A SYSTEMATIC APPROACH TO MEDICALLY UNEXPLAINED SYMPTOMS

PATHOPHYSIOLOGY OF CENTRAL SENSITIZATION

Chris Aakre, MD, MSc

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The Ritz-Carlton, Half Moon Bay

@MayoClinicGIM
DISCLOSURES

Relevant Financial Relationships
• None

Off-Label and/or Investigational Uses
• Gabapentin, Ketamine, Dextromethorphan, Methadone, SPMs, Ambroxol, TCAs, naltrexone
• Neuromodulation devices
LEARNING OBJECTIVES

- Define central sensitization and recognize common central sensitization syndromes
- Describe microscopic neurological mechanisms leading to central sensitization
- Describe macroscopic central nervous system mechanisms involved in central sensitization
- Describe how commonly recommended treatments for CS syndromes target these mechanisms
HAVE YOU HEARD OF THE TERM CENTRAL SENSITIZATION?

A. Yes
B. No
C. Maybe
HOW COMFORTABLE ARE YOU WITH EXPLAINING CENTRAL SENSITIZATION TO AN UNFAMILIAR COLLEAGUE?

A. Very comfortable
B. Comfortable
C. Neutral
D. Uncomfortable
E. Very uncomfortable
F. What is central sensitization?
HOW COMFORTABLE ARE YOU WITH EXPLAINING CENTRAL SENSITIZATION TO A PATIENT?

A. Very comfortable
B. Comfortable
C. Neutral
D. Uncomfortable
E. Very uncomfortable
F. What is central sensitization?
“... I know it when I see it ...”

Supreme Court Justice Potter Stewart
(Jacobellis v. Ohio, 1964)
## CHARACTERIZING CS: THE CS INVENTORY

Please circle the best response to the right of each statement. (Range: 0-4)

<table>
<thead>
<tr>
<th></th>
<th>Statement</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I feel unrefreshed when I wake up in the morning.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>My muscles feel stiff and achy.</td>
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<tr>
<td>3</td>
<td>I have anxiety attacks.</td>
<td></td>
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<td>4</td>
<td>I grind or clench my teeth.</td>
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<tr>
<td>5</td>
<td>I have problems with diarrhea and/or constipation.</td>
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<tr>
<td>6</td>
<td>I need help in performing my daily activities.</td>
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</tr>
<tr>
<td>7</td>
<td>I am sensitive to bright lights.</td>
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<tr>
<td>8</td>
<td>I get tired very easily when I am physically active.</td>
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<tr>
<td></td>
<td>Description</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
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</tr>
<tr>
<td>9</td>
<td>I feel pain all over my body.</td>
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</tr>
<tr>
<td>10</td>
<td>I have headaches.</td>
<td></td>
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</tr>
<tr>
<td>11</td>
<td>I feel discomfort in my bladder and/or burning when I urinate.</td>
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</tr>
<tr>
<td>12</td>
<td>I do not sleep well.</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>13</td>
<td>I have difficulty concentrating.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>14</td>
<td>I have skin problems such as dryness, itchiness or rashes.</td>
<td></td>
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</tr>
<tr>
<td>15</td>
<td>Stress makes my physical symptoms get worse.</td>
<td></td>
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</tr>
<tr>
<td>16</td>
<td>I feel sad or depressed.</td>
<td></td>
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</tr>
<tr>
<td>17</td>
<td>I have low energy.</td>
<td></td>
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</tr>
<tr>
<td>18</td>
<td>I have muscle tension in my neck and shoulders.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>19</td>
<td>I have pain in my jaw.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>20</td>
<td>Certain smells, such as perfumes, make me feel dizzy and nauseated.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>21</td>
<td>I have to urinate frequently.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>22</td>
<td>My legs feel uncomfortable and restless when I am trying to go to sleep at night.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>23</td>
<td>I have difficulty remembering things.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>24</td>
<td>I suffered trauma as a child.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>25</td>
<td>I have pain in my pelvic area.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
</tbody>
</table>

**Total=**
CHARACTERIZING CS: THE CS INVENTORY
### CHARACTERIZING CS: SENSORY HYPERSENSITIVITY SCALE

Please circle the best response to the right of each statement. (Range: 1-5)

