MEDICINA NEI SECOLI
Journal of History of Medicine and Medical Humanities
37/2 (2025) 43-52

Received: 10.03.2025
Accepted: 30.05.2025
DOI: 10.13133/2531-7288/3161

Corresponding Author:
grignolio.andrea@hsr.it

The Last Four Centuries of Pain: Philosophical Roots, Physiological Discoveries, and the Neurocognitive Frontiers of Treatments

Andrea Grignolio Corsini

History of Medicine, Faculty of Medicine & Surgery, Vita-Salute S. Raffaele, Milan, Italy

Abstract

This paper traces the evolution of pain theory from René Descartes' 17th-century mechanistic model, which linked pain to neural signals and the pineal gland, through the Enlightenment's integration of physiology and psychology by von Haller, Cabanis, and Bichat. The 19th century's Specificity Theory, advanced by Bell, Magendie, and Müller, identified distinct neural pathways and sensory receptors but faced debate over pain's uniqueness. The 20th century introduced temporal and integrative perspectives, highlighting central modulation and cognitive influences on pain perception. Melzack and Wall's Gate Control Theory revolutionized pain science by demonstrating spinal gating mechanisms modulated by both peripheral and brain signals. Later, multidimensional models emphasized sensory, emotional, and cognitive components, supported by neuroimaging evidence of complex brain networks involved in pain processing. This historical and scientific overview underscores pain as a dynamic, multifaceted experience shaped by biological, psychological, and social factors, informing contemporary approaches to pain diagnosis and treatment.

Keywords: Pain - Chronic pain - History of neuroscience - History of Medicine

Introduction

The birth and history of medicine were made possible by pain. Since its dawn, the figure of the healer in its various incarnations, first and foremost that of the shaman, has played the role of the "mediator of pain" in the early human villages and communities. Despite being at the center of medical reflection, though, the concept of pain is still one of the most elusive.

The understanding of pain has undergone a profound transformation from metaphysical interpretations to neurobiological frameworks. Early conceptions, such as those proposed by René Descartes in the 17th century, framed pain through a mechanistic and dualistic lens, laying the groundwork for the Specificity Theory, which posited distinct neural pathways dedicated to pain, as discussed in the next paragraph.

The Enlightenment era catalyzed a paradigm shift, integrating physiology, psychology, and nervous system anatomy into pain science through the work of thinkers like von Haller, Cabanis, and Bichat. The 19th century further refined the Specificity Theory through discoveries in neuroanatomy by Bell, Magendie, and Müller, advancing the idea of sensory specialization. However, challenges to this model prompted the emergence of temporal-integrative and multidimensional theories, recognizing pain as a complex, subjective experience shaped by central processing and emotional states. Recent advances in neuroimaging and molecular neuroscience have revealed that pain arises from dynamic brain networks, especially in chronic conditions, where plasticity and connectivity are altered. This paper explores the evolution of pain theories, tracing their philosophical, anatomical, and psychological foundations.

1. Descartes and the Dawn of the "Theory of Specificity"

The Specifity theory saw pain as an independent sensation with its own sensory apparatus[1]. René Descartes was among the first Western philosophers to provide a detailed description of the somatosensory pathways in humans. In the *Principles of Philosophy* (1644) he put forth his insights on phantom limb pain, originally advanced in the *Sixth Meditation* (1641), proposing that the experience of pain originated in the brain rather than in the phantom limb[2].

He linked the sensation of pain to persistent neural agitation and suggested that the "soul of pain" resided in the pineal gland. The concept of the soul was incorporated by Descartes to align his theories with Church doctrine—where pain was considered a consequence of original sin. He rejected the idea that pain was a specific sensation, instead viewing it as a general response linked to touch. His dualistic model of pain separated it into sensory (physical) and psychic domains, presenting them as reciprocally exclusive[3].

