Theories of pain: from specificity to gate control

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Moayedi M, Davis KD. Theories of pain: from specificity to gate control. J Neurophysiol 109: 5–12, 2013. First published October 3, 2012; doi:10.1152/jn.00457.2012.—Several theoretical frameworks have been proposed to explain the physiological basis of pain, although none yet completely accounts for all aspects of pain perception. Here, we provide a historical overview of the major contributions, ideas, and competing theories of pain from ancient civilizations to Melzack and Wall’s Gate Control Theory of Pain:

 specifier areas in the brain. Similarly, noxious stimuli would activate a nociceptor, which would project to higher “pain” centers through a pain fiber. These ideas have been emerging over several millennia but were experimentally tested and formally postulated as a theory in the 19th century by physiologists in Western Europe.

Descartes’ description of the pain system. René Descartes was one of the first Western philosophers to describe a detailed somatosensory pathway in humans. Descartes’ manuscript, Treatise of Man (originally written in French), was illustrated, edited, and published posthumously, first in Latin in 1662 (Descartes 1662) and then in French in 1664 (Descartes et al. 1664). In Treatise of Man, based on the French edition by Louis La Forge (who was also one of the illustrators), Descartes describes pain as a perception that exists in the brain and makes the distinction between the neural phenomenon of sensory transduction (today, known as nociception) and the perceptual experience of pain. What is essential to the development of Descartes’ theory is his description of nerves, which he perceived as hollow tubules that convey both sensory and motor information. This understanding of neural function was by no means novel. In the third century BCE, Herophilus demonstrated the existence of sensory and motor nerves, and Erasistratus demonstrated that the brain influenced motor activity (Rey 1995). One-half of a millennium later, Galen demonstrated that sectioning the spinal cord caused sensory and motor deficits (Ochs 2004). Within the spirit of scientific enquiry that resurfaces in the renaissance, anatomical studies by Vesalius published in 1543 reiterated and confirmed Galen’s findings (Ochs 2004). In relation to this, Galen had postulated that three conditions be met for perception: 1) an organ must be able to receive the stimulus, 2) there must be a connection from the organ to the brain, and 3) a processing center that converts the sensation to a conscious perception must exist (Rey 1995). Descartes contributed to Galen’s model by postulating that a gate existed between the brain and the tubular structures (the connections), which was opened by a
sensory cue (Descartes et al. 1664). A sensory cue would “tug” on the tube, which would then open a gate between the tube and the brain. The opening of this gate would then allow “animal spirits” (an extension of the Greek pneuma\(^4\)) to flow through these tubes and within the muscles to move them. Although this sensory system was not specific to pain, La Forge’s drawing (based on Descartes’ concept and La Forge’s understanding of contemporaneous anatomy) of a foot near a flame is one of the most famous figures in neuroscience (Fig. 2).

This example describes the pathway for promptly moving one’s foot away from a hot flame. In the figure (and its description in the text), the heat of the flame near the foot activates a fibril (or fiber) within the nerve tubule that traverses up the leg, to the spinal cord, and finally, to the brain. Descartes compared this fiber with a cord attached to a bell—by pulling on the other end of cord, the bell will ring. The proverbial bells, in this case, are the pores that line the ventricles in the brain. Once these pores open in response to the sensory input, the animal spirits were thought to flow through the tubule and elicit a motor response. This motor response included turning the head and the eyes to see the flame and raising the hands and folding the body away from the flame for protection. Descartes conceived that there are many of these fibrils and that their movements elicit the sensations. For example, the perception of pain would be felt in the brain when there is a significant tug on the fiber, which caused it to sever. In contrast, a tug of the same magnitude that does not cause the fiber to break would evoke a tickling (or tingling; Descartes uses the French word chatouillement) perception. Although La Forge’s figure of the boy and the flame suggests that there is a dedicated pain pathway, a closer read of the text indicates that Descartes believed that the pattern and rate of firing (intensity of tugging) of a fiber provided the adequate information to the brain about the stimulus intensity and quality. In fact, it is likely that the misconception of a dedicated pathway in the somatosensory system by Descartes is an extension of his proposal that the visual system requires a labeled line (where the image is carried and projected in the brain).

