Narrative Review Article

How Does Stress Influence the Psychological Amplification of Chronic Pain, and Can Psychological Therapies Modify the Emotional and Cognitive Components of Pain?

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ABSTRACT

Psychological factors have become increasingly recognized as critical components in the experience of chronic pain, alongside its physical mechanisms. Although existing literature highlights the links between stress, memory networks, and pain, the precise neurobiological and cognitive pathways driving stress-induced pain amplification remain unclear. To address this critical gap, this comprehensive review evaluates how these interconnected systems modulate subjective pain perception, while assessing the efficacy of integrated psychological interventions. Centrally, stress activates the hypothalamic-pituitary-adrenal (HPA) axis, releasing cortisol that facilitates the consolidation and retrieval of negative, pain-related memories via the amygdala-hippocampal complex. This neurological loop drives cognitively mediated pain amplification through anticipatory processing, pain imagery, and negative expectations. Regarding clinical applications, systematic evidence indicates that psychological therapies – primarily cognitive behavioral therapy (CBT) and mindfulness – alleviate functional disability and improve coping strategies rather than consistently reducing physical pain intensity. Because therapeutic outcomes vary significantly based on the intervention type, patient demographics, and clinical timing, treatment models must evolve into precision-based, collaborative care plans. Finally, this review highlights the critical need for advanced neuroimaging and biomarker developments to successfully distinguish psychologically driven pain amplification from progressive tissue damage, paving the way for targeted, precision pain management.

Keywords: Chronic pain; biological mechanisms; psychological mechanisms; stress; perception of pain; memory networks; psychological interventions

INTRODUCTION

As life expectancy continues to increase, ensuring quality of life has become even more important. Therefore, chronic pain, which is defined as long-standing pain that persists beyond the usual recovery period (1), can be one of the factors that have the greatest impact on people's prolonged life.

In the United States of America, more than 51.6 million American adults, which makes up 21% of the population, live with chronic pain (2). Even the estimated national prevalence of chronic pain in children 6–17 years was 10.6% in 2019 (3), which indicates that chronic pain represents a significant public health concern across various age groups, rather than being confined to older populations. The reason why chronic pain should be a

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global priority is that it not only creates economic and medical burdens or pressure but also contributes to anxiety and depression (4).

Although chronic pain management is recognized as essential for improving patients' quality of life, researchers often focus on the physical causes and overlook the psychological aspect of chronic pain. With regards to the psychological aspect, stress, in particular, can significantly affect the perception of pain (5).

As well as the connection between pain perception and stress, memory formation has also been shown to be closely related to pain perception (6). To address these interconnected factors, this review specifically aims to evaluate the neurobiological and cognitive mechanisms through which stress and negative pain-related memories modulate and amplify chronic pain perception, thereby providing a comprehensive rationale for integrating psychological interventions with physical treatments in multidisciplinary pain management.

SYMPTOMS AND BIOLOGICAL MECHANISMS OF CHRONIC PAIN

To effectively address these psychological dimensions, it is first essential to establish a clear baseline of how chronic pain manifests clinically and biologically. The common symptoms of chronic pain include persistent aching, fatigue, poor sleep, anxiety or depression, no treatment response, appetite changes, and cognitive issues (7, 8). Chronic pain can vary depending on whether it is caused by a specific injury or a disease/condition, such as rheumatoid arthritis or fibromyalgia (9). The biological mechanisms that mediate chronic pain can be categorized into two types: central and peripheral sensitization.

In chronic pain, post-translational and transcriptional changes in nociceptor neurons, which are specialized for encoding noxious stimuli, exhibit increased excitability. This process is known as peripheral sensitization (10). This increased peripheral excitability enhances sensory input to the dorsal horn of the spinal cord – the primary site for processing and integrating painful signals – leading to central sensitization, a state of sustained nervous system hyperactivity, that results in increased neuronal excitability and enhanced synaptic transmission (11). While these two types of pain pathways differ from each other, evidence suggests that they can both contribute to plasticity within the pain pathways, potentially leading to sensory misprocessing (12). Beyond the spinal cord, critical brain regions, such as the amygdala, anterior cingulate cortex (ACC), insular cortex, prefrontal cortex (PFC), and thalamus, are also strongly associated with the perception of pain and promote pain amplification (13).

