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Nataliia Koliada
candidate of Psychological Science, Senior Lecturer at the Department of Psychology, Political Science and Socio-Cultural Technologies, Sumy State University, Sumy, tel.: (050) 307-40-09, https://orcid.org/0000-0002-6108-3482

Kyrylo Deineka
Bachelor's student of the Department of Psychology, Political Science and Sociocultural Technologies, Sumy State University, Sumy, tel.: +380 (99) 722 84 14, https://orcid.org/0009-0000-2584-1832

THE BIOPSYCHOSOCIAL NATURE OF PAIN: FROM NOCICEPTION TO AFFECTIVE DISORDERS

Анотація. Біль розглядається як комплексний феномен, який не може бути описаним виключно ушкодженням тканин. За сучасними біопсихосоціальними концепціями, відчуття болю формується від лінійного кодування ноцицептивних сигналів у периферичній сенсорній системі, до інтеграції інформації у спинній нервові системі та мозку, з модуляцією завдяки когнітивним механізмам. Метою цієї роботи є комплексний аналіз та систематизація наявних наукових даних щодо процесів формування суб'єктивного сприйняття болю від нижчих до вищих.

У статті розглядаються типи периферичних нейронів, зокрема ноцицептивні А-дельта та С волокна сенсорних нейронів, а також механізми обробки інформації у спинному мозку за теоріями популяційного кодування, комбінаційного кодування та механізмами латеральної інгібіції, центральної сенситизації та просторової сумації. Щодо інтеграції больової інтеграції у мозку, розглядається теорія нейроматриці, яка постулює розподілення функцій між усім мозком, радше наявність незамінних регіонів, які відповідають за сприйняття болю.

Особлива увага приділяється двонаправленій взаємодії між спинною нервовою системою та мозком. Стаття розглядає найактуальнішу теорію низхідної модуляції болю, яка називається теорією предиктивного кодування. Вона описує роль помилок прогнозування, що опрацьовуються в межах таких структур мозку, як передня поясна кора та острівкова кора, у формуванні суб'єктивного сприйняття болю. Додатково, основними психологічними модулянтами цього процесу є увага, очікування, інтерпретація, тривога, стрес та депресія. У роботі описуються результати досліджень щодо нейробіологічних та психологічних механізмів медіації у формуванні суб'єктивного сприйнятті болю та фізіологічної реакції нервової системи.

Окремо розглядається явище хронічного болю при впливі тривалого стресу, а також його спільні нейрологічні процеси та висока коморбідність з депресією.

Ключові слова: сприйняття болю, ноцицептори, низхідна модуляція, предиктивне кодування, хронічний біль, стрес, депресія

Abstract. Pain is considered a complex phenomenon that cannot be described solely as tissue damage. According to modern biopsychosocial concepts, the sensation of pain is formed from the linear coding of nociceptive signals in the peripheral sensory system to the integration of information in the spinal nervous system and brain, with modulation by cognitive mechanisms. The aim of this work is to comprehensively analyse and systematise existing scientific data on the processes of forming subjective pain perception from lower to higher levels.

The article discusses the types of peripheral neurons, in particular nociceptive A-delta and C fibre types of sensory neurons, as well as the mechanisms of information processing in the spinal cord according to the theories of population coding, combination coding and the mechanisms of lateral inhibition, central sensitisation and spatial summation. Regarding the integration of pain in the brain, the Neuromatrix theory is considered, which postulates the distribution of functions throughout the brain, rather than the presence of irreplaceable regions responsible for pain perception.

Particular attention is paid to the bidirectional interaction between the spinal nervous system and the brain. The article discusses the most current theory of descending pain modulation, called Predictive Coding Theory. It describes the role of prediction errors, which are processed within brain structures such as the anterior cingulate cortex and insular cortex, in the formation of subjective pain perception.

Additionally, the main psychological modulators of this process are attention, expectation, interpretation, anxiety, stress, and depression. The paper describes the results of studies on the neurobiological and psychological mechanisms of mediation in the formation of subjective pain perception and the physiological response of the nervous system.

