

Theories of pain: from specificity to gate control

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

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

Submitted 30 May 2012; accepted in final form 1 October 2012

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.

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

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).

SPECIFICITY THEORY OF PAIN

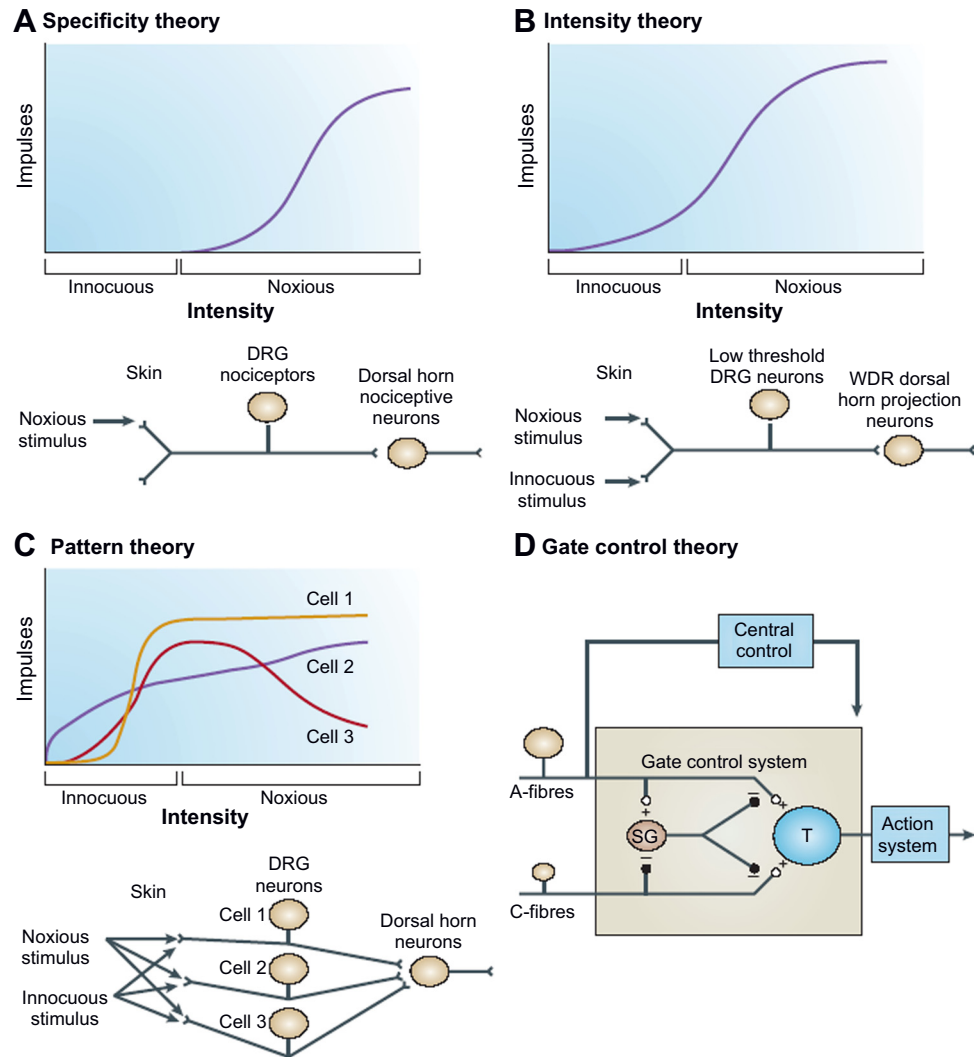
The Specificity Theory refers to the presence of dedicated pathways for each somatosensory modality. The fundamental tenet of the Specificity Theory is that each modality has a specific receptor and associated sensory fiber (primary afferent) that is sensitive to one specific stimulus (Dubner et al. 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-

tive 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 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 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

Address for reprint requests and other correspondence: K. D. Davis, Div. of Brain, Imaging and Behaviour-Systems Neuroscience, Toronto Western Research Inst., Toronto Western Hospital, Univ. Health Network, 399 Bathurst St., Rm. MP14-306, Toronto, Ontario, Canada M5T 2S8 (e-mail: kdavis@uhnres.utoronto.ca).

