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PSYCHOLOGICAL VULNERABILITY AND CHRONIC PAIN IN MUSCULOSKELETAL DISORDERS: INTEGRATING NEUROENDOCRINE, IMMUNE, AND BEHAVIORAL MECHANISMS

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ABSTRACT
Chronic musculoskeletal pain is a complex phenomenon that involves the influence of biological, psychological and behavioral factors. This review will explore the concept of psychological vulnerability in terms of the mechanisms and pathways by which psychological vulnerability is related to the development, exacerbation and maintenance of pain in musculoskeletal conditions, including neuroendocrine pathways, immune pathways, molecular pathways and behavioural pathways. Depression, anxiety, chronic stress, pain catastrophizing, fear avoidance, hypervigilance, and low resilience may affect pain perception and contribute to functional disability. These all occur in relation to hypothalamic–pituitary–adrenal axis dysregulation, abnormal cortisol secretion, sympathetic activation and endogenous pain inhibition. Peripheral and central sensitization are further perpetuated by persistent immune activation, release of pro-inflammatory cytokines and neuroimmune signaling between microglia and astrocytes. Additionally, epigenetic changes and genetic susceptibility could account for variations in pain sensitivity, chronicity, and response to treatment. These biological and psychological processes are reinforced by behavioral mechanisms such as sleep disturbance, physical inactivity, social withdrawal, and maladaptive coping that perpetuate pain and disability. There is supporting evidence for an integrated biopsychosocial approach to the assessment and management of chronic MSK-pain. Applying psychological screening, sleep and activity assessment, molecular biomarkers, physical rehabilitation, stress management and suitable pharmacological treatment could enhance patient stratification and treatment outcomes. The need for future studies in this field is the use of validated multidimensional biomarkers and personalized interventions that target multiple mechanisms involved in this isthmus between vulnerability to pain and persistence in chronic pain.

KEYWORDS: chronic musculoskeletal pain; psychological vulnerability; neuroendocrine dysregulation; neuroimmune mechanisms; biopsychosocial management

INTRODUCTION
Musculoskeletal pain is a major cause of disability globally and negatively impacts on physical function, psychological health and quality of life. Acute pain is a biological protective response to tissue damage while chronic musculoskeletal pain occurs when the pain persists beyond the expected time of healing, has complex relationships with the peripheral tissues, central nervous system, and social and psychological factors (Cohen et al., 2021). The burden of common musculoskeletal conditions (CMCs), such as osteoarthritis, rheumatoid arthritis, chronic low back pain, neck pain, and fibromyalgia include costs of care, long-term disability, and decreased work productivity (El-Tallawy et al., 2021). Therefore, the term chronic pain is now used to describe a multi-factorial disease process that must be understood in terms of biological, psychological and behavioral factors in order to approach it effectively, instead of only through a structural or anatomical approach. Recent progress in pain neuroscience has led to the identification of central sensitization, central neural processing, and maladaptive neuroplasticity as all contributing to persistent musculoskeletal pain, in addition to peripheral nociceptive input (Nijs et al., 2021). These mechanisms can lead to increased sensitivity to pain even when there is little to no tissue pathology present or even when the tissues are already healed.
Additionally, the understanding of nociplastic pain has further advanced the current understanding of pain, focusing on the dysfunction of pain-processing pathways rather than just ongoing tissue damage (Fitzcharles et al., 2021). This paradigm shift underscores the need to explore the systemic biological mechanisms underlying the chronicity of pain such as neuroendocrine dysregulation, immune activation and molecular signaling pathway alterations. Psychological

vulnerability has proven to be one of the most powerful predictors of onset, persistence, and disability from chronic pain in people with MSDs. Depression, anxiety, perceived stress, pain catastrophizing, fear-avoidance beliefs, and decreased resilience are also factors that affect pain intensity and functional recovery by altering cognitive and emotional reactions to painful stimuli (Martinez-Calderon et al., 2020). These psychological attributes are not simply present along with chronic pain but are also part of a set of maladaptive behaviors that may help to sustain chronic pain.

Emotional distress can exacerbate attention to pain, decrease physical activity, decrease coping, and increase long-term disability, thus perpetuating a cycle of emotional dysfunction and chronic pain (Dueñas et al., 2020). There is accumulating evidence that psychological vulnerability is mediated by complex neuroendocrine and immune system mechanisms. Long-term psychological stress has been found to affect the regulation of the hypothalamic–pituitary–adrenal (HPA) axis, leading to abnormalities in cortisol production, and changes in autonomic nervous system functioning and physiological responses to stress (Karin et al., 2020). Chronic activation of these stress response pathways has been linked to an increase in pain sensitivity, reduced endogenously produced pain inhibition and increased risk of chronic musculoskeletal pain (Hannibal & Bishop, 2020). At the same time, sustained stress leads to chronic low-grade systemic inflammation via up-regulation of pro-inflammatory cytokines and immune mediators, which also sensitize peripheral nociceptors and central pain pathways (Ji et al., 2020). Activated microglia and astrocytes have also been identified as crucial players responsible for maintaining inflammatory signaling in the central nervous system (CNS), contributing to chronic pain (Donnelly et al., 2020).

In molecular terms, progress in genetics and epigenetics has led to an understanding of the individual differences in susceptibility to pain and in psychological resilience. There are a number of genetic loci associated with chronic musculoskeletal pain and genetic variation exists across the population, which indicates that inherited variation in the biological system is a part of pain vulnerability (Suri et al., 2020). Epigenetic processes like changes to DNA methylation, and expression changes to genes, have been linked to the development of chronic pain by their ability to modulate inflammatory pathways, neuronal plasticity, and stress responsive signaling networks (D'Agnelli et al., 2021).

