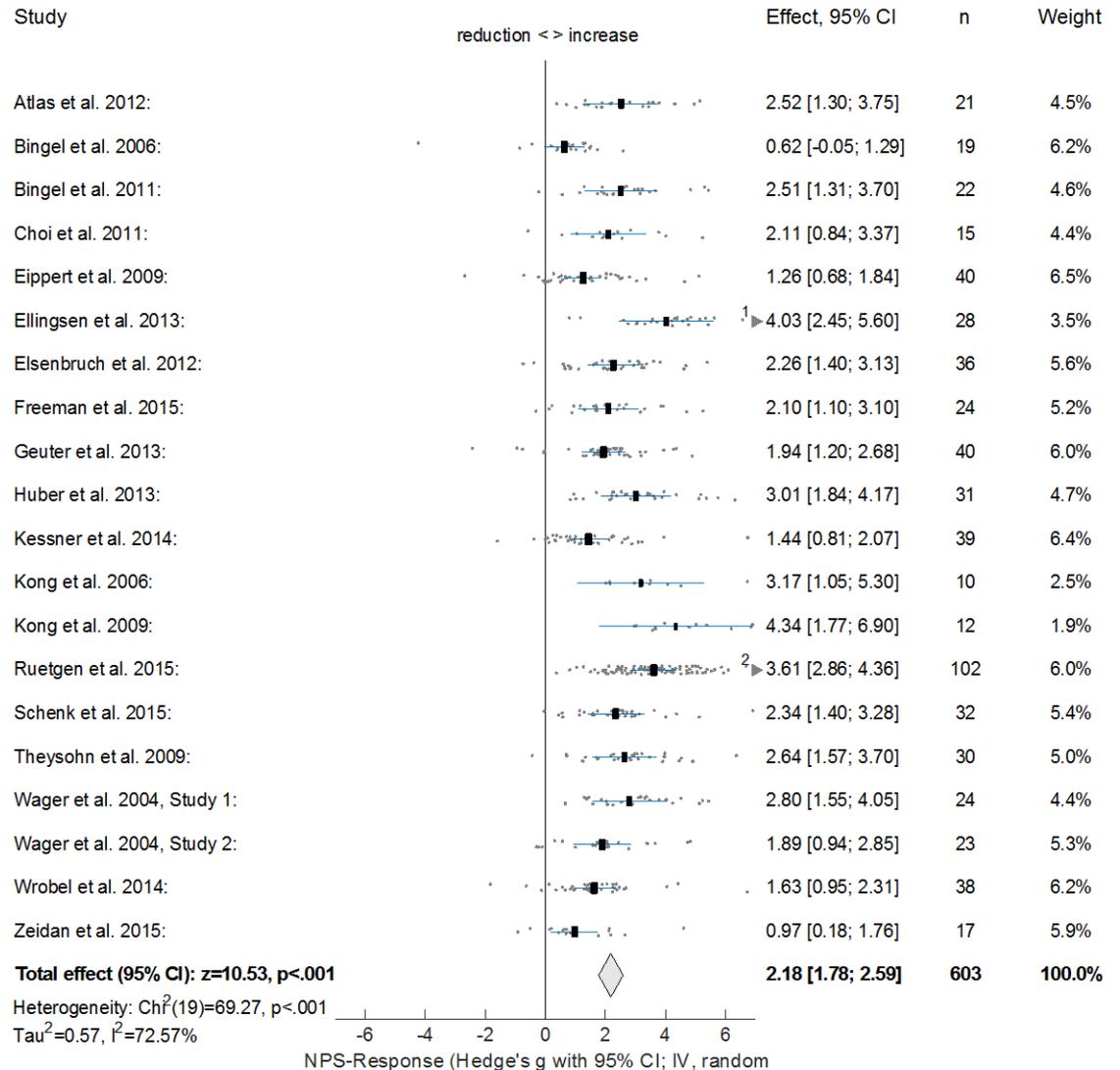
Generalization: NPS responds to diverse types of evoked pain



