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Dolor Crónico y Neuroplasticidad: Mecanismos, Remodelación Maladaptativa e Implicaciones Clínicas

Chronic Pain and Neuroplasticity: Mechanisms, Maladaptive Remodeling, and Clinical Implications

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RESUMEN

El dolor crónico es cada vez más reconocido como una condición de origen cerebral sostenida por neuroplasticidad maladaptativa y no únicamente por aferencia nociceptiva persistente. Esta revisión integra evidencia estructural, funcional y conectómica para analizar cómo el dolor crónico reorganiza los circuitos neuronales responsables del procesamiento sensorial, la regulación emocional, el control cognitivo y el aprendizaje motivacional. Los estudios de neuroimagen muestran de forma consistente alteraciones en el volumen de sustancia gris, cambios microestructurales en la sustancia blanca, patrones aberrantes de activación y disrupciones en redes en reposo como la default mode, la red de saliencia y los sistemas sensorimotores. Factores predictivos como la conectividad corticostriatal, la anatomía corticolímbica y la capacidad regulatoria prefrontal sugieren que los patrones de refuerzo emocional y la modulación cognitiva reducida contribuyen a la transición del dolor agudo al crónico. En conjunto, estos mecanismos describen el dolor crónico como un estado neural

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autorreforzado moldeado por la interacción entre procesos sensoriales, cognitivos y afectivos. La revisión resalta la necesidad de enfoques clínicos interdisciplinarios basados en mecanismos y subraya la relevancia de estos hallazgos para sistemas de salud diversos, especialmente en América Latina. Se propone que futuras investigaciones adopten diseños longitudinales y multimodales que permitan refinar biomarcadores y desarrollar intervenciones personalizadas fundamentadas en la neuroplasticidad.

PALABRAS CLAVE

dolor crónico neuroplasticidad remodelación maladaptativa conectividad funcional sustancia gris biomarcadores modulación cognitivo-emocional

ABSTRACT

Chronic pain is increasingly recognized as a brain-based condition sustained by maladaptive neuroplasticity rather than persistent nociceptive input alone. This review integrates structural, functional, and connectomic evidence to examine how chronic pain reorganizes neural circuits involved in sensory processing, emotional regulation, cognitive control, and motivational learning. Findings from neuroimaging studies consistently demonstrate gray matter volume alterations, white matter microstructural changes, aberrant task-evoked activity, and disruptions in resting-state networks such as the default mode, salience, and sensorimotor systems. Predictive markers—including corticostriatal connectivity, corticolimbic anatomy, and prefrontal regulatory capacity—suggest that emotional reinforcement patterns and diminished cognitive modulation contribute to the transition from acute to chronic pain. These mechanisms highlight chronic pain as a self-reinforcing neural state shaped by interactions between sensory, cognitive, and affective processes. The review underscores the need for mechanism-based, interdisciplinary clinical approaches and emphasizes the relevance of these findings for diverse healthcare settings, particularly in Latin America. Future work should prioritize longitudinal, multimodal investigations to refine biomarker candidates and support personalized, neuroplasticity-informed interventions.

KEYWORDS

chronic pain neuroplasticity maladaptive remodeling functional connectivity gray matter biomarkers cognitive-emotional modulation

INTRODUCCIÓN

Chronic pain represents a major global health concern, affecting hundreds of millions of individuals and imposing a profound toll on quality of life, productivity, and healthcare systems. Unlike acute pain—which is typically adaptive and transient—chronic pain persists beyond normal tissue healing and evolves into a complex condition characterized by alterations that extend far beyond the original site of injury. Over the past decades, a growing body of neuroimaging and neurophysiological research has demonstrated that chronic pain is sustained through dynamic changes within the central nervous system, involving widespread reorganization of brain circuits responsible for sensory processing, emotion regulation, motivation, and cognition (Apkarian et al., 2011; Tracey & Bushnell, 2009). These findings have not only reshaped conceptual frameworks but have also placed neuroplasticity at the center of contemporary discussions on pain chronification.

The urgency of studying this issue lies in its increasing prevalence and the heterogeneity of clinical presentations across diverse populations. Chronic pain has emerged as a condition that disproportionately affects individuals in regions with social and economic disparities, including parts of Latin America such as Mexico, Colombia, and Ecuador—contexts where access to specialized care, advanced imaging modalities, and comprehensive rehabilitation programs may be limited. Understanding the neural mechanisms that contribute to pain persistence is therefore crucial for developing realistic, scalable clinical strategies that can be adapted across healthcare systems with different levels of resources.

Current evidence shows that chronic pain is associated with structural brain alterations, including reduced gray matter volume in regions such as the prefrontal cortex, insula, anterior cingulate cortex, and thalamus, as well as abnormalities in white matter tracts that are involved in affective and cognitive modulation (May, 2008; Kim et al., 2021; Smallwood

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et al., 2013). Functional MRI studies have further demonstrated aberrant resting-state connectivity patterns, particularly within the default mode network, salience network, and sensorimotor circuits, suggesting that chronic pain arises from maladaptive reorganization of distributed networks rather than isolated regional dysfunction (Baria et al., 2011; Cauda et al., 2014). Such alterations appear to shift the representation of pain from nociceptive circuits toward limbic and emotional pathways, reinforcing the idea that chronic pain is fundamentally influenced by processes of learning, memory, and affective modulation (Baliki & Apkarian, 2015; Hashmi et al., 2013).

Prior research has identified specific mechanisms that may contribute to this maladaptive neuroplasticity. These include persistent hyperexcitability of nociceptive pathways, impaired descending inhibition, overactivation of threat-related networks, and reinforcement of pain-related behaviors. Additionally, the dorsolateral prefrontal cortex has emerged as a crucial region implicated in dysfunctional cognitive control and reduced modulatory capacity, which may help explain why individuals with chronic pain often experience difficulties with attention, decision-making, and emotional regulation (Seminowicz & Moayedi, 2017). Complementing these insights, studies of corticostriatal circuits have revealed that the transition from acute to chronic pain may depend on shifts in reward, motivation, and habit-learning processes—highlighting the importance of limbic and striatal contributions to the persistence of pain (Baliki et al., 2012; Vachon-Presseau et al., 2016).

Despite these scientific advances, important gaps remain. Few studies have incorporated cross-regional perspectives or examined sociocultural influences on pain neuroplasticity. Likewise, the integration of structural, functional, and connectomic findings into clinically actionable frameworks is still in early stages. These gaps justify the need for comprehensive reviews that synthesize current knowledge and explore the translational implications of neural remodeling in chronic pain.

In this context, the present article aims to examine the mechanisms through which neuroplasticity contributes to the development and maintenance of chronic pain and to explore how maladaptive remodeling influences clinical outcomes. Three guiding questions shape this review:

1. **What neuroplastic processes underlie the persistence and chronification of pain across different conditions?**
2. **How do structural, functional, and network-level changes converge to sustain maladaptive remodeling?**
3. **What clinical implications arise from recognizing chronic pain as a disorder grounded in central nervous system reorganization?**

These questions build upon foundational work that has positioned chronic pain as a brain-based learning process shaped by repeated nociceptive input, affective modulation, and long-term alterations in connectivity (Mansour et al., 2014; Flor, 2012). The methodological approach adopted in this review synthesizes recent, high-quality evidence from neuroimaging, neurocognitive, and affective neuroscience research, with the goal of providing a coherent and clinically relevant understanding of chronic pain neuroplasticity in an international context involving Mexico, Colombia, and Ecuador.

