Neuroimaging Pain: functional MRI to assess activity and connectivity

Vitaly Napadow, PhD

Athinoula A. Martinos Center
MGH, Harvard Medical School, Boston, MA, USA
Overview

• Introduce functional MRI (fMRI), and functional connectivity MRI (fcMRI) – a newer fMRI technique that has dominated fMRI research in recent years.

• How can these different imaging techniques be applied to better understand the multi-dimensional elements of chronic pain.
Functional Neuroimaging Modalities:
Hemodynamics, Metabolism, Electrophysiology, Neurochemistry

Neuronal Activity

Electromagnetic Response

Neurotransmitter Response

↑ Glu, GABA, endorphin
↑ Receptor (e.g. µ-opioid) Binding

Hemodynamic Response

↑ Blood Flow
↑ Blood Volume
↑ Blood Oxygenation

PET
H-MRS
Optical
fMRI

EEG
MEG
fMRI Contrast: **BOLD** – Blood Oxygenation Level Dependent

**Basal State**
- basal neuronal activity
- basal blood flow
- basal [HbO\(_2\)], [Hbr]
- basal MRI signal

**Activated State**
- Increased blood flow
- Incr. [HbO\(_2\)], decr. [Hbr] → lower field gradients around vessels
- Increased MRI signal (from lower field gradients)

\[ \uparrow \text{Activation} \rightarrow \uparrow \text{HbO}_2/\text{deoxy-Hb} \rightarrow \uparrow \text{T2*} \rightarrow \uparrow \text{fMRI signal} \]
What Does fMRI Data Look Like?
...a time series of MRI signal brightness

MRI signal from one of ~40,000 brain voxels
How to evoke pain in MRI scanner?

- Heat pain
- Cuff pressure pain
- Thumb nail pressure pain
- Electrical pain
- Hypertonic saline pain
- Laser pain
Evoked ("acute") pain neuroimaging

- ALE meta-analysis from 266 evoked, cutaneous pain fMRI studies

Tanasescu et al., 2016

Schweinhardt et al., 2010

Sprenger et al., J Neurosci 2015
From fMRI to fcMRI: Resting State Connectivity can assess Intrinsic Brain Networks

• The brain is 2% of our body weight but consumes 20% of body energy

• Stimulus-evoked increase in metabolism is small (<5%) when compared to the large (and much less studied) resting energy metabolism…

• fMRI fluctuations at rest are NOT random or chaotic, but instead correlate across network-specific, distant brain regions.
Connectivity Analysis: from social to brain networks

Washington Post, July 2017
Connectivity Analysis: from social to brain networks
Functional Connectivity: fMRI Signal Fluctuates Synchronously within Distinct Brain Networks

Resting State Networks: Somatomotor Network (SMN)

- One of the first reports of connectivity in low frequency dominated resting state fMRI data - somatomotor network

- Similar to brain activation attributed to a motor task using a block design protocol

Biswal et al., 1995
Different resting fMRI signal analysis methods

- Seed voxel correlation

- Data-driven methods such as independent component analysis (ICA)

- Spectral power analysis of the resting fMRI signal
Which networks are closely linked with pain?
Default Mode Network (DMN)

- Anatomically defined brain regions more active at rest (internal focus) than during externally focused tasks (e.g. visual, motor, somatosensory, etc.)… *When is DMN activated??* ⇒ tasks relating to self-referential cognition, autobiographical memory, etc. (see Buckner, 2007)
- Includes inferior parietal lobule (IPL), posterior cingulate cortex / precuneus (PCC), medial prefrontal cortex (MPC)

Shulman et al., 1997; Fox et al. 2005
The Salience Network responds to stimuli that are “salient” = stand out from other stimuli (e.g. pain?)

Key nodes include ACC, anterior insula, TPJ

SLN may control dynamic switching between internal (DMN) and external (CEN) modes

Uddin, Nat Rev Neurosci 2015

Yeo, J Neurophysiol 2011

Uddin, Nat Rev Neurosci 2015
How do connectivity networks apply to pain?