A separate consideration is given to the phenomenon of chronic pain under the influence of prolonged stress, as well as its common neurological processes and high comorbidity with depression.

Keywords: pain perception, nociceptors, descending modulation, predictive coding, chronic pain, stress, depression

Statement of the problem. There have been many breakthroughs in neuroscience, but despite this, pain can still be viewed as a physiological response to tissue damage, explained by simplified models of linear conduction of nociceptive impulses [5; 15; 20]. However, this approach is outdated and does not explain recent discoveries demonstrating that pain is a complex phenomenon shaped by a complex biopsychosocial structure [1; 26]. The problem lies in the insufficient recognition of the significant role of the brain in the formation of subjective pain perception, in which nociceptive impulses are actively processed in the central nervous system through bidirectional communication rather than being passively received [5; 20; 26].

Another important aspect of pain research concerns the limitations of classical neurophysiological models with modern theories, in particular predictive coding theory [4; 14; 24]. Although empirical data confirm the role of prediction and prediction errors in modulating pain perception, their systematic application to understanding pain remains limited. As a result, existing widespread models cannot fully explain interindividual differences in subjective pain perception, especially in cases where there are no tissue pathologies or differences in stimulus intensity [1; 5; 16].

The lack of a consistent theoretical explanation for the problem has direct clinical implications, as chronic pain has a high comorbidity with affective disorders, creating complex and ambiguous clinical cases [2; 9]. The lack of models that take into account both neurobiological pathologies (e.g., serotonin and noradrenaline pathways) and psychological factors such as catastrophising, attention, and anticipation limits the effectiveness of existing treatment approaches [10; 22; 25]. Therefore, there is an urgent need to develop an integrative approach capable of addressing both somatic and psychological aspects of pain within a single model.

Analysis of recent research and publications. The main neurobiological and psychological processes of pain perception have been described in the studies of J. P. Pinel & S. J. Barnes [20], R. C. Coghill [5], I. Tracey & P. W. Mantyh [26], and A. V. Apkarian [1]. The mechanisms of central sensitisation, lateral inhibition, and spatial summation are discussed in the works of R. Baron [3], Quevedo et al. [23]. The concept of the neuromatrix for pain processing in the brain was discussed in the works of R. Melzack and J. Katz [16]. Cognitive modulators were described in the works of Sprenger et al. [25], Valet et al. [29], Petrovic et al. [19]. Recent publications by Song et al. [24], Z. S. Chen [4], Lersch et al. [14] examined the mechanisms of descending regulation of pain perception according to Predictive Coding Theory.

The aim of this work is to conduct a comprehensive analysis and systematization of current scientific data regarding the neurobiological and psychological mechanisms of pain formation, ranging from peripheral nociception to central processing and cognitive modulation.

Objectives:

1. To describe the anatomical and physiological pathways of pain transmission (from nociceptors to the cerebral cortex).
2. To analyze the role of descending control and Predictive Coding Theory in pain perception.
3. To determine the influence of psychological factors (attention, expectation, anxiety, stress) on the intensity of pain sensations.
4. To elucidate the bidirectional relationship between pain and depression through shared neural and biochemical mechanisms.

Presentation of the main material of the study. According to the definition provided by the International Association for the Study of Pain, pain is ‘an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage’ [13]. Three types of neurons are involved in pain-related aspects: sensory, interneurons, and motor neurons [20]. Peripheral sensory neurons are those that transmit stimuli to the central nervous system. The leading theory regarding the transmission of stimuli by sensory neurons is the labelled line theory. It states that there are specific

neurons for each type of sensory information. This theory is confirmed by the presence of different types of sensory neurons depending on fibre types. A-alpha fibre type neurons are responsible for proprioception, A-beta for touch, A-delta for mechanical and thermal pain, and C-type neurons are responsible for the perception of mechanical, thermal and chemical pain. A-delta and C fibre type neurons are called nociceptors, i.e. those responsible for the perception of pain. Nociceptors in the peripheral sensory system are not attached to individual receptors but are free endings, i.e. they receive information about noxious stimuli through transmembrane proteins on their surface, which trigger an action potential in the event of tissue damage. However, unlike other types, C type has a non-myelinated sheath, so its conduction speed is much lower. This gives rise to the concepts of first and second pain. In the case of noxious stimuli, neurons with A-delta fibres transmit acute, localised sensation, while neurons with C fibres transmit dull and diffuse pain that follows the initial pain [20].