Generalization:
N = 600 across diverse
population

Electrical, heat, laser,
mechanical

Average effect size:
d = 2.18



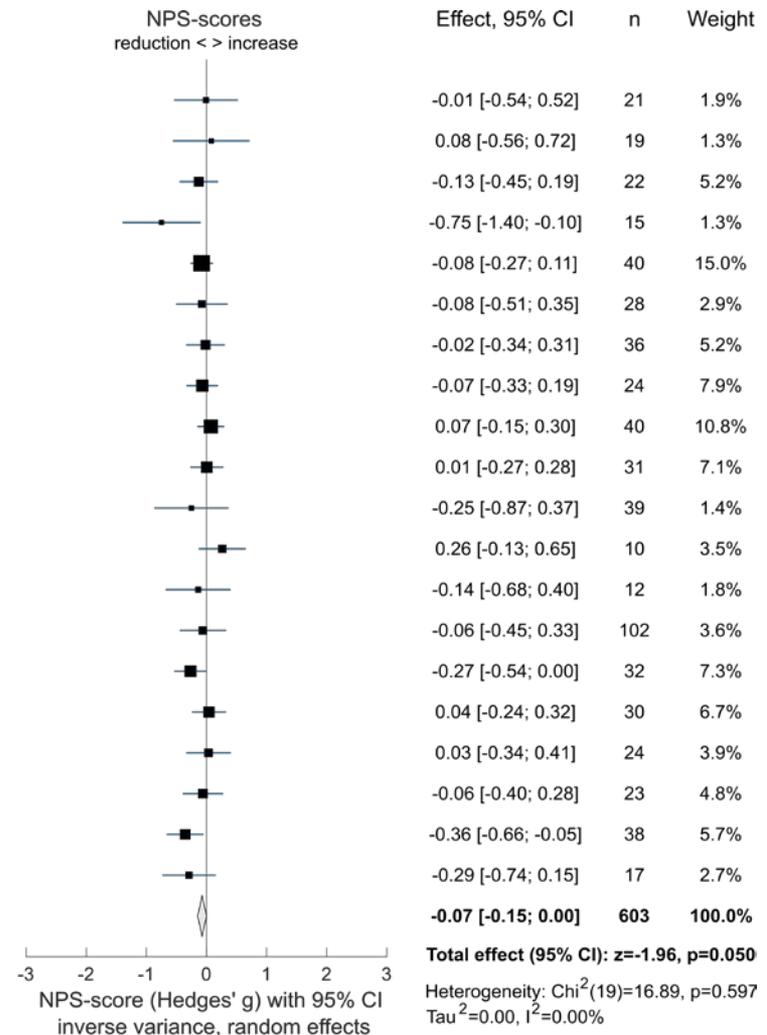
Placebo treatment: No (or little) effect on the NPS