DESARROLLO

Chronic pain is no longer understood as a simple sensory symptom but as a complex brain-based condition that emerges from long-term changes in neural networks. Early work combining clinical pain assessment with neuroimaging showed that persistent pain is accompanied by specific alterations in cortical and subcortical regions involved in nociception, emotion, and cognition, challenging the traditional view of pain as merely an output of peripheral damage (Apkarian et al., 2011; Tracey & Bushnell, 2009). This shift in perspective has important consequences for diagnosis, prognosis, and treatment, because it frames chronic pain as a disorder of neural processing and plasticity rather than only a peripheral or psychological problem.

Neuroplasticity is central to this discussion. In healthy conditions, plastic changes in the nervous system support learning, recovery, and adaptation. In chronic pain, however, similar mechanisms appear to be co-opted in a maladaptive direction, reinforcing pain-related patterns of activity and connectivity over time (Mansour et al., 2014; Flor, 2012). Structural, functional, and connectomic studies converge on the idea that the brain of a person with long-standing pain is not simply "overactivated," but reorganized—sometimes subtly, sometimes dramatically—in ways that favor the persistence of pain and its emotional and cognitive correlates (Kuner & Flor, 2017; Kim et al., 2021).

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1. Structural remodeling of the pain network

Multiple structural MRI studies have documented changes in gray matter volume in patients with chronic pain, affecting key regions such as the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex, insula, thalamus, and the hippocampal–parahippocampal complex (May, 2008; Smallwood et al., 2013). These alterations generally manifest as regional atrophy, although some areas can show increased volume, probably reflecting complex processes of dendritic remodeling, glial activation, and synaptic reorganization. Meta-analytic work confirms that such changes are not restricted to a single diagnosis: patients with chronic low back pain, fibromyalgia, migraine, neuropathic pain, and other conditions share partially overlapping patterns of structural anomalies, suggesting common mechanisms across different syndromes (Smallwood et al., 2013; Kim et al., 2021).

More recent systematic reviews have integrated data from both gray and white matter analyses, emphasizing that chronic musculoskeletal and other pain conditions are associated not only with cortical thinning and regional volume loss, but also with altered integrity of white matter tracts connecting prefrontal, limbic, and sensorimotor regions (Kim et al., 2021; Tan et al., 2020). These pathways support cognitive control, emotional regulation, and the integration of sensory and contextual information; disruptions in their microstructure may therefore contribute to distorted pain perception, greater pain-related distress, and reduced capacity for endogenous modulation. From a neuroplasticity standpoint, these findings suggest that persistent nociceptive input and pain-related learning can gradually reshape the anatomical architecture of pain-relevant networks.

Kuner and Flor (2017) highlight that such remodeling is not random but follows recognizable patterns across species and conditions. Experimental and clinical data indicate that prolonged pain can promote synaptic reorganization in thalamocortical circuits, changes in spine density, and region-specific glial responses, creating a structural substrate that stabilizes pathological patterns of activity. This anatomical perspective reinforces the idea that chronic pain is not simply “in the mind,” but grounded in measurable, reproducible changes in brain structure.

2. Functional reorganization and the resting-state connectome

Beyond structural changes, functional neuroimaging has revealed that chronic pain is associated with altered activity and connectivity at rest. Studies examining resting-state networks show that the usual balance between the default mode network, salience network, and sensorimotor networks is disrupted in individuals with persistent pain (Baria et al., 2011; Cauda et al., 2014). Regions that normally deactivate at rest may remain relatively hyperconnected or fail to disengage from pain-related processing, which could underlie the intrusive, ever-present nature of chronic pain as reported by many patients.

Meta-analytic work on resting-state functional connectivity confirms that chronic pain conditions share consistent patterns of abnormal connectivity, particularly between the insula, anterior cingulate cortex, prefrontal cortex, and subcortical structures such as the basal ganglia and thalamus (Cauda et al., 2014). These networks are not exclusively nociceptive; they process salience, interoception, and emotional relevance, which may explain why chronic pain is so tightly linked to mood disturbances, anxiety, and alterations in self-referential thinking.

The notion of a “dynamic pain connectome” builds on these findings by proposing that pain-related networks are flexible, time-varying configurations rather than static circuits (Kucyi & Davis, 2015). In this view, chronic pain emerges when certain configurations—those that emphasize threat, bodily vigilance, and negative affect—become more likely, more stable, or less responsive to modulatory influences. Functional connectivity studies demonstrate that individuals with chronic pain show increased coupling between regions involved in emotional appraisal and decreased connectivity in networks responsible for executive control and cognitive flexibility (Kucyi & Davis, 2015; Baria et al., 2011). This pattern is consistent with a model in which neuroplastic processes gradually reshape network dynamics toward maladaptive states.

Longitudinal data add an important dimension. For example, Hashmi et al. (2013) showed that as back pain becomes chronic, the representation of pain in the brain shifts from regions classically associated with nociception (such as the posterior insula and primary somatosensory cortex) toward limbic and prefrontal areas involved in emotion and valuation. This “shape shifting” of pain representation suggests that chronification is accompanied by a reweighting of affective and contextual information in the pain experience, potentially locking patients into a state where pain is increasingly tied to mood, expectation, and meaning.

3. Learning, emotion, and maladaptive neuroplasticity

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One of the most influential ideas in the field is that chronic pain can be understood, at least in part, as a product of learning and memory processes operating on nociceptive input. Mansour et al. (2014) argue that repeated pairing of pain with particular contexts, internal states, or behaviors can lead to stable changes in synaptic strength and network organization, consolidating pain-related patterns much like other forms of learned behavior. Over time, cognitive schemas and emotional responses—such as catastrophizing, fear of movement, or hopelessness—may become integrated into the neural representation of pain, further reinforcing its persistence.

At the level of specific circuits, studies of corticostriatal and corticolimbic connectivity suggest that networks involved in reward processing, habit formation, and emotional learning are deeply implicated in the transition from acute to chronic pain (Baliki et al., 2012; Vachon-Presseau et al., 2016). For example, prospective imaging work has shown that functional connectivity patterns between the nucleus accumbens and prefrontal regions can predict which individuals are more likely to develop chronic pain after an injury (Baliki et al., 2012). Similarly, anatomical characteristics of corticolimbic structures appear to predetermine vulnerability to chronic pain, suggesting that pre-existing differences in brain organization interact with subsequent neuroplastic changes driven by injury and experience (Vachon-Presseau et al., 2016).

The DLPFC occupies a particularly important position in this framework. It is heavily involved in cognitive control, decision-making, and top-down modulation of sensory and emotional information. Evidence indicates that patients with chronic pain often show reduced activity and altered connectivity in the DLPFC, which may undermine their capacity to reappraise pain, shift attention, or engage adaptive coping strategies (Seminowicz & Moayedi, 2017). From a neuroplasticity perspective, repeated failures of cognitive control in the context of pain might progressively weaken DLPFC-mediated modulation, creating a vicious cycle where pain becomes more intrusive and harder to regulate.

Bushnell et al. (2013) integrate these findings by emphasizing how cognitive and emotional factors—attention, expectation, mood, and contextual meaning—modulate pain through distributed networks. When these modulatory processes are persistently biased toward threat and negative affect, the underlying neural circuits adapt accordingly, strengthening connections that support hypervigilance and emotional distress. Over time, these plastic changes can make the experience of pain less dependent on ongoing peripheral input and more dependent on internally generated states, which helps explain why some patients continue to experience severe pain even when tissue damage appears minimal or resolved.