The cell bodies of peripheral sensory neurons are located in the dorsal root ganglion, from where information is transmitted to the grey matter in the spinal cord, where various types of spinal interneurons are located [20]. Previously, dorsal horns were considered only a passive station for transmitting information to the brain, but they are a place of active processing of stimuli, namely inhibition, excitation, and modulation [15]. In isolation, they are responsible for establishing the intensity and localisation of pain, as well as forming withdrawal responses [5]. The precise localisation of pain is established by means of a mechanism of lateral inhibition. This mechanism involves the most activated neuron in the spinal cord inhibiting neighbouring secondary neurons, which helps to accurately determine the spatial signal that is then sent to the brain [20]. A study Quevedo et al. [23], investigated the phenomenon of lateral inhibition, where the skin was heated with a laser in the form of a line or two points. In conclusion, it was found that regardless of the length of the lines, the level of pain did not change. When the skin was heated at two points, a distance of 4 centimetres had the same pain input as a line of that length, but at a distance of 8 centimetres, the pain was stronger. Accordingly, the closer the pain stimuli are to each other, the greater the lateral inhibition, and the longer the distance, the greater the facilitation through the mechanism of spatial summation. The phenomenon of spatial summation is that stimuli at a certain distance, when lateral inhibition does not work, can be summed up and increase in intensity. The main theories of integration of information from the periphery into the spinal cord are population coding theory [5] and combination coding theory [20]. Population coding theory considers that wide dynamic range neurons (WDR) play a role in pain integration [5]. These are neurons that integrate both noxious and non-noxious stimuli and identify pain stimuli by recruiting a large number of WDRs. High-intensity stimuli are layered, helping interneurons identify pain. In addition, the mechanism of spatial summation is at work, so greater coverage of the WDR receptive field by stimuli increases the likelihood of interpreting a painful stimulus. Combination coding theory posits that the sensation of pain is formed through the interaction of afferent neurons and interneurons [20]. For example, A-beta fibre type neurons can inhibit pain signals from C fibre type neurons by activating Substantia Gelatinosa (SG) interneurons, which in turn inhibit pain-specified neurons. This is why we can rub the affected area to reduce the sensation of pain. Another example of combination coding theory is a study [3] that investigated the effect of capsaicin on pain perception. High activity of C fibre type neurons enhanced the response of spinal interneurons, leading to a phenomenon called central sensitisation. This caused primary hyperalgesia, i.e. increased sensitivity to pain, in the primary injection site of capsaicin, and secondary hyperalgesia, i.e. non-nociceptive neurons transmitted pain stimuli through a change in transmission mechanisms. In addition, central sensitisation created allodynia, i.e. pain from non-painful stimuli.

Information about pain stimuli is transmitted through the dorsal horns to the brain. The thalamus acts as a station that simultaneously distributes information to different regions of the brain. However, this is not the only route, as some regions receive information bypassing the thalamus. For example, the parabrachial nucleus (PBN) transmits information directly to the amygdala. Pathways that are processed quickly help to subconsciously respond to pain stimuli through fight/flight [20]. According to the pain neuromatrix theory [16; 15], the processing of sensory, emotional, and cognitive information occurs in the brain's neural network, rather than in a specific region, and leads to the formation of subjective pain. A meta-analysis by Apkarian et al. [1] showed that the main regions of the brain that are activated during pain are: primary and secondary somatosensory cortices, which are responsible for sensory features of pain; insular and anterior cingulate cortices, which are responsible for the affective perception of pain; prefrontal cortices, which are responsible for cognitive evaluation; and the thalamus. In addition, it is noted that the ACC is also involved in the cognitive-evaluation stages of pain perception. However, there is no universal pain matrix [26], as many different elements can perform the same function in pain perception [5].

