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From the gate to the neuromatrix

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Abstract

The gate control theory's most important contribution to understanding pain was its emphasis on central neural mechanisms. The theory forced the medical and biological sciences to accept the brain as an active system that filters, selects and modulates inputs. The dorsal horns, too, were not merely passive transmission stations but sites at which dynamic activities (inhibition, excitation and modulation) occurred. The great challenge ahead of us is to understand brain function. I have therefore proposed that the brain possesses a neural network — the body-self neuromatrix — which integrates multiple inputs to produce the output pattern that evokes pain. The body-self neuromatrix comprises a widely distributed neural network that includes parallel somatosensory, limbic and thalamocortical components that subserve the sensory-discriminative, affective-motivational and evaluative-cognitive dimensions of pain experience. The synaptic architecture of the neuromatrix is determined by genetic and sensory influences. The 'neurosignature' output of the neuromatrix — patterns of nerve impulses of varying temporal and spatial dimensions — is produced by neural programs genetically built into the neuromatrix and determines the particular qualities and other properties of the pain experience and behavior. Multiple inputs that act on the neuromatrix programs and contribute to the output neurosignature include, (1) sensory inputs (cutaneous, visceral and other somatic receptors); (2) visual and other sensory inputs that influence the cognitive interpretation of the situation; (3) phasic and tonic cognitive and emotional inputs from other areas of the brain; (4) intrinsic neural inhibitory modulation inherent in all brain function; (5) the activity of the body's stress-regulation systems, including cytokines as well as the endocrine, autonomic, immune and opioid systems. We have traveled a long way from the psychophysical concept that seeks a simple one-to-one relationship between injury and pain. We now have a theoretical framework in which a genetically determined template for the body-self is modulated by the powerful stress system and the cognitive functions of the brain, in addition to the traditional sensory inputs. © 1999 International Association for the Study of Pain. Published by Elsevier Science B.V.

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1. Introduction

In 1959, Patrick Wall had already achieved a reputation as a brilliant young scientist who had done important research on spinal cord physiology. As a result, when I arrived at the Massachusetts Institute of Technology in September 1959 as an Assistant Professor of Psychology, I was eager to meet Pat, who was a Professor in M.I.T.'s prestigious Department of Biology. We met more quickly than I expected because I was appalled to discover on the day of my arrival that research with animals could not be done in my building and I would have to go elsewhere to do it. A colleague suggested that I call Pat Wall, who might be able to help me.

Pat detected the desperation in my voice and invited me over. After a warm, friendly conversation, Pat said that some research space might be available for me. Members of the Department of Food Technology in Pat's building had funds from a U.S. Space Agency to discover what might happen to cans of food that make a hard landing on the moon's surface. To find out, these investigators used an

apparatus that resembled the catapult in the comic-strip 'Hager the Horrible' and flung cans of food against a cement surface. Happily for me, Pat convinced them that they could dispense with some of their space to allow me to continue my research on the effects of early sensory deprivation on the perception of pain. Thus began a life-long friendship that has been one of the highlights of my life.

During periodic visits to Pat's lab, where he was invariably doing an experiment on the spinal cord, he and I talked often about our interests in somesthesia and the particularly challenging problem of pain. W.K. Livingston visited me from time to time, and he was delighted to join Pat and me during one of our discussions on alternatives to specificity theory. This topic — the need for a new theory — was foremost in our minds, and after a year or so, Pat and I decided to write a paper together.

When we began our discussions that led to the gate control theory of pain, we were convinced that (1) brain processes had to be integrated into the theory, including feedforward and feedback transmission; and (2) the new hypothetical spinal cord mechanism would need sufficient

explanatory power to challenge spinal-cord physiologists and entice them away from the concept of specificity.

How the theory actually came into being involves an amusing sequence of events. My early research in psychology and physiology led me to speculate that the brain exerts a powerful, continuous descending inhibitory control over the input that is transmitted through the dorsal horns (Melzack et al., 1958). But this notion of modulation of input by the brain does not constitute a conceptual model of pain. It could be part of one, but more was needed. In 1959, Pat was examining the different nerve impulse patterns evoked in dorsal horn cells by various stimuli and the way in which vibration modulated the pattern evoked by noxious stimulation. In 1961 I published an article in *Scientific American* which reviewed the psychology and physiology of pain as it was understood at the time. It emphasized patterning, modulation in the dorsal horns, multiple ascending pathways and the multidimensional qualities of pain experience. But it was not a cohesive, succinct theory. In 1962, Pat and I (Melzack and Wall, 1962) proposed a general theory of somesthesia in the form of eight propositions. The paper, published in *Brain*, evoked some interest but had little impact. We then toyed with the idea of using this general 'theory' as the basis for a theory that dealt exclusively with pain but we made no headway and put the project aside.

