Setting the Stage for Pain

Allegorical Tales from Neuroscience

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The growth of knowledge and scholarship in biology, the social sciences, and humanities in the recent past has been remarkable. A by-product of this growth is the creation of a multitude of experts. The sheer expanse of knowledge challenges the capacity of individuals to maintain their expertise without losing touch with areas outside their own discipline. The increasing isolation of disciplines that have significant potential to inform each other is particularly unfortunate. Because advances in understanding often occur at the boundaries between academic areas of scholarship and research, it is essential to create a venue for interdisciplinary collaboration. The choice of pain as a focus for such collaboration is both imaginative and prescient. Pain is a powerful force in human behavior, and the biology of pain is a fairly advanced science. However, biological explanations are often not satisfying to scholars in the social sciences and humanities. The problem is in the area of meaning. The humanists do not find meaning in discussions of neural activity, and the neuroscientists usually are not looking for it.

On the other hand, the distance between the two camps is not that great. Because the impact of pain is so highly dependent on the meaning ascribed to it by the individual, a fuller understanding of pain in human beings requires an interdisciplinary approach that transcends the usual biomedical model. A major limitation in our ability to relieve the suffering of patients with chronic pain is an insufficient understanding of the role of meaning.

In this chapter, "meaning" will refer primarily to a set of associations. For example, a sound may initially have little meaning for an individual. It acquires meaning over time through the process of association. We first learn that the sound "mama" is associated with a particular person. The meaning could be general, coming to signify a general relationship of a female to a child. It could, in a different context, refer to a particular person. In the latter case, the meaning is enriched by a potentially very large set of associations related to the individual's life. Clearly, associations build over time, are context dependent, and can be culturally determined. A major challenge in neuroscience is to determine how the neural connections that underlie associations are made and maintained by the central nervous system.

To the extent that we seek to understand the human experience of pain as fully as possible we must address the issue of meaning. This requires constant interchange between neuroscience, the social sciences, and the humanities.

Meaning and Brain Activity

The brain provides the interface of biology with culture. Although the brain is a bodily organ, it has the unique property that its operation is completely symbolic. Patterns of neural activity are representational. Some patterns produce sensations; others produce language and memory. Unique patterns of neural activity represent the body, the external world, and memories. Although these activity patterns symbolize very different things, the representations themselves are all ontologically identical. They are all messages written in the same code, that is, spatiotemporal patterns of neural activity. Because they are coded in the same way, they can interact. Whether conscious or unconscious, bodily or cultural memories, current perceptions, and imagined futures are written in the same language, that is, electrochemical changes in nerve cells. The evolutionary history of the species as recorded in its nucleic acid, the accumulated icons of culture and clan, and the narrative of the individual are all written in the language of neural activity. The brain translates these different aspects of individual experience and weaves each of them into the seamless web of subjective experience and behavior.

Although few dispute that the nervous system is the organ of mental activity, the impact of this idea in the social sciences and humanities is minimal. Even natural scientists rarely delve into the broad implications of this idea. Since all human endeavors, from breathing to philosophy, depend on a set of rules governing the action and interaction of nerve cells, understanding brain function can inform a broad range of disciplines from aesthetics and history to anthropology and political science. Conversely, knowledge of neural activity and connectivity is insufficient to provide a complete understanding of the function of the human brain. Such understanding requires knowledge of concurrent contextual factors as well as the past experience and the goals of the individual. While not ignoring the power of genetics to explain individual differences, it is clear that the moment-to-moment experience of each person is interpreted with reference to his or her individual narrative and belief system. Furthermore, because of the rich tools that have evolved for human communication, our past histories include information derived in symbolic form from other people. This information is represented in the nervous system and has a profound effect on brain function. What we see is only partly shaped by what we are looking at. It is also determined by our past experience, which influences what we are looking for and which, in turn, is conditioned by what we want. Beyond our biological needs for survival, what we want depends on who we are. Who we are is constrained by our biology, but it is also shaped by cultural, interpersonal, and experiential factors.

The Natural Science of Meaning, or Why the Brain Is Not Like Other Organs

In the era of modern neuroscience, the triumph of the reductionist method is magnificent and undeniable. We have learned how nerve cells communicate with each other, how the right anatomical connections are determined during development, and how the strength of these connections is altered during learning. Insofar as brain cells are like cells in other organs, our knowledge is extensive and is growing exponentially. We are very close to having the entire human genome described. With this knowledge in hand, it becomes technically feasible to know the amino acid sequence of every protein in the body. We will

then know all the building blocks that go into nerve cells. To the extent that we can stick electrodes into it and take pieces out of it, we have made enormous strides in understanding *how* the brain works. We are close to knowing how it works; the question is, *What does it do?* What is the meaning of brain activity? Analyzing the connections and electrical properties of nerve cells in isolation would not answer this question, because the meaning of neural activity lies *outside* the brain *(vide infra)*. It is this crucial insight that enables the interdisciplinary project.

Brain activity can be understood, that is, has meaning, only to the extent that it is a representation of the state of the body, of the external world, or of a potential behavior. Just as it would be pointless to analyze a book by investigating the chemical composition of paper and ink, a reductionist analysis of brain activity, that is, taking it apart and analyzing its nucleic acids, enzymes, receptors, and ion channels, fails to explain what brain activity accomplishes. The neuroscience of meaning requires experiments that study brain activity as the body moves through the world or as people describe their experience.

In an operational sense, the function of the brain has more in common with that of language than with that of other bodily organs. Because the brain operates symbolically, objects and events encoded by neural activity are not constrained by space or time. Brain activity can represent things experienced in the past or in an anticipated future. Furthermore, since representations can interact and be combined in novel ways, they are not constrained by objective reality. Neural activity can represent completely imaginary things like unicorns or a moon of blue cheese.

