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Review Article

Neuronal Mechanisms and Treatment Approaches to Emotional and Physical Pain

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Abstract

The feeling of pain encompasses a range of mental and physical states, sharing the scale of mild annoyance to debilitation. Pain is the most common symptom reported to health care professionals. Psychological pain results from negative emotions induced by any feeling of loss. Physical pain is an aversive state that originates from an injury or disease. Pain is a complex and bio-psycho-social phenomenon, arising from interactions of anatomical and chemical systems of neural networks and involving several cognitive processes. Medicine still regards pain as a symptom of physical injury, despite evidence of many people suffering from psychological-based pain. The concept of pain requires broadening and inclusion to accommodate the basic science of pain originating from various sources, that is, physical and psychological. Research on emotional psychology and pain has proliferated in many aspects with overlapping and non-linear networks. Psychology could be an essential contributor to understanding and depicting chronic pain treatment approaches, as psychological illness and pain are viewed as a reciprocal relationship that involves the expression of the disease and the pain that showcases specific effects on the behavior and emotional state. Persistent pain is complex, with emotions only scaling as a contributing factor supported by anecdotal evidence with the frequent association. Other factors such as genetic, environmental, contingencies, placebo, and cognition also play an essential role in studying the aspect. This review provides an overview of chronic and emotional pain and its underlying neuronal mechanisms and treatment approaches.

Keywords: *Cognitive-Behavioral Therapy; Depression; Inflammation; Limbic System; Sickle Cell Disease; Osteoarthritis; Prostaglandins*

Abbreviations

ACC: Anterior Cingulate Cortex; CBT: Cognitive-Behavioral Therapy; CPS: Chronic Pain Syndrome; CRPS: Complex Regional Pain Syndrome; GPCR: G Protein-Coupled Receptor; NGF: Nerve Growth Factor; TNF: Tumor Necrosis Factor; PAG: Periaqueductal Gray; RCT: Randomized Controlled Trial

Introduction

Chronic pain is persistent in characteristics and is defined as lasting for at least 3 months. Therefore, it is more complicated to assess and treat than acute pain conditions. In addition, the nosology of pain is continuously evolving and inconsistent, as some forms and types of pain are related to specific diseases such as osteoarthritis (joint degeneration), neuropathic pain (nerve damage), and sickle cell disease (tissue anoxia or severe hypoxia or loss of oxygen) [1]. Both chronic pain syndrome (CPS) and complex regional pain syndrome (CRPS) were first described by Silas Weir Mitchell in 1864 [2]. In 1901, Paul Sudeck described the CRPS type I lesion as "acute reflex bone atrophy after inflammation and injuries of the extremities and their clinical appearances" [3]. In 1936, James Evans coined "reflex sympathetic dystrophy" [4].

Mental pain, emotional pain, or psychological pain is unpleasant suffering or feeling of a non-physical origin. In 1998, Edwin S. Shneidman, a pioneer in the field of suicidology, described this feeling as "how much you hurt as a human being" [5]. In 1962, Sandler elaborated on psychological pain associated with a discrepancy between the perception of the ideal and the actual self [6]. Bakan, in 1968, observed the feeling of separation from the significant other in his patients [7]. In 1990, Baumeister revealed that mental pain has an indirect suicidal influence. In addition, it impacts the psychological quality of life with the primary emotion of self-disappointment [8].

Melzack and Casey (1968) have described the composition of human pain experience expanded into 3 dimensions (Figure 1). First, the sensory-discriminative dimension identifies the stimulus's timing, location, and mechanical (or physical) characteristics and prompts reflexes to withdraw and avoid tissue damage. The cognitive-evaluative dimension plays a role in influencing the evaluation and consequences of any specific injury or pain. Finally, the affective-motivational dimension is closely related to emotion with exposure to the stimulus, thus activating defensive behaviors such as escaping the noxious stimulus [9].