The molecular results confirm that chronic pain is the result of dynamic interactions between genes and psychological and other environmental factors, such as chronic stress and negative behavior patterns. The multidimensionality of chronic musculoskeletal pain is reinforced by behavioral factors. Sleep disturbances, physical inactivity, maladaptive coping strategies and decreased social participation can contribute to worsening inflammatory reactions, poorer recovery and higher levels of pain (Santos et al., 2023). Biopsychosocial approach is now advocated by contemporary pain management which combines biological mechanisms with psychological evaluation and behavioural therapy to enhance long-term clinical outcomes (George et al., 2021).

The purpose of this review is to provide a broad overview of the link between psychological vulnerability and chronic pain in musculoskeletal disorders in order to synthesize the findings from neuroendocrine, immune, genetic, molecular and behavioral research. It includes ongoing research on the biological mechanisms (neuroendocrine dysregulation, neuroimmune interactions, inflammatory mechanisms, molecular markers, and behavioral factors) linking psychological stress with chronicity of pain, as well as factors that affect the progression of the disease and treatment efficacy. The aim is to compile the current evidence and arrive at a sound mechanistic understanding that could be used to better inform personalized assessment, diagnosis, and multimodal treatment pathways for chronic musculoskeletal pain.

2. Biological Basis of Chronic Musculoskeletal Pain

2.1 Peripheral and Central Sensitization Mechanisms

Chronic musculoskeletal pain is a result of chronic changes in both peripheral nociceptive pathways and central pain-processing systems. Peripheral sensitization is defined as the decrease in activation threshold of nociceptors by the release of inflammatory mediators from injured or stressed tissue. This results in greater sensitivity to mechanical, thermal and chemical stimuli and can cause pain with normal motion or gentle touch. Excessive repetitions of a noxious stimulus can maintain the sensitivity of the tissue even after the initial tissue healing process has started (El-Tallawy et al., 2021). Repeated peripheral input can then lead to central sensitization (over-excitability of neurons in the spinal cord and brain). Central sensitization leads to heightened responses to painful stimuli and can also give the sensation of pain from non-painful stimuli. Hyperalgesia, allodynia, temporal summation and an increase of pain areas beyond the damaged tissue are well described accompanying the CPS (Nijs et al., 2021). The idea of the nociplastic pain concept has helped to explain why in some cases, patients can have high intensity and persistent musculoskeletal pain despite a limited extent of structural injury. Nociplastic pain is a type of pain that occurs when there is still no evidence of ongoing tissue damage or direct damage to the somatosensory system (Fitzcharles et al., 2021). Specific clinical features of nociplastic musculoskeletal pain therefore focus on regional or widespread pain, pain hypersensitivity, fatigue, cognitive dysfunction and sleep disturbance (Kosek et al., 2021).

2.2 Genetic and Molecular Regulation of Pain Perception

Genetic variation contributes to the individual susceptibility to chronic musculoskeletal pain. Genes of neurons that regulate their excitability, inflammatory signaling, stress regulation, and neurotransmitter metabolism can alter pain sensitivity and the risk of chronic pain. Genetic studies conducted across the genome have identified genetic regions that are linked to chronic back pain, suggesting that inherited differences in biological systems can make some populations more vulnerable to developing chronic back pain than others (Suri et al., 2020). Molecular mechanisms also affect the detection, transmission and maintenance of painful stimuli.

Persistent pain signalling can be reinforced by pro-inflammatory cytokines, chemokines, neuropeptides, ion channels and growth factors which can increase nociceptor excitability. Elongation of immune to nervous system communication and activation of glial cells may be other activities of inflammatory mediators (Matsuda et al., 2020). There are also epigenetic

mechanisms that could influence gene expression in relation to pain, as a result of environmental stress or psychological experiences. Patients who have chronic low back pain have been found to have altered DNA methylation, which could affect pathways affecting immune function, neuronal signalling and stress responses (Aroke et al., 2020). The variation in pain and disability in people with the same tissue pathology may therefore be explained by epigenetic regulation.

2.3 Neuroplastic Changes Associated With Persistent Pain

Chronic pain can induce structural and functional alterations in neural networks involved in sensation, emotion, attention and threat appraisal. Chronic pain exposure could increase the strength of the excitatory synapses and diminish the strength of inhibitory pain-control pathways. These changes can diminish the ability to engage in endogenous pain inhibition and enhance the likelihood of perceiving sensory information as threatening (Woolf, 2023). In addition, the neuroplasticity includes changes in activity in the prefrontal cortex, insula, anterior cingulate cortex, amygdala, and somatosensory regions. These regions of the brain are involved in the perception of pain, emotional reactions, memory and fear, and behavioral reactions. The ongoing activation of these networks can exacerbate pain-related anxiety, hypervigilance, and avoidance, which in turn can sustain pain even with a stable peripheral pathology.

An activation of the glia is especially significant in maintaining maladaptive neuroplasticity. Astrocytes and microglia secrete inflammatory mediators that affect synaptic transmission and increase neuronal excitability (Ji et al., 2020). The persistent central pain amplification, thus, may result from the prolonged glial signalling, which can transform short-term nociceptive activity into persistent central pain amplification (Donnelly et al., 2020). Chronic musculoskeletal pain is a process involving peripheral sensitization, central sensitization, nociplastic pain processing, genetic/molecular regulation and maladaptive neuroplastic changes as illustrated in figure 1. Table 1 provides a summary of peripheral sensitization, central sensitization, nociplastic pain, genetic susceptibility, epigenetic modification and activation of the glia cells.