The Symbolic Brain: Neural Activity, Networks, and Representations

The minimal meaningful unit of nervous system function is the *network*. A network is a set of interconnected neurons whose coordinated activity produces an observable action or a subjective experience. The spatiotemporal pattern of *activity* of neurons in a network that produces an action (or perception) is a *representation.* Neuroscientists say that representations *encode* such things as stimuli or intended movements. Thus, representations relate to things and/or events external to

the brain. The very concept of the representation depends on the thing that is represented. Although representations can be unrelated to the external world (e.g., those associated with introspection, imagination, expectation), even these representations are usually understood in the context of things external to the brain. Since our subjective experience of self, body, and world is an *emergent property* of dynamic networks of coordinated neural activity, the brain must contain representations of the body, the self (mind), and the external world. These representations give rise to the ongoing subjective experience of the individual.

Representations are a neural (physical) embodiment of meaning that is often understood in the context of intention. Intention assumes goals; goals imply values. A major task of the brain is to make choices between goals, and this in turn depends on values and predictions of consequences. Since biological, cultural, and personal factors play a major role in the determination of value, value is another critical area for the interdisciplinary enterprise.

In summary, the nervous system is poised at the interface of organism and environment. It is made up of bits of the body that generate a dynamically changing representation of the environment and body in relation to each other. The organism's biological program for survival and reproduction is reified in the neural analysis of this virtual body / virtual context relationship. This analysis of representations guides the physical organism through the external environment. The interacting dyad of brain and context is the canvas upon which "we" continually create ourselves. The brain is the site where culture and biology interact. It is an interface constrained by the laws of physics but liberated by imagination and hope.

The Fallacy of the Faithful Representation: Vision and Television

Old ideas fade slowly, particularly simple, elegant ideas that are consistent with our personal experience. One such idea is that the brain generates sensations by recreating an image of an object in the external world. This idea implies that a process occurs in the brain that is conceptually similar to what happens when a television camera monitors an object and converts it to (i.e., encodes as) a set of electrical signals

that is then decoded by the tuner. The tuner then produces a visual image on the television screen that looks like the object in the camera. In this case the wavelength and pattern of light coming from the object completely determine the shape and color of the image on the television screen. The object is the ultimate cause of the image.

Many people, including some neuroscientists, assume that the human visual system works in a roughly analogous manner. In other words, that the object we are looking at completely determines the image we perceive. To a certain extent, this attitude is reinforced by certain arbitrary properties of the brain. Thus, for example, the visual cortex contains topographically accurate maps of visual space, and some cells in the visual cortex respond to lines of specific orientations, while others respond to specific colors. It is not a huge leap from these observations to the idea that there is a unique neural representation of the visual image that is completely determined by the wavelength and spatial pattern of light arriving at the retina from the external object. This representation would then generate the perceived image.

Although simple, this idea is hard to reconcile with the fact that people have vivid visual imagery during dreaming, when no visual stimuli impinge upon the retina. Hallucinations induced by drugs, trance, or mental illness are also difficult to reconcile with the brain as television monitor. These are only the most dramatic examples of processes that are in continual operation coloring our moment-to-moment experience. A purely bottom-up explanation of sensory experience is inconsistent with the facts.

The Perceptual Process: Selection or Reconstruction?

In fact, sensory stimuli impinge on a brain that is conditioned by genetics and learning. The process that leads from visual input to a subjectively experienced image is more akin to a computation about the likely cause of the stimulus than a photographic reproduction of the object. It is more selective and synthetic than reconstructive.

Dramatic and compelling evidence for this idea are the observations of Wilder Penfield and others who electrically stimulated the cerebral cortex in awake patients undergoing surgery for epilepsy. Depending on the location of the electrodes, stimulation could produce a variety

of projected sensations (Penfield 1958; also see Gloor 1990). Of greatest interest were the effects of stimulation of the temporal lobes, which elicited complex narrative reports with strong emotional coloring. It is unlikely that the neural activity producing the experience is localized to the small area actually stimulated. What is more likely is that the stimulation activated a set of "prepackaged" representations. These representations could have a genetic component, but it is likely that they evolve over time through a combination of sensory experience and synthesis. The point is that, rather than passively reproduce images from sensory stimuli, the brain actively uses these inputs to combine and shape images that are selected from a potentially large but limited preexisting file.

Here is another potential interface for neurobiology: the social sciences and the humanities. Each individual will have a nervous system that is shaped by his or her unique experience. This is powerfully influenced by language, religion, and other cultural factors. A key point is that this influence is a two-way street: not only do bodily and environmental factors create central representations; these representations strongly influence the interpretation of ongoing experience. I will expand upon this point later.

Projection and the Illusion of the Mind-Body Dichotomy

The studies of Penfield as outlined above illustrate the process of *projection.* The process of projection is critical to understanding the experience of pain. Penfield's studies proved that electrical stimulation of the brain can elicit fully formed experience that is projected beyond the body to a "virtual" external world. Electrical stimulation of pain-transmitting neural pathways results in an experience of pain that is projected onto a specific body part (see, e.g., Craig and Dostrovsky 1999). In this case, there is nothing happening in that body part. The only thing that is "happening" is electrical activity in nerve cells activated either directly or indirectly by electrical stimulation. A neural representation has been activated and has produced the subjective experience of pain. The same thing happens when there is actual tissue injury (e.g., due to a broken bone), and the pain pathways are activated by the usual route. The experience of pain is the result of

activating a neural representation in the brain and is projected in space to the site of tissue injury. The point is that the pain is generated at a site distant from the injury but is perceived to be at the injury site due to projection. The pain is generated in the brain. It is neural and mental. It is physical pain in the sense that nerve cells and their activity are physical. It is mental pain in the sense that it is subjectively experienced "in" what we generally call the mind.