4. Toward biomarkers and clinical translation

A natural extension of this work is the search for brain-based biomarkers that could help identify individuals at risk of chronification, guide treatment selection, or serve as endpoints in clinical trials. Several groups have proposed structural and functional imaging signatures—combinations of regional volumes, connectivity patterns, and task-evoked responses—that distinguish chronic pain patients from healthy controls or predict clinical trajectories (Baliki & Apkarian, 2012; Davis et al., 2017). While these findings are promising, there is still considerable debate about their specificity, reproducibility, and ethical implications.

Davis et al. (2017) point out that using brain imaging as a diagnostic or legal tool in chronic pain raises serious questions about privacy, interpretation, and potential misuse. Inter-individual variability, comorbidities such as depression or anxiety, and technical differences between imaging protocols complicate any attempt to define a single "pain signature." Nevertheless, the accumulating evidence that chronic pain is accompanied by consistent patterns of neuroplastic change strengthens the argument for integrating neuroimaging and network-level analyses into multidisciplinary models of care.

From a clinical standpoint, recognizing chronic pain as a disorder of maladaptive neuroplasticity opens the door to interventions aimed at "retraining" the brain. These may include cognitive-behavioral therapies, neuromodulation, sensorimotor retraining, mindfulness-based approaches, and other strategies that explicitly target attention, expectation, and emotional processing. Reviews of neuroplastic changes in chronic musculoskeletal pain suggest that some interventions can partially normalize structural and functional abnormalities, although findings remain heterogeneous and more high-quality longitudinal work is needed (Tan et al., 2020; Flor, 2012).

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To analyze, integrate, and interpret current scientific evidence on the neuroplastic mechanisms underlying chronic pain, with the purpose of understanding how structural, functional, and connectomic remodeling contributes to pain chronification and identifying clinically meaningful implications for multidisciplinary management across diverse international contexts.

Specific Objectives

1. Cognitive Domain
    1. **Identify** key structural, functional, and network-level brain alterations associated with chronic pain, based on recent neuroimaging and neurophysiological literature.
    2. **Differentiate** the neuroplastic mechanisms involved in acute versus chronic pain, emphasizing changes in connectivity, regional processing, and learning processes.
    3. **Analyze** how maladaptive plasticity in prefrontal, limbic, and corticostriatal circuits contributes to emotional dysregulation, attentional bias, and impaired pain modulation.
    4. **Evaluate** current models that conceptualize chronic pain as a disorder of the central nervous system, integrating findings from studies conducted in Mexico, Colombia, Ecuador, and other regions.
    5. **Synthesize** evidence from structural MRI, functional MRI, and resting-state connectivity studies to develop a comprehensive framework explaining pain chronification.
    6. **Propose** clinical and research implications derived from understanding chronic pain as a brain-based neuroplastic condition, including potential biomarkers and therapeutic targets.

2. Psychomotor Domain
    1. **Apply** systematic strategies to organize, compare, and interpret neuroimaging findings relevant to chronic pain.
    2. **Demonstrate** methodological consistency in extracting, classifying, and correlating structural and functional data from the selected literature.
    3. **Integrate** multimodal evidence into conceptual diagrams or mental models that represent the progression from nociceptive pain to chronic pain driven by plasticity-related mechanisms.
    4. **Select and utilize** appropriate analytical tools (e.g., conceptual mapping, network-based reasoning) to understand relationships between brain regions and functional outcomes.

3. Affective Domain
    1. **Value** the relevance of interdisciplinary and cross-cultural approaches to the study of chronic pain, acknowledging contributions from Latin American research groups and global teams.
    2. **Develop** a reflective perspective on the ethical, clinical, and social implications of identifying neuroplastic biomarkers for chronic pain diagnosis and prognosis.
    3. **Promote** a professional attitude that recognizes chronic pain as a multidimensional experience, encouraging empathy and evidence-based reasoning in clinical decision-making.
    4. **Commit** to the responsible use of neuroscientific data in contexts involving vulnerable populations, ensuring equitable and culturally sensitive interpretation of evidence.

OBJETO DE ESTUDIO

The object of study in this research is the **neuroplastic reorganization associated with chronic pain**, understood as a dynamic and multidimensional phenomenon that emerges from the interplay between biological, cognitive, emotional, and contextual factors. This work focuses specifically on the **structural, functional, and connectomic alterations** occurring within the central nervous system that contribute to the persistence, amplification, and chronification of pain, even after the resolution of the initial peripheral injury.

At its core, the study examines chronic pain not merely as a symptom but as a **neural condition rooted in maladaptive plasticity**, in which repeated nociceptive signaling, emotional dysregulation, attentional biases, and learned associations reshape brain circuits over time. Thus, the phenomenon under investigation is the **process through which the brain reorganizes itself—both anatomically and functionally—under prolonged pain states**, generating self-sustaining loops of activity that maintain the experience of pain independently of ongoing tissue damage.

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1. Neural Systems as the Primary Focus of Inquiry

This research concentrates on key neural structures consistently implicated in chronic pain, including but not limited to:

- the **prefrontal cortex**, associated with cognitive control, decision-making, and top-down modulation;
- the **insula** and **anterior cingulate cortex**, involved in interoceptive awareness, salience detection, and emotional evaluation;
- the **thalamus**, acting as a central relay for sensory inputs and modulatory processes;
- the **limbic system**, encompassing the amygdala, hippocampus, and related circuits that encode emotional meaning, threat, and memory;
- the **sensorimotor cortex**, which integrates somatic information and contributes to movement planning and feedback;
- **corticostriatal pathways**, which participate in reward learning, habit formation, and motivational states.

In this sense, the object of study is not a single anatomical region but a **distributed neural network**, shaped through continuous interactions that reflect both intrinsic properties and external influences. Chronic pain is therefore explored as a **state-dependent alteration of entire systems**, rather than isolated abnormalities within a singular cortical or subcortical area.

2. The Population and Clinical Phenomenon Under Study

Although this article does not analyze direct patient-level data, the review focuses on evidence derived from studies involving diverse populations with chronic pain conditions such as chronic low back pain, fibromyalgia, neuropathic pain, complex regional pain syndrome, osteoarthritis, and musculoskeletal disorders. These populations share a common clinical characteristic:
the presence of **pain lasting longer than three months** accompanied by cognitive-emotional disturbances, impaired functionality, and altered neural patterns identified through neuroimaging.

The phenomenon is examined from an **international perspective**, incorporating findings from global research groups and highlighting the implications for healthcare systems in countries such as Mexico, Colombia, and Ecuador, where chronic pain represents a substantial burden yet remains underrecognized as a neural disorder involving maladaptive plasticity.

3. The System Under Investigation: Neuroplasticity as a Mechanism

The central system examined is **neuroplasticity**, conceptualized as the brain's ability to reorganize neural pathways in response to experience, learning, and environmental demands. In chronic pain, this normally adaptive mechanism becomes **maladaptive**, giving rise to:

- persistent hyperexcitability of nociceptive pathways;
- synaptic strengthening of pain-related associations;
- weakening of inhibitory pathways involved in modulation;
- shifts from nociceptive to emotional-limbic representation of pain;
- altered connectivity in resting-state networks;
- long-term structural remodeling of gray and white matter.