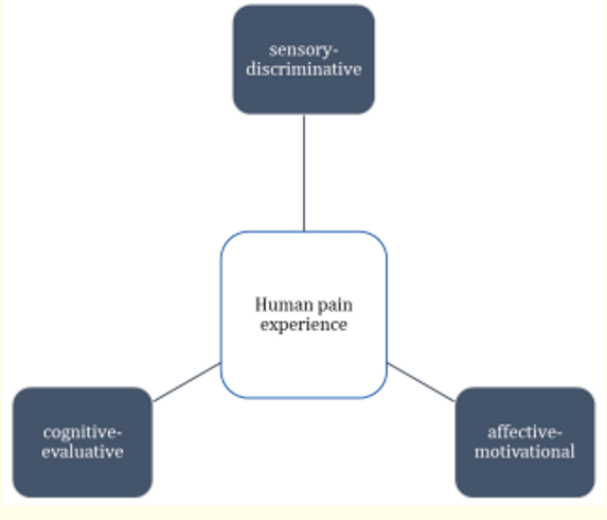

Figure 1: *Three dimensions of the human pain experience as described by Melzack R., et al. (1968) [9].*

The dimensions sensory-discriminative and affective-motivational are supported by a parallel but separate neural network of systems. The lateral pain system supports the sensory-discriminative dimension and expands the axons to the spinal cord through the spinothalamic tract. The medial pain system supports the affective-motivational dimension and projects axons to the spinal cord and brain stem through the spinothalamic tract, thus forming the synapse and expanding further to the limbic system and the cingulate cortex [9]. Clinical studies reported by Ploner., *et al*. (1999) [10] and Kulkarni., *et al*. (2005) [11] have presented data supporting the distinction between the lateral and medial pain systems.

Discussion

Neuroscience of psychological (emotional) pain

The definition of psychological pain is complicated and can be understood as a lasting unpleasant feeling with an unsustainable feeling that can be characterized by the inability and perception of self-deficiency of an individual, leading to social disconnect and frustration in achieving psychological needs [12]. Papini., *et al.* (2006) supported the idea of endogenous opioid involvement in psychological pain studied in animal research [13]. Physical pain regulation is also operated by cannabinoid receptors and therefore is expected to influence the psychological pain scale [14]. Chronic pain is distressing; however, the familiar and complex problem deeply affects individuals and, therefore, social interactions [15]. It is commonly represented because injury or disease has its taxonomy and medical definitions and is therefore defined as a separate condition in the current scenario based on data supported by structural, functional, and molecular imaging studies [16,17]. Chronic health pain is a significant concern to most of the population.

Acute pain is elicited by the acute level of inflammation or wounded tissue, whereas chronic pain is maladaptive and is characterized by specific observations of burning (spontaneous pain) in response to noxious or non-noxious stimuli. Neuronal plasticity is part of chronic pain's neural coding pathways and circuits. Sensory neurons from the dorsal root ganglia, the trigeminal ganglia, and central sensory effects produced by neurons in the brain and spinal cord are involved in pain processing through orthopedic stressors. Nociceptors are the primary response elements activated in any tissue injury.

The response is sensitized by inflammatory mediators, such as prostaglandins, nerve growth factors (NGF), bradykinin, pro-inflammatory cytokines such as interleukins, tumor necrosis factors (TNF), and pro-inflammatory chemokines such as CXCL5 and CCL2 that act by direct binding and stimulation of the G protein-coupled receptor (GPCR) pathway and tyrosine kinase receptors [18-20].

The concept that sustained, repeated, and intense stimuli are required for central sensitization is historically considered medical dogma. The evolving data support persistent peripheral nociceptive input, not necessarily central sensitization. It results from a continuous change in the properties of neurons in the central nervous system that increases as an independent factor for peripheral input [21]. However, according to researchers, central sensitization, neuroinflammation, and chronic pain can occur without a peripheral injury in injuries such as traumatic brain injury, spinal cord injury, and multiple sclerosis [22]. Therefore, future studies must explore bi-directional pathways and central and peripheral sensitization interactions.

Neuroscience of chronic pain

Understanding the complex process of chronic pain has become challenging during treatment because the mechanisms interact with neural circuits that involve emotional, sensory, and cognitive processing. Therefore, researchers are exploring a mechanistic approach to implement psychology-based treatments for chronic pain, as it is an ideal model to attempt to understand multiple types of processes in the context of integrated and localized neural networks.

