Towards fMRI-based biomarkers for pain and emotion

Tor D. Wager
Department of Psychology and Neuroscience
And the Institute for Cognitive Science
The University of Colorado, Boulder
“…the patient, though conscious that his condition is perilous, may recover his health simply through his contentment with the goodness of the physician”

Pain and emotional distress are core causes of disability in many disorders of the brain and body, and other life events.
Faith by the numbers

$235,400,000,000

$89,000,000,000
Pharma R&D budget (2004)

$4,746,000,000
NIH behavioral science spending, 2013 (est).

• Most research directed towards molecular/genetic causes and treatments, rather than psychology and behavior

• …even when we know behavior is very important (heart disease, lung cancer, pain, depression, anxiety)


Gagnon, Lexchin et al. 2008 (2004 data)

InnoThink Center For Research In Biomedical Innovation; Thomson Reuters Fundamentals via FactSet Research Systems; CDC Advance Data Report #343. 2004; NIH
Drugs for mental health: Very limited success

- Few (any unequivocal?) successes, and few new drugs.
- Pain drugs are often ineffective, and have adverse long-term effects (e.g., Borsook, 2011)
- Criticism of publication bias and small effect sizes in antidepressant studies (e.g., Kirsch 1998, 2008, Fournier 2010)
- Limited success of antipsychotics in reducing disability
- Much effort in rebranding old drugs and marketing

“We don't really understand how the brain actually works, what goes awry when you have mental illness, and therefore you're not able to target your treatment to that specific circuit in the brain.”

- Zul Merali

What is the role of the mind in health?

How to intervene?

Psychological interventions, drugs, both?
Complexity of the “emotional brain”: vertically integrated circuits

- Conceptual pattern generators: Situational schemas
- Social context
- Interoceptive context
- Expected future events
- NTS Vagal
- Visceral pattern generators
- Thermoregulation, emesis, nociception, etc.
- Fight, escape, submit, pursue, recover, etc.
- Affective pattern generators
- Memory, place context
- vmPFC
- DMPFC
- OFC
- Insula
- vmPFC
- Hipp
- PAG
- Hy
- NAC
- Amy

Wager & Atlas, under review; Saper 2002; Bandler 2001
We need neuroimaging-based biomarkers

- **Biomarker**: physiological process that is objectively measured as an indicator of normal or pathological responses
  - (Biomarker Definitions Working Group; Borsook et al., 2011)

**Disease-relevant mental features**

- Varieties of pain
- Cognitive performance
- Autonomic dysregulation
- Sadness, anhedonia

Identifying strongly predictive human brain patterns: A major goal of cognitive neuroscience

Patterns can a) be mapped to animal systems, b) inform us about the nature of underlying representations, and c) be used as markers for treatment effects
Overlap logic:
Similar brain = similar process

"Pain-processing"

Wager lab, N=115, Thermal pain on left arm, p < .05 FWE corrected

e.g., Apkarian et al. 2005; Coghill et al. 1999, many others
Anterior cingulate and insula: Shared representations of “pain?”

Physical pain

Anterior cingulate

Anterior Insula

Social pain (rejection)

Green = self, red = other

Coghill 1999; Apkarian 2005; Atlas 2010, 2012; Many others

Singer 2004; Jackson 2005; Fan 2012; others

Using brain patterns/regions as markers

“Pain-processing”

Wager lab, N=115, Thermal pain on left arm, p < .05 FWE corrected

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Modulation of pain processing

- Expectation (Atlas et al. 2010)
- Emotion (Roy et al. 2010)
- Religious symbols (Wiech et al.)
- Meditation (Zeidan et al. 2010)
Biomarkers for mental events?

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

- Reward (ventral striatum)
- Value (medial prefrontal cortex)
- Memory (hippocampus)
- Visual processing (V1)
- Social cognition (dorsomedial prefrontal cortex)
- Specific emotions (fear: amygdala; disgust: insula)
- Etc.
The problem with current approaches

These brain results are not **biomarkers**.