In his posthumously published *L'Homme* (1644), Descartes illustrated his pain model using the famous example of a boy withdrawing his foot from a fire. He described pain

as the activation of a thread-like fiber traveling from the foot to the brain. This mechanistic explanation was influenced by William Harvey's model of blood circulation, which described valves as doors regulating the flow of fluids and preventing reflux[4].
The great French philosopher's work marked a significant milestone in pain research, paving the way for the localization of cerebral functions and distinguishing pain from emotional states like sadness. He argued that sadness followed pain as the soul's recognition of the body's fragility.
Descartes' groundbreaking ideas stood in opposition to English empiricism, which emphasized inductive reasoning and profoundly shaped British scientific traditions. In contrast, Descartes' mechanistic and reductionist approach guided the development of French science. This intellectual divide influenced research methodologies and scientific paradigms throughout the 18th century[3].

Progress in Pain Theories During the 18th Century

The age of Enlightenment, influenced by the decline of Church authority, marked significant changes in medical thought, a shift extended to the understanding and definition of pain. The legacy of 18th-Century can be summarized by the contributions of von Haller, Cabanis, and Bichat who, in different biomedical areas, marked a paradigm shift in pain science. Their work transitioned from purely mechanical models to a holistic understanding of pain that integrated physiology, psychology, and nervous system functions[5].
The Swiss physiologist von Haller (1708-1777) played a pivotal role in reshaping pain theories according to a mechanistic view. He differentiated the irritability of muscle fibers (contractibility) from the excitability of nerve fibers (sensitivity). He argued that only nerves produce sensations and that parts of the body disconnected from the nervous system cannot experience pain. von Haller's strict division between conscious nerve sensitivity and unconscious muscle irritability laid the groundwork for modern research into pain mechanisms. His work highlighted the roles of muscle fibers and nerves, a focus that remains relevant in pain science today[6].
The French physiologist Pierre Jean George Cabanis (1757-1808) opposed von Haller's theories, highlighting the emotional and psychological aspects of pain. He adopted a unique vitalistic stance, advocating for an intermediate perspective that balanced vitalism with scientific empiricism. This approach positioned him as a precursor to psychophysiology[7].
He proposed that pain, inherently tied to pleasure and sensitivity, serves physiological and therapeutic purposes, such as stabilizing the nervous and muscular systems. This perspective led to innovations like electrical stimulation as a pain treatment. Cabanis also introduced the idea that pain can arise spontaneously in the brain, linking physical pain to mental processes, then restoring the Galenic concept of "hypochondria"

in physiological terms. He understood pain as a dynamic interaction between internal and external sensations, where dominant stimuli suppress weaker ones, shaping the overall perception. Cabanis' psychophysiological approach marked a significant shift in treating pain, combining physical and emotional components, and laid the foundation for holistic treatment strategies[5].

The third key representative of the Enlightenment concept of pain is the French anatomist Xavier Bichat (1771-1802). He advanced pain research by distinguishing between the sympathetic and parasympathetic nervous systems. He proposed that these systems have separate centers—one in the brain and the other in ganglia—and produce distinct types of pain. His perspective was also in line with the vitalist school and consequently represented a further criticism of von Haller's mechanistic view.

Bichat's work highlighted the importance of the sympathetic nervous system in pain processing and supported a more integrated understanding of pain. His findings, along with Cabanis' theories, contributed to the rise of psychophysiological and multidisciplinary approaches to pain management, including the increased use of opium for treatment.

By fostering a shift from mystical and theological explanations of suffering toward empirical observation and rational analysis, Enlightenment thinkers catalyzed the development of medicine as a scientific discipline. This intellectual transformation encouraged the integration of anatomy, physiology, psychology, and later neurology in understanding pain as both a biological and subjective experience, paving the way for modern approaches to pain diagnosis and treatment[8].

The 19th Century development of Specificity Theory

The concept of a dedicated pain pathway, known as the "Specificity Theory", was pioneered by the Scottish neurologist Charles Bell (1774-1842) in his essay *Idea of a New Anatomy of the Brain* (1811), later republished in 1868. Bell challenged Descartes' notion of the brain as a "common sensorium" and, drawing on earlier work by the English anatomist Thomas Willis, proposed that the brain is a heterogeneous structure. He provided evidence that nerves consist of bundles of specialized neurons for distinct functions, including sensory, motor, and "vital" neurons connected to the mind rather than the brain. Bell distinguished between sensory perception (e.g., nociception) and its experiential counterpart (e.g., pain), laying the foundation for the idea of a pain-specific pathway.

The French physician and founder of experimental physiology François Magendie (1783-1855) developed Bell's research by determining distinct motor and sensory nerve routes (dorsal roots and ventral roots) in the spinal cord, a discovery codified as the Bell-Magendie Law. His contributions, alongside those of the Mauritian physiologist Charles-Édouard Brown-Séquard (1817-1894), advanced neurophysiology and clarified the organization of the nervous system[9,10].

The German physiologist Johannes Peter Müller (1801-1858) further synthesized these discoveries in his *Manual of Physiology* (1833-1840), proposing that each sensory receptor responds to a unique "specific energy", such as warmth or pain, regardless of how it is stimulated. This idea influenced subsequent work on sensory specificity, such as Erasmus Darwin's early evidence for heat-specific nerves.

The identification of specialized cutaneous receptors—such as Pacini and Meissner's corpuscles—reinforced the concept of sensory specialization. However, the lack of a distinct nociceptor, a structure dedicated to processing pain stimuli, fueled discussions on whether pain constitutes an independent sense or merely a psychological construct. This debate echoes Platonic and Aristotelian perspectives, which frame pain as an emotional experience and the opposite of pleasure.

Additional support for the Specificity Theory emerged in the mid-19th century. Schiff and Woroschiloff demonstrated the existence of two distinct spinal cord pathways: the anterolateral tract for pain and temperature and posterior bundles for tactile sensation. Their work, corroborated by William Richard Gowers, showed that these pathways had unique characteristics, such as decussation patterns, further reinforcing the theory[3].

By the late 19th century, researchers such as Magnus Blix (1849-1904), Alfred Goldscheider (1858 -1935), and Max von Frey (1852-1932) investigated sensory spots on the skin, each responsible for a specific sensation: warmth, cold, pressure, or pain. von Frey's experiments, utilizing calibrated "von Frey hairs" (precursors to modern aesthesiometers), demonstrated that pain and innocuous pressure originated from distinct spots on the skin, associated with free nerve endings and Meissner's corpuscles, respectively. He proposed a mosaic-like distribution of sensory modalities across the skin, offering an anatomical basis for the Specificity Theory[11,12,1].

Despite its advancements, the Specificity Theory faced challenges, including the lack of identified pain receptors and pathways specific to pain. These gaps fueled alternative models, such as the Temporal Theory, yet the Specificity Theory remains a cornerstone in understanding somatosensory processes and the neuroanatomy of pain.

The Temporal-Integrative Theory

During the early 20th century, pain research underwent a paradigm shift, moving from a receptor-centric model to a focus on temporal dynamics, neural conduction speed, and central integration. Researchers began to understand pain as a complex interaction between peripheral stimuli and central processing mechanisms influenced by both cognitive and emotional factors.

One of the foundational contributions came, again, from Goldscheider, who identified the temporal summation of pain—where repeated, low-intensity stimuli resulted in disproportionate increases in perceived pain. His findings are now recognized as early

evidence for central sensitization, a key mechanism in chronic pain conditions. He also discovered distinct skin zones that transformed from pressure-sensitive to pain-sensitive areas, suggesting dynamic plasticity in sensory processing[11].

Henry Head (1861-1940) advanced these ideas by proposing a model linking the thalamus and cortex, based on his observations of the thalamic pain syndrome. He emphasized the affective-motivational dimension of pain, arguing that lesions in the thalamus altered emotional responses to sensory input. Head's integrative model laid the foundation for later theories, including Melzack and Wall's Gate Control Theory, and positioned the optic thalamus as central to conscious sensory experience[13].