Fig. 1. Schematic diagrams of pain theories. *A*: based on the Specificity Theory of Pain; 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. DRG, dorsal root ganglion. *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 determines the intensity of a stimulus. The primary afferent neurons synapse onto wide-dynamic range (WDR) 2nd-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 1st 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).



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 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

¹ 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).

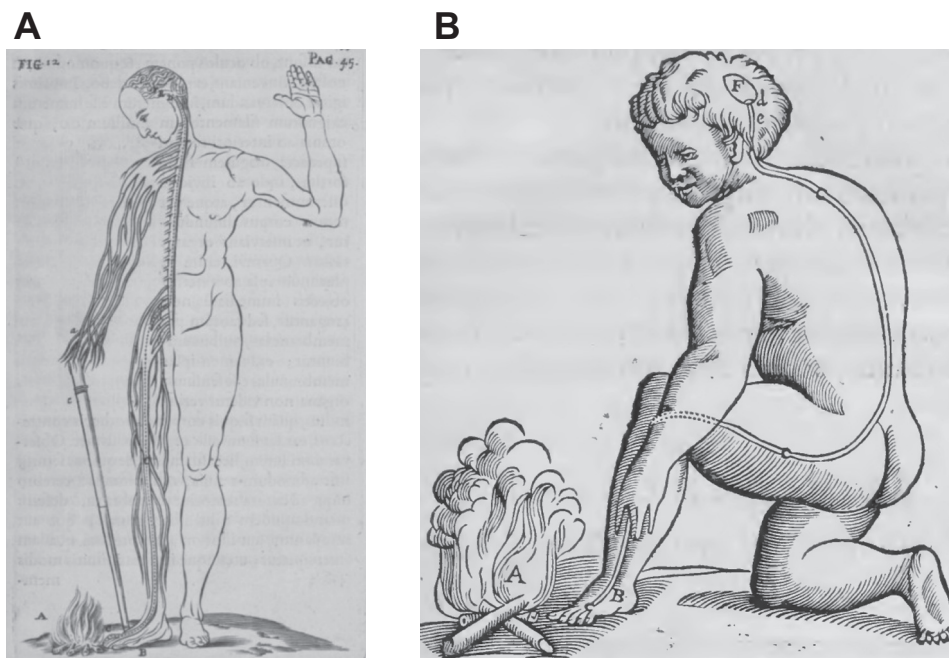


Fig. 2. Line drawing of the pain system by (A) Florentius Schuyl and (B) Louis La Forge based on Descartes' description in *Treatise of Man* (see text). The fire (letters A) is close to the foot (letters B). Particles from the fire move and press the skin and tug on the fibril (letters C), which opens the pore (letters d and 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 (letters F) into the fibril; part of them activates the muscles to move the foot away from the fire, part of them activates the muscles to turn the eyes and the head toward the fire to look at it, and part of them is used to bring forth the hands and fold the body to protect it. [A is reproduced from Descartes (1662), and B and text are reproduced from Descartes et al. (1664), out of copyright; translated by M. Moayedli.]

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, respec-

tively) (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 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 somesthesia 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., 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 "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 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 [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 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 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 Moayed (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, neuro-

imaging 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 somaesthesia 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.

ACKNOWLEDGMENTS

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

GRANTS

Funding for K. D. Davis is provided by operating grants from the Canadian Institutes of Health Research.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: M.M. prepared figures; M.M. drafted manuscript; M.M. and K.D.D. edited and revised manuscript; M.M. and K.D.D. approved final version of manuscript.

