Can We Image Pain

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Disclosure

• None
Overview

• What is the science behind attempts to localize a pain generator?

• Is it possible to tell if it is “all in the head”?
Imagine

- Looks bad
- Easy to see his pain
- What does he feel or sense?
Fibromyalgia

- It hurts here
- No incident cause
- Hard to see her pain
- Psychological factors
- Because we cannot identify a cause or pathology - does not mean it is not real
Back Pain

Why does my back hurt so much?
First Step: History & Diagnosis

• Central
• Radicular
• Referred
Mimics:
referral patterns for visceral pain
Back Pain: *The Easy* Dx/Tx

- Identify The Source - A Fracture
- Concordant with exam
- Feels better after augmentation
Functional pain: *The Enigma*

- Black disc phenom
- Schmorl’s nodes

Spinal inflammation can explain some of the causes of pain

- Detected by magnetic resonance
- Nuclear medicine
- Molecular imaging

Ability of MRI to detect inflammatory changes
Need to have concordance for pain

Effusion in cavity of atlanto-odontoid joint
Facet osteoarthritis

SPECT

Radiology 2008 vol 238 issue
Utility of single photon emission computed tomography/computed tomography imaging in evaluation of chronic low back pain
Twenty-one-year-old man with duration of AS 3 years; with lumbar IBP for 6 months

Right Costovertebral joint

both costotransversal joints with concomitant osteitis of the adjacent rib and transversal processes

Ankylosing Spondylitis
intense thoracic IBP for 6 months

Bone marrow oedema in right costo-transversal joint (short arrow), erosions and subchondral bone oedema right and left costovertebral joints (long arrows).

Identifiable Causes
Right Radiculopathy

epidural fibrosis

Bony Mass Effect
Pearl

- Treat based on sophisticated and intuitive imaging
- With clinical concordance
Isolated septic facet joint arthritis as a rare cause of acute and chronic low back pain

WE are visualizing..

- Edema
- Enhancement
- Mass effect
- Fracture lines
- Misalignment

- These are indirect signs
Three-Dimensional MR Neurography of the Lumbosacral Plexus
Chhabra et al., Semin Musculoskelet Radiol 2015; 19(02): 149-159
Brachial Plexus

• Advancement in 3D imaging, better fat-suppression techniques, and superior coil designs

• Imaging supported by clinical and/or EMG/surgical data,

Chhabra et al., AJNR 2013 34: 486-497
Neurotmesis

- A 43-year-old woman with loss of function in the left upper extremity following recent neck surgery
- Coronal MIP 3D STIR SPACE image shows severed, enlarged, and hyperintense C5 and C6 nerve roots with distal end bulb neuromas

Chhabra et al., AJNR 2013 34: 486-497
On The Horizon
Imaging Nerves and Physiological Changes

Neuropathic Pain Mechanisms and Imaging
Tung et al., Semin Musculoskelet Radiol 2015; 19(02): 103-111
Elliot Krane

• “We think of pain as a symptom, but there are cases where the nervous system develops feedback loops and pain becomes a terrifying disease in itself”
CRPS / RSD

- Long after the injury is healed
- There is persistent pain
Perception

• Understanding of the plasticity and complexity of pain processing...
• The strength and unpleasantness of pain is neither simply nor directly related to the nature and extent of tissue damage
Perception of Pain

- The first pain pathway sends signals via nerves about the intensity of painful stimuli to a number of regions in the brain.
- Typically the anterior cingulate cortex has been associated with pain perception.
Anatomy of the pain pathway

Cell. 2009 October 16; 139(2): 267–284
Pain is usually an aversive signal processed by at least three pathways:

- 2 ascending pain-evoking pathways
- At least one descending pain-inhibitory pathway
- The medial pain pathway encodes the motivational/affective component of pain i.e., the unpleasantness
- The lateral pathway encodes the discriminatory/sensory component
- The descending pathway suppresses ongoing pain in a state dependent manner
- The medial and lateral pain pathways are processed in parallel and can be individually modified without affecting the other pathway

DE RIDDER & VANNESTE Neuromodulation September 2015
**Ascending and descending pain pathways**

The lateral ascending pathway processes the discriminatory components of pain whereas the medial pathway processes the motivational, affective, attentional components of pain.

