Gate Control Theory

On the Evolution of Pain Concepts

Ronald Melzack

Descartes' concept that pain is produced by a direct, straight-through transmission system from injured tissues in the body to a pain center in the brain has dominated pain research and therapy until recently. The gate control theory of pain, published in 1965, proposes that a mechanism in the dorsal horns of the spinal cord acts like a gate that inhibits or facilitates transmission from the body to the brain on the basis of the diameters of the active peripheral fibers, as well as the dynamic action of brain processes. As a result, psychological variables such as past experience, attention, and other cognitive activities have been integrated into current research and therapy on pain processes. The gate control theory, however, is not able to explain several chronic pain problems, such as phantom limb pain, which require a greater understanding of brain mechanisms. A new theory of brain function, together with recent research that has derived from it, are described. They throw light on complex pain problems and have important implications for basic assumptions in psychology and neuroscience. **Key words:** *gate control theory, pain, dorsal horn, neuromatrix*

Theories of pain, like every other kind of theory, evolve in conjunction with the accumulation of scientific facts. Theories give rise to experiments, which generate new facts, and these, in turn, reveal the inadequacies of older theories and provide the foundations for new ones. This article discusses the gate control theory of pain in the perspective of earlier theories and outlines the data that call for a new one. In particular, phantom limb pain cannot be explained by any current theories and reveals that the study of brain function, in general, is in a state of crisis. We have a multitude of facts but no adequate framework to incorporate them into a meaningful whole.

From the Department of Psychology, McGill University, Montreal, Quebec, Canada.

Reprint requests: Ronald Melzack, Department of Psychology, McGill University, 1205 Dr. Penfield Avenue, Montreal, Quebec H3A 1B1, Canada.

A BRIEF HISTORY OF PAIN

The theory of pain we inherited in the 20th century was proposed by Descartes three centuries earlier (see Melzack and Wall [32]). Descartes was the first philosopher to be influenced by the scientific method that flourished in the 17th century, and he achieved a major revolution by arguing that the body works like a machine that can be studied by using the experimental methods of physics pioneered by Galileo and others. Although humans, Descartes proposed, have a soul (or mind), the human body is, nevertheless, a machine, like an animal's body.

The impact of Descartes' theory was enormous. The history of experiments on the anatomy and physiology of pain during the first half of this century (reviewed in Melzack and Wall [32]) is marked by a search for specific pain fibers and pathways and a pain center in the brain. The result was a concept of pain as a specific, straight-through sensory projection system. This rigid anatomy of pain in the 1950s led to attempts to treat severe chronic pain by a variety of neurosurgical lesions. Descartes' specificity theory, then, determined the "facts" as they were known up to the middle of this century, and even determined therapy.

Specificity theory proposed that injury activates specific pain receptors and fibers that, in turn, project pain impulses through a spinal pain pathway to a pain center in the brain. The psychological experience of pain, therefore, was virtually equated with peripheral injury. In the 1950s, there was no room for psychological contributions to pain, such as attention, past experience, and the meaning of the situation. Instead, pain experience was held to be proportional to peripheral injury or pathology. Patients who suffered back pain without presenting signs of organic disease were labeled as psy-

chologically disturbed and sent to psychiatrists. The concept, in short, was simple and, not surprisingly, generally failed to help patients who suffered severe chronic pain. To thoughtful clinical observers, specificity theory was clearly wrong.

There were several attempts to find a new theory. The major opponent to specificity was labeled as "pattern theory," but there were several different pattern theories and they were generally vague and inadequate. However, seen in retrospect, pattern theories gradually evolved and set the stage for the gate control theory (Fig. 1). Goldscheider [5] proposed that central summation in the dorsal horns is one of the critical determinants of pain. Livingston's [16] theory postulated a reverberatory circuit in the dorsal horns to explain summation, referred pain, and pain that persisted long after healing was completed. Noordenbos's theory [33] proposed that large-diameter fibers inhibited small-diameter fibers, and he even suggested that the substantia gelatinosa in the dorsal horns plays a major role in the summation and other dynamic processes described by Livingston. However, in none of these theories was there an explicit role for the brain other than as a passive receiver of messages. Nevertheless, the successive theoretical concepts moved the field in the right direction: into the spinal cord and away from the periphery as the exclusive answer to pain.

THE EVOLUTION OF NEW CONCEPTS

Progress in science, according to historians of science such as Thomas Kuhn [12], occurs in two ways: by the gradual accumulation of information that we call "facts" and by the rapid jumps in the integration of facts that occur when a new theory, concept, or "paradigm" is proposed. The former is "normal science"; the latter is a "revolution." The process occurs in a cycle that may involve generations of scientists and take centuries to complete. This historical process is depicted in Figure 2, with specific reference to the history of pain.

The power of theory was summarized briefly by Donald O. Hebb: "The 'real world' is a construct, and some of the peculiarities of scientific thought become more intelligible when this fact is recognized . . . Einstein himself in 1926 told Heisenberg it was nonsense to found a theory on observable facts alone: 'In reality the very opposite happens. It is theory which decides what we can observe' " (Hebb [7] pp. 5–9). In the case of pain, theory not only determines what we observe in physiology, but it determines how we treat people in pain. We now know that neurosurgical lesions to abolish chronic pain usually fail and the pain tends to return. Yet theory and so-called facts about pain fibers and pathways said they should work and neurosurgeons—notwithstanding their own observations on the tendency for pain to return after surgery—continued to carry out cordotomies, rhizotomies, cortical ablations, and so forth. The emphasis was on the temporary successes, not on the long-term follow-up failures [3,37].