<table>
<thead>
<tr>
<th></th>
<th>Allergies</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I suffer from allergies</td>
<td>SD</td>
<td>D</td>
<td>N</td>
<td>A</td>
<td>SA</td>
</tr>
<tr>
<td>2</td>
<td>I am allergy-free</td>
<td>SD</td>
<td>D</td>
<td>N</td>
<td>A</td>
<td>SA</td>
</tr>
<tr>
<td>3</td>
<td>I have a number of allergies</td>
<td>SD</td>
<td>D</td>
<td>N</td>
<td>A</td>
<td>SA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Cold</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>I often feel too hot in an environment where others don’t seem to be bothered</td>
<td>SD</td>
<td>D</td>
<td>N</td>
<td>A</td>
<td>SA</td>
</tr>
<tr>
<td>5</td>
<td>I am easily disturbed by high temperatures</td>
<td>SD</td>
<td>D</td>
<td>N</td>
<td>A</td>
<td>SA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Heat</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>I often feel too cold in an environment where others don’t seem to be bothered</td>
<td>SD</td>
<td>D</td>
<td>N</td>
<td>A</td>
<td>SA</td>
</tr>
<tr>
<td>7</td>
<td>I am easily disturbed by low temperatures</td>
<td>SD</td>
<td>D</td>
<td>N</td>
<td>A</td>
<td>SA</td>
</tr>
</tbody>
</table>

# CHARACTERIZING CS: SENSORY HYPERSENSITIVITY SCALE

<p>| | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Light</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>8</td>
<td>My eyes are sensitive to sunlight</td>
<td>SD</td>
<td>D</td>
<td>N</td>
<td>A</td>
<td>SA</td>
</tr>
<tr>
<td>9</td>
<td>I am sensitive to bright light</td>
<td>SD</td>
<td>D</td>
<td>N</td>
<td>A</td>
<td>SA</td>
</tr>
<tr>
<td>10</td>
<td>I am not really bothered by bright lights</td>
<td>SD</td>
<td>D</td>
<td>N</td>
<td>A</td>
<td>SA</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>I am quite sensitive to pain</td>
<td>SD</td>
<td>D</td>
<td>N</td>
<td>A</td>
<td>SA</td>
</tr>
<tr>
<td>12</td>
<td>I can tolerate a large amount of pain</td>
<td>SD</td>
<td>D</td>
<td>N</td>
<td>A</td>
<td>SA</td>
</tr>
<tr>
<td>13</td>
<td>Things that would ordinarily hurt others are not painful to me</td>
<td>SD</td>
<td>D</td>
<td>N</td>
<td>A</td>
<td>SA</td>
</tr>
<tr>
<td><strong>Smell</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>I often react to odors that others do not initially notice</td>
<td>SD</td>
<td>D</td>
<td>N</td>
<td>A</td>
<td>SA</td>
</tr>
<tr>
<td>15</td>
<td>I seem to notice smells that others people do not</td>
<td>SD</td>
<td>D</td>
<td>N</td>
<td>A</td>
<td>SA</td>
</tr>
<tr>
<td>16</td>
<td>I rarely notice smells</td>
<td>SD</td>
<td>D</td>
<td>N</td>
<td>A</td>
<td>SA</td>
</tr>
</tbody>
</table>
### CHARACTERIZING CS: SENSORY HYPERSENSITIVITY SCALE