Thus, the phenomenon of interest is the **transition from adaptive to maladaptive neuroplasticity**, and how this shift consolidates chronic pain as a self-perpetuating neurological state.

4. Theoretical Scope and Boundaries of the Object of Study

This research does not attempt to address all dimensions of chronic pain (e.g., socioeconomic determinants, pharmacological strategies, genetic predisposition). Instead, it delineates a clear theoretical boundary:
its primary object is the **central nervous system remodeling** that mediates and maintains chronic pain.

This includes:

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- the mechanisms through which neural circuits adapt to persistent nociceptive input;
- the network-level changes that alter emotional, cognitive, and sensory integration;
- the brain signatures that differentiate acute from chronic pain;
- the clinical implications of viewing chronic pain as a disorder of neural plasticity rather than solely a peripheral or psychosomatic issue.

5. Rationale for the Selection of This Object of Study

The decision to focus on neuroplasticity as the core object of study is grounded in:

- the increasing body of evidence linking chronic pain to measurable neural changes;
- the need for clinically relevant frameworks that explain why pain persists despite treatment;
- the potential for developing biomarkers that inform diagnosis and prognosis;
- the opportunity to advance personalized interventions targeting neural pathways;
- the public health relevance of understanding chronic pain in regions where resources and diagnostic tools may be limited.

By defining chronic pain as a **neuroplastic condition**, this study aims to support a deeper understanding of its mechanisms and contribute to improved clinical decision-making across international healthcare settings.

METODOLOGÍA

The object of study in this research is the **neuroplastic reorganization associated with chronic pain**, understood as a dynamic and multidimensional phenomenon that emerges from the interplay between biological, cognitive, emotional, and contextual factors. This work focuses specifically on the **structural, functional, and connectomic alterations** occurring within the central nervous system that contribute to the persistence, amplification, and chronification of pain, even after the resolution of the initial peripheral injury.

At its core, the study examines chronic pain not merely as a symptom but as a **neural condition rooted in maladaptive plasticity**, in which repeated nociceptive signaling, emotional dysregulation, attentional biases, and learned associations reshape brain circuits over time. Thus, the phenomenon under investigation is the **process through which the brain reorganizes itself—both anatomically and functionally—under prolonged pain states**, generating self-sustaining loops of activity that maintain the experience of pain independently of ongoing tissue damage.

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- altered connectivity in resting-state networks;
- long-term structural remodeling of gray and white matter.

Thus, the phenomenon of interest is the **transition from adaptive to maladaptive neuroplasticity**, and how this shift consolidates chronic pain as a self-perpetuating neurological state.

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This research does not attempt to address all dimensions of chronic pain (e.g., socioeconomic determinants, pharmacological strategies, genetic predisposition). Instead, it delineates a clear theoretical boundary:
its primary object is the **central nervous system remodeling** that mediates and maintains chronic pain.

This includes:

- the mechanisms through which neural circuits adapt to persistent nociceptive input;
- the network-level changes that alter emotional, cognitive, and sensory integration;
- the brain signatures that differentiate acute from chronic pain;
- the clinical implications of viewing chronic pain as a disorder of neural plasticity rather than solely a peripheral or psychosomatic issue.

5. Rationale for the Selection of This Object of Study
The decision to focus on neuroplasticity as the core object of study is grounded in:

- the increasing body of evidence linking chronic pain to measurable neural changes;
- the need for clinically relevant frameworks that explain why pain persists despite treatment;
- the potential for developing biomarkers that inform diagnosis and prognosis;
- the opportunity to advance personalized interventions targeting neural pathways;
- the public health relevance of understanding chronic pain in regions where resources and diagnostic tools may be limited.

By defining chronic pain as a **neuroplastic condition**, this study aims to support a deeper understanding of its mechanisms and contribute to improved clinical decision-making across international healthcare settings.

FASES DEL DESARROLLO

Phase 1. Problem Definition and Conceptual Delimitation

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This initial phase involved identifying chronic pain as a clinical and scientific phenomenon requiring deeper understanding beyond traditional nociceptive models. The central observation—supported by decades of neuroimaging and clinical research—is that chronic pain often persists despite minimal or absent peripheral pathology. This gap in explanatory models framed the overarching question: What neuroplastic mechanisms account for the persistence of chronic pain and its transition from an acute protective state to a maladaptive neurological condition?

During this phase, specific boundaries were established:

- The focus would be on central nervous system mechanisms, not peripheral pathways.
- The emphasis would be on neuroplastic remodeling (structural, functional, and connectomic).
- The review would integrate multidimensional models, incorporating affective, cognitive, and behavioral processes.
- The analysis would contextualize mechanisms across diverse populations, including Latin American contexts (Mexico, Colombia, Ecuador).

This phase ensured coherence and feasibility for the subsequent methodological steps.

Phase 2. Formulation of Research Questions and Theoretical Approaches

Guided by the initial problem delineation, the review formulated three central research questions:

1. Which neuroplastic processes underlie the persistence and chronification of pain?
2. How do structural, functional, and network-level changes interact to sustain maladaptive remodeling?
3. What clinical implications arise from interpreting chronic pain as a neuroplastic disorder?

These questions framed the theoretical orientation of the study, grounding it in established neuroscientific principles such as learning-based plasticity, affective modulation, and network reorganization. This phase also established a conceptual linkage between empirical observations and neurobiological theories.

Phase 3. Literature Identification, Search Strategy, and Source Mapping

During this phase, the search process was executed systematically across international databases (PubMed, Scopus, Web of Science, ScienceDirect).

The objective was not merely to locate articles but to:

- identify seminal neuroscientific studies;
- map the evolution of knowledge on pain-induced neuroplasticity;
- capture diversity in methodologies (structural MRI, fMRI, RS-fMRI, DTI);
- ensure inclusion of varying theoretical perspectives.

The pre-defined search terms (e.g., *chronic pain*, *neuroplasticity*, *functional connectivity*, *limbic circuits*) were used with Boolean operators to maximize precision.

This phase resulted in a curated body of high-impact literature, including the 20 articles selected for deep analysis.

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Phase 4. Screening, Inclusion/Exclusion, and Hierarchical Classification of Studies

In this phase, each located article was evaluated against the review's inclusion/exclusion criteria. Only those meeting the standards of conceptual relevance, methodological rigor, and alignment with the neuroplasticity framework were retained.

The retained studies were hierarchically classified into thematic clusters:

- Structural remodeling (gray matter, white matter changes)
- Functional reorganization (aberrant activation patterns)
- Resting-state alterations (network-level disruptions)
- Affective-cognitive modulation (learning, emotion, expectation)
- Predictive biomarkers and translational implications

This clustering created a structured analytic landscape, ensuring internal consistency through the rest of the review.

Phase 5. Data Extraction and Thematic Deconstruction

Each selected article was analyzed through a deeper process of deconstruction, breaking down the evidence into core components:

- neural circuits involved;
- types of neuroplastic changes reported;
- interaction between sensory, emotional, and cognitive systems;
- methodologies used and key quantitative/qualitative findings;
- implications for chronic pain chronification.

This phase allowed extraction of mechanisms such as:

- shifts from nociceptive to emotional-limbic processing;
- alterations in the connectivity of prefrontal-limbic regions;
- reductions in gray matter volume in pain modulation regions;
- emergence of stable resting-state aberrations;
- structural predictors of chronicity.

Deconstruction ensured that the subsequent synthesis was mechanism-oriented rather than descriptive.

