A New Paradigm for Managing Chronic Pain: Focus on the Mechanism(s) Rather Than the Disease

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Learning Objective

Analyze the current paradigms for diagnosing and treating chronic pain

Evidence-Based Medicine: Bibliography (Pain)


Which Person Has Pain?
Our Current Paradigms for Diagnosing and Treating Chronic Pain Are Antiquated

We've Been Looking for Pain in All the Wrong Places

- There is no chronic pain state where degree of damage or inflammation in the periphery (i.e., nociceptive input) correlates well with level of pain
- Yet our diagnostic paradigms—and terms we use to describe chronic pain states—imply otherwise
- Until recently, many assumed that when there was a disparity between peripheral findings and pain, this was primarily due to psychological factors


Our Current Paradigms for Diagnosing and Treating Chronic Pain Are Antiquated

- Many non-psychological neurobiological factors can increase or decrease sensitivity to pain, and these are operative in many chronic pain states
- Because these central factors play prominent roles in most individuals with chronic pain, it is imperative that we modify our diagnostic and therapeutic paradigms to better identify and treat central pain


Mechanistic Characterization of Pain

Any Combination May Be Present in a Given Individual

<table>
<thead>
<tr>
<th>Peripheral (nociceptive)</th>
<th>Neuropathic</th>
<th>Central (non-nociceptive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation or mechanical damage in tissues</td>
<td>Damage or dysfunction of peripheral nerves</td>
<td>Characterized by central disturbance in function (e.g., hypothalamic/amygdaloid)</td>
</tr>
<tr>
<td>NSAID-, opioid-responsive</td>
<td>Responds to both peripheral (NSAIDs, opioids, serotonin-reuptake inhibitors) and central pharmacological therapy (e.g., tricyclic antidepressants, other neuroactive compounds)</td>
<td>Responds to neuroactive compounds that alter levels of neurotransmitters involved in pain transmission</td>
</tr>
<tr>
<td>Responds to procedures</td>
<td>Classic examples: Acute pain due to injury, osteoarthritis, rheumatoid arthritis, cancer pain</td>
<td>Classic examples: Fibromyalgia</td>
</tr>
</tbody>
</table>

**Evolution of Thinking Regarding Fibromyalgia**

American College of Rheumatology (ACR) Criteria

- Discrete illness
- Focal areas of tenderness
- Psychological and behavioral factors nearly always present and negative
- Final common pathway
- Part of a larger continuum
- Many somatic symptoms, diffuse tenderness
- Psychological and behavioral factors play roles in some individuals
- Chronic widespread pain
- Tenderness in ≥11 of 18 tender points


**Overlap Between Central Pain Syndromes and Psychiatric Disorders**

- Fibromyalgia
  - 2%-4% of population
  - Defined by widespread pain and tenderness
- Regional Pain Syndromes
  - Irritable bowel syndrome
  - Interstitial cystitis/pelvic pain syndrome
  - Temporomandibular joint disorders
  - Tension headache
  - Vulvodynia

Psychiatric Disorders

- Major depression
- Obsessive-compulsive disorder
- Bipolar disorder
- Posttraumatic stress disorder
- Generalized anxiety
- Panic attack
- Somatoform Disorders
  - 4% of population
  - Multiple unexplained symptoms — no organic findings


**Clinical Characteristics of Central or Centralized Pain**

- Typically characterized by:
  - Multifocal pain
  - Higher current and lifetime history of pain
  - Multiple other somatic symptoms (fatigue, memory difficulties, and sleep disturbances)
- Not a Yes or No — occurs over a wide continuum
  - Diagnostic labels (e.g., fibromyalgia, irritable bowel syndrome, temporomandibular joint disorder) largely historical and irrelevant

Clinical Characteristics of Central or Centralized Pain (cont’d)

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


Pain-Prone Phenotype

The Same Features:
- Are the seminal clinical findings seen in individuals with central pain states such as fibromyalgia
- Can identify the individuals within a cohort of mixed pain states that have centralized their pain
- Are baseline features of individuals in the population that are at risk of higher levels of pain and other symptoms after an acute stimulus
- Predict who will progress from acute to chronic pain, including who will develop new post-surgical pain


Evolution From Chronic Pain-Prone to Chronic Pain

Central Pain-Prone Phenotype
- Female
- Genetics
- Early life trauma
- Family history of chronic pain and mood disturbances
- Personal history of chronic, centrally mediated symptoms (multifocal pain with neuropathic descriptors, fatigue, sleep disturbances, psychological distress, memory difficulties)
- Cognitions such as catastrophizing
- Lower mechanical pain threshold; descending analgesic activity