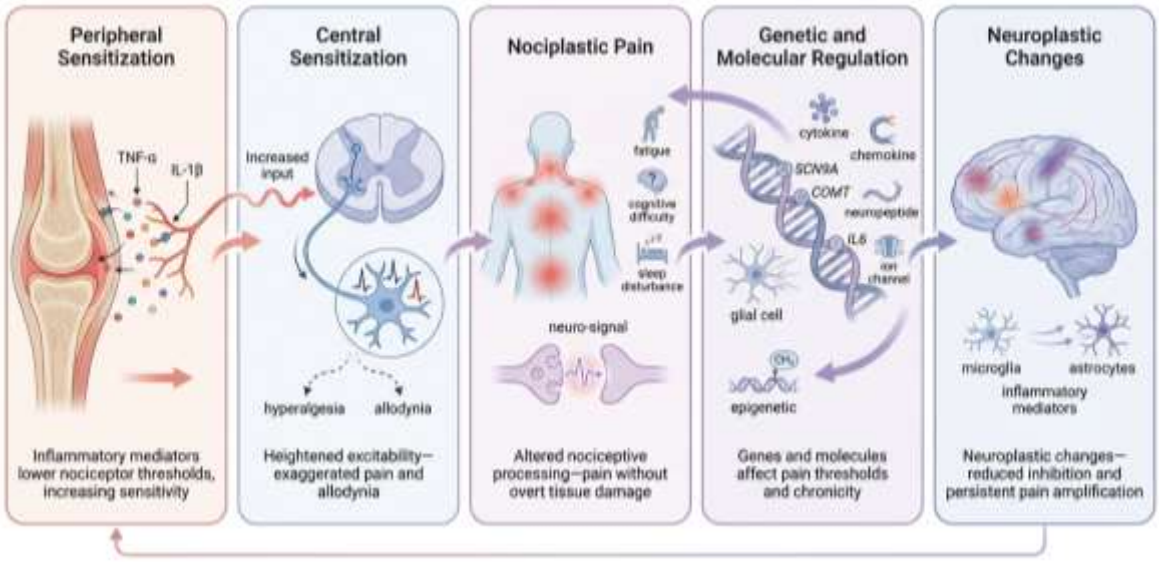

Figure 1. Biological Basis of Chronic Musculoskeletal Pain

Table 1. Major Biological Mechanisms Involved in Chronic Musculoskeletal Pain

Mechanism	Biological effect	Clinical manifestation	Supporting reference
Peripheral sensitization	Reduced nociceptor activation threshold	Local tenderness and movement-related pain	El-Tallawy et al. (2021)
Central sensitization	Increased spinal and cortical excitability	Hyperalgesia and allodynia	Nijs et al. (2021)
Nociplastic pain processing	Altered nociception without clear tissue damage	Widespread pain, fatigue, and sleep problems	Kosek et al. (2021)
Genetic susceptibility	Variation in pain- and inflammation-related genes	Differences in pain persistence	Suri et al. (2020)
Epigenetic modification	Altered pain-related gene expression	Variable pain sensitivity and disability	Aroke et al. (2020)
Glial-cell activation	Sustained neuroinflammatory signalling	Persistent central pain amplification	Ji et al. (2020)

3. Psychological Vulnerability and Pain Experience

3.1 Depression, Anxiety, Stress, and Pain Catastrophizing

Vulnerabilities are a major factor in the development, maintenance, and aggravation of chronic musculoskeletal pain. Depression and anxiety are common concurrent conditions with chronic pain, and can worsen the experience of pain, hinder treatment engagement, and exacerbate functional disability. Emotional distress can exacerbate one's awareness of sensations within the body, and increase the feeling of pain as if it were a greater threat, thus perpetuating a cycle of pain,

worry, and decreased activity (Dueñas et al., 2020). Repeated exposure to psychological stress can also change pain processing pathways, decrease endogenous pain inhibitory pathways and increase pain chronicity. People under chronic stress have reported more pain intensity, less recovery and higher sensitivity to mechanical stimulation (Hannibal & Bishop, 2020).

The effects of these may be especially strong if stress is associated with sleep disturbance, work pressure or reduced social support. Pain catastrophizing is a heightened negative attitude to real or perceived pain. Usually has rumination, magnification and hopelessness. When structural pathology is unchanged, catastrophizing can contribute to greater attention to pain, emotional distress, and movement avoidance, leading to increased disability (Martinez-Calderon et al., 2020). Therefore, a comprehensive clinical evaluation of chronic musculoskeletal pain should measure the severity of the symptoms as well as the patient's cognitive understanding of pain.

3.2 Fear Avoidance, Hypervigilance, and Emotional Dysregulation

Patients learn fear-avoidance beliefs if they think that moving or exercising is unsafe and may result in more injury. This can lead to lack of activity, muscle deconditioning, social isolation and decreased confidence in movement. These behavioral changes can over time lead to an increase in disability and the belief that the pain is uncontrollable (Wertli et al., 2021). Hypervigilance is hyperattention to pain-related sensations and the potential signs of physical damage. People who are very aware of their body can often feel and make sense of the small changes in symptoms as a sign of a worsening illness.