Then, things unexpectedly and suddenly started to fall into place. It began in the fall of 1962, when I first stumbled onto William Noordenbos' 1959 book on pain (Noordenbos, 1959). That brilliant little book led me to have a 'flash of insight'.

Fig. 1A shows Noordenbos' concept of pain. He did not fill in the circle in the dorsal horns to show how large fibers inhibit small ones. He just said that they did, and showed a picture of the substantia gelatinosa to illustrate the complexity of dorsal horn anatomy. He then went on to explain temporal and spatial summation, referred pain, and other properties of pain after nerve injury. However, Noordenbos' story stops at the thalamus — the T at the top. My idea was to put a cortex on Bill's thalamus, show the dorsal column projection as a rapid, precise feedforward system to activate psychological processes, with a feedback to the circle to modulate the input (Fig. 1B). Here, at last, was the beginning of a conceptual model in which brain processes can select, filter and modulate pain signals.

When I discussed all this with Pat, he began to have ideas too. He soon developed a concept, based on his research on the substantia gelatinosa, for a hypothetical mechanism to put in the circle. A few weeks later he gave me his picture (Fig. 1C). It may seem an easy step from our two pictures to the final gate model, but it was not. We invented and rejected a variety of names for the theory and the components of the model. It took countless drafts, changes and compromises to produce the final paper (Melzack and Wall, 1965). I moved to McGill University in 1963, so that most of the paper was written by exchanging drafts

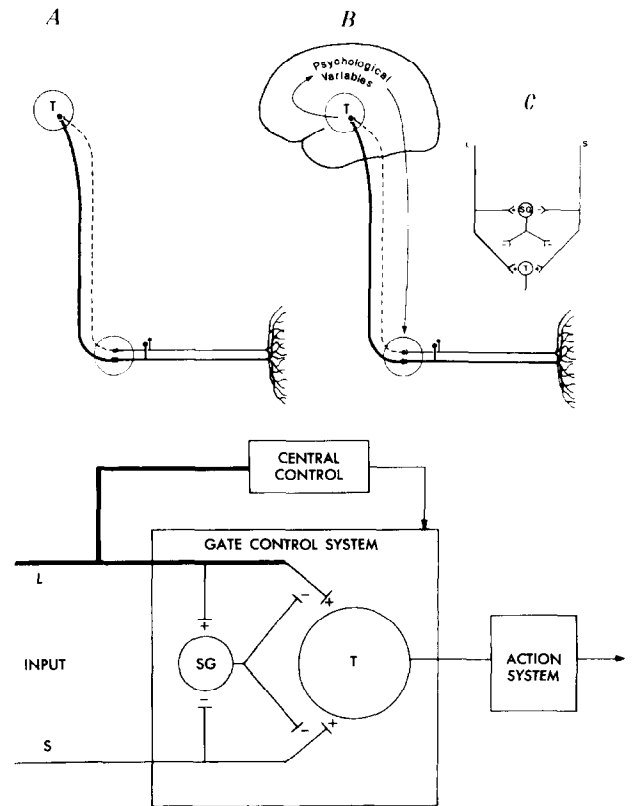


Fig. 1. The evolution of the gate control theory. (A) shows Noordenbos' model in which large, fast-conducting fibers inhibit small, multisynaptic, slowly conducting fibers. Noordenbos (1959) says of the circle that represents the dorsal horns: 'In this circle which includes the substantia gelatinosa of Rolandi and its immediate adjacent parts, the multifiber pattern of afferent impulses is modified... The nature of this inhibitory interaction will not be further discussed...' (B) An early development that led to the gate control theory in which the large fiber system is shown to activate psychological variables (such as meaning and past experience) that then project down to the dorsal horns and modulate the input. (C) Shows a further development toward the gate control theory which comprises a theoretical presynaptic inhibition exerted by the substantia gelatinosa. The ideas gradually evolved into the model of the gate control theory shown at the bottom.

by mail or during my many visits to Boston where we consumed large amounts of duty-free whiskey and talked late into the night at Pat's home.

When the gate control theory of pain was published in 1965, we 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-1970's 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 healthcare professionals who use a multitude of sensory modulation techniques were brought into the picture, and TENS became an important modality for the treatment of chronic and acute pain.