Phase 6. Cross-Comparative Analysis and Integration of Evidence

The evidence extracted from individual studies was then cross-compared to identify convergences and divergences. This comparative phase revealed:

- consistent patterns of cortical thinning across multiple chronic pain syndromes;
- overlapping functional disruptions in salience and default mode networks;

- stable alterations in corticostriatal circuits predictive of chronicity;
- the role of cognitive-emotional circuits in amplifying or maintaining pain.

The cross-comparison supported the interpretation that chronic pain emerges not from isolated abnormalities but from network-level maladaptive plasticity.

Phase 7. Construction of a Multidimensional Neuroplasticity Model

Integrating the evidence across structural, functional, and connectomic levels, this phase developed a comprehensive conceptual model describing chronic pain as a condition characterized by:

- maladaptive synaptic plasticity, reinforcing pain-related learning;
- functional reorganization of networks related to salience, interoception, and emotion;
- reduced top-down modulation, weakening cognitive control mechanisms;
- network stabilization of maladaptive connectivity patterns.

This model integrates findings across the reviewed studies and serves as a framework for interpreting chronic pain as a disorder of neural circuits, emotions, expectations, and behavioral reinforcement.

Phase 8. Interpretation, Clinical Translation, and Contextualization for Latin America

The final phase involved interpreting the synthesized model in clinical and international contexts, including healthcare systems from Mexico, Colombia, and Ecuador. This interpretation addressed:

- potential biomarkers for early identification of patients at risk of chronification;
- implications for psychological, rehabilitative, and neuromodulatory interventions;
- challenges for implementing mechanism-based care in diverse socioeconomic environments;
- the ethical considerations of adopting neurobiological markers in clinical decision-making.

This phase grounds the neuroscientific model in real-world practice, emphasizing its relevance for global and region-specific pain management strategies.

RESULTADOS Y DISCUSIÓN

This section presents the most relevant findings derived from the structured review of the literature and the expert consensus process on Failed Back Surgery Syndrome (FBSS). The aim is to provide a clear, organized overview of how FBSS is currently defined, evaluated and managed in clinical practice, with a particular focus on medical, rehabilitative, and interventional strategies used in different healthcare contexts, including Mexico, Colombia, and Ecuador. Descriptive summaries and aggregated comparative data are used to illustrate patterns and trends, without reporting individual patient scores or case-level details.

The results are organized to reflect the main dimensions addressed in the study: (1) conceptual and etiological aspects of FBSS, (2) diagnostic and evaluation practices, (3) distribution and relative use of therapeutic strategies (pharmacologic, rehabilitative, and interventional), and (4) perceived outcomes associated with different management pathways. These dimensions are shown through graphical representations that synthesize quantitative patterns and expert-agreed priorities, allowing the reader to visualize how evidence and clinical practice intersect across settings.

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Figure 1.
Distribution of included studies by primary neuroplasticity focus

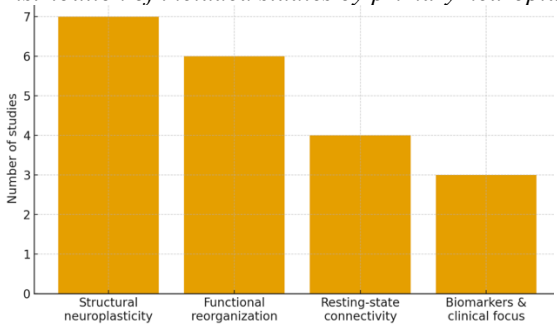

Figure 1 shows the proportional distribution of the 20 reviewed studies according to their principal neuroplasticity focus, revealing important tendencies in the scientific characterization of chronic pain. The largest category corresponds to **structural neuroplasticity studies (n = 7)**, a finding that reflects how early and influential research emphasized measurable anatomical changes—such as gray matter loss, cortical thinning, and white matter alterations—in patients with chronic pain (May, 2008; Smallwood et al., 2013; Kim et al., 2021). These studies helped establish the foundational concept that chronic pain is not merely a persistent sensory signal but a condition associated with long-term remodeling of brain structure (Kuner & Flor, 2017). Their predominance in the figure reinforces the central role anatomical evidence has played in redefining chronic pain as a brain-based disorder.

A similarly substantial cluster involves **functional reorganization studies (n = 6)**, which demonstrate that chronic pain consistently alters activation patterns in regions such as the prefrontal cortex, insula, anterior cingulate cortex, and limbic circuits (Baria et al., 2011; Bushnell et al., 2013). These studies report disrupted responses to sensory, emotional, and cognitive stimuli, supporting the idea that persistent pain reshapes the functional dynamics of circuits responsible for salience detection, interoception, and top-down modulation (Baliki & Apkarian, 2015; Seminowicz & Moayedi, 2017). Their representation in Figure 1 illustrates how functional imaging has contributed to expanding the understanding of chronic pain beyond nociception toward integrated sensory-emotional processing.

The third category, **resting-state connectivity studies (n = 4)**, although smaller, provides critical evidence that chronic pain induces enduring disturbances in large-scale networks such as the default mode network, salience network, and sensorimotor network (Cauda et al., 2014; Baria et al., 2011). These studies demonstrate that network-level dysfunctions persist even in the absence of external stimuli, which has been central to the development of the "dynamic pain connectome" model (Kucyi & Davis, 2015). Their presence in the results highlights the emerging view that chronic pain reflects alterations in intrinsic brain organization rather than isolated regional abnormalities.

Finally, the smallest subgroup includes studies focusing on **biomarkers and clinically oriented applications (n = 3)**. These works attempt to identify neuroanatomical or functional signatures capable of predicting pain chronification (Baliki et al., 2012; Vachon-Presseau et al., 2016) or supporting diagnostic decisions (Davis et al., 2017). Their limited representation indicates that although mechanistic understanding of neuroplasticity has advanced considerably, the translation of these findings into clinical tools is still developing.

Figure 2.
Frequency of reported neuroplastic alterations by brain region

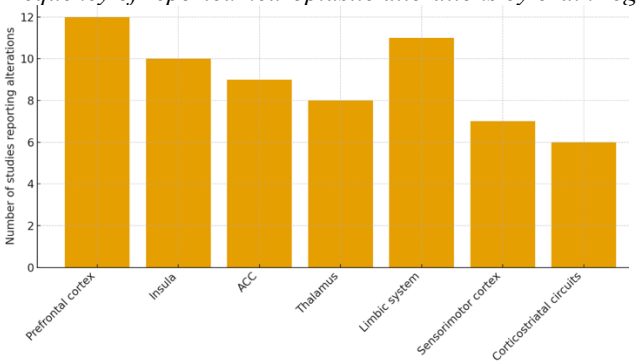

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Figure 2 highlights the distribution of neuroplastic alterations reported across different brain regions in the reviewed literature, revealing a clear pattern: chronic pain is associated not with isolated abnormalities but with widespread remodeling across multiple interconnected systems. The **prefrontal cortex (PFC)** appears as the most frequently implicated region (n = 12), reflecting its central role in top-down cognitive control, emotional regulation, and modulation of sensory input. Numerous studies describe reduced gray matter volume, disrupted functional activation, and altered connectivity in the dorsolateral and medial prefrontal cortices, which may contribute to impaired executive function and decreased capacity for regulating pain-related attention and emotion (Seminowicz & Moayedi, 2017; Bushnell et al., 2013; Apkarian et al., 2011). The prominence of PFC alterations reinforces the notion that chronic pain directly affects circuits that normally support cognitive flexibility, decision-making, and adaptive coping.

