Cognitive aspects of acute and chronic pain: 10 advances in 10 years

David A. Seminowicz, PhD
Department of Neural and Pain Sciences
University of Maryland School of Dentistry
dseminowicz@umaryland.edu

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A retrospective ...
And a look ahead ...
Back in 2006...

IV. COGNITIVE AND EMOTIONAL ASPECTS OF PAIN Moderator: Ray Dionne

Cognitive Factors That Enhance Pain Processing

The Placebo Effect: New Insights

Jennifer Haythornthwaite

Roger Fillingim

Ted Kaptchuk

Individual Differences in Pain and Analgesia: Genes, Gender, and Ethnicity
Catastrophizing: Cognitive/affective response to pain

- **Negative Emotions**
  - Anxiety, Depression, Rumination
  - “I worry about whether it will end”
- **Attention to pain**
  - Magnification, Exaggeration, Hypervigilance
  - “I can’t seem to keep it out of my mind”
- **Beliefs about pain**
  - Threat, Helplessness, Pessimism
  - “I become afraid that the pain will get worse”

Slide courtesy of Jennifer Haythornthwaite, presented at 2006 NIH Pain Consortium meeting
2006: What are the neural correlates of pain catastrophizing in healthy subjects?
Individual differences: pain catastrophizing

**Mild Pain**

- Left rostral ACC: (-13, 45, 10)
  - $r = 0.643$
  - $p < 0.005$

- Right mid Insula: (34, 2, 13)
  - $r = 0.731$
  - $p < 0.0005$

**Moderate Pain**

- Right DLPF: (18, 42, 42)
  - $r = -0.605$
  - $p < 0.005$

- Left DLPF: (-19, 35, 47)
  - $r = -0.630$
  - $p < 0.005$

Seminowicz and Davis 2006 Pain
2007: Is pain a cognitive load?
Seminowicz and Davis 2007 J Neurophysiol
2008: are cognitive networks disrupted in chronic pain?
Beyond Feeling: Chronic Pain Hurts the Brain, Disrupting the Default-Mode Network Dynamics

Baliki et al., 2008 JNeurosci
2009: what drives attention-related pain modulation?
Strength of prefrontal activation predicts intensity of suggestion-induced pain

Raij et al. 2009 Hum Brain Mapp
2010: what brain regions mediate the pain experience?
Brain mediators of predictive cue effects on perceived pain

Pain predictive cue (H vs L) → Path c → PPNM pain-evoked response → Reported pain

Path a
Cue-evoked anticipatory response

Path b

Assimilation
Inverse of assimilation
Expected intensity
Expectancy violation

Atlas et al. 2010 J Neurosci
2011: can treatment reverse abnormal cognitive-related activity in chronic pain?
Treatment reverses left DLPFC GMV loss

Patients vs. controls

Patients pre-Tx vs. post-Tx

Seminowicz et al. 2011 J Neurosci
Left DLPFC has abnormal activity in CLBP, normalizes with treatment

Seminowicz et al. 2011 J Neurosci
2012: can we modulate activity in the left DLPFC and affect pain?
Endogenous opioids mediate left DLPFC rTMS-induced analgesia

Mindfulness meditation engages left DLPFC

Taylor et al., 2012 Pain

Allen et al. 2012 J Neurosci
2013: are there catastrophizing-related treatment effects?
CBT for chronic pain: reduced catastrophizing, increased gray matter

Seminowicz et al., 2013 J Pain
2014: does catastrophizing (rumination) disrupt cognitive networks in chronic pain patients?
Enhanced default mode connectivity in chronic pain is associated with pain rumination

Kucyi et al. 2014 J Neurosci
2015: can we restore cognitive network function with treatment?
Cognitive networks in chronic low back pain

Test connectivity to whole brain using these regions as seeds

Patients pre- vs. post-treatment: left DLPFC identified

Patients vs. Controls: bilateral a/mINS identified

PARTIAL REVERSAL

Čeko et al, 2015 Hum Brain Mapp
Hypothesized cognitive network dysfunction in CLBP

Čeko et al, 2015 Hum Brain Mapp
Summary 2006-2015

• Catastrophizing affects pain-related activity
• Pain has a cognitive load that affects cognitive network function
• Left DLPFC might be a particularly good target
The future?
Three newish trends