The “Neurologic Pain Signature” is insensitive to placebo

Average effect size $d = -0.07$

Points to contributions from other systems



Use cases



For clinical trialists and treatment design



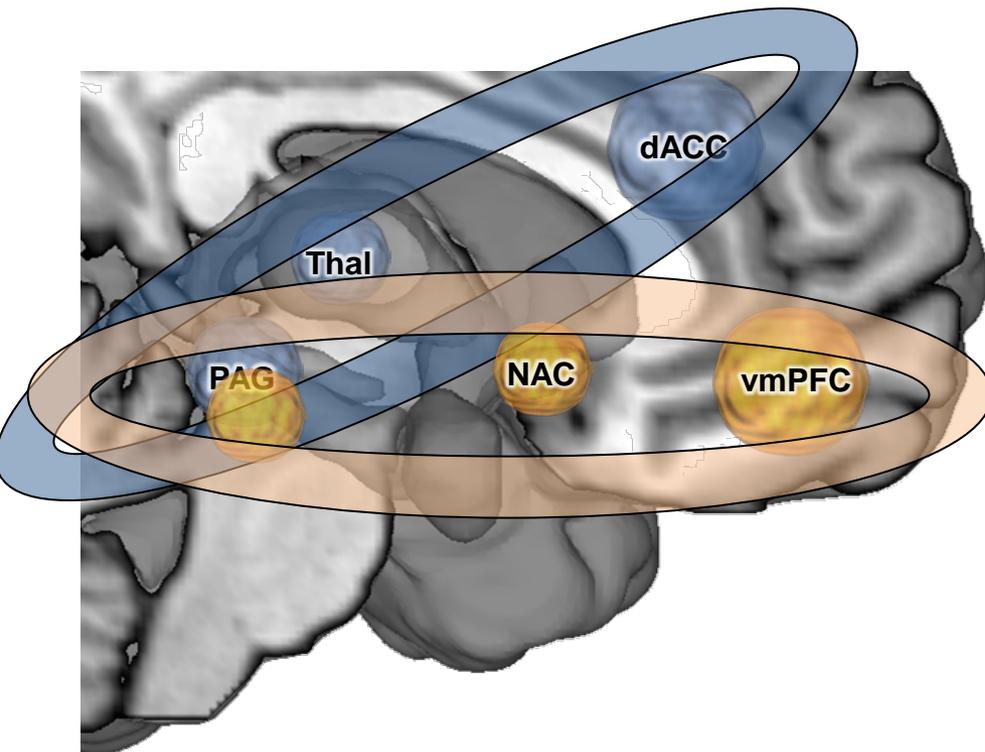
Penetrance
Pharmacodynamics
Efficacy
Mechanism

Intermediate outcomes that are
sensitive to **pain**, but not
placebo

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)

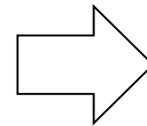
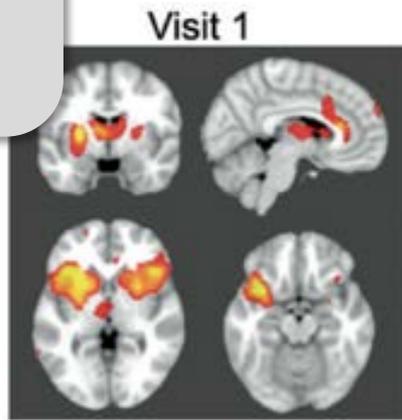
2. Emotion, pain avoidance systems

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

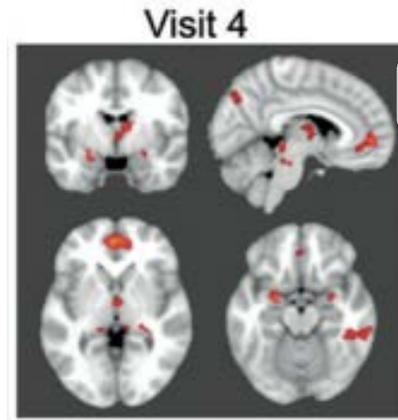


Nociceptive targets:
Cingulate, insula, thalamus

Back pain persists

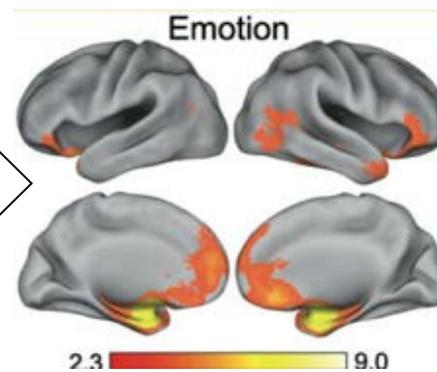
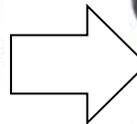
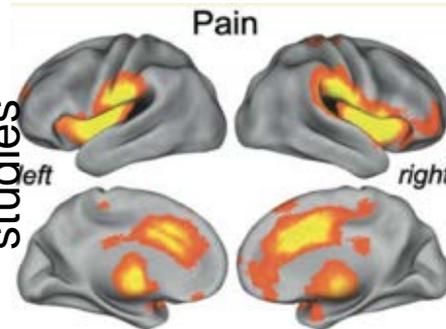