- **Definition**
  - We do not agree on precisely what these patterns are (which voxels?)
  - Lack of exact replication

- **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. \[ P(\text{brain} \mid \text{absence of psych})? \]

- **Thus, we do not know their diagnostic value.**
  \[ P(\text{psych} \mid \text{brain})? \]

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e.g., Button et al. 2013 Nat Neurosci; Ioannidis 2005
We need to do better…and we can

PAWEŁ ŁÓJDŻENIA

The vast majority of brain research is now drowning in uncertainty. It’s time to build a more complete understanding of the mind, says Ingefei Chen

Hidden depths

The vast majority of brain research is now drowning in uncertainty. It’s time to build a more complete understanding of the mind, says Ingefei Chen.

It's four in the afternoon when I meet John Kanzius, but lines of fatigue are deepening under his eyes. He’s exhausted with yet another set of preparatory meetings at his day job as a professor of neuroscience at the University of California. He has two young children and spends most of his time thinking about the brain and its mysteries. Kanzius is a neuroscientist and a psychologist, and he has been working on the mechanisms that underlie learning and memory for over 20 years. He has made significant contributions to our understanding of how the brain learns and remembers, and his research has been widely cited in the scientific literature.

Kanzius is sitting in a comfortable chair, surrounded by books and papers. He looks at me and smiles, clearly enjoying our conversation. "I’m not sure what you mean by ‘drowning in uncertainty’," he says, "but I do think that we need to do better." He goes on to explain that many of the biggest questions in neuroscience remain unanswered, and that our understanding of the brain is still evolving. "We need to do better and we can," he concludes.

Kanzius is a firm believer in the power of collaboration and interdisciplinary approaches to solving complex problems. "We need to bring together experts from different fields to tackle the challenges that face us," he says. "This is how we will make real progress in our understanding of the brain."

Kanzius is an advocate for open science and the sharing of data and results. "We need to be more transparent about our research and more open to new ideas," he says. "This will help us to build a more complete understanding of the mind."
The problem of specificity

Desired inference: Pain ← anterior cingulate and insula
Observed data: Pain → anterior cingulate and insula
Emotion
Attention
Decision-making

Base rate, P(activation) across 3489 neuroimaging studies Yarkoni et al. (2012)

Yarkoni, Poldrack, Van Essen, & Wager, 2011, Nature Methods
A new approach: Multi-study validation of brain markers

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

Characterize:
Properties of marker across studies

Replicate:
Assess generalizability across individuals, studies

Use biomarkers to understand mental phenomena
Machine learning: Key to specificity

- Machine learning oriented towards
  a) Optimizing prediction, b) assessing specificity across defined alternatives

Predicting the orientation of perceived lines

Predicting the semantic category of words, pictures

So far: Mostly requires training data and knowledge of “ground truth” for individuals
Few applications to health-related outcomes

Kamitani & Tong, 2005

Predicting Human Brain Activity Associated with the Meanings of Nouns

Mitchell et. al, 2008
fMRI-based biomarkers for pain
Analysis framework

Multivariate approach: Multiple brain regions predict pain

Manipulation
- Noxious input

Brain
- Anterior cingulate
- Thalamus
- Anterior insula
- Posterior insula/SII

...etc.

Behavior
- Pain reports
- Predictive map

- Many predictors (200,000!!)
- Use *machine learning* to stabilize maps
- Test *generalization*: Train on some subjects, test on others
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

Anticipatory activity  Pain-related activity  Report-related activity

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<tr>
<td>Cue</td>
<td>Anticipation</td>
<td>Heat</td>
<td>Rest</td>
<td>Rate pain</td>
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<td>2 s</td>
<td>6 s</td>
<td>10 s</td>
<td>14 s</td>
<td>4 s</td>
</tr>
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Time during Trials

Wager et al. 2013, NEJM
Study 1, Neurologic Pain Signature: Pain-predictive map

Threshold for display: $q < .05$ FDR (bootstrap)

Wager et al. 2013, NEJM
Study 1, NPS results, predicting pain in new individuals

Pain vs. other affective events

Threshold for display: q < .05 FDR (bootstrap)

Sensitivity and specificity

- pain vs. warm, pain cue, pain recall
- Forced-choice: Which is more painful?
- 100% sensitivity/specificity
- Single-interval: Is this condition painful?
  >= 94% sensitivity and specificity

Wager et al. 2013, NEJM
What does the NPS track? Is it just a ‘fancy skin thermometer’?

