Pain and Depression: What is the relationship?

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The University of Michigan
Disclosures

- Consulting
  - Pfizer, Forest, Eli Lilly, Pierre Fabre, Cypress Biosciences, Wyeth, UCB, Astra Zeneca, Merck, J & J, Nuvo, Jazz, Abbott, Cerephex, Iroko, Tonix, Theravance

- Research support
  - Pfizer, Cypress Biosciences, Forest, Merck, Nuvo, Cerephex

- One-time licensing fee paid to University of Michigan by Eli Lilly
Pain and Depression

- How often do they co-occur?
- Which comes first?
- Shared (and distinct) neurobiological factors
- (Some) future directions
Pain and Depression

- How often do they co-occur?
- Which comes first?
- Shared neurobiological factors
- (Some) future directions
How often do pain and depression co-occur?

Depends on how you look, and where

- **How?**
  - Diagnostic clinical interview vs. questionnaire
  - What is the questionnaire really measuring?
  - Need to dissociated somatic symptoms from cognitive/affective symptoms (“contaminated” measures)

- **Where?**
  - Population-based vs. primary care vs. tertiary care
  - Nociceptive vs. centralized pain conditions

- **Realize**
  - Relative risk of other psychiatric disorders being co-morbid is often relatively higher than depression
Pain and Depression

- How often do they co-occur?
- Which comes first?
- Shared neurobiological factors
- (Some) future directions
Which comes first, pain or depression?

- Nearly all studies suggest chronic pain increases risk of subsequent depression

- Most but not all studies suggest depression is a risk factor for developing pain
  - These risks are very modest from relative standpoint in population-based studies (adjusted OR of 1.1 – 1.6) but are high from absolute standpoint because depression is common
  - When studies are done using same methodology, multiple other factors are typically stronger predictors of subsequent pain than baseline depression or distress
    - Early life stressors
    - Other psychiatric conditions e.g. PTSD, anxiety
    - Prior pain
    - Prior somatic symptoms
    - Poor sleep

Pain and Depression

■ How often do they co-occur?
■ Which comes first?
■ Shared (and distinct) neurobiological factors
■ (Some) future directions
Shared neurobiological factors between pain and depression

- Triggered by a variety of types of stress
- Involvement in medial/limbic structures in both pain processing and depressed mood
  - Areas such as anterior insulae, amygdala, hippocampus more strongly activated with painful stimulus in depressed pain patients but no affect of depression on more lateral structures\(^1\)
- Pain is pain but physical pain can be differentiated on imaging from emotional pain (e.g. S2, posterior insulae)\(^2\)

**Neurotransmitter similarities**

Neural Influences on Pain and Sensory Processing

Facilitation
- Substance P
- Glutamate and EAA
- Serotonin (5HT\textsubscript{2a, 3a})
- Nerve growth factor

Inhibition
- Descending antinociceptive pathways
- Norepinephrine-serotonin (5HT\textsubscript{1a,b}), dopamine
- Opioids
- GABA
- Cannabimimetics

Distinct neurobiological factors between pain and depression

- Neurotransmitters are like real estate – location, location, location¹

- Pain processing not generally abnormal (e.g. hyperalgesia, diminished CPM) in depression²,³

- Antidepressants vs. centrally acting analgesics
  - Time course of treatment response different
  - Many effective anti-depressants (e.g. highly selective SSRIs) not effective analgesics
  - Analgesic response to drugs that work for both pain and depression is generally not better in depressed than non-depressed pain patients⁴,⁵

Following pregabalin treatment, FM patients display reductions in posterior insula Glx, but not following placebo. This was not seen for the anterior insula or occipital lobe.

Harris et. al. Anesthesiology 2013
DMN Connectivity to Right Insula is Correlated with Clinical Pain at the time of the Scan

Intrinsic DMN Connectivity vs. Spontaneous Pain

Napadow et al, Arthritis & Rheumatism 2010
DMN Connectivity to the Insula is Reduced Following 4-weeks of Therapy

p<0.05 corrected

R Ant Insula

Default Mode Network

Pain During fMRI Scan

McGill Scale Score

- Pre-Therapy
- Post-Therapy

McGill Sensory
McGill Affective

Z = 6mm
X = 36mm
Reduction in Insular-DMN Connectivity is Correlated with Change in Clinical Pain

\[ p < 0.05 \text{ corrected} \]
Pain and Depression

- How often do they co-occur?
- Which comes first?
- Shared neurobiological factors
- (Some) future directions
(Some) Future Directions

- Why do we just focus on negative mood/affect?

- New mechanisms being explored in depression and pain
  - Immune mechanisms/glial cell activation
  - Microbiome

- The 800 lb gorilla in the room . . . . .
What is the CNS 800 lb gorilla we should be focusing on rather than depression?