1. Shift to limbic circuits (Baliki et al 2012, Hashmi et al 2013)
2. Maladaptive stress (Borsook et al 2012)
3. Refinement of treatment targets
1: Development of chronic pain

Healthy acute chronic

2: Treatment

Chronic pain intervention recovery Healthy

3. Disease-related vs ongoing pain

Healthy or chronic pain no pain ongoing pain
1. Shift to limbic circuits
Gray matter changes in sensory- and affective-related brain regions

Hyperalgesia

- ACC (24)
- Bregma +3.2
- S1HL
- Bregma -1.0
- Insula

SNI

Mean relative voxel size

Log(50% von Frey threshold (g))

Number of exits from closed arms

Weeks relative to injury

Seminowicz et al., 2009 Neuroimage
SNI > SHAM – EARLY (4 wks post-injury)

Hubbard et al., 2015 Neuroimage
SNI > SHAM – LATE (20 wks post-injury)
Spinal cord injury pain model: S1(hind limb) resting state connectivity

Seminowicz et al. 2012 J Neurosci
2. Maladaptive stress
Burning Mouth Syndrome

- 7 am: Psychophysics & Questionnaires
- 8:15 am: fMRI
- 10 am - 3 pm: Break
- 3 pm: Psychophysics & Questionnaires
- 4:15 pm: fMRI

Khan et al, 2014 Pain
Burning Mouth Syndrome

Gray matter volume

Resting state connectivity

R-Hc (patients > controls)  L-mPFC (controls > patients)

Increased mPFC connectivity to right Hc BMS PM - controls

Increased mPFC connectivity to right Hc BMS PM - BMS AM

Khan et al, 2014 Pain
Hippocampus in chronic pain: maladaptive stress

Vachon-Presseau et al., 2013 Brain
3. Refinement of treatment targets

- A good target:
  - Does something when you hit it
  - Doesn’t move
  - Might not always do what you expect
Treatment normalizes left DLPFC anatomy and function

Patients pre-Tx vs. post-Tx

Daily left prefrontal repetitive transcranial magnetic stimulation for medication-resistant burning mouth syndrome.

Seminowicz et al. 2011 J Neurosci
### Left DLPFC in CLBP

Apkarian et al 2004 JNeurosci

### Table: Chronic pain disorder

<table>
<thead>
<tr>
<th>Chronic pain disorder</th>
<th>Reference</th>
<th>Thal</th>
<th>BG</th>
<th>S1</th>
<th>S2</th>
<th>IC</th>
<th>ACC</th>
<th>MCC</th>
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<th>PFC</th>
<th>Brainstem</th>
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<td>Schmidt-Wilcke et al., 2006</td>
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<td>Buckalew et al., 2008</td>
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<td>↓ PPC</td>
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Davis & Moayedi 2012 J Neuroimmune Pharmacol
Enhanced left DLPFC cognitive-related activity in migraine

Mathur et al., 2015 Neuroimage: Clin
Catastrophizing related to structural differences

Hubbard et al. 2014 eNeuro
Catastrophizing related to pain-related brain activity

Mathur et al., in prep
Effectiveness of mindfulness for migraine

Migraine Pain month (omnibus LMM p=.01)

PCS Total (omnibus LMM p=.07)

PCS magnification (omnibus LMM p=.02)

PCS helplessness (omnibus LMM p=.008)

Mathur et al., in prep
Reduction in pain-related activity?

Mathur et al., in prep
Change in relationship between pain catastrophizing and pain-related activity

L aINS
R aINS

Mathur et al., in prep
The future?

1. Shift to limbic circuits
   – Can we prevent the shift?
2. Maladaptive stress
   – Can we break the cycle?
3. Refinement of treatment targets
   – Can we use it for individualized medicine?
DAS lab
Shana Burrowes
Andrew Furman
Catherine Hubbard
Li Jiang
Michael Keaser
Shariq Khan
Vani Mathur
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Janell Payano Sosa
Joyce Teixeira da Silva
Sooyoung Yoo

University of Maryland, Baltimore
Joel Greenspan (NPS)
Radi Masri (EPOD)
Tim Meiller (OMC)
Jeremy Rietschel (VA)
Richard Traub (NPS)

Johns Hopkins University
Jennifer Haythornthwaite
Madhav Goyal
B. Lee Peterlin
Patrick Finan

Ali Mazaheri (U. Amsterdam)
Magdalena Naylor (U. Vermont)
Alexander Shackman (UM College Park)
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