STRESS AND PERCEPTION OF PAIN

These central brain structures do not operate in isolation; rather, they are continuously modulated by the individual's psychological state, particularly under conditions of stress. Daily stress from work demands, future uncertainties, or family responsibilities can negatively impact the body, disrupting homeostasis and acting as a trigger or aggravating factor for many diseases and pathological conditions (14). Stress is known to be an important modulator of pain perception and responses, which means that chronic pain can be amplified by the increased level of stress (5, 15). One study conducted by Etienne and colleagues in 2018 also demonstrates that chronic pain patients have been shown to exhibit maladaptive responses to stress in general, as well as to pain (16).

STRESS AND MEMORY NETWORKS

Stress strongly influences multiple parts of the body, including the hypothalamic-pituitary-adrenal (HPA) axis, amygdala, and hippocampus (17). The common feature of these regions is that they closely connect stress and memory networks (18, 19).

The HPA axis is a crucial communication system responding to stress. Its main function is to release cortisol, a steroid hormone released in stressful situations. Dysfunction of the HPA axis may also play a role in memory loss and memory-related disorders (20). HPA axis dysregulation and increased amounts of cortisol may lead to negative memory formation, which can also be seen in post-traumatic stress disorder (PTSD) and anxiety disorders, where heightened cortisol responses are associated with the persistence and reinforcement of traumatic or fear-related memories (21).

The hippocampus, a region of the brain that is primarily associated with memory (22), is also one of the major components of the brain that may be altered in response to stress. Structurally, human and animal studies have demonstrated that stress changes neuronal morphology and reduces hippocampal volume (23), which eventually impairs memory. Although a study of stress effects on neuronal structure conducted by McEwen and colleagues argues that acute stress can

even enhance excitability and promote memory over minutes to hours, this is only when the stressor is not overly intense; intense stress can have the opposite effect, which influences memory negatively (17). In this context, 'negative' refers both to reduced memory performance and the reinforcement of negative emotional memories. Another study of the relationship between stress and memory conducted in 2019 revealed that cortisol modulation can affect emotional memory retrieval and potentially reconsolidation (24), which implies the possible connections between stress and negative emotions formed as well as direct memory issues such as remembering or memorizing (21).

Because emotional stimuli are closely linked with memory and stress, the role of the amygdala becomes even more critical. The amygdala and hippocampal complex work together when emotion meets memory (19); the hippocampus is central to declarative memory, while the amygdala modulates emotional aspects of memory.

Therefore, cortisol-induced changes in the brain and alterations in memory caused by elevated cortisol, as well as the emotional modulation of these memories during stress, help link the HPA axis, amygdala, and hippocampus, highlighting how stress can influence memory formation and ultimately contribute to distorted pain perceptions.

MEMORY NETWORKS AND PAIN PERCEPTION

While the neurobiological effects of stress map directly onto memory consolidation pathways, the clinical consequence of this intersection is its profound impact on how pain is ultimately processed and felt. The connection between stress and memory networks highlights the fact that stress can enhance the consolidation of negative pain-related memories, leading to heightened retrieval of these negative memories in future contexts when the patients get re-exposed to similar conditions, including similar environment or stimuli (25). This retrieval of negative pain-related memories can be caused by specific behaviors or thoughts that patients might have engaged in consciously or unconsciously. Pain imagery and negative expectation are the two main reasons for cognitively mediated amplification of pain (26,27).

For example, the study conducted by Vetterlein and colleagues in 2024 revealed that the same brain areas related to pain-control or -regulation, such as PFC, supplementary motor area (SMA), primary motor cortex (M1), primary somatosensory cortex (S1), posterior parietal cortex (PPC), and cerebellum, can be activated only by pain imagery instead of experiencing the physical pain in real life (26). This study shows that similar brain activity patterns occur between actual pain experiences and painful imaginations. In addition, negative expectation of pain can activate pain-related brain networks as well. According to recent clinical evidence on the fear-avoidance model in 2025, individuals who are fearful of pain and re-injury and who seek only a physical cause and solution to the injury generally experience delayed functional recovery, which can turn into chronic pain (27, 28). This emphasizes that the severity of chronic pain is heavily modulated by the patient's cognitive appraisal of their condition. Another study conducted by Henderson and colleagues supports the findings reported by the aforementioned study and explores anticipatory pain processing through the nocebo effect and stimulus-expectancy (29).

