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Review Article

MULTIPLE PAIN GENERATORS AND CENTRAL AMPLIFICATION IN CHRONIC PAIN: A NARRATIVE REVIEW OF PERIPHERAL-CENTRAL MECHANISM

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ABSTRACT

Introduction: Chronic pain is increasingly recognized as a complex condition involving interactions between peripheral nociceptive sources and central nervous system amplification mechanisms. Traditional models that focus solely on tissue damage are inadequate to explain the persistence and widespread distribution of many chronic pain conditions.
Material and Methods: This narrative review synthesizes current theoretical frameworks and empirical evidence regarding the interplay between peripheral pain generators and central amplification mechanisms. Literature from clinical, experimental, and neurobiological studies was reviewed to examine mechanisms of central sensitization, neuroimmune interactions, descending pain modulation, and patterns of chronic pain comorbidity.
Discussion: Current evidence suggests that central sensitization is a key mechanism linking multiple chronic pain conditions. Persistent peripheral nociceptive inputs, including tissue inflammation, nerve injury, and musculoskeletal disorders, may initiate and maintain central sensitization through neuroimmune activation and altered descending pain modulation. Epidemiological and mechanistic evidence supports integrated peripheral–central models of chronic pain, although uncertainties remain regarding the relative contributions of peripheral and central mechanisms, the temporal evolution of sensitization, and the identification of reliable mechanistic biomarkers.
Conclusion: Chronic pain is best understood as the result of dynamic interactions between peripheral pain generators and central amplification mechanisms rather than isolated pathological processes. Recognizing these bidirectional mechanisms has important implications for comprehensive clinical assessment and multimodal management. Future research should prioritize longitudinal studies, validated mechanistic biomarkers, and personalized approaches that integrate peripheral, central, and psychosocial factors.

Keywords: pain; mental state; multidimensional; biopsychosocial; pain assessment

INTRODUCTION

Chronic pain is generally defined as pain that persists or recurs for more than three months and is increasingly seen as a disease in its own right rather than just a symptom (IASP classification). It affects about 20-30% of adults worldwide and represents a major public health challenge with significant personal suffering and societal costs. Traditional biomedical models,

which treat chronic pain as a direct consequence of tissue damage or peripheral issues, have proven inadequate in explaining the complexity, persistence, and treatment resistance present in many chronic pain conditions. Modern pain science increasingly recognizes chronic pain as a complex phenomenon involving dynamic interactions between peripheral nociceptive mechanisms and processing and amplification within the central nervous system.[1,2]

Two complementary conceptual frameworks have developed to explain the pathophysiology of chronic pain. First, the idea of "multiple pain generators" suggests that chronic pain conditions often involve several distinct peripheral and central sources of nociceptive input that may interact synergistically.[3,4,5] Second, the theory of "central amplification" or "central sensitization" argues that persistent or intense nociceptive input can cause neuroplastic changes in central pain pathways, leading to increased pain sensitivity, expanded receptive fields, and pain responses to normally harmless stimuli.[6,7,8] These frameworks are not mutually exclusive; rather, growing evidence indicates complex bidirectional interactions in which peripheral pain generators can trigger and sustain central sensitization, and central amplification can reduce the activation thresholds for additional peripheral pain sources.[9,10]

This narrative review critically examines the current understanding of multiple pain generators and central amplification in chronic pain. The objectives are to:

1. Synthesize key theoretical models and their development
2. Evaluate research methods used to study pain mechanisms
3. Assess empirical evidence for both peripheral and central contributions to chronic pain
4. Identify areas of agreement and ongoing debates among researchers
5. Critically evaluate the strengths and limitations of existing studies
6. Highlight critical knowledge gaps that need further research. The review is aimed at a postgraduate academic audience and explicitly notes uncertainties

where evidence is limited or conflicting

MATERIAL AND METHODS

Literature Search Strategy

This narrative review was conducted using a structured literature search to identify current evidence regarding the interaction between peripheral pain generators and central amplification mechanisms in chronic pain. Literature searches were performed in March 2026 using five primary academic databases and search platforms: PubMed, Google Scholar, SciSpace (including Deep Search, Paper Search, and Full-Text Search functions), ArXiv, and the author's SciSpace Library. Multiple databases were used to maximize literature coverage and capture diverse clinical, experimental, and translational perspectives.

Search strategies combined controlled vocabulary and free-text keywords related to three principal concepts: (1) multiple pain generators (e.g., *multiple pain sites*, *comorbid pain conditions*, *peripheral pain generators*, and *polyalgesic*); (2) central amplification mechanisms (e.g., *central sensitization*, *central nervous system sensitization*, *pain amplification*, *central pain mechanisms*, and *central processing*); and (3) chronic pain conditions (e.g., *chronic pain*, *widespread pain*, *diffuse pain*, and *chronic pain syndromes*). Boolean operators (AND, OR) were used to combine search terms appropriately. PubMed searches incorporated Medical Subject Headings (MeSH) when available alongside free-text terms, whereas Google Scholar searches used exact phrase matching and synonym combinations to broaden retrieval.

Although no formal date restrictions were initially applied to ensure adequate historical context, emphasis was placed on studies published within the past ten years. Seminal earlier publications were retained when considered essential for understanding foundational theoretical concepts. No language restrictions were imposed during the initial search process

Study Selection

Retrieved records from all databases were merged and duplicate publications were removed prior to

screening. A total of 307 unique records underwent title, abstract, and full-text evaluation according to their relevance to the review objectives. Studies were selected based on their contribution to understanding the interaction between peripheral nociceptive mechanisms and central amplification in chronic pain.