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Hearing</th>
<th>SD</th>
<th>D</th>
<th>N</th>
<th>A</th>
<th>SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>When I read, it must be totally quiet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>I cannot study or read if there is any conversation or noise around</td>
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</tr>
<tr>
<td>19</td>
<td>I can work even in noisy circumstances</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>Taste</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>20</td>
<td>I tend to be a picky eater</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>There are many foods that taste bad to me</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>I can eat almost anything</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>Touch</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>23</td>
<td>I am generally unable to wear clothes made of rough material</td>
<td></td>
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</tr>
<tr>
<td>24</td>
<td>I am sensitive to rough textures</td>
<td></td>
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</tr>
<tr>
<td>25</td>
<td>I can wear almost any kind of fabric without it bothering me</td>
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</tr>
<tr>
<td>SHS Scale</td>
<td>FM</td>
<td>OA</td>
<td>FM+OA</td>
<td>HC</td>
<td>F score</td>
<td>P value</td>
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<td>------------</td>
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<tr>
<td>Cold</td>
<td>3.75</td>
<td>3.01</td>
<td>3.49</td>
<td>2.93</td>
<td>6.24</td>
<td>0.0004</td>
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<tr>
<td>Heat</td>
<td>3.34</td>
<td>3.33</td>
<td>3.74</td>
<td>2.33</td>
<td>9.51</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Allergies</td>
<td>3.54</td>
<td>3.32</td>
<td>3.78</td>
<td>2.86</td>
<td>5.05</td>
<td>0.002</td>
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<tr>
<td>Smell</td>
<td>3.91</td>
<td>3.44</td>
<td>3.75</td>
<td>3.17</td>
<td>4.50</td>
<td>0.005</td>
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<tr>
<td>Pain</td>
<td>3.64</td>
<td>3.06</td>
<td>3.32</td>
<td>2.77</td>
<td>9.20</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Touch</td>
<td>3.64</td>
<td>3.04</td>
<td>3.58</td>
<td>2.69</td>
<td>7.68</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Hearing</td>
<td>3.19</td>
<td>2.80</td>
<td>2.75</td>
<td>2.66</td>
<td>2.74</td>
<td>0.045</td>
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<tr>
<td>Light</td>
<td>4.01</td>
<td>3.77</td>
<td>3.94</td>
<td>3.12</td>
<td>7.58</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Taste</td>
<td>2.83</td>
<td>2.38</td>
<td>2.47</td>
<td>2.15</td>
<td>4.30</td>
<td>0.006</td>
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<tr>
<td>Total</td>
<td>3.53</td>
<td>3.13</td>
<td>3.41</td>
<td>2.75</td>
<td>17.65</td>
<td>&lt; 0.0001</td>
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</table>
CHARACTERIZING CS: COMPASS 31

- Condensed original COMPASS scale for autonomic dysfunction
  - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3541923/bin/mmc2.pdf
- 6 domains:
  - Orthostatic intolerance
  - Vasomotor
  - Secretomotor
  - Gastrointestinal
  - Bladder
  - Pupillomotor
### CHARACTERIZING CS: COMPASS 31 AND FM

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient M(SD)</th>
<th>Controls M(SD)</th>
<th>P value</th>
<th>Adjusted p</th>
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</thead>
<tbody>
<tr>
<td>Orthostatic Intolerance</td>
<td>9.2 (8.5)</td>
<td>2.9 (6.4)</td>
<td>0.0020</td>
<td>0.0008</td>
</tr>
<tr>
<td>Vasomotor</td>
<td>0.8 (1.3)</td>
<td>0.1 (0.3)</td>
<td>0.0019</td>
<td>0.0023</td>
</tr>
<tr>
<td>Secretomotor</td>
<td>4.9 (3.2)</td>
<td>1.1 (2.4)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>8.4 (4.4)</td>
<td>3.1 (2.7)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bladder</td>
<td>1.8 (1.6)</td>
<td>0.5 (0.9)</td>
<td>0.0003</td>
<td>0.0044</td>
</tr>
<tr>
<td>Pupillomotor</td>
<td>2.4 (1.1)</td>
<td>1.2 (0.8)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COMPASS-31 total</td>
<td>27.5 (14.2)</td>
<td>8.9 (8.7)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

A lot of symptoms, but few objective abnormalities on autonomic testing
CENTRAL SENSITIZATION: A MENTAL MODEL FOR MUS
Latremloliere and Woolf (2009)

• An enhancement in the function of neurons and circuits in nociceptive pathways caused by increases in membrane excitability and synaptic efficacy as well as to reduced inhibition and is a manifestation of the remarkable plasticity of the somatosensory nervous system in response to activity, inflammation, and neural injury.