Two illustrative examples of the phenomenon of projection are phantom limb and referred pain. Following amputation of an arm or leg, the amputee continues to feel the presence of the limb even though he knows it is not present. Of course, this is not surprising since the brain's representation of the limb is intact. Over time, the perceived size of the experienced phantom limb shrinks as the brain's representation changes (Flor, Elbert, and Muhlmickel 1998). In the case of referred pain, projection is also at work. The gall bladder is located just below the liver, but when it is inflamed, it often generates a pain that is felt as if it were in the right shoulder. This is because the sensory fibers from the gall bladder enter the nervous system along with the sensory fibers from the shoulder. Under normal conditions there is almost never a neural signal from the gall bladder, but when it is inflamed, it generates a signal that activates central pathways that are frequently activated by sensory input from the shoulder. The mislocalization of the source of the pain is due to the projection of the sensation to the usual source of the sensory signal.

Once one understands and accepts the concept of projection, it becomes obvious that all pain is mental. Furthermore, what most people call mental, or emotional, pain is ontologically identical to what they call organic, physical, or bodily pain. This point is counterintuitive, and failure to appreciate it has compounded the confusion about the nature of pain. Once this point is appreciated, many confusing phenomena, such as the placebo response, somatization, psychologically induced headache, and analgesia in trance, become less surprising and arcane.

Projection is a psychobiological phenomenon of great relevance to the interdisciplinary project (see my concluding remarks). It illustrates dramatically the metaphorical nature of neural activity. Furthermore, it reveals to us that everyday life requires an ongoing

suspension of disbelief as our brains displace our subjective experiences from their intracranial generators (representations) out to our bodies and the external world. It seems to me that understanding these aspects of brain function provides one "humanities-friendly" ground of neuroscience.

The Neurobiology of Pain and Suffering: Pain as Sensation, Pain as Emotion

Up to this point I have focused on properties of brain function that relate to perception in general. This section will focus specifically on the neural mechanisms of pain perception. This will be a traditional bottom-up approach, covering brain areas that mediate different components of the pain experience. I will suggest how the meaning of pain associated with tissue damage can be shaped by personal and cultural factors. I will then discuss the evolution of current ideas about how activity in neuronal circuits elicited by tissue-damaging stimuli give rise to pain. This brief introduction to the neurobiology of pain transmission will be followed by a review of top-down factors that influence pain: specifically, the pain modulatory networks through which contextual factors interact with pain pathways to suppress, enhance, or even create the sensation of pain.

The rough outlines of the pain sensory system have been known since the late nineteenth century. Tissues are innervated by sensory nerve fibers that respond selectively to intense, potentially injurious events. These nerves propagate messages to the central nervous system. These messages activate numerous parallel circuits in the central nervous system that produce a variety of objective and subjective responses. For example, if you inadvertently touch a hot iron, you will automatically turn toward the iron and pull your hand away well before you experience a painful sensation. If you cannot pull away quickly enough, your blood pressure and heart rate will rise. Each of these responses depends on a separate circuit in the central nervous system; none requires the cortex.

Turning to the subjective experience: there are three distinct components (Melzack and Casey 1968; Fields 1999). First, there is the purely

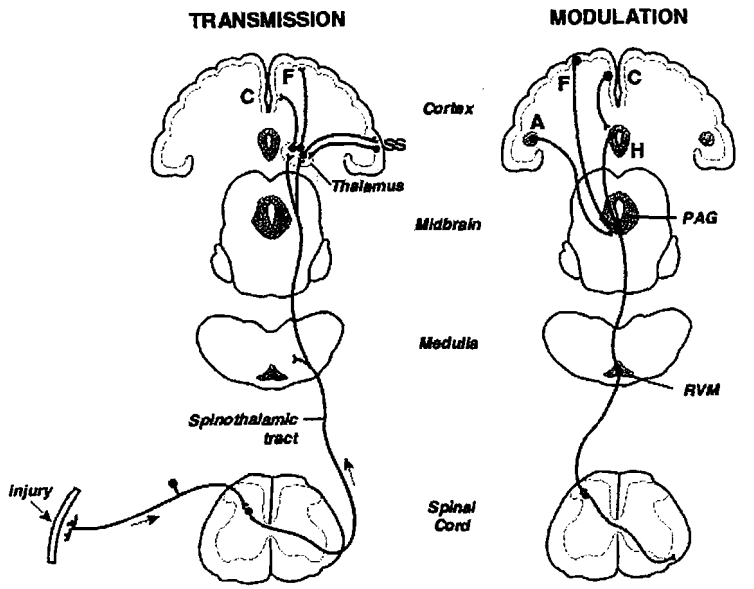

Figure 4.1. Pain Transmission and Modulation. Left: transmission pathway. Tissue injury activates primary afferent sensory fibers that relay information to the spinal cord. Initial processing takes place at the level of the dorsal horn and is then conducted in the spinothalamic tract to the thalamus. At this level, the pathway diverges into a medial projection to the front lobe (F), which includes the anterior cingulate cortex (C), the lateral pathway that projects to the somatosensory cortex (SS). Right: modulation pathway. Signals depending upon memories and contextual cues arise from the frontal cortext and amygdala (A) and project to the midbrain periaqueductal gray (PAG), which controls the spinothalamic pathway via the rostral ventromedial medulla (RVM).

discriminative part that includes recognizing the quality of the sensation as a burn and localizing it to your hand. Second, there is the motivational aspect associated with the desire to pull your hand away or to terminate the sensation. Third, there is an evaluative component—the thought of the damage that has been done to your hand and how that will affect your life in the hours and days ahead. All three subjective components of the pain experience are triggered by activity in peripheral nerves that enter the spinal cord and activate cells that project to the contralateral thalamus (see Figure 4.1, Transmission). This is the spinothalamic tract, which is required for all components of the

sensation of pain in normal individuals. At the level of the thalamus, the pain signal diverges into separate pathways that underlie the different components of the experience. The discriminative component (what and where) largely involves the somatosensory cortex. In contrast, forebrain areas known as the limbic system mediate the motivational and emotional component of pain (how bad it feels). The limbic system includes the cingulate gyrus and anterior insula of the frontal cortex and the subcortical structure known as the amygdala. The neurobiology of the evaluative component is still an open question.