Psychological and behavioral response to pain or stressor

New or different region of chronic pain

Exposure to stressors or acute, peripheral nociceptive input

Stressors Capable of Triggering These Illnesses

Supported by Case-Control Studies1-6

- Early-life stressors3
  - Children born in 1958 who had experienced a motor traffic accident or who were institutionalized were 1.5X – 2X more likely to have chronic widespread pain (CWP) 42 years later
- Peripheral pain syndromes (e.g., rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis)4
- Physical trauma (automobile accidents)5
- Certain catastrophic events (war…not natural disasters)6
- Infections7
- Psychological stress/distress

Supported by Case-Control Studies


Pain Sensitivity in the General Population

- Like most other physiological processes, we have a volume-control setting for how our brain and spinal cord processes pain1
- This is probably set by the genes that we are born with2-4 and modified by neurohormonal factors and neural plasticity
- The higher the volume-control setting, the more pain we will experience, irrespective of peripheral nociceptive input


Conditions Characterized by Hyperalgesia / Allodynia

- Fibromyalgia
- Temporomandibular joint disorder1,2
- Irritable bowel syndrome2,4
- Headache (tension > migraine)2,6
- Idiopathic low back pain2,4
- Osteoarthritis9
- Rheumatoid arthritis10

Genetics of Pain

- Pain is known to be very genetic in that it strongly runs in families in humans, and differs within species of inbred rats and mice.
- Three specific genes have been shown to play major roles in pain sensitivity thus far:
  - A genetic mutation that leads to loss of function of the Nav1.7 channel is associated with insensitivity to pain, whereas mutations (1.8, 1.9) that lead to increased function leads to erythromelalgia or paroxysmal extreme pain disorder.
  - GTP cyclohydrolase 1 (GCH1)
  - Catechol-O-methyltransferase (COMT)
  - KCNS1


Genetics of Fibromyalgia

- Familial predisposition
  - Most recent work by Arnold, et al. suggests >8 odds ratio (OR) for first-degree relatives, and much less familial aggregation (OR 2) with major mood disorders.
  - Much stronger with bipolarity, obsessive-compulsive disorder.
- Genes that may be involved
  - 5-HT2A receptor polymorphism T/T phenotype
  - Serotonin transporter
  - Dopamine D4 receptor exon III repeat polymorphism
  - COMT (catecholamine-o-methyl transferase)


Neural Influences on Pain and Sensory Processing

- Facilitation
  - Substance P
  - Glutamate and EAA
  - Serotonin
  - Nerve growth factor
  - CCK
- Inhibition
  - Descending anti-nociceptive pathways
  - Norepinephrine-serotonin (5-HT1a/b), dopamine
  - Opioids
  - GABA
  - Cannabinoids
  - Adenosine

EAA = excitatory amino acid; CCK = Cholecystokinin; GABA = gamma-aminobutyric acid

Specific Underlying Mechanisms Leading to Central Augmentation

Decreased Descending Analgesic Activity

- Absent or attenuated DNIC in many pain conditions, including osteoarthritis, fibromyalgia, and irritable bowel syndrome1-3
- Duloxetine leads to increased DNIC in healthy controls4

DNIC = diffuse noxious inhibitory controls


A Deficiency of Descending Analgesic Activity in Fibromyalgia1,2: Which One?

Opioid Agents

- Normal or high levels of CSF enkephalins2
- Never administered in randomized controlled trials; most feel opioids are ineffective or marginally effective
- Harris used PET to show decreased mu-opioid receptor-binding in fibromyalgia4

Noradrenergic/Serotonergic Agents

- Low levels of biogenic monoamines in CSF in fibromyalgia5
- Nearly any class of drug that raises both serotonin and norepinephrine has demonstrated efficacy in fibromyalgia6


Specific Underlying Mechanisms in Central Pain States

- Global problem with sensory processing (i.e., interoception)
- Patients with fibromyalgia are equally sensitive to loudness of auditory tones1
- Insular hyper-reactivity is consistently seen2-4
- H-MRS studies of glutamate levels in posterior insula5