- Since chronic, clinical pain is typically in a steady but fluctuating state, can resting functional connectivity MRI (fcMRI) be used to better understand clinical pain state-specific brain circuitry?
Networks may differentially link to the *multi-dimensional* aspects of chronic pain

DMN activity and connectivity is linked with clinical pain

• DMN response to stimuli is modified by chronic pain:

Brain response to visual tracking task

Healthy adults  cLBP  Healthy > cLBP

Why don’t pain patients deactivate DMN as much as healthy adults? Is the DMN engaged differently at “rest” by chronic pain patients?
DMN brain regions are involved in pain-associated negative affect

• Negative affect is well known to significantly modify pain

• Pain catastrophizing is the tendency to describe a pain experience in more exaggerated terms than the average person, to ruminate on it more (e.g., "I kept thinking 'this is terrible'"), and/or to feel more helpless about the experience ("I thought it was never going to get better").
Neural circuitry supporting catastrophizing

- “read these statements and reflect on the degree to which they relate to you on a typical day of FM pain” – block design fMRI

fMRI contrast of interest:
CAT vs. NEU

Lee et al., A&R 2018
Neural circuitry supporting catastrophizing

% fMRI signal change to CAT

BPI (severity)

CAQ score

CAQ = catastrophizing applicability questionnaire

Lee et al., A&R 2018
Resting DMN Connectivity is Altered in FM patients

- In FM, DMN shows greater resting connectivity to SN (insula), and SMN (SII) regions outside conventional DMN boundaries.

- note: all FM vs. HC differences driven by greater connectivity for FM patients.

Napadow et al., Arth & Rheum 2010
DMN Connectivity to ant./mid. Insula is Correlated with Clinical Pain at the time of the Scan

Napadow et al., Arth & Rheum 2010
Increased DMN / SN connectivity in chronic pain?

• Several other groups have now also found increased DMN/insula or more generalized DMN/SLN connectivity linked to chronic pain.

Basu et al., A&R 2018

Hemington et al., Brain Struct Func, 2015
Therapy that reduces pain also reduces DMN-insula connectivity.

- fcMRI performed at baseline and following 4 weeks of real and sham acupuncture therapy.

Napadow et al., Arth & Rheum 2012
What about models that increase pain?

- N=16 chronic low back pain patients with radiculopathy
- 6min resting ASL fMRI scan
- Maneuvers then used to exacerbate clinical pain
- 6min post-maneuvers resting ASL fMRI scan

DMN connectivity in cLBP

- At baseline, clinical pain severity correlated with the strength of connectivity between DMN and right insula (rINS-DMN).

Loggia et al. Pain 2012
DMN connectivity in exacerbated cLBP

- Changes in pain induced by the maneuvers (post-maneuvers minus baseline) correlated with the change in rINS-DMN connectivity

Loggia et al. Pain 2012
Pain alters SLN, DMN, SMN connectivity: a large N replication and extension

HC (N=54)  cLBP (N=127)

pain intensity (0-100)

31.9 ± 19.9

physical maneuvers

53.7 ± 22.5

Kim et al., in review
Clinical pain increases SLN connectivity to somatotopically specific S1 brain regions
Pain-specific change in $S_{1_{\text{back}}}$ connectivity

- maneuvers-induced change in $S_{1_{\text{back}}}$ connectivity to L alns is associated with post-maneuver change in clinical pain

Kim et al., in review
Machine Learning for Pain Biomarkers

- Paired Support Vector Machine classifier: low vs. high clinical pain states
- rCBF, S1CONN, HRV-HF vs. combined

![Graph showing pain intensity before and after maneuvers](image)

![ROC curve comparison](image)

<table>
<thead>
<tr>
<th>dataset (n=53)</th>
<th>Accuracy (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBF</td>
<td>81.13</td>
<td>81.13</td>
<td>81.13</td>
<td>0.9051</td>
</tr>
<tr>
<td>S1CONN</td>
<td>79.24</td>
<td>79.24</td>
<td>79.24</td>
<td>0.8473</td>
</tr>
<tr>
<td>HRVHF</td>
<td>67.92</td>
<td>67.92</td>
<td>67.92</td>
<td>0.8067</td>
</tr>
<tr>
<td>rCBF+S1CONN</td>
<td>90.56</td>
<td>90.56</td>
<td>90.56</td>
<td>0.9633</td>
</tr>
<tr>
<td>rCBF+HRVHF</td>
<td>86.79</td>
<td>86.79</td>
<td>86.79</td>
<td>0.9220</td>
</tr>
<tr>
<td>S1CONN+HRVHF</td>
<td>81.13</td>
<td>81.13</td>
<td>81.13</td>
<td>0.8902</td>
</tr>
<tr>
<td>rCBF+S1CONN+HRVHF</td>
<td><strong>92.45</strong></td>
<td>92.45</td>
<td>92.45</td>
<td><strong>0.9699</strong></td>
</tr>
</tbody>
</table>

Lee, Mawla et al., *in review*

→ multimodal metrics improve prediction
What about DMN/insula connectivity?

