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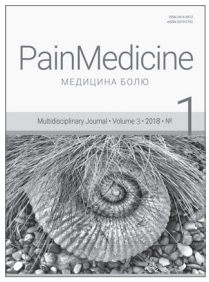

Theories of pain, up to Descartes and after neuromatrix: what role do they have to develop future paradigms?

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Abstract. *The article represents a synthesis of literature about antique, medieval and modern pain theories. In short there are described the most relevant theories about nociception and pain. Chronologically there are presented the discoveries in physiology, anatomy, histology and other methods and investigations of pain. There is discussed the character of past pain theories and its influence on elaboration of the new ones. There was elaborated the hypothesis about the neuromatrix theory and impact of human microbiota on pain perception or other comorbidities with psychological and pain component.*

Key words: *history of medicine, pain theories, neuromatrix, human microbiota.*

There is occasions and causes why and wherefore in all things
William Shakespeare (1564–1616), King Henry V, V.i.
Mighty things from small beginnings grow
John Driden (1631–1700), Annus Mirabilis

Introduction

Periodically, in the scientific medical journals are published articles on the history of medicine, including in the field of pain. The result of working in the archives of medical history of the enthusiasts, is already synthesized, integrated and accessible today, to practically everyone. Although it is impressive, viewed from a historical perspective, the amount of knowledge held is somewhat constant, finite as available information, in particular, relative to the scale of today's information age.

Consequently, most authors give the same data, depending on the possibility of access to archives or the degree of documentation in the field, data, that are seen from one point of view or another. Thus, traditionally, there are presented the ancient and medieval theories (up to Descartes), philosophical of pain, which reflect the thinking, culture and conceptions of the world of the civilization of that time [1, 2, 3].

The modern age is reflected in the structural and functional theories of pain, starting from nociceptor and reaching the central nervous system. Typically, they describe the microscopic level of structures, which at this level maintain certain functions (potentials of action, coded by intensity and frequency or centrifuge axiomatic biochemical flow) [1–3, 7].

The theories and contemporary models of pain (control gate theory, neuromatrix theory, multidimensional model of pain etc.) hold the full conceptual power at present. And these theories are based on structures and functions, which, however, in the light of today's technology, are viewed, described and explained on a submolecular, informational or oversized interaction scale.

Undoubtedly, sooner or later, these theories and patterns will be updated with new ones...

In view of the above, I propose, however, an article of history of pain theories... Why another article on pain theories?

I consider, that new generations of specialists in trening, would be useful to review the evolution of pain theories over the centuries. These theories, in their time, were the basis for the development of pain-fighting methods and techniques, the pharmacological industry with analgesics, institutional and national organizational measures to fight pain. The new theories of pain go beyond the pure pharmacological and physical approach to pain, requiring a biopsychosocial, multidimensional and interdisciplinary approach.

I intend not break the "traditions" of displaying history articles, but up to a certain point. After that, I will try, based on "history", to formulate a hypothesis of a (future?) pain theory: what beyound neuromatrix? Because, "Progress is not an accident, but a necessity... It is a part of nature". (Herbert Spencer [1820–1903], Social Statistics).

Pain Theories up to Descartes

The ancient theories of pain reflected the philosophical ideas of time about life, existence, perception of the world, based on empirical reflections. Their essence is presented in Table 1.

The main questions about pain, have remained unresolved for centuries: pain appears as a result of the activity of a dedicated neural device or is the product of a less specific process?

Modern age: from specificity of structures and functions to gate control theory

Until the second century. XIX, it was thought that the senses depend on the transport of some substance out of the brain or heart.

Century. XIX has been characterized by the co-existence of three concepts: (1) pain is an emotion (the ancient philosophers and the psychologists of the times); (2) pain is a sensation, with sense organs and own transmissions (Avicenna, Schiff); (3) Intense stimulation of other related systems that serve other sensations generates pain over a certain threshold (Erb, psychologists, doctors).

One of the arguments, against the theory of pain specificity, was that pain can also be produced by mechanical, thermal or chemical stimuli, which are different in terms of the receptive structure and the nociceptive pathway. The polemics in the "specificity theory" continued until the 1970s, XX century.

The most important findings on nociception and pain between 1911 and 2003 years, are listed in Table 2.

Fig. 1. The humoral theory of pain (Hippocrates and Galen).