In addition to its role in pain perception, the limbic system mediates emotional responses to a variety of factors including personal loss, anticipation of harm, and so on. The dysphoric states such as depression and anxiety share limbic system circuits with somatic pain. It is thus no accident that the word "pain" is often used to denote emotional pain that has no somatic component. For the purposes of our multidisciplinary project, it is important to keep the distinction between somatic and emotional pain clear. Although somatic injury can produce both somatic and emotional pain, the neural representations of these two aspects of the experience are largely separate. For example, patients with frontal lobotomies selectively lose the motivational (suffering) component of pain, but the discriminative component is spared. When these patients sustain tissue injury, they report intense pain and can give a precise description of its quality and location and yet have no emotional response to it (Fields 1999).

The motivational and evaluative aspects of pain are tightly bound. Imagine the difference between a headache sustained after a bout of heavy drinking and an equally severe headache the week after learning that one's identical twin brother with a similar headache was diagnosed with a malignant brain tumor. In these two examples, although a similar peripheral signal was at work, the meaning was completely different. The point is that the response to the "pain" signal does not occur in a vacuum, and the cognitive response to it depends in large part on the context in which the pain arises. Since the context depends on interpersonal dynamics, cultural factors, and the individual's personal narrative, their analysis requires the tools and concepts of the social sciences.

The Evolution of Ideas about the Neural Mechanisms of Pain

The focus on pain as a sensation as opposed to an emotion stimulated research on specific pain pathways. The success of these studies on sensation reinforced the tendency of investigators to focus on this aspect of pain. In the early nineteenth century the pioneering work of Bell and Magendie had established the differences between sensory and motor nerves (e.g., see chapter 5 in Keele 1957). The definition of a distinct system for somatic sensation, including pain, fit in well with the law of specific nerve energies proposed by the German physiologist Muller. This law postulates that each sensory modality (vision, smell, hearing, somatic sensation) is subserved by a distinct set of neural structures in peripheral nerves and in the brain. This idea received strong confirmation through the mid-nineteenth-century experimental and clinical studies of Brown-Sequard that clearly identified the anterolateral quadrant of the spinal cord as a discrete spinal pathway for pain. More specialized anatomical techniques allowed later investigators to determine that the thalamus is the relevant target for this pathway.

Primary Afferents for Pain: The Rise and Apparent Fall of Specificity Theory

Pain sensation requires primary afferents to transform tissue pathology (e.g., injury and inflammation) into a code (nerve impulses) that can be interpreted by the brain (see Chapter 3). Primary afferents are neurons that have their cell bodies in the dorsal root ganglia near the spinal cord. They send one process (axon) out to innervate the peripheral tissues, and another axon carries the message into the spinal cord. By the late nineteenth century, anatomists had discovered a variety of different skin specializations innervated by cutaneous primary afferent nerves. These discoveries led von Frey to propose that each anatomical specialization conferred specific sensitivity to a specific type of stimulus energy (e.g., warm, cold, touch, pain, itch). Perhaps because of its elegance and simplicity, this idea held sway until the mid-twentieth century, when it was thoroughly discredited by anatomical studies showing a dissociation between any of the known skin specializations and the

sensations of cold, warm, and pain. On the other hand, von Frey's idea that a class of primary afferent is specialized to encode information about intense, tissue-damaging stimuli was ultimately vindicated, but not until after a period of strong controversy.

After World War II, a new method emerged that revolutionized neuroscience. This was the ability to record the activity of single nerve cells. This method enabled investigators to determine precisely what stimuli a given nerve fiber responds to optimally. The first rush of data stimulated specific theories. As is often the case, the first interpretations were based on incomplete information. The earliest studies found few primary afferent nerve fibers specialized to respond to intense tissue-damaging stimuli. Furthermore, the first pain-responsive neurons studied in central pain pathways responded across a broad range of stimuli, including innocuous mechanical stimulation. These findings appeared at odds with the dominant idea of a labeled line that consisted of specialized primary afferent receptors and central pathways for pain sensation. In addition, there were behavioral studies in animals, clinical observations, and human psychophysical data that were at odds with the idea of a simple one-to-one relationship between stimulus intensity and perceived pain intensity. First, there were the experimental studies of Russian physiologist Ivan Pavlov. When he trained dogs by consistently preceding food administration with tissue-damaging stimulation, over time, they began to salivate instead of whining and cowering when the noxious stimuli were applied. Somehow the pairing of the intense stimulus with food changed its meaning. These findings were complemented by the observations in people that psychological factors such as fear and expectation could powerfully alter pain perception. The most famous of these were the reports by Beecher (1959; see also 1946) of American soldiers in World War II who denied feeling pain despite grievous injuries. Not only do these observations illustrate the importance of learning and context; they clearly imply that the brain has mechanisms that allow it to suppress typical responses to intense, tissue-damaging stimuli, including the perception of pain. Finally, peripheral nerve lesions or selective blockade of large myelinated axons in peripheral nerve were shown to produce exaggerated responses to stimuli that were normally innocuous or only mildly painful. This suggested that the large myelinated fibers inhibited central pain pathways.

This evidence of interaction of stimuli from different sensory channels smacked of pattern theory, that is, the idea that sensation has as much to do with the interactions and *patterns* of neural activity as with their specific sensitivity. As it turns out, both ideas were eventually incorporated into our current concepts of the neural coding relevant to pain perception.