The pain inhibitory pathway suppresses ongoing pain.
“Pain Matrix”

• *Psychological concept* to illustrate that our perception of pain varies based on a number of other factors like mood, energy state, attention, social situation

• The regions of the brain involved in pain perception are also unsurprisingly are also involved in general perception
Measures of neuroreceptors and neurotransmitters

- Two main approaches have been used to study the neurochemistry of pain
- Examination of brain metabolic function in response to relevant pharmacological agents, and direct measurement of receptors for neurotransmitters
Brain imaging studies

- Indicate the cortical and sub-cortical substrate that underlies pain perception
- Instead of locating a singular “pain center” in the brain, neuroimaging studies identify a network of somatosensory (S1, S2, IC), limbic (IC, ACC) and associative (PFC) structures receiving parallel inputs from multiple nociceptive pathways
Lyrics

• It hurts when I laugh sometimes, feels good when I cry
• Tell me when you looking at me
• Can you see the pain in my eyes

• [Trey Songz - Pain Lyrics | MetroLyrics](http://www.metrolyrics.com/pain-lyrics-trey-songz.html)
Immediately after pain onset, there was a significant pupil dilation which reached its maximum about 2 s after pain onset. While this maximum pupil dilation did not differ with pressure intensity, the pupil dilation was larger for the higher pressure intensity in the period from 10 s after pressure onset to pressure offset.
• How we connect Physiology and imaging
• With increased neuronal activity
  ...the brain needs more nutrients (glucose, O2)
• Functional MRI
  ...indirectly measures neuronal activity
BOLD: fMRI

- **BOLD** = **B**lood **O**xygenation **L**evel–**D**ependent fMRI

- *indirectly* measures blood flow via blood oxygenation, and local metabolic changes due to increased neuronal activity
At rest

Visual task

Youssef et al.,
NeuroImage 2016

• Data reveal brainstem circuitry activated during acute noxious orofacial stimuli
• And its relationship with conditioned pain modulation (CPM) analgesia
Brainstem activation during brief noxious stimuli applied to the right side of the mouth
All in the Head?

An fMRI-Based Neurologic Signature of Physical Pain

Tor D. Wager, Ph.D., Lauren Y. Atlas, Ph.D., Martin A. Lindquist, Ph.D.,
Mathieu Roy, Ph.D., Choong-Wan Woo, M.A., and Ethan Kross, Ph.D.
Original Article

An fMRI-Based Neurologic Signature of Physical Pain

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N Engl J Med
Volume 368(15):1388-1397
April 11, 2013
Study Overview

• The experience of pain is poorly understood.
• The authors describe a neurologic signature that discriminates between the sensations of painful heat and nonpainful heat, is specific to physical pain, and is responsive to the analgesic agent remifentanil.
Prediction of Physical Pain on the Basis of Normative Data from Other Participants in Study 1.

Application of the Neurologic Signature to Physical and Social Pain Stimuli in Study 3.