REFERENCES

- Aminoff MJ.** Historical perspective Brown-Sequard and his work on the spinal cord. *Spine (Phila PA 1976)* 21: 133–140, 1996.
- Avivi-Arber L, Martin R, Lee JC, Sessle BJ.** Face sensorimotor cortex and its neuroplasticity related to orofacial sensorimotor functions. *Arch Oral Biol* 56: 1440–1465, 2011.
- Baliki MN, Baria AT, Apkarian AV.** The cortical rhythms of chronic back pain. *J Neurosci* 31: 13981–13990, 2011.
- Basbaum A.** Specificity versus patterning theory: continuing the debate. In: *Pain Research Forum*, edited by McCaffrey P and Andrews N. <http://www.painresearchforum.org/forums/discussion/7347-specificity-versus-patterning-theory-continuing-debate> [24 June 2011].

- Bassett DS, Bullmore ET.** Human brain networks in health and disease. *Curr Opin Neurol* 22: 340–347, 2009.
- Bell C, Shaw A.** Reprint of the “Idea of a New Anatomy of the Brain,” with Letters, &c. *J Anat Physiol* 3: 147–182, 1868.
- Bernard C, Magendie F.** Leçon d’ouverture du Cours de Médecine du Collège de France. Baillière, Paris, 1856.
- Bessou P, Perl ER.** Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. *J Neurophysiol* 32: 1025–1043, 1969.
- Bingel U, Herken W, Teutsch S, May A.** Habituation to painful stimulation involves the antinociceptive system—a 1-year follow-up of 10 participants. *Pain* 140: 393–394, 2008.
- Boring EG.** *Sensation and Perception in the History of Experimental Psychology*. New York, London: D. Appleton-Century, 1942.
- Borsook D.** Pain and motor system plasticity. *Pain* 132: 8–9, 2007.
- Bryan CP.** *The Papyrus Ebers/Translated from the German Version by Cyril P. Bryan with an Introd. by Professor G. Elliot Smith*. London: Geoffrey Bles, 1930.
- Budge EAW.** *The Book of Medicines: Ancient Syrian Anatomy, Pathology and Therapeutics (Kegan Paul Library of Aracana)*. London: Routledge, 2002.
- Burgess PR, Perl ER.** Myelinated afferent fibres responding specifically to noxious stimulation of the skin. *J Physiol* 190: 541–562, 1967.
- Cauna N, Mannan G.** The structure of human digital Pacinian corpuscles (*corpus cula lamellosa*) and its functional significance. *J Anat* 92: 1–20, 1958.
- Cauna N, Ross LL.** The fine structure of Meissner’s touch corpuscles of human fingers. *J Biophys Biochem Cytol* 8: 467–482, 1960.
- Colloca L, Benedetti F.** Placebos, and painkillers: is mind as real as matter? *Nat Rev Neurosci* 6: 545–552, 2005.
- Colloca L, Benedetti F, Porro CA.** Experimental designs and brain mapping approaches for studying the placebo analgesic effect. *Eur J Appl Physiol* 102: 371–380, 2008.
- Dallenbach KM.** Pain: history and present status. *Am J Psychol* 52: 331–347, 1939.
- Darwin E, Darwin RW.** *Zoonomia; or, The Laws of Organic Life*. London: J. Johnson, 1794.
- Davis KD.** Neuroimaging of pain: what does it tell us? *Curr Opin Support Palliat Care* 5: 116–121, 2011.
- Davis KD, Moayed M.** Central mechanisms of pain revealed through functional and structural MRI. *J Neuroimmune Pharmacol*, July 24, 2012 Epub ahead of print.
- Descartes R.** *De Homine—Figuris et Latinitate Donatus Florentio Schuyl*. Leiden, Germany: Leffer & Moyardus, 1662.
- Descartes R, Clersefier C, La Forge L, Schuyl F.** *L’homme et un Traité de la formation du Fœtus du Mesme Autheur*. Paris: Charles Angot, 1664.
- Dubner R, Sessle BJ, Storey AT.** *The Neural Basis of Oral and Facial Function*. New York: Plenum, 1978.
- Duncan GH, Bushnell MC, Lavigne GJ.** Comparison of verbal and visual analogue scales for measuring the intensity and unpleasantness of experimental pain. *Pain* 37: 295–303, 1989.
- Eippert F, Bingel U, Schoell ED, Yacubian J, Klingner R, Lorenz J, Buchel C.** Activation of the opioidergic descending pain control system underlies placebo analgesia. *Neuron* 63: 533–543, 2009.
- Eroglu C, Barres BA.** Regulation of synaptic connectivity by glia. *Nature* 468: 223–231, 2010.
- Goldscheider A.** *Ueber den Schmerz in Physiologischer und Klinischer Hinsicht: Nach einem Vortrage in der Berliner Militärärztlichen Gesellschaft*. Ann Arbor, MI: University of Michigan Library, 1894.
- Iggo A, Muir AR.** The structure and function of a slowly adapting touch corpuscle in hairy skin. *J Physiol* 200: 763–796, 1969.
- Kenins P.** The functional anatomy of the receptive fields of rabbit C polymodal nociceptors. *J Neurophysiol* 59: 1098–1115, 1988.
- Kropotov JD, Crawford HJ, Polyakov YI.** Somatosensory event-related potential changes to painful stimuli during hypnotic analgesia: anterior cingulate cortex and anterior temporal cortex intracranial recordings. *Int J Psychophysiol* 27: 1–8, 1997.
