

# Pain and the Neuromatrix in the Brain

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*Abstract:* The neuromatrix theory of pain proposes that pain is a multidimensional experience produced by characteristic “neurosignature” patterns of nerve impulses generated by a widely distributed neural network—the “body-self neuromatrix”—in the brain. These neurosignature patterns may be triggered by sensory inputs, but they may also be generated independently of them. Acute pains evoked by brief noxious inputs have been meticulously investigated by neuroscientists, and their sensory transmission mechanisms are generally well understood. In contrast, chronic pain syndromes, which are often characterized by severe pain associated with little or no discernible injury or pathology, remain a mystery. Furthermore, chronic psychological or physical stress is often associated with chronic pain, but the relationship is poorly understood. The neuromatrix theory of pain provides a new conceptual framework to examine these problems. It proposes that the output patterns of the body-self neuromatrix activate perceptual, homeostatic, and behavioral programs after injury, pathology, or chronic stress. Pain, then, is produced by the output of a widely distributed neural network in the brain rather than directly by sensory input evoked by injury, inflammation, or other pathology. The neuromatrix, which is genetically determined and modified by sensory experience, is the primary mechanism that generates the neural pattern that produces pain. Its output pattern is determined by multiple influences, of which the somatic sensory input is only a part, that converge on the neuromatrix.

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Pain has many valuable functions. It often signals injury or disease and produces a wide range of actions to stop it and treat its causes. Toothache, for example, is usually a signal of caries, and forces us to seek dental help. Memories of earlier pain and suffering also warn us to avoid potentially dangerous situations. Yet another effect of pain, especially after serious injury or disease, is to make us rest, thereby promoting the body’s healing processes. All of these actions induced by pain—to seek help, avoid, or rest—have obvious value for survival.

Yet despite these valuable features of pain, there are negative aspects that challenge our attempts to understand the puzzle of pain. What is the value of persistent phantom limb pain to amputees whose stump has healed completely? The pain, not the physical disability, prevents them from leading normal lives. Similarly, most backaches, headaches, muscle pains, nerve pains, pelvic pains, and facial pains serve no discernible purpose, are difficult to treat, and are a disaster for the people who suffer them.<sup>1,2</sup>

Pain may be the warning signal that saves the lives of some people, but it destroys the lives of countless others. Chronic pains, clearly, are not a warning to prevent physical injury or disease. They *are* the disease—the result of neural mechanisms gone awry. The neuromatrix concept suggests brain mechanisms that may underlie some kinds of chronic pain and points to new forms of treatment.

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## Phantom Limbs and the Concept of a Neuromatrix

The gate control theory of pain,<sup>3</sup> proposed in 1965, highlighted the role of spinal and brain mechanisms in acute and chronic pain, and triggered an explosive advance in pain research and therapy. 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<sup>4</sup> 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<sup>5</sup> indicate that we need to go beyond the foramen magnum and into the brain.<sup>6,7</sup>

Now let me make it clear that I mean more than just the sensory thalamus and cortex. These are important, of course, but they mark just the beginning of the neural activities that underlie perception. The

cortex, White and Sweet<sup>8</sup> have made amply clear, is not the pain center, and neither is the thalamus.<sup>9</sup> The areas of the brain involved in pain experience and behavior are very extensive. They must include the limbic system as well as somatosensory projections. 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<sup>6,7</sup> 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.

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## 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 in-

teractions 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 that 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 neural networks to produce movement. That is, the 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 neural networks that eventually activate 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.

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## 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,<sup>10</sup> 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. Although the neurosignature may be triggered or modulated by input, the input is only a “trigger” and does not produce the neurosignature 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 possessing a sense of self. The stream of neurosignature output with constantly varying patterns riding on the main signature pattern produces the feelings of the body-self with constantly changing perceptual and emotional qualities.

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## 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 producing “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.<sup>11,12</sup>

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.<sup>13</sup> 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. 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.<sup>14,15</sup> 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 among 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 percent of adults who suffer from an autoimmune disease, two out of three are women. Pain diseases also show a sex difference, as Berkley<sup>16</sup> has argued, with the majority prevalent in women and a smaller number prevalent in men. Of particular importance is the change in sex ratios concurrently 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.<sup>15</sup> 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.

The cortisol output by itself may not be sufficient to cause any of these problems, but rather provides the conditions so that other contributing factors may, in combination, produce them. Sex-related hormones, genetic predispositions, and psychological stresses derived from social competition and the hassles of everyday 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 Gold<sup>14</sup> 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 caused by depletion of cortisol as a result of prolonged stress. Indeed, Sapolsky<sup>15</sup> 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 are also classified as chronic pain syndromes—such as Crohn's disease, multiple sclerosis, rheumatoid arthritis, scleroderma, and lupus—suggests that the study of these syndromes in relation to stress effects and chronic pain could be fruitful.<sup>11,12</sup> 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.

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## 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. Figure 1 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

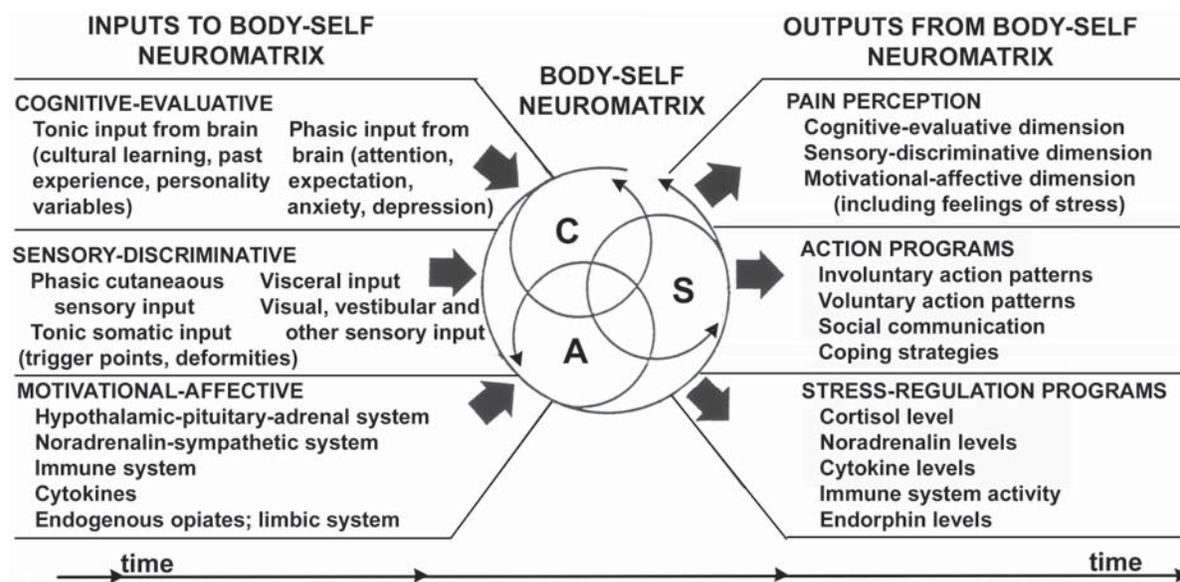


Figure 1. Factors that contribute to the patterns of activity generated by the body-self neuromatrix, which comprises sensory, affective, and cognitive neuromodules. The output patterns from the neuromatrix produce the multiple dimensions of pain experience as well as concurrent homeostatic and behavioral responses.

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. The expansion of the field of pain to include endocrinology and immunology may lead to insights and new research strategies that will reveal the underlying mechanisms of chronic pain and give rise to new therapies to relieve the tragedy of unrelenting suffering.

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