Hippocrates and Galen believed that all the illnesses came from the four fluids of the body: the phlegm, the yellow ball, the black ball and the blood. The flow and reflux of each of the fluids is a response to changes in the body or the environment. Pain is caused by increased blood viscosity, which stops flowing from each narrow passage in its path

Theories of specificity

The essence of the theory lies in the fact that each somato-sensorial mode (somatosensorial modality) is dedicated to a specific way of transmission. A specific receptor that is sensitive to a particular stimulus is connected to a primary sensory nerve fiber. For example, mechanical stimuli are detected by low threshold mech-

Table 1. The ancient concepts of pain (synthesis 1–3, 7)

Century. VIII BC	*Homer*	Telemachus, son of Ulises and Penelope (Iliad and Odyssey), use opium to relieve pain and drive out sadness
Approx. 460–370 BC	*Hippocrates of Kos*	Pain comes from the body fluids. The heart is the main organ of pain perception (Fig. 1)
437–347 BC	*Platon*	Pain, as well as pleasure, is a passion for the soul
384–322 BC	*Aristoteles*	Evil spirits penetrate the body through various injuries. The heart is the center of the senses. He did not consider pain as a special sense, but was an emotion
130–201 AD	*Galen*	The brain is the organ of the senses, and the pain was placed in the sphere of sensations
Dark ages	–	Pain exists everywhere outside of the human body. This, being sinful, suffers. Only prayer (or fire) can alleviate the pain. Pain and suffering is a divine test
980–1037 AD	*Avicenna*	Pain is an independent feeling, different from touch or thermal
1596–1650	*René Descartes*	The body is a machine. I think, therefore I am
1642–1727	*Isaac Newton*	Neural messages are the vibration of the substance in the nerves
1705–1757	*David Hartley*	Neural messages are the vibration of the substance in the nerves

anoreceptors, and the primary sensory nerve fiber transmits the impulse to the second neuron, and it is "mechanoreceptive", in the spinal cord or the cerebral trunk. The secondary "mechanoreceptive" neurons, in turn, project to the cortical structural receptors. Similarly, noxious stimuli will be projected to "higher pain centers" through nociceptive fibers (Dubner et al., 1976).

Gate control theory

Proposed in 1965 by Ronald Melzack and Patrick Wall, the theory provides a physiological explanation of the findings made in the psychology of pain perception. She "reconciled" the theories of specificity and patterns, revolutionized research into nociception and pain.

Table 2. The most important findings on nociception and pain (According to Edward R. Perl [7], with adaptation)

Year	Scientist	The essence of the discovery or concept
1811	*Bell C.*	The medial dorsal and ventral pathways have different function, the ventral ones being responsible for muscle contraction. Sensory nerves have specialized functions to detect and transmit a particular stimulus
1822	*Magendie F.*	Dorsal medullary transmit sensitive messages
1840	*Müller J.*	He developed Bell's idea. Related neurons have specific (specialized) functions
1848–1849	*Dubois-Reimond E.*	Identifying the potential for action in the nerve, which is electrochemical in nature (inspired by Müller's ideas). Nerve impulses transmit to the brain some of the information about the nature of the stimulus
1858	*Schiff J.*	Magendie's student. Medullary lesions induce different reactions to the application of painless peripheral stimuli. Pain is a specific sensitivity. Spinal lesion produces loss of tactile sensitivity to painfulness
1860	*Brown-Séquard C.*	Has demonstrated dissociation of painful sensation from tactile sensitivity in experimental spinal lesions. He found loss of contralateral pain distally and distally from transverse medial hemispheres
1874	*Erb W.*	Issues the theory of intensity for pain. Strong stimulation of other sensory ways is painful. The intensity determines the response
1878	*Gowers W.*	Describes the dissociation of painful sensation from tactile sensation into bone marrow lesions in humans
1884	*Blix M., Goldscheider A.*	Skin sensitivity is discontinuous. They described the mosaic of nociceptive and sensory (pressure, warm, cold) receptor fields. The last – the follower of Erb's theory of intensity
1890	*Edinger L.*	Identified the cross-linking of the related (spinotalamic) tract in the spinal cord. The dorsal medial paths consist of the middle beam, made up of large diameter and lateral fibers (thin fibers)
1891	*Waldeyer W.*	The brain is not a syncytium, but consists of distinct cells. Synapses are functional connections between cells
1896	*Von Frey M.*	Described circumstantial correlations between the number of skin sensory receptors and structured nerve endings. Ultimate demonstration that pain is an independent sensory way
1905	*Head H.*	Describes somatic (epicritic, discriminative) and protopathic (diffuse) sensory innervation, consistent with Edinger L.'s anatomical descriptions
1906	*Sherrington C.*	Because pain is usually produced by tissue damage, it has been proposed to introduce the lesion (noxious) stimulant category that is painful regardless of its physical nature. Specialized structures for pain are responsible for nociception. In addition to excitation, inhibition of excitation in neuronal circuits is essential for integrative activity
1906–1911	*Dejerine J., Roussy G., Head H., Holmes G.*	Describe the role of the thalamus in pain
1912	*Spiller W., Martin E.*	They presented a ventral lateral medullar cordotomy to relieve rebel pain, located on the opposite side of the section
1915	*Ranson S.*	Primary afferent primary diameters are protopathic and lead, in part, painful stimuli
1924–1928	*Erlanger J., Gasser H., Bishop G.*	Describe the complexity of the peripheral nerve potential and its relationship to the diameter of the nerve fiber. Nerve fibers with different driving speed are involved in pain