A major force in this exciting epoch was John Bonica, who had been trying valiantly to convince his medical colleagues that pain is a syndrome in its own right that merits special attention, research and funding. The arrival of the gate control theory encouraged John to pursue his cause even more vigorously. At the same time, he promoted the gate control theory as a focus for new medical approaches. Out of all this ferment of theory, research and clinical advances, John brought together a host of scientists and clinicians and formed the International Association for the Study of Pain (Bonica, 1974). At the same time, the journal *Pain* was created, with Pat as its founding Editor. He has done, and continues to do, a brilliant job of it. The journal helped establish the field of pain as a major specialty in the health sciences and professions.

What was the gate control theory's most important contribution to biological and medical science? I believe it was the emphasis on CNS mechanisms. Never again, after 1965, could anyone try to explain pain exclusively in terms of peripheral factors. The theory forced the medical and biological sciences to accept the brain as an active system that filters, selects and modulates inputs. The dorsal horns, too, were not merely passive transmission stations but sites at which dynamic activities — inhibition, excitation and modulation — occurred. This then was the revolution: we highlighted the central nervous system as an essential component in pain processes.

2. The neuromatrix

Where do we go from here? I believe the great challenge ahead of us is to understand brain function. My analysis of phantom limb phenomena (Melzack, 1989; Melzack et al., 1997) has led to four conclusions which 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 which 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 a new conceptual model.

How can we explain our experience of the body? I propose that a genetically built-in matrix of neurons for the whole body produces characteristic nerve-impulse patterns for the body and the myriad somatosensory qualities we feel. I have termed the network, whose spatial distribution and synaptic links are initially determined genetically and are later sculpted by sensory inputs, a 'neuromatrix'. Thalamocortical and limbic loops that comprise the neuromatrix diverge to permit parallel processing in different components of the neuromatrix and converge to permit interactions between the output products of processing. The cyclical processing and synthesis of nerve impulses in the neuromatrix imposes a characteristic output pattern or 'neurosignature'.

Loeser and I (Melzack and Loeser, 1978) have presented a model, consistent with the gate control theory of pain, which proposes that synaptic areas along the transmission routes of the major sensory projection systems — from the dorsal horns to the somatosensory projection areas in the thalamus and cortex — may become pattern generating mechanisms. Their activity is capable of producing patterns of nerve impulses which exceed a critical firing level per unit time (or have a particular pattern, or both) and project to other areas that subserve pain experience and the localization of pain at specific sites.

This concept is consistent with the fact that injury may produce high firing levels that signal pain as well as with the observation that loss of input to central structures by deafferentation after amputation, root section or cord transection also produce high firing levels and abnormal bursting patterns that may provide the necessary conditions for pain. Thus, any input to the hyperactive central cells — from nearby injured tissues, from visceral sensory nerve, from small afferents in the sympathetic chain and from higher psychoneuronal processes — can trigger abnormal, prolonged firing and produce severe, persistent pains in discrete areas of the denervated limbs or other body parts.

3. Pain and stress

We are so accustomed to considering pain as a purely sensory phenomenon that we have ignored the obvious fact that injury does not merely produce pain: it also disrupts the brain's homeostatic regulation systems, thereby produ-

cing 'stress' and initiating complex programs to reinstate homeostasis. By recognizing the role of the stress system in pain processes, we discover that the scope of the puzzle of pain is vastly expanded and new pieces of the puzzle provide valuable clues in our quest to understand chronic pain (Melzack, 1998, 1999).

Hans Selye, who founded the field of stress research, dealt with stress in the biological sense of physical injury, infection and pathology, and also recognized the importance of psychological stresses. In recent years, the latter sense of the word has come to dominate the field. However, it is important for the purpose of understanding pain to keep in mind that stress is a biological system that is activated by physical injury, infection or any threat to biological homeostasis as well as by psychological threat and insult of the body-self. Both are correct and important.

The disruption of homeostasis by injury activates programs of neural, hormonal and behavioral activity aimed at a return to homeostasis. The particular programs that are activated are selected from a genetically determined repertoire of programs and are influenced by the extent and severity of the injury.

When injury occurs, sensory information rapidly alerts the brain and begins the complex sequence of events to reinstate homeostasis. Cytokines are released within seconds after injury. These substances, such as gamma-interferon, interleukins 1 and 6, and tumour necrosis factor, enter the bloodstream in 1–4 min and travel to the brain. The cytokines, therefore, are able to activate fibers that send messages to the brain and, concurrently, to breach the blood–brain barrier at specific sites and have an immediate effect on hypothalamic cells. The cytokines together with evaluative information from the brain rapidly begin a sequence of activities aimed at the release and utilization of glucose for necessary actions, such as removal of debris, the repair of tissues and (sometimes) fever to destroy bacteria and other foreign substances. At sufficient severity of injury, the noradrenergic system is activated. Adrenalin is released into the blood stream and the powerful locus coeruleus/norepinephrine (LC/NE) system in the brainstem projects information upward throughout the brain and downward through the descending efferent sympathetic nervous system. Thus the whole sympathetic system is activated to produce readiness of the heart, blood vessels and other viscera for complex programs to reinstate homeostasis (Chrousos and Gold, 1992; Sapolsky, 1992).