- I don’t know what to call it but similar to Justice Potter view of obscenity
  - ”I know it when I see it”

- Called by different names by different subspecialists
  - Somatization/somatoform disorders
  - Central sensitization
  - Regional idiopathic pain syndromes (tension headache, irritable bowel, TMJD, interstitial cystitis, vulvodynia, dry eye disease)
  - Centralized pain
  - Fibromyalgia

- Often ignored with inordinate focus on peripheral factors
The F-Word
Evolution of Thinking Regarding Fibromyalgia

American College of Rheumatology (ACR) Criteria

- Final common pathway (i.e. centralization)
- Part of a larger continuum
- Many somatic symptoms, diffuse tenderness
- Psychologic and behavioral factors play roles in some individuals
- Chronic widespread pain
- Tenderness in $\geq 11$ of 18 tender points

- Discrete illness
- Focal areas of tenderness
- Psychologic and behavioral factors nearly always present and negative

Anterior

Posterior
Fibromyalgia

Centralized pain in individuals with any chronic pain condition
### Mechanistic Characterization of Pain

Any combination may be present in a given individual

#### Peripheral (nociceptive)
- Inflammation or mechanical damage in tissues
- NSAID, opioid responsive
- Responds to procedures
- Classic examples
  - Acute pain due to injury
  - Osteoarthritis
  - Rheumatoid arthritis
  - Cancer pain

#### Peripheral Neuropathic
- Damage or dysfunction of peripheral nerves
- Responds to both peripheral (NSAIDs, opioids, Na channel blockers) and central (TCA's, neuroactive compounds) pharmacological therapy
- Classic examples
  - Diabetic neuropathic pain
  - Post-herpetic neuralgia

#### Centralized Pain
- Characterized by central disturbance in pain processing (diffuse hyperalgesia/allodynia)
- Responsive to neuroactive compounds altering levels of neurotransmitters involved in pain transmission
- Classic examples
  - Fibromyalgia
  - Irritable bowel syndrome
  - TMJD
  - Tension headache

#### Mixed Pain States
Clinical Characteristics of “Central” or Centralized Pain ─ I

- Typically characterized by:
  - Multifocal pain (use pain diagram)
  - Use or “neuropathic” verbal descriptors of pain
  - Higher current and lifetime history of pain
  - Multiple other somatic symptoms (fatigue, memory difficulties, and sleep disturbances)
  - Sensitivity to multiple sensory stimuli

- Not “yes” or “no” — occurs over a wide continuum
  - Diagnostic labels (eg, FM, IBS, TMJD) largely historical and irrelevant
  - Wolfe et al. has shown that degree of “fibromyalgia-ness” predicts pain intensity, symptoms, and disability over a wide range of rheumatic disorders (RA, OA, regional musculoskeletal pain, FM).

Clinical Characteristics of Central or Centralized Pain — II

- 1.5 to 2x more common in females
- Strong familial/genetic underpinnings\(^1\)
  - Take family history of pain
- Triggered or exacerbated by stressors\(^2\)
- Generally normal physical examination except for diffuse tenderness and nonspecific neurological signs\(^3\)

Centralization Continuum

Proportion of individuals in chronic pain states that have centralized their pain

Peripheral

Acute pain
Osteoarthritis
RA

Centralized

SC disease
Ehler’s Danlos
Low back pain

Fibromyalgia
Tension HA
TMJD
IBS
# Pharmacological Therapies for Fibromyalgia (i.e. Centralized Pain)

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong</strong></td>
<td>Dual reuptake inhibitors such as</td>
</tr>
<tr>
<td><strong>Modest</strong></td>
<td>Tramadol</td>
</tr>
<tr>
<td><strong>Weak</strong></td>
<td>Growth hormone, 5-hydroxytryptamine, tropisetron, S-adenosyl-L-methionine (SAMe)</td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>Opioids, corticosteroids, nonsteroidal anti-inflammatory drugs, benzodiazepine and nonbenzodiazepine hypnotics, guanifenesin</td>
</tr>
</tbody>
</table>

Clauw JAMA 2014
Neural Influences on Pain and Sensory Processing

Facilitation
- Substance P
- Glutamate and EAA
- Serotonin \((5HT_{2a, 3a})\)
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- Norepinephrine-serotonin \((5HT_{1a,b})\), dopamine
- Opioids
- GABA
- Cannabinoids

Ongoing Study of Predictors of Outcomes in OA Patients Undergoing TKA and THA
Brummett et. al., Anesthesiology, 2013

- Primary hypothesis of study is the measures of centralized pain in OA (Fmness) will predict failure to respond to arthroplasty
- Extensive preoperative phenotype using validated self-report measures of pain, mood, and function
- Two outcomes of interest:
  - Postoperative opioid consumption
  - Pain relief from procedure at 6 months
Variables Analyzed