H-MRS = proton magnetic resonance spectroscopy

Functional Neuroimaging of Pain

- A number of functional neuroimaging techniques have been used to study acute and chronic pain
- Functional MRI (fMRI) allows the examination of changes in blood flow (i.e., neuronal activation) associated with various tasks (e.g., giving a pressure or heat stimulus and viewing the response)
- Variations also being used to examine connectivity between structures and subtle changes in brain volume
- Other imaging techniques enable examination of level or binding of certain neurotransmitters
- Positron emission tomography
- Proton magnetic resonance spectroscopy


fMRI in Chronic Pain States

- There is objective evidence of augmented pain processing in a broad range of hyperalgesic pain states
- Depression and pain are overlapping neurobiological processes
- How individuals think about their pain can affect both the sensory and affective processing of pain


Default Mode Network

- Anatomically defined brain regions more active at rest (internal focus) than during externally focused tasks (visual, motor, somatosensory, etc.)
- Includes inferior parietal lobule (IPL), posterior cingulate cortex / precuneus (PCC), medial prefrontal cortex (MPC)

Intrinsic Brain Connectivity Is Altered in Patients With Fibromyalgia

In fibromyalgia, DMN and rEAN show greater intrinsic connectivity within component DMN (PCC), and rEAN (IPS) as well as limbic (insula), and sensorimotor (SII) regions outside conventional network boundaries.

All fibromyalgia vs. healthy control differences driven by greater connectivity for patients with fibromyalgia.


DMN Connectivity to Right Insula Is Correlated With Clinical Pain at the Time of the Scan

VAS = visual analog scale.


Is Chronic Pain a Neurodegenerative Disease?

Apkarian was first to show that chronic pain may be a neurodegenerative disease, showing

- Decreased gray matter density in DLPFC and thalamus
- Related to length of pain
- More recently seen in other pain states including
  - Headache (insula and ACC)
  - Irritable bowel syndrome (insula and ACC)
  - Fibromyalgia (multiple regions)
  - Posttraumatic stress disorder (insula)

DLPFC = Dorsolateral prefrontal cortex; ACC = anterior cingulated cortex.

Osteoarthritis of the Knee

- Classic "peripheral" pain syndrome
- Poor relationship between structural abnormalities and symptoms\(^1\)
- In population-based studies:
  - 30% – 40% of individuals who have grade 3/4 K/L radiographic osteoarthritis have no symptoms
  - 10% of individuals with severe pain have normal radiographs
- Psychological factors explain very little of the variance between symptoms and structure\(^2\)
- We sometimes delude ourselves into thinking that our current therapies are adequate
- NSAIDs, acetaminophen, and even opioids have small effect sizes\(^3,4\)
- Arthroplasty does not predictably relieve pain


Osteoarthritis of the Knee (cont’d.)

- Subsets of patients with osteoarthritis of the knee display hyperalgesia and attenuated DNIC.\(^1\)
- In past years, two classes of neuroactive drugs likely acting on volume control of pain processing have been shown to be effective:
  - SNRIs (formerly tricyclic drugs had shown the same effect but have not gained wide usage)\(^2\)
  - Tanezumab, a nerve growth factor inhibitor\(^2\)
- Functional and structural neuroimaging results from Tracey group\(^2\)
- Identify hyperalgesia/central sensitization in osteoarthritis\(^3\)
- Show that thalamic atrophy on VBM at baseline in knee osteoarthritis normalizes after arthroplasty\(^4\)

DNIC = diffuse noxious inhibitory controls; VBM = voxel-based morphometry

Chronic Low Back Pain (CLBP)

- Well-known, poor relationship between structural abnormalities and pain
- Several studies have demonstrated diffuse hyperalgesia at neutral sites in individuals with CLBP\(^1,3\)
  - Tenderness at thumb a greater predictor of pain and functional status than psychological factors or X-ray/MRI of back\(^1\)
- Functional MRI studies have demonstrated central pain augmentation very similar to that seen in fibromyalgia\(^2\)
- GCH1 haplotype predicts decreased pain after discectomy\(^3\)

Clinical Connections

- Most practitioners have historically considered most chronic pain to be from peripheral nociceptive input (i.e., damage or inflammation), and data increasingly suggest this is simply not the case.
- When thinking about central factors in pain, focus on psychological factors.
- We now understand that non-psychological central nervous system factors can markedly increase sensitization or decrease pain sensitivity.
- The central nervous system is now thought of as setting the volume control on pain processing.
- Clinicians should incorporate a broader understanding of factors that can increase or decrease pain sensitivity into practice.

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