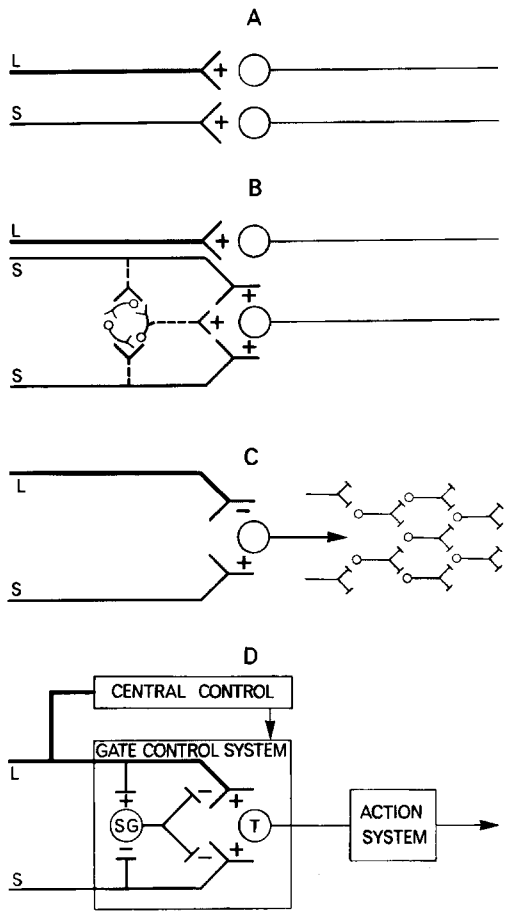

Figure 1. Schematic representation of conceptual models of pain mechanisms. (A) Specificity theory. Large (L) and small (S) fibers are assumed to transmit touch and pain impulses respectively, in separate, specific, straight-through pathways to touch and pain centers in the brain. (B) Goldscheider's summation theory, showing convergence of small fibers onto a dorsal horn cell. The central network projecting to the central cell represents Livingston's (1943) conceptual model of reverberatory circuits underlying pathological pain states. Touch is assumed to be carried by large fibers. (C) Sensory interaction theory, in which large (L) fibers inhibit (–) and small (S) fibers excite (+) central transmission neurons. The output projects to spinal cord neurons, which are conceived by Noordenbos (1959) to comprise a multisynaptic afferent system. (D) Gate control theory. The large (L) and small (S) fibers project to the substantia gelatinosa (SG) and first central transmission (T) cells. The central control trigger is represented by a line running from the large fiber system to central control mechanisms, which in turn project back to the gate control system. The T cells project to the entry cells of the action system. +, excitation; –, inhibition. From Melzack [23]. With permission.