Threshold for display: $q < .05$ FDR (bootstrap)

Predicted vs. actual temperature across phases of trial

Time course of stimulation vs. pain report

Pain signature time course correlates better with pain than stimulus
Average $r = 0.9$ vs. $r = 0.8$, $p < .001$

Wager et al., 2013, NEJM
Study 2: New sample, new scanner
Exact replication of the NPS pattern

- Pain vs. warm: 93% sensitivity/specificity
- 90+% sensitivity/specificity for 1 degree increments
- Tracks pain more closely than temperature

Wager et al. 2013, NEJM
Study 3: Social pain

N = 40 participants
All romantically rejected

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

A

<table>
<thead>
<tr>
<th>Fixation Cross</th>
<th>Ex-Partner (vs. Friend)</th>
<th>Rating</th>
<th>Visuospatial Control Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>15</td>
<td>5</td>
<td>18</td>
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</table>

B

<table>
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<th>Fixation Cross</th>
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Kross et al., 2011, PNAS
Rejection is very similar to physical pain

Regions activated in both [Hot vs. Warm] and [Reject – Friend] contrasts

- Anterior cingulate
- Anterior insula
- Medial thalamus
- SII

Red: Physical pain, emotional pain overlap
Blue: OP, containing SII; Eickhoff, 2009

Kross et al., 2011, PNAS
Biomarker 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

- **Test Hot vs. Warm**
- **Test Reject vs. Friend**

Pain biomarker expression

- **Pain**
- **Rejector**
- **Photo**

Pain biomarker response

- **High Pain**
- **Low Pain**

Wager et al. 2013, NEJM
Study 4: Treatment response

Continuous infusion of remifentanil (N = 21)

Atlas et al. 2012, J Neuro
Wager et al. 2013, NEJM
A new look at shared representations for affective events
Anterior cingulate and insula: Shared representations of “pain?”

Physical pain

Anterior cingulate

Anterior Insula

Social pain (rejection)

Pain empathy (observed pain)

Green = self, red = other

Coghill 1999; Apkarian 2005; Atlas 2010, 2012; Many others

Singer 2004; Jackson 2005; Fan 2012; others

Pain and rejection:
Common regions, different patterns

Discrimination accuracy

Correlations in predictive patterns

Rej - Friend

Hot - Warm

Physical pain
Social pain

Test Hot vs. Warm
Test Reject vs. Friend

Woo, Koban et al., in prep
Anterior cingulate and insula: Shared representations of “pain?”

**Physical pain**

- Anterior cingulate
- Anterior insula

**Social pain (rejection)**

**Pain empathy (observed pain)**

- Green = self, red = other

Coghill 1999; Apkarian 2005; Atlas 2010, 2012; Many others

Singer 2004; Jackson 2005; Fan 2012; others

Study 5: Vicarious vs. experienced pain (N = 28)

- Location: Arm vs. foot
- Intensity: Low, medium, high

Overlap between somatic and vicarious pain (FDR q < .01)

- Activation overlap
- Pattern similarity
- Somatotopy

Vicarious Pain
Somatic Pain
Overlap

Location:

\[ x = -5 \]
\[ x = 3 \]
\[ x = -40 \]
\[ x = 44 \]
Neurologic Pain Signature response: Generalizability and specificity

- Transfer across body sites (hand and foot)
- Specificity relative to Vicarious pain