Both the nocebo effect and stimulus-expectancy demonstrate that negative anticipatory beliefs – specifically the expectation of symptom worsening – profoundly alter subjective pain perception. Nevertheless, these two concepts can be differentiated in the following way: the nocebo effect describes a situation in which a patient develops side effects or symptoms following administration of a drug or therapy as a result of negative expectations of the treatment (30). This definition ultimately implies that psychological factors in the absence of any physically harmful elements can play a significant role in pain perception and impact physical symptoms. Similarly, stimulus expectancy refers to an expectation of the intensity of coming pain or stimulation itself. Henderson and colleagues examined the participants after giving them certain cues or instructions on the intensity of their expected pain. Their conclusion was that pain-related experiences are not a simple intensity-dependent issue but a changeable variable that is altered depending on individuals' expectations of their own pain. They also found that this stimulus-expectancy manipulation of pain intensity alters activity in both higher brain and brainstem centers, which are known to modulate pain under various conditions (29).

In summary, evidence from multiple studies emphasizes the relationship between memory processes and anticipatory pain perception. Two major psychological mechanisms have been proposed: pain imagery and expectation-related pain modulation, the latter including the nocebo effect and stimulus-expectancy. Together, these mechanisms can be understood as the recreation

and recall of pain-related memories, that might amplify pain perception in chronic pain patients.

CLINICAL AND THERAPEUTIC IMPLICATIONS

As many studies mentioned throughout this paper demonstrate the interaction between psychological factors and pain perception, psychological aspects ultimately play a significant role in different kinds of treatments and in various aspects of therapy for chronic pain patients. In addition to the connection between stress, negative memories, and their effects on pain perception, other studies have also shown specific positive effects of psychological interventions for the treatment/management of chronic pain. An article about positive pain management written by Susan McGarvie, Ph.D. indicates that techniques like mindfulness and cognitive-behavioral therapy (CBT) can reduce pain perception and improve coping skills (31). A systematic review by Bérubé and colleagues in 2021 also discusses the importance of pain education on self-management and the role of psychological interventions, such as psychoeducation, cognitive-behavioral interventions, and self-care enhancement interventions. Introduction of these interventions early after pain onset in order to prevent pain from becoming chronic was introduced as an interesting solution for preventing pain chronicity in improving pain-related disability and coping mechanisms (32). In addition, psychological interventions can be in other forms as well: for example, enhancing resilience skills with motivation and engagement, involving patients in the goal-setting process, and the reinforcement of coping strategies can also support chronic pain patients by reducing their pain perception. As such, many studies reported numerous findings regarding psychological interventions for chronic patients' psychophysical well-being, like quality of life and personal satisfaction, suggesting that these modalities hold the potential to favorably modulate pain perception and enhance overall coping capacity (33).

However, some studies present a different perspective, arguing that psychological interventions have limited impact on altering immediate pain intensity. According to a systematic review and meta-analysis written by Bérubé and colleagues, there is no significant effect of psychological interventions on pain intensity; furthermore, the current evidence remains insufficient to confirm whether early psychological interventions can definitively prevent pain from becoming chronic (32). Nevertheless, they emphasize that such modalities are highly valuable for reducing pain-related disability and improving patients' coping mechanisms (32). Another study conducted by Pike and colleagues in 2016 reported no benefits of psychological interventions in reducing medication in chronic pain patients (34).

The contrasting results regarding the implications of psychological interventions on chronic pain can be reconciled by a comprehensive biopsychosocial framework. While psychological therapies may not directly decrease physical pain severity, they significantly alleviate the associated functional disability and emotional distress (32). Leccese and colleagues substantiated this by demonstrating that targeted psychological interventions significantly improve patients' psychosocial well-being and coping capacity specifically through the reduction of pain catastrophizing and the enhancement of psychological resilience (33). Similarly, McGarvie's study reported that psychological interventions on pain management, such as pain catastrophizing, placebo effect, and mindfulness-based intervention, help chronic pain patients more effectively, enhancing their quality of life and reducing pain intensity (31).

CONCLUSION

By synthesizing insights from multiple studies on chronic pain and its psychological influences, our understanding of its underlying mechanisms can be expanded toward a more comprehensive, integrated framework. Specifically, stress engages neural circuits, including the HPA axis and limbic structures, where elevated cortisol levels modulate the consolidation of pain-related memories. Through these cortisol-mediated effects on memory-related brain regions, stress ultimately strengthens the association between pain, fear, and anxiety.