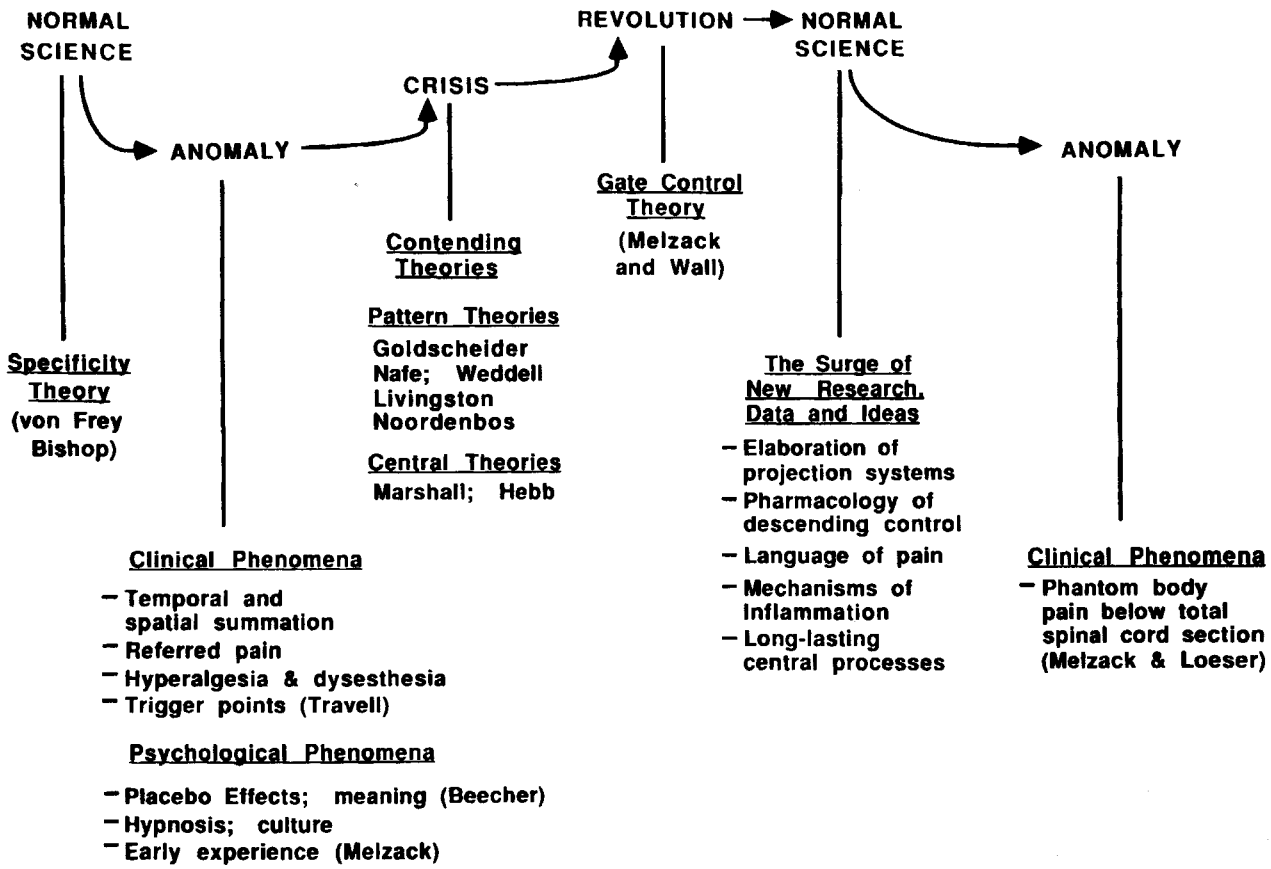

Figure 2. The pattern of scientific progress according to Kuhn (1970). "Normal science" is a generally tranquil stage in which scientific data are acquired within the framework of a theory or "paradigm" that is generally accepted by all or most scientists. During this period, data are obtained that represent an anomaly—they do not fit the accepted paradigm. These data usually lead to several new theories to explain the anomalous data and produce a contentious and unsettled period. Finally, a single theory emerges that becomes the new paradigm and represents a revolution from the old paradigm to the new one. Within this new paradigm, normal science produces new data and proceeds until a period of anomaly again arises, thus leading to a new cycle that culminates in the revolution of a new paradigm. This sequence is shown specifically for pain, with the major events and scientists associated with each stage. From Melzack [23]. With permission.

Descartes' views have so thoroughly permeated our concepts about physiology and anatomy that we still cannot escape them. In addition to the concept of a specific pain projection system, Descartes left us another legacy that has perverted our understanding of how the nervous system works: it led to psychophysics, the idea that the relationships between sensation and stimulus energy can be expressed in elegant mathematical formulas, suggesting mechanical, immutable laws, like the physics of long ago. Certainly we find these laws—when we use rats and students in artificial laboratory chambers. In the normal world, perception and behavior are highly variable, with a multitude of contributing factors. Fortunately, psychology has recently undergone major changes [13]. Behaviorism, which ignored the brain and its functions, is vanishing; cognitive psychology, which recognizes the variability of perception, the malleability of memory, thought, and imagery, has now become the dominant concept.

This new approach in psychology is, happily, being paralleled by major changes in our views of brain function. We now know that the brain possesses widely distributed, parallel processing networks and that it produces an excess of neurons and synapses, so that we can conceive of memory as a sculpting process rather than a slow "cementing" of synapses. This new, dynamic picture of the brain is gradually having an impact on our understanding of pain.

THE GATE CONTROL THEORY OF PAIN

Science is a highly personal endeavor and it is necessary for me, therefore, to discuss the milieu in which I first approached the problem of pain. The careers of

many scientists are launched during the formative years of working on a doctoral thesis, and the concept of "gating" by the brain evolved during that exciting period of my life. I had the good fortune, in the early 1950s, to have a superb research advisor—Donald O. Hebb—and a challenging problem: pain. Happily, Hebb was then engaged in a long correspondence on the problem of pain with George H. Bishop—a brilliant physiologist who shared Hebb's fascination with the nervous system. Bishop was convinced that pain would one day be explained entirely (or primarily) in terms of the sizes of fibers (which his research helped to sort out) and their projections to the brain. However, the brief section on pain in Hebb's book [7], *The Organization of Behavior*, which ascribed pain to abnormal patterns of firing in the brain, intrigued Bishop. In the course of the exchange of ideas, Hebb described his ongoing research on the role of early sensory experience on adult behavior in Scottish terriers and stated his hope that experiments such as these might throw light on the role of learning in pain perception.

Here, suddenly, a possible PhD thesis topic leaped out at me. Scottish terriers were already being raised in social isolation in Hebb's laboratory in special sensory-restriction cages (kennel cages with boards on the side and top), and littermate controls were being raised in homes as pets. Hebb was interested in the effects of sensory-social restriction on intelligence. I was now curious to know whether this kind of restriction had an effect on pain perception.

When the restricted dogs were removed from their cages, they became extremely excited. They ran wildly around the laboratory rooms, in sharp contrast to the controls who cautiously explored every important place and object. At a suitable time, I lit a match in the presence of a restricted dog. He sniffed it, withdrew reflexively for a moment and sniffed again—and again and again. The other restricted dogs behaved essentially the same way. The control dogs, in sharp contrast, carefully avoided the flaming match so that I had to chase after them. The few that ventured one sniff would not try another. Similar behavior was observed when the stimulus was pricking the skin with a dissecting needle.

More litters of dogs and more elegant testing sessions led to similar observations [27]. The question raised by these observations was this: Did the dogs really not feel pain or did they have to learn the meaning of different stimuli until they learned that flaming matches or sharp needles were different and more dangerous than other kinds of inputs? Several years of research subsequently led me to conclude that the restricted dogs had difficulty in discriminating among stimuli, largely because of their high level of arousal [18]. I developed the hypothesis that part of the input from an object such as a flaming match must travel rapidly up the largest fibers and fastest pathways to the brain and activate neural processes that act down on the more slowly conducted input. The information descending from the brain, I proposed, acted at levels that had to be below the brainstem reticular formation. The brains of restricted dogs, without the advantage of prior learning, allowed all information to ascend to the brain. Flaming matches and dissecting needles were no more important than anything else in the environment, and the massive, unfiltered sensory input produced high levels of reticular arousal. The restricted dogs, I believed, could indeed feel pain, but the irrelevant messages were not being inhibited below the level of the reticular formation, and the relevant injury signals failed to rise above the background noise.