This increased awareness can heighten the feeling of pain and stress leading up to movement or treatment. Fear-avoidance beliefs have also been linked to increased chronic pain rates among the working population, suggesting that the occupational and psychosocial environment can have an impact on pain-related behavior (Wakaizumi et al., 2021). Emotional dysregulation can also exacerbate chronic pain by interfering with the capacity to regulate distressing thoughts, fears, frustrations and uncertainties. Emotional dysregulation can contribute to a rise in physiological arousal and promote maladaptive coping such as avoidance, inactivity, and reliance on passive treatment. The ongoing nature of these patterns can diminish recovery of function and lead to chronic pain-related disability.

3.3 Influence of Personality, Coping Capacity, and Resilience

Coping styles and personality traits may affect the way that people react to musculoskeletal pain. Passive coping patients may be preoccupied with symptom management; limit activities, and become more dependent on health care interventions. The other active coping strategies, however, promote incremental steps, self-management, problem-solving, and participation in relevant activities. Acceptance of pain is a key adaptive process that enables people to participate in activities they value without requiring complete pain relief. Pains acceptance is correlated with good psychological adaptation to pain and reduced pain interference (Esteve et al., 2020). Acceptance isn't a sign of giving up, but a change in attitude from feeling in control of all pain to having function and quality of life.

Resilience is the ability to embrace adversity and make positive changes despite ongoing pain and suffering. Resilient people might employ coping mechanisms that are more flexible, stay socially connected and bounce back better from setbacks during the pain. Resilience and acceptance are considered as protective psychological resources for adaptation to chronic musculoskeletal pain (Ramírez-Maestre et al., 2022). In contrast, having a limited coping capacity may make it more likely that an acute pain becomes chronic, especially when coupled with anxiety, fear, and low self-efficacy (Hruschak & Cochran, 2020). Table 2 lists the main psychological risk factors for chronic pain, such as depression, anxiety, chronic stress, catastrophizing, fear avoidance, pain acceptance, and resilience, and associated clinical implications.

Table 2. Psychological Factors Influencing Chronic Musculoskeletal Pain

Psychological factor	Principal effect on pain	Likely clinical consequence	Supporting reference
Depression and anxiety	Increase negative attention and emotional distress	Greater pain intensity and disability	Dueñas et al. (2020)
Chronic stress	Disrupts pain regulation and stress adaptation	Increased pain sensitivity	Hannibal and Bishop (2020)
Pain catastrophizing	Promotes rumination and helplessness	Increased pain interference	Martinez-Calderon et al. (2020)
Fear avoidance	Restricts movement and activity	Deconditioning and functional decline	Wertli et al. (2021)
Pain acceptance	Supports engagement despite symptoms	Better psychological adjustment	Esteve et al. (2020)
Resilience	Improves adaptation to persistent pain	Better coping and functional recovery	Ramírez-Maestre et al. (2022)

4. Neuroendocrine Mechanisms Linking Psychological Stress and Pain

4.1 Hypothalamic–Pituitary–Adrenal Axis Dysregulation

Psychological stress has a strong impact on chronic musculoskeletal pain via the hypothalamic–pituitary–adrenal (HPA) axis. Under stress, the hypothalamus secretes corticotropin-releasing hormone that activates the release of adrenocorticotropic hormone from the pituitary, and cortisol from the adrenal cortex. This is a normal response that is temporary and that helps maintain physiological stability under normal conditions. But chronic or chronic-like stress can

alter the feedback mechanisms and lead to over- or under-activity of cortisol (Herman et al., 2020). Continued HPA-axis activation can affect immunity, sleep, energy use and pain sensitivity.
Disturbed cortisol patterns can impair the body's ability to react to new stressors in an adequate way and also can make them more susceptible to chronic pain. The long-term effects of sustained stress exposure are also suggested by mathematical and biological models of the HPA axis (Karin et al., 2020). Depression and other stress-related conditions frequently seen with chronic musculoskeletal pain have also been linked to abnormal functioning of the HPA axis. Dysfunction of the glucocorticoid receptor sensitivity and dysfunction of negative feedback might facilitate long-lasting emotional dysregulation and changes in pain processing (Mikulska et al., 2021). Based on these results, it is suggested that neuroendocrine dysfunction could be a significant link between psychological vulnerability and the chronicity of pain.

4.2 Cortisol, Catecholamines, and Stress-Response Pathways

Cortisol is involved in a complicated manner in the regulation of pain. Normally, acute release of cortisol can help adapt to stress but chronic dysregulation can lead to an imbalance in the immune system and sensitivity to pain. People under chronic stress can have a flattened daily cortisol pattern, abnormal morning levels of cortisol, or less sensitivity to stress. This pattern can be linked to fatigue, sleep problems and impaired recovery from musculoskeletal pain. Chronic stress also may affect mechanical pain sensitivity and temporal processing of painful stimuli. Experimental studies show that basal mechanical pain sensitivity is enhanced in women with chronic stress, which indicates that chronic psychological stress can influence somatosensory processing (Kuehl et al., 2021). These changes can happen even if there is no significant tissue damage. Another stress pathway is the sympathetic–adrenal–medullary system.
Psychological stress leads to the release of catecholamines, especially adrenaline and noradrenaline, and thus to an increase in cardiovascular activity and physiological arousal. Persistent activation of the sympathetic nerves may increase muscle tension, decrease peripheral blood flow and increase peripheral nociceptor sensitivity. In chronic lower back pain, neck pain, and myofascial pain, for example, the arousal of the sympathetic system could exacerbate pain. Maintaining pain may be due to dysfunction in cortisol and long-lasting activation of the autonomic nervous system, which could act together on the impairment of pain recovery, inflammation, and the reduced descending pain inhibition. This psychoneuroendocrine communication is a rationale for incorporating stress reduction techniques into multidisciplinary pain rehabilitation (Hannibal & Bishop, 2020).