The cognitive and emotional aspects of chronic pain involve the interconnected network and action of brain regions such as the somatosensory cortex, thalamus, insula, prefrontal cortex, anterior cingulate cortex, spinal cord; midbrain regions, cerebellum, and periaqueductal gray; subcortical structures, hippocampus, amygdala, and basal ganglia [23].

Neuroscience of interaction between psychological (emotional) pain and chronic pain

Pain is a nociceptive-stimulated response that forces people to seek treatment when they experience pain, ache, or suffering. The psychological state (the state of mind) is altered once pain reaches the chronic stage, displaying the same band of physical, emotional, or psychological pain [23]. Physical and emotional pain exists on the scaffold of the same continuum [24,25] that involves standard neural networks [26], resulting in eccentric behavior (Figure 2).

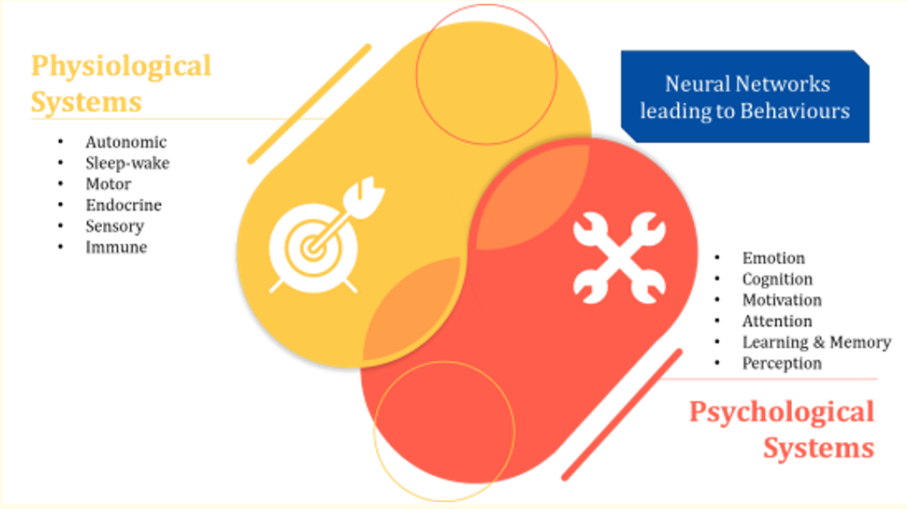

Figure 2: *Pain behavior integrating physiological and psychological systems.*

The two main points to be considered when exploring the approach of the brain system to psychological pain processing are: 1) experiencing pain can trigger a cascade of neurological events that begin with sensory networks that lead to an altered psychological state of mind and b) data have also revealed that earlier psychological states can increase the risk of chronic scale due to cross-sensitization due to greater sensitivity to stressful events, such as childhood trauma, addiction, and loss of a parent [27–29].

Chronic pain and depression (for example) have common comorbidities such as higher levels of stress and disturbance of sleep patterns compared to patients who have no symptoms of chronic pain or depression. Any cause leading to chronic pain has a prevalence of 21.9%, and of this, approximately 35% of patients have comorbid depression associated with it. Logistic analysis has shown a higher probability that the younger population experiences comorbid pain along with depression compared with chronic pain alone.

The findings have also revealed demographic groups as an essential factor in determining the prevalence of comorbid pain and depression in a particular community and assessing the benefits [30,32]. Feelings of worry, anxiety, frustration, and depression are caused by

chronic pain. However, evidence of a reverse causal relationship has also supported evidence of negative mood and emotion leading to or exacerbating the pain.

The association can be elaborated on and explained by a distorted scale of pain sensitivity. Clinical studies have described the positive association between a higher score of pain and negative emotions [32], together with solid evidence supporting the association of negative emotions that reduce sensitivity to pain [33,34]. Possible neural mechanisms of modulatory influences suggest that the amygdala, periaqueductal gray (PAG), anterior insula, and the anterior cingulate cortex (ACC) are critical players in pain processing [32].