**Anatomical discoveries inform physiology.** The modern concept of a dedicated pain pathway (also known as Specificity Theory; see Fig. 1A) was developed by Charles Bell in his landmark essay, *Idea of a New Anatomy of the Brain, submitted for the observation of his friends*, first published as a conference proceeding in 1811 and later reproduced in a journal (Bell

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\(^4\) In ancient Greek medicine, the concept of pneuma represents air, breath, or motion. It was also called the breath of life and the spirit of man (Stead 1998).
and from the spinal cord (the ventral and dorsal roots, respectively) (Stahnisch 2009). This differentiation of spinal nerves is known as the Bell-Magendie Law, which is a fundamental aspect of the organization of the nervous system.

Concurrently, in Germany, Johannes Müller published a Manual of Physiology, which echoed Charles Bonnet’s manual published one century earlier (Rey 1995). Müller’s manual, published in 1840, sought to summarize and synthesize findings in physiology. The purpose of this synthesis was to understand how different stimuli were so clearly sensed and how the brain could distinguish them from one another. He, like Bonnet, concluded that specific receptors must have specific energy of stimulation and that there were infinite numbers and types of fibers, each to a specific sensory stimulus; e.g., there is a specific fiber for the smell of bananas, another for the scent of an apple, and yet another for the scent of an orange. Furthermore, because of a sense organ’s specific energy, the sensory neuron will only encode a single perceptual quality. For example, if a warm fiber is artificially stimulated by an electric current, the brain will perceive warmth. In line with these findings, Erasmus Darwin (Charles Darwin’s grandfather) provided the first evidence for a set of specific nerves for the perception of heat (Darwin and Darwin 1794).

The discovery of specific, cutaneous touch receptors, such as Pacinian corpuscles [Pacini 1835; cited in Cauna and Mannan (1958)], Meissner’s corpuscles [Meissner 1853; cited in Cauna and Ross (1960)], Merkel’s discs [Merkel 1875; cited in Iggo (1958)], Meissner’s corpuscles [Meissner 1853; cited in Cauna and Ross (1960)], Merkel’s discs [Merkel 1875; cited in Iggo and Muir (1969)], and Ruffini’s end-organs (Ruffini 1893), in the latter one-half of the 19th century, provided further evidence that specific sensory qualia were encoded by dedicated nerve fibers. However, there remained a debate about the nature of pain as part of the five senses, as an end-organ specific to pain stimuli (nociceptor) had not yet been discovered. In contrast to the idea of a dedicated pain pathway, it was argued that pain was different than the other senses in that it is inherently unpleasant (Boring 1942; Dallenbach 1939). These ideas persisted from Plato’s and Aristotle’s writings of pain as an emotion (Schmitter 2010). This inherently makes pain the...
antithesis of pleasure, and because pleasure is a characteristic of the mind (i.e., an emotion), it was inferred that pain was also a characteristic of the mind and not a percept of the body.

Further evidence for the Specificity Theory came from Schiff and Woroschiloff’s findings of a pain pathway in the spinal cord in a series of experiments between 1854 and 1859 (Rey 1995). These findings built on Charles-Édouard Brown-Séquard’s observations that sensory fibers decussate in the spinal cord (Aminoff 1996; Dallenbach 1939). Schiff and Woroschiloff established the presence of two pathways through observations of the effect of incisions at different levels of the spinal cord: the anterolateral pathway for pain and temperature and the posterior bundles for tactile sensibility (Dallenbach 1939; Rey 1995). However, Schiff and Woroschiloff noted that the tactile pathway did not decussate at the level of the spinal cord. These findings were supported by a case study by William Richard Gowers, a physician in London, who reported that a patient with a bullet wound to the gray matter of the spinal cord lost the sense of pain and temperature but not touch (Rey 1995). He concluded that there were specific pathways for pain and temperature, separate from that of touch. However, those who held onto the Aristotelian dogma argued strenuously against the Specificity Theory. They insisted that pain is a quality of all senses—a percept of the mind. Only when Blix and Goldscheider published their findings of sensory spots on the skin independently did the Specificity Theory gain momentum and did pain become a recognized sense (Dallenbach 1939). Sensory spots were defined as tiny areas of the skin that elicit a specific sensation when touched. These sensory spots were specific to warmth, cold, pressure, or pain. However, both Blix and Goldscheider moved away from the Specificity Theory some years later and moved toward the Intensity Theory of Pain, a concurrent theory (see below).