Year	Scientist	The essence of the discovery or concept
1926	*Adrian E., Zotterman Y.*	Recording the potentials of action on unique nerve fibers. Different stimuli (thermal, brushing, stretching etc.) produce selective discharges into distinct nerve fibers
1929	*Nafe J.*	Issues the theorem patterns for the description of nerve activity, which gives specific characteristics to the applied stimulus. Stimulation mode allows the formation of a compound signal, emitted by a population of related nerve fibers
1933	*Heinbecker P., Bishop G., O'Leary J.*	Pain in humans is produced by activating thin nerve fibers
1936–1939	*Zotterman Y.*	Intense stimulation of type C nerve fibers causes pain. Some are activated by fine tactile stimuli (gentle stimuli). The existence of nociceptors was questionable
1942–1952	*Lewis T., Hardy J., Woolf H., Goodell H.*	Description of primary and secondary hyperalgesia
1948–1955	*Weddell G., Sinclair D.*	Neuronal Specificity in Skin Sensitivity
1962–1965	*Melzack R., Wall P.*	Spatial and temporal patterns of nerve activity underlie skin sensory perceptions. Portion Control Theory (1965)
1967	*Burgess P., Perl E.*	Describe free myelinated nerve fibers as nociceptors
1969	*Bessu P., Perl E.*	Describe polyimodal nociceptors of C-fibers and the phenomenon of sensitization
1970	*Christensen B., Perl E.*	Describes nociceptive neurons in marginal medullary areas
1972	*Mantih P., Trevino D.*	Identification of spinotalamic neurons by antidromic and retrograde tracing
1973	*Pert C., Snyder S.*	Identifies opioid receptors
1973–1977	*Price D., Mayer D.*	Describe the wide dynamic range (WDR) neurons in the spinotalamic tract
1975	*Hökfelt T.*	Identifies expression peptide (P-peptide-linked calcitonin gene) migration into the primary afferent fibers
1981–1983	*Konietzny F., Ochoa J.*	Micronucleus stimulation in conscious individuals, has shown that nociceptor excitement, but not the downward, threshold mechanism mechanoreceptors, causes pain
1983	*Woolf C.*	Demonstrates central sensitization in spinal nociceptive pathways
1997	*Rainville P.*	Using positron emission tomography (PET-scan) and fMRI has been demonstrated differentiated cortical activation previously cingulated by painful stimuli
1997	Caterina M.	Describes the receptors for capsaicin and notes that they confer properties responsive to polymodal nociceptors
2003	Craig A.	Pain is a homeostatic emotion

The essence of the theory is that the painless impulses transmitted through thicker, myelinated (Aβ) fibers will close the "gate" of painful impulses (transmitted through the myelinated Aδ and unmyelinated fibers, type C), thus preventing them from reaching the central nervous system. Inhibition is presynaptic and involves interneurons in the structure (Fig. 2). Although the conceptual structure of the neural circuit is simple schematized, it is much more complex, both as a network and biochemical composition.