• Recruit previously subthreshold synaptic inputs to nociceptive neurons, generating an increased or augmented action potential output: a state of facilitation, potentiation, augmentation, or amplification.
CENTRAL SENSITIZATION: A MENTAL MODEL FOR MUS

• Centralized pain dysregulation
• CNS amplification of sensory input
• CNS-mediated alterations in pain processing

Augmented central pain and sensory processing

"Sensory sensitivity syndrome“¹

Dorris. doi:10.3389/fpain.2022.926331
CONDITIONS ASSOCIATED WITH CENTRAL SENSITIZATION

- Chronic fatigue syndrome
- Insomnia
- POTS
- Chronic headaches
- Chronic low back pain
- Interstitial cystitis/painful bladder syndrome
- Temporomandibular joint disorders
- Chronic pelvic pain syndromes
- Anxiety/Depression

@MayoClinicGIM
Pathophysiology of Central Sensitization

Altered sensory processing
# Classification of Pain Mechanisms

<table>
<thead>
<tr>
<th></th>
<th>Nociceptive pain</th>
<th>Neuropathic pain</th>
<th>Centralized pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause</strong></td>
<td>Inflammation or tissue damage</td>
<td>Nerve damage or entrapment</td>
<td>CNS or systemic problem</td>
</tr>
</tbody>
</table>
| **Clinical features** | Localized pain  
Activity affects pain consistently | Follows nerve distributions/dermatomes  
Lancinating, numbness, tingling | Widespread  
Accompanied by fatigue, sleep, memory, and/or mood difficulties  
History of sustained pain elsewhere in body |
| **Treatment** | NSAIDs, injections, surgery, topicalics, opioids         | CNS-acting drugs or local treatments                  | CNS-acting drugs, non-pharmacologic                    |
| **Examples**  | OA, Tissue injury, Cancer                                | Diabetic neuropathy, sciatica, post-herpetic neuralgia | Fibromyalgia, functional GI disorders, TMJ, chronic tension headache, interstitial cystitis |
PHYSIOLOGIC CHANGES SEEN IN CS

• Dysregulation of the CNS (thalamus, hypothalamus, and amygdala)
  • Temperature dysregulation/VMS
• Changes in neurotransmitter concentrations
  • Mood symptoms
• Neuroplasticity (predominantly central)
  • Learned pain response
• HPA axis changes (reduced diurnal variability)
  • Sleep dysfunction, fatigue
• Hyperactive sympathetic and endogenous opioid systems
  • Insomnia/Fatigue
• Amplification of ascending excitatory signals (pain, senses)
  • Global sensory amplification
• Reduction in descending inhibitory signaling
  • Migratory, aching pain (noise-signal breaking through)
  • Paresthesias
Neuroscience of Widespread Pain Augmentation

Zooming in
CNS Pain Volume Control

Low Setting

Peripheral pain signals

Moderate tissue injury

High Setting

Central pain signals

High PAIN

Minimal tissue injury

Clauw D. Central sensitization. Controversies in Fibromyalgia 2019. Vienna
(Neuro) Inflammation and chronic pain

It’s all about the glia
INFLAMMATION

• Commonly used by our patients to explain symptoms of Fibromyalgia and other chronic pain conditions

• Pain doesn’t respond well to typical anti-inflammatories (NSAIDs or steroids)

• They may be right...

“I feel like my whole body is on fire.”
Many activate cytotoxic immunity (CD8 and NK)
  - IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-15, IL-11, TNF

Other activate humoral immunity (B-cell)
  - IL-2, IL-4, IL-5, IL-6, IL-9

Mast cells
  - Major activator: c-kit ligand (stem cell factor)
  - Minor: IL-3, IL-5, IL-6, IL-9, IL-10, IL11
  - Release IL-6, IL-17
  - Involved in BBB, can activate microglia
CYTOKINE & CHEMOKINE PRIMER

• **TNF-α**
  - Activates neutrophils
  - Pro-inflammatory
  - Primary mediator for sepsis
  - Hyperalgesia, myalgia, fatigue

• **IL-1**
  - Activates T-cells
  - Increases B-cell proliferation and Ig synthesis
  - Increases IL-2 production
  - Acute phase reactant production
  - Lethargy, fever, sleepiness, anorexia

• **IL-6**
  - Most potent inducer of acute phase reactants
  - Matures B-cells into plasma cells
  - Activates T-cell growth and diff
  - Inhibits IL-1 and TNF synthesis
  - Hyperalgesia, fatigue