One year later



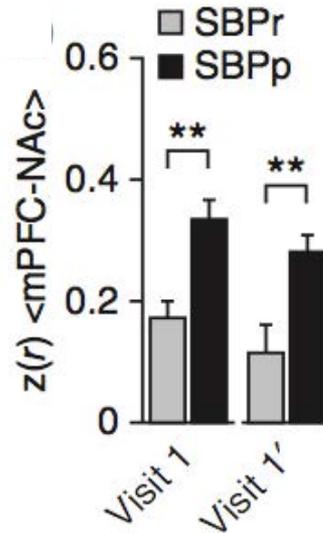
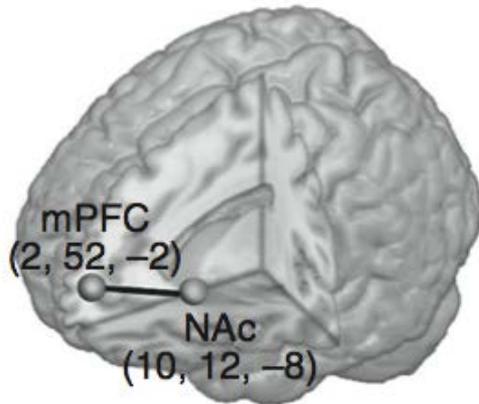
vmPFC

Meta-analysis of basic studies

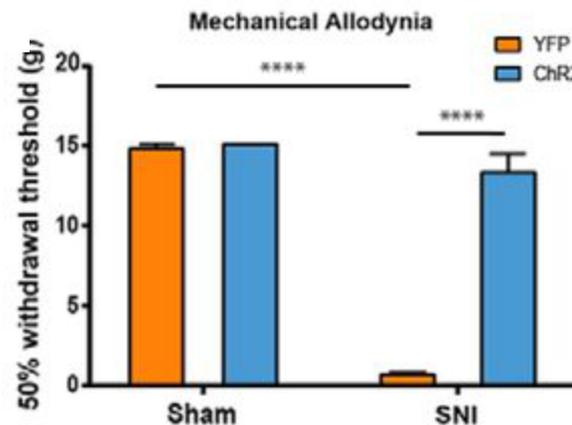
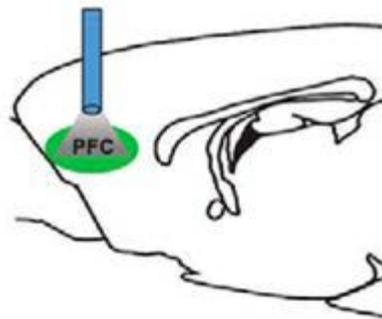