von Frey’s and Goldscheider’s skin spots. Between 1894 and 1896, Max von Frey carried out experiments that advanced the Specificity Theory (Rey 1995). von Frey indicated that there were four somatosensory modalities: cold, heat, pain, and touch and that all of the other skin senses were derivatives of these four modalities. To test this idea, he developed his now well-known “von Frey hairs” (termed an aesthesiometer), which consisted of a hair—usually from a human, but sometimes he used a horsehair or a hog bristle—attached to a wooden stick (Perl 1996). By measuring the hair’s diameter, length, and precise maximal weight that it could support without breaking off of the stick (maximal tension), it was possible to measure the force applied to a very specific spot. Today, von Frey hairs are made of fine nylon filaments of varying thicknesses (and hence, stiffness to deliver different forces and pressures upon bending). With the use of these hairs, he could carefully determine the pressure required to elicit a sensation at each of the skin spots identified by Blix and Goldscheider. Furthermore, his experimental setup allowed him to determine which spots responded to innocuous pressure and which ones responded to noxious pressure. von Frey demonstrated that there were distinct spots for innocuous pressure and for noxious pressure. He presented a model of the skin that comprised a “mosaic of distinct tactile, cold, warm, and pain spots distributed across the skin with distinctive regional variation” (Perl and Kruger 1996). von Frey related the distribution of the pressure points to the distribution of Meissner’s corpuscles, whereas pain points were related to the distribution of free nerve endings in the skin. Despite these remarkable findings, the Specificity Theory made a number of assumptions about the anatomical, physiological, and psychological bases of somesthesis and pain. For instance, when von Frey postulated the theory, pain receptors had yet to be identified nor were the peripheral pathways and brain centers specific to pain sensation established, as well as other factors [for a review, see Dallenbach (1939) and Rey (1995)].

Landmark discoveries. Charles Scott Sherrington (1947) addressed some of the assumptions of the Specificity Theory in his proposed framework of nociception. He applied a Virchowian (i.e., based on the cell theory) and Darwinian (i.e., evolutionarily) approach to study integration in the nervous system. Specifically, he examined what he conceived to be the functional basic unit (the simple reflex arc) to understand the nervous system. With the use of this method, he described the specificity of neurons, which included the four basic modalities recognized by von Frey. Furthermore, he postulated that behavior in animals is the temporal and spatial pattern of activity, resulting from the interaction of these specific neurons. His studies allowed him to conclude that “the main function of the receptor is [...] to lower the excitability threshold of the [reflex] arc for one kind of stimulus and heighten it for all others” (Sherrington 1906, 1955). This “selection” approach resolved the divide between the Intensity Theory (see below) and Specificity Theory (Rey 1995), because it accounts for the specificity of neurons, which included the four basic modalities recognized by von Frey. He also coined the term “nocicipient” (Sherrington 1903) to describe the specificity of the cutaneous end-organ for noxious stimuli, later termed nociceptor (Sherrington 1906). Sherrington developed a framework that advanced the Specificity Theory of Pain even further. However, the nociceptor had yet to be identified definitively.