# Pain-Classification Performance, According to Study.

<table>
<thead>
<tr>
<th>Study</th>
<th>Discrimination between Pain and No Pain†</th>
<th>Effect Size‡</th>
<th>P Value</th>
<th>Performance on Forced-Choice Test¶</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Signature-Response Threshold</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Positive Predictive Value</td>
</tr>
<tr>
<td>Study 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painful vs. warm¶</td>
<td>1.40</td>
<td>95 (86–100)</td>
<td>95 (86–100)</td>
<td>95 (85–100)</td>
</tr>
<tr>
<td>Pain vs. pain anticipation</td>
<td>0.36</td>
<td>100 (100–100)</td>
<td>99 (96–100)</td>
<td>95 (86–100)</td>
</tr>
<tr>
<td>Pain vs. pain recall</td>
<td>0.54</td>
<td>95 (85–100)</td>
<td>94 (89–98)</td>
<td>79 (64–92)</td>
</tr>
<tr>
<td>Study 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Painful vs. warm</td>
<td></td>
<td></td>
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<tr>
<td>Painful vs. near pain threshold</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High vs. low warmth</td>
<td>1.00</td>
<td>56 (36–75)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
</tr>
<tr>
<td>Study 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Painful vs. warm</td>
<td>1.40</td>
<td></td>
<td></td>
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<tr>
<td>Painful vs. rejecter</td>
<td>1.40</td>
<td></td>
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<tr>
<td>Rejector vs. friend</td>
<td>1.40</td>
<td></td>
<td></td>
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<tr>
<td>Study 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Painful vs. warm, before drug treatment</td>
<td>1.40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painful vs. warm, during drug treatment</td>
<td>1.61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painful before vs. during drug treatment</td>
<td>1.61</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* Study 1 included 12 trials each in painful and warm conditions. Study 2 included a mean (±SD) of 24±13 trials for pain and 36±9 trials for warmth, depending on the ratings. Study 3 included 8 trials each in painful and warm conditions. Study 4 included 3 trials for pain and 3 for warmth in the before-drug-treatment condition and in the condition with peak drug concentration. CI denotes confidence interval.
† The tradeoff between sensitivity and specificity at different thresholds was assessed by means of receiver-operating-characteristic (ROC) plots; the signature-response threshold that minimized overall classification errors is reported here.
‡ For the area under the ROC curve, chance is 0.5. Discriminability is a measure of effect size under a gaussian model. Performance varied across studies, according to the number of trials averaged to form the condition maps.
§ For the two-choice (forced-choice) discrimination test, the classification threshold for the difference between paired observations is 0. The sensitivity, specificity, and positive predictive value are the same and are equal to the decision accuracy.
¶ Painful conditions were defined as temperatures greater than 44.5°C and as ratings of more than an average of 5.80 points on a visual-analogue scale (VAS), and warm conditions as temperatures of less than 44.5°C and ratings of less than 3.34 points on the VAS.
** Study 2 was conducted with the use of a scanner with a different field strength (3 T), so the threshold was reestimated.
†† Participants rated pain or warmth intensity on a continuous VAS, with scores ranging from 0 to 99 points for warmth and from 100 to 200 points for pain. Pain was defined as a score of more than 125 points, near the pain threshold as a score of 75 to 125 points, high warmth as a score of 50 to 100 points, and low warmth as a score of 0 to 50 points.
†‡ The threshold derived from study 1 was applied.

Study Conclusions

- It is possible to use fMRI to assess pain elicited by noxious heat in healthy persons.
- Future studies are needed to assess whether the signature predicts clinical pain.
Close, But no cigar

• Signatures useful when self-reports (of Pain) are suspect

• Before fMRI-based signatures for pain can be tested in medical decision-making ... generalizability of our findings must be assessed.
Empathy Imaged

- Neuroimaging evidence suggests that observing others’ suffering and pain
- Elicits activations of the anterior insular and the anterior cingulate cortices
- Associated with subjective empathetic responses in the observer

journal *Brain* 2012 Liberati et al
Anterior Insular Cortex Is Necessary for Empathetic Pain Perception
Liberati et al.

- study included six patients who had electrodes implanted in the insula as part of the programme of treatment for their epilepsy (intracerebral recording)
- Recorded local field potentials from a total of 72 different sites across all patients, 47 of which were in the insula
- Painful stimuli were provided using a small laser

journal *Brain* 2012 Liberati et al
Anterior Insular Cortex Is Necessary for Empathetic Pain Perception
Summary

• Physical pain is an affliction associated with enormous cognitive, social, and economic costs
Summary

- It is primarily assessed by means of self-report, an imperfect measure of subjective experience.
• The capacity to effectively report pain is limited in many vulnerable populations (e.g., the very old or very young, persons with cognitive impairment, and those who are minimally conscious)
Implications

- Pain
- Suffering
As a result, current approaches to pain assessment focus on a convergence of biologic, behavioral, and self-report measures.
Conclusions