In 1959, then, when I was appointed assistant professor of psychology at Massachusetts Institute of Technology and met a young professor of biology, Patrick Wall, we both had ideas that we shared: pain is due to patterns of nerve impulses rather than straight-line transmission of modality-specific impulses to a pain center; information that arrives at the spinal cord is filtered and selected on the basis of the total pattern of activity in stimulated fibers as well as by descending information from the brain. Wall and I wrote a paper on somesthesis that was published in *Brain* in 1962 [30], and we then decided to write a paper specifically on pain, which was published in *Science* in 1965 [31]. The development of the gate control theory has been described elsewhere [22]. The final model is shown in Figure 1 in the context of earlier theories of pain. It is evident that it is the first theory of pain that incorporated the central control processes of the brain.

The gate control theory of pain (Fig. 1D) is based on the following propositions:

1. The transmission of nerve impulses from afferent fibers to spinal cord transmission (T) cells is modulated by a spinal gating mechanism in the dorsal horn.
2. The spinal gating mechanism is influenced by the relative amount of activity in large-diameter (L) and small-diameter (S) fibers: activity in large fibers tends to inhibit transmission (close the gate) while small-fiber activity tends to facilitate transmission (open the gate).
3. The spinal gating mechanism is influenced by nerve impulses that descend from the brain.
4. A specialized system of large-diameter, rapidly conducting fibers (the central control trigger) activates selective cognitive processes that then influence, by way of descending fibers, the modulating properties of the spinal gating mechanism.
5. When the output of the spinal cord transmission (T) cells exceeds a critical level, it activates the action

system—those neural areas that underlie the complex, sequential patterns of behavior and experience characteristic of pain.

When the gate control theory was published, Wall and I were astonished by the reception. The theory generated vigorous (sometimes vicious) debate, as well as a great deal of research to disprove or support the theory. The search for specific pain fibers and spinal cells by our opponents now became almost frantic. It was not until the mid-1970s that the gate control theory was presented in almost every major textbook in the biological and medical sciences. At the same time there was an explosion in research on the physiology and pharmacology of the dorsal horns and the descending control systems.

The theory's emphasis on the modulation of inputs in the spinal dorsal horns and the dynamic role of the brain in pain processes had a clinical as well as a scientific impact. Psychological factors, which were previously dismissed as "reactions to pain," were now seen to be an integral part of pain processing and new avenues for pain control were opened. Similarly, cutting nerves and pathways was gradually replaced by a host of methods to modulate the input. Physical therapists and other health care professionals who use a multitude of modulation techniques were brought into the picture, and transcutaneous electrical nerve stimulation became an important modality for the treatment of chronic and acute pain. The current status of pain research and therapy has been evaluated [32] and indicates that, despite the addition of a massive amount of detail, the conceptual components of the theory remain basically intact after more than 30 years.

BEYOND THE GATE

I believe the great challenge ahead of us is to understand brain function. Kenneth Casey and I [25] made a start by trying to convince our colleagues that specialized systems in the brain are involved in the sensory-discriminative, motivational-affective, and evaluative dimensions of pain (Fig. 3). These phrases seemed strange when we coined them, but they are now used so frequently and seem so "logical" that they have become part of our language. So too, the McGill Pain Questionnaire, which taps into subjective experience—one of the functions of the brain—is widely used to measure pain [19,29]. Later articles tried to understand the spinal and cerebral systems that underlie acute and chronic pain [2], and we have gained a far better understanding of the analgesic effects of morphine [21,39].

The gate control theory had another, unexpected effect. The increasing visits to China by Westerners, beginning in the early 1970s, led to a fascination with acupuncture. Interestingly, the explanation for the ability of acupuncture to relieve some kinds of pain, given by Chinese scientists with a "Western" training and orientation, was the gate control theory. Acupuncture needles were assumed to activate large fibers that closed the gate to inputs from slowly conducting "pain fibers." This explanation lent credibility to acupuncture for pain, and a surge of research on the topic occurred in Western laboratories of physiology, psychology, and pharmacology [24].

An early study I carried out with W. K. Livingston during three postdoctoral years in his laboratory led to the discovery that the area surrounding the aqueduct in the

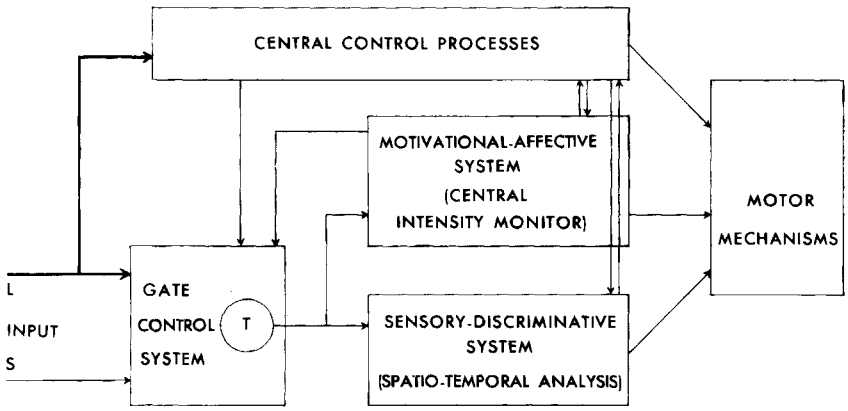

Figure 3. Conceptual model of the sensory, motivational, and central control determinants of pain. The output of the T (transmission) cells of the gate control system projects to the sensory-discriminative system and the motivational-affective system. The central control trigger is represented by a line running from the large fiber system to central control processes; these, in turn, project back to the gate control system, and to the sensory-discriminative and motivational-affective systems. All three systems interact with one another, and project to the motor system. From Melzack and Casey [25]. With permission.

