Theories of pain: from Specificity to Gate Control

Massieh Moayedi\textsuperscript{1,3} and Karen D. Davis\textsuperscript{1,2,3}

\textsuperscript{1}Institute of Medical Science, \textsuperscript{2}Department of Surgery, University of Toronto, Toronto, Ontario, Canada; \textsuperscript{3}Division of Brain, Imaging and Behaviour - Systems Neuroscience, Toronto Western Research Institute, University Health Network, Toronto, Ontario, Canada.

Running Title: A history of pain theories

Correspondence to:
Karen D. Davis, Ph.D.
Division of Brain, Imaging and Behaviour – Systems Neuroscience
Toronto Western Research Institute
Toronto Western Hospital,
University Health Network
399 Bathurst Street, Room MP14-306
Toronto, Ontario, Canada M5T 2S8
(416) 603-5662 ph; (416) 603-5745 fax
Email: kdavis@uhnres.utoronto.ca
Several theoretical frameworks have been proposed to explain the physiological basis of pain, although none yet completely account 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.
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.

- A. Goldscheider, *Ueber den Schmerz*, 1894

The current definition of pain, established by 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) Theory, the Intensity Theory, the Pattern Theory and the Gate Control Theory of Pain (see Figure 1).

1. **Specificity Theory**

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 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” mechanoreceptive 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 nineteenth century by physiologists in Western Europe.

57

58 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 3rd century BCE, Herophilus demonstrated the existence of sensory and motor nerves, and Erasistratus demonstrated that the brain influenced motor activity (Rey, 1995). Half a millennium later, Galen demonstrated that sectioning the spinal cord
caused sensory and motor deficits (Ochs, 2004). Within the spirit of scientific enquiry that resurfaced 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 to be able to receive the stimulus, (2) a connection from the organ to the brain, and (3) a processing center that converts the sensation to a conscious perception (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\(^1\)) 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 LaForge’s understanding of contemporaneous anatomy) of a foot near a flame is one of the most famous figures in neuroscience (see Figure 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 to 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 doesn’t 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 Figure 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 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 seventeenth 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., colour and pain, respectively). Importantly for 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 Specificity theory, which postulates that there is a dedicated fiber that leads up 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 Figure 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 a 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, and 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 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), Merkel’s discs
(Merkel, 1875 cited in Iggo and Muir, 169), and Ruffini’s end-organs (Ruffini, 1893) in the latter
half of the nineteenth 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 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’s and Woroschiloff’s findings of a pain pathway in the spinal cord in a series of experiments between 1854 and 1859. These findings built upon 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 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 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 Specificity theory some years later, and moved towards the Intensity theory of pain, a concurrent theory (see below).
Between 1894 and 1896, Max von Frey’s carried out experiments that advanced the Specificity theory. 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) that 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 the maximal weight precisely it could support (maximal tension) without breaking off of the stick, and therefore 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). Using these hairs, he could carefully determine the pressure required to elicit a sensation at each of the skin spots identified by Blix and Goldscheider. Further, his experimental setup allowed him to determine which spots responded to innocuous pressure, and which ones responded 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 of 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; Rey, 1995)).

Landmark Discoveries

Charles Scott Sherrington 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., 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 determine understand the nervous system. Using this method, he described the specificity of neurons, which included the four basic modalities recognized by von Frey. Furthermore, he postulated that behaviour 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 that are intense or excessive activate the “pain” reflex arc because this is their common feature). 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 (HTM). 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).

2. **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 4th century BCE by Plato in his œuvre *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 (1794) 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 (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 per second, 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, in order for the subthreshold stimuli to become unbearably painful. Goldscheider suggested a neurophysiological model to describe this summation effect: repeated subthreshold stimulation or suprathreshold hyper-intensive stimulation could cause pain (see Figure 1b). He further suggested 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 Specificity theory; and postulated the existence of sensory receptors that are specialized to respond to noxious stimuli, for which he coined the term “nociceptor”.

3. 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 Figure 1c). Lele, Sinclair and Weddell (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).

4. **Gate control theory of pain**

In 1965, Ronald Melzack and Charles Patrick (Pat) Wall proposed a theory that would revolutionize pain research: the Gate Control theory of pain. The Gate Control theory recognized the experimental evidence that supported Specificity theory and Pattern theory, and provided a model that could explain these seemingly opposed findings. In a landmark paper, Melzack and Wall (Melzack and Wall, 1965) carefully discussed the shortcomings of the specificity and pattern theories – the two dominant theories of the era, 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 dorsal horn of the spinal cord: cells in the substantia gelatinosa and the “transmission” cells. The model (see Figure 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 behaviours. 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.