- fMRI and research just starting to understand pain pathways, neurochemistry, and its true meaning
Future

• fMRI not a lie detector test (yet)

• May in future *objectively* measure pain

• Monitor treatment for pain

• Diagnose pain in non-verbal patients
“On the plus side, you’ve cured my back pain.”
Thank you

• Abrook@montefiore.org
Implications

- Legal
spondyloarthritis on active inflammatory lesions MRI before and after treatment with etanercept

Song et al., Ann Rheum Dis 2011;70:590–596.
Pathways

- Appears to mediate the effects of cognitive regulation on pain perception
- Increasing activity in the medial prefrontal cortex and nucleus accumbens

journal *Brain* 2012
Figure 3. Application of the Neurologic Signature to Physical and Social Pain Stimuli in Study 3.

Panel A shows the signature response in each condition. The dashed horizontal line shows the threshold derived from the classification of pain versus warmth in study 1. I bars indicate standard errors. Panel B shows the receiver-operating-characteristic plots for the forced-choice test, assessed only from the pattern within a single region of interest. A physical-pain signature would ideally show high sensitivity and specificity for pain versus warmth (orange line) and pain versus rejecter (dark blue line) but chance performance for rejecter versus friend (light blue line). The brain images (insets) show the positive (yellow) and negative (blue) signature weights in each region of interest, with the magnitude of the weights represented by the intensity of the colors.
• It is plausible that neurologic signatures (patterns of activity across brain regions) derived from brain imaging could provide direct measures of pain intensity and be used to compare analgesic treatments
ROSS-VALIDATED PREDICTION OF PAIN

• In study 1, the neurologic signature included significant positive weights in regions including the bilateral dorsal posterior insula, the secondary somatosensory cortex, the anterior insula, the ventrolateral and medial thalamus, the hypothalamus, and the dorsal anterior cingulate cortex
• The signature response increased nonlinearly with increasing stimulus intensity during thermal stimulation, but as expected, it was uniformly low for the pain-anticipation and pain-recall periods
• The neurologic signature response was substantially stronger for physical pain than for any of the other conditions (warmth, rejecter, or friend)
Next Steps

• Developing neurologic signatures for multiple types of pain and other cognitive and affective processes
fMRI circa 20th Century

Brain activity during experimentally induced thermal pain

http://neuroimaging.northwestern.edu/research-team-3/kenneth-weber/
fMRI circa 21st Century

- **Arterial Spin Labeling (ASL)**
- Better fMRI technique for evaluating persistent (ongoing, chronic) pain
- *Directly* measures blood flow
- Not dependent on difference in signal between active and resting states

ASL: Blood is labeled

fMRI changes in chronic pain
fMRI reveals Psychologic factors

- **Attention**
  - modulates pain
- **Emotions**
  - Anxiety \[\uparrow\] pain response
  - Depression \[\uparrow\] pain response
- **Anticipation of pain**
  - \[\uparrow\] pain response
- **Placebo effect**
  - \[\downarrow\] pain response

fMRI in chronic pain

- Spatial representation changes over time
  - Rostral shift (? Assoc. with emotion)

- ↓ inhibition, ↑ facilitation

- ↓ Noxious inhibitory control
  - Ability to “distract” ↓

fMRI in chronic pain

- Structural alterations
- ↓ diffusion directionality (fractional anisotropy)
- ↓ white matter in frontal and parietal areas — migraines


http://www.cedars-sinai.edu/Patients/Programs-and-Services/Imaging-Center/Research/Clinical-Trials/#.Uml_znA3u84
Chronic pain remains one of the most prevalent and challenging health problems. As central factors play a prominent role in the development and maintenance of chronic pain, structural and functional brain imaging has become a primary tool for discovery of the pathophysiologic mechanisms of chronic pain and evaluation of novel treatments.
MRI of Macrophage Trafficking