The discovery of myelinated primary afferent fibers that respond only to mechanical noxious stimuli occurred much later, in 1967 (Burgess and Perl 1967). Soon thereafter, Bessou and Perl (1969) discovered nociceptive, unmyelinated afferent fibers: polymodal nociceptors and high-threshold mechanoreceptors. These findings revolutionized the field of pain research and helped advance and develop a number of theories of pain. Since Sherrington’s endorsement of the Specificity Theory of Pain, this became the dominant theory at the time. However, its popularity waned with the postulation of the Gate Control Theory of Pain (see below) by Melzack and Wall (1965).

INTENSITY THEORY OF PAIN

An Intensive (or Summation) Theory of Pain (now referred to as the Intensity Theory) has been postulated at several different times throughout history. First, conceptualized in the fourth century BCE by Plato in his oeuvre Timaeus (Plato 1998), the theory defines pain, not as a unique sensory experience but rather, as an emotion that occurs when a stimulus is stronger than usual. Centuries later, Erasmus Darwin (Darwin and Darwin 1974) reiterated this concept in Zoonomia. One hundred years after Darwin, Wilhelm Erb also suggested that pain occurred in any sensory system when sufficient intensity was reached rather than being a stimulus modality in its own
right [cited in Dallenbach (1939)]. Arthur Goldscheider further advanced the Intensity Theory, based on an experiment performed by Bernhard Naunyn in 1859 [cited in Dallenbach (1939)]. These experiments showed that repeated tactile stimulation (below the threshold for tactile perception) produced pain in patients with syphils who had degenerating dorsal columns. When this stimulus was presented to patients 60–600 times/s, they rapidly developed what they described as unbearable pain. Naunyn reproduced these results in a series of experiments with different types of stimuli, including electrical stimuli. It was concluded that there must be some form of summation that occurs for the subthreshold stimuli to become unbearably painful. Goldscheider suggested a neurophysiological model to describe this summation effect: repeated subthreshold stimulation or suprathreshold hyperintensive stimulation could cause pain (see Fig. 1B). He suggested further that the increased sensory input would converge and summate in the gray matter of the spinal cord. This theory competed with the Specificity Theory of Pain, which was championed by von Frey. However, the theory lost support with Sherrington’s evolutionary framework for the Specificity Theory and postulated the existence of sensory receptors that are specialized to respond to noxious stimuli, for which he coined the term “nociceptor”.

PATTERN THEORY OF PAIN

In an attempt to overhaul theories of somaesthesia (including pain), J. P. Nafe postulated a “quantitative theory of feeling” (1929). This theory ignored findings of specialized nerve endings and many of the observations supporting the specificity and/or intensive theories of pain. The theory stated that any somaesthetic sensation occurred by a specific and particular pattern of neural firing and that the spatial and temporal profile of firing of the peripheral nerves encoded the stimulus type and intensity (see Fig. 1C). Lele et al. (1954) championed this theory and added that cutaneous sensory nerve fibers, with the exception of those innervating hair cells, are the same. To support this claim, they cited work that had shown that distorting a nerve fiber would cause action potentials to discharge in any nerve fiber, whether encapsulated or not. Furthermore, intense stimulation of any of these nerve fibers would cause the percept of pain (Sinclair 1955; Weddell 1955).