Yarkoni et al. 2011, Neurosynth.org

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

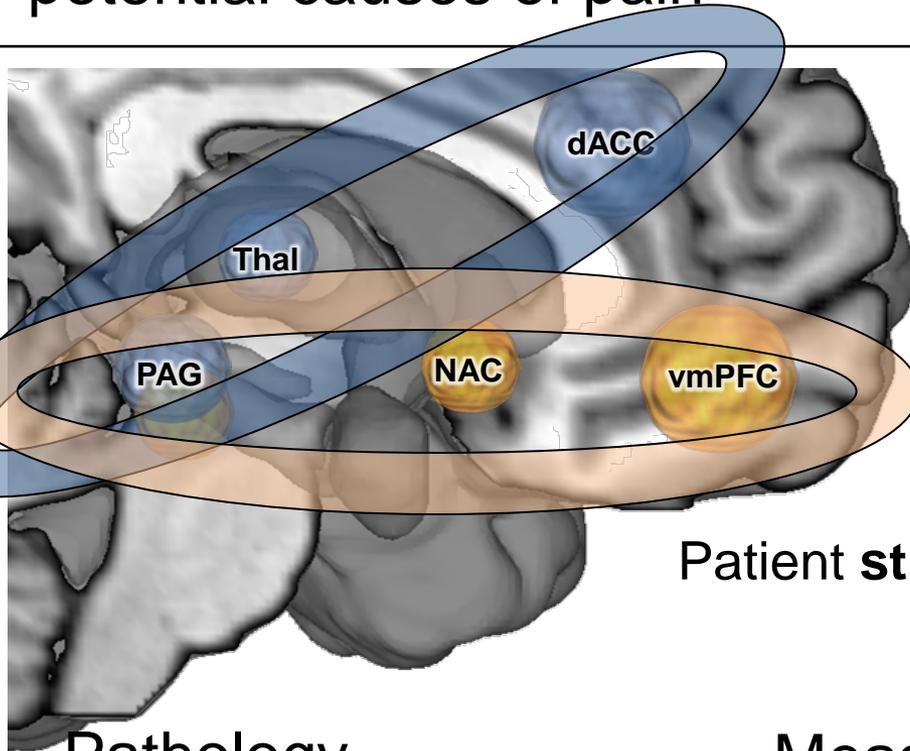


vmPFC-accumbens connectivity predicts development of chronic back pain 1 year later



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

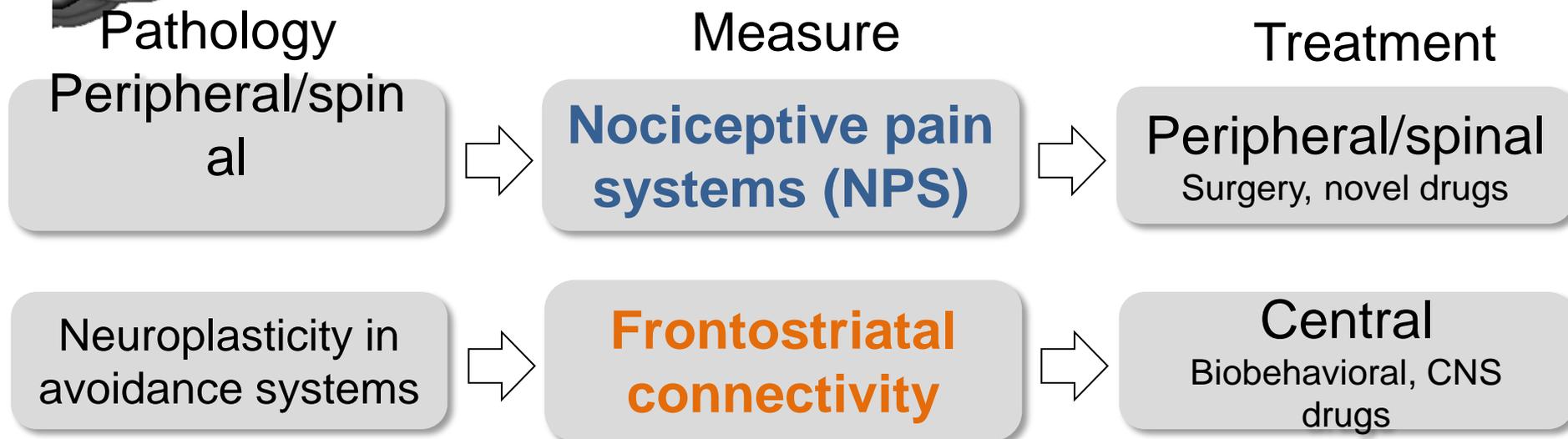
Future treatment decisions? Brain measures for multiple potential causes of pain



1. **Nociceptive pain** system(s)

2. **Pain avoidance** systems

Patient **stratification**: Which treatment is best?