• **IL-8**
  - Allodynia, sympathetic pain

• **Chemokines (CC, CXC, CXCL)**
  - Typically inflammatory
  - Recruit and activate leukocytes to start immune response

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PERIPHERAL SENSITIZATION IN CHRONIC PAIN

Inflammation has a protective role and helps with healing

Inflammatory mediators
- Bradykinin
- Prostaglandins
- CGRP
- TNF-α
- IL-1ra*
- IL-6*
- IL-8*
- IL-17*
- CXCL2
- CXC5

Inflammatory cytokine receptors on cell bodies and terminals of nociceptors
- Released by glia and cause negative feedback loop

Activation leads to hypersensitivity and hyperexcitability of nociceptors by modulating ion channels
- Peripheral sensitization
- (Hyperalgesia and allodynia)

*Elevated in fibro
CYTOKINES HAVE PAIN NEUROMODULATORY EFFECTS

Periphery
- Keratinocytes: ATP, PGE2, ET, β-END
- Macrophages: TNF, IL-1β, IL-10, SPM
- Schwann cells: TNF, IL-1β, IL-10
- Cancer cells: NGF, VEGF, β-END
- Bacteria: LPS, β-hemolysin, flagellin, Mycolactone

Dorsal root ganglion
- Macrophages: TNF, IL-1β, IL-10, SPM
- Satellite glial cells: TNF, IL-1β, ATP
- Nociceptors
- Bone marrow stem cells: TGF-β

Spinal cord
- Oligodendrocytes: IL-33
- T cells: IFN-γ, IL-10, IL-4
- Microglia: TNF, IL-1β, BDNF
- IL-10, SPM?
- Spinal nociceptive neurons

KEY
- Pro-nociceptive
- Anti-nociceptive

Pain (to brain)
ACTIVATED GLIAL CELLS MODULATE PERIPHERAL & CENTRAL NERVOUS SYSTEM SYNAPSES
WIND-UP PHENOMENON (CENTRAL)

• Repeated noxious stimulation of C-fibers increases release of:
  • Glutamate, substance P, CGRP, BDGF
  • Wind up = Prolonged discharge in dorsal horn cells (increase in number of actional potentials elicited per stimulus)

• Sustained release (Long term potentiation) increases afferent nerve hyperactivity and hypersensitivity in the spinal cord
  • Hyperalgesia
  • Allodynia

• This process induces and maintains central sensitization in some patients

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors also involved
## SEX DIFFERENCES IN IMMUNE RESPONSES

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<th>Prepuberty</th>
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RESULTING CHANGES AT CELLULAR LEVEL

- Increased membrane excitability and synaptic strength
- Decreased inhibitory signaling
- Spontaneous neuronal activity
  - Mediated (in part) by reduced activation threshold
- Enlarged receptive sensory and pain fields

Sensations dissociate from association with location, duration, or intensity of stimulus
(alldynia & hyperalgesia)
Anesthesiology 2018; 129:343-66

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KEY POINTS

• Pro-inflammatory cytokines stimulate glial cells, causing neuromodulation of central and peripheral nerves

• AMPA-R, NMDA-R activation can initiate and maintain central sensitization and sensory augmentation in some patients

• Adaptive immune response primes the sensory system to amplify **ALL** sensory inputs
  • Sex-related differences in mechanism exist
  • Pain amplification: Fibro (and fatigue)
Brain re-wiring in chronic pain

Zooming out
BRAIN REGIONS INVOLVED IN PAIN PROCESSING


Image courtesy of Apollo Marcom.
DESCENDING INHIBITION

• Endogenous opioid system in the periaqueductal grey matter (PAG) and neurons in the rostral ventral medulla (RVM) are involved in pain modulation.
  • PAG gets input from frontal cortex, amygdala, hypothalamus
  • RVM adjacent to the RVLM, which regulates sympathetic NS
  • 5HT and NE important NT in descending pain regulatory pathway
    • Some patients have reduced endogenous activity, respond to SNRIs or TCAs
    • Iron deficiency – Fe cofactor for 5HT and NE synthesis
    • Pathway also affected by sleep and exercise
  • Some patients have increased release of endogenous opioids with high baseline opioid receptor occupancy
    • Target of low-dose naltrexone (4.5 mg daily)
INCREASED GRAY MATTER VOLUME IN AND CONNECTIVITY TO SENSORY CORTEX IN WIDESPREAD PAIN

NEUROLOGICAL SIGNATURE OF WIDESPREAD PAIN INCLUDES SENSORY AND INSULAR CORTICES

Increased glutaminergic activity between insula (prop nociceptive brain region) and the "default mode network" (brain at rest) predictive of gabapentinoid response.