Meanwhile, Charles Sherrington (1857–1952), who together with E. D. Adrian were awarded the Nobel Prize in 1932 for their research on the functions of the nervous system, revolutionized the understanding of pain by integrating evolutionary theory with neurophysiology. He coined the term "synapse", described reflex arcs, and highlighted how motor and sensory responses were coordinated across neural circuits. His classification of stimuli (proprioceptive, exteroceptive, interoceptive) and assertion that the nervous system functions as a coherent, integrative whole shaped modern somatosensory science[14].

Building on electrophysiological methods, Edgar Douglas Adrian (1889-1977) used the cathode ray oscillograph to study neural transmission, discovering that nerve impulses travel at different speeds depending on fiber size. His findings on stimulus duration, intensity, and summation contributed significantly to understanding how the central nervous system interprets pain signals[15].

Finally, Thomas Lewis (1881-1945) distinguished between fast and slow-conducting fibers, laying groundwork for identifying nociceptive pathways still recognized today. He classified sensory receptors into proprioceptive, exteroceptive, and interoceptive categories, providing a broader framework for the study of somatic and visceral pain. Collectively, these advances represented a departure from Specificity Theory, steering pain research toward a multi-dimensional, integrative approach that considered evolutionary, neurophysiological, and emotional dimensions[1].

The Gate Control Theory

In 1965, Ronald Melzack (1929-2019) and Patrick Wall (1925-2001) introduced the Gate Control Theory of Pain, a groundbreaking model that transformed pain science by integrating and reconciling elements of the two dominant theories of the time: the Specificity Theory and the Pattern Theory. Both earlier theories had experimental backing, but they couldn't fully explain the complexity of pain perception. Melzack and Wall's Gate Control Theory offered a comprehensive neurophysiological framework that bridged these gaps[16].

According to the theory, pain signals are not transmitted passively from the skin to the brain but are modulated by a "gate" mechanism in the spinal cord, specifically in a

region called the substantia gelatinosa within the dorsal horn. The spinal gate controls whether pain signals reach the brain through a dynamic interaction between large-diameter (non-nociceptive) and small-diameter (nociceptive) nerve fibers: a) Large fibers (touch, pressure) inhibit pain signals by closing the gate; b) Small fibers (pain, temperature) facilitate transmission by opening the gate. Additionally, descending signals from the brain can influence this gate, allowing higher brain centers to suppress or enhance pain perception based on cognitive or emotional states[17].

The Gate Control Theory marked a major shift by introducing the idea that pain is not purely a sensory experience but a modulated process involving both peripheral and central mechanisms, including psychological influences. This theory laid the foundation for modern pain management approaches, including psychological and cognitive interventions[1].

The Multidimensional Theory

By the 1950s, William K. Livingston (1892-1966) emerged as a pivotal figure in transforming pain research from a mechanistic and reductionist paradigm to an integrated, neuropsychological framework. His research shifted attention away from simple stimulus-response models to the dynamic interplay of sensory input, central processing, and emotional modulation. Livingston asserted that pain is not always proportional to stimulus intensity and highlighted the brain's active role in modulating nociceptive signals, even before they reach conscious perception. He noted that emotional states can amplify pain, making it a subjective and individualized experience[18].

Livingston's investigations demonstrated that the anterolateral tract in the spinal cord was not the exclusive pathway for pain. Rather, pain signals could ascend via multiple, indirect routes, bypassing interruptions in the spinal cord and reaching subcortical brain regions outside the primary somatosensory cortex. These findings led to his conclusion that the cerebral cortex is not the sole center for pain perception, and that subcortical structures play a central role in the affective dimension of pain. His perspective emphasized the top-down influence of the brain on sensory processing, anticipating contemporary understandings of central sensitization and neuroplasticity[19,1].

In his work *Pain and Suffering*, Livingston further argued against the traditional dualism between psychological and physiological interpretations of pain. He maintained that all pain is inherently psychological, as perception is ultimately constructed by the brain. Consequently, the labeling of certain pain types as "psychogenic" was, to him, both arbitrary and scientifically unsound. This rejection of Cartesian dualism positioned Livingston as a bridge between historical biomedical views and modern biopsychosocial approaches to pain.

This intellectual groundwork paved the way for Melzack's later work with Wall and Kenneth Lyman Casey (1935-), which introduced in 1968 a multidimensional model of pain[20]. This model delineated three interrelated components: the sensory-

discriminative, affective-motivational, and cognitive-evaluative dimensions[3]. While these components are functionally interdependent, they are also partially dissociable, meaning that cognitive processes can differentially modulate specific aspects of the pain experience[10].

Typically, the greater the intensity of a noxious stimulus, the more unpleasant the experience. However, cognitive modulation can disrupt this correlation. For instance, hypnosis has been shown to alter the unpleasantness of pain without affecting its sensory intensity, suggesting a selective modulation of the affective component[21,22]. This illustrates how higher-order cognitive states can influence pain perception, particularly through the affective-motivational system[23].

Further evidence of cognitive modulation is seen in the placebo and nocebo effects, where expectations and beliefs influence pain outcomes via top-down neural mechanisms[24]. Such phenomena underscore the role of cognitive-evaluative processing in shaping subjective pain experiences.

Recent advances in neuroimaging have shifted the conceptualization of brain function from modular localization to network-based processing. In the context of pain, distinct but overlapping brain networks—including the default mode network, salience network, and sensorimotor network—have been implicated in pain perception and modulation[25,26].

Moreover, in chronic pain conditions, alterations in brain structure and function have been observed, suggesting neuroplastic changes that affect the connectivity and functionality of pain-related networks. These findings emphasize that chronic pain is not merely a prolonged acute pain state but reflects complex reorganizations in the central nervous system.

As our understanding of the neurophysiological and neuroanatomical foundations of pain deepens, contemporary theories of pain continue to evolve. The integration of data from neuroimaging, molecular biology, and systems neuroscience is essential for the development of more effective, personalized approaches to pain management[3]. A thorough grasp of the historical and scientific progression of pain models is critical to advancing both clinical and theoretical knowledge in this field.

Conclusion

The history of pain research, from Descartes' dualistic model to contemporary multidimensional and network-based theories, reveals a progressive shift toward an increasingly nuanced understanding of pain as a complex, integrated experience shaped by sensory, emotional, and cognitive factors. Foundational theories like the Specificity Theory, Temporal-Integrative models, and the Gate Control Theory have each contributed to unraveling the physiological and psychological underpinnings of pain, culminating in the modern recognition of pain as both a neurobiological and subjective phenomenon. Advances in neuroscience, particularly neuroimaging and molecular

studies, have revealed the plasticity of pain networks and underscored the importance of top-down modulation in shaping individual pain experiences.

However, even as science has clarified the mechanisms behind pain perception and modulation, socioeconomic disparities in pain experience and treatment remain poorly understood. Emerging epidemiological data consistently shows that individuals from lower socioeconomic backgrounds report higher pain intensity and frequency and are more likely to use opioid analgesics[27]. Future research must therefore delve deeper into the biopsychosocial, environmental, and structural determinants that explain why the less well-off perceive more pain and rely more heavily on pharmacological interventions than their wealthier counterparts. Addressing this inequity is essential not only for advancing pain science but also for ensuring just and effective pain care across all social strata.

Bibliography, notes and references

1. Olson K, History of pain: a brief overview of the 19th and 20th centuries. Pract Pain Manag 2013;13(6).
2. Lott TL, Descartes on phantom limbs. Mind Lang 1986;1:243-271. doi:10.1111/j.1468-0017.1986.tb00103.x
3. Moayedi M, Davis KD, Theories of pain: from specificity to gate control. J Neurophysiol 2013;109(1):5-12.
4. Gorham G, Mind-body dualism and the Harvey-Descartes controversy. J Hist Ideas 1994;55(2):211-234. doi:10.2307/2709897
5. Rey R, The History of Pain. Cambridge (MA): Harvard University Press; 1995. (Original: Histoire de la douleur. Paris: La Découverte; 1993.)
6. Moravia S, Dall' 'homme machine' all' 'homme sensible'. Meccanicismo, animismo e vitalismo nel secolo XVIII. Belfagor 1974;29(6):633-648.
7. Massimo S, Istinto e materialismo. Cabanis e Condillac a confronto. Noctua 2020;7(2). doi:10.14640/NoctuaVII7.
8. Shoja MM, Tubbs RS, Loukas M, Shokouhi G, Ardalan MR, Marie-François Xavier Bichat (1771-1802) and his contributions to the foundations of pathological anatomy and modern medicine. Ann Anat 2008,20;190(5):413-20. doi: 10.1016/j.aanat.2008.07.004. Epub 2008 Aug 20. PMID: 18819786
9. Finger S, Minds Behind the Brain: A History of the Pioneers and Their Discoveries. Oxford: Oxford University Press; 2000.
10. Tracey I, Mantyh PW, The cerebral signature for pain perception and its modulation. Neuron 2007;55(3):377-391. doi:10.1016/j.neuron.2007.07.012
11. Perl ER, Ideas about pain: a historical view. Nat Rev Neurosci 2007;8(1):71-80. doi:10.1038/nrn2042
12. Vierck CJ, Mechanisms underlying development of chronic pain: a review of current literature. Brain Res Bull 2012;87(2-3):144-153. doi:10.1016/j.brainresbull.2011.10.014
13. Melzack R, Wall PD, Pain mechanisms: a new theory. Science 1965;150(3699):971-979. doi:10.1126/science.150.3699.971
14. Sherrington CS, The Integrative Action of the Nervous System. New Haven: Yale University Press; 1906.

15. Adrian ED, The Basis of Sensation: The Action of the Sense Organs. New York: W\.W. Norton & Company; 1928.
16. Melzack R, Casey KL, Sensory, motivational, and central control determinants of pain: a new conceptual model. In: Kenshalo DR (ed.), The Skin Senses. Springfield (IL): Charles C. Thomas; 1968. pp. 423-443.
17. Fields HL, Pain modulation: expectation, opioid analgesia and virtual pain. Prog Brain Res 2000;122:245-253. doi:10.1016/S0079-6123(08)62137-1
18. Melzack R, Wall PD, Pain mechanisms: a new theory. Science 1965;150(3699):971-979.
19. Livingston WK, Pain mechanisms: a physiologic interpretation of causalgia and its related states. New York: Macmillan; 1943.
20. Melzack R, Casey KL, Sensory, motivational, and central control determinants of pain: a new conceptual model. In: Kenshalo DR (ed.), The skin senses. Springfield, IL: Charles C Thomas; 1968. p. 423-443.
21. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC, Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 1997;277(5328):968-971.
22. Wik G, Fischer H, Bragée B, Finer B, Fredrikson M, Functional anatomy of hypnotic analgesia: a PET study of patients with fibromyalgia. Eur J Pain 1999;3(4):285-299.
23. Rainville P, Brain mechanisms of pain affect and pain modulation. Curr Opin Neurobiol 2002;12(2):195-204.
24. Colloca L, Benedetti F, Placebos and painkillers: is mind as real as matter? Nat Rev Neurosci 2005;6(7):545-552.
25. Baliki MN, Geha PY, Apkarian AV, Chialvo DR, Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. J Neurosci 2008;28(6):1398-1403.
26. Apkarian AV, Baliki MN, Geha PY, Towards a theory of chronic pain. Prog Neurobiol 2009;87(2):81-97.
27. Prego-Domínguez J, Khazaeipour Z, Mallah N, Takkouche B, Socioeconomic status and occurrence of chronic pain: a meta-analysis. Rheumatology 2021;2;60(3):1091-1105. doi: 10.1093/rheumatology/keaa758. PMID: 33276382.

Andrea Grignolio Corsini ORCID: 0000-0002-6538-5584