midbrain exerted a tonic inhibitory effect on pain [28]. This experiment was, in large part, the basis for postulating a descending inhibitory control in the gate theory. It also led directly to Reynolds' demonstration [24] that electrical stimulation of the periaqueductal gray produced analgesia. This study was followed by Liebeskind and Paul's [15] research on the mechanisms of the descending inhibition and by the discovery of pharmacological substances such as endorphins that contribute to it [4]. My interest in the observation that "pain takes away pain," in which I postulated that descending inhibition tends to be activated by intense inputs, led to a series of studies on intense transcutaneous electrical nerve stimulation [20]. Later, a series of definitive studies on "diffuse noxious inhibitory controls" was carried out by Besson and colleagues [14], which firmly established the power of descending inhibitory controls.

In 1978, John Loeser and I [26] described severe pains in the phantom body of paraplegics with verified total sections of the spinal cord and proposed a central "pattern generating mechanism" above the level of the section (Fig. 4). This concept represented a major advance: it did not merely extend the gate, it said that pain could be generated by brain mechanisms in paraplegics in the absence of a spinal gate because the brain is completely disconnected from the cord. Psychophysical specificity, in such a concept, makes no sense and we must explore how patterns of nerve impulses generated in the brain can give rise to somesthetic experience. This concept does not diminish the role of sensory inputs and spinal processing in pain due to injury, inflammation, and other pathology. It simply provides a new perspective in which the brain synthesizes raw sensory inputs and generates perceptual experience. This approach seems radical and difficult to comprehend, but I am convinced that it is the logical extension of concepts that began with the gate control theory's incorporation of the brain in the attempt to understand pain.

PHANTOM LIMBS AND THE CONCEPT OF A NEUROMATRIX

It is evident that the gate control theory has taken us a long way. Yet, as historians of science have pointed out, good theories are instrumental in producing facts that eventually require a new theory to incorporate them. And this is what has happened. It is possible to make adjustments to the gate theory so that, for example, it includes long-lasting activity of the sort Wall [41] has described. But there is a set of observations on pain in paraplegics that just does not fit the theory. This does not negate the gate theory, of course. Peripheral and spinal processes are obviously an important part of pain, and we need to know more about the mechanisms of peripheral inflammation, spinal modulation, midbrain descending control, and so forth. But the data on painful phantoms below the level of total spinal section [26] indicate that we need to go beyond the foramen magnum and into the brain [22,23].

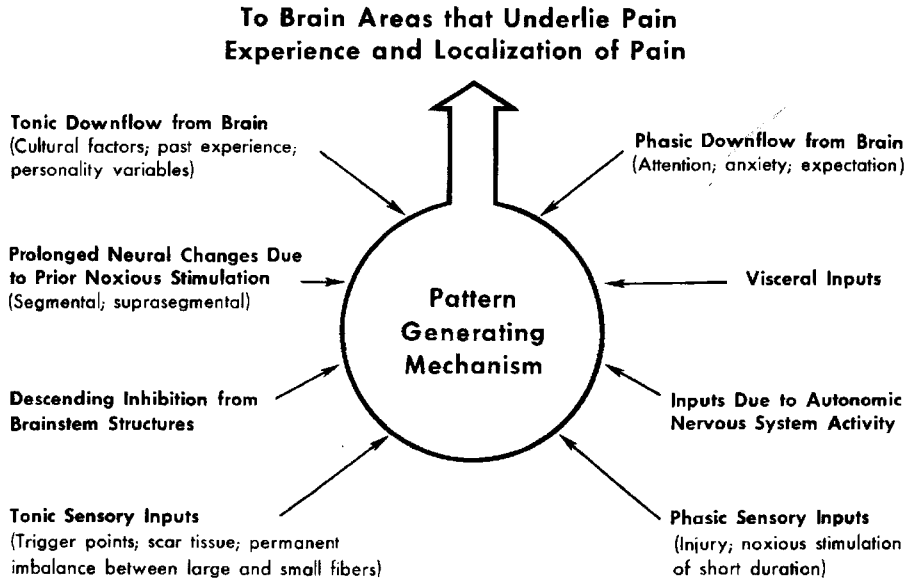

Figure 4. Concept of a pattern generating mechanism controlled by multiple inputs. From Melzack and Loeser [26]. With permission.

Now let me make it clear that I mean more than just the spinal projection systems to thalamus and cortex. These are important, of course, but they mark just the beginning of the psychological process that underlies perception. The cortex, White and Sweet [44] have made amply clear, is not the pain center and neither is the thalamus [37]. The areas of the brain involved in pain experience and behavior are very extensive. They must include somatosensory projections as well as the limbic system. Furthermore, because our body perceptions include visual and vestibular mechanisms as well as cognitive processes, widespread areas of the brain must be involved in pain. Yet the plain fact is that we do not have an adequate theory of how the brain works.