Prolonged pain response after noxious event

Hyperalgesia response enhanced by stressors/anxiety
KEY POINTS: FUNCTIONAL / STRUCTURAL

• Increased activation on fMRI or PET
  • Somatosensory cortex (sensation)
  • Insula (emotional context of sensation, sensory appraisal)
  • Anterior cingulate (autonomics, emotions)
  • Amygdala (mood, emotional control)

• Reduced descending inhibitory anti-nociceptive activity

• Increased connections between default mode network and pain augmentation centers (ie the insula)
SENSORY AMPLIFICATION IN RELATED CS SYNDROMES

Pain amplification
• Interstitial cystitis/painful bladder syndrome
• Temporomandibular joint disorders
• Chronic tension headaches/migraines
• Chronic pelvic pain syndromes
• Chronic low back pain

Fatigue
• Chronic Fatigue Syndrome

Hypervigilance & Sympathetic activation
• Insomnia
• Global sensory hyperresponsiveness
• Mixed chemical sensitivity
• Misophonia
• Light/sound sensitivity
• POTS
Leveraging CS Pathophysiology for Treatment

Insight on common and investigational treatments
TREATING CS: TARGETING CYTOKINES

- TNF-α (Intrathecal): Slight reduction
- IL-1β (SQ): No effect
- IL-1ra: No trials
- IL-6 (Intra-articular, systemic): Slight reduction. IA > systemic
- IL-8: No trials
- CXCL1/2 (SQ/IT): Slight reduction

Challenge: Peripheral or central target more effective?

Area of active research in CS and inflammatory pain syndromes

Mediators Inflamm. 2020; 2020: 2076328
TREATING CS: TARGETING NEUROINFLAMMATION

- Exercise can also cause mild decrease in neuroinflammation
- Ambroxol: + effect in small studies

TREATING CS: TARGETING WIND-UP

• Glutamate NMDA-R and AMPA-R potential therapeutic targets
  • Ketamine
    • Effective in some, but side effect limited
  • Dextromethorphan
    • Mixed results in trials
  • Methadone
    • Side effects, complicated pharmacokinetics
    • Low glutamate diet – mild reduction is pain

TREATING CS: BLOCKING NOCICEPTIVE PAIN PATHWAYS

- SNRIs – Increase NE reuptake in DRG, which inhibits propagation of nociceptive signal
  - Duloxetine
  - Milnacipran
  - Other agents (TCAs) with peripheral NE reuptake activity have similar activity, but different side effect profiles.

- Gabapentinoids – Indirectly block release of glutamate (main NT in nociceptive pathway) and glutamate activity in insula
  - Gabapentin
  - Pregabalin

Do not modulate neuroinflammation
PATHOPHYSIOLOGY SUMMARY

The combination of changes at central and peripheral nerve terminals and modification of specific brain signaling pathways from neuroinflammation leads to pain amplification seen in fibromyalgia and sensory amplification seen in related conditions.

Reducing neuroinflammation and pharmacologically targeting pain signaling pathways is key to improving symptom control for CS syndromes.
HOW COMFORTABLE ARE YOU WITH EXPLAINING CENTRAL SENSITIZATION TO AN UNFAMILIAR COLLEAGUE?

A. Very comfortable
B. Comfortable
C. Neutral
D. Uncomfortable
E. Very uncomfortable
F. What is central sensitization?
HOW COMFORTABLE ARE YOU WITH EXPLAINING CENTRAL SENSITIZATION TO A PATIENT?

A. Very comfortable
B. Comfortable
C. Neutral
D. Uncomfortable
E. Very uncomfortable
F. What is central sensitization?
QUESTIONS & ANSWERS

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