4.3 Neurotransmitter and Neuropeptide Alterations in Chronic Pain

Neurotransmitter systems of mood, motivation, arousal, and pain inhibition are also affected by psychological stress and chronic pain. Descending pain-modulatory pathways in the brainstem are mediated by serotonin and noradrenaline. Any impairment of the activity of these pathways can diminish endogenous pain inhibitory systems and enhance vulnerability to chronic pain. Dopamine is involved in reward processing, motivation and pain-related learning. Increased fatigue, decreased motivation for physical activity, and decreased interest (anhedonia) may be related to reduced dopaminergic function. These effects can further perpetuate behavioral withdrawal and/or functional decline for patients with chronic musculoskeletal disorder.
Nociceptive transmission can further be increased by stress-related neuropeptides, such as corticotropin-releasing hormone (CRH) and substance P. The role of substance P is to induce neurogenic inflammation and to help sensory neurons to communicate with immune cells. This prolonged release of these mediators could lead to heightened peripheral sensitivity and central amplification of pain. Figure 2 illustrates the activation of stress hormone systems (the sympathetic–adrenal–medullary system and the hypothalamic–pituitary–adrenal axis) in response to psychological stress, which leads to the release of catecholamines and cortisol into the bloodstream that can affect inflammation and pain sensitivity. Table 3 details the ways in which HPA-axis dysfunction, altered cortisol rhythms, glucocorticoid signalling, sympathetic activation, mechanical pain sensitivity, and neurotransmitter imbalance play a role in the persistence of pain (Ali et al., 2025).

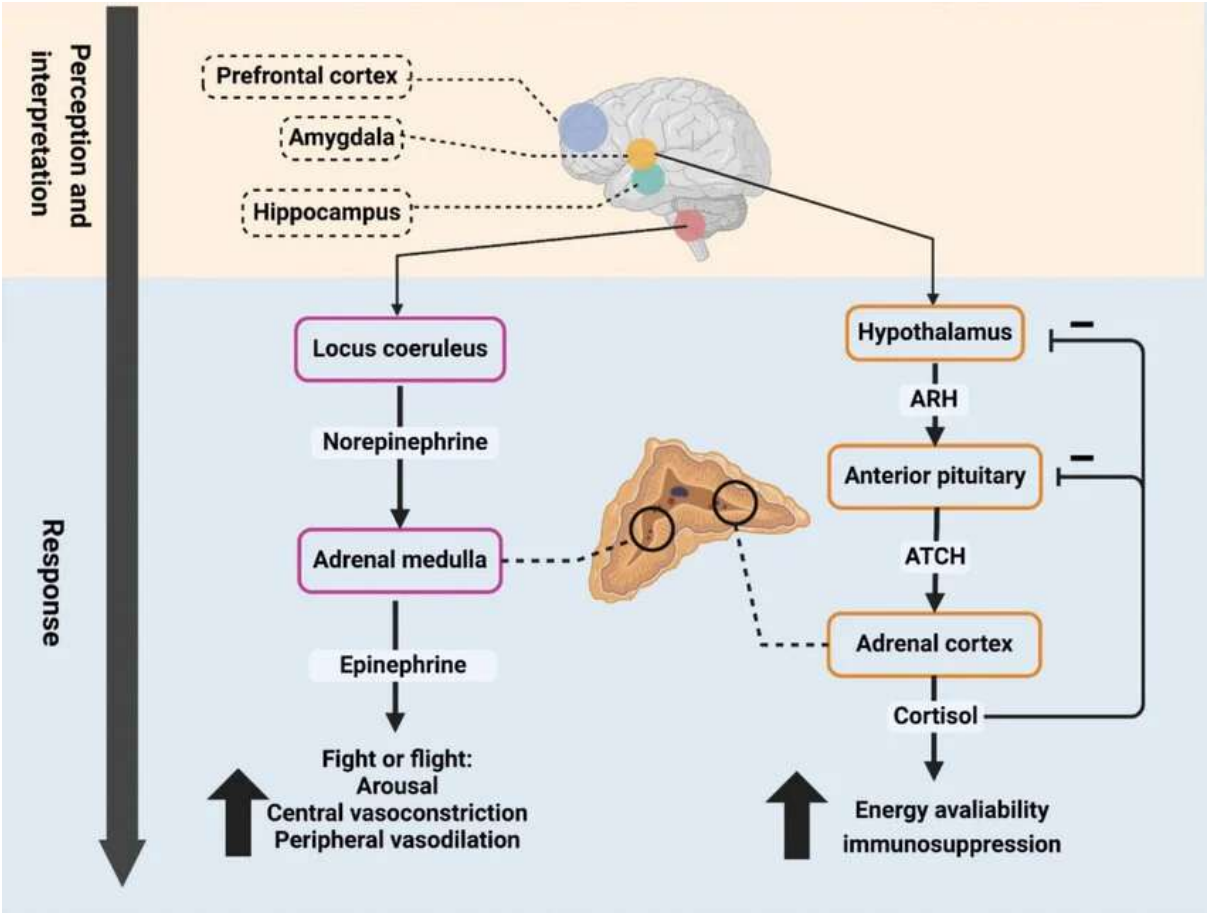

Figure 2. Neuroendocrine Pathways Linking Psychological Stress and Chronic Pain (Ali et al., 2025)