Contemporary theories

The theory of neuromatrix

According to Ronald Melzack (2005) [citation]: "The neuromatrix theory of pain proposes that pain is a multidimensional experience produced by characteristic "neurosignature" patterns of nerve impulses generated by a widely distributed neural network – the "body-self neuromatrix" – in the brain. These neurosignature patterns may be triggered by sensory inputs, but they may also be generated independently of them. Acute pains evoked by brief noxious inputs have been meticulously investigated by neuroscientists, and their sensory transmission mechanisms are generally well understood. In contrast, chronic pain syndromes, which are often characterized by severe pain associated with little or no discernable injury or pathology, remain a mystery. Furthermore, chronic psychological or physical stress is often associated with chronic pain, but the relationship is poorly understood. The neuromatrix theory of pain provides a new conceptual framework to examine these problems. It proposes that the output patterns of the body-self neuromatrix activate perceptual, homeostatic, and behavioral programs after injury, pathology, or chronic stress. Pain, then, is produced by the output of a widely

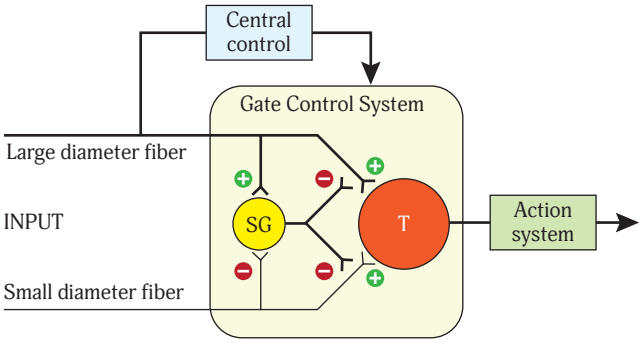

Fig. 2. Gate control theory of pain

distributed neural network in the brain rather than directly by sensory input evoked by injury, inflammation, or other pathology. The neuromatrix, which is genetically determined and modified by sensory experience, is the primary mechanism that generates the neural pattern that produces pain. Its output pattern is determined by multiple influences, of which the somatic sensory input is only a part, that converge on the neuromatrix" [4, 5].

What beyound neuromatrix?

As it observed, most of the pain theories are not "global" but "localized" to body structures or functions: receptors (intensity and specificity), coding of information (neural patterns), dorsal medulla (portion control theory), central nervous system (neuromatrix theory). Other important elements are the figures of a puzzle – beliefs, memory, previous experiences, stress, central and peripheral sensitization, downward modulation, cortical plasticity and retography, neuroimmuno-humoral mechanisms etc. (Fig. 3).

The human body is whole. Any structure and function at any scale can be studied and presented individually, separately. In reality, however, "everything is connected to everything", functioning as a whole. In this way, each pain theory has its place, reflecting an element in the puzzle. Could a new theory of pain go beyond the neuromatrix scale, so that the puzzle is the final picture?

What would be after neuromatrix? Which elements could complement it?

Here we can mention nonperceptual influences on neuromatrix, its interaction with other body analyzers (seeing, hearing, smell, taste, touch). Recent studies have found the connections between the olfactory analyzer and the visual eye with neuromatric pain. Applications, which will clarify these issues, are of the future [8, 9, 10].

Brain matrix and the missing element of pain: gut microbiota

From a certain point of view, humans can be considered superorganisms, which are composed of the human and the microbial component. With the help of contemporary biotechnology and information technologies, it has been found that microbial communities within the human body can alter their lifestyle, behavior, influence the perception of pain or induce/favor the occurrence of many diseases (Fig. 4).

The human intestine hosts, under anaerobic conditions, over 100 trillion microorganisms, which are representative of over 1.000 distinct species. Recently, there was a bidirectional link between the intestine and the brain, where the microbial composition can influence behavior and cognition, and the nervous system in turn – the microbial composition of the intestine. Bacterial metabolites (up to 99% undetected), vagus nerve, immune system, hypothalamic-pituitary-adrenal axis