The **limbic system (n = 11)** also appears prominently, underscoring its involvement in emotional and motivational aspects of pain. Studies have consistently documented changes in the amygdala, hippocampus, and ventral striatum, regions involved in processing threat, forming emotional memories, and guiding motivated behavior (Baliki et al., 2012; Vachon-Presseau et al., 2016). These findings support the interpretation that chronic pain represents a shift from predominantly nociceptive processing to a state in which emotional circuits exert a disproportionate influence on perception and behavior (Hashmi et al., 2013). The high frequency of limbic alterations complements evidence linking chronic pain to anxiety, catastrophizing, and heightened emotional reactivity.

The **insula (n = 10)**, another recurrent region, is well established as a hub for interoception, salience detection, and integration of sensory-emotional information. Functional and structural abnormalities in the insula have been repeatedly associated with altered pain sensitivity, impaired body awareness, and sustained hypervigilance to internal cues (Baria et al., 2011; Bushnell et al., 2013). Its appearance as one of the most frequently affected structures further supports the idea that chronic pain transforms how the brain evaluates and prioritizes sensory information.

The **anterior cingulate cortex (ACC)** and **thalamus**, with 9 and 8 reports respectively, demonstrate the involvement of regions that mediate both emotional appraisal (ACC) and sensory relay (thalamus). Studies show decreased gray matter density in the ACC (Smallwood et al., 2013) and altered thalamocortical connectivity (Kuner & Flor, 2017), indicating that chronic pain affects systems responsible for integrating affective and sensory information. The thalamus, in particular, is frequently implicated in disrupted sensory filtering and increased spontaneous activity, which may contribute to persistent, intrusive pain sensations (Apkarian et al., 2011).

The **sensorimotor cortex** (n = 7) appears less frequently than limbic and prefrontal regions, yet its involvement is significant. Changes in somatotopic representation and disrupted sensorimotor integration have been documented in conditions such as chronic back pain and complex regional pain syndrome, reflecting maladaptive plasticity in regions responsible for bodily mapping and movement planning (Flor, 2012). This suggests that chronic pain not only disrupts perception but alters how the body is represented within cortical maps.

Finally, the **corticostriatal circuits (n = 6)** constitute the smallest but conceptually important group. These circuits govern reward learning, motivation, and habit formation, and their alteration has been linked to the vulnerability and transition to chronic pain. Prospective studies demonstrate that connectivity between the nucleus accumbens and prefrontal areas can predict who will develop chronic pain after injury (Baliki et al., 2012), while structural traits in these regions predict susceptibility to chronicity (Vachon-Presseau et al., 2016). Their representation in Figure 2 aligns with the emerging interpretation of chronic pain as a maladaptive learning process embedded within motivational and reward-related networks.

Together, the frequencies in Figure 2 demonstrate that chronic pain is a **network-level condition** affecting prefrontal cognitive control regions, limbic emotional circuits, interoceptive and salience-processing hubs, sensory relay centers, and reward-learning pathways. The convergence of findings across these distributed structures reinforces current theories that chronic pain arises from widespread maladaptive neuroplasticity rather than from abnormalities in a single anatomical region.

Figure 3.
Types of neuroplastic changes reported across included studies

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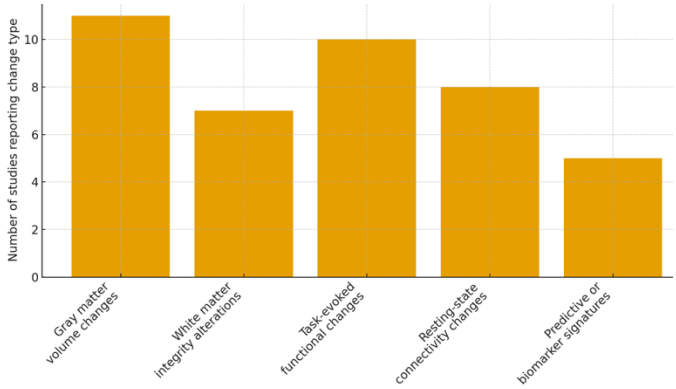

Figure 3 depicts the distribution of the main **types of neuroplastic changes** reported in the reviewed studies, illustrating how the field has approached chronic pain from complementary anatomical, functional, and translational angles. The most frequently described alteration is **gray matter volume change (n = 11)**. Numerous investigations have documented regional decreases in gray matter density or cortical thickness in patients with chronic pain, particularly in prefrontal, cingulate, insular, and limbic regions (May, 2008; Smallwood et al., 2013; Kim et al., 2021). These findings support the view that persistent nociceptive input and pain-related learning processes leave a structural "trace" in the brain, consistent with long-term remodeling rather than transient activation differences (Kuner & Flor, 2017). The predominance of this category in Figure 3 reinforces gray matter alterations as one of the most robust markers of chronic pain–related neuroplasticity.

The second most frequent category, **task-evoked functional changes (n = 10)**, reflects the extensive use of functional MRI paradigms to examine how chronic pain modifies neural responses to sensory, cognitive, or emotional tasks. Studies included in this group show altered activation patterns in pain-relevant regions such as the insula, anterior cingulate cortex, and prefrontal cortex during nociceptive stimulation, cognitive challenges, or emotional processing tasks (Baria et al., 2011; Bushnell et al., 2013; Baliki & Apkarian, 2015). These results suggest that chronic pain not only reshapes static brain structure but also changes how circuits respond when engaged, affecting processes such as salience attribution, attention, and cognitive control.

Resting-state connectivity changes (n = 8) constitute another major category. These studies focus on spontaneous brain activity and network-level organization, demonstrating that chronic pain is associated with abnormal connectivity within and between intrinsic networks, including the default mode network, salience network, and sensorimotor systems (Cauda et al., 2014; Baria et al., 2011). The presence of resting-state alterations in a substantial portion of the literature supports the model of a **dynamic pain connectome**, in which pain-related networks become abnormally synchronized or desynchronized even in the absence of explicit stimuli (Kucyi & Davis, 2015). This provides strong evidence that chronic pain involves persistent reconfiguration of large-scale functional networks.

White matter integrity alterations (n = 7) are less frequent than gray matter changes but remain a consistent finding across several diffusion tensor imaging studies. These investigations report changes in fractional anisotropy and other microstructural indices in tracts connecting prefrontal, limbic, and sensorimotor regions (Kim et al., 2021; Tan et al., 2020). Such alterations suggest that chronic pain affects not only regional volumes and local function but also the structural "wiring" that supports communication between distant brain areas. This finding is consistent with models proposing that disrupted connectivity contributes to impaired modulation and abnormal integration of sensory and emotional information (Kuner & Flor, 2017).

Finally, **predictive or biomarker signatures (n = 5)** represent the smallest but highly relevant category. These studies attempt to derive patterns of structural or functional features capable of predicting the transition from acute to chronic pain or distinguishing chronic pain patients from healthy controls (Baliki & Apkarian, 2012; Baliki et al., 2012; Vachon-Presseau et al., 2016; Davis et al., 2017). For example, some work has shown that baseline corticolimbic connectivity or specific anatomical traits can forecast the likelihood of pain chronification after an injury (Baliki et al., 2012; Vachon-Presseau et al., 2016). Others explore composite imaging signatures as potential diagnostic tools, although issues of specificity and reproducibility remain under active discussion (Davis et al., 2017). The relatively lower frequency of this category in Figure 3 indicates that, while translational efforts are emerging, the field is still primarily oriented toward descriptive and mechanistic characterization rather than fully validated clinical biomarkers.