A study by M Von Korff., *et al*. (1996) highlighted the bi-directional relationship between pain and depression with underlining depression as a positive predictor in developing the symptoms of chronic pain, and in turn, the chronic pain scale increases the risk of depression. Epidemiological studies on the comorbidity of pain and depression have shown that a) pain has a strong relationship with anxiety and depression disorders; b) pain that interferes with certain activities is a vital characteristic of predicting depression; c) specific psychological symptoms (such as disturbed sleep), low level of energy, and worry are prominently observed in patients affected by pain, whereas guilt and loneliness are not; d) pain dysfunction with depression is observed in the early phase of pain, while distress is often transient; and e) depression levels do not improve in patients with chronic dysfunction; however, it also does not increase over the period with increasing chronicity [35].

Research to explore the connection

Targeted research would advance the contribution and better understanding of psychological processes in chronic pain conditions. The method of pain itself cascades the changes in the processing of psychological alteration. Integrating psychological science into pain neurobiological pathways is progressing into clinical translation data. Data sets extracted from functional imaging are attractive in treating approaches. Clinical research programs and drug trials are now integrating psychological issues and stigmas into pain to improve research strategies. The correlations and interconnections of the brain system network are depicted in figure 3 that are included in altering the psychological state of the respective chronic pain conditions.

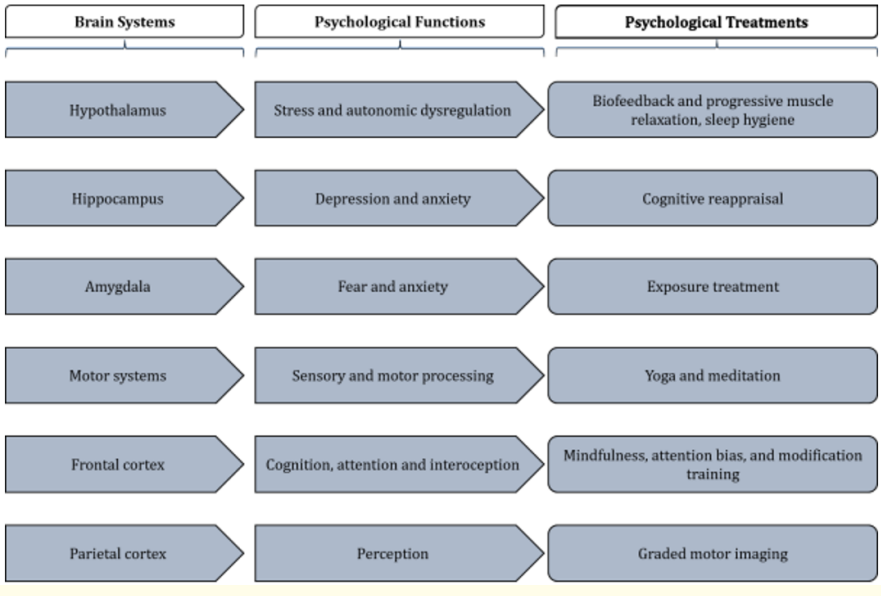

Figure 3: *Brain system network altering the psychological functions in chronic pain.*

Evidence supports the fact that pain negatively affects cognitive performance and attention by activating the ACC, altered by hypnotic suggestion in healthy subjects, leading to decreased activity in attention processing. Altered perception is another fine example of the inability of limb movements despite intact and proper motor functioning.

This occurrence has also been associated with significant disease states, such as Parkinson's and schizophrenia. Treatment approaches in these scenarios include sensory stimulation, visio-spatial specific training, and hypokinesia enhancement of the affected limb. The physiological condition also depends on emotional well-being and maintained stress levels. Rewarding and aversion stimuli also have a dynamic ability to modify one's behavior, and therefore it is essential to derive pleasure and happiness from ordinary activities [23].

Fear originating from pain is another psychological mechanism of feeling that has significant implications for psychological and physical functioning in chronic pain. This fear reflects a fear of injury or deterioration of the health condition, triggering pain [36]. The enlightened process of the reward-deficit syndrome is related to neural circuit dysfunction that can help study contributing factors to prepare a treatment approach [23]. Evidence highlights that pain-related fear also contributes to disability, and if left unaddressed or untreated, it can catastrophize pain and related fear and contribute uniquely to the generation of physical disability and pain [37].

Current approaches to behavioral therapies include cognitive-behavioral therapy (CBT) and acceptance and commitment therapy. The reversal of the butterfly effect can also enhance the enhancement of the therapeutic effect. The recently established psychological flexibility model has gained attention and is defined as the ability to adjust or maintain behavior by consistently participating in achieving goals and values [38,39].