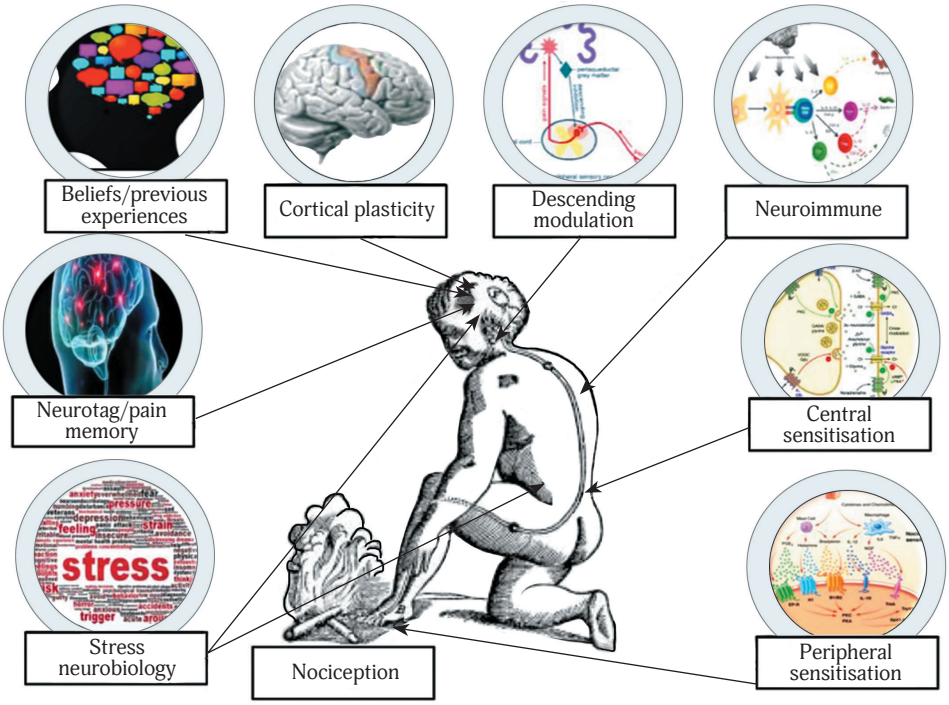

Fig. 3. The Puzzle of Pain: each element with its own picture (According to: Ben Cormack, 2017)