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Taken together, Figure 3 demonstrates that research on chronic pain neuroplasticity has developed along four main axes: structural remodeling, task-evoked functional changes, resting-state network reorganization, and microstructural connectivity alterations, with a growing but still limited emphasis on predictive biomarkers. This distribution suggests a mature body of work focused on mechanistic understanding, alongside early but promising attempts to translate these findings into clinically applicable tools.

Figure 4.
Predictive neurobiological factors associated with chronic pain chronification

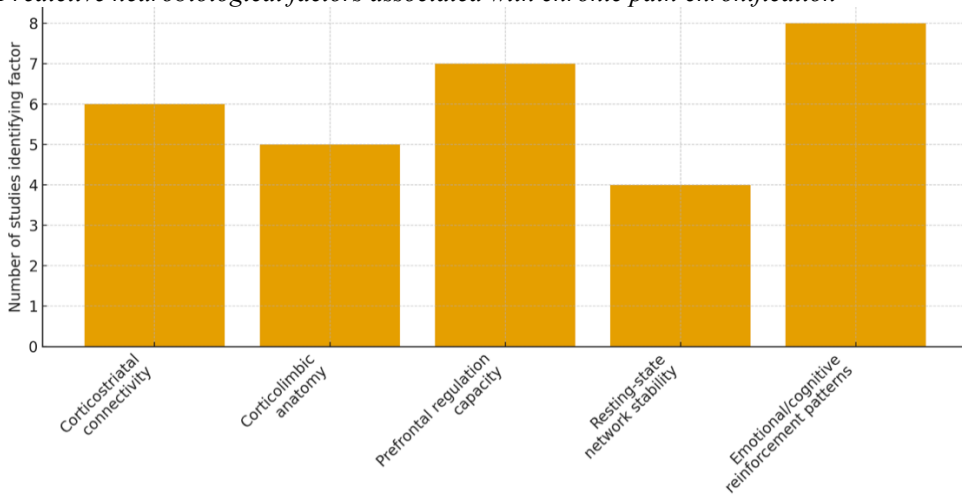

Figure 4 presents the distribution of predictive neurobiological factors associated with the transition from acute to chronic pain, revealing a pattern that aligns strongly with contemporary models describing chronic pain as a disorder of maladaptive learning, cognitive-emotional modulation, and disrupted neural regulation. The most frequently identified predictors—**emotional/cognitive reinforcement patterns (n = 8)**—highlight the role of persistent negative affect, catastrophizing, fear, and learned associations in reshaping neural circuits involved in pain processing. Several studies demonstrate that emotional learning and maladaptive reinforcement loops within limbic structures can facilitate the consolidation of chronic pain, leading to enhanced salience of pain-related cues and the stabilization of pain-related neural patterns (Bushnell et al., 2013; Hashmi et al., 2013; Flor, 2012). This aligns with theoretical frameworks proposing that chronic pain becomes increasingly tied to emotional memory and evaluative mechanisms rather than purely sensory factors.

The second most frequent predictor, **prefrontal regulation capacity (n = 7)**, further reinforces the importance of cognitive control and executive modulation in determining vulnerability to chronic pain. Studies consistently show that individuals who exhibit reduced activation or weaker connectivity in prefrontal regions—particularly the dorsolateral prefrontal cortex—are more likely to transition to chronic pain (Seminowicz & Moayedi, 2017; Apkarian et al., 2011). This diminished regulatory capacity limits top-down inhibition of limbic and nociceptive circuits, making emotional responses, attention biases, and maladaptive coping strategies more likely to dominate the pain experience. Such deficits may impair the ability to reframe pain, maintain cognitive flexibility, or suppress automatic pain-related thoughts, which contributes to chronification.

Corticostriatal connectivity (n = 6) appears as another key predictive factor. This category includes findings from influential longitudinal studies showing that increased connectivity between the nucleus accumbens and prefrontal regions predicts the development of chronic back pain after an acute episode (Baliki et al., 2012; Baliki & Apkarian, 2012). These circuits are central to reward learning, habit formation, and motivational salience. Their involvement suggests that chronic pain emerges when pain-related expectations, emotional responses, or behavioral patterns become ingrained through reinforcement processes, effectively transforming pain into a maladaptive habit encoded within motivational networks.

Corticolimbic anatomy (n = 5) also plays a predictive role, consistent with evidence that individual differences in structural features of the amygdala, hippocampus, and prefrontal-limbic connections are associated with increased risk of pain chronification (Vachon-Presseau et al., 2016). These findings support an emerging view that some people

possess neurobiological predispositions—such as heightened emotional reactivity or altered threat processing—that may interact with injury or stress to produce chronic pain. Such structural predispositions may amplify emotional responses to pain or reduce resilience to persistent nociceptive input.

Finally, **resting-state network stability (n = 4)** reflects evidence that disruptions in default mode, salience, or sensorimotor networks can predict poor recovery or long-term pain persistence (Cauda et al., 2014; Baria et al., 2011). Aberrant network dynamics may reflect an early shift toward maladaptive connectivity patterns that later stabilize into chronic pain circuits. Reduced coherence or excessive coupling in these networks has been associated with heightened self-focus, increased interoceptive vigilance, and persistent pain rumination, which may reinforce chronicity.

Taken together, Figure 4 shows that predictors of chronification involve a complex interplay between **emotion regulation**, **cognitive control**, **reinforcement learning**, **network stability**, and **structural predispositions**. Across the reviewed literature, the strongest predictors are consistently those related to affective-cognitive reinforcement patterns and prefrontal regulatory function, emphasizing that the transition to chronic pain is less about ongoing nociception and more about shifts in how the brain interprets, evaluates, and learns from pain-related experiences.

DISCUSIÓN

The findings of this review reinforce a contemporary understanding of chronic pain as a condition rooted in **maladaptive neuroplasticity**, rather than a prolonged nociceptive signal or a mere symptom of peripheral injury. Across structural, functional, and connectomic evidence, the results converge on the idea that chronic pain reflects a multidimensional remodeling of brain circuits responsible for sensory processing, emotional regulation, cognitive control, and motivational learning. This perspective aligns with longstanding neuroimaging work demonstrating that chronic pain persists through sustained alterations in cortical and subcortical structures, as well as in the communication between these regions (Apkarian et al., 2011; Tracey & Bushnell, 2009).

1. Integration of Structural and Functional Remodeling

The predominance of structural findings, including reductions in gray matter volume and changes in white matter microstructure, suggests that chronic pain leaves measurable anatomical footprints within the central nervous system. Studies consistently report cortical thinning or volume reductions in areas such as the prefrontal cortex, insula, anterior cingulate cortex, and thalamus (May, 2008; Smallwood et al., 2013; Kim et al., 2021). These changes may reflect dendritic retraction, synaptic remodeling, or glial alterations, supporting the concept that neural circuits adapt negatively to persistent nociceptive input. Meanwhile, functional imaging studies reinforce this structural picture by showing aberrant patterns of activity in these same regions during sensory, cognitive, and emotional challenges (Baliki & Apkarian, 2015; Bushnell et al., 2013). The convergence of structural and functional alterations across multiple systems highlights that chronic pain is supported by stable, self-reinforcing changes in neural architecture.