- Legrain V, Iannetti GD, Plaghki L, Mouraux A.** The pain matrix reloaded: a salience detection system for the body. *Prog Neurobiol* 93: 111–124, 2011.
- Lele PP, Sinclair DC, Weddell G.** The reaction time to touch. *J Physiol* 123: 187–203, 1954.
- Meier W, Klucken M, Soyka D, Bromm B.** Hypnotic hypo- and hyperalgesia: divergent effects on pain ratings and pain-related cerebral potentials. *Pain* 53: 175–181, 1993.
- Melzack R, Casey KL.** *Sensory, motivational, and central control determinants of pain: a new conceptual model*. In: *The Skin Senses*, edited by Kenshalo D. Springfield, IL: C. C. Thomas, 1968, p. 423–439.
- Melzack R, Wall PD.** Pain mechanisms: a new theory. *Science* 150: 971–979, 1965.
- Merkel F.** Tastzellen und Tastkörperchen bei den Hausthieren und beim Menschen. *Arch. Mikr. Anat. EntwMech.* 11: 636–652, 1875.
- Meissner G.** Beitrage zur Anatomie und Physiologie der Haut. Leopold Voss: Leipzig, Germany, 1853.
- Müller J.** *Handbuch der Physiologie des Menschen für Vorlesungen*. Coblenz, Germany: Verlag von J. Hölscher, 1840.
- Nafe JP.** A quantitative theory of feeling. *J Gen Psychol* 2: 199–211, 1929.
- Nathan PW, Rudge P.** Testing the gate-control theory of pain in man. *J Neurol Neurosurg Psychiatry* 37: 1366–1372, 1974.
- Ochs S.** *A History of Nerve Functions: from Animal Spirits to Molecular Mechanisms*. New York; Cambridge, UK: Cambridge University Press, 2004.
- Pacini F.** *Sopra un Particolare 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.)*, 1835.
- Perl ER.** Ideas about pain, a historical view. *Nat Rev Neurosci* 8: 71–80, 2007.
- Perl ER.** Pain and the discovery of nociceptors. In: *Neurobiology of Nociceptors*, edited by Belmonte C and Cervero F. New York: Oxford University Press, 1996, p. 5–36.
- Perl ER, Kruger L.** Nociception and pain: evolution of concepts and observations. In: *Pain and Touch*, edited by Kruger L. San Diego, CA: Academic, 1996, p. 180–212.
- Plato.** *Timaeus*. Salt Lake City, UT: Project Gutenberg, 1998.
- Rainville P.** Brain mechanisms of pain affect and pain modulation. *Curr Opin Neurobiol* 12: 195–204, 2002.
- Rainville P, Carrier B, Hofbauer RK, Bushnell MC, Duncan GH.** Dissociation of sensory and affective dimensions of pain using hypnotic modulation. *Pain* 82: 159–171, 1999.
- Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC.** Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 277: 968–971, 1997.
- Rey R.** *The History of Pain*. Cambridge, MA: Harvard University Press, 1995.
- Ruffini A.** *Sur un nouvel organe nerveux terminal et sur la presence des corpuscules Golgi-Mazzoni dans le conjonctif souscutané de la pulpe des doigts de l’homme. Mémoires de l’Academie Royale*. Italy: L’Accademia Nazionale dei Lincei Lincei, 1893, 249–265.
- Salomons TV, Johnstone T, Backonja M, Shackman AJ, Davidson RJ.** Individual differences in the effects of perceived controllability on pain perception: critical role of the prefrontal cortex. *J Cogn Neurosci* 19: 993–1004, 2007.
- Salomons TV, Johnstone T, Backonja MM, Davidson RJ.** Perceived controllability modulates the neural response to pain. *J Neurosci* 24: 7199–7203, 2004.
- Schmitter AM.** 17th and 18th century theories of emotions. In: *The Stanford Encyclopedia of Philosophy*, edited by Zalta EN. <http://plato.stanford.edu/archives/win2010/entries/emotions-17th,18th/> [15 Oct 2010].
- Scholz J, Woolf CJ.** The neuropathic pain triad: neurons, immune cells, and glia. *Nat Neurosci* 10: 1361–1368, 2007.
- Sechzer JA.** The ethical dilemma of some classical animal experiments. *Ann N Y Acad Sci* 406: 5–12, 1983.
- Seifert F, Maihofner C.** Functional, and structural imaging of pain-induced neuroplasticity. *Curr Opin Anaesthesiol* 24: 515–523, 2011.
- Sharp TJ.** Chronic pain: a reformulation of the cognitive-behavioural model. *Behav Res Ther* 39: 787–800, 2001.
- Sherrington CS.** *Man on His Nature*. Cambridge, UK: Cambridge University Press, 1955.
- Sherrington CS.** Observations on the scratch-reflex in the spinal dog. *J Physiol* 34: 1–50, 1906.
- Sherrington CS.** Qualitative difference of spinal reflex corresponding with qualitative difference of cutaneous stimulus. *J Physiol* 30: 39–46, 1903.
- Sherrington CS.** *The Integrative Action of the Nervous System*. Cambridge, UK: Cambridge University Press, 1947.
- Sinclair DC.** Cutaneous sensation and the doctrine of specific energy. *Brain* 78: 584–614, 1955.
- Stahnisch FW.** Francois Magendie (1783–1855). *J Neurol* 256: 1950–1952, 2009.