GATE CONTROL THEORY OF PAIN

In 1965, Ronald Melzack and Charles Patrick (Pat) Wall (Melzack and Wall 1965) proposed a theory that would revolutionize pain research: the Gate Control Theory of Pain. The Gate Control Theory recognized the experimental evidence that supported the Specificity and Pattern Theories and provided a model that could explain these seemingly opposed findings. In a landmark paper, Melzack and Wall (1965) carefully discussed the shortcomings of the Specificity and Pattern Theories—the two dominant theories of the era—and attempted to bridge the gap between these theories with a framework based on the aspects of each theory that had been corroborated by physiological data. Specifically, Melzack and Wall accepted that there are nociceptors (pain fibers) and touch fibers and proposed that these fibers synapse in two different regions within the dorsal horn of the spinal cord: cells in the substantia gelatinosa and the “transmission” cells. The model (see Fig. 1D) proposed that signals produced in primary afferents from stimulation of the skin were transmitted to three regions within the spinal cord: 1) the substantia gelatinosa, 2) the dorsal column, and 3) a group of cells that they called transmission cells. They proposed that the gate in the spinal cord is the substantia gelatinosa in the dorsal horn, which modulates the transmission of sensory information from the primary afferent neurons to transmission cells in the spinal cord. This gating mechanism is controlled by the activity in the large and small fibers. Large-fiber activity inhibits (or closes) the gate, whereas small-fiber activity facilitates (or opens) the gate. Activity from descending fibers that originate in supraspinal regions and project to the dorsal horn could also modulate this gate. When nociceptive information reaches a threshold that exceeds the inhibition elicited, it “opens the gate” and activates pathways that lead to the experience of pain and its related behaviors. Therefore, the Gate Control Theory of Pain provided a neural basis for the findings that supported and in fact helped to reconcile the apparent differences between the Pattern and Specificity Theories of Pain.

SHORTCOMINGS OF THE COMPETING PAIN THEORIES

Each of the major pain theories discussed in the previous sections adequately described a series of observations about the nociceptive system and pain perception. However, none adequately accounted for the complexity of the pain system. For instance, although the Specificity Theory appropriately described sensory receptors that are specific to nociceptive stimuli and primary afferents that show responses only to suprathreshold stimuli, it did not account for neurons in the central nervous system (CNS) that respond to both non-nociceptive and nociceptive stimuli (e.g., wide-dynamic range neurons). Although these neurons are well characterized, their function in pain perception has yet to be determined.

Another shortcoming of these theories is that they focus on cutaneous pain and do not address issues pertaining to deep-tissue, visceral, or muscular pains. Although Sherrington does discuss visceral and muscular pain (Sherrington 1947), these observations are not fully accounted for within his model. Additionally, these models are focused on acute pain and do not address mechanisms of persistent pain or the chronicification of pain, likely because at the time, it was assumed that the nervous system was hard wired. Although the mechanisms of persistent and chronic pain are still not fully understood, it is now clear that peripheral and central plasticity can arise following repeated nociceptive stimulation in healthy subjects (Bingel et al. 2008; Teutsch et al. 2008) and in chronic pain [for a review, see Davis and Moayedi (2012)]. In addition, recent work has demonstrated that plasticity is not limited to changes in neurons but can also involve changes in glial cells (Eroglu and Barres 2010; Streit et al. 1988), which may relate to the maintenance of persistent and chronic pains (Scholz and Woolf 2007; Zhuo et al. 2011).

The Gate Control Theory is the most promulgated of pain theories and led to some of the most fruitful research in the field of pain. However, many of the details of this theory have been shown to be inaccurate. For example, there were oversimplifications and flaws in the presentation of the neural architecture of the spinal cord, the location and the model pertaining to how large afferent fiber stimulation inhibits or...
Empire (circa 200 BCE). In ancient texts, dating as far back as the Syriac medical tradition, certain foods make the body “warm”, whereas others make the body “cool”. These concepts are not unique to the Egyptians who were the first to record medical texts, e.g., The Papyrus Ebers (Bryan 1930), to the Greeks (e.g., most famously, Hippocrates and Galen), to the Babylonians, and to the Assyrians.