At the same time, the perception of injury activates the hypothalamic-pituitary-adrenal (HPA) system, in which corticotropin-releasing hormone (CRH) produced in the hypothalamus enters the local blood stream which carries the hormone to the pituitary, causing the release of adrenocorticotrophic hormone (ACTH) and other substances. The ACTH then activates the adrenal cortex to release cortisol, which must inevitably play a powerful role in determining chronic pain. Cortisol also acts on the immune system and the endogenous opioid system. Although these opioids are

released within minutes, their initial function may be simply to inhibit or modulate the release of cortisol. Experiments with animals suggest that their analgesic effects may not appear until as long as 30 min after injury.

Cortisol, together with noradrenergic activation, sets the stage for response to life-threatening emergency. If the output of cortisol is prolonged, excessive or of abnormal patterning, it may produce destruction of muscle, bone and neural tissue and produce the conditions for many kinds of chronic pain.

Cortisol is an essential hormone for survival after injury because it is responsible for producing and maintaining high levels of glucose for rapid response after injury, threat or other emergency. However, cortisol is potentially a highly destructive substance because, to ensure a high level of glucose, it breaks down the protein in muscle and inhibits the ongoing replacement of calcium in bone. Sustained cortisol release, therefore, can produce myopathy, weakness, fatigue and decalcification of bone. It can also accelerate neural degeneration of the hippocampus during aging. Furthermore, it suppresses the immune system.

A major clue to the relationships between injury, stress and pain is that many autoimmune diseases, such as rheumatoid arthritis and scleroderma, are also pain syndromes. Furthermore, more women than men suffer from autoimmune diseases as well as chronic pain syndromes. Among the 5% of adults who suffer from an autoimmune disease, two out of three are women. Pain diseases also show a sex difference, as Berkley (1997) has argued, with the majority prevalent in women, and a smaller number prevalent in men. Of particular importance is the concurrent change in sex ratios with changes in sex hormone output as a function of age. Estrogen increases the release of peripheral cytokines, such as gamma-interferon, which in turn produce increased cortisol. This may explain why more females than males suffer from most kinds of chronic pain as well as painful autoimmune diseases such as multiple sclerosis and lupus.

I propose that some forms of chronic pain may occur as a result of the cumulative destructive effect of cortisol on muscle, bone and neural tissue. Furthermore, loss of fibers in the hippocampus due to aging reduces a natural brake on cortisol release which is normally exerted by the hippocampus. As a result, cortisol is released in larger amounts, producing a greater loss of hippocampal fibers and a cascading deleterious effect. This is found in aging primates and presumably also occurs in humans. It could explain the increase of chronic pain problems among older people.

Cortisol output by itself may not be sufficient to cause any of these problems, but rather it provides the conditions so that other contributing factors may, all together, produce them. Sex-related hormones, genetic predispositions, psychological stresses derived from social competition and the hassles of every day life may act together to influence cortisol release, its amount and pattern, and the effects of the target organs.

These speculations are supported by strong evidence.

Chrousos and his colleagues (Chrousos and Gold, 1992) have documented the effects of dysregulation of the cortisol system: effects on muscle and bone, to which they attribute fibromyalgia, rheumatoid arthritis and chronic fatigue syndrome. They propose that they are caused by hypocortisolism, which could be due to depletion of cortisol as a result of prolonged stress. Indeed, Sapolsky (1992) attributes myopathy, bone decalcification, fatigue and accelerated neural degeneration during aging to prolonged exposure to stress.

Clearly, consideration of the relationship between stress-system effects and chronic pain leads directly to examination of the effects of suppression of the immune system and the development of autoimmune effects. The fact that several autoimmune diseases, such as Crohn's disease, multiple sclerosis, rheumatoid arthritis, scleroderma and lupus, are also classified as chronic pain syndromes suggests that the study of these syndromes in relation to stress effects and chronic pain could be fruitful. Immune suppression, which involves prolonging the presence of dead tissue, invading bacteria and viruses, could produce a greater output of cytokines, with a consequent increase in cortisol and its destructive effects. Furthermore, prolonged immune suppression may diminish gradually and give way to a rebound, excessive immune response. The immune system's attack on its own body's tissues may produce autoimmune diseases that are also chronic pain syndromes. Thorough investigation may provide valuable clues for understanding at least some of the terrible chronic pain syndromes that now perplex us and are beyond our control.

4. The multiple determinants of pain

The neuromatrix theory of pain proposes that the neurosignature for pain experience is determined by the synaptic architecture of the neuromatrix, which is produced by genetic and sensory influences. The neurosignature pattern is also modulated by sensory inputs and by cognitive events, such as psychological stress. It may also occur because stressors, physical as well as psychological, act on stress-regulation systems, which may produce lesions of muscle, bone, and nerve tissue, thereby contributing to the neurosignature patterns that give rise to chronic pain. In short, the neuromatrix, as a result of homeostasis-regulation patterns that have failed, produces the destructive conditions that may give rise to many of the chronic pains that so far have been resistant to treatments developed primarily to manage pains that are triggered by sensory inputs. The stress regulation system, with its complex, delicately balanced interactions, is an integral part of the multiple contributions that give rise to chronic pain.

The neuromatrix theory guides us away from the Cartesian concept of pain as a sensation produced by injury, inflammation, or other tissue pathology and toward the concept of pain as a multidimensional experience produced

by multiple influences. These influences range from the existing synaptic architecture of the neuromatrix — which is determined by genetic and sensory factors — to influences from within the body and from other areas in the brain. Genetic influences on synaptic architecture may determine, or predispose toward, the development of chronic pain syndromes. Fig. 2 summarizes the factors that contribute to the output pattern from the neuromatrix that produce the sensory, affective and cognitive dimensions of pain experience and behavior.

We have traveled a long way from the psychophysical concept that seeks a simple one-to-one relationship between injury and pain. We now have a theoretical framework in which a genetically determined template for the body-self is modulated by the powerful stress system and the cognitive functions of the brain, in addition to the traditional sensory inputs.

The neuromatrix theory of pain — which places genetic contributions and the neural-hormonal mechanisms of stress on a level of equal importance with the neural mechanisms of sensory transmission — has important implications for research and therapy. An immediate recommendation is that interdisciplinary pain clinics should expand to include specialists in endocrinology and immunology. Such a collaboration may lead to insights and new research strategies

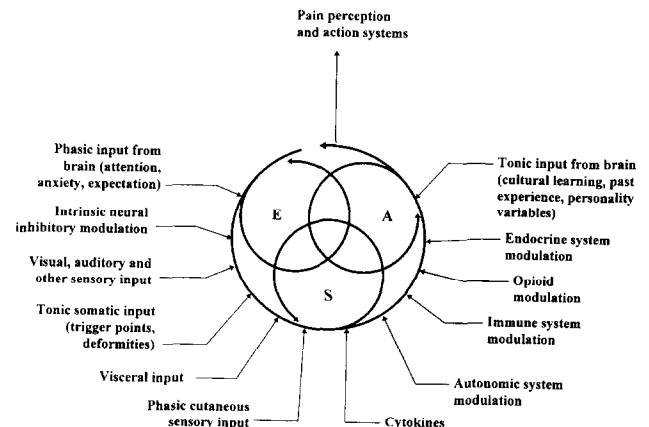


Fig. 2. The body-self neuromatrix. The body-self neuromatrix, which comprises a widely distributed neural network that includes somatosensory, limbic, and thalamocortical components, is schematically depicted as a circle containing smaller parallel networks that contribute to the sensory-discriminative (S), affective-motivational (A), and evaluative-cognitive (E) dimensions of pain experience. The synaptic architecture of the neuromatrix is determined by genetic and sensory influences. The 'neurosignature' output of the neuromatrix—patterns of nerve impulses of varying temporal and spatial dimensions—is produced by neural programs genetically built into the neuromatrix and determines the particular qualities and other properties of the pain experience and behavior. Multiple inputs that act on the neuromatrix programs and contribute to the output neurosignature include (1) sensory inputs from somatic receptors (phasic cutaneous, visceral and tonic somatic inputs); (2) visual and other sensory inputs that influence the cognitive interpretation of the situation; (3) phasic and tonic cognitive and emotional inputs from other areas of the brain; (4) intrinsic neural inhibitory modulation inherent in all brain function; and (5) the activity of the body's stress-regulation systems, including cytokines as well as the endocrine, autonomic, immune and opioid systems.

that may reveal the underlying mechanisms of chronic pain and give rise to new therapies to relieve the tragedy of unrelenting suffering.

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