5. **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 supra-threshold stimuli, it did not account for neurons in the 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 hardwired. 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).
Additionally, 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., 2004), that 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 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 and the location and the model pertaining to how large
afferent fiber stimulation inhibits or modulates C-fibres (Nathan and Rudge, 1974), and the
hypothesized modulatory system which we now know includes descending small-fibre
projections from the brainstem (Treede, 2006). Nonetheless, the Gate Control theory spurred
many studies in the field, and this significantly advanced our understanding of pain.
6. 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 a cognitive-evaluative components. Additionally, recent work has shown that pain can also 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 which 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 are rather 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 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., 1999; Rainville et al., 1997; 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 behavioural therapy (Salomons et al., 2007; Salomons et al., 2004; 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 somaesthesis 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 versus Pattern theory has recently reemerged 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 and Howard Fields (the three commentators on Basbaum’s posting) agree that experimental data has 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 are essential, in order for us to progress in understanding pain, and to develop effective treatments to alleviate this most common of ailments.

AKNOWLEDGEMENTS

We would like to thank Drs. Jonathan Dostrovsky, Barry Sessle and Howard Tenenbaum for feedback on earlier versions of this paper.
REFERENCES


Moayedi and Davis  A history of pain theories  JN-00457-2012R2

460
462
464
466
467  Melzack R, Casey KL, 1968. Sensory, motivational, and central control determinants of pain: a
new conceptual model. In: Kenshalo D (Ed.), The Skin Senses. C.C. Thomas,
468
470
472
474
Psychiatry 37: 1366-1372.
476
478
479  Pacini F (1835) Sopra un particolar genere di piccoli Corpi globulosi scoperti nel corpo umano
da Filippo Pacini Alunno interno degli Spedali riunti di Pistoia. (Letter to Accademia
Medico-fisica di Firenze).
480
481  Perl ER, 1996. Pain and the discovery of nociceptors. In: Belmonte C, Cervero F (Eds.),
482
484
486
488
12: 195-204.
490
and affective dimensions of pain using hypnotic modulation. Pain 82: 159-171.
492
493  Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC (1997) Pain affect encoded in


Sherrington CS (1903) Qualitative difference of spinal reflex corresponding with qualitative difference of cutaneous stimulus. J Physiol 30: 39-46.


**Figure 1:** Schematic diagrams of pain theories. (a) Based on the Specificity theory of pain and each modality (touch and pain) is encoded in separate pathways. Touch and pain stimuli are encoded by specialized sense organs. Impulses for each modality are transmitted along distinct pathways, which project to touch and pain centers in the brain, respectively. (b) Based on the Intensity theory of pain, there are no distinct pathways for low- and high-threshold stimuli. Rather, the number of impulses in neurons determine the intensity of a stimulus. The primary afferent neurons synapse onto wide-dynamic range (WDR) second order neurons in the dorsal horn of the spinal cord, where low levels of activity encode innocuous stimuli, and higher levels of activity encode noxious stimuli. (c) The Pattern theory of pain posits that somatic sense organs respond to a dynamic range of stimulus intensities. Different sense organs have different levels of responsivity to stimuli. A population code, or the pattern of activity of different neurons encodes the modality and location of the stimulus. (d) The Gate Control theory of pain proposes that both large (A-fibers) and small (C-fibers) synapse onto cells in the substantia gelatinosa (SG) and the first central transmission (T) cells. The inhibitory effect exerted by SG cells onto the primary afferent fiber terminals at the T cells is increased by activity in A-fibers and decreased by activity in C-fibers. The central control trigger is represented by a line running from the A-fiber system to the central control mechanisms; these mechanisms, in turn, project back to the Gate Control system. The T cells project to the entry cells of the action system. +, Excitation; –, inhibition. (Figure is reproduced with permission from: (Perl, 2007)).

**Figure 2:** Line drawing of the pain system by (a) Florentius Schuyl (left) and (b) Louis La Forge (right) based on Descartes description in *Treatise of Man*: (see text). The fire (A) is close to the
foot (B). Particles from the fire move and press the skin, and tug on the fibril (C), which opens
the pore (d, e) where the fibril terminates. Opening the pore is akin to tugging on a rope attached
to a bell, thus ringing the bell. The open pore allows the “animal spirits” to flow from the cavity
(F) into the fibril and, part of them activate the muscles to move the foot away from the fire, and
part of them activate the muscles to turn the eyes and the head toward the fire to look at it, and
part of them are used to bring forth the hands and fold the body to protect it. (Image on the left is
reproduced from (Descartes, 1662), and the image on the right and text is reproduced from
(Descartes et al., 1664), out of copyright; translated by Massieh Moayedi).