The Gate Control Hypothesis in Perspective

In 1965, Melzack and Wall suggested a specific neural model, the gate control hypothesis, to account for these and other findings at odds with specificity theory. This model was revolutionary in that it was the first serious attempt to incorporate the puzzling clinical features of pain and the newly emerging data from studies of single neurons. Their theory was consistent with what was known at the time, and it was simple, highly specific, and testable. At that time it was generally accepted that the smaller-diameter, most slowly conducting primary afferents had the highest threshold for activation, and the larger-diameter fibers responded maximally to light-innocuous stimuli. The core of Melzack and Wall's idea was as follows: (1) the different primary afferents responding to either innocuous (large-diameter primary afferents) and noxious stimuli (small-diameter primary afferents) converge onto, and directly excite, pain transmission neurons (T cells) that produce responses to pain-including sensation; (2) there is also an interneuron (SG cell) in the spinal cord dorsal horn that inhibits both types of primary afferent by preventing neurotransmitter release from their terminals onto the T cells; (3) the SG cell is inhibited by the small-diameter primary afferent and excited by the large-diameter afferent. Excitation of SG interneurons by large-diameter fibers suppresses pain responses. Furthermore, the model predicts that strong inhibition of the SG cells by the small-diameter primary afferents would block the inhibitory effect of the large-diameter fibers so that they would *produce pain* rather than inhibiting it.

This last prediction presented the greatest challenge for specificity (labeled line) theory, since the large-diameter myelinated fibers do not respond differentially to intense stimuli. In fact, subsequent research has shown conclusively that selective stimulation of large-diameter

fibers in awake human beings under normal conditions produces a nonpainful vibratory or tingling feeling but never pain. However, following selective activation of small-diameter fibers, selective stimulation of the same large-diameter fibers produces a burning pain. The activation of the small-diameter fibers has produced a change in the pain pathways so that the large myelinated fibers now have access to it. There has thus been a modality shift such that the same fibers that produce an innocuous feeling of touch under one condition can produce pain when tissue damage has occurred. There is no way that this robust finding can be accounted for by a labeled central line for pain. Modality shifting is the ultimate vindication of a core concept of the pattern theory idea because it clearly demonstrates that the perceptual impact of activity in a primary afferent can be robustly changed by activity in other primary afferents.

It is difficult to overestimate the impact that the Melzack/Wall hypothesis had. By proposing a specific and testable neural hypothesis for pain perception, it stimulated an explosion of experiments and invigorated the field of pain research. By providing a neural explanation for the paradoxical dissociation of stimulus and perception, it not only shook the foundations of specificity theory, but it brought the most clinically relevant aspects of pain out of the realm of pure psychology and into the realm of neuroscience. A corollary of this was to provide enhanced respectability for pain patients, for the physicians who cared for them, and for the scientists working in the field. Instead of asking, "What's wrong with this person?" the question became, "What's wrong with his/her nervous system?" The latter question is clearly more susceptible to investigation with the tools of modern biological science. The gate control hypothesis was a heuristic success.

Despite the huge impact of the gate control hypothesis, critical observations upon which it was based were either incomplete or misleading, and most of its specific assertions have crumbled under the weight of investigation. Later discoveries provided better explanations for most of the phenomena that the model addressed. First, it turns out that there are, in fact, many primary afferents that respond selectively to intense, tissue-damaging stimuli. More problematic for the hypothesis is the discovery of dorsal horn neurons that respond

selectively to noxious and to thermal stimuli. The prolonged excitatory changes in pain transmission neurons are now known to result from changes intrinsic to the primary afferents and the central transmission neurons as opposed to inhibition of inhibitory SG interneurons. Thus, many primary afferents show increased sensitivity and spontaneous activity following intense tissue damage or when they themselves are damaged. Furthermore, most substantia gelatinosa neurons are excitatory, not inhibitory, and the weight of evidence indicates that the shift in modality of large myelinated fibers from touch to pain is due to long-term excitation of the pain transmission (T) cells themselves, not disinhibition (Doubell, Mannion, and Woolf 1999). While there are some inhibitory SG neurons, there is no evidence that they are inhibited by small-diameter primary afferents, which is a key component of the gate control model. Finally, and most relevant to our multidisciplinary project, there is no compelling evidence to support a role for the dorsal columns in the "central control trigger."

In summary, our understanding of the primary afferent nociceptor and the spinal transmission neurons they excite has evolved dramatically. A subset of primary afferents responds selectively to tissue-damaging stimuli and shows lowered thresholds and spontaneous activity when exposed to prolonged or repeated intense stimuli or when damaged. The spinal neurons (T cells) activated by nociceptive primary afferents also become sensitized following prolonged or repeated intense stimuli. When (and only when) the second-order (T) cells are sensitized, they can be activated by light (normally innocuous) mechanical stimuli that only activate the large myelinated fibers. It is this sensitization that accounts for the modality shift from touch to pain in large-diameter primary afferents, which was a major impetus for the gate control hypothesis. Nearly four decades after the theory was proposed, we have better explanations for most of the observations that it attempted to explain. Yet its impact is undeniable. The advances in our understanding since mid-1965, while dramatic in their cumulative effect, have been incremental, and none have had anything like the revolutionary impact as the gate control hypothesis. Specificity theory is now generally understood to be inadequate. The importance of convergence and plasticity in the connections to spinal cord pain transmission neurons remains

unchallenged, as is the idea that forebrain control is exerted via descending connections to a spinal "gate."

Top-Down Influences on Pain: Modulatory Systems

A major impetus for the gate control hypothesis was the recognition that learning, attention, expectation, and mood can exert powerful control over pain. At the time of the original proposal, much less was known about these top-down factors than about primary afferent nociceptors and spinal cord pain processing. Melzack and Wall clearly realized that unless these factors could be accounted for, any theories of pain would be woefully inadequate. Pain research was able to progress precisely because scientists doing psychophysical studies could control these modulating factors and isolate the mechanisms specific to the bottom-up sensory process. To a certain extent, the emphasis on the ascending sensory pathways remains the dominant theme in pain research. However, there is a growing interest in studying the neural systems that underlie the top-down modulatory factors.

While descending pathways were known to impinge on and control spinal cord pain transmission neurons, their origin and function were unknown (Fields, Basbaum, and Heinricher 2006). The gate control hypothesis incorporated these descending pathways by proposing a vague "central control trigger." The central control was activated by a bodily stimulus that, via large-diameter afferents in the dorsal column, triggered an evaluative forebrain process that generated a signal sent back down to the spinal cord "gate" to close it before the slowly conducting input from the small fibers arrived. This idea has not been supported by experiment. No bodily stimulus is required for activation of evaluative processes known to precede and modify pain. Furthermore, there is no compelling evidence that the dorsal column pathway contributes significantly to pain modulation.