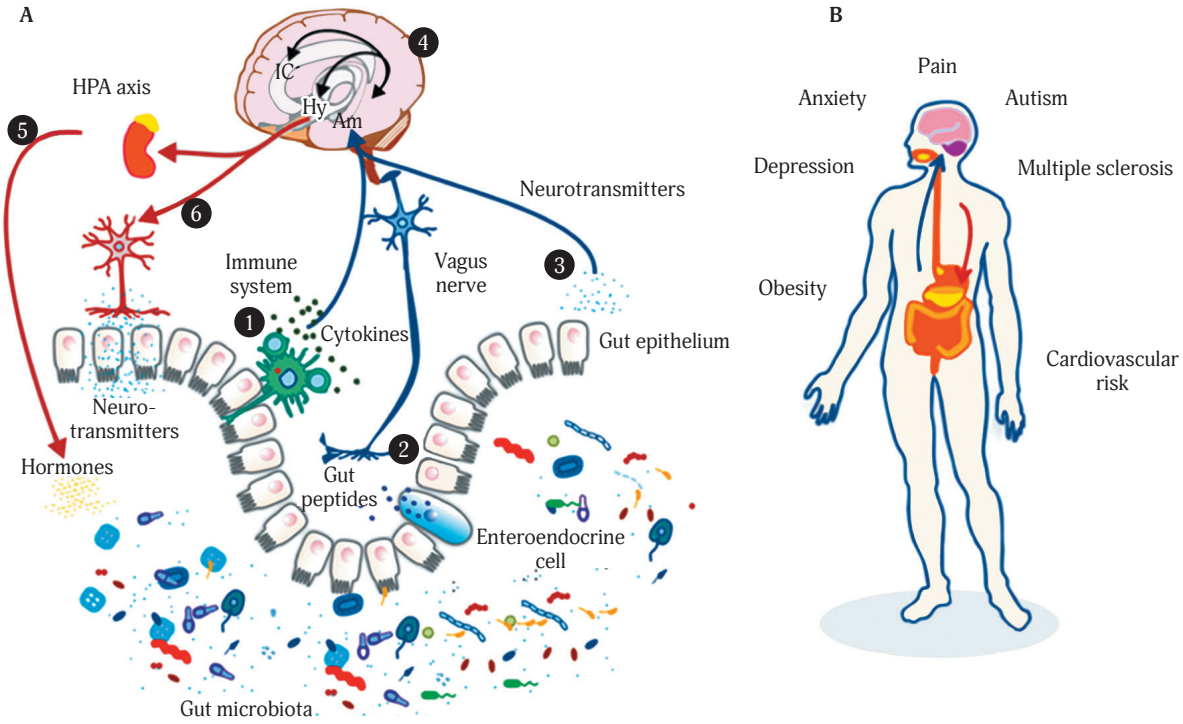

Fig. 4. Gut microbiota, pain and other health-related conditions. Exact citation, according to Montiel-Castro A. et al., 2013 [11]): *(A)* "Direct and indirect pathways support the bidirectional interactions between the gut microbiota and the central nervous system (CNS), involving endocrine, immune and neural pathways. On the afferent arm (blue arrows): (1) lymphocytes may sense the gut lumen and internally release cytokines which can have endocrine or paracrine actions, (2) Sensory neuronal terminals, such as on the vagus nerve may be activated by gut peptides released by enteroendocrine cells, (3) Neurotransmitters or its precursors produced as microbiota metabolites may reach the gut epithelium having endocrine or paracrine effects. (4) Centrally, after brainstem relays (e.g., nucleus tractus solitarii) a discrete neural network has been described consistently involving the amygdala (Am) and the insular cortex (IC) as main integrators of visceral inputs. Consistently hypothalamic (Hy) activation initiates the efferent arm (red arrows): (5) corticosteroids, release as results of the hypothalamic–pituitary–adrenal (HPA) axis activation, modulates gut microbiota composition. (6) Neuronal efferent activation may include the so called "anti-inflamatory cholinergic reflex" and/or sympathetic activation, both liberating classica neurotransmitters that may affect directly the gut microbiota composition. *(B)* Health conditions affected by the MGB axis. Recent and growing evidence suggests that several health conditions may be affected by intestinal microbiota, including: visceral pain (McKernan et al., 2010; Wang et al., 2010; Clarke et al., 2012), autism spectrum disorders (Adams et al., 2011; de Theije et al., 2011; Thomas et al., 2012; Wang et al., 2012), obesity (Turnbaugh and Gordon, 2009; Davey et al., 2012; Manco, 2012), cardiovascular risk (Tang et al., 2013), anxiety/depression (Bravo et al., 2011; Heijtz et al., 2011; Foster and McVey Neufeld, 2013), and multiple sclerosis (Berer et al., 2011; Lee et al., 2011)"

are involved in generating various pathological conditions: depression, anxiety, irritable bowel syndrome, neurodevelopmental disorders (autism, Parkinson's disease, Alzheimer's disease).

Bacterial metabolites, in particular, of the bioactive lipid class (N-acylethanolamine [NAE] class – N-arachidonoylethanolanine [AEA], palmitoylethanolamide [PEA], oleoylethanolamide [OEA], short chain fatty acids, such as butyrate[short chain fatty acids, SCFAs]) are able to modulate peripheral and central pathological processes. The role of these substances has already been demonstrated in the generation and maintenance of inflammation, neuroinflamation, acute and chronic pain, obesity, central nervous system disorders [6].

And this new direction of study will, as far as we can see, significantly complement our knowledge of ourselves, including those related to nociception and pain.

Instead of conclusions

Even the most contemporary theories of pain were based on the knowledge gained from older theories. In turn, they will be the platform for generating new knowledges to formulate the next generation of pain theories.

"This is not the end...
It is perhaps the end of the beginning"
Whinston Churchill (1874–1965)
Speech at the Mansion House, 10 November 1942.

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Теорії болю: до Декарта і після нейроматрикса: яка їхня роль в розвитку майбутніх парадигм?

Яна Бурмістр

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Резюме. *Стаття є синтезом літератури щодо античних, середньовічних і сучасних теорій болю. Якщо коротко, описано найважливіші теорії ноцицепції та болю. У хронологічному порядку представлено відкриття фізіології, анатомії, гістології та інших методів діагностики болю. Обговорюється роль теорій минулих століть і їх впливу на розробку нових. Було сформульовано гіпотезу щодо розвитку теорії нейроматриксу, враховуючи появу нових даних про вплив людської мікробіоти на появу і перцепцію болю або інших супутніх патологій із психологічним або больовим компонентом.*

Ключові слова: *історія медицини, теорії болю, нейроматрикс, людська мікробіота.*

Теории боли: до Декарта и после нейроматрикса: какова их роль в развитии будущих парадигм?

Яна Бурмистр

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Резюме. *Статья является синтезом литературы относительно античных, средневековых и современных теорий боли. Вкратце, описаны наиболее важные теории о ноцицепции и боли. В хронологическом порядке представлены открытия физиологии, анатомии, гистологии и других методов диагностики боли. Обсуждается роль теорий прошлых веков и их влияния на разработку новых. Была сформулирована гипотеза относительно развития теории нейроматрикса, учитывая появление новых данных о влиянии человеческой микробиоты на появление и перцепцию боли или других сопутствующих патологий с психологическим или болевым компонентом.*

Ключевые слова: *история медицины, теории боли, нейроматрикс, человеческая микробиота.*