Eligible studies included original research articles, systematic reviews, meta-analyses, and theoretical papers addressing mechanisms of chronic pain, central sensitization, central nervous system pain processing, peripheral pain generators, pain comorbidity, neuroinflammation, or related mechanistic concepts. Both human and animal studies were considered eligible when they provided mechanistic insights relevant to peripheral–central pain interactions.

Studies were excluded if they focused exclusively on acute pain, evaluated pharmacological interventions without discussing underlying mechanisms, consisted solely of case reports or case series involving fewer than ten participants (unless they offered unique mechanistic insights), described surgical techniques without mechanistic discussion, or represented non-peer-reviewed publications such as editorials, conference abstracts, or opinion articles lacking substantial empirical or theoretical evidence.

Following screening, the 30 most relevant publications were selected for detailed synthesis. Selection was based on overall relevance to the review objectives, scientific quality, citation impact, and contribution to current understanding of peripheral pain generators, central sensitization, neuroimmune interactions, and chronic pain mechanisms

Narrative Synthesis

The selected literature was narratively synthesized using a thematic approach rather than quantitative pooling of study findings. Evidence was critically reviewed and organized into major conceptual themes reflecting the objectives of this review. These themes included:

1. Current concepts of peripheral pain generators and central sensitization

2. Evidence supporting peripheral–central interactions
3. Neurophysiological and neuroimmune mechanisms of central amplification
4. Areas of scientific consensus and ongoing controversy
5. Methodological considerations across the literature
6. Clinical implications and future research directions.

Rather than estimating pooled effect sizes, this review emphasizes the interpretation and integration of evidence across different study designs. Particular attention was given to identifying recurring concepts, conflicting findings, methodological strengths and limitations, and existing knowledge gaps to provide a comprehensive overview of current understanding regarding peripheral–central mechanisms in chronic pain

DISCUSSION

Current Concepts of Peripheral Central Pain Interaction

Current understanding of chronic pain recognizes that persistent pain is rarely driven by a single mechanism. Instead, chronic pain results from dynamic interactions between peripheral nociceptive inputs and central nervous system processes that progressively amplify pain perception. Ongoing peripheral pain generators may initiate peripheral sensitization and neuroimmune activation, which subsequently promote central sensitization and central amplification. These mechanisms facilitate cross-sensitization between different body regions, ultimately contributing to the development of multiple chronic pain conditions, as illustrated in Figure 1.

1. Central Sensitization Theory

Central sensitization is a state of increased excitability of neurons in the pain pathways of the central nervous system, leading to amplified pain responses to nociceptive stimuli (hyperalgesia) and to normally harmless stimuli (allodynia).[6,11] This condition was first described in experimental animal models, which

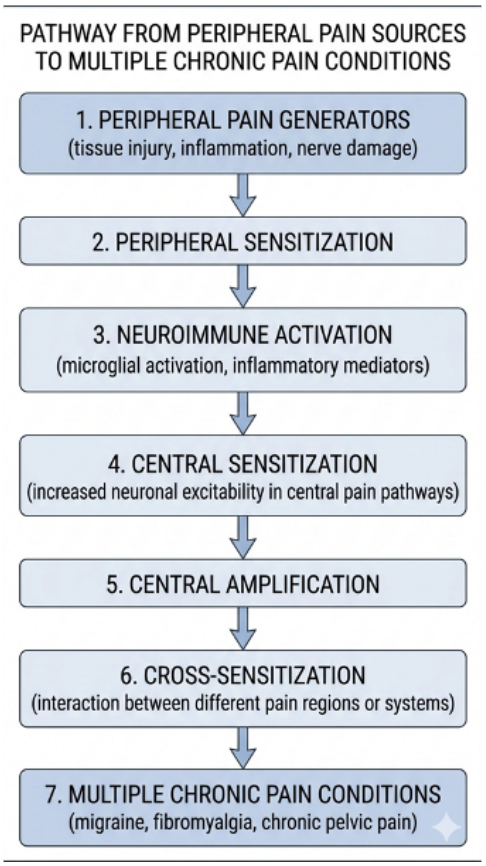

Figure 1. Proposed conceptual framework of peripheral–central interactions leading to multiple chronic pain condition

showed that repetitive C-fiber stimulation causes progressive increases in the excitability of dorsal horn neurons a process known as "wind-up".[24] Later research has shown that central sensitization involves multiple molecular and cellular mechanisms, including strengthened synaptic connections through long-term potentiation; changes in ion channel expression and function; decreased inhibitory neurotransmission; activation of microglia and astrocytes; and reorganization of cortical and subcortical pain processing networks.[2,11,22]

Central sensitization theory has been used to explain key features of chronic pain conditions that cannot be explained by peripheral tissue damage alone, such as ongoing pain despite healing, pain spreading beyond the original injury, and widespread pain.[24] The theory is

especially relevant for conditions like fibromyalgia, where diffuse pain and hyperalgesia happen without clear signs of peripheral tissue damage.[6,11,28] Yunus has suggested "central sensitivity syndromes" as a broad category for conditions sharing central sensitization as a common mechanism, including fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, and temporomandibular disorders.[6]

However, the central sensitization concept has evolved significantly since its introduction. Modern models acknowledge that central sensitization is not a single phenomenon but involves multiple distinct neurobiological processes that operate at different times and locations.[2,22] Moreover, recent evidence indicates that central sensitization can be sustained by ongoing peripheral nociceptive input in many conditions, disputing earlier ideas that focused on autonomous central mechanisms separate from peripheral input.[4,14,15]

2. Peripheral Pain Generator Concepts

The idea of peripheral pain generators relates to specific anatomical locations or pathophysiological processes that produce nociceptive input, which can initiate or sustain chronic pain.[5,14] These generators can include damaged or inflamed tissues; sites of nerve compression or injury; myofascial trigger points; joint issues; visceral organ dysfunction; and ectopic neural activity.[3,5,13,20] The peripheral pain generator model highlights that, even in conditions with central sensitization, ongoing peripheral nociceptive input may significantly contribute to maintaining central hyperexcitability.[14,15]