The study of pain modulation began in earnest about five years after Melzack and Wall published their hypothesis, and our knowledge in this area has since grown explosively. Briefly, brain regions comprising the limbic system (the cingulate and prefrontal cortex, the medial temporal lobe and amygdala, and the hypothalamus) connect via neurons in certain brainstem structures that descend to and control the dorsal

horn neurons that receive inputs from the primary afferents that specifically respond to noxious stimuli (Fields and Price 1997; Fields, Basbaum, and Heinricher 2006; see again Figure 4.1, Modulation). The structures in this pain-modulating circuit are linked by endogenous opioid peptides (endorphins), and the evidence is compelling that the circuit mediates the pain-relieving effect of powerful narcotic analgesics such as morphine. In addition to suppression of pain, neurons in the circuit can *facilitate* pain. In other words, pain modulation is bidirectional. The impact of our improved understanding of pain-modulating systems has been extraordinary and rivals that of the gate control hypothesis and subsequent research in pain transmission. Research on pain modulatory systems has been crucial for increasing understanding of how centrally acting analgesic drugs relieve pain, how drug tolerance develops, and how cognitive factors modify pain.

The Brain as a Hypothesis Machine: The Biological Function of Reward and Punishment

After this brief introduction to the basic neurobiology of pain, let us return to more general issues. It is essential to put the neurobiology of pain into a broader functional perspective in order to move toward a rigorous dialogue with the humanities. This requires identifying points where the neurobiology of pain informs such key interdisciplinary bridging concepts as meaning and expectancy. Up to this point, we have focused on the subjective experience of pain. After all, pain is defined in those terms, and most scientific work on pain to date has focused on mechanistic explanations of the perceptual experience. However, a deeper and broader understanding requires that we put the subjective experience into a biological perspective. To ask, "What is the biological purpose of the neural systems that mediate and modulate the experience of pain?" is clearly quite a different matter than to ask, "What are the neural mechanisms underlying pain sensation?" The former question requires us to address the general issue, "How does the brain use sensory information?"

Earlier in this chapter we discussed representation and projection and put the relationship of stimulus to perception in perspective. As mentioned earlier, representations are best understood in the context

of goals, which in turn imply a set of values. Biological values are determined by the survival and reproductive success of the individual. Nervous systems are designed to enable an organism to respond to potentially tissue-damaging or life-sustaining objects or processes in the internal or external environment. As the repertoire of potential responses expands, more complex neural computations are required to choose the response most likely to be beneficial. Whether to run, fight, or pay someone else to fight, the more options there are, the more possibilities to "succeed." The brain gathers all the information and makes a computation about which course of action is most likely to achieve the desired end. In other words, the computation leads to a prediction of consequences in the form of a hypothesis: If I carry out action A, the consequence will be B. If I carry out C, the consequence will be D. B is more desirable than D; therefore I will carry out A. The role of pain (and pleasure) is to inform the organism of the cost (and benefit) of the chosen action. This information allows the brain to reevaluate the accuracy of its predictions. The point is that the sensory system is not a passive conduit for transmitting information about stimuli. The sensory system is active in the context of goal-directed behaviors and provides data the brain uses to evaluate the consequences of specific actions. The brain is not passive; it is actively probing and exploring. At any given time, what the brain "perceives" depends as much on what questions it is asking and what happened in the past as it does on what stimuli are presented to it. The modifications that take place can be thought of as transformations of the meaning of the neural activity produced by tissue-damaging stimuli.

Pain Transforms Meaning, Meaning Transforms Pain

Although our interdisciplinary project is still in a nascent stage, it is not too soon to ask whether we can conceptualize a neurobiological model for the transformative process. How could pain transform meaning, and how could meaning transform pain? There is no doubt that these transformations occur, but we have yet to develop a common language. First we have to agree on what the phenomenon is that we want to explain. Consider this section a preliminary attempt to get the conversation going.

One aspect of this conversation is straightforward. By the process of association, pain can transform the meaning of contextual cues, intentions, and behaviors. It is no accident that the Latin root of the word "pain" is punishment. Punishment is a core interpersonal transaction that leads to social control and the reinforcement of cultural norms. For example, take the dictum Honor thy parents. Parents may inflict pain on their children if they lie, deliberately break things, or simply act in a defiant manner. Through the agency of punishment, the (actual or intended) performance of the punished act acquires new meaning. One could argue that obedience becomes a good because of its association with the avoidance of pain. The threat of pain can become incorporated into cultural myths that serve the same purpose as punishment. For example, in some ideas of hell, physical pain plays a prominent role. Conversely, pain can transform behaviors in the opposite direction. You might say that defiance is transformed from disrespect to courage when it is done in the anticipation of physical punishment. What the parent views as evil, the child's peers might view as a good. In this case, the concept of courage (or defiance) requires cultural insights and is usefully informed by anthropology and/or sociology. Courage is generally thought to be good, but again, good and bad are not scientific constructs. Here one must call on scholars in philosophy and religion. Through the analysis of such specific behaviors, the interdisciplinary project of the Mind/Brain/Behavior Initiative can be advanced.

How can we inject neurobiology into this conversation? In this specific case it would be difficult. At some point it might be possible to develop a neurobiology of courage; however, the neurobiology of culturally defined personal qualities is virtually nonexistent. What is possible, now, is to find a model for a *behavioral* transformation produced by pain.

An Animal Model to Study the Neurobiology of Pain-Induced Transformation: Conditioned Fear and Pain-Modulating Pathways

An excellent animal model of transformation is *conditioned fear* in rodents. One rodent response to threat is to freeze and become analgesic.