Aim for future treatment

People tend to adapt themselves to stressful conditions, and thus rejecting any chronic condition would require a data-driven and focused mechanism-based approach as treatment. While most clinical psychology studies may be related to 'pain' or 'sick feelings', only a few clinical training programs are available focusing on pain neurobiology. There is a tremendous advancement in understanding brain functioning and its related impact. Psychology is now very well positioned to take advantage of treating brain-related pathways and networks in chronic pain conditions [23].

Health care professionals are exploring the adaptation of psychological interventions to manage chronic pain symptoms. A recently published theory of chronic pain has described how the aversive stimulus can be passed to neutral stimuli in physical movement and behavior, ultimately contributing to the adjustment or avoidance of behavior. The exclusive use of behavioral approaches to pain management has demonstrated efficacy in treating lower back pain. Similarly, exposing the patient to pain-related fear has improved functional disability and pain [37].

CBT expands the bio-psycho-social approach to chronic pain treatment and targets cognitive responses to pain and maladaptive behavior along with environmental and social contingencies and modifying reactions to pain [40]. The principles of CBT have shown efficacy for a wide range of physical illnesses such as chronic lower back pain, cancer, chronic migraines, irritable bowel syndromes, and spinal cord injury, to name a few, and psychiatric disorders such as helplessness, fear of acceptance, and commitment, to name a few [37].

Health care professionals should be cautioned in assuming homogeneity in the characteristics among patients. Turk (2005) highlighted the need to understand better the different treatment approaches resulting in similar outcomes and thus, proposed that patients show distinct patterns of response to pain that can be clustered into subclasses of patients with the same or similar medical diagnoses such as dysfunctional, interpersonally distressed, and adaptive copers. Designing clinical studies in this manner will validate the approach to demonstrate any specific characteristic of the interconnected network [41].

The subgrouping of patients expands and clarifies the overview of specific responses, thus supporting the efficacy of interdisciplinary treatment [42]. Identifying subgroups through a detailed assessment of disability and chronic level (or score) of pain can be achieved and maintained as an insight-focused therapy and self-management approach [43].

Understanding the safety profile

Any treatment decision can be harmful to patients. There are reported side effects of psychotherapy; however, the complete understanding and scope are still unclear. Psychological therapies for pain management are assumed to have a low risk of safety concerns or adverse effects. However, this field needs more investigation to reach a consensus and explore how to detect the concern or handle it if any concern arises.

There is a dire need to establish specific mechanisms and methods to examine potential ingredients, moderators, outcomes, and a broad spectrum of outcome measures over time. The study designs of randomized controlled trials (RCTs) must be validated with real-world clinical practice to maintain and strengthen knowledge. [44].

Conclusion

Pain is rarely concentrated from a psychological point of view, while the relationship and indivisible nature between physical and psychological (emotional) suffering is the epitome of pain. However, the relationship between pain and psychology is intricate and reciprocal, and it has supporting evidence from clinical data of overlapping presentations between anatomical structures [45]. The multidimensional network of pain has regained the strength to explore psychophysiological phenomena.

Common and divergent aspects of physical and psychological pain provide a framework for exploring more RCT, followed by studies of real-world evidence to support the data. Wager (2013) has presented additional evidence suggesting a significant degree of specificity in the underlying neural mechanisms directly associated with physical pain and the processing of social pain [46]. The neuro signature pattern is a characteristic generated by a widely distributed neural network in the brain and proposes pain as a multidimensional experience.

Physical and psychological pain are now understood to be controlled and regulated by similar and overlapping neural network mechanisms, which require more data to support. The neuromatrix components of both networks that encompass behavioral output have not yet been identified [47]. Further examinations of different forms of pain will undoubtedly support the knowledge of the psychological and biological mechanisms that contribute to the onset and maintenance pathways of the phenomena.

Considering the brain as an orchestra and aiming to correlate the components to harmonize the tuning will facilitate focusing on the theoretical issues of brain functioning and learning and the evolutionary aspect. This understanding will help design future studies on depression, chronic pain, addiction, and anxiety disorders.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

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