N = 28, University of Colorado, Boulder
- Thermal pain on left arm or foot
- Vicarious pain on hand or foot

Krishnan et al., in prep; scaling of signature response is study dependent
Vicarious vs. experienced pain: Different patterns in overlapping regions

C Overlap between somatic and Vicarious pain (FDR q < .01)

<table>
<thead>
<tr>
<th>Vicarious Pain</th>
<th>Somatic Pain</th>
<th>Overlap</th>
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<tbody>
<tr>
<td>S2</td>
<td>dACC</td>
<td>dpINS</td>
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</table>

Krishnan et al., in prep
Is there a *different* pattern for vicarious pain?
Vicarious vs. experienced pain: Different predictive patterns

Neurologic pain signature (NPS) pattern (Wager et al., 2013, NEJM)

LASSO-PCR Vicarious pain (SIMP) ratings

Krishnan et al., in prep
Why does it work?

Machine-learning derived patterns provide more fine-grained information.

Brain regions include many neurons with different functional properties.

Visual orientation columns

Anterior cingulate:
Separate neurons respond to mechanical and thermal pain (25% respond to both).

But overall activation of anterior cingulate is non-specific...

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

Sikes and Vogt (1982)
Using biomarkers to understand how treatments work

A new look at the cognitive regulation of pain
Understanding treatments: Same pain relief, different mechanisms?

- Anti-inflammatory treatments
- Cognitive reappraisal
- Cognitive therapy
- Mindfulness
- Music
- SSRIs
- Placebo
- Opiates
- Meditation
- Catastrophizing
- Hypnosis
- Relaxation
- Virtual reality
- Acceptance therapy
- Anxiolytics

e.g., Fields, 2004, NRN
Cognitive reappraisal

- “Rethinking” the meaning of emotional events
- An analogue to clinical psychologically focused therapies

Wager, et al., 2008; Silvers, Buhle et al. 2013
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
Reappraisal effects

Regulation vs. Passive experience

Regulate-up vs. Regulate-down

SMA
cluster p < .05

NAc (L)

cluster p < .05

voxel-wise
p < .001

Activity

Conditions

Activity

Conditions

Reappraisal effects
Reappraisal effects:

• Large and reliable effect on pain report (gold standard for assessing pain)

• Effects on prefrontal cortex and ‘value-related’ subcortical regions comparable to previous emotion regulation studies

• Satisfies conditions for a meaningful test of reappraisal on pain processing using the Neurologic Pain Signature
Cognitive reappraisal of pain

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

If no: Appraisal mainly influences post-nociception judgment
Results: Does reappraisal influence PPBN? No.
Nucleus Accumbens-Medial PFC: A possible second route to pain

Stronger connectivity at Time 1 predicts persistent back pain (black) vs. recovery (gray) up to 1 year.

Baliki et al. 2012, Nat Neurosci

Nac-mPFC pathway mediates reappraisal effect on pain

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

β₁: 0.05 (0.01)***
β₂: 0.55 (0.05)***
β₃: -6.12 (0.76)***

β₄: -13.34 (2.90)***
β₄': -12.13 (2.43)***

Appetitive vs. aversive Reappraisal

Pain rating
Implications: “Cognitive bias” or multiple pain systems?

Interpretation 1: NAc-VMPFC activity reflects ‘decision bias’

Interpretation 2: NAc-VMPFC activity is a separate, functionally significant pathway that contributes to pain

VMPFC/NAc increases and/or connectivity predict real world behaviors (see Berkman & Falk, 2011)
• Transition to chronic pain (Baliki et al. 2012)
• Subsequent reductions in smoking (Falk et al., 2011)
• Weight gain (Demos et al. 2012)

VMPFC projects directly to spinal autonomic centers and may be critical for conceptually driven affect (e.g., Roy et al. 2012)
Dissociating brain and peripheral sources of pain

“Pathology” diagnosed by three neuroradiologists, in the absence of pain


Carragee et al. 2005 (N = 100): Psychosocial variables, not peripheral pathology, strongly predicted both long- and short-term disability with low back pain over 6 years
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
Biomarkers for other affective responses
Overlap in systems for pain and emotion?
Biomarkers for aversive emotional responses

- Can brain activity predict individual subjects’ negative emotion ratings?
- Is the predictive pattern similar to that for physical pain?