My analysis of phantom limb phenomena [22,23] has led to four conclusions that point to a new conceptual nervous system. First, because the phantom limb (or other body part) feels so real, it is reasonable to conclude that the body we normally feel is subserved by the same neural processes in the brain; these brain processes are normally activated and modulated by inputs from the body, but they can act in the absence of any inputs. Second, all the qualities we normally feel from the body, including pain, are also felt in the absence of inputs from the body; from this we may conclude that the origins of the patterns that underlie the qualities of experience lie in neural networks in the brain; stimuli may trigger the patterns but do not produce them. Third, the body is perceived as a unity and is identified as the "self," distinct from other people and the surrounding world. The experience of a unity of such diverse feelings, including the self as the point of orientation in the surrounding environment, is produced by central neural processes and cannot derive from the peripheral nervous system or spinal cord. Fourth, the brain processes that underlie the body-self are, to an important extent that can no longer be ignored, "built-in" by genetic specification, although this built-in substrate must, of course, be modified by experience. These conclusions provide the basis of the new conceptual model.

Outline of the Theory

The anatomical substrate of the body-self, I propose, is a large, widespread network of neurons that consists of loops between the thalamus and cortex as well as between the cortex and limbic system. I have labeled the entire network, whose spatial distribution and synaptic links are initially determined genetically and are later sculpted by sensory inputs, as a *neuromatrix*. The loops diverge to permit parallel processing in different components of the neuromatrix and converge repeatedly to permit interactions between the output products of processing. The repeated cyclical processing and synthesis of nerve impulses through the neuromatrix imparts a characteristic pattern: the neurosignature. The neurosignature of the neuromatrix is imparted on all nerve impulse patterns that flow through it; the neurosignature is produced by the patterns of synaptic connections in the entire neuromatrix. All inputs from the body undergo cyclical processing and synthesis so that characteristic patterns are impressed on them in the neuromatrix. Portions of the neuromatrix are specialized to process information related to major sensory events (such as injury, temperature change, and stimulation of erogenous tissue) and may be labeled as neuromodules, which impress subsignatures on the larger neurosignature.

The neurosignature, which is a continuous outflow from the body-self neuromatrix, is projected to areas in the brain—the sentient neural hub—in which the stream of nerve impulses (the neurosignature modulated by ongoing inputs) is converted into a continually changing stream of awareness. Furthermore, the neurosignature patterns may also activate a neuromatrix to produce movement. That is, the signature patterns bifurcate so that a pattern proceeds to the sentient neural hub (where the pattern is converted into the experience of movement), and a similar pattern proceeds through a neuromatrix that eventually activates spinal cord neurons to produce muscle patterns for complex actions.

The four components of the new conceptual nervous system, then, are (1) the body-self neuromatrix; (2) cyclical processing and synthesis, in which the neurosignature is produced; (3) the sentient neural hub, which converts (transduces) the flow of neurosignatures into the flow of awareness; and (4) activation of an action neuromatrix to provide the pattern of movements to bring about the desired goal.

The Body-Self Neuromatrix

The body is felt as a unity, with different qualities at different times and, I believe, the brain mechanism that underlies the experience also comprises a unified system that acts as a whole and produces a neurosignature pattern of a whole body. The conceptualization of this unified brain mechanism lies at the heart of the new theory and I believe the word "neuromatrix" best characterizes it. "Matrix" has several definitions in Webster's dictionary [43], and some of them imply precisely the properties of the neuromatrix as I conceive of it. First, a matrix is defined as "something within which something else originates, takes form or develops." This is exactly what I wish to imply: the neuromatrix (not the stimulus, peripheral nerves, or "brain center") is the origin of the neurosignature; the neurosignature originates and takes form in the neuromatrix. Though the neurosignature may be triggered or modulated by input, the input is only a "trigger" and does not produce the neurosigna-

ture itself. Matrix is also defined as a "mold" or "die" that leaves an imprint on something else. In this sense, the neuromatrix "casts" its distinctive signature on all inputs (nerve impulse patterns) that flow through it. Finally, matrix is defined as "an array of circuit elements . . . for performing a specific function as interconnected." The array of neurons in a neuromatrix, I propose, is genetically programmed to perform the specific function of producing the signature pattern. The final, integrated neurosignature pattern for the body-self ultimately produces awareness and action.

For these reasons, the term *neuromatrix* seems to be appropriate. The neuromatrix, distributed throughout many areas of the brain, comprises a widespread network of neurons that generates patterns, processes information that flows through it, and ultimately produces the pattern that is felt as a whole body. The stream of neurosignature output with constantly varying patterns riding on the main signature pattern produces the feelings of the whole body with constantly changing qualities.

Psychological Reasons for a Neuromatrix

It is incomprehensible to me how individual bits of information from skin, joints, or muscles can all come together to produce the experience of a coherent, articulated body. At any instant in time, millions of nerve impulses arrive at the brain from all the body's sensory systems, including the proprioceptive and vestibular systems. How can all this be integrated in a constantly changing unity of experience? Where does it all come together?

I cannot imagine how all these bits are added up to produce a whole. But I can visualize a genetically built-in neuromatrix for the whole body, producing a characteristic neurosignature for the body that carries with it patterns for the myriad qualities we feel. The neuromatrix, as I conceive of it, produces a continuous message that represents the whole body in which details are differentiated within the whole as inputs come into it. We start from the top, with the experience of a unity of the body, and look for differentiation of detail within the whole. The neuromatrix, then, is a template of the whole, which provides the characteristic neural pattern for the whole body (the body's neurosignature), as well as subsets of signature patterns (from neuromodules) that relate to events at (or in) different parts of the body.