- Age
- Sex
- Surgery (Knee vs Hip)
- Primary anesthetic (GA vs neuraxial)
- Home opioids (IVME)
- Pain severity (BPI)
  - Overall
  - Surgical site
- Neuropathic pain score (PainDETECT)
- Depression (HADS)
- Anxiety (HADS)
- Catastrophizing
- Physical function-WOMAC
Concept of “Fibromyalgia-ness”

Distribution of FMness

Brummett CM et al. Unpublished data
## Phenotypic Differences by FM Score

<table>
<thead>
<tr>
<th></th>
<th>Low FM (FM = 0-4)</th>
<th>Moderate FM (FM = 5-8)</th>
<th>High FM (FM = 9-31)</th>
<th>p-value</th>
<th>p(Group 1-Group 2)</th>
<th>p(Group 1-Group 3)</th>
<th>p(Group 2-Group 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>184</td>
<td>209</td>
<td>159</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean(SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>64.8 (10)</td>
<td>61.6 (11.7)</td>
<td>60 (11.6)</td>
<td>&lt;0.001</td>
<td>0.01254</td>
<td>&lt;0.001</td>
<td>0.377</td>
</tr>
<tr>
<td>Body mass index</td>
<td>29.9 (10.4)</td>
<td>31.3 (5.72)</td>
<td>30.3 (6.09)</td>
<td>0.183</td>
<td>0.1797</td>
<td>0.9025</td>
<td>0.419</td>
</tr>
<tr>
<td>Overall Pain Severity</td>
<td>4.11 (2.05)</td>
<td>4.73 (1.83)</td>
<td>5.81 (1.96)</td>
<td>&lt;0.001</td>
<td>0.00457</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgical site pain severity</td>
<td>4.45 (2.07)</td>
<td>4.86 (1.78)</td>
<td>5.75 (1.95)</td>
<td>&lt;0.001</td>
<td>0.09514</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PainDETECT</td>
<td>7.62 (5.01)</td>
<td>9.14 (5.79)</td>
<td>12.7 (6.78)</td>
<td>&lt;0.001</td>
<td>0.03816</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3.81 (2.8)</td>
<td>5.55 (3.18)</td>
<td>7.69 (4.24)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>3.09 (2.25)</td>
<td>4.59 (2.75)</td>
<td>7.21 (3.85)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WOMAC- Function</td>
<td>33.1 (10.8)</td>
<td>37.5 (10.2)</td>
<td>42.5 (10.1)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Catastrophizing</td>
<td>2.43 (3.4)</td>
<td>4.19 (4.58)</td>
<td>9.22 (7.35)</td>
<td>&lt;0.001</td>
<td>0.01716</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Home opioids (mg)</td>
<td>0.366 (1.61)</td>
<td>2.01 (6.87)</td>
<td>5.74 (12.9)</td>
<td>&lt;0.001</td>
<td>0.1149</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## Acute Pain Outcomes by FM Score

<table>
<thead>
<tr>
<th></th>
<th>Low FM (FM = 0-4)</th>
<th>Moderate FM (FM = 5-8)</th>
<th>High FM (FM = 9-31)</th>
<th>p-value</th>
<th>p(Group 1-Group 2)</th>
<th>p(Group 1-Group 3)</th>
<th>p(Group 2-Group 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesia (%Neuraxial)</td>
<td>56%</td>
<td>52.00%</td>
<td>44%</td>
<td>0.119</td>
<td>0.4479</td>
<td>0.0276</td>
<td>0.1227</td>
</tr>
<tr>
<td>Days Inpatient</td>
<td>2.86 (0.916)</td>
<td>2.98 (0.871)</td>
<td>3.19 (1.3)</td>
<td>0.014</td>
<td>0.4999</td>
<td>0.01029</td>
<td>0.1336</td>
</tr>
<tr>
<td>PACU opioids (mg)</td>
<td>5.96 (7.32)</td>
<td>6.98 (8.49)</td>
<td>11.1 (13.6)</td>
<td>&lt;0.001</td>
<td>0.5636</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient opioids (mg)</td>
<td>50.3 (33.3)</td>
<td>62.9 (49.3)</td>
<td>90.6 (82.1)</td>
<td>&lt;0.001</td>
<td>0.07493</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total postop opioids (mg)</td>
<td>56.3 (36.9)</td>
<td>69.8 (53.5)</td>
<td>102 (87)</td>
<td>&lt;0.001</td>
<td>0.07193</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## ANCOVA: Post-Op Opioid Consumption