Presumably, the biological significance is that the rodent is less likely to be seen by a predator if it is absolutely still. In the conditioned fear paradigm, rodents are exposed for a few seconds to a painful stimulus in a small box from which they cannot escape. After a couple of brief exposures to such stimuli, when the rodents are returned to the box in which they had previously been shocked, they freeze and become completely analgesic. What has happened is that the sensory features that are unique to the shock-box have been transformed. Where once the box was considered safe, it is now threatening. In other words, through associative conditioning the contextual stimuli (color, texture, odor of the box) have acquired new meaning. One can do the same thing by cueing the shock with an innocuous tone or light.

From the neurobiological standpoint, the mechanism of conditioned fear is well understood. The underlying circuit includes the endogenous opioid-mediated pain-modulating pathway described earlier (e.g., see Helmstetter and Tershner 1994). Furthermore, the sites of plasticity that underlie the "transformation" in meaning of the cues that have been paired with the shock have been localized in specific limbic system structures. The synaptic changes underlying the learning are partially understood. The point is that we have a model for discussing meaning at a biological level. The nervous system objectively embodies meaning and renders it accessible to scientific study. By virtue of the physical interaction of representations, new representations emerge that change behavior and perception. When referring to this process, substitute the word "learning" for "transformation," and neuroscientists become comfortable.

How Meaning Modifies Pain

Because it is such a powerful motivating force, and can signal the threat of irreversible harm, it is not surprising that pain has transformative power for individuals. What is surprising, however, is the power of symbolic manipulation to change the experience of pain. The placebo analgesic response is an excellent example of the power of expectation to alter the pain experience (Fields and Price 1997).

There is compelling evidence that placebo analgesia requires the same opioid-mediated pain-modulating circuitry that underlies the analgesic effect of conditioned fear in rodents. In human subjects with experimental pain, placebo analgesic responses are associated with activity in brain areas that largely overlap those activated when opioids are administered (Petrovic et al. 2002). This circuitry is homologous to that activated by opioids and conditioned fear in rodents. In view of the fact that placebo analgesia in humans is blocked by the opioid antagonist drug naloxone, this observation demonstrates the importance of specific pain-modulating circuitry in mediating the suppressing effects of meaning and expectancy on pain. It seems to me that the placebo analgesic effect, with its powerful cultural and personal determinants, and a partially described neural mechanism, is an ideal place to focus an interdisciplinary discussion.

Another dramatic example of the power of verbal instruction to alter pain perception is a study by Dworkin and colleagues at the University of Washington. They used the method of tooth pulp stimulation to deliver a standard noxious stimulus in normal human volunteers (Dworkin et al. 1983). Subjects were stimulated at an intensity adjusted to produce the same reported subjective pain intensity. Following this, all subjects were given nitrous oxide. The independent variable was what the subjects were told. One group was simply told they were receiving nitrous oxide; the other group was told that nitrous oxide actually enhanced awareness. Those told simply that they were receiving nitrous oxide reported significant pain relief, whereas those told that nitrous oxide enhanced awareness experienced a significant increase in their pain levels. In this case, the physical manipulations resulted in different outcomes based on different verbal instructions.

Even more dramatic is the study by Bayer and colleagues (Bayer, Baer, and Early 1991). They examined normal volunteers who had electrodes placed on their temples. The subjects were told that they would receive electrical stimulation at increasing intensity and were to report the level of pain they experienced. The stimulus intensity was signaled by an intensity gauge that the subject could view and by a tone whose pitch increased in increments that were parallel with the

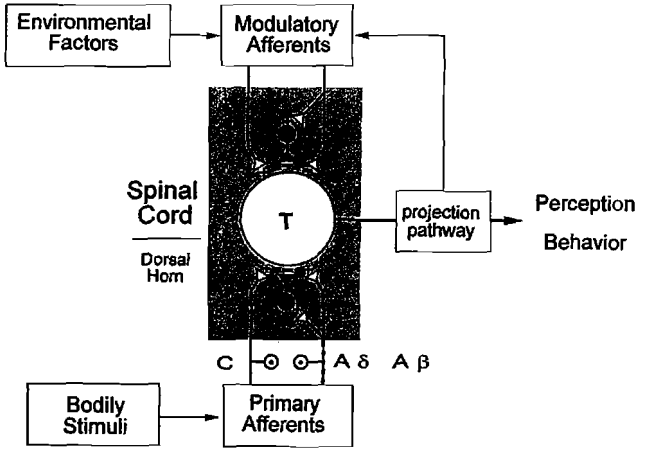

Figure 4.2. Top-down Factors in Pain. Pain depends on both potentially injurious bodily stimuli and the context in which those stimuli are given. The pain transmission system integrates both somatic stimuli (shown coming up from below to contact the T, or transmission neuron). Of equal or greater importance are top-down inputs from modulatory systems that are determined by behavioral state (both internal motivations and external contextual cues). Cultural factors can be powerful determinants of the state of the T neuron. Aδ and C fibers include nociceptors, while Aβ fibers are activated by light, normally innocuous stimuli. Bottom-up and top-down systems can be either inhibitory (acting via the small, dark inhibitory neurons) or excitatory.

gauge readings. One hundred subjects were included in the study. They were divided into five groups and given different instructions. Although no stimulus was actually delivered (the electrodes were not connected to a power source), up to 50 percent of subjects reported pain at the electrode site, and up to 25 percent requested pain medication. This study is very important because severe pain was elicited in the absence of any stimulation. It illustrates the power of meaning to influence the pain experience. There is evidence that the pain modulatory systems described here may be involved in these cognitively generated pain responses. The pain modulatory system is known to exert bidirectional control; that is, it can generate as well as suppress pain. Furthermore, recent functional imaging studies are consistent with the notion that brain regions identified as part of this system are activated during the time when a painful stimulus is expected (Hsieh, Stone-Elander, and

Ingvar 1999; Sawamoto et al. 2000; Tracey et al. 2002; Keltner et al. 2006).