In conclusion, the clinical utility of integrating psychological and physical modalities remains nuanced and characterized by mixed evidence rather than a uniform solution. While such integrated approaches may not consistently yield direct reductions in physical pain intensity, they offer significant clinical value in mitigating functional disability and fostering positive coping mechanisms. Crucially, the overall effectiveness of these interventions is not absolute; rather, it heavily depends on specific treatment modalities – such as CBT and mindfulness-based practices – distinct patient populations, targeted clinical outcomes, and the timing

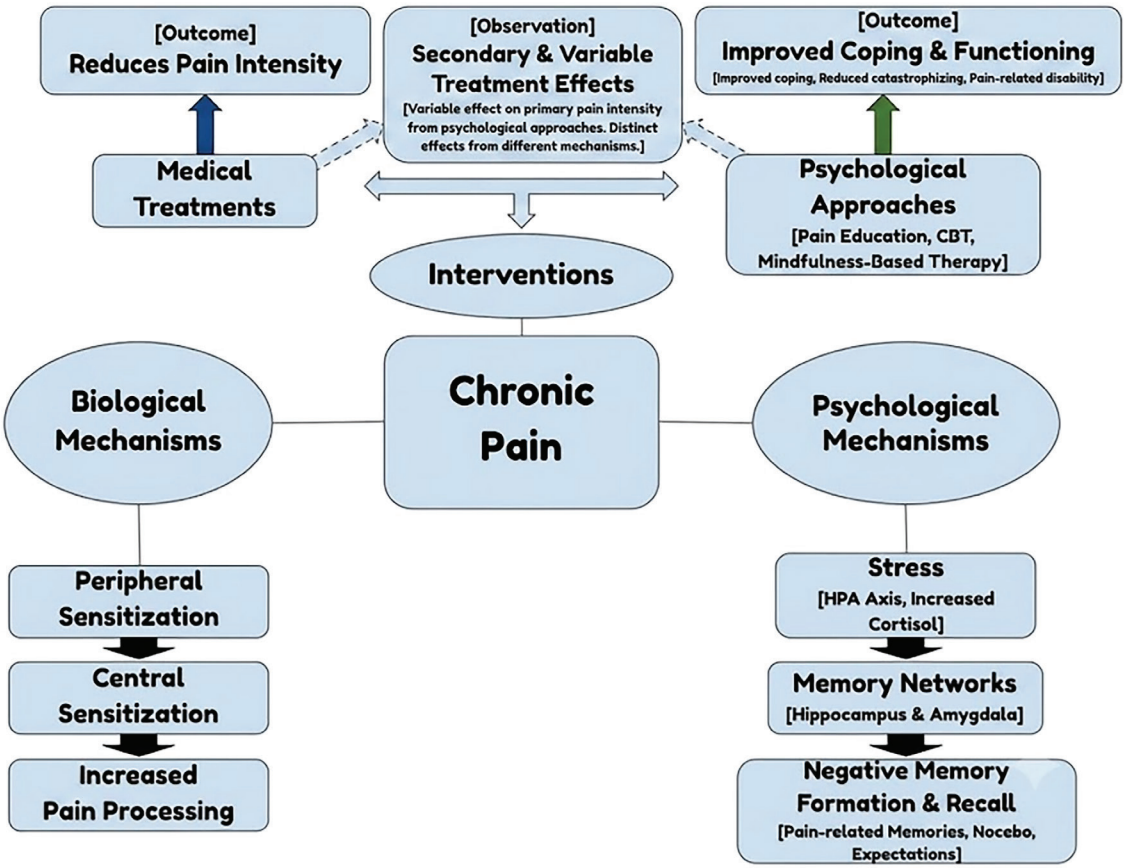

Figure 1. *Interaction of biological and psychological mechanisms in chronic pain and their modulation by intervention. Chronic pain is mediated by both biological mechanisms and psychological mechanisms. With increased stress, elevated cortisol levels influence memory-related brain regions, thereby facilitating the consolidation of negative, pain-related memories. Interventions targeting these pathways yield distinct outcomes: medical treatments primarily act to reduce pain intensity, whereas psychological approaches predominantly target coping, emotional distress, catastrophizing, and pain-related disability, with variable direct effects on pain intensity. Comprehensive management of chronic pain thus involved integrating both biological and psychological interventions.*

of the intervention – particularly given the currently insufficient evidence regarding early-stage chronic pain prevention. Accordingly, future clinical applications and research must shift from generalized integration to highly tailored, patient-specific multidisciplinary regimens.

However, translating this framework into clinical practice presents a key challenge: distinguishing pain that is amplified by the progression of the underlying physical injury from pain that is exacerbated by psychological factors. Therefore, future research and clinical development should focus on developing neuroimaging and biomarker approaches that can differentiate these mechanisms, enabling more targeted, precision-driven, and effective interventions for holistic chronic pain management.

CONFLICT OF INTEREST

The author declares no conflicts of interest related to this work.

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