Table 3. Principal Neuroendocrine Pathways Linking Stress and Chronic Pain

Neuroendocrine component	Effect of prolonged psychological stress	Contribution to chronic pain	Supporting reference
HPA axis	Disrupted hormonal feedback regulation	Altered stress adaptation and pain sensitivity	Herman et al. (2020)
Cortisol rhythm	Flattened or abnormal secretion pattern	Fatigue, inflammation, and impaired recovery	Karin et al. (2020)
Glucocorticoid signalling	Reduced receptor sensitivity	Persistent stress and emotional vulnerability	Mikulska et al. (2021)
Sympathetic nervous system	Sustained catecholamine release	Muscle tension and nociceptor sensitization	Hannibal and Bishop (2020)
Mechanical pain processing	Increased sensitivity under chronic stress	Greater pain response to pressure	Kuehl et al. (2021)
Neurotransmitter imbalance	Reduced descending inhibition	Enhanced pain persistence and emotional distress	Hannibal and Bishop (2020)

5. Immune and Molecular Mechanisms

5.1 Pro-Inflammatory Cytokines and Chronic Low-Grade Inflammation

Chronic musculoskeletal pain is now well recognised as an immune mediated disease in which chronic inflammatory processes are thought to lead to chronic pain and tissue dysfunction. Immune cells release pro-inflammatory cytokines such as Interleukin (IL)-1β, Interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α) and a number of chemokines after injury or repetitive mechanical stress. These mediators lower activation threshold of peripheral nociceptors and make them more sensitive towards mechanical and thermal stimulation (Matsuda et al., 2020). Acute inflammation plays a crucial role in healing, but if it persists, the production of cytokines can keep the body in pain, even after the tissues are repaired.

Low-grade systemic inflammation also affects central pain processing via the promotion of communication between peripheral immune cells and the central nervous system. Circulating inflammatory mediators may alter the excitability of the neurons, reduce natural pain modulation and are associated with fatigue, mood changes, and cognitive dysfunction. Immune dysregulation has been found in a number of chronic musculoskeletal diseases, indicating that this is a common pathway of an inflammatory response driving chronic pain (Sommer et al., 2021). Changes have also been observed in cytokine profiles in fibromyalgia and nociplastic pain syndromes. While there are marked differences in cytokine levels, the use of inflammatory mediators as biologic markers in the severity of symptoms and pain persistence is supported by

a systemic evidence (Üçeyler et al., 2021). Therefore, inflammatory markers are starting to be studied as markers of disease activity and therapeutic response.

5.2 Neuroimmune Interactions and Glial-Cell Activation

Immune system and nervous system interactions are key to sustaining chronic pain. With continued nociceptive stimulation, resident immune cells in the central nervous system (CNS), including microglia and astrocytes, are activated and begin to secrete inflammatory cytokines, chemokines, nitric oxide, and reactive oxygen species. These molecules intensify the transmission of pain signals across synapses found in the spine and boost the excitability of neurons, thereby strengthening central sensitization (Ji et al., 2020). Microglia are thought to be the first cells to respond to damage to neurons and to contribute to the onset of neuroinflammatory responses. These are activated and lead to a chronic inflammatory signal that continues to sustain pain without any current peripheral tissue injury. Astrocytes then play roles in long-term maintenance of pain through manipulating neurotransmitter uptake, synaptic plasticity and production of inflammatory mediators (Donnelly et al., 2020).

New studies also show that there is a two-way flow between the nervous system and the immune system. Signaling molecules released by neurons activate immune cells and immune mediators affect neuronal activity and pain transmission. This back-and-forth feedback loop creates a self-sustaining inflammatory environment that can sustain chronic musculoskeletal pain over a long period of time (Grace et al., 2021). Recent studies also indicate that dysbiosis of the gut microbiota can affect neuroimmune signaling via immune modulation and microbial metabolites. The gut–brain axis is therefore a growing field of research to elucidate the mechanisms underlying chronic pain and as a potential target for novel therapeutic strategies (Fiore et al., 2020).

5.3 Genetic, Epigenetic, and Molecular Biomarkers of Pain Vulnerability

Chronic pain susceptibility is partly due to individual differences that include genetic and epigenetic variations. Several genes have been identified, through genome-wide association studies, as being linked to chronic musculoskeletal pain, including genes that are associated with neuronal signaling, inflammation, regulation of extracellular matrix, and stress response. These genetic differences can affect pain sensitivity, recovery ability and treatment efficacy (Suri et al., 2020).

In addition to inherited genetic variation, epigenetic mechanisms offer a crucial link between exposure to the environment and expression of genes. The inflammatory pathways, neuronal plasticity and stress-response genes can be regulated by DNA methylation, histone modifications, and non-coding RNAs without the underlying DNA sequence being changed. Patients with chronic low back pain have been found to have epigenetic changes which indicates that chronic psychological stress and environment may affect pain persistence by reversible molecular changes (Aroke et al., 2020).

Research on fibromyalgia also suggests that epigenetic changes can impact genes that control neurotransmission, immune function, and neuroendocrine processing. These molecular changes can be factors in pain perception, fatigue, cognitive symptoms and emotional vulnerability that distinguish individuals (D'Agnelli et al., 2021). Research also is underway on molecular biomarkers that circulate in the blood, such as inflammatory cytokines, chemokines, microRNAs, neuropeptides, and stress-related hormones, for their potential applications in precision medicine for pain. No single biomarker has yet proven to be sufficiently diagnostic for general use in clinical practice, but molecular markers might be more useful in the context of psychological and clinical evaluation for patient stratification and tailoring treatment. In sustaining chronic pain, there is interplay between pro-inflammatory cytokines, activation of glial cells, neuroimmune communication, gut–brain signalling, genetic susceptibility and epigenetic regulation, as well as molecular biomarkers (see Figure 3). Table 4. Increase in awareness of key immune and molecular mechanisms involved in chronic musculoskeletal pain.Enhanced understanding of important immune and molecular mechanisms in chronic musculoskeletal pain.