These views are in sharp contrast to the classical specificity theory, in which the qualities of experience are presumed to be inherent in peripheral nerve fibers. Pain is not injury; the quality of pain experiences must not be confused with the physical event of breaking skin or bone. Warmth and cold are not "out there"; temperature changes occur "out there," but the qualities of experience must be generated by structures in the brain. There are no external equivalents to stinging, smarting, tickling, itch; the qualities are produced by built-in neuromodules whose neurosignatures innately produce the qualities.

We do not learn to feel qualities of experience; our brains are built to produce them. The inadequacy of the traditional peripheralist view becomes especially evident when we consider paraplegics with high-level complete spinal breaks. In spite of the absence of inputs from the body, virtually every quality of sensation and affect is experienced. It is known that the absence of input produces hyperactivity and abnormal firing patterns in spinal cells above the level of the break [26]. But how, from this jumble of activity, do we get the meaningful experience of movement, the coordination of limbs with other limbs, cramping pain in specific (nonexistent) muscle groups, and so on? This must occur in the brain, in which neurosignatures are produced by neuromatrixes that are triggered by the output of hyperactive cells.

When all sensory systems are intact, inputs modulate the continuous neuromatrix output to produce the wide variety of experiences we feel. We may feel position, warmth, and several kinds of pain and pressure all at once. It is a single unitary feeling, just as an orchestra produces a single unitary sound at any moment even though the sound comprises violins, cellos, horns, and so forth. Similarly, at a particular moment in time, we feel complex qualities from all of the body. In addition, our experience of the body includes visual images, affect, "knowledge" of the self (versus not-self), as well as the meaning of body parts in terms of social norms and values. I cannot conceive of all of these bits and pieces coming together to produce a unitary body-self, but I can visualize a neuromatrix that impresses a characteristic signature on all the inputs that converge on it and thereby produces the neverending stream of feeling from the body.

The experience of the body-self involves multiple dimensions—sensory, affective, evaluative, postural, and many others. The sensory dimensions are subserved, in part at least, by portions of the neuromatrix that lie in the sensory projection areas of the brain; the affective dimensions, I assume, are subserved by areas in the brainstem and limbic system. Each major psychological dimension (or quality) of experience, I propose, is subserved by a particular portion of the neuromatrix that contributes a distinct portion of the total neurosignature. To use a musical analogy once again, it is like the strings, tympani, woodwinds, and brasses of a symphony orchestra, which each comprise a part of the whole; each makes its unique contribution yet is an integral part of a single symphony that varies continually from beginning to end.

The neuromatrix resembles Hebb's "cell assembly" by being a widespread network of cells that subserves a particular psychological function. However, Hebb [7] conceived of the cell assembly as a network developed by gradual sensory learning, while I, instead, propose that the structure of the neuromatrix is predominantly determined by genetic factors, although its eventual synaptic architecture is influenced by sensory inputs. This emphasis on the genetic contribution to the brain does not diminish the importance of sensory inputs. The neuromatrix is a psychologically meaningful unit, developed by both heredity and learning, that represents an entire unified entity.

Action Patterns: The Action-Neuromatrix

The output of the body neuromatrix, I have proposed above, is directed at two systems: the neuromatrix that produces awareness of the output and a neuromatrix involved in overt action patterns. In this discussion, it is important to keep in mind that, just as there is a steady stream of awareness, there is also a steady output of behavior (including movements during sleep).

It is important to recognize that behavior occurs only after the input has been, at least partially, synthesized and recognized. For example, when we respond to the experience of pain or itch, it is evident that the experience has been synthesized by the body-self neuromatrix (or relevant neuromodules) sufficiently for the neuromatrix to have imparted the neurosignature patterns that underlie the quality of experience, affect, and meaning. Apart from a few reflexes (such as withdrawal of a limb, eye-blink, and so on), behavior occurs only after inputs have been analyzed and synthesized sufficiently to produce meaningful experience. When we reach for an apple, the visual input has clearly been synthesized by a neuromatrix so that it has three-dimensional shape, color, and meaning as an edible, desirable object, all of which are produced by the brain and are not in the object "out there." When we respond to pain (by withdrawal or even by telephoning for an ambulance), we respond to an experience that has sensory qualities, affect, and meaning as a dangerous (or potentially dangerous) event to the body.

I propose that after inputs from the body undergo transformation in the body-neuromatrix, the appropriate action patterns are activated concurrently (or nearly so) with the neuromatrix for experience. Thus, in the action-neuromatrix, cyclical processing and synthesis produces activation of several possible patterns and their successive elimination until one particular pattern emerges as the most appropriate for the circumstances at the moment. In this way, input and output are synthesized simultaneously, in parallel, not in series. This permits a smooth, continuous stream of action patterns.

The command, which originates in the brain, to perform a pattern such as running activates the neuromodule, which then produces firing in sequences of neurons that send precise messages through ventral horn neuron pools to appropriate sets of muscles. At the same time, the output patterns from the body-neuromatrix that engage the neuromodules for particular actions are also projected to the sentient neural hub and produce experience. In this way, the brain commands may produce the experience of movement of phantom limbs even though there are no limbs to move and no proprioceptive feedback. Indeed, reports by paraplegics of terrible fatigue as a result of persistent bicycling movements (like the painful fatigue in a tightly clenched phantom fist in arm-amputees) indicate that feelings of effort and fatigue are produced by the signature of a neuromodule rather than particular input patterns from muscles and joints.

