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. These second-order neurons project to “higher” mechanoreceptors, which are associated with dedicated primary afferents in the spinal cord or brainstem (depending on the source of the input).

Pain; gate control; medicine; Descartes; specificity; labeled line; pattern theory; somatosensory

SPECIFICITY THEORY OF PAIN

The Specificity Theory refers to the presence of dedicated pathways for each somatosensory modality. The fundamental tenet of the Specificity Theory is that each modality has a specific receptor and associated sensory fiber (primary afferent) that is sensitive to one specific potential stimulus (Dubner et al. 1978). For instance, the model proposes that non-noxious mechanical stimuli are encoded by low-threshold mechanoreceptors, which are associated with dedicated primary afferents that project to “mechanoreceptive” second-order neurons in the spinal cord or brainstem (depending on the source of the input). These second-order neurons project to “higher” mechanorecep-

IT IS A SHAME THAT WE POSSESS such insufficient knowledge concerning the character of pain—those symptoms which represent the essential part of all bodily suffering of man (Goldscheider 1894).

The current definition of pain, established by the International Association for the Study of Pain (IASP) in 1986, defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of tissue damage, or both.” This definition is the culmination of centuries of ideas and work that have explored the concept of pain.

A number of theories have been postulated to describe mechanisms underlying pain perception. These theories date back several centuries and even millennia (Kenins 1988; Perl 2007; Rey 1995). This review will mainly focus on theories postulated since the 17th century and then provide an overview of current thinking. The four most influential theories of pain perception include the Specificity (or Labeled Line), Intensity, Pattern, and Gate Control Theories of Pain (Fig. 1).
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 pneuma⁴) 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).

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 Shaw 1868). In this essay, Bell provided an alternative perspective about the organization of the nervous system. First, he suggested that the brain is not “common sensorium”, as suggested by Descartes, which was the accepted model of the brain at the time. Instead, he provided anatomical evidence that the brain was a heterogeneous structure, a theory first postulated by Willis in the 17th century (Rey 1995). He then suggested that nerves were bundles of heterogeneous neurons that have specialized functions and that their bundling was only for ease of distribution. Thus Bell spoke of different sensory neurons for different types of stimuli, motor neurons, and so-called “vital” neurons that are wired to the mind rather than the brain. He did, however, maintain that perception of stimulus (such as vision and nociception) is different than the perceptual experience (e.g., sight and pain, respectively). Importantly, for the Specificity Theory, Bell states:

...that while each organ of sense is provided with a capacity of receiving certain changes; to be played upon it, as it were, yet each is utterly incapable of receiving the impressions destined for another organ of sensation. It is also very remarkable that an impression made on two different nerves of sense, though with the same instrument, will produce two distinct sensations; and the ideas resulting will only have relation to the organ affected (Bell and Shaw 1868).

This is the fundamental tenet of the Specificity Theory, which postulates that there is a dedicated fiber that leads to a dedicated pain pathway to the sensory modality’s region of the brain. This model, therefore, suggests that a pathway specific to pain exists (see Fig. 1A).

François Magendie was a French physician considered by some as the father of experimental physiology (Bernard and Magendie 1856; Sechzer 1983; Stahnisch 2009). Magendie made substantial contributions to neurophysiology, including reiterating Bell’s findings regarding the existence of both motor and sensory nerves and that these have separate paths to 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 [Merkel 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 von Frey's and Woroschiloff's findings of a pain pathway in the peripheral nervous system. Through observations of the effect of incisions at different levels of the spinal cord, they established the presence of two pathways for pain and temperature, separate from that of touch (Dallenbach 1939). However, both Blix and Goldscheider moved away from the Specificity Theory in their proposed framework of noception. They applied a Von Freyian (i.e., based on the cell theory) and Darwinian (i.e., evolutionary) 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 findings of specific pain points (i.e., receptors that are specific to pain) and also accounts for the Intensity Theory (i.e., somatosensory stimulation, which is intense or excessive, activates the pain reflex arc because this is its common feature).

He also coined the term “nociceptor” (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 1794) reiterated this concept in Zoologia. 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 syphilis 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 somaesthesis (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 chronification 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
modulates C-fibers (Nathan and Rudge 1974), and the hypothesized modulatory system, which we now know includes descending small-fiber projections from the brain stem (Treede 2006). Nonetheless, the Gate Control Theory spurred many studies in the field, and this significantly advanced our understanding of pain.

CONTEMPORARY VIEWS AND THE MULTIDIMENSIONAL ASPECTS OF PAIN

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 [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 unpleasantness 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; Legrain 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 Maihofner 2011).

Theories about somatoesthesia 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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