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>SE</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>92.06</td>
<td>13.32</td>
<td>6.92</td>
<td>&lt;0.000001</td>
</tr>
<tr>
<td>Home opioids (mg; means)</td>
<td>2.77</td>
<td>0.26</td>
<td>10.8</td>
<td>&lt;0.000001</td>
</tr>
<tr>
<td>Age (means)</td>
<td>-1.47</td>
<td>0.19</td>
<td>-7.81</td>
<td>&lt;0.000001</td>
</tr>
<tr>
<td>TKA (vs THA)</td>
<td>20.87</td>
<td>4.18</td>
<td>4.99</td>
<td>&lt;0.000001</td>
</tr>
<tr>
<td>Days Inpatient (means)</td>
<td>16.04</td>
<td>1.99</td>
<td>8.05</td>
<td>&lt;0.000001</td>
</tr>
<tr>
<td>Neuraxial (vs GA)</td>
<td>-16.49</td>
<td>4.08</td>
<td>-4.04</td>
<td>0.000061</td>
</tr>
<tr>
<td>Fibromyalgia-ness</td>
<td>2.70</td>
<td>0.49</td>
<td>5.55</td>
<td>&lt;0.000001</td>
</tr>
</tbody>
</table>
### 6 month pain and global outcomes

#### Model without fibromyalgia survey score included

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>SE</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-0.53</td>
<td>0.22</td>
<td>0.017</td>
</tr>
<tr>
<td>Pain severity surgical site</td>
<td>-0.94</td>
<td>0.036</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>African American race</td>
<td>2.38</td>
<td>0.47</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Other race</td>
<td>0.96</td>
<td>0.37</td>
<td>0.0093</td>
</tr>
<tr>
<td>TKA (vs THA)</td>
<td>0.76</td>
<td>0.13</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>0.06</td>
<td>0.02</td>
<td>0.0015</td>
</tr>
<tr>
<td>WOMAC stiffness</td>
<td>0.081</td>
<td>0.04</td>
<td>0.044</td>
</tr>
</tbody>
</table>

#### Model including fibromyalgia survey score included

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>SE</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-0.51</td>
<td>0.17</td>
<td>0.0034</td>
</tr>
<tr>
<td>Pain severity surgical site</td>
<td>-0.91</td>
<td>0.03</td>
<td>&lt;0.00001</td>
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<tr>
<td>Fibromyalgia survey score</td>
<td>0.073</td>
<td>0.014</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>African American race</td>
<td>2</td>
<td>0.37</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Other race</td>
<td>0.74</td>
<td>0.31</td>
<td>0.019</td>
</tr>
<tr>
<td>TKA (vs THA)</td>
<td>0.88</td>
<td>0.12</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

#### Preoperative predictors patient global impression of change 6-months postoperatively

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>SE</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not married</td>
<td>0.51</td>
<td>0.2</td>
<td>0.012</td>
</tr>
<tr>
<td>Education (technical degree)</td>
<td>-0.12</td>
<td>0.25</td>
<td>0.62</td>
</tr>
<tr>
<td>Education advanced</td>
<td>-0.57</td>
<td>0.29</td>
<td>0.049</td>
</tr>
<tr>
<td>Homemaker or retired</td>
<td>-0.22</td>
<td>0.2</td>
<td>0.27</td>
</tr>
<tr>
<td>Unemployed</td>
<td>-0.62</td>
<td>0.29</td>
<td>0.033</td>
</tr>
<tr>
<td>TKA (vs THA)</td>
<td>-2.05</td>
<td>0.24</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Catastrophizing</td>
<td>-0.052</td>
<td>0.016</td>
<td>0.0014</td>
</tr>
<tr>
<td>WOMAC stiffness</td>
<td>0.12</td>
<td>0.052</td>
<td>0.028</td>
</tr>
</tbody>
</table>
Summary

- Depression is a common co-morbidity in chronic pain but . . .

- We have historically focused too much on the co-morbid depression in pain - and on classic definitions of the “disease” depression

- Need to dissociate the cognitive affective component of depression from the CNS-mediated symptom cluster of
  - Multifocal pain and sensory symptoms
  - Fatigue
  - Sleep problems
  - Memory problems
Summary

- Whatever we want to call this, it makes by far the biggest difference in determining what the underlying pathogenesis of pain or other irritative sensory symptoms is and what will work and what won’t regarding our common treatments for pain.

- Within any chronic pain state:
  - some individuals have that pain because of a problem in the area of the body they are experiencing symptoms
  - others have a lifelong disease characterized by multifocal pain and other sensory experiences, fatigue, sleep, memory and mood difficulties
  - most have something in between

- So . . . .
Of course identifying and treating depression is important

But that’s so 70’s
Been there, done that, doesn’t help much
Identifying and appropriately treating centralized pain is likely much more important.

You can ignore the tip of the iceberg – but ignore what is below the surface and you’re missing what is likely the most important CNS contribution to pain.