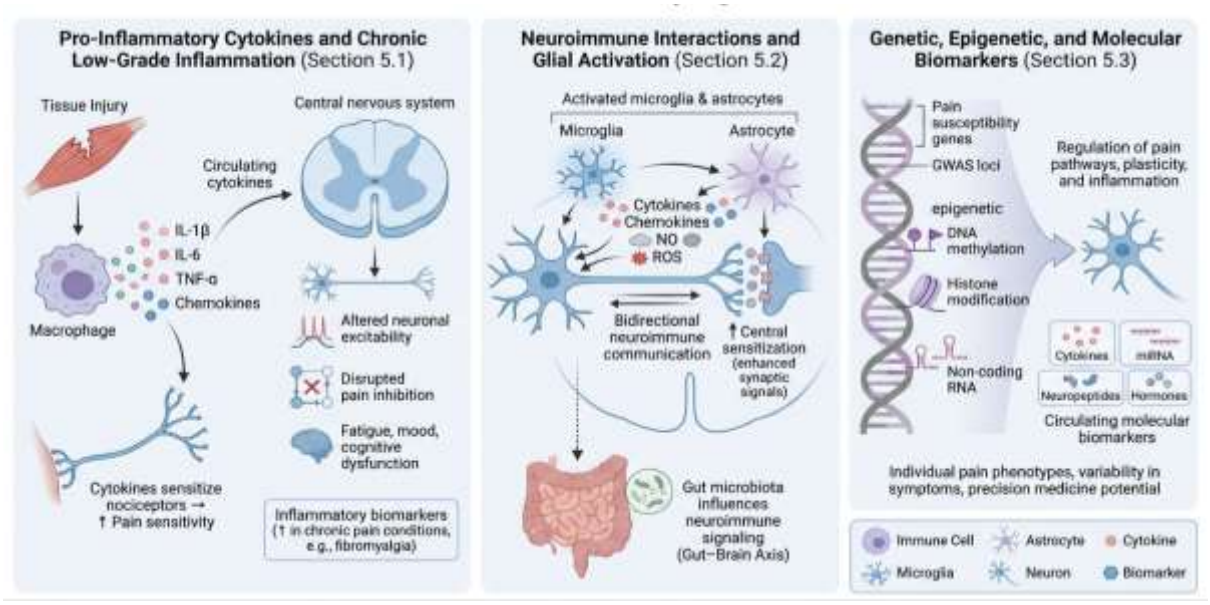

Figure 3. Immune and Molecular Mechanisms Underlying Chronic Musculoskeletal Pain

Table 4. Major Immune and Molecular Mechanisms Associated with Chronic Musculoskeletal Pain

Mechanism	Biological function	Role in chronic pain	Supporting reference
Pro-inflammatory cytokines (IL-1β, IL-6, TNF-α)	Promote inflammatory signaling	Peripheral nociceptor sensitization and persistent pain	Matsuda et al. (2020)
Chronic low-grade inflammation	Sustained immune activation	Enhanced pain sensitivity and fatigue	Sommer et al. (2021)
Microglial activation	Neuroinflammatory response	Initiation of central sensitization	Ji et al. (2020)
Astrocyte activation	Regulation of synaptic signaling	Maintenance of chronic pain	Donnelly et al. (2020)
Neuroimmune communication	Bidirectional neuron–immune signaling	Persistent pain amplification	Grace et al. (2021)
Gut–brain immune interactions	Immune modulation through microbiota	Influence on neuroinflammation and pain	Fiore et al. (2020)
Genetic susceptibility loci	Regulation of neuronal and inflammatory pathways	Individual pain vulnerability	Suri et al. (2020)
Epigenetic modifications	Alteration of gene expression	Long-term regulation of pain mechanisms	Aroke et al. (2020)
Molecular biomarkers	Cytokines, microRNAs, neuropeptides	Potential for precision diagnosis and prognosis	D'Agnelli et al. (2021)

6. Behavioral Mechanisms and Clinical Implications

6.1 Sleep Disturbance, Physical Inactivity, and Maladaptive Behaviors

There is a significant role for behavioural factors in the maintenance and exacerbation of chronic musculoskeletal pain. Patients with chronic pain often report sleep disturbances, such as difficulty falling asleep, frequent awakenings, non-restorative sleep, or shorter sleep. Bad sleeping can lead to heightened sensitivity to pain, lower emotional regulation, delayed immune system recovery, and diminished endogenous pain inhibitory systems (Santos et al., 2023). Bidirectional since pain affects sleep and sleep quality affects pain intensity and fatigue the next day. The day-to-day changes in sleep quality also can impact pain intensity, physical functioning, and psychological distress. Extended lack of sleep over multiple nights can lead to heightened sensitivity to mechanical or movement-related discomfort and decreased tolerance levels (De Baets et al., 2024). Thus, sleep should be viewed as a regular part of a chronic pain assessment and not a secondary symptom. Another important behavior risk factor is the lack of exercise.

Avoidance of movement due to fear of it causing pain and/or re-injury potentially leads patients to adjust their work, play, and social habits to decrease activities. Inactivity over a long period of time can result in muscle weakness, decreased joint mobility, poor cardiovascular fitness, and a reliance on passive modes of care. Fear-avoidance beliefs can thus be a catalyst for a change in an initially protective response to an extended disability (Wertli et al., 2021). Common maladaptive coping behaviors are excessive rest, repeated seeking of reassurance, social isolation, relying on medication and avoiding meaningful activities. These behaviors can feed into feelings of helplessness and decrease self-confidence. In contrast, supporting functional adjustment rather than complete symptom resolution, such as through active coping, gradual activity, and pain acceptance can be supported even if symptoms are not fully resolved (Esteve et al., 2020).