The connection between the brain and spinal cord is bidirectional, where the descending pain modulatory system helps us regulate nociceptive processing in the dorsal horn through inhibition or facilitation [26]. The brainstem, namely the periaqueductal gray matter (PAG), nucleus cuneiformis (NCF), dorsolateral pontine tegmentum (DLPT) and rostral ventromedial medulla (RVM), is the region through which different parts of the brain send descending signals to the spinal cord [26]. This descending nociceptive control is opioid-mediated. The periaqueductal gray matter (PAG) collects information about the necessary amount of anti-nociception, according to information from higher regions of the brain, and sends it to the spinal cord via the rostral ventromedial medulla (RVM) and dorsolateral pontine tegmentum (DLPT) [20].

The main theory of descending control is Predictive Coding Theory, which explains how the central nervous system encodes sensory stimuli [14; 24; 4]. It states that descending information is encoded in the form of predictions about sensory stimuli, including pain. In turn, actual inputs that do not match expectations are called prediction errors (PE), which move in an ascending path. In accordance with PE, predictions are updated, which helps to process information more efficiently in the central nervous system. In the context of pain, PE is influenced by nociception and modulating factors [14]. Modulating factors are those that change the way PE affects our expectations (enhances or inhibits the effect). According to Chen [4], the ACC-insula hub is central to Predictive Coding Theory. ACC signals in the VTA are associated with prediction, while reverse signals are associated with error-related feedback integration. In addition, the ACC processes the difference between prediction and prediction error. Speaking of the insula, the AIC encodes prediction errors (PE), while the PIC encodes pain intensity and expectations. The active inference algorithm described in the article suggests that with PE, the CNS either changes expectations or behaviour to avoid errors.

What are the modulators of subjective pain perception? One of the main ones is attention. Research by Sprenger et al. [25], has shown that with greater cognitive load, pain perception decreases due to activity in the dorsal horns. In addition, the partial role of opioids has been proven, since naloxone, an opioid receptor antagonist, increases pain perception, which negates the effect of cognitive load. The authors consider the rACC and PAG to be the main regions involved in the influence of attention on pain perception. Moreover, a study [6] found a direct connection between the ACC and the spinal cord. The results of a study by Tracey et al. [27] showed that less attention to pain stimuli was associated with greater PAG activity and, accordingly, a reduction in subjective pain. Another study by Valet et al. [29] showed a strengthening of the connection between the orbitofrontal (OFC) and perigenual anterior cingulate cortex (ACC), PAG and the posterior thalamus when distracted from pain perception, but not when in pain alone. The authors suggest that top-down signals from the OFC and ACC to the PAG and posterior thalamus may modulate pain perception during distraction. In addition, attention affects the spatial summation of pain. Thus, a study by Quevedo and Coghill [22] showed that when attempting to discriminate between pain stimuli, the effect of spatial summation disappears. The authors believe that the OFC, ACC, DLPFC and PAG are involved in this.

Speaking of other modulators of subjective pain perception, interpretation also plays an important role. Thus, **the placebo effect in the context of pain is interpreted as analgesic**. A study by Petrovic et al. [19] proves that the use of placebo anaesthesia is associated with the activation of the ACC and the opioid system, which may indicate the involvement of cognitive mechanisms in pain reduction. In addition, Gracely [10] found that catastrophising pain, i.e., perceiving it as terrible, unbearable, or catastrophic, increases the subjective perception of pain. People who catastrophise pain have increased attention (activation of ACC, DLPFC), anticipation (medial PFC), emotional response (claustrum, anterior insula), and motor components (lentiform nuclei).