Gerwin has argued that peripheral pain mechanisms remain important even in conditions traditionally seen as primarily central, such as fibromyalgia and chronic widespread pain.[14] Evidence supporting this includes: (1) identification of specific peripheral tender points and myofascial trigger points in fibromyalgia patients; (2) demonstration that local anesthetic blockade of peripheral pain sites can offer temporary relief; and (3) findings that peripheral tissue

pathology (e.g., small fiber neuropathy) exists in some patients with fibromyalgia and other central sensitivity syndromes.[11,14] Staud has similarly noted that peripheral pain mechanisms contribute to chronic widespread pain through sustained nociceptive input that promotes central sensitization.[15]

The peripheral pain generator concept has significant clinical implications, indicating that targeting specific peripheral sources can reduce central sensitization and offer therapeutic benefits even in conditions with prominent central features.[5,14] However, the importance of peripheral versus central mechanisms varies among conditions and individuals, and identifying relevant peripheral pain generators remains difficult in many cases.[3,14]

3. Integrated Models of Peripheral-Central Interactions

Contemporary theoretical models increasingly highlight bidirectional interactions between peripheral and central pain mechanisms, rather than treating them as separate explanations.[9,10,15,21] These integrated models suggest that chronic pain usually involves both peripheral nociceptive input and central amplification, with complex feedback loops where peripheral input causes central sensitization, which then lowers thresholds for activating additional peripheral pain sources.[1,9,30]

Several lines of evidence support integrated peripheral-central models. First, studies demonstrate dose-response relationships between the number or intensity of peripheral pain sources and the severity of central sensitization markers such as allodynia and widespread pain.[1,9,21] Tietjen et al. found a graded relationship between the number of comorbid pain conditions and the severity of cutaneous allodynia in migraine patients, suggesting that cumulative peripheral input drives central sensitization.[1] Second, research indicates that central sensitization can expand pain beyond the original peripheral source through mechanisms including enlarged receptive fields, recruitment of silent nociceptors, and enhanced temporal summation. [15,21,24] Third, evidence shows that central

sensitization can facilitate the development of new peripheral pain generators through mechanisms such as neurogenic inflammation and altered descending modulation.[21,30]

McNamara et al. have proposed a comprehensive model of peripheral, central, and cross-sensitization in endometriosis-associated pain that exemplifies integrated thinking.[21] This model suggests that peripheral endometriotic lesions produce nociceptive input that triggers central sensitization in the spinal cord and brain. Central sensitization then heightens pain from the original lesions. It promotes the development of related pain conditions through cross-sensitization—the process where sensitization in one area increases pain sensitivity in other regions. Similar integrated models have been proposed for chronic pelvic pain, chronic low back pain, and other conditions.[3,7,22]

Despite the appeal of integrated models, significant uncertainties remain about the timing of peripheral-central interactions, individual differences in susceptibility to sensitization, and the specific mechanisms driving bidirectional effects.[2,77,22] These questions are key areas for future research

Research Methodologies in Pain Mechanism Studies

1. Clinical Assessment Approaches

Research on pain mechanisms uses various methodological approaches, each with its own strengths and limitations. Clinical assessment studies usually employ cross-sectional or longitudinal observational designs to explore relationships between pain features, comorbid conditions, and potential markers of central sensitization or peripheral pain sources.[1,3,7] Common assessment tools include validated questionnaires for pain intensity, distribution, and quality; standardized diagnostic criteria for specific pain conditions; tender point examinations; and measures of pain-related disability and psychological factors.[1,7,23,29]

Large-scale cross-sectional studies have offered valuable evidence on comorbidity patterns and relationships between pain conditions. For example, Tietjen et

al. studied 1,413 migraineurs from 11 headache centers using standardized questionnaires to assess allodynia and comorbid pain condition.[1] Hah et al. conducted a retrospective cohort study of 1,607 patients with abdominal pain to examine overall pain distribution and risk factors for widespread pain [9]. These large samples provide the statistical power to identify associations and control for confounding variables through multivariable regression analyses.[1,9]

However, cross-sectional designs have significant limitations. They cannot determine temporal precedence or causality, which creates uncertainty about whether observed associations indicate peripheral input causing central sensitization, central mechanisms promoting peripheral pain, or shared underlying vulnerability factors.[1,7,9] Self-report measures may be prone to recall bias and do not directly assess underlying neurobiological mechanisms.[1,9] Additionally, relying on clinical diagnosis without objective biomarkers can lead to heterogeneous patient samples that obscure mechanistic relationships.[6,11]

2. Experimental Pain Testing

Quantitative sensory testing (QST) offers standardized methods to evaluate somatosensory function and detect signatures of altered pain processing.[15,23,27] QST protocols generally assess detection and pain thresholds across various stimulus modalities (mechanical, thermal, electrical) at multiple body sites, along with measures of temporal pain summation and conditioned pain modulation.[15,23,27] Findings such as reduced pain thresholds at sites distant from the original pain site, increased temporal summation, or impaired descending inhibition are considered signs of central sensitization.[15,23,27]

Several studies have used QST to examine central sensitization in chronic pain conditions. Jespersen et al. assessed pressure-pain thresholds in patients with lateral epicondylalgia and found reduced thresholds at sites away from the elbow, indicating central sensitization.[27] Chaves et al. used QST to show that patients with both migraine and temporomandibular disorders experienced greater heat pain hyperalgesia and cephalic

cutaneous allodynia compared to those with only one condition, supporting the idea that multiple pain sources increase central sensitization.[23] Drummond et al. measured mechanical and thermal hyperalgesia in the limbs and forehead of patients with complex regional pain syndrome, finding greater ipsilateral cranial hyperalgesia in those with co-occurring migraine.[30]

QST offers a more objective evaluation of pain processing than self-report alone and can identify subclinical changes in somatosensory function.[15,23,27] However, QST has drawbacks, including significant variability between individuals, a lack of standardized normative data, and uncertainty regarding the specificity of findings for particular underlying mechanisms.[15,27] Lower pain thresholds may indicate peripheral sensitization, central sensitization, psychological factors, or a combination of these.[15,27] Additionally, QST measures evoked pain responses to experimental stimuli, which may not fully reflect the mechanisms underlying spontaneous clinical pain.[15]

3. Neurobiological and Molecular Investigations

Advances in neuroscience have facilitated the study of molecular and cellular mechanisms underlying chronic pain. Animal models enable controlled manipulation of peripheral and central pain mechanisms and allow direct assessment of neuronal activity, neurotransmitter systems, and molecular signaling pathways.[16,18] For instance, Harvey et al. used a mouse model of endometriosis to show that multiple lesion inductions increase central sensitization driven by neuroinflammation.[16] Cai et al. used neuroimaging in rat models to demonstrate differential cortico-thalamic reorganization in opioid-induced hyperalgesia compared to neuropathic pain.[17]

Human neuroimaging studies utilizing functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and electroencephalography (EEG) have identified changes in brain structure and function associated with chronic pain conditions, including alterations in pain processing regions, default

mode network connectivity, and descending modulation systems.[2,22,28] However, interpreting neuroimaging findings remains difficult because it is often unclear whether the observed brain changes are causes or effects of chronic pain, or if they reflect comorbid psychological factors.[2,22]

Molecular studies have examined inflammatory mediators, neurotrophic factors, ion channels, and genetic polymorphisms associated with chronic pain.[2,18,19] Jung's review emphasizes the roles of nociceptor sensitization, neurogenic inflammation, neuroimmune interactions, and gut microbiota dysbiosis in the development of chronic pain.[2] Argueta et al. demonstrated neuroprotective, anti-inflammatory, and pain-relieving effects of palmitoylethanolamide in a sickle cell mouse model, indicating neuroimmune mechanisms.[18] These molecular investigations offer mechanistic insights but often do not translate directly to human clinical pain because of species differences and the complex nature of human pain conditions.[2,18]

A major challenge in neurobiological research is establishing causal links between molecular or neural changes and clinical pain experiences.[2,22] Longitudinal studies that track the timing of neurobiological changes in relation to the development of pain are uncommon but crucial for understanding causality.[2,16,22]

Evidence for Multiple Pain Generators

1. Comorbidity Patterns and Pain Condition Clustering

Substantial epidemiological evidence shows that chronic pain conditions often co-occur more frequently than expected by chance, indicating shared underlying mechanisms .[1,6,7,9,29] Tietjen et al. found that 60% of migraine patients reported at least one allodynic symptom, and the severity of allodynia increased with the number of coexisting pain conditions (irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia), even after controlling for demographic factors, migraine features, and mood disorders. Patients with three or more co-occurring pain conditions had three times higher odds of severe allodynia compared to those without

coexisting conditions.[1]

Hah et al. examined 1,607 patients with abdominal pain and found that 44% reported pain in multiple body areas. Widespread pain was linked to female sex, younger age, higher pain intensity, and the presence of anxiety or depression. The distribution of pain extended beyond anatomically connected regions, indicating central rather than purely peripheral mechanisms.[9] Similarly, Palit et al. found that individuals with chronic pelvic pain and multiple overlapping pain conditions showed increased central sensitization markers and that negative affect mediated the relationship between pain conditions and central sensitization.[7]

The idea of "central sensitivity syndromes" proposed by Yunus includes conditions like fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, temporomandibular disorders, tension-type headache, and migraine. These conditions often occur together and share features of central sensitization [6]. However, the scientific validity and usefulness of this concept are still debated [6]. Critics claim that grouping diverse conditions under a single label can obscure important mechanistic differences and that the boundaries between central sensitivity syndromes and other chronic pain conditions are unclear [6].

Comorbidity patterns offer important evidence for shared mechanisms but also have limitations. Comorbidity may indicate common underlying vulnerability factors (genetic, psychological, environmental) rather than direct mechanistic links between conditions [1], [7], [9]. Cross-sectional comorbidity data cannot determine whether one condition predisposes individuals to others or whether they develop independently from shared risk factors [1], [9]. Longitudinal studies that examine the temporal sequence of condition onset are necessary but remain limited.[7,9]

2. Peripheral Nociceptive Sources

Although contemporary pain research often emphasizes central mechanisms, substantial evidence shows that peripheral nociceptive input plays a crucial role in many chronic pain conditions.[4,5,14,15] Borg-Stein reviewed evidence for

peripheral pain generators in fibromyalgia, including myofascial trigger points, cervical spine issues, and peripheral nerve entrapments, and argued that targeting these peripheral sources can offer clinical benefits.[5] Similarly, Gerwin highlighted that peripheral pain mechanisms remain significant in fibromyalgia and chronic widespread pain, citing evidence that local anesthetic blockade of peripheral sites provides temporary relief.[14]

In chronic pelvic pain, Hoffman identified multiple potential peripheral sources of pain, including endometriosis, adenomyosis, pelvic floor muscle dysfunction, bladder issues, and nerve entrapment.[3] A patient-centered assessment requires a systematic evaluation of these possible sources to guide targeted treatment.[3] McNamara et al. emphasized that peripheral endometriotic lesions produce ongoing nociceptive input through inflammatory mediators and nerve fiber infiltration, which can trigger and sustain central sensitization.[21]

Staud reviewed evidence that peripheral pain mechanisms contribute to chronic widespread pain through sustained nociceptive input from muscles, joints, and other tissues. Experimental studies show that sustained muscle pain can cause central sensitization and that ongoing peripheral input is necessary to maintain central hyperexcitability in many cases. However, Staud also noted that the relative contributions of peripheral versus central mechanisms vary among individuals, with some patients showing predominantly peripheral mechanisms and others predominantly central.[15]

The identification of small fiber neuropathy in some patients with fibromyalgia and other conditions traditionally seen as purely central has challenged the separation between peripheral and central pain mechanisms. Di Tommaso et al. reviewed neurophysiological and morphological evidence for small fiber neuropathy in fibromyalgia, suggesting that peripheral nerve pathology may play a role in pain for some patients. However, the prevalence and clinical importance of small fiber neuropathy in fibromyalgia are still uncertain, and

its link to central sensitization remains unclear.[11]

Macionis proposed a new hypothesis that chronic pain in usually painless conditions, including neuromas, may result from compressive proximal neural lesions that sensitize distal nerve segments. This hypothesis suggests that peripheral nerve pathology may be more widespread than currently recognized but needs further empirical validation.[13]

3. Neuroinflammatory Mechanisms

Neuroinflammation the activation of immune cells and inflammatory signaling within the nervous system has become a key mechanism connecting peripheral and central pain processes.[2,10,16,18,19,21] Jung's review highlighted that neurogenic inflammation involves the release of inflammatory mediators from sensory nerve terminals, which sensitize peripheral nociceptors and recruit immune cells, thus creating a positive feedback loop. Interactions between the immune system and the nervous system in the spinal cord and brain, including microglial and astrocytic activation, contribute to the development and persistence of central sensitization.[2]

Harvey et al. demonstrated in a mouse model that multiple endometriotic lesions strengthen central sensitization through neuroinflammatory mechanisms, with increased spinal cord microglial activation and pro-inflammatory cytokine expression. This finding suggests that the number of peripheral inflammatory sites may influence the extent of central sensitization via cumulative neuroinflammatory drive.[16] Argueta et al. showed that palmitoylethanolamide, an endogenous lipid mediator with anti-inflammatory properties, reduced pain behaviors and neuroinflammation in sickle cell mice, supporting the role of neuroimmune mechanisms in chronic pain.[18]

Alzamora-Schmatz et al. reviewed evidence showing that endometriosis-associated pain involves complex interactions between peripheral lesion-derived inflammatory mediators, peripheral nerve sensitization, and central

nervous system changes.[12] Inflammatory cytokines, prostaglandins, and nerve growth factor released from endometriotic lesions sensitize pelvic nociceptors and promote nerve fiber growth into lesions.[12] These peripheral inflammatory processes can trigger central sensitization, which then intensifies pain and may lead to the development of additional pain conditions.[21]

Demir et al. examined pain mechanisms in chronic pancreatitis, explaining how pancreatic inflammation causes peripheral nerve damage, neurogenic inflammation, and central sensitization. The authors used the metaphor of "a master and his fire" to describe how peripheral inflammatory processes (the fire) are amplified by central mechanisms (the master). This analogy highlights the interconnected role of peripheral and central factors in chronic pain.[25] Despite increasing recognition of neuroinflammatory mechanisms, significant uncertainties still exist regarding which inflammatory mediators are most critical for pain, how neuroinflammation evolves in relation to pain development, and the individual differences in neuroinflammatory responses.[2,12,16,21] Additionally, translating neuroinflammatory findings from animal models to human chronic pain conditions remains a challenge.[16,18]

Central Amplification Mechanisms

1. Neurophysiological Basis of Central Sensitization

Central sensitization involves multiple neurophysiological mechanisms that increase the excitability of central pain pathways and decrease inhibitory control.[2,6,11,15,22,24] At the spinal level, central sensitization is marked by: heightened responsiveness of dorsal horn neurons to peripheral input; expansion of neuronal receptive fields; lowered activation thresholds; and prolonged after-discharges following stimulation.[15,24] These changes result from molecular mechanisms, including increased glutamate receptor activity (especially NMDA receptors), altered expression of ion channels, decreased GABAergic and glycinergic inhibition, and structural

synaptic plasticity.[2,15,24]

Vierck presented a detailed model of how chronic, spatially distributed pain like fibromyalgia develops through central sensitization mechanisms.[24] The model suggests that ongoing nociceptive input from various peripheral sources causes cumulative sensitization of spinal and brain pain pathways, eventually leading to widespread hyperalgesia and allodynia.[24] Key mechanisms include temporal summation (wind-up), in which repetitive C-fiber input causes progressively stronger responses in dorsal horn neurons, and spatial summation, in which converging input from multiple body regions increases central excitability.[24] Once established, central sensitization can be maintained by normally harmless input, explaining why pain persists even after the initial tissue damage has healed.[24]

Supraspinal mechanisms also play an essential role in central amplification. Lee et al. reviewed evidence for the involvement of the central nervous system in rheumatoid arthritis, osteoarthritis, and fibromyalgia, describing changes in brain structure and function in pain-processing areas, the default mode network, and descending modulation systems.[2,17,22,28] Cai et al. demonstrated distinct cortico-thalamic reorganization in opioid-induced hyperalgesia compared to neuropathic pain in rats, indicating that different central mechanisms may lead to various chronic pain conditions.[17] Li et al. reviewed the peripheral and central pathological mechanisms of chronic low back pain, emphasizing that central sensitization involves reorganization of cortical pain processing and altered connectivity between pain-related brain regions.[22]

However, significant uncertainties still exist about the neurophysiological basis of central sensitization. The specific molecular and cellular mechanisms that are most essential for triggering versus maintaining sensitization are unclear.[2,15,22] The extent to which central sensitization involves reversible functional changes versus structural neuroplastic changes is debated.[2,22,24] Additionally, the connection between

neurophysiological measures of central sensitization and clinical pain experiences remains only partially understood.[15,22]

2. Neuroimmune Interactions

Neuroimmune interactions are a vital mechanism linking peripheral inflammation to central sensitization. Glial cells, especially microglia and astrocytes, play crucial roles in regulating synaptic transmission and neuronal excitability in pain pathways. Peripheral inflammatory signals can activate spinal cord microglia through various pathways, including: direct activation by inflammatory mediators crossing the blood-spinal cord barrier; activation by damage-associated molecular patterns released from injured tissues; and stimulation by neurotransmitters and neuropeptides released from primary afferent terminals.[2,16,18,21]

Activated microglia and astrocytes release pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines, prostaglandins, and reactive oxygen species, which increase neuronal excitability and synaptic transmission. [2,16]These neuroimmune mediators can also decrease inhibitory neurotransmission and promote structural synaptic changes, contributing to the maintenance of central sensitization. Harvey et al. demonstrated that multiple endometriotic lesions elicit greater spinal cord microglial activation and central sensitization than single lesions, suggesting a dose-dependent neuroimmune response.[16]

Jung's review highlighted that gut microbiota dysbiosis can contribute to chronic pain through neuroimmune mechanisms. Dysbiosis increases intestinal permeability and systemic inflammation, and disrupts gut-brain communication, thereby sensitizing central pain pathways. This may explain the high co-occurrence of chronic pain conditions and gastrointestinal disorders. However, the specific microbiota changes most relevant to pain and the mechanisms mediating gut-brain signaling in chronic pain remain only partly understood.[2]

Systemic factors, including adrenal insufficiency and weakened cholinergic anti-inflammatory

pathways, may also contribute to chronic pain by lowering endogenous anti-inflammatory capacity. Jung pointed out that chronic stress and hypothalamic-pituitary-adrenal axis dysfunction can impair cortisol production, reducing the body's ability to resolve inflammation and potentially promoting chronic pain development. However, the causal relationships between these systemic factors and chronic pain need further research.[2]

3. Descending Modulation and Inhibitory Control

Descending pain modulation systems originating in the brainstem can either inhibit or facilitate spinal nociceptive transmission, and changes in descending modulation contribute to chronic pain.[2,22,28] Normally, descending inhibitory pathways involving serotonergic and noradrenergic projections from the rostral ventromedial medulla and locus coeruleus suppress spinal nociceptive processing.[22,28] However, in chronic pain conditions, descending inhibition may be impaired while descending facilitation is increased, leading to a net amplification of pain signals.[22,28]

Lee et al. reviewed evidence that patients with fibromyalgia, rheumatoid arthritis, and osteoarthritis exhibit reduced conditioned pain modulation a psychophysical measure of descending inhibitory control compared to healthy controls. Impaired descending inhibition may indicate altered brainstem function, decreased endogenous opioid or monoamine signaling, or increased descending facilitation.[28] Li et al. similarly observed that chronic low back pain is associated with changes in descending modulation, with some patients exhibiting predominantly impaired inhibition and others showing increased facilitation.[22]

The mechanisms behind altered descending modulation in chronic pain are still not fully understood.[22,28] Possible contributing factors include: chronic stress and hypothalamic-pituitary-adrenal axis dysfunction; mood disorders such as depression and anxiety that affect monoaminergic neurotransmission; sleep disturbances that hinder restorative processes; and

neuroplastic changes in brainstem pain modulation circuits caused by persistent nociceptive input.[2,22,28,29] Di Tommaso et al. found that headache patients with fibromyalgia also experienced higher levels of anxiety, sleep problems, and pericranial tenderness, suggesting that psychological and sleep factors might play a role in central sensitization by impacting descending modulation.[29]

However, the direction of causation remains unclear. It is uncertain whether changes in descending modulation are a primary vulnerability factor that predisposes individuals to chronic pain or a secondary result of ongoing pain and related psychological distress.[22,28] Longitudinal studies that track changes in descending modulation over time in relation to pain onset are necessary to clarify this issue.[22,28]

Critical Evaluation: Consensus and Controversy

1. Areas of Scientific Consensus

Despite ongoing debates, several key conclusions regarding multiple pain sources and central amplification have reached a strong consensus in the pain research community. First, there is broad agreement that central sensitization—marked by increased excitability of central pain pathways—represents a common mechanism behind many chronic pain conditions.[1,2-7,21-24] Clinical signs of central sensitization, including allodynia, hyperalgesia, widespread pain, and enhanced temporal summation, have been consistently observed across different conditions1.[7,15,23,27,30]

Second, researchers generally agree that chronic pain conditions often co-occur at rates higher than chance, indicating shared pathophysiological mechanisms.[1,6,7,9] The clustering of conditions such as fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, migraine, and temporomandibular disorders is well-documented.[1,6,29] This pattern of comorbidity supports the idea that central sensitization can promote the development of multiple pain conditions through mechanisms including expanded receptive fields, cross-sensitization, and altered descending modulation.[6,7,21]

Third, there is consensus that

neuroinflammatory mechanisms, including peripheral and central immune activation, play important roles in chronic pain pathophysiology.[2,12,16,18,21] The involvement of inflammatory mediators, microglial and astrocytic activation, and neuroimmune signaling in pain sensitization is supported by converging evidence from animal models and human studies.[2,16,18]

Fourth, researchers agree that psychological factors, including depression, anxiety, and stress, interact with neurobiological pain mechanisms and contribute to chronic pain.[1,7,9,22,28,29] However, the specific mechanisms mediating these interactions and the directionality of causation remain areas of active investigation.[7,22,28]

2. Ongoing Debates and Conflicting Evidence

Although there are areas of agreement, significant debates remain about the relative importance of peripheral versus central mechanisms in chronic pain. A key issue is whether central sensitization can become autonomous and self-sustaining without ongoing peripheral input or if peripheral nociceptive drive is necessary to maintain central hyperexcitability.[4,5,14,15] Gerwin and Staud argue that peripheral pain mechanisms remain important, even in conditions such as fibromyalgia, which are often considered mainly central, citing evidence that peripheral treatments can be beneficial.[14,15] However, others stress that central mechanisms dominate in fibromyalgia and that peripheral findings might be secondary effects.[6,11,24]

This debate has significant clinical implications. If central sensitization is autonomous, treatments should focus on central mechanisms using medications that affect central neurotransmission, psychological interventions, or neuromodulation.[6,28] If peripheral input is necessary to sustain central sensitization, treatments targeting peripheral pain sources may be effective even in conditions with dominant central features.[5,14,15] The evidence indicates that the answer likely varies across conditions and individuals, but methods to assess the relative

peripheral versus central contributions in individual patients remain underdeveloped.[3,14,15]

A related controversy concerns the nosological validity of "central sensitivity syndromes" as a distinct diagnostic category.[6] While Yunus and others have argued that grouping conditions sharing central sensitization provides conceptual clarity and may guide treatment, critics contend that this construct obscures important mechanistic differences between conditions and that the boundaries with other chronic pain conditions are unclear. The clinical utility of the central sensitivity syndrome concept remains debated.[6]

Conflicting evidence exists about the role of small fiber neuropathy in fibromyalgia and related conditions. Some studies have found small fiber damage in certain fibromyalgia patients, indicating that peripheral nerve injury may play a part in pain. However, other research has not replicated these results, and the prevalence, clinical significance, and association with central sensitization remain uncertain.[11] This debate highlights broader difficulties in understanding how peripheral and central factors interact in conditions often viewed as purely central.[11,14]

The mechanisms underlying comorbidity patterns remain debated.[1,7,9] While some researchers highlight that comorbidity reflects central sensitization, which facilitates multiple pain conditions through shared mechanisms, others contend that comorbidity may stem from common underlying vulnerability factors (genetic, psychological, environmental) rather than direct mechanistic links.[1,7,9] The timing and development of comorbidity whether one condition predisposes others or they develop independently remain unclear due to limited longitudinal data.[7,9]

3. Methodological Strengths and Limitations

Research on pain mechanisms has used various methods, each with its own strengths and limitations that affect how results are interpreted. Cross-sectional observational studies have provided useful evidence about comorbidity patterns and links between pain features and potential

markers of central sensitization.[1,7,9,23,29] Their strengths include large sample sizes, the ability to detect statistically significant associations, the ability to control for confounders, and the study of clinically relevant populations.[1,9] However, cross-sectional designs cannot determine the temporal order of events or causality, leaving fundamental questions about cause-and-effect relationships unresolved.[1,7,9]

Quantitative sensory testing offers a more objective evaluation of pain processing compared to self-reporting alone and can detect subclinical changes in somatosensory function.[15,23,27] However, QST has limitations, including considerable variability between individuals, the absence of standardized normative data, and uncertainty about the specificity of findings to particular underlying mechanisms.[15,27] Lower pain thresholds may indicate peripheral sensitization, central sensitization, psychological factors, or a combination of these.[15,27] Additionally, QST measures evoked pain responses to experimental stimuli, which might not fully reflect the mechanisms driving spontaneous clinical pain.[15]

Animal models enable controlled manipulation of pain mechanisms and direct assessment of neurobiological processes.[16,17,18] Harvey et al.'s demonstration that multiple endometriotic lesions increase central sensitization through neuroinflammation in mice offers mechanistic insights that are hard to obtain in humans.[16] However, translating findings from animal models to human chronic pain is difficult because of species differences in pain processing, the complexity of human pain conditions, and the challenge of modeling psychological and social factors in animals.[16,18]

Human neuroimaging studies have identified changes in brain structure and function associated with chronic pain, but interpreting these findings remains difficult.[2,17,22,28] It is often unclear whether the observed brain alterations are causes or effects of chronic pain, or if they reflect comorbid psychological factors.[2,22] Longitudinal neuroimaging studies

that track brain changes over time in relation to the development of pain are uncommon but crucial for understanding causality.[2,22]

A widespread challenge across methodologies is the variability in diagnostic criteria, assessment techniques, and patient populations.[3,6,11,14] Conditions such as fibromyalgia, chronic pelvic pain, and chronic widespread pain include diverse patient groups that may have different underlying mechanisms.[3,6,11,14] This diversity can hide mechanistic relationships and lead to conflicting results across studies. The development of validated biomarkers to identify mechanistic subgroups is a crucial need.[2,11,22]

Future Direction

Despite significant progress in understanding multiple pain sources and central amplification, critical knowledge gaps still exist. First, the temporal dynamics of sensitization processes are not well understood.[2,7,9,16,22] Long-term studies that examine how peripheral and central mechanisms evolve from acute to chronic pain are rare but essential for understanding causality and finding intervention opportunities.[2,7,9,22] Specifically, research is needed to determine when and how central sensitization develops after peripheral injury or inflammation; whether there are critical periods when interventions are most effective; and whether central sensitization can be reversed with treatment or persists indefinitely.[2,16,22]

Second, individual vulnerability factors that determine who develops chronic pain and central sensitization following similar peripheral injuries remain poorly understood.[2,7,9,22,24] These factors may include genetic polymorphisms affecting pain processing, early life stress and trauma, psychological factors, and baseline differences in descending modulation.[2,7,22] However, the significance of each factor and its interactions remains unclear.[2,7,22] Prospective studies examining these vulnerability factors before pain onset are necessary to fill this gap.[7,29]

Third, the mechanisms behind comorbidity patterns and the development of multiple pain

conditions need further research.[1,6,7,9,21] Important questions include: Does one pain condition causally lead to others through central sensitization and cross-sensitization, or do multiple conditions develop independently due to shared vulnerability factors? What influences which particular comorbid conditions occur in individual patients? Can treating one pain condition help prevent or improve other comorbidities?.[1,7,9,21] Long-term studies that track the order in which conditions appear and experimental research on cross-sensitization mechanisms are essential.[7,9,21]

Fourth, methods to evaluate the relative roles of peripheral versus central mechanisms in individual patients remain underdeveloped.[3,14,15] Although research has identified group-level differences in pain processing between conditions, clinical tools to characterize individual patients and guide personalized treatment are lacking. Developing and validating clinical assessment algorithms that incorporate pain characteristics, quantitative sensory testing, and potentially biomarkers to identify mechanistic subgroups is a critical need.[3,11,14,15]

Fifth, the specific neuroinflammatory mechanisms most crucial for chronic pain and their temporal dynamics need further clarification.[2,12,16,21] Questions include: Which inflammatory mediators are most important for initiating versus maintaining sensitization? What factors influence individual differences in neuroinflammatory responses? Can neuroinflammatory processes be targeted therapeutically in humans?.[2,12,16,21] Translating neuroinflammatory findings from animal models to human chronic pain conditions remains a significant challenge.[16,18]

Sixth, the role of small fiber neuropathy and other peripheral nerve pathologies in conditions traditionally seen as central needs clarification.[11,13] The prevalence of small fiber neuropathy in fibromyalgia and related conditions, its clinical importance, and its connection to central sensitization remain uncertain.[11] Standardized assessment methods and larger

studies are necessary to resolve this controversy.[11]

Finally, the mechanisms that mediate interactions between psychological factors and neurobiological pain processes need further study.[1,7,9,22,28,29] Although links between depression, anxiety, stress, and chronic pain are well-known, the specific mechanisms behind these relationships and the direction of causality are still unclear.[7,22,28] Possible mechanisms include effects on descending modulation, hypothalamic-pituitary-adrenal axis function, sleep, and health behaviors, but their relative importance remains uncertain.[2,22,28,]

CONCLUSION

Multiple pain generators and central amplification are interconnected mechanisms in chronic pain pathophysiology. Strong evidence supports the role of central sensitization heightened excitability of central pain pathways as a common factor in various chronic pain conditions, explaining key clinical features such as allodynia, hyperalgesia, widespread pain, and comorbidity patterns. Neuroinflammatory processes involving both peripheral and central immune activation have become important mechanisms linking peripheral nociceptive input to central sensitization. Nonetheless, substantial evidence also shows that peripheral pain generators and ongoing peripheral nociceptive input are crucial in initiating and maintaining central sensitization in many conditions.

Contemporary theoretical models increasingly highlight bidirectional interactions between peripheral and central mechanisms, rather than viewing them as competing explanations. Peripheral nociceptive input can trigger and sustain central sensitization, while central amplification can reduce activation thresholds for additional peripheral pain sources, creating positive feedback loops. The relative roles of peripheral versus central mechanisms likely vary across conditions and individuals, but methods to determine these roles in individual patients remain underdeveloped.

Critical knowledge gaps include understanding the timing of sensitization processes, individual vulnerability factors, mechanisms behind comorbidity patterns, and the integration of psychological and neurobiological factors. Limitations of current research especially the dominance of cross-sectional designs, inconsistent diagnostic criteria, and the scarcity of mechanistic biomarkers hinder causal inference and mechanistic insight.

Future research priorities include: longitudinal studies examining the progression of pain mechanisms from acute to chronic states; development of validated biomarkers to identify mechanistic subgroups; experimental studies of cross-sensitization and the development of comorbidities; translating neuroinflammatory findings to human chronic pain; and integrating peripheral, central, and psychological assessments to support personalized treatment options. Addressing these gaps will require multidisciplinary collaboration that combines clinical, experimental, and neurobiological approaches.

Understanding multiple pain sources and central amplification has important clinical implications. Recognizing that chronic pain usually involves both peripheral and central mechanisms suggests that comprehensive assessment and multimodal treatment targeting both peripheral sources and central sensitization may be most effective. However, the evidence supporting this approach remains limited, and further research is necessary to develop and validate integrated assessment and treatment strategies.

The clinical implications of this conceptual framework are important for patient assessment and treatment planning. In clinical practice, many chronic pain conditions involve the interaction of peripheral pain sources and central amplification mechanisms. For example, migraine patients often have comorbid temporomandibular disorders or cervical myofascial pain, which may provide ongoing peripheral nociceptive input that contributes to central sensitization. Similarly, chronic pelvic pain can involve cross-sensitization between visceral and somatic structures, where

peripheral issues like endometriosis interact with central pain processing. In fibromyalgia, although central sensitization is key, evidence suggests that peripheral nociceptive sources such as myofascial trigger points or small fiber neuropathy may also help sustain central hyperexcitability. These findings highlight the importance of comprehensive clinical evaluations aimed at identifying both peripheral pain sources and central amplification mechanisms, guiding more effective multimodal treatment approaches. For neurologists and pain specialists, understanding this peripheral–central interaction can improve diagnostic reasoning and enable the development of individualized treatment strategies targeting both nociceptive sources and central pain regulation

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