IMPLICATIONS OF THE NEW CONCEPT

Phantom Limb Pain

The new theory of brain function, proposed on the basis of phantom limb phenomena, provides an explanation for phantom limb pain. Amputees suffer burning, cramping, and other qualities of pain. An excellent series of studies [8,11] found that 72% of amputees had phantom limb pain a week after amputation and that 60% had pain 6 months later. Even 7 years after amputation, 60% still continued to suffer phantom limb pain, which means that only about 10% to 12% of amputees obtain pain relief. The pain is remarkably intractable; although many forms of treatment have been tried, none has proved to be particularly efficacious [36].

Why is there so much pain in phantom limbs? I believe that the active body-neuromatrix, in the absence of modulating inputs from the limbs or body, produces a neurosignature pattern, including the high-frequency, bursting pattern that typically follows deafferentation, which is transduced in the sentient neural hub into a hot or burning quality. The cramping pain, however, may be due to messages from the action-neuromodule to move muscles in order to produce movement. In the absence of the limbs, the messages to move the muscles become more frequent and "stronger" in the attempt to move the limb. The end result of the output message may be felt as cramping muscle pain. Shooting pains may have a similar origin, in which action-neuromodules attempt to move the body and send out abnormal patterns that are felt as shooting pain. The origins of these pains, then, lie in the brain.

Recent Research

Surgical removal of the somatosensory areas of the cortex or thalamus fails to relieve phantom limb pain [44]. However, the new theory conceives of a neuromatrix that extends throughout selective areas of the whole brain. Thus, to destroy the neuromatrix for the body-self, which generates the neurosignature pattern for pain, is impossible. However, if the neurosignature for pain is generated by cyclical processing and synthesis, then it may be possible to block it by injecting a local anesthetic into a discrete area. Such an injection would be relatively easy and harmless to carry out and could bring relief that extends beyond the duration of the anesthetic.

In the first study on this problem, Tasker and I [38] injected the local anesthetic lidocaine into the lateral hypothalamus—an area we considered to be strategic for a neuromatrix for the body-self and pain. We found that freely moving rats that received the injection showed a significant reduction of pain in the formalin test, which produces a moderately intense pain for 1 to 2 hours and has many of the characteristics of injury-produced pain in humans. However, the injection had no effect on tail-flick pain, which is primarily a spinally mediated reflex. Moreover, lidocaine injected into adjacent hypothalamic structures (including the medial hypothalamus) had no effect on the formalin-test pain, indicating that the analgesia was produced by local anesthesia of a specific group of neurons. Since the analgesia was bilateral, it is reasonable to assume that the lateral hypothalamus contains neurons that are important for producing the neurosignature for pain in both sides of the body.

Recently, Vaccarino and I [40] injected lidocaine into the cingulum bundle and other areas that seem to be strategically located in the neuromatrix for the synthesis of the neurosignature for pain. The results showed that the lidocaine produces striking decreases in pain in the formalin test, as well as in self-mutilation produced by pain or dysesthesia after peripheral nerve lesions. McKenna and I [17] obtained similar results after injection of lidocaine into the dentate nucleus. These exciting results suggest a valuable new approach for the study of pain. If, ultimately, they lead to the relief of pain and suffering, the neuromatrix theory will have served at least one valuable function.

My students and I have also gathered some direct evidence supporting my suggestion that the brain—and, by implication, the neuromatrix—can generate sensation on its own. The formalin pain test produces an "early" pain that rapidly rises and falls in intensity during the first 5 minutes after the injection, followed by a "late" pain, which begins about 15 minutes after the injection and persists for about an hour. By means of this test, Coderre, Vaccarino, and I [1] found that an anesthetic block of the paw completely obliterates the late pain, but only if the anesthetic is delivered in time to prevent the early response. Once the early pain occurs, the drug only partly reduces the later response. This observation of pain continuing even after the nerves carrying pain signals are blocked implies that long-lasting pain (such as that in phantoms) is determined not only by sensory stimulation during the discomfort but also by brain processes that persist without continual priming.

In a related study, Katz et al. [10] showed that an injury of a rat's paw before it is totally denervated leaves a lasting memory that influences the rat's later perception of pain in the "phantom" of the denervated paw. These "pain memories" are consistent with earlier observations that the pain felt in phantom limbs in humans often resembles the pains of earlier injuries of the limbs prior to amputation [9].

The phenomenon of phantom limbs has allowed me to examine some fundamental assumptions in psychology. One assumption is that sensations are produced only by stimuli and that perceptions in the absence of stimuli are psychologically abnormal. Yet phantom limbs, as well as phantom seeing [35], indicate this notion is wrong. The brain does more than detect and analyze inputs; it generates perceptual experience even when no external inputs occur.

Another entrenched assumption is that perception of one's body results from sensory inputs that leave a memory in the brain; the total of these signals becomes the body image. But the existence of phantoms in people born without a limb or who have lost a limb at an early age suggests that the neural networks for perceiving the body and its parts are built into the brain. The absence of inputs does not stop the networks from generating messages about missing body parts; they continue to produce such messages throughout life. In short, phantom limbs are a mystery only if we assume the body sends sensory messages to a passively receiving brain. Phantoms become comprehensible once we recognize that the brain generates the experience of the body. Sensory inputs merely modulate that experience; they do not directly cause it.

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