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## SPECIAL ARTICLES

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# Evolution of the Neuromatrix Theory of Pain. The Prithvi Raj Lecture: Presented at the Third World Congress of World Institute of Pain, Barcelona 2004

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Ronald Melzack, PhD

*Department of Psychology, McGill University, Montreal, Quebec, Canada*

■ **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 discernable 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 mod-

ified 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. ■

**Key Words:** neuromatrix, chronic pain, phantom limb pain

We all know that 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. Chest pains, for example, may be a signal of heart disease, and may force us to seek medical help. Memories of earlier pain and suffering also warn us to avoid potentially dangerous situations. Still 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 escape, avoid, or rest—have obvious value for survival.

However, 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 a normal life. Similarly, most backaches, headaches, muscle pains, nerve

Address correspondence and reprint requests to: Ronald Melzack, PhD, Department of Psychology, McGill University, 1205 Dr. Penfield Avenue, Montreal, Quebec, Canada H3A 1B1. E-mail: rmelzack@ego.psych.mcgill.ca.

pains, pelvic pains, and facial pains serve no discernable purpose, are difficult to treat, and are a disaster for the people who suffer them.

Pain may be the warning signal that saves the lives of some people or animals, 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.

### PHANTOM LIMBS AND THE CONCEPT OF A NEUROMATRIX

The gate control theory of pain highlighted the role of spinal and brain mechanisms in acute and chronic pain.<sup>1</sup> However, 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.<sup>1</sup> 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>2</sup> indicate that we need to go beyond the foramen magnum and into the brain.

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>3</sup> have made amply clear, is not the pain center and neither is the thalamus.<sup>4</sup> 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. However, