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Neuroplastic mechanisms of chronic pain: Implications and future directions

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Abstract

Chronic pain is now increasingly viewed as aberrant neuroplasticity rather than a protracted expression of peripheral nociception. This review integrates current knowledge through the lens of a peripheral-to-central paradigm, whereby peripheral sensory sensitization contributes to pain initiation, spinal excitation–inhibition imbalance and glia–neuron signaling amplify and sustain central sensitization, and supraspinal corticolimbic and reward-network remodeling contributes to persistent pain as well as affective or cognitive comorbidities. Across neuropathic, inflammatory, osteoarthritis-related, pelvic, postoperative, visceral, and diabetic pain, higher-level processes show broad cross-disorder convergence, whereas the dominant molecular mediators, immune-cell populations, and circuit mechanisms frequently remain disease- and model-specific. The strongest mechanistic evidence comes from animal studies, while neuroimaging, behavioral phenotyping, and molecular markers are complementary but not yet clinically validated measures of pain-related plasticity. Pharmacological and non-pharmacological interventions have shown preclinical potential for modulating these mechanisms, although evidence for mechanism-guided precision treatment remains limited. Future studies need to implement longitudinal, sex-inclusive, and cross-model designs that integrate cell-specific manipulation, multimodal imaging, multi-omics, and prospective clinical validation in order to differentiate causal drivers from secondary adaptations and translate knowledge of neuroplastic mechanisms into clinically actionable strategies.

Keywords: Chronic pain, Neuroplasticity, Central sensitization, Neuroinflammation, Neural circuit remodeling

1 INTRODUCTION

Chronic pain is a prevalent and debilitating public health issue globally. Besides persistent or recurrent pain, it is commonly associated with affective disturbances, sleep impairment, and markedly reduced quality of life [1, 2]. Acute pain is protective and adaptive, whereas chronic pain persists long after the injury has healed and arises from persistent and complicated neurobiological changes. Chronic stress has been linked to the development of a range of pain syndromes such as fibromyalgia, and prolongation of nociceptive input during acute pain increases the risk of subsequent pain chronification [3, 4].

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These findings imply that in addition to sustained peripheral noxious input, chronic pain is also a consequence of long-lasting functional changes within the nervous system.

Neuroplasticity is the ability of the nervous system to achieve functional stability through developmental processes, learning, and adaptation to environmental changes. However, with ongoing injury or inflammation, this adaptive process may turn maladaptive and perpetuate dysregulated sensory processing. These changes correlate with remodeling at several hierarchical levels [5, 6]. At the level of synapses, the balance between excitatory and inhibitory inputs shifts, lowering neuronal response thresholds and increasing inappropriate firing [6]. The molecular underpinnings of synaptic remodeling include alterations in neurotrophic factors, receptor-mediated signaling pathways, and transcriptional regulatory networks [5]. Circuit-level functional reorganization of cortico–limbic networks and descending modulatory pathways augments nociceptive signaling, while the capacity for endogenous inhibitory control is diminished [2, 6]. These overlapping adaptations represent the neurobiological basis for chronic pain maintenance.

Chronic pain also correlates with extensive functional reorganization across central neural networks, including sensory processing, emotional regulation, and cognitive appraisal. Patients frequently experience cognitive fatigue and have higher activity in pain-related brain regions [7]. Accumulating evidence from animal studies has indicated an association between maladaptive connectivity among specific brain regions and changes in pain-related behavior [8]. Collectively, these data imply that chronic pain represents lasting dysregulation within distributed neural circuits.

Neuroplastic changes in chronic pain are multi-scale, comprising structural and functional changes at the molecular, circuit, and systems levels. These include convergent processes of peripheral sensory-neuron plasticity, spinal plasticity, glia–neuron signaling, and supraspinal network remodeling, while the initiating pathology and dominant molecular and cellular pathways may remain condition- and model-specific [9-11]. The ensuing sections identify these common processes and differentiate them from mechanisms that are preferentially supported in individual pain conditions or experimental models.

2 PATHOPHYSIOLOGICAL MECHANISMS OF CHRONIC PAIN

2.1 Neuroplastic alterations in the central nervous system (CNS)

In chronic pain, there is not only persistent nociceptive input but also long-lasting functional reorganization in the CNS. Neuroplastic adaptations across levels mark both its onset and persistence. These adaptations may become maladaptive and reinforce pain chronicity [9, 12]. Such changes occur in distributed brain networks related to the transmission and integration of nociceptive signals. A systems-level view of the reconfiguration of pain-modulatory circuits is briefly summarized in **Table 1**.

Plasticity in opioid signaling pathways is a fundamental mechanism of analgesic tolerance. Spinal T-cell lymphoma invasion and metastasis 1 (Tiam1)-mediated signaling contributes to aberrant plasticity in spinal nociceptive circuits associated with morphine tolerance and opioid-induced hyperalgesia [39]. Adaptive reorganization of pain circuitry is induced by chronic opioid exposure and repetitive nociceptive stimulation. Such restructuring is exemplified by changes in receptor sensitivity, synaptic transmission, and long-term reprogramming of intracellular signaling pathways. These coordinated changes impair the inherent pain-relieving properties of the endogenous opioid system, while enabling CNS sensitization to pain. However, the differential effects of κ-opioid receptor antagonists on pain aversion and mechanical hypersensitivity support functional dissociation between the sensory and affective components of neuropathic pain [40].

Chronic pain induces widespread neuroplastic changes in affective and motivational processing. Persistent nociceptive input alters synaptic plasticity and ensemble neuronal activity within the anterior cingulate cortex (ACC), a pivotal hub for integrating the emotional dimension of pain. These changes strengthen neural circuits associated with aversion, anxiety, and other negative affective states. Recent evidence suggests that discrete closed-loop pathways transmit aversive pain-related information to the ACC, and that inhibition of these circuits can effectively dampen allodynia [41]. Neuropathic pain induces long-lasting inhibition of thalamocortical projections to the ACC, which in turn reshapes thalamocortical integration and modulates nociceptive processing within affective networks [42].

With pain progression, neuroplastic adaptations to pain extend beyond interregional connectivity to the architecture of large-scale brain networks. Across several structures, system-wide reorganization of functional connectivity takes place, including in the somatosensory cortex, prefrontal cortex (PFC), limbic system, and thalamus. Cross-species association studies further indicate that chronic pain-related alterations favor increased randomness in global brain connectivity, consistent with a wide-scale topological reorganization [43].

In summary, chronic pain-related CNS plasticity includes opioid modulation, ACC-centered affective circuits, and large-scale brain networks. These changes are, however, pathway specific and not uniformly increased. κ-Opioid signaling has a greater influence on pain aversion than on mechanical hypersensitivity, and ACC-related pathways have a more direct impact on affective and motivational abnormalities [40-42]. Global network disruption may underpin the maintenance of

Table 1. Neuroplastic changes associated with chronic pain in the CNS organized by mechanistic pathway category

Central structure	Type of plasticity	Main cell types	Key molecule/pathway	Functional change	Pain-related significance	Reference
Neurotrophic, cytokine, neuropeptide, and neuromodulatory signaling						
PFC	Altered neurochemical plasticity	Neurons and glial cells	BDNF, tumor necrosis factor alpha (TNF-α), and IL-10	Upregulated levels of related factors	Reverses hyperalgesia and pain hypersensitivity	[13]
Hippocampus	Synaptic plasticity	Hippocampal neurons	BDNF/TrkB/CREB signaling pathway	Upregulation of synapse-related proteins	Alleviates chronic inflammatory pain and associated depressive-like behaviors	[14]
Spinal dorsal horn	Presynaptic plasticity	Sensory neurons	PreNMDARs/Ca^{2+}/SK channels/BDNF-PKG-I	State transition between presynaptic inhibition and facilitation	Regulates nociceptive transmission and pain sensitization	[15]
Hippocampus	Synaptic and structural plasticity	Pyramidal neurons, microglia	Synaptamide	Restored LTP and increased dendritic spine density	Alleviates pain hypersensitivity and cognitive impairment	[16]
Bed nucleus of the stria terminalis (BNST)	Enhanced inhibitory synaptic plasticity	Cocaine- and amphetamine-regulated transcript (CART)-positive BNST neurons	CART	Increased excitability of CART neurons and inhibition of LH-projecting BNST neurons	Induces anxiety-like behaviors associated with chronic pain	[17]
PBN	Increased neuronal excitability	Calca neurons	Calca neuronal activity	Increased neuronal excitability	Drives and sustains nociceptive plasticity	[18]
Spinal dorsal horn	Synaptic plasticity	Microglia, dorsal horn neurons	IL-10/GLP-1R pathway and β-endorphin/MOR	Inhibition of glutamatergic synaptic transmission	Suppresses neuropathic hyperalgesia	[19]
Epigenetic, nuclear receptor, and cellular stress regulation						
mPFC	Synaptic plasticity and epigenetic alterations	Pyramidal neurons	DNMT3a/Gabrb1 pathway	Enhanced inhibitory synaptic transmission	Alleviates chemotherapy-induced pain hypersensitivity and anxiety	[20]
ACC	Synaptic plasticity	ACC neurons	Retinoic acid (RA)/RARB signaling pathway	Reversal of aberrant synaptic plasticity	Alleviates neuropathic pain and anxiety	[21]
Hippocampus	Synaptic plasticity	Microglia	LXRβ/PI3K/AKT pathway	Upregulated synaptic protein expression	Alleviates pain-related cognitive deficits	[22]
Hippocampal CA1 region	Altered synaptic plasticity	Glutamatergic neurons	SIRT1	Impaired synaptic plasticity and cognitive function	Mediates chronic pain-associated cognitive impairment	[23]
Dorsal CA1 region of the hippocampus	Impaired synaptic plasticity	CaMKIIα neurons	CHOP/UPR pathway	Reduced synaptic function and neuronal activity	Leads to pain-related cognitive deficits	[24]
Rho GTPase and cytoskeletal remodeling						
ACC	Synaptic plasticity	ACC neurons	Tiam1/Ras-related C3 botulinum toxin substrate 1 (Rac1) pathway	Actin reorganization and stabilization of synaptic NMDARs	Drives pain-associated depressive-like behaviors	[25]
Spinal dorsal horn	Structural and functional synaptic plasticity	Dorsal horn neurons	Tiam1/Rac1 pathway	Actin reorganization and stabilization of synaptic N-methyl-D-aspartate (NMDA) receptors	Coordinates the initiation and maintenance of neuropathic pain	[26]

Spinal dorsal horn	Synaptic plasticity	Dorsal horn neurons	Dedicator of cytokinesis 4 (DOCK4)/Rac1/Glutamate ionotropic receptor NMDA type subunit 2B (GluN2B)	Enhanced excitatory synaptic transmission and synaptogenesis	Promotes the development of neuropathic pain	[27]
ACC	Aberrant central plasticity	ACC neurons	MAP2, GAP43, and tau	Reversal of altered expression of related proteins	Reduces mechanical hypersensitivity in chronic neuropathic pain	[28]
Glutamatergic, excitatory synaptic, and neuronal output regulation						
Primary somatosensory cortex	Synaptic plasticity	Astrocytes	Metabotropic glutamate receptor 5 (mGluR5)	Increased excitatory synaptogenesis	Leads to mechanical allodynia	[29]
Amygdala	Synaptic plasticity	Amygdalar neurons	PRKCG/CaMKII/GRIA1 pathway	Weakened functional synaptic connectivity	Contributes to chronic pain and associated emotional disturbances	[30]
CeA	Enhanced synaptic plasticity	CeA neurons	CRF/CRFR1 and GluN2B-NMDAR	Enhanced LTP and excitatory synaptic transmission	Promotes stress-induced hyperalgesia	[31]
Spinal dorsal horn	Synaptic plasticity	Dorsal horn neurons	NWD1/GluN2B	Enhanced synaptic transmission and excitatory synaptogenesis	Promotes the progression of neuropathic pain	[32]
Spinal dorsal horn	Synaptic structural remodeling	Spinal dorsal horn neurons	NR2B/PSD-95 receptors and glutamate	Altered synaptic structure and increased expression of synaptic proteins	Alleviates pain through synaptic structural remodeling	[33]
Spinal dorsal horn	Remodeling of neuronal output	Dorsal projection neurons	Ca^{2+} signaling	Altered encoding of low-intensity stimuli and activation of high-threshold neurons	Differentially regulates spinal output under pain conditions	[34]
Neuroimmune, glial, and multisystem regulation						
Prefrontal cortex–nucleus accumbens pathway	Impaired LTP	Prefrontal and limbic neurons	Immune/inflammatory pathways	Impaired circuit activity and reduced neuronal activity	Drives the affective component and long-term consequences of neuropathic pain	[35]
Amygdala	Excitatory synaptic plasticity	Microglia, neurons	iNOS/NO/cGMP/PRKG2 pathway	Enhanced excitatory synaptic transmission	Drives chronic pain and depressive-like behaviors	[36]
CNS	Enhanced synaptic plasticity	Microglia, neurons	MHCII genes and inflammatory pathways	Improved synaptic structure and reduced glutamatergic transmission	Alleviates neuropathic pain	[37]
Multiple brain regions (GrN, PBN, RMN, PAG, BLA, and hippocampus)	Neuroplastic alterations	Microglia, astrocytes, neurons	Proinflammatory cytokines, GAD67, serotonin, and GluN2B	Enhanced sensory transmission and disrupted neurogenesis	Leads to chronic hyperalgesia	[38]

Notes: Unless otherwise specified, the effects summarized in this table were reported in preclinical experimental models and indicate mechanistic involvement or candidate therapeutic relevance rather than clinically validated efficacy.

chronic pain beyond localized circuits [43]. The question of whether these changes drive pain chronification or result from persistent nociceptive input remains unresolved and requires longitudinal and pathway-specific studies.

2.2 Peripheral nervous system (PNS) contributions to pain modulation

The PNS acts as the primary interface for detection of potentially damaging thermal, mechanical, and chemical stimuli and transmission of nociceptive information to the CNS. Peripheral injury or inflammation induces plastic changes in primary afferent neurons, including changes in ion-channel expression, membrane excitability, and gene regulation, which contribute to increased neuronal responsiveness and provide an important peripheral substrate for pain initiation and the transition to chronicity [44-46].

Among these sensory transduction mechanisms, mechanosensitive ion channels play essential roles in mediating the initiation of peripheral signals. These channels transduce mechanical signals into electrical ones that can initiate sensory transmission. Aberrant activation of Piezo1, which is broadly expressed in neuronal and non-neuronal populations within peripheral sensory pathways, has been linked to pain following nerve injury [47]. Increased expression of mechanosensitive channels and receptors during peripheral nerve injury or chronic inflammation reduces activation thresholds, leading to enhanced responsiveness of sensory neurons to mechanical stimuli. Greater multimodal responsiveness also increases the sensitivity of primary afferents and allows tactile, thermal, and chemical inputs to be integrated into nociceptive encoding. During neuropathic pain development, aberrant sensory input is reinforced through this process [48].

Collectively, disrupted mechanotransduction and multisensory sensitization of primary afferents provide a peripheral substrate primarily at the level of pain initiation and the transition to chronicity [47, 48]. Nevertheless, it remains a matter of debate whether the continuing presence of peripheral nociceptive input is required for sustaining neuropathic pain once central sensitization has been established [49]. Clarifying this issue is necessary to pinpoint those phases of the disease when peripheral interventions may warrant further therapeutic evaluation.

2.3 Neuroinflammation and pain perception

Chronic pain-associated neuroinflammation can be arranged as a peripheral-to-central pathological cascade comprising peripheral nociceptive initiation, central inflammatory amplification, and cerebral pain perception. After peripheral injury, reciprocal signaling between sensory neurons and immune cells can promote sensory-neuron sensitization and altered synaptic transmission, thereby linking persistent tissue injury to pain sensitization [50, 51]. These peripheral, spinal, and cortical processes can be conceptualized as a sequential but context-dependent neuroimmune cascade connecting peripheral nociceptive initiation with altered pain perception, as summarized in **Figure 1**.

At the peripheral level, the dorsal root ganglion (DRG) acts as a significant neuroimmune interface. It has been reported that crosstalk between sensory neurons and macrophages after nerve injury contributes to the initiation and persistence of neuropathic pain [50]. Injury or chronic inflammation can reshape the DRG immune microenvironment by recruiting macrophages, T cells, and other immune populations. Inflammatory macrophages can transfer microRNA-155 (miR-155) into sensory neurons via extracellular vesicles (EVs), leading to increased expression of interleukin-6 (IL-6) in DRG tissue and enhanced neuronal excitability and nociceptive hypersensitivity [52]. These data suggest that recruitment of peripheral immune cells and macrophage–neuron signaling can promote nociceptive initiation before central amplification becomes established.

Persistent peripheral nociceptive input then recruits central inflammatory responses in the spinal cord. Inflammatory signaling from resident microglia and astrocytes alters neuronal excitability and synaptic transmission. Morphine administration may paradoxically prolong neuropathic pain by enhancing spinal NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome activation [53]. By contrast, administration of intrathecal platelet-rich plasma (PRP) has been reported to reduce neuropathic pain symptoms in rats and has also been associated with decreased astrocytic activation in the spinal dorsal horn [54]. Taken together, these findings indicate that distinct interventions can differentially modulate spinal glial responses associated with pain-related plasticity.

Other immune pathways contribute to pain modulation in disease- and cell-specific contexts. In lupus-prone mice, blockade of colony-stimulating factor 1 receptor (CSF1R) signaling ameliorates chronic pain and restores impaired glial glutamate transporter function, indicating that CSF1R-dependent signaling contributes to pain maintenance in this disease context [55]. The B cell–immunoglobulin G (IgG)–Fc gamma receptor (FcγR) axis represents a distinct immune pathway that promotes neuropathic pain sensitization [56]. These results suggest that pain may be influenced by distinct immune-cell populations and signaling pathways through model-specific mechanisms.

Synchronized activity of DRG neurons can induce cortical synchrony in neuropathic pain at the supraspinal level [11]. Together with the spinal neuroinflammatory changes described above, this finding supports a conceptual peripheral-to-central sequence linking peripheral nociceptive initiation, spinal inflammatory amplification, and subsequent cortical changes associated with pain perception.

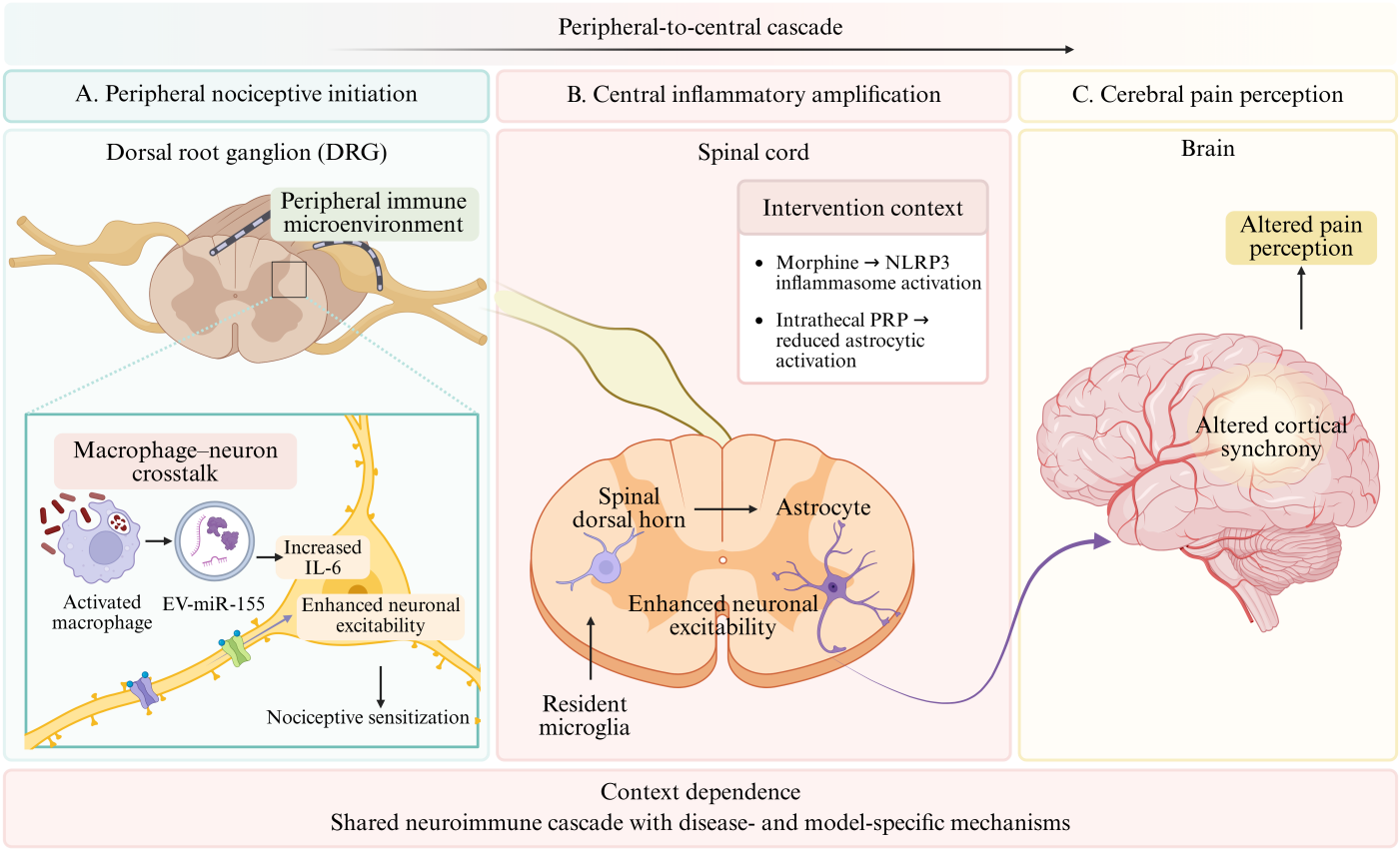


Figure 1. Context-dependent peripheral-to-central neuroimmune cascade in chronic pain. (A) Peripheral nociceptive initiation. The DRG immune microenvironment is reshaped in response to peripheral injury or inflammation. Crosstalk between macrophages and neurons involving extracellular vesicle-mediated transfer of miR-155 is associated with increased IL-6, enhanced neuronal excitability, and nociceptive sensitization. (B) Central inflammatory amplification. Persistent peripheral nociceptive input is associated with activation of resident microglia and astrocytes in the spinal dorsal horn and increased neuronal excitability. In certain experimental contexts, morphine may increase NLRP3 inflammasome activation, whereas intrathecal platelet-rich plasma has been associated with decreased astrocytic activation. (C) Cerebral pain perception. Peripheral and spinal nociceptive processing is followed by supraspinal alterations, including altered cortical synchrony associated with altered pain perception. Arrows represent the proposed direction of signaling, modulation, or progression across the peripheral-to-central cascade. This overarching framework is context-dependent, with broadly shared neuroimmune processes coexisting with disease- and model-specific mechanisms. Created with BioRender.com.

When considered collectively, peripheral immune–sensory neuron communication, spinal glial activation, and neuroimmune amplification constitute broadly convergent processes across multiple chronic pain conditions. However, the immune pathways involved are not necessarily common. DRG macrophage–neuron communication and spinal glial responses illustrate relatively common levels of neuroimmune regulation, while CSF1R-dependent signaling in lupus-prone mice and the B cell–IgG–FcγR axis in neuropathic pain are examples of disease- or model-specific mechanisms [50, 52-56]. Synchronized sensory input is thought to subsequently reorganize cortical dynamics associated with pain perception [11]. Accordingly, the general process of immune activation at peripheral sites followed by central amplification may be common, but the specific immune-cell populations and molecular pathways involved may differ depending on the etiology of pain, its anatomical site, stage of disease progression, and experimental model.

3 MOLECULAR AND CELLULAR MECHANISMS

3.1 Neurotransmitters and receptor dynamics

Chronic pain is mediated by long-term plasticity in neural circuits, while persistent neurochemical changes and altered receptor expression also contribute to the onset and maintenance of a chronic pain state. In response to persistent injury, neurotransmitter signaling, receptor expression, and transcriptional regulation in sensory neurons and neural circuits can change over time, thereby altering the encoding and transmission of nociceptive information. These changes not only modify nociceptive signaling but also lead to long-term reprogram-

ming of receptor expression and gene regulation, thereby reinforcing pain hypersensitivity [57, 58].

Modulation of neurotransmitter receptor systems is a key mechanism underlying chronic pain. In particular, opioid and cannabinoid receptor systems play central roles in analgesic control. However, transcription of Oprd1 and Cnr1 is downregulated in primary sensory neurons following nerve injury through the transcriptional repressor RE1-silencing transcription factor (REST), suggesting that opioid- and cannabinoid-mediated analgesic pathways are attenuated [58]. This preclinical evidence highlights REST as a potential therapeutic target for neuropathic pain. In experimental models, inhibition of REST may reverse receptor-gene repression and enhance endogenous analgesic signaling, but its clinical therapeutic relevance remains unestablished. Epigenetic repression also regulates receptor expression. In the DRG, methyl-CpG-binding domain protein 1 (MBD1) recruits DNA methyltransferase 3 alpha (DNMT3a) to silence opioid receptor-related genes such as Oprm1, thereby contributing to acute and neuropathic pain regulation [59]. These mechanisms induce long-lasting changes in receptor expression profiles, maintaining elevated neuronal responsiveness under persistent stimulation.

In addition to receptor expression, changes in neurotransmitter metabolism also affect nociceptive transmission. Sensory neurons upregulate glutaminase 1 (GLS1) following peripheral nerve injury, resulting in increased glutamate synthesis and release. This alteration is correlated with mechanical allodynia, indicating that peripheral GLS1 may be a candidate analgesic target based on preclinical evidence [57]. Concomitantly, nociceptive signaling is regulated by functional coupling between opioid receptors and ion channels. Following chronic nerve injury, Kir3 channels remain functionally coupled with μ-opioid receptors in peripheral sensory neuron somata, consistent with persistent opioid-mediated signaling [60]. In addition, δ-opioid receptor signaling has been implicated as a critical modulator of maladaptive pathology following peripheral nerve injury, particularly via endogenous activation [61].

Collectively, altered neurotransmitter synthesis, receptor expression, and receptor–effector coupling may represent broadly relevant modalities of neuroplastic regulation in chronic pain. However, the exact mechanisms discussed here, including REST- and MBD1-mediated receptor-gene repression, GLS1 upregulation, and persistent opioid receptor–ion channel coupling, were largely defined in peripheral nerve injury models [57-61]. Hence, their generalizability remains an open question for inflammatory, osteoarthritis-related, pelvic, postoperative, visceral, and diabetic pain. This distinction suggests that a common functional endpoint, for example, increased excitability or weakened endogenous analgesia, may be reached through different molecular mechanisms across different pain conditions.

3.2 Gene regulation and epigenetic mechanisms

Chronic pain persists not only through circuit-level rewiring but also through long-term alterations in gene regulatory networks. Pain-related gene expression is altered at the transcriptional, RNA-splicing, and translational levels via multilayered processes triggered by nerve injury and inflammation that contribute to persistent changes in neuronal function [10, 45, 62]. Gene-regulatory and epigenetic mechanisms such as RNA modifications, transcriptional regulation and DNA methylation mediate gene expression without changing the DNA sequence, forming a molecular substrate for chronic pain.

Recent work has revealed that RNA-modifying enzymes are important regulators of neuropathic pain-related plasticity. In sensory neurons, FOXD3-mediated transactivation of ALKBH5 promotes N6-methyladenosine (m6A)-dependent stabilization of 5-hydroxytryptamine receptor 3A (5-HT3A) mRNA and promotes neuropathic pain [63]. In addition, NAT10 is upregulated following injury and promotes pain hypersensitivity by modulating N4-acetylcytidine (ac4C) modification and the stability of synaptotagmin IX mRNA [64].

Chronic pain is influenced by both transcriptional control and alternative splicing. After nerve injury, the activity of transcription factors and splicing regulators changes, altering both the expression levels and protein isoform composition of pain-associated genes. The RNA splicing factor Rbfox1 regulates the alternative splicing of Nrcam in primary sensory neurons, contributing to neuropathic pain in the DRG [65]. This type of alternative splicing may produce protein isoforms with altered roles in neuronal excitability, synaptic transmission, and nociceptive signaling.

Relatively stable epigenetic processes such as DNA methylation may contribute to the persistence of chronic pain. DNA methylation provides sustained transcriptional regulation through changes in chromatin structure and transcription-factor accessibility. For example, DNMT1 represses the potassium channel gene Kcna2 in the DRG, thereby contributing to neuropathic pain [66]. Zinc-finger protein ZFP612 contributes to chronic pain by epigenetically silencing Il1rl1 [67]. At the central level, downregulation of sirtuin 1 (SIRT1) in the hippocampal cornu ammonis area 1 (CA1) region has been demonstrated to impair synaptic plasticity, thereby mediating chronic pain-associated cognitive dysfunction [23].

Collectively, RNA modification, alternative splicing, and DNA methylation modulate persistent pain-related gene reprogramming, whereas hippocampal SIRT1-dependent regulation is more directly associated with chronic pain-related cognitive dysfunction [23, 63-67]. Nevertheless, whether these regulatory and epigenetic changes induce or maintain chronic pain or merely accompany it remains unclear [46, 68]. Longitudinal,

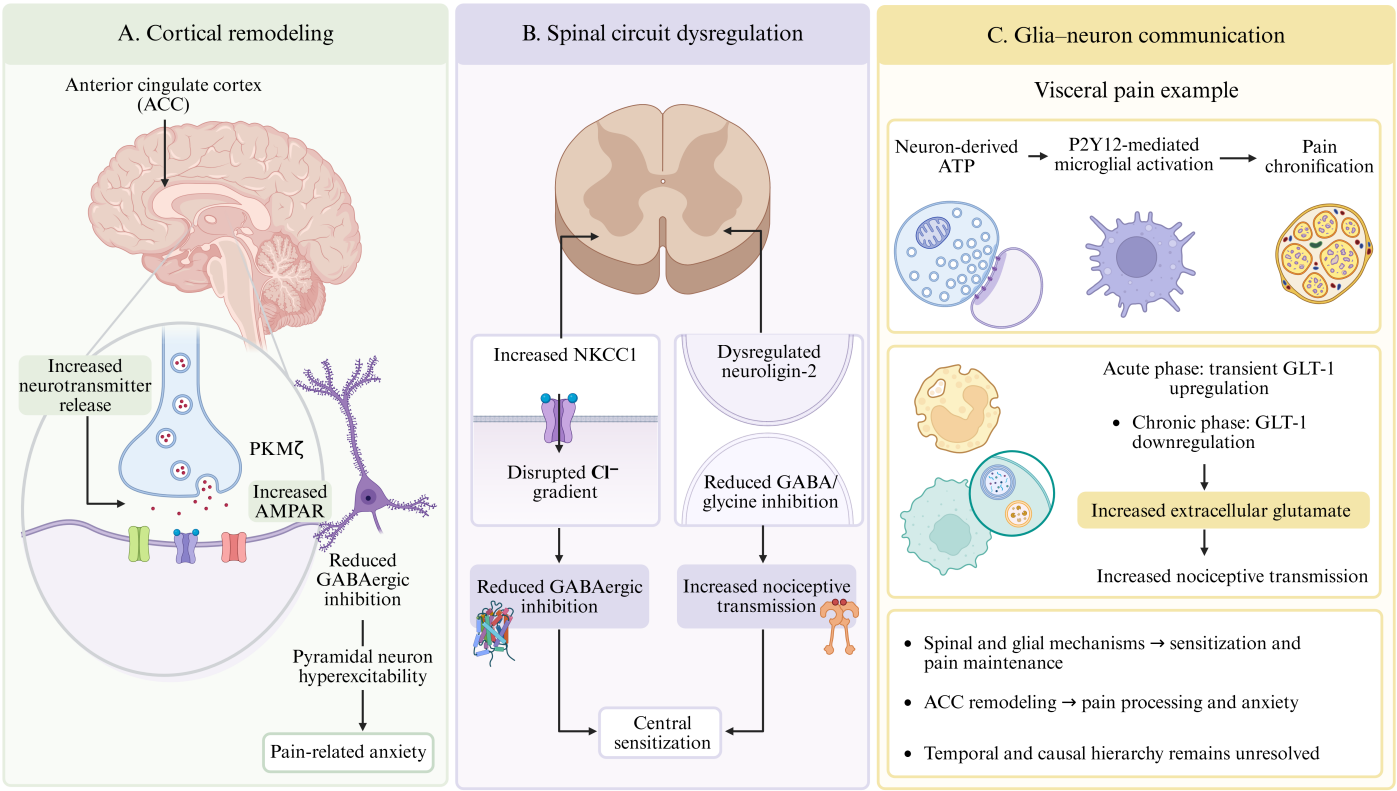


Figure 2. Multilevel intercellular signaling and neural network remodeling in chronic pain. (A) Cortical remodeling. Persistent pain-related plasticity in the ACC includes enhanced excitatory synaptic signaling, PKMζ-related synaptic alterations, reduced GABAergic inhibition, and pyramidal neuron hyperexcitability, which may contribute to persistent pain processing and pain-related anxiety. (B) Spinal circuit dysregulation. Changes in NKCC1-dependent chloride homeostasis and neuroligin-2-associated inhibitory networks can compromise GABAergic and glycinergic inhibition, amplify nociceptive transmission, and thus contribute to central sensitization. (C) Glia–neuron communication. Specifically, neuron-derived ATP can be extracellularly converted to ADP, which activates P2Y12-dependent microglial signaling and may facilitate pain chronification in visceral pain. Dynamic changes in glial GLT1 can impair glutamate clearance, elevate extracellular glutamate, and facilitate nociceptive transmission. Spinal and glial mechanisms mainly contribute to sensitization and pain maintenance, while ACC remodeling is associated with persistent pain processing and pain-related anxiety. The temporal and causal hierarchy among these mechanisms remains incompletely resolved. Arrows indicate the proposed direction of signaling, regulation, or functional progression between the depicted processes. Created with BioRender.com.

cell-specific studies are required to define their temporal and causal roles.

3.3 Intercellular signaling and neural network remodeling

Chronic pain is not only driven by hyperexcitability at the level of individual neurons but is also maintained by multilevel remodeling of intercellular signaling and neural circuits [9, 11]. Persistent injury or inflammation changes synaptic transmission and intracellular signaling, thereby fostering maladaptive plasticity that perpetuates pain [9]. These changes can include changes in cortical synchrony and synaptic remodeling, disruption of inhibitory signaling within the spinal cord, and dysregulated glia–neuron communication that can enhance nociceptive signaling and pain maintenance [9, 11, 69]. Collectively, these cortical, spinal, and glial adaptations comprise a multilevel neuroplastic framework connecting ongoing nociceptive input to chronic pain, as summarized in **Figure 2**.

Chronic pain-related plasticity at the cortical level can increase synaptic transmission and change network connectivity. Sustained nociceptive input may increase presynaptic neurotransmitter release and postsynaptic receptor sensitivity, thereby facilitating excitatory transmission and long-term potentiation (LTP). Cortical synaptic remodeling mediates the propagation of pain-related signals in models of chronic orofacial pain [70]. Consistent with this, peripheral nerve injury upregulates ACC protein kinase M zeta (PKMζ) expression, and inhibition of the enzyme partially reduces pain-related behavior in an experimental model, suggesting a role for PKMζ in persistent pain-associated synaptic plasticity [71]. In addition, the loss of GABAergic inhibition within the ACC elicits pyramidal neuron hyperexcitability and augments pain-related anxiety, thereby contributing to the affective component of pain [72].

The spinal dorsal horn is a key sensory relay whose circuit dynamics are thought to underlie the development of chronic

pain. Persistent injury disrupts the balance between excitatory and inhibitory signaling, thereby amplifying nociceptive transmission. The dysregulation of neuroligin-2 within the spinal dorsal horn has been demonstrated to disrupt GABAergic inhibitory networks and mediate spinal synaptic plasticity during hyperalgesic priming (HP), thereby contributing to the transition from acute to persistent pain [73]. Na^+-K^+-2Cl– cotransporter 1 (NKCC1) is a broadly expressed ion cotransporter that regulates chloride gradients influencing inhibitory signaling and pain processing in multiple neuronal and non-neuronal populations [74]. Perturbed chloride homeostasis may reduce inhibitory signaling or shift it toward excitation, increasing network excitability.

At the intercellular level, glial cells influence neural circuit remodeling through defined transmitter- and transporter-dependent pathways. Adenosine triphosphate (ATP) derived from spinal neurons activates purinergic receptor P2Y12 (P2Y12) on microglia, thereby promoting visceral pain chronification [75]. In particular, expression of glial glutamate transporter 1 (GLT1) within pain-related neural circuits undergoes dynamic changes during the progression to chronic pain. While transient changes in GLT1 regulate glutamate clearance during the acute phase, later GLT1 downregulation contributes to persistent glutamate accumulation and promotes nociceptive transmission [76].

In general, this suggests that chronic pain encompasses distinct cortical, spinal, and glial changes. Spinal inhibitory and ionic plasticity, as well as glial signaling, primarily contribute to central sensitization and pain maintenance, whereas ACC signaling contributes to both persistent pain processing and pain-related anxiety [71-76]. The cortical structural and functional changes may represent maintenance mechanisms or consequences of prolonged nociceptive activity [70]. Their temporal and causal hierarchy remains only partially defined, and longitudinal studies are needed to disentangle initiating mechanisms from maintenance mechanisms and late-stage adaptations [12, 77].

4 ANIMAL MODELS AND EXPERIMENTAL STUDIES

4.1 General features and research value of chronic pain animal models

Animal models are controlled experimental systems for studying the biology of chronic pain, but their reproducibility and translational relevance depend on etiology, species, sex, induction methodology, and behavioral readout. These models allow for direct analysis of the initiation and maintenance of pain under standardized conditions by modeling nerve injury, inflammation, or disease-associated pain states. These models not only reproduce pain-related behaviors but also allow assessment of structural and functional adaptations at the molecular, cellular, and circuit levels.

Immune responses and neuroinflammatory processes have major modulatory effects in models of chronic pain. Chronic inflammation or nerve injury elicits the recruitment or activation of macrophages and microglia within the dorsal root ganglia, spinal dorsal horn, and pain-related brain regions, along with the release of cytokines and inflammatory mediators. These responses alter neuronal excitability and synaptic transmission, leading to persistent sensitization of nociceptive signaling [51, 78, 79]. Importantly, immune regulatory pathways may also have context- and sex-dependent effects. For example, models of inflammatory pain exhibited sex-based differences in tactile hypersensitivity. Intrathecal co-administration of interferon beta (IFN-β) and anti-tumor necrosis factor (TNF) therapy has been shown to partially counteract pain-related behaviors in males but not in females, suggesting sexually dimorphic immunomodulation of pain transmission [80].

Alterations in CNS structure and function are a common feature of chronic pain models. Neuronal activity patterns in pain-related regions, including the cortex, thalamus, and limbic system, are reorganized by nerve injury or disease-related stimuli. With ongoing stimulation, synaptic transmission and network connectivity undergo gradual changes that favor the central integration of nociceptive input. Central post-stroke pain models reproduce thalamic lesion-associated pain hypersensitivity and supraspinal plasticity, providing a disease-specific platform to investigate chronic pain after CNS injury [81].

Animal models have allowed for detailed characterization of behavioral phenotypes and central sensitization. These paradigms consistently produce mechanical allodynia, thermal hyperalgesia, and persistent tactile hypersensitivity. As such, these paradigms are applicable to mechanistic studies. In the case of nerve injury or persistent inflammation, spinal nociceptive processing changes over time, with increased neuronal excitability, impaired inhibitory signaling, and enhanced excitatory synaptic transmission [9, 32, 69]. These alterations are typical features of central sensitization. Evidence from quantitative sensory testing in a naturally occurring canine model of osteoarthritis revealed widespread somatosensory sensitivity, suggesting that this model may capture clinically relevant features of centralized osteoarthritic pain [82].

Increased neuronal excitability, reduced inhibitory control, augmented synaptic transmission, and central sensitization appear to be convergent features of a number of chronic pain models. The initiating pathology and dominant neuroplastic manifestations are nonetheless model-specific in nature. Sex-dependent immune regulation is particularly evident in inflammatory arthritis models, lesion-associated supraspinal plasticity characterizes central post-stroke pain, and widespread somatosensory hypersensitivity is prominent in canine osteoarthritis [80-82]. Consequently, these findings are complementary rather than directly interchangeable. Importantly, since withdrawal-based tests alone may not fully capture spontane-

ous pain or affective components of pain, model selection and behavioral validation should be consistent with the disease-specific pathology, clinical phenotype, and research question [83, 84]. Representative animal models of chronic pain and their corresponding neuroplasticity features are summarized in **Table 2**.

4.2 Experimental approaches to investigating neuroplasticity

Multiscale methods for studying molecular, cellular, and network-level changes are utilized in the examination of neuroplasticity related to chronic pain. Advances in molecular biology, neuroimaging, and multimodal recording now allow investigation of nervous system activity across many spatial and temporal scales. These strategies facilitate systems-level analyses of pain generation and modulation.

The role of glial cells in chronic pain can be studied with the use of immunohistochemistry, in situ hybridization, transgenic labeling, and chemogenetic manipulation. Molecular markers can be used to identify glial populations and activation-associated states, whereas chemogenetic approaches allow cell-type-specific testing of their contributions to pain-related behavior [51].

Integrated analytical platforms are commonly applied to study both molecular and circuit-level changes in pain-relevant brain regions. Large-scale approaches to the molecular characterization of pain states, including protein-expression profiling, transcriptomics, and single-cell sequencing, have proved useful in identifying molecular signatures and regulatory networks involved in neuronal excitability and synaptic remodeling. Gene-level analyses have identified synaptic regulators such as CASKIN1. Caskin1 deletion influences gait, nociceptive responses, memory, and stress-related behavior, consistent with its proposed role in neural integration and pain-related neuroplasticity [109]. At the same time, synaptic ultrastructural imaging, circuit tracing, and electrophysiological recording provide information on connectivity and activity transmission, thereby connecting molecular changes to circuit function. Additionally, time-gated bioimaging of lanthanide-based luminescent in situ hybridization allows background-free visualization of pain-related gene transcription in the CNS [110].

Global brain activity at the systems level can be interrogated using neuroimaging and multimodal neural recording techniques. Functional imaging captures patterns of connectivity across brain regions, whereas calcium imaging and in vivo electrophysiology enable real-time measurement of neuronal population dynamics. Functional ultrasound imaging studies in arthritic rat models have shown evidence of global inter-regional connectivity changes and dynamic brain states related to pain behaviors [111]. These results indicate that chronic pain involves both local pathological mechanisms and large-scale brain reorganization.

Collectively, multiscale methods offer complementary but non-equivalent evidence. While chemogenetics allows for cell-specific causal testing, knockout phenotyping, in situ hybridization, and functional ultrasound characterize broader behavioral, spatial, and network-level changes [51, 109-111]. As chronic pain-related plasticity entails molecular, cellular, circuit, and behavioral changes, longitudinal cross-modal validation continues to be necessary [112].

4.3 Key findings and emerging insights from experimental studies

Recent animal studies have begun to shift from descriptive associations toward causal testing via genetic, pharmacological, and cell-type-specific perturbations. These methods assist in determining whether modifying a specific neuroimmune, molecular, or synaptic pathway alters pain-related behavior and whether the observed mechanism remains consistent across experimental models.

Both genetic and pharmacological manipulations support the view that neuroimmune pathways can causally influence pain-related behavior. The genetic deletion of the cystine/glutamate antiporter xCT or the pharmacological inhibition of system xc^- reduces pain hypersensitivity, decreases spinal glial responses, and is associated with a change from a pro-inflammatory to an anti-inflammatory microglial phenotype [113]. However, as decreased pain behavior, reduced glial responses, and altered microglial polarization occur together, it is unknown whether the latter response directly underlies analgesia or can be considered secondary to reduced nociceptive activity. In addition, differences in injury models, timing of intervention, and behavioral phenotype assessments may account for inconsistent findings across studies [50, 114, 115].

A separate line of causal evidence comes from synaptic mechanisms. In neuropathic rats receiving morphine, bulleyaconitine A decreases morphine tolerance through inhibition of LTP at C-fiber synapses and reduction of protein kinase Cγ signaling in the spinal dorsal horn [116]. This result supports a role for spinal synaptic plasticity in treatment-related adaptations and does not directly demonstrate a mechanism involving DRG glial activation. In chronic constriction injury (CCI), TNFR2 signaling and regulatory T cells contribute to recovery, supporting a role for neuroimmune pathways not only in pain initiation and maintenance but also in spontaneous or treatment-associated recovery [117]. Nevertheless, it remains to be clarified whether TNFR2-related effects can be generalized across sexes, injury models, and disease stages.

During pain-related neuroplasticity, alterations extend beyond inflammatory and immune mechanisms to neurotransmitter

Table 2. Common animal models of chronic pain and their neuroplasticity features

Model type	Modeling method	Major central site of alteration	Representative plasticity features	Research value	References
CCI model	CCI of the sciatic nerve	Hippocampus	Impaired hippocampal synaptic plasticity	Useful for elucidating the dsRNA/TLR3 signaling pathway and pain-related cognitive dysfunction	[85]
		Spinal cord and spinal dorsal horn	M1 microglial polarization and CX3CR1 signaling; complement component 3/complement component 3a receptor (C3/C3aR)-mediated microglial polarization; microglial activation and inflammation; nuclear STAT2 downregulation; Rac2/JNK/SIRT1 signaling; EGR2-mediated microglial phagocytosis; and extracellular signal-regulated kinase (ERK)/CEBPB dysregulation	Useful for comparing microglial polarization, neuroinflammatory signaling, and intervention-responsive glial mechanisms in CCI-induced neuropathic pain	[86-94]
		Spinal cord	Glial interactions and myelin pathology; regulation of A1 astrocyte phenotype activation	Allows integrated investigation of microglia–astrocyte interactions, myelin injury, and astrocyte-associated plasticity	[95, 96]
		Spinal cord	Mitophagy-related mitochondrial regulation; transmembrane protein 34 (TMEM34)/SGK1/FOXO3 signaling; and KCNQ1 opposite strand/antisense transcript 1 (Kcnq1ot1)/MyD88 regulation	Useful for investigating mitochondrial, transcriptional, and intracellular regulatory mechanisms in neuropathic pain	[97-99]
		Spinal dorsal horn	Microglial activation and enhanced synaptic transmission	Useful for elucidating novel analgesic mechanisms of SCS	[100]
	CCI of the median nerve	Cuneate nucleus	Microglial phenotypic switching	Useful for clarifying the mechanism by which curcumin regulates glial polarization	[101]
Spared nerve injury model	Selective ligation and transection of sciatic nerve branches	Spinal cord	Microglial phenotypic switching through CTRP9/AdipoR1/AMPK signaling; anti-inflammatory effects mediated by miR-26a-5p targeting Wnt5a	Useful for studying microglial regulation and extracellular vesicle-mediated analgesic mechanisms	[102, 103]
Spinal nerve ligation (SNL) model	SNL	Spinal cord	Improvement of synaptic structure and function; regulation of glutamatergic signaling; NFAT1/c-MYC-dependent microglial activation; and NLRP3-mediated microglial PANoptosis and synaptic loss	Useful for studying synaptic repair, microglial transcriptional regulation, neuroinflammation, and PANoptosis	[104-107]
	L5/L6 SNL	DRG and spinal dorsal horn	Hyperexcitability of dorsal horn neurons, activation of the ERK signaling pathway, and increased release of pro-inflammatory cytokines	Reveals the multitarget analgesic mechanisms of NS5806	[108]

transport systems and synaptic signaling. Glutamate is the predominant excitatory neurotransmitter involved in nociceptive transmission, and changes to both its release and reuptake modulate neuronal excitability and synaptic efficacy. A key regulator of this process is the glutamate transporter GLT1. Its inhibition by dihydrokainate produces hyperalgesia comparable to that induced by water-avoidance stress, whereas its upregulation by ceftriaxone ameliorates pain and urinary dysfunction induced by water-avoidance stress [118]. Localized neurotransmitter alterations also modulate the affective dimensions of pain. In the medial prefrontal cortex (mPFC), altered serotonergic signaling increases anxiety-like behavior following neuropathic injury [119].

Peripheral neural structures and sensory transduction have also been studied to provide mechanistic insights. Peripheral sensory neurons are initial sites of nociceptive transduction, their axonal growth, ion-channel expression and function, and signaling pathways being dynamically modulated following injury or inflammation [44, 120, 121]. Studies in animals have shown that peripheral nerve injury causes structural remodeling of sensory fibers and alters the responsiveness of neurons to mechanical, thermal, and chemical stimuli such that innocuous stimuli are abnormally encoded as being painful. Evidence for the contribution of peripheral sensory neuron activity to maintaining pain is provided by chemogenetic inhibition of trigeminal ganglion neurons, which blunts trigeminal neuropathic pain [122].

In aggregate, this pattern of experimental studies suggests that different mechanisms contribute to specific phases and facets of chronic pain. While trigeminal sensory activity is more closely tied to nociceptive initiation and maintenance, spinal system xc^- and GLT1 regulation contribute to central amplification and persistent hypersensitivity [113, 118, 122]. In contrast, prefrontal plasticity is more closely associated with pain-related anxiety, and TNFR2-dependent regulatory T cells play a role in facilitating recovery rather than promoting pain [117, 119]. Such findings should thus be interpreted according to the anatomical site, pain model, disease stage, and outcome measure. As these observations were gleaned mostly from experimental models, they illustrate mechanistic involvement and preclinical therapeutic relevance but not clinically validated treatment efficacy.

5 CLINICAL PRESENTATION AND DIAGNOSTIC STRATEGIES

5.1 Clinical phenotypes and pathological features of chronic pain

Chronic pain is markedly heterogeneous. It is characterized not only by persistent or recurrent nociception but also by aberrant sensory processing and dysregulated neural modulation. Its evolution is intrinsically associated with long-lasting neuroplastic modifications in the CNS. Peripheral injury or inflammation can increase neuronal excitability in the spinal dorsal horn and alter activity in supraspinal pain-control circuits while decreasing inhibitory control, thereby promoting central sensitization. These changes can result in low-intensity stimuli being perceived as painful, pain thresholds decreasing, and endogenous pain modulation weakening, thus perpetuating nociceptive amplification [123, 124].

Such dysregulation of neural processing often manifests as distinct pain-sensitivity profiles in specific patient populations. Diffuse somatosensory hypersensitivity has been linked to comorbidity among chronic overlapping pain conditions (COPCs), whereas the Sleep, Pain, Affect, Cognition, Energy (SPACE) phenotype correlates with disability severity and urinary symptom indices. These features may therefore collectively represent a continuum of symptom expression, wherein increased symptom burden correlates with a more centralized pain phenotype [125]. Similar patterns exist in several chronic pain disorders. Many women suffering from endometriosis or chronic pelvic pain (CPP) have increased pelvic floor (PF) tenderness, consistent with heightened pain sensitivity and altered central pain modulation that may influence treatment responses [126]. Similarly, patients with urological chronic pelvic pain syndromes (UCPPS), including bladder pain syndrome/interstitial cystitis, have heightened pain sensitivity outside the pelvis, further supporting the involvement of CNS-mediated amplification of visceral nociception in symptom generation [127]. Such spatially distributed changes suggest that focal nociceptive input can be transformed by central integration into relatively large areas of hypersensitivity.

Risk phenotypes of chronic pain are the result not only of disease-specific pathology, but also of systemic physiological load and individual differences in neural regulation. Elevated cardiometabolic burden has been associated with increased temporal summation of nociceptive flexion reflex (TS-NFR) and depressed conditioned pain modulation–nociceptive flexion reflex (CPM-NFR); however, the correlation with subjective pain perception has been shown to be poor. This finding suggests that cardiometabolic stress may represent a risk factor for spinal sensitization [128]. Neuroimmune interactions at the cellular level may also regulate pain sensitization. Enhanced glial fibrillary acidic protein (GFAP) immunoreactivity in pain-processing regions correlated with increased pain-related behaviors, suggesting that supraspinal astrocytes are involved in the plasticity of networks mediating affective and nociceptive processing [129].

Chronic pain phenotypes arise through the interplay of peripheral injury, neuroplasticity, and systemic physiological regulation. Widespread hypersensitivity is associated with central sensitization, whereas affective and cognitive symptoms are correlated with remodeling of prefrontal–hippocampal circuits [130, 131]. These manifestations should therefore be seen as

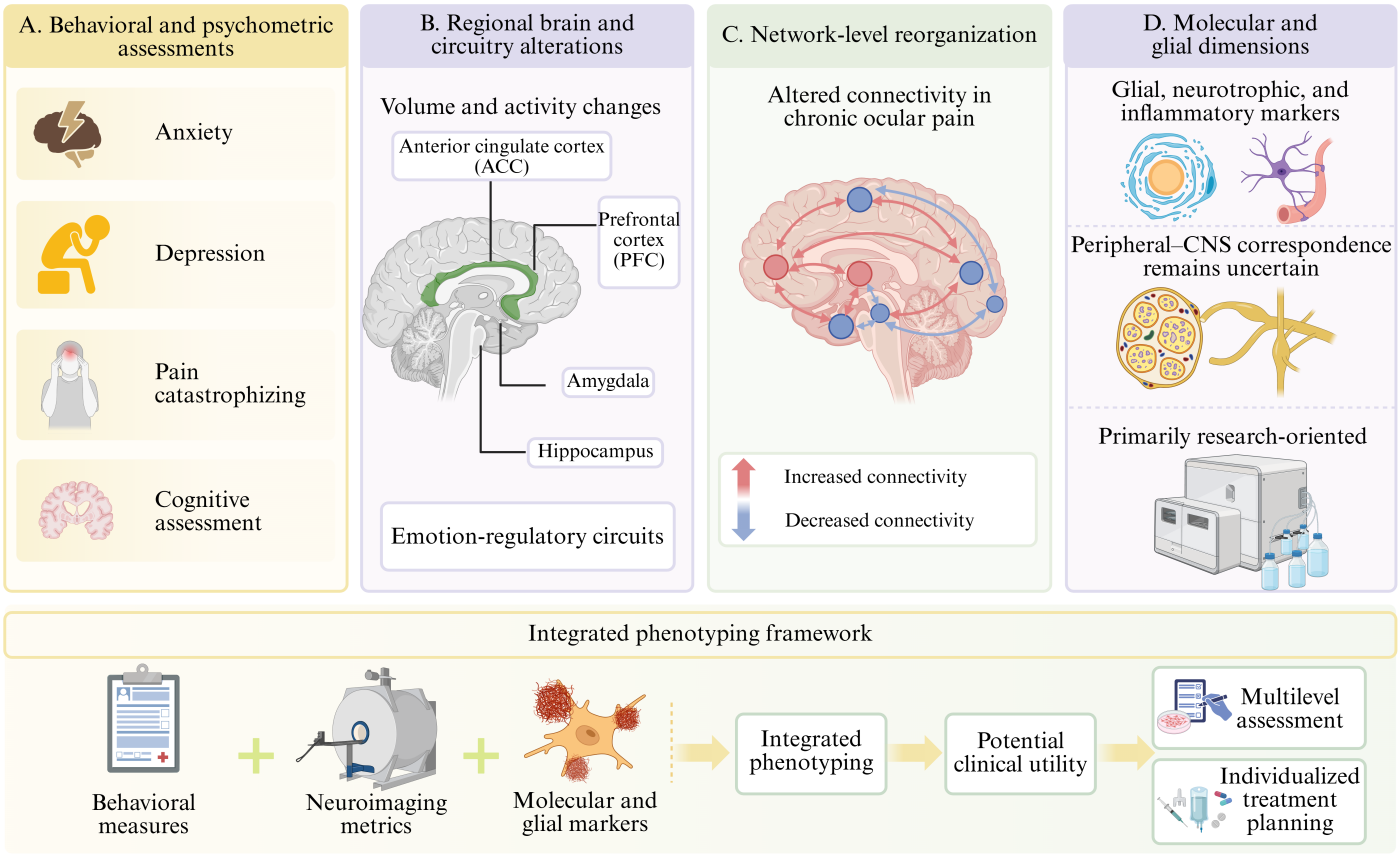


Figure 3. Integrated multimodal framework for assessing pain-related neuroplasticity in chronic pain. (A) Behavioral and psychometric assessments. Anxiety, depression, pain catastrophizing, and cognitive measures reflect the affective and cognitive dimensions of chronic pain. (B) Regional brain and circuitry alterations. Structural and functional changes in the ACC, PFC, amygdala, and hippocampus reflect alterations in emotion-regulatory circuits. (C) Network-level reorganization. In chronic ocular pain, increased and decreased functional connectivity has been reported across distributed brain regions involved in pain processing. (D) Molecular and glial dimensions. Although peripheral–CNS correspondence remains unclear, glial, neurotrophic, and inflammatory markers may serve as adjuncts to behavioral and neuroimaging assessments. These complementary measures may be integrated to support multilevel phenotyping and individualized treatment planning. Upward and downward arrows depict increased and decreased connectivity, respectively; plus signs represent the integration of assessment modalities, and horizontal arrows indicate progression toward integrated phenotyping and potential clinical utility. Created with BioRender.com.

overlapping but mechanistically distinct domains of chronic pain. The systematic identification of these manifestations may ultimately aid in clinical stratification as well as guide the future development and prospective assessment of precision interventions.

5.2 Clinical metrics for assessing neuroplasticity

Neuroplasticity and its role in chronic pain are being increasingly explored in clinical studies. Chronic pain is related to altered sensory processing and CNS adaptations that may become maladaptive, leading to altered pain perception [132, 133]. Multisource assessments integrated across behavioral measures, neuroimaging, and biological biomarkers can provide a characterization of changes in pain-related circuits, network reorganization, and associated neurochemical alterations [133, 134]. These strategies may support multilevel phenotyping and future individualized treatment planning. Thus, pain-related neuroplasticity can be assessed across behavioral, regional brain, network, molecular, and glial levels using an integrated blend of behavioral phenotyping, psychometric scales, neuroimaging, and molecular assays, as summarized in **Figure 3**.

At the regional level, brain areas related to emotional and memory processing, including the temporal and frontal cortices as well as the hippocampus, exhibit both volumetric and functional alterations [135]. Therefore, structural and functional changes in areas associated with emotion regulation might be considered candidate imaging biomarkers. Nonetheless, their utility for diagnosis, prognosis, and treatment prediction needs to be validated prospectively. Disruption of activity in emotional regulation networks is associated with neuroplastic dysregulation and chronic pain. Continued nociceptive signaling

influences neural circuits in limbic and prefrontal regions, which can lead to changes in emotional experience, attentional control, and cognitive evaluations of pain. Clinically, chronic pain and heightened pain sensitivity are often associated with affective disorders such as anxiety and depression. In patients with chronic low back pain, for instance, negative affect is associated with ACC glial activation and altered functional connectivity [136]. Integration of psychometric assessments with neuroimaging metrics enables partial characterization of the functional state of emotion-related circuits.

In addition to local changes, chronic pain results in large-scale reorganization of functional brain networks. While the thalamus acts as a relay and integrator for sensory information, the trigeminal nucleus, amygdala, and cortical regions are implicated in pain perception and affective evaluation. In patients with chronic ocular pain, functional connectivity analyses show both increased and decreased connectivity differences involving the trigeminal nucleus, amygdala, nucleus accumbens, putamen, caudate, and various thalamic subregions [137]. These results indicate that nociceptive processing is integrated with interoceptive, affective, and sensorimotor circuits, changing the broader organization of pain-related signaling.

At the molecular level, candidate neurotrophic, inflammatory, and glial markers may complement behavioral and neuroimaging evaluations of pain-related neuroplasticity. Their clinical interpretation is complicated by marker variability, tissue specificity, and the uncertain correspondence between peripheral data and CNS processes [138, 139]. Molecular markers may be integrated into research-oriented multimodal assessment frameworks; however, they should not be considered clinically validated stand-alone indicators of neuroplastic changes in chronic pain.

5.3 Challenges and prospects in early diagnosis

Early identification of chronic pain is clinically relevant yet challenging due to the intricate interplay among neural, immune, and psychological systems. The subjective nature of pain leaves current assessments heavily dependent on patient-reported outcomes and rating scales, while reliable objective biomarkers remain limited for diagnostic and prognostic use [132, 134]. High interindividual variability in pain sensitivity, affective state, and neural regulatory capacity contributes to phenotypic heterogeneity. Chronic pain arises over time through progressive neuroplastic adaptations that can precede overt symptoms, complicating early detection and thereby prompting the development of predictive markers and integrated assessment models.

At the level of clinical phenotyping and risk prediction, specific symptom patterns have been associated with the development of chronic pain. Evidence from clinical cohorts supports an association between the preoperative PainDETECT score and postoperative pain risk. Knee osteoarthritis patients with neuropathic-like pain features on PainDETECT have an increased risk of chronic postsurgical pain following total knee arthroplasty [140]. Hence, heightened sensory sensitivity, impaired pain modulation, and neuropathic-like features may be viewed as early abnormalities in pain processing. Sensory-processing measures are also indicators of central sensitization and pain modulation, including pain sensitivity, temporal summation, and CPM-NFR [141]. Quantifying these features might aid perioperative risk stratification. Prospective interventional validation is required to ascertain whether phenotype-guided management improves clinical outcomes.

Circulating inflammatory mediators, neurotrophic factors, and neurotransmitter-related molecules have been investigated as candidate markers for early risk stratification. Neuropeptide Y (NPY) dynamics may reflect an adaptive peripheral response that is more specific to diabetic peripheral neuropathy (DPN) [142]. Blood cytokine profiles may reflect systemic inflammatory burden but are not specific to a single chronic pain condition [143]. Thus, these markers should be viewed in the context of disease and not considered interchangeable or clinically validated indicators.

Chronic pain patients may exhibit both neurobiological changes and systemic metabolic abnormalities. Disease-associated metabolic disorders may influence pain susceptibility through changes in inflammation and sensory-neuron function [144, 145]. As a result, paradigms for early diagnosis are moving away from symptom-based evaluation toward multiparametric predictive models that incorporate clinical phenotypes, biomarkers, and metabolic profiles. These candidate diagnostic and stratification models might be supported by data-analytic approaches leveraging multi-omics. Prospective validation is needed to determine the utility of these models for personalized management and precision intervention.

6 THERAPEUTIC STRATEGIES AND INTERVENTIONS

6.1 Pharmacological modulation of neuroplasticity

Neuroplastic mechanisms represent a potential area for pharmacological investigation given the close relationship between persistent maladaptive plasticity in the nervous system and chronic pain. Emerging strategies may target neural network remodeling and cellular functional changes beyond conventional symptom-oriented approaches [146]. These interventions seek to normalize pathological network activity, mitigate pain-promoting signaling, and restore functional activity by modulating neuronal excitability, synaptic transmission, and neuroimmune crosstalk [147]. As a general principle within this section, the majority of interventions described have been tested in cellular or animal models and should be interpreted

as suggesting preclinical therapeutic relevance rather than established clinical efficacy.

Brain-derived neurotrophic factor (BDNF) signaling exerts region- and model-dependent effects in preclinical studies. Experimental models indicate that morphine-induced mechanical analgesia involves BDNF-expressing neurons in the rostral ventromedial medulla, which recruit spinal glycinergic neurons through BDNF/tropomyosin receptor kinase B (TrkB) signaling [148]. BDNF also contributes to the transition from acute to chronic pain through sensory neuron-dependent mechanisms in some experimental models [149]. These observations implicate BDNF signaling in pain modulation and pain chronification, but do not identify BDNF as a clinically validated therapeutic target.

Distinct components of glial inflammatory signaling have been investigated in preclinical pharmacological studies. In animal models, bioactive compounds in Duhuo Jisheng decoction inhibit peroxisome proliferator-activated receptor gamma-related pro-inflammatory microglial responses, whereas praeruptorin C reduces complete Freund's adjuvant (CFA)-induced microglial activation and cytokine production in the ACC and modifies the expression of excitatory synaptic proteins [79, 150]. Together, these findings point to potential therapeutic relevance of glial inflammatory regulation, but the corresponding targets and compounds need clinical validation. Each effect was detected in a particular experimental model, so it remains unclear whether similar microglial alterations represent a common therapeutic mechanism across different pain etiologies and disease stages.

Glia-targeted interventions are also emerging as candidate pharmacological strategies. In a Phase I open-label clinical trial involving patients with chronic orofacial neuropathic pain, six weeks of treatment with the glial modulator palmitoylethanolamide (PEA) was associated with reduced pain intensity and decreased infra-slow oscillatory activity along the ascending trigeminal pain pathway, particularly in treatment responders [151]. These findings provide preliminary human evidence supporting the translational potential of glial modulation in neuropathic pain. However, whether modulation of astrocytic activity represents a primary mechanism underlying the analgesic effects of PEA or forms part of a broader glial and anti-inflammatory response remains unclear.

Collectively, these studies support the concept that pharmacological interventions may engage specific mechanistic components of maladaptive plasticity, including region-specific BDNF signaling, microglial inflammatory responses, and astrocyte-associated network activity. Although these mechanisms show preclinical therapeutic relevance, their reproducibility requires further validation, while the safety and efficacy of interventions targeting these mechanisms need to be evaluated using clinically relevant models and in prospective human studies.

6.2 Potential and applications of non-pharmacological therapies

Chronic pain is characterized by enduring neuroplastic changes, and pharmacotherapy alone rarely achieves sufficient symptom control. Non-pharmacological therapies have been increasingly incorporated into pain management. These strategies may not only dampen nociceptive signaling but may also influence neural circuit activity, synaptic transmission, and neuroimmune interactions to restore more physiological pain processing and ultimately stabilize synaptic function.

Preclinical data indicate that these interventions may engage spinal and supraspinal pain-processing networks through mechanisms related to neuroplasticity and central sensitization. In animal models, electroacupuncture reduces spinal sensitization, partly through inhibition of the calcium/calmodulin-dependent protein kinase II (CaMKII)/cAMP response element-binding protein (CREB)/BDNF signaling cascade [152]. Notably, environmental enrichment reduces stress-induced visceral pain-related behavior and microglia-associated neuronal plasticity in the amygdala [153]. Together, these results suggest possible involvement of distinct spinal and affect-related circuits but do not establish clinical efficacy.

These studies highlight commonalities and differences in the targets of non-pharmacological intervention across models. Spinal sensitization is a convergent neuroplastic process found in both cervical radiculopathy and osteoarthritis models [152, 154]. By contrast, CaMKII/CREB/BDNF signaling was examined in cervical radiculopathy, microglia-associated plasticity in the amygdala was identified in stress-induced visceral pain, and combined cartilage injury and spinal glial modulation were demonstrated in the monosodium iodoacetate-induced osteoarthritis model [152-154]. These pathways should therefore be viewed as disease- or model-specific mechanisms converging on broader processes such as central sensitization and altered affective pain processing. More needs to be established regarding the generalizability of these pathways and the clinical efficacy of interventions targeting them.

6.3 Integrated therapeutic strategies: Exploration and prospects

Chronic pain involves persistent, multilevel remodeling of the nervous system that may limit the efficacy of single-target therapies. Modulating neural circuits, molecular signaling, and neuroimmune states can alter maladaptive plasticity. Chronic pain is associated with reward-circuit dysfunction, aberrant neurotrophic signaling, and neuroimmune dysregulation [149, 155, 156]. Multitarget interventions in these domains have conceptual and preclinical therapeutic relevance, but whether

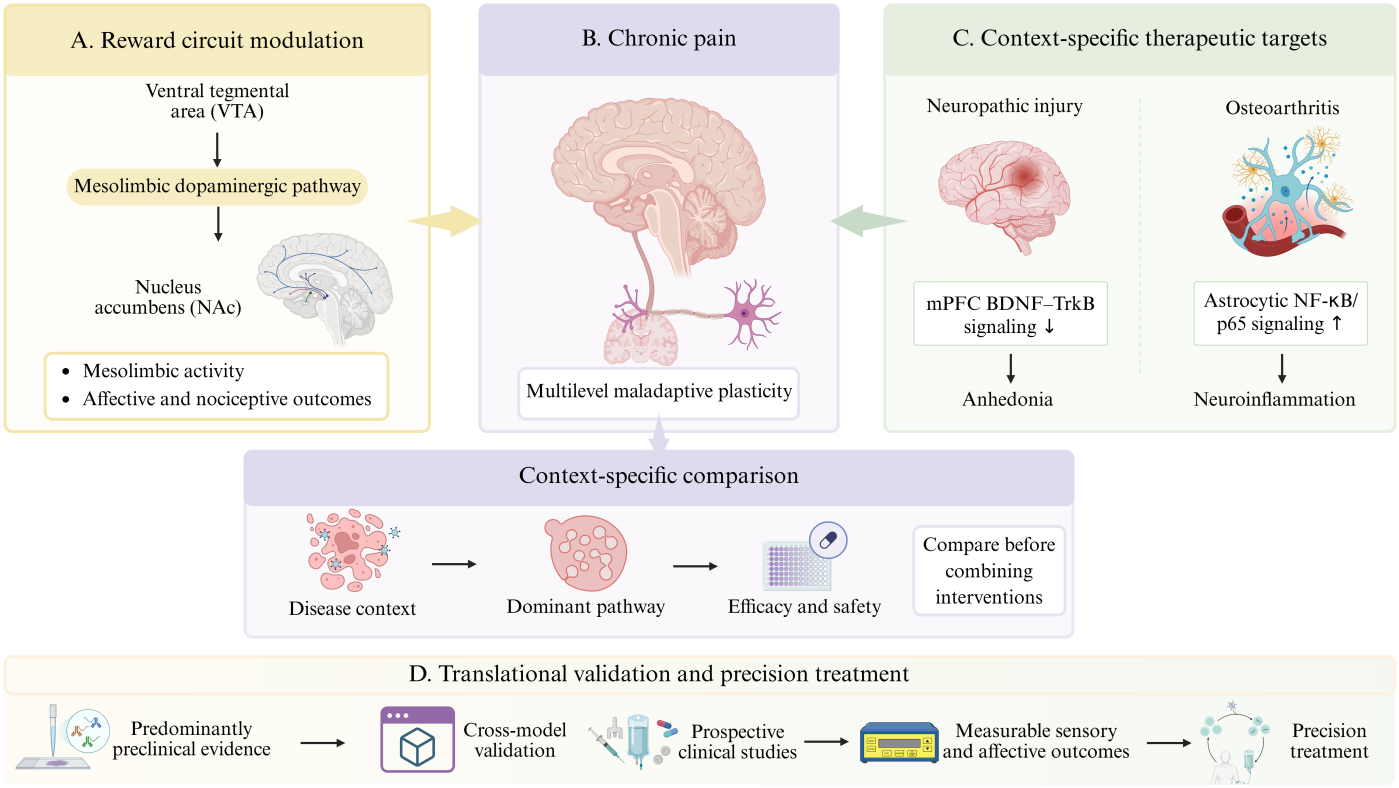


Figure 4. Hypothetical framework for integrated and context-specific therapeutic strategies targeting maladaptive plasticity in chronic pain. (A) Reward circuit modulation. Modulating the VTA–nucleus accumbens mesolimbic dopaminergic pathway may influence mesolimbic activity and nociceptive and affective outcomes. (B) Chronic pain. Chronic pain embodies a multilevel state of maladaptive plasticity involving neural, glial, and circuit-level dysfunction. (C) Context-specific therapeutic targets. Different pain conditions may involve distinct dominant pathways, including impaired mPFC BDNF–TrkB signaling during neuropathic injury and increased spinal astrocytic NF-κB/p65 signaling in osteoarthritis. Thus, disease context and dominant pathways should be considered, and the efficacy and safety of the corresponding interventions should be evaluated before combination strategies are pursued. (D) Translational validation and precision treatment. Since current evidence is mostly preclinical, cross-model validation, prospective clinical studies, and measurable sensory and affective outcomes are necessary before these strategies are used to inform precision treatment. Arrows indicate proposed pathway relationships, context-specific comparison, or translational progression. Created with BioRender.com.

these interventions improve sensory and affective outcomes in patients remains to be established. Collectively, these candidate approaches provide a context-dependent and still hypothetical basis for comparing and potentially integrating interventions that target maladaptive plasticity, as illustrated in **Figure 4**.

The modulation of reward circuitry, especially dopaminergic pathways, is one potential approach supported primarily by preclinical evidence. Chronic pain not only changes sensory processing but also disrupts mesolimbic activity and may reduce motivation while increasing anhedonia and affective disturbances. Recent studies have shown nociceptive modulation of mesolimbic circuits, emphasizing the integration of pain with emotional and motivational networks [157]. For instance, projections from dopaminergic neurons in the ventral tegmental area (VTA) regulate both nociceptive processing and depressive-like behaviors, further emphasizing the bidirectional relationship between pain and affect [158].

Chronic pain plasticity may involve broadly relevant neurotrophic and neuroimmune regulation, but the dominant pathways vary as a function of pain condition. In neuropathic injury, impaired mPFC BDNF–TrkB signaling has been associated especially with anhedonia, while spinal astrocytic nuclear factor kappa B p65 (NF-κB/p65) signaling has been demonstrated in models of osteoarthritis [159, 160]. These findings support convergence at the level of affective-circuit and neuroimmune dysfunction but do not necessarily imply convergence at the level of molecular pathways. These findings therefore support approaches that compare, rather than directly combine, circuit-, neurotrophic-, and immune-directed strategies across disease contexts. Evidence supporting such strategies remains largely preclinical.

Future studies should further investigate whether reward-circuit modulation can be safely and effectively combined with context-specific regulation of neurotrophic and neuroimmune

pathways. These approaches require cross-model validation and prospective clinical studies using measurable outcomes before they can guide precision therapy.

7 DISCUSSION

Chronic pain represents a complex neurobiological state involving long-term functional remodeling of the nervous system. Its development and maintenance involve peripheral input together with multilevel plastic changes within the CNS. Robust and reproducible evidence of peripheral and central sensitization in neuropathic pain has been obtained from experimental nerve-constriction models [161]. Accumulating evidence suggests that chronic pain is not simply the result of a single lesion or persistent inflammation but instead reflects interactions among peripheral sensitization, central circuit reorganization, and neuroinflammatory processes. In this regard, targeted modulation of defined neuronal circuits has shown preclinical therapeutic relevance. In animal models, chemogenetic silencing of somatostatin (SST)-expressing neurons in the central nucleus of the amygdala (CeA), or blockade of brainstem inputs to these neurons, decreased pain-related and anxiety- or depression-like behaviors [162]. While these findings reveal candidate circuit mechanisms, they do not establish clinically applicable interventions.

Collectively, these patterns support an overlapping progression whereby peripheral sensitization and DRG neuroimmune signaling are primarily involved in pain initiation, spinal synaptic and glial plasticity promote central amplification and pain maintenance, while supraspinal remodeling contributes to persistent pain perception and affective or cognitive comorbidities. Molecular and epigenetic regulation may help stabilize these changes, although their temporal and causal roles remain incompletely defined.

Peripheral sensitization, spinal excitation-inhibition imbalance, glia-neuron signaling, and supraspinal network remodeling are broadly shared mechanisms across chronic pain conditions. Nevertheless, the dominant associated pathways remain specific to particular conditions, including transcriptional and epigenetic changes in neuropathic pain, sex-dependent immune regulation in inflammatory arthritis, thalamic plasticity in post-stroke pain, joint pathology with central sensitization in osteoarthritis, sensory and affective circuit changes in pelvic and visceral pain, and NPY regulation in DPN [58, 59, 63-67, 80-82, 125-127, 142, 153, 154, 160]. As such, chronic pain conditions may share higher-order neuroplastic processes while differing in both initiating pathology and molecular mediators, although direct cross-condition comparisons remain limited.

Three unanswered questions appear across Sections 2–4. First, the extent to which chronic pain depends on ongoing peripheral input or is maintained by plasticity within spinal and supraspinal neural circuits remains unclear [9, 18, 163]. Second, neuroimmune mechanisms vary across cell types, anatomical sites, pain etiologies, and disease stages: DRG macrophages contribute to both initiation and maintenance of neuropathic pain, system xc^--related neuroinflammation promotes hypersensitivity, and TNFR2-dependent regulatory T cells support recovery [50, 113, 117]. Third, while numerous molecular, epigenetic, and network changes are associated with persistent pain, their roles as drivers, maintenance factors, or secondary consequences remain insufficiently defined [12, 68]. Differences in experimental approaches, behavioral readouts, time points, and models may contribute to this uncertainty [114, 164]. Future studies should implement longitudinal, sex-inclusive, and cross-model designs that couple cell-specific manipulation with molecular, circuit-level, and behavioral analyses.

Long-lasting changes in neuronal excitability, synaptic efficacy, and circuit connectivity following prolonged injury or stimulation can transform adaptive plasticity into maladaptive processes that maintain pain. Chemogenetic inhibition of the parabrachial nucleus (PBN)→CeA pathway partially relieved acute but not chronic neuropathic pain [12]. These observations indicate that chronic pain is not simply an extension of acute pain but rather involves persistent circuit reconfiguration. These changes alter nociceptive signaling and the affective and cognitive processing of pain without necessarily changing the underlying tissue injury, thereby promoting pain persistence.

Recent developments reflect a move away from reductionist descriptions toward mechanistic analyses. Accumulating evidence has pointed to multiple molecular and circuit mechanisms involved in the chronification of pain. C-X-C motif chemokine ligand 1 (CXCL1) derived from the DRG is a key mediator of pain maintenance and contributes to the transition to persistent pain in the HP model [165]. Moreover, available preclinical evidence indicates that microglial transient receptor potential vanilloid 4 (TRPV4) channels contribute to the transition from peripheral nerve injury to central sensitization and may represent a plausible candidate therapeutic target along the spinal neuroimmune axis [166]. The safety, target specificity, and clinical efficacy of TRPV4-targeted interventions remain to be established. These findings indicate that chronic pain can be viewed as a systems-level disorder characterized by dysregulated tissue-resident neuronal function, microenvironmental changes, and immune signaling.

Despite progress, significant challenges remain. Clinical application is complicated by variability across experimental models, limited translational validation, and considerable patient heterogeneity. Consequently, longitudinal and cross-model studies are needed to address methodological differences in model selection, intervention timing, behavioral outcomes, and clinical phenotyping.

8 CONCLUSION

Chronic pain can be characterized as a maladaptive neuroplastic state with features of peripheral sensitization, spinal excitation–inhibition imbalance, glia–neuron signaling, and supraspinal network remodeling. Although the initiating pathology, dominant molecular mediators, neuroimmune mechanisms, and neural circuits may remain disease-, sex-, and model-specific, broader neuroplastic processes may still recur across chronic pain conditions. This framework may help account for the persistence of pain beyond tissue healing, as well as the common coexistence of sensory abnormalities with affective, cognitive, and motivational disturbances. Some pharmacological and non-pharmacological interventions show preclinical potential for modulating these mechanisms, but clinically validated evidence for mechanism-guided precision treatment remains limited. Upcoming studies should bring together longitudinal, sex-inclusive designs with cross-model validation, cell-specific manipulation, multimodal imaging, multi-omics, and clinical phenotyping. Prospective clinical studies are needed to distinguish causal drivers from secondary adaptations, identify reproducible biomarkers, and assess whether neuroplasticity-based stratification can improve treatment selection and long-term outcomes.

ABBREVIATIONS

5-HT3A, 5-hydroxytryptamine receptor 3A; ac4C, N4-acetylcytidine; ACC, anterior cingulate cortex; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; BNST, bed nucleus of the stria terminalis; C3/C3aR, complement component 3/complement component 3a receptor; CA1, cornu ammonis area 1; CaMKII, calcium/calmodulin-dependent protein kinase II; CART, cocaine- and amphetamine-regulated transcript; CCI, chronic constriction injury; CeA, central nucleus of the amygdala; CFA, complete Freund's adjuvant; CNS, central nervous system; COPCs, chronic overlapping pain conditions; CPM-NFR, conditioned pain modulation–nociceptive flexion reflex; CPP, chronic pelvic pain; CREB, cAMP response element-binding protein; CSF1R, colony-stimulating factor 1 receptor; CXCL1, C-X-C motif chemokine ligand 1; DNMT3a, DNA methyltransferase 3 alpha; DOCK4, dedicator of cytokinesis 4; DPN, diabetic peripheral neuropathy; DRG, dorsal root ganglion; ERK, extracellular signal-regulated kinase; EVs, extracellular vesicles; FcγR, Fc gamma receptor; GFAP, glial fibrillary acidic protein; GLS1, glutaminase 1; GLT1, glutamate transporter 1; GluN2B, glutamate ionotropic receptor NMDA type subunit 2B; HP, hyperalgesic priming; IFN-β, interferon beta; IgG, immunoglobulin G; IL-6, interleukin-6; Kcnq1ot1, KCNQ1 opposite strand/antisense transcript 1; LTP, long-term potentiation; m6A, N6-methyladenosine; MBD1, methyl-CpG-binding domain protein 1; mGluR5, metabotropic glutamate receptor 5; miR-155, microRNA-155; mPFC, medial prefrontal cortex; NF-κB/p65, nuclear factor kappa B p65; NKCC1, Na^+-K^+-$2Cl^-$ cotransporter 1; NLRP3, NOD-like receptor family pyrin domain-containing 3; NMDA, N-methyl-D-aspartate; NPY, neuropeptide Y; P2Y12, purinergic receptor P2Y12; PBN, parabrachial nucleus; PEA, palmitoylethanolamide; PF, pelvic floor; PFC, prefrontal cortex; PKMζ, protein kinase M zeta; PNS, peripheral nervous system; PRP, platelet-rich plasma; RA, retinoic acid; Rac1, Ras-related C3 botulinum toxin substrate 1; REST, RE1-silencing transcription factor; SIRT1, sirtuin 1; SNL, spinal nerve ligation; SPACE, Sleep, Pain, Affect, Cognition, Energy; SST, somatostatin; Tiam1, T-cell lymphoma invasion and metastasis 1; TMEM34, transmembrane protein 34; TNF, tumor necrosis factor; TNFR2, tumor necrosis factor receptor 2; TNF-α, tumor necrosis factor alpha; TrkB, tropomyosin receptor kinase B; TRPV4, transient receptor potential vanilloid 4; TS-NFR, temporal summation of nociceptive flexion reflex; UCPPS, urological chronic pelvic pain syndromes; VTA, ventral tegmental area; xCT, cystine/glutamate antiporter xCT.

DECLARATIONS

Author contributions

Kaikai Wang, Yanhu He, and Jinhai Liu contributed equally to the conception and design of this review, literature retrieval, and drafting of the manuscript. Shaobai Li, Chengyi Yuan, Xinyu Wang, Guoliang Hou, Jingru Ma, Rui Yin, and Jinge Yang contributed to literature collection and critical revision of the manuscript. Xiaoguang Qin and Yana Wu conceived and supervised the review and critically revised the manuscript. All authors read and approved the final version of the manuscript.

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