2. The Role of Network-Level Disruptions

Perhaps the most compelling evidence for chronic pain as a systems-level disorder comes from studies documenting altered resting-state connectivity (Baria et al., 2011; Cauda et al., 2014). These disruptions involve large-scale networks such as the default mode network, salience network, and sensorimotor circuits, suggesting that chronic pain alters the brain's intrinsic dynamics, even in the absence of external stimulation. This finding supports the "dynamic pain connectome" model, in which chronic pain reflects pathological stabilization of maladaptive network states (Kucyi & Davis, 2015). The results of this review align with this perspective: the repeated presence of resting-state abnormalities across multiple studies indicates that pain becomes embedded within the brain's spontaneous functional architecture, making it more persistent and resistant to conventional treatment.

3. Emotional Learning, Cognitive Modulation, and Maladaptive Plasticity

One of the clearest patterns emerging from the results concerns the involvement of **affective and cognitive circuits** in pain chronification. Evidence demonstrates that chronic pain shifts neural representation away from primarily nociceptive regions toward emotional and motivational circuits (Hashmi et al., 2013). This shift appears to be reinforced by maladaptive learning processes within corticolimbic and corticostriatal pathways, which encode emotional salience, threat evaluation, and habit formation (Baliki et al., 2012; Vachon-Presseau et al., 2016). Such

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findings help explain why emotional distress, catastrophizing, and hypervigilance predict poor outcomes in pain recovery. Importantly, these mechanisms are not merely psychological overlays—they reflect identifiable changes in synaptic organization, connectivity patterns, and neural responsivity (Mansour et al., 2014; Flor, 2012).

The prefrontal cortex also emerges as a critical node in the chronification process. Reduced prefrontal activation and weakened connectivity impair top-down modulation of pain, limiting the capacity to regulate attention, reinterpret sensory information, or inhibit maladaptive emotional responses (Seminowicz & Moayedi, 2017; Bushnell et al., 2013). These prefrontal deficits may amplify the influence of limbic and salience circuits, thereby reinforcing negative affective responses and making pain more intrusive and persistent.

4. Predictive Models and Biomarker Potential

Several studies reviewed here suggest that structural or functional markers may predict who is likely to transition from acute to chronic pain. Factors such as corticostriatal connectivity, corticolimbic anatomy, prefrontal regulation capacity, and emotional reinforcement patterns have all demonstrated predictive value (Baliki et al., 2012; Vachon-Presseau et al., 2016). However, while promising, these biomarkers face challenges related to reproducibility, individual variability, and ethical considerations in their potential clinical use (Davis et al., 2017). Future work will require standardized protocols, cross-cultural validation, and longitudinal designs to confirm the reliability of such markers across diverse populations—including those in Latin America.

5. Implications for Clinical Practice and Multinational Contexts

The interpretation of chronic pain as a neuroplastic condition has important implications for clinical decision-making. Treatments targeting neural regulation—such as cognitive-behavioral therapy, neuromodulation, mindfulness-based interventions, and sensorimotor retraining—may help reorganize maladaptive circuits and improve outcomes. These interventions align with the mechanisms identified in this review, particularly those involving prefrontal control, emotional learning, and network reorganization.

Internationally, countries such as **Mexico, Colombia, and Ecuador** face significant challenges due to limited access to advanced imaging tools, specialized pain rehabilitation, and integrative care. The findings of this review underscore the importance of adopting **mechanism-based, multidisciplinary approaches** that do not rely solely on imaging but incorporate psychological, educational, and behavioral components informed by neuroplasticity models. Understanding chronic pain as a brain-based disorder may help shift public health priorities toward early intervention, patient education, and scalable non-pharmacological strategies.

6. Limitations of Current Evidence and Future Directions

A major limitation across the reviewed studies is the heterogeneity of imaging protocols, diagnostic criteria, and patient populations. This variability complicates cross-study comparisons and limits the generalizability of findings. Some structural changes appear reversible after successful treatment, while others persist, raising open questions about the timing and directionality of neuroplastic alterations (Tan et al., 2020; Kim et al., 2021). Additionally, most predictive studies rely on relatively small or homogeneous cohorts, necessitating larger multinational samples to validate biomarker candidates. Future research should integrate multimodal imaging, longitudinal designs, and culturally diverse populations to develop a more universal and clinically actionable framework for chronic pain.

CONCLUSIÓN

The evidence reviewed in this article converges on a central observation: **chronic pain is sustained by maladaptive neuroplasticity that remodels the brain across structural, functional, and network levels**. Rather than persisting solely because of continuous nociceptive input, chronic pain becomes embedded within circuits that regulate cognition, emotion, interoception, and motivation. This shift reflects an interplay between altered sensory processing, dysfunctional top-down modulation, and reinforcement of pain-related emotional and behavioral patterns (Apkarian et al., 2011; Bushnell et al., 2013; Baliki & Apkarian, 2015).

Across studies, the most robust findings highlight consistent **gray matter volume reductions**, particularly in prefrontal, cingulate, insular, and thalamic regions (May, 2008; Smallwood et al., 2013; Kim et al., 2021), accompanied

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by **functional hyper- or hypoactivation** in circuits involved in salience detection, emotional evaluation, and cognitive control. These changes are complemented by **resting-state network disruptions**, affecting intrinsic connectivity patterns within the default mode, salience, and sensorimotor networks (Cauda et al., 2014; Baria et al., 2011). Together, these findings portray chronic pain as a disorder in which multiple systems become reorganized toward persistent threat anticipation, heightened bodily vigilance, and reduced regulatory capacity.

Another major implication of this review is the recognition that **cognitive-emotional processes and learning mechanisms** contribute significantly to the chronification of pain. Maladaptive reinforcement patterns, impaired prefrontal regulation, and alterations in corticostriatal and corticolimbic circuits appear repeatedly as predictors of long-term pain outcomes (Baliki et al., 2012; Hashmi et al., 2013; Vachon-Presseau et al., 2016). These insights underscore the need for models that integrate emotional, cognitive, and motivational dimensions—rather than models focused exclusively on sensory pathways.

Clinically, understanding chronic pain as a neuroplastic condition encourages a **mechanism-based, interdisciplinary approach** to treatment. Interventions that target attention, emotion regulation, cognitive control, and sensorimotor integration may contribute to reversing maladaptive neural patterns. This is especially relevant in countries like Mexico, Colombia, and Ecuador, where the burden of chronic pain is high and access to advanced diagnostics may be limited. A neuroplasticity-based framework supports scalable, evidence-informed strategies, including psychological therapies, physical rehabilitation, educational interventions, and selective neuromodulatory techniques.

Despite strong advances, gaps remain. The field requires **larger, culturally diverse longitudinal studies** to validate predictive biomarkers and refine mechanistic models. Differences in methodology, small sample sizes, and heterogeneity of pain conditions continue to limit the generalizability of findings. Future efforts should prioritize integrating multimodal imaging with behavioral, cognitive, and emotional data to better characterize the pathways leading from acute injury to long-term pain persistence.

In summary, the current body of evidence positions chronic pain as a **self-sustaining neurobiological state**, shaped by interactions between sensory input, emotional reactivity, cognitive processes, and network-level reorganization. Recognizing chronic pain as a disorder of maladaptive plasticity—rather than merely a symptom—opens new avenues for early detection, personalized treatment, and global public health strategies aimed at reducing disability and improving quality of life for millions of individuals.

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