Melzack and Casey (1968) described pain as being multidimensional and complex, with sensory-discriminative, affective-motivational, and cognitive-evaluative components. In addition, recent work has shown that pain can affect and interact with motor systems (Avivi-Arber et al. 2011; Borsook 2007). The concept of pain as a multidimensional experience has been described in ancient texts, dating as far back as the Syriac Empire (circa 200 BCE). In The Book of Medicines (Budge 2002), it is suggested that pain is the product of bile and phlegm mingled with cold and heat. These simple combinations occur in the brain, and according to Syriac medicine, pain is a product of the brain (a concept that has passed the test of time and that we still hold true today). Different types of pains would thus arise from differential combinations of these substances affecting the type of pain. It is noteworthy that the concepts of bile and phlegm and even those of cold and hot were understood in a different paradigm of philosophical thought; these are not the simple compounds we know today but rather, are used as a classification of the world. For instance, certain foods make the body “cool”, whereas others make the body “warm”. These concepts are not unique to the Syrians, since they follow a long tradition of ancient medicine passed down from the Egyptians. It is notable that the concepts of bile and phlegm and even those of cold and hot were understood in a different paradigm of philosophical thought; these are not the simple compounds we know today but rather, are used as a classification of the world. For instance, certain foods make the body “cool”, whereas others make the body “warm”. These concepts are not unique to the Syrians, since they follow a long tradition of ancient medicine passed down from the Egyptians who were the first to record medical texts, e.g., The Papyrus Ebers (Bryan 1930), to the Greeks (e.g., most famously, Hippocrates and Galen), to the Babylonians, and to the Assyrians.

The contemporary definition of pain used by the IASP is based on the divisional (multidimensional) definition proposed by Melzack and Casey (1968). These dimensions include the sensory-discriminative (intensity, location, quality, and duration), the affective-motivational (unpleasantness and the subsequent flight response), and the cognitive-evaluative (appraisal, cultural values, context, and cognitive state) dimensions of pain. These three dimensions are not independent but rather, interact with one another. They are, however, partially dissociable: the cognitive state of a person can modulate one or both of these dimensions of pain perception. In general, the more intense that a noxious stimulus is, the more unpleasant it will be (Duncan et al. 1989). However, there are exceptions to this rule: hypnosis has been shown to modulate pain unpleas-antness without affecting intensity; that is, the person felt the pain but was not as bothered by the sensation (Kropotov et al. 1997; Meier et al. 1993; Rainville 2002; Rainville et al. 1997, 1999; Wik et al. 1999). This is an example of how the cognitive state can modulate the percept of the affective-motivational component of pain and can be referred to as cognitive modulation. Cognitive modulation of pain is reflected in the effects of placebo and nocebo (Colloca and Benedetti 2005; Colloca et al. 2008; Eippert et al. 2009; Wager et al. 2004), cognitive behavioral therapy (Salomons et al. 2004, 2007; Sharp 2001), and other treatments for chronic pain. More recently, neuroimaging suggests that brain function may not be modular but rather, likely involves networks (Bassett and Bullmore 2009). In the context of pain, various networks have been implicated in the experience of pain (Davis 2011; Legmore et al. 2011). Furthermore, recent studies have demonstrated that in chronic pain conditions, brain structure and function undergo plasticity and that network dynamics are altered (Baliki et al. 2011; Davis 2011; Seifert and Mairhofner 2011).

Theories about somesthesia and pain have continued to evolve as knowledge accumulates concerning the structure and function of pathways underlying pain perception and pain modulation. Recent advances in neuroimaging and cellular and molecular medicine have vastly expanded our understanding of pain, and as we continue to study the normal and abnormal neurophysiological and neuroanatomical bases of pain, we will continue to modify our working hypothesis. The discussion of Labeled Line vs. Pattern Theory has re-emerged recently in the field (Basbaum 2011). This discussion has highlighted the differences between the peripheral encoding of nociceptive stimuli and CNS processing and perception of pain. Specifically, Allan Basbaum, Ken Casey, Clifford Woolf, Howard Fields, and Vania Apkarian (the four commentators on Basbaum’s posting) agree that experimental data have clearly demonstrated that peripheral sensory encoding does occur in a labeled-line fashion. However, at the level of the second- and third-order neurons in the CNS, we lack empirical data to determine how pain is perceived. Therefore, future work is required to address this key question. To do so, a clear understanding of the emergence of the current ideas in pain research and the data that have built the models is essential for us to progress in understanding pain and to develop effective treatments to alleviate this most common of ailments.

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