- In the entire cLBP cohort in this study, DMN/insula connectivity was not increased following physical maneuvers.

- However, in high catastrophizing patients (highest PCS tertile), DMN connectivity was in fact increased to a/mIns.

- Moreover, $\Delta$DMN/insula connectivity was linked with $\Delta$pain intensity… but only in cLBP patients reporting high pain catastrophizing!

Kim et al., in review
Chronic Pain → Blurred Network Connectivity

What aspects of pain does this overlap encode?
Clues from other studies: Evoked pressure pain increases SLN connectivity to S1 representations

- 6-min rest vs. 6-min sustained cuff pressure pain fMRI
- Sustained deep receptor pressure pain significantly modulates SMN and SLN resting connectivity

Kim et al., Pain 2013
S1 resting brain connectivity is reduced (i.e. between different SMN nodes) in FM

Kim et al., A & R 2015
Sustained deep tissue pain alters S1 connectivity in FM

Kim et al., A & R 2015
Chronic Pain → Blurred Network Connectivity

Somatotopic specificity

S1 back representations

Saliency directed toward the location and intensity of clinical pain

What about blurring between DMN and SLN?
Why might DMN-insula connectivity be associated with clinical pain?

- DMN associated with self-referential cognition

- SLN and insula commonly activated by pain stimuli, and insula is thought to integrate subcortical homeostatic information (e.g. pain) into higher-order conscious awareness.

- Speculation: Is this linkage a neural substrate for chronic pain patients’ common perception that pain becomes part of who they are? A core part of their self-referential state?

- Is linkage originated and maintained by pain catastrophizing?

Lee et al., 2017

Kim et al., in review
Hypothesis: Catastrophizing about pain activates specific DMN regions (i.e. PCC), setting up a state with increased linkage of DMN regions to SLN.

Catastrophizing influences DMN connectivity

Chronic Pain

Saliency directed toward the patient’s ruminations about suffering from clinical pain

Uddin, Nat Rev Neurosci 2015
Conclusions

• Functional MRI (fMRI) can be used to assess:
  • Brain response to evoked ("acute") pain
  • Brain circuitry supporting hyperalgesia (e.g. capsaicin cream)
  • Brain circuitry supporting temporal summation of pain, conditioned pain modulation, onset/offset analgesia, etc.
  • Placebo/nocebo effects on brain circuitry

• Functional connectivity MRI (fcMRI) can be used to assess:
  • All of the above… plus
  • Chronic pain states
Conclusions

• The brain is composed of multiple primary sensory and associative networks that activate and deactivate over time as distinct assemblies… multiple analysis approaches

• These networks become blurred when chronic, pain-associated activation of network nodes is maintained,

• **Blurring of different networks supports different aspects of chronic pain, suggesting potential biomarkers to target w. therapy.**
Acknowledgements

Martinos Center for Biomedical Imaging, MGH, HMS, Boston, MA

- Dan-Mikael Ellingsen, PhD
- Kylie Isenburg
- Jeungchan Lee, PhD
- Marco Loggia, PhD

- Ishtiaq Mawla
- Bruce R Rosen, MD PhD
- Jessica Gerber, MS LAc
- Roberta Sclocco, PhD

Pain Management Center, BWH, Boston, MA

- Robert Edwards, PhD

Dept. Anesthesiology, University of Michigan, Ann Arbor, MI

- Richard E Harris PhD
- Daniel Clauw MD

Korean Institute for Oriental Medicine, Daejeon, Korea

- Changjin Jung
- Jieun Kim, PhD

NCCIH, NIAMS (R61-AT009306, P01-AT002048, R01-AR064367, R01-AT007550); KIOM (K15050)
Neuroimaging pain pathways: a bright future ahead