- Aversive photographs: International affective picture system (IAPS); Lang, Bradley and Cuthbert, 1999

- N = 121 subjects (cross-validation sample) and N = 61 (holdout test sample)

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<th>3</th>
<th>4</th>
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<tr>
<td>Mean</td>
<td>1.08</td>
<td>4.32</td>
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</table>

Chang, Gianaros, Manuck, & Wager, In Prep
Is it just for pain?
Biomarkers for aversive emotional responses

Training (cross-validation Data (n=121)
Predict Emotion Ratings
LASSO-PCR, LOSO Cross-Validation

Aversion Pattern Weights

Activity predicts:
- Increased negativity
- Decreased negativity

Test Data (n=61)

Emotion Rating
High – low aversion
Accuracy 100%

Chang, Gianaros, Manuck, & Wager, In Prep
Is it just for pain?
Biomarkers for aversive emotional responses

Training (cross-validation Data (n=121)
Predict Emotion Ratings
LASSO-PCR, LOSO Cross-Validation

Aversion Pattern Weights

Neurologic Pain Signature Weights (Wager et al. 2013)

Aversion and pain patterns are uncorrelated
(r = 0.04)

Chang, Gianaros, Manuck, & Wager, In Prep
Brain representation of emotion categories

• Database
  – 148 human neuroimaging studies of emotion categories (excluding general affect)
  – 377 maps
  – 2519 participants

• Model
  – Generative, hierarchical Bayesian spatial point process model of joint activation, conditional on a particular category of emotion (Kang et al., 2011, JASA)
The model

• Model joint likelihood of set of activation points for a given study contrast
### ‘Decoding’ emotion type

<table>
<thead>
<tr>
<th>Emotion</th>
<th>Anger</th>
<th>Disgust</th>
<th>Fear</th>
<th>Happy</th>
<th>Sad</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual</td>
<td>0.43</td>
<td>0.76</td>
<td>0.86</td>
<td>0.58</td>
<td>0.65</td>
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<tr>
<td>Classification accuracy</td>
<td>0.07</td>
<td>0.08</td>
<td>0.06</td>
<td>0.11</td>
<td>0.09</td>
</tr>
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43 – 86% accurate  
Chance is 20%

Valence:
Figure 2. Characterizing emotion categories based on known functional networks

A

Resting-state networks

Anatomically defined regions

Cortex

Basal ganglia

Cerebellum

Hippocampus

Thalamus

Prefrontal

Premotor

Motor

Somato-sensory

Parietal

Visual

Anger

Disgust

Fear

Happy

Sad

Cortex

Basal Ganglia

Cerebellum/Brainstem

Thalamus

Amygdala

Hippocampus
Figure 3. Network characterization and graphical properties

A

Anger
Disgust
Fear
Happy
Sad

B

dAN
SMN
VAN
FPN
Vis
Def
Lim

Cortex
Basal Ganglia
Cerebellum/Brainstem
Thalamus
Amygdala
Hippocampus

C

anger
disgust
fear
happy
sad

Connectivity
Summary

• Too little research on the role of emotion in health, and it is costing us in mental health

• It may be possible to develop human brain markers for specific types of affective experience

• Specific patterns – not ‘one size fits all’

• Integrate animal and human neuroscience approaches to studying affect, physiology, and health
“Modern medicine will become really scientific only when physicians and their patients have learned to manage the forces of the body and mind...