Anxiety also affects the perception of pain stimuli. Thus, Ploghaus et al. [21] found that, given the same stimulus, the one accompanied by anxiety caused more subjective pain. Anxiety activates the entorhinal cortex, which is part of the hippocampal formation, and sends amplifying signals of pain perception. In addition, the ACC and insula are activated. A meta-analysis by Ocañez et al. [17] investigated the influence of Anxiety Sensitivity (AS), i.e. the tendency to interpret anxiety symptoms as threatening, on pain perception. AS emotionally amplifies pain perception.

The connection between pain and stress is very significant [16; 15]. First, nociceptive input itself causes a biological stress response due to a disturbance in homeostasis. Immediately after injury, cytokines are released, sending a signal to the brain about the injury, most quickly reaching the hypothalamus. Together with the information processed in the brain, they trigger the necessary actions, such as tissue repair, destruction of bacteria, etc. If the injury is serious, the noradrenergic system is activated, releasing adrenaline to activate the sympathetic nervous system to prepare the body for complex homeostasis

restoration. Then the hypothalamic–pituitary–adrenal (HPA) system is activated, releasing cortisol, which suppresses the immune system and affects the endogenous opioid system. Prolonged release of cortisol depletes the body, which can lead to the development of chronic pain, creating a vicious cycle [16; 15]. Psychological stress can negatively affect pain perception. For example, a study by Padhy et al. [18] found that preoperative stress lowers patients' pain thresholds and pain tolerance. Anxiety and previous negative experiences can also modulate this process.

Pain and depression have a high comorbidity. Thus, approximately 30-60% of patients with pain have comorbid depression [2]. However, the relationship between them is bidirectional, i.e., pain can cause depression, just as depression can cause chronic pain [9]. For example, psychological distress can cause chronic widespread pain [11], and baseline pain increases the risk of developing depression [7]. There is an overlap between psychological pain and the affective-emotional aspects of physical pain in brain regions such as the anterior insula, PFC, ACC, thalamus [9], amygdala and hippocampus [8]. This may explain how pain and affective disorders reinforce each other. There are also similarities in neurotransmitters, as serotonin and noradrenaline are involved in both pain and mood processing [9]. This also explains why antidepressants may be recommended for pathological pain due to their analgesic effect [12]. In addition, cognitive aspects can also influence both pain and depression. One of the main ones is catastrophising [30].

Also, negative affectivity in people with chronic pain may be a risk factor for depression [9]. In addition, in people with chronic pain, risk factors for the development of depression may include behaviours that contribute to insufficient sleep [28] and behaviours associated with fear avoidance [31]. Therefore, despite the absence of direct causal models, there are many biological and psychological factors that influence and interrelate pain and depression.

Conclusion. This article describes the complex, multidimensional process of pain perception, demonstrating that it is not limited to passive sensory responses to tissue damage through the conduction of pain stimuli from the peripheral sensory system to the central nervous system. Analysis of the mechanisms of the peripheral sensory system and the integration of sensory information in the spinal cord and brain confirms that pain perception is an active process modulated not only by physiological aspects. The combination of common theoretical concepts, such as labelled line theory, population coding theory, combination coding theory, and modern concepts of neuromatrix and predictive coding theory, emphasises the integrative ability of the central nervous system.

The key conclusion of this paper is the role of descending modulation within the framework of predictive coding theory. To preserve energy and respond appropriately to pain stimuli, the brain does not simply passively receive nociceptive signals, but actively predicts them. Subjective pain, without somatic causes, often arises from prediction errors processed in the anterior cingulate cortex and insular cortex. This explains why cognitive factors such as attention, expectation, anxiety, and catastrophising can modulate pain intensity through direct connections to the spinal cord or opioid system, which includes the PAG and RVM.

In addition, the high comorbidity of chronic pain and depression highlights a bidirectional relationship that may involve shared neurobiological processes, including serotonergic and noradrenergic pathways. Available data indicate that psychological stress not only modulates the increase or decrease in pain perception, but also exhausts the body, which can lead to the development of chronic pain. Therefore, understanding the mechanisms of subjective pain perception for effective application in further research and practice requires a transition to a comprehensive biopsychosocial approach that focuses not only on neurobiological processes but also on psychological mechanisms that modulate the experience of pain.

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