Although a complete understanding of contextual influences on pain is many years in the future, a general model is emerging. The basic idea is that through the process of association environmental stimuli gain the ability to exert powerful influences on perceived pain intensity. The process of association changes the neural representations (meaning) of the relevant contextual stimuli. Consequently, the contextual stimuli gain the power to change the neural representations elicited by actual or anticipated tissue-damaging stimuli. These changes are exerted via a specific pain-modulatory system with links in limbic forebrain, amygdala, and brain stem. This circuit projects to, and selectively controls, pain-transmitting spinothalamic tract neurons. Thus the old view that the experience of pain is a bottom-up process determined largely by the stimulus must be revised. In the current view, activity in the pain pathways is determined not only by tissue injury but by expectation (see Figure 4.2). This, in turn, is conditioned by the individual's past history and by current contextual stimuli. In this view, pain normally has both stimulus-bound and context-determined components. The study of the stimulus-bound components is advanced and is largely the province of neurobiology. The study of the context-determined components is an inherently interdisciplinary endeavor and is in its infancy.

References

Bayer, T. L., P. E. Baer, and C. Early. 1991. "Situational and Psychophysiological Factors in Psychologically Induced Pain." *Pain* 44: 45–50.

Beecher, H. K. 1946. "Pain in Men Wounded in Battle." *Ann. Surg.* 123: 96–105.

———. 1959. *Measurement of Subjective Responses: Quantitative Effects of Drugs.* New York: Oxford University Press.

Craig, A. D., and J. O. Dostrovsky. 1999. "Medulla to Thalamus." In P. D. Wall and R. Melzack, eds., *Textbook of Pain,* 4th ed. Edinburgh: Churchill-Livingstone, 183–214.

Doubell, T. P., R. J. Mannion, and C. J. Woolf. 1999. "The Dorsal Horn: State-Dependent Sensory Processing, Plasticity and the Generation of

Pain." In P. D. Wall and R. Melzack, eds., *Textbook of Pain,* 4th ed. Edinburgh: Churchill-Livingstone, 165–182.

Dworkin, S. F., A. C. C. Chen, L. LeResche, and D. W. Clark. 1983. "Cognitive Reversal of Expected Nitrous Oxide Analgesia for Acute Pain." *Anesth. Analg.* 62: 1073–1077.

Fields, H. L. 1999. "Pain: An Unpleasant Topic." *Pain* supplement 6: S61–S69.

Fields, H. L., A. I. Basbaum, and M. M. Heinricher. 2006. "Central Nervous System Mechanisms of Pain Modulation." In S. B. McMahon and M. Koltzenburg, eds., *Wall and Melzack's Textbook of Pain,* 5th ed. Edinburgh: Elsevier Churchill Livingstone, 125–142.

Fields, H. L., and D. D. Price. 1997. "Toward a Neurobiology of Placebo Analgesia." In A. Harrington, ed., *The Placebo Effect: An Interdisciplinary Exploration.* Cambridge, Mass.: Harvard University Press.

Flor, H., T. Elbert, and W. Muhlmickel. 1998. "Cortical Reorganization and Phantom Phenomena in Congenital and Traumatic Upper-Extremity Amputees." *Exp. Brain Res.* 119: 205–212.

Gloor, P. 1990. "Experiential Phenomena of Temporal Lobe Epilepsy: Facts and Hypotheses." *Brain* 113: 1673–1694.

Helmstetter, F. J., and S. A. Tershner. 1994. "Lesions of the Periaqueductal Gray and Rostral Ventromedial Medulla Disrupt Antinociceptive But Not Cardiovascular Aversive Conditional Responses." *J. Neurosci.* 14: 7099–7108.

Hsieh, J. C., S. Stone-Elander, and M. Ingvar. 1999. "Anticipatory Coping of Pain Expressed in the Human Anterior Cingulate Cortex: A Positron Emission Tomography Study." *Neurosci. Lett.* 26 (262): 61–64.

Keele, K. D. 1957. *Anatomies of Pain.* Oxford: Blackwell Press.

Keltner, J. R., A. Furst, C. Fan, R. Redfern, B. Inglis, and H. L. Fields. 2006. "Isolating the Modulatory Effect of Expectancy upon Pain Transmission: An fMRI Study." *J. Neurosci.* 26: 4437–4443.

Melzack, R., and K. L. Casey. 1968. "Sensory, Motivational, and Central Control Determinants of Pain." In D. Kenshalo, ed., *The Skin Senses.* Springfield, Ill.: C. C. Thomas, 423–439.

Melzack, R., and P. D. Wall. 1962. "On the Nature of Cutaneous Sensory Mechanisms." *Brain* 85: 331–356.

———. 1965. "Pain Mechanisms: A New Theory." *Science* 150: 971–979.

Penfield, W. 1958. *The Excitable Cortex in Conscious Man.* Springfield, Ill.: C. C. Thomas.

Petrovic, P., E. Kalso, K. M. Petersson, and M. Ingvar. 2002. "Placebo and Opioid Analgesia: Imaging a Shared Neuronal Network." *Science* 295: 1737–1740.

Sawamoto, N., M. Honda, T. Okada, T. Hanakawa, M. Kanda, H. Fukuyama, J. Konishi, and H. Shibasaki. 2000. "Expectation of Pain Enhances Responses to Nonpainful Somatosensory Stimulation in the Anterior Cingulate Cortex and Parietal Operculum/Posterior Insula: An Event-Related Functional Magnetic Resonance Imaging Study." *J. Neurosci.* 20: 7438–7445.

Tracey, I., A. Ploghaus, J. S. Gati, S. Clare, S. Smith, R. S. Menon, and P. M. Matthews. 2002. "Imaging Attentional Modulation of Pain in the Periaqueductal Gray in Humans." *J. Neurosci.* 22: 2748–2752.

Wall, P. D., and R. Melzack, eds. 1999. *Textbook of Pain,* 4th ed. Edinburgh: Churchill-Livingstone.