-Rene Dobos
Discoverer of the first clinically used antibiotic
<table>
<thead>
<tr>
<th>Postdocs</th>
<th>Graduate Students</th>
<th>Staff</th>
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<tbody>
<tr>
<td>Matheiu Roy</td>
<td>Scott Schafer</td>
<td>Luka Ruzic</td>
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<tr>
<td>Marina López-Solà</td>
<td>Jenna Reinin</td>
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<tr>
<td>Luke Chang</td>
<td>ChoongWan Woo</td>
<td>Leonie Koban</td>
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<td>Anjali Krishnan</td>
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<td>Liane Schmidt</td>
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<td>Jessica Andrews-Hanna</td>
</tr>
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<td></td>
<td></td>
<td>Yoni Ashar</td>
</tr>
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</table>
CU Collaborators (actual and projected)

Joanna Arch
Marie Banich
Dan Barth
Sona Dimidjian
Naomi Friedman
John Hewitt
June Gruber
Tiffany Ito
Matt Jones
Matt Keller
Chris Lowry
Steve Maier
Francois Meyer
Akira Miyake
Yuko Munakata
Randy O’Reilly
Soo Rhee
Mark Whisman

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NIMH

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Gatsby Comp. Neuroscience
DRG (Germany)
CIRC (Canada)
Swiss NSF
Catalan government (Spain)
What systems mediate reappraisal effects on pain?

Nuc. accumbens/Ventral striatum

Wager et al. 2008 Neuron (aversive images)

Baliki et al. 2012 Nat Neuro
mPFC-NAC connectivity predicts development of chronic pain 1 year later
What systems mediate reappraisal effects on pain?

- No effect of temperature increases on this pathway

\[ \beta_1: -0.05 (0.01)*** \]
\[ \beta_2: 0.55 (0.05)*** \]
\[ \beta_3: -6.12 (0.76)*** \]

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

Regulate-up vs. -down

\[ \text{Direct}(\beta_4'): 12.13 (2.43)*** \]

Pain rating

• No effect of temperature increases on this pathway
Cognitive bias…or conceptually driven pain genesis?

Interpretation 1:
NAc-VMPFC activity reflects ‘decision bias’

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VMPFC projects directly to spinal autonomic centers and may be critical for conceptually driven affect (e.g., Roy et al. 2012)
Psychological modulation of pain: Current projects

What is the contribution of “nociceptive pain” and “value-driven” pain systems to:

Psychological modulation of pain

- **Placebo** effects (Scott Schafer, Jason Buhle, Leonie Koban)
- Pain **expectancy** (Lauren Atlas, Anjali Krishnan)
- **Mindful acceptance** (Hedy Kober, Buhle, Kevin Ochsner, others)
- **Distraction** (Jason Buhle)
- **Meditation** (David Perlman and Richie Davidson, Josh Grant and Bob Coghill)
- **Emotion** (Mathieu Roy)
- **Social support** (Marina Lopez-Sola)
- **Social emotions** (Leonie Koban)

Cultural and individual differences

- **Gender and ethnicity differences in pain reporting** (Liz Losin and Luke Chang)

Clinical pain

- **Fibromyalgia** (Marina Lopez-Sola, Jesus Pujol)
- Chronic **low back pain** (Etienne Vachon-Presseau, Mathieu Roy, Pierre Rainville)
Can we identify neuroimaging-based markers for other affective states?
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Classification based on brain pattern

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<td>0.02</td>
<td>0.04 0.86 0.06 0.03</td>
</tr>
<tr>
<td>happy</td>
<td>0.00</td>
<td>0.07 0.23 0.58 0.11</td>
</tr>
<tr>
<td>sad</td>
<td>0.00</td>
<td>0.07 0.20 0.09 0.65</td>
</tr>
</tbody>
</table>

43 – 86% accurate
Chance is 20%

Valence:
Figure 2. Characterizing emotion categories based on known functional networks

A

Resting-state networks

Anatomically defined regions

Anger

Disgust

Fear

Happy

Sad

Legend:
- Red: Cortex
- Green: Basal Ganglia
- Pink: Amygdala
- Blue: Cerebellum/Brainstem
- Yellow: Thalamus
- Turquoise: Hippocampus