Use cases



For clinical trialists and treatment design



Penetration

Pharmacodynamics

Efficacy —————

Mechanism

Stratification —————

Intermediate outcomes that are sensitive to **pain**, but not

placebo

Select patients likely to benefit

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



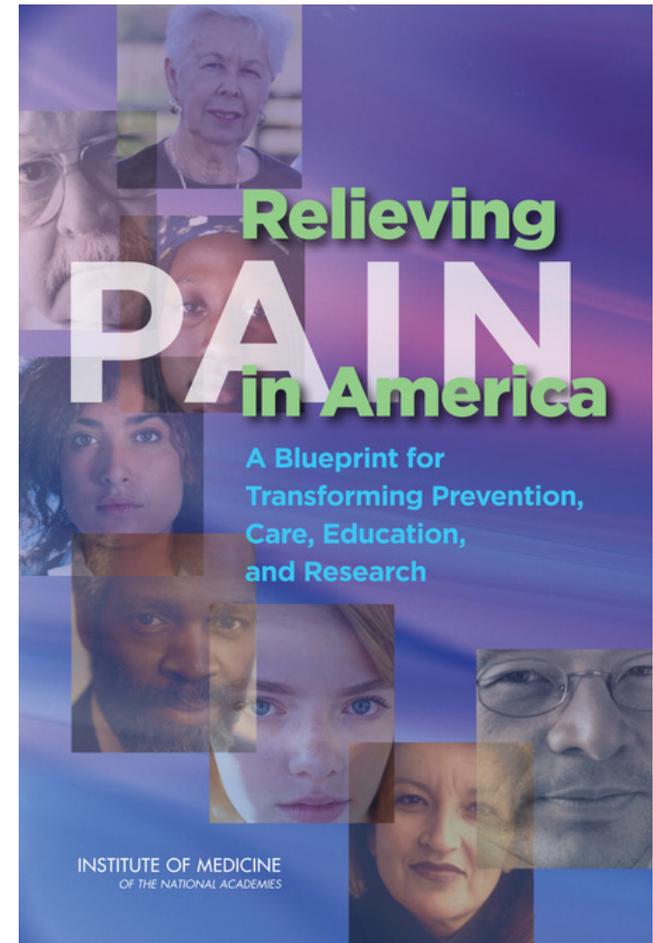
- ~65 yr old male
- Back strain while loading a suitcase onto an airport conveyor belt
- Two weeks later, lower back pain and spasm, left mid-buttock area.
- Disk herniation suspected, but normal MRIs of spine, pelvis, hip
- 5 months of twice-daily physical therapy, acupuncture, deep tissue massage, 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**

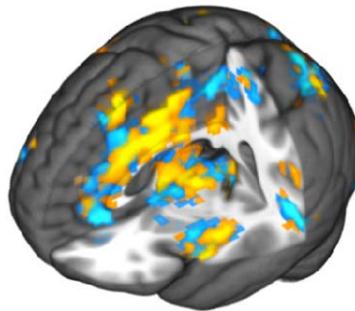
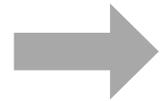


Biomarker: physiological, objectively measured process that indicates a mental experience or process

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



Noxious event



Biomarker:
Measured pattern

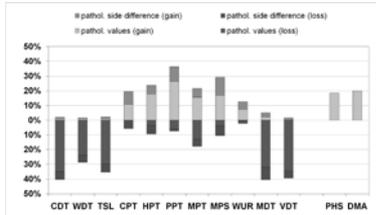


Cognitive impairment
Fear and avoidance
Long-term outcomes
(disability)

Biomarkers for pain – **scalable**, cost-effective **measures**



Behavior (QST)



Genetics

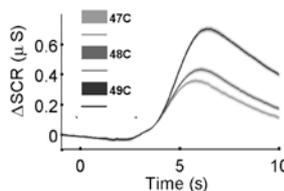
EEG



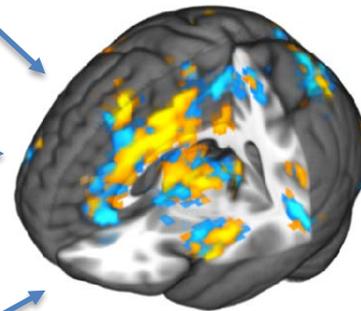
Face and voice



Physiology



Inflammation



Pain

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



Neuroimaging can be useful
for **understanding** and
validating other measures

Biomarkers for pain – **interventions** for prevention and treatment



Behavioral health
(sleep, exercise)

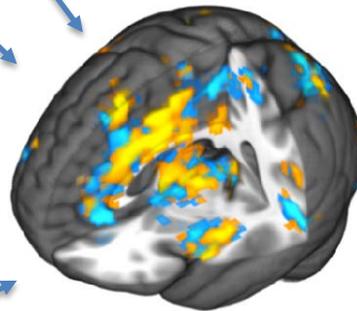
Pharmacotherapy

Physiotherapy

Psychotherapy

Neurofeedback

Neuromodulation



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

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

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