- Macrophages and microglia play a critical role in the nerve damage repair process.
- However, inflammatory mediators released by these cells add to the pathogenesis of chronic pain by potentiating and maintaining heightened sensitivity of pain-sensing neurons.
- Localization of these pro-nociceptive cells near neural structures of interest may elucidate potential pain generators.
Peripheral mediators of inflammation
“inflammatory soup”
But brain imaging can put an image to the invisible.
An fMRI-Based Neurologic Signature of Physical Pain

Tor D. Wager, Ph.D., Lauren Y. Atlas, Ph.D., Martin A. Lindquist, Ph.D., Mathieu Roy, Ph.D., Choong-Wan Woo, M.A., and Ethan Kross, Ph.D.
• four studies involving a total of 114 participants
• developed an fMRI-based measure that predicts pain intensity at the level of the individual person
In study 1, we used machine-learning analyses to identify a pattern of fMRI activity across brain regions — a neurologic signature — that was associated with heat-induced pain. The pattern included the thalamus, the posterior and anterior insulae, the secondary somatosensory cortex, the anterior cingulate cortex, the periaqueductal gray matter, and other regions.
• In study 2, we tested the sensitivity and specificity of the signature to pain versus warmth in a new sample.
In study 3, we assessed specificity relative to social pain, which activates many of the same brain regions as physical pain.
In study 4, we assessed the responsiveness of the measure to the analgesic agent remifentanil.
new drugs will be developed that are not symptom-modifying drugs that simply mask the problem, as we have now, but that will be disease-modifying drugs that will actually go right to the root of the problem and attack those glial cells, or those pernicious proteins that the glial cells elaborate, that spill over and cause this central nervous system wind-up, or plasticity, that so is capable of distorting and amplifying the sensory experience that we call pain. So I have hope
Optimizing Central Nervous System Drug Development Using Molecular Imaging

Figure 7  Framework for the assessment of new candidate pain analgesia drugs in terms of whether new drugs have comparable effects on brain systems to other, known drugs using fMRI with a multivariate pattern analysis methods (left). Critical goals of future research include the understanding of how the multivariate, complex fMRI patterns of drug effects relate to clinical and health outcomes (e.g., chronic pain, depression, etc.), and the systems-level brain processes (e.g., sensory, affective, or meaning systems) that mediate them (right). With thanks to Tor Wager (adapted from Wager, T.D. & Woo, C.-W. fMRI in analgesic drug discovery. Sci. Transl. Med. 7, 274fs6 [2015]).
• AS is the most frequent inflammatory rheumatic disease that affects the spine, peripheral joints and entheses
• The disease starts relatively early in life at a mean age of 26 years and is only somewhat more frequent in male than in female patients, with inflammatory back pain (IBP) being a characteristic symptom
• The disease usually takes a chronic course that is characterized by new bone formation with syndesmophytes and ankylosis
Molecular and cellular imaging of neuropathic pain, utilizing the myriad of receptors and inflammatory mediators involved in nociceptive activity, is a promising approach toward objectively identifying peripheral pain generators.

Neuropathic conditions arise from injured and inflamed nerves, which have been shown to elaborate several molecular and cellular elements that give rise to the neuropathic phenotype and can be exploited for imaging purposes.
Take-Home Points

• Neuropathic pain remains a challenging diagnosis because anatomical abnormalities seen on conventional imaging do not always correspond to clinical presentation.

• Molecular imaging promises to bridge the gap between anatomical imaging and the clinical diagnosis of neuropathic pain.

• Hybrid imaging techniques such as PET/MRI afford radiologists both functional and anatomical imaging information, allowing us to visualize both anatomical abnormalities and biological pathologic processes in studies that were seemingly normal on conventional imaging techniques.

• Molecular mechanisms explored for imaging of neuropathic nerves include: (1) cellular response, (2) inflammatory mediation and reception, (3) ion channel expression, and (4) metabolic response
• You think of pain as a symptom of a disease, and that's true most of the time
• It's the symptom of a tumor or an infection or an inflammation or an operation
• But about 10 percent of the time, after the patient has recovered from one of those events, pain persists
• It persists for months and oftentimes for years, and when that happens, it is its own disease