Brain regions:
- dAN
- SMN
- FPN
- vAN
- Def
- Limbic
- Basal ganglia
- Cerebellum
- Hippocampus
- Thalamus
- Prefrontal
- Premotor
- Somato-sensory
- Parietal
- Vis
- Temporal
- CM
- LB
- Limbic
- FPN
- vAN
- SMN
- dAN

Figure 3. Network characterization and graphical properties

A

Anger
Disgust
Fear
Happy
Sad

B

dAN
SMN
vAN
Vis
Def
Lim

Cortex
Basal Ganglia
Cerebellum/Brainstem
Thalamus
Amygdala
Hippocampus

C

anger
disgust
fear
happy
sad

Connectivity

1
2
3
4
5
6
7
“Emotions” are important because they are labels for integrated brain states highly relevant for survival and well being

Emotion reports are very complex, and brain measures can help provide objective measures of some critical ‘ingredients’

Neuroimaging can yield biomarkers for pain
- patterns of brain activity diagnostic of acute pain in normative (non-clinical) cases

Biomarker patterns can be used to examine:
- The nature of brain representations (anterior cingulate / salience?)
- How different treatment effects (psychological, drug) may be mediated through different systems

We may be able to develop similar neuroimaging-based markers for other emotional states
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Social and physical pain: Shared mechanisms?

Study 1, Biomarker results predicting new individuals

Threshold for display: $q < .05$ FDR (bootstrap)

Forced-choice classification
“which is more painful?”

- Pain vs. pain anticipation: 100% accurate
- Pain vs. pain recall period: 100% accurate
- High vs. low pain: 100% accurate

Wager et al., in press, NEJM
If we could develop neuroimaging measures that track emotion, what would they look like?

- **Patterns** across multiple systems
- **Models** of connections and interactions across systems conditional on particular emotional experiences

![Brain diagram with arrows indicating connections between different functions: attention, action, perception, prospection, memory, organ function, metabolism.](image-url)
Pain prediction

- A biomarker for pain should:
  - Predict the magnitude of pain experience in normative samples
  - Apply to individual persons
  - Apply across samples, scanners, and populations (i.e., exact replication of the biomarker response)
  - Be specific to physical pain (i.e., not “salience” or any negative emotion)
  - Respond to known analgesic treatments

- Strategy
  - Train brain patterns to predict self-reports in normative samples, when pain reports are known to be reliable
  - Test those patterns in cases in which the ground truth is unknown
Depression

High placebo response rates in meta-analyses of antidepressant trials (Kirsch, 2008; Fournier et al., 2010)

- Placebo vs. wait-list controls: Placebo effects 2x active drug (Kirsch & Saperstein, 1998;1999)

- Placebo vs. wait-list controls: (Kirsch & Saperstein, 1998;1999)

- Comparator vs. double-blind trials: (Sneed et al., 2008; Rutherford et al., 2009)

- 60% vs. 46% Response rate
- OR = 1.53, P < .001

Active Placebo, 5.1 points
Active drug, 2.4 points
Natural history, 2.5 points

http://www.columbia.edu/cu/psychology/tor/
• Direct projections from medial prefrontal cortex to sympathetic ganglia (also via hypothalamus and PAG)
“Modern medicine will become really scientific only when physicians and their patients have learned to manage the forces of the body and mind…

-Rene Dobos
Discoverer of the first clinically used antibiotic
Premises:

- Understanding emotion and pain are central to understanding well-being …and central to understanding how to intervene

- We have neglected psychology, and emotion in particular, in the study of health and disease. And it has cost us.
Emotions at the center of life

Happiness and well being

Social relationships
- Empathy
- Loneliness
- Sadness
- Joy

Physical and mental health
- Pain
- Shame
- Comfort
- Emotional pain
- Anger
- Satisfaction

Exploration and learning

Physical performance

Optimal cognitive function

Happiness and well being