- Stead C.** Pneuma. In: *Routledge Encyclopedia of Philosophy*, edited by Craig E. London: Routledge, 1998. <http://www.rep.routledge.com/article/A092SECT1> [4 Sept 2012].
- Streit WJ, Graeber MB, Kreutzber GW.** Functional plasticity of microglia: a review. *Glia* 1: 305–307, 1988.
- Teutsch S, Herken W, Bingel U, Schoell E, May A.** Changes in brain gray matter due to repetitive painful stimulation. *Neuroimage* 42: 845–849, 2008.
- Treede RD.** Pain and hyperalgesia: definitions and theories. In: *Handbook of Clinical Neurology*, edited by Cervero F and Jensen TS. Amsterdam: Elsevier, 2006, vol. 81, p. 3–10.
- Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD.** Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science* 303: 1162–1167, 2004.
- Weddell G.** Somesthesia and the chemical senses. *Annu Rev Psychol* 6: 119–136, 1955.
- Wik G, Fischer H, Bragee B, Finer B, Fredrikson M.** Functional anatomy of hypnotic analgesia: a PET study of patients with fibromyalgia. *Eur J Pain* 3: 7–12, 1999.
- Zhuo M, Wu G, Wu LJ.** Neuronal and microglial mechanisms of neuropathic pain. *Mol Brain* 4: 31, 2011.