6.2 Integrated Biopsychosocial Assessment and Patient Stratification

Assessment should be broader than imaging findings and pain intensity to reflect the interacting biological, psychological, and behavioral processes that underlie chronic musculoskeletal pain. A biopsychosocial assessment of pain should encompass pain duration, distribution, functional limitations and sleep, emotional distress and catastrophizing, fear avoidance, coping ability, social context, and pain-related medical comorbidities. Stratified care (Lin et al., 2020), in which treatment intensity and content are matched to patient risk profile and dominant pain mechanisms, has been increasingly supported by clinical practice recommendations.

Treatment might be tailored to the site of the painful tissue for nociceptive pain, while multidisciplinary treatment is more appropriate for central sensitization, psychological distress or generalized symptoms. Psychological Screening may aid in recognition of patients who are at higher risk for chronic disability. Depression, anxiety, chronic stress, and diminished resiliency could signal the need for behavioral support as well as physical rehabilitation. There is pre-existing evidence that psychosocial factors play a significant role in the development of acute to chronic pain (Hruschak & Cochran, 2020). Therefore, to stratify patients, factors beyond a single biomarker or a diagnostic label should be included, such as psychological and behavioral indicators.

6.3 Psychological, Pharmacological, and Lifestyle-Based Interventions

A multimodal approach is generally the most effective for the management of chronic musculoskeletal pain. Cognitive behavioral therapy, ACT, Pain education, Relaxation training, and Stress Management can help to decrease catastrophizing and coping skills. These strategies are especially helpful when fear, emotional distress and avoidance behavior are causes of disability. Graded physical activity and exercise still play a major role in treatment as it enhances strength, mobility, confidence and participation. Education, self-management, exercise and tailored treatment are recommended to replace prolonged rest or unnecessary reliance on passive treatment, as recommended in best-practice

guidelines (Lin et al., 2020). Selected patients may benefit from pharmacological therapy in addition to non-pharmacological therapy. Treatment should be personalized based on the diagnosis, co-morbidity, the severity of symptoms and risk of treatment.

The modern way of dealing with chronic musculoskeletal pain focuses on function, medication safety and ongoing reassessment instead of solely relying on analgesics (El-Tallawy et al., 2021). Additional lifestyle modifications that address sleep hygiene, stress reduction, physical activity, nutrition and social participation may also help to decrease pain burden. Rehabilitation should aim for more than symptom reduction; it should seek to bring about restoration of meaningful activity, independence and quality of life. Table 5 summarizes major behaviors and clinical characteristics that influence chronic pain and correlates these with recommended treatment, such as sleep management, graded activity, psychological screening, biopsychosocial assessment, and multimodal treatment.

Table 5. Behavioral Factors and Clinical Management Strategies

Behavioral or clinical factor	Effect on chronic pain	Recommended response	Supporting reference
Sleep disturbance	Increases pain sensitivity and fatigue	Sleep assessment and sleep-hygiene intervention	Santos et al. (2023)
Daily sleep variability	Influences next-day pain and function	Monitoring and individualized sleep management	De Baets et al. (2024)
Fear-driven inactivity	Produces deconditioning and disability	Graded activity and reassurance	Wertli et al. (2021)
Maladaptive coping	Reinforces helplessness and avoidance	Acceptance-based and cognitive interventions	Esteve et al. (2020)
Psychosocial risk factors	Increase the likelihood of pain persistence	Early psychological screening	Hruschak and Cochran (2020)
Multidimensional pain presentation	Limits the value of single-domain care	Biopsychosocial stratification	Lin et al. (2020)
Persistent musculoskeletal pain	Requires combined treatment strategies	Multimodal and individualized management	El-Tallawy et al. (2021)

7. CONCLUSION

Chronic musculoskeletal pain does not only occur as a result of tissue damage or structural problems. It emerges from a complex interplay between psychological vulnerability, impaired pain processing, neuroendocrine disturbances, immune system activation, molecular predisposition and maladaptive behaviors. Depression, anxiety, stress, catastrophizing, fear avoidance, and diminished resilience can increase the perception of pain and lead to decreased functional status. These psychological factors are closely related to hypoactive hypothalamic–pituitary–adrenal axis, abnormal cortisol regulation, activation of the sympathetic system and impaired endogenous pain inhibition. Simultaneously, peripheral and central sensitization may be maintained by activation of pro-inflammatory cytokines, neuroimmune signaling, microglial and astrocytic activation, and chronic low-grade inflammation. Genetic variation and epigenetic modification adds to the variation in pain vulnerability, symptom severity, and treatment response between individual cases. These biological and psychological pathways can be reinforced by behavioral factors like poor sleeping patterns, physical inactivity, avoidance, and poor coping, which can create a vicious cycle of pain and disability. Thus, a biopsychosocial model is important for the understanding and management of chronic musculoskeletal pain. Evaluation of clinical symptoms should include physical findings, psychological screening, sleep assessment, behavioral analysis, and biological markers if applicable. Multimodal interventions combining education, graded physical activity, psychological therapy, stress management, improving sleep and appropriate pharmacological treatment increase the likelihood of long-term improvements. Future studies need to confirm combined neuroendocrine, immune, genetic markers, and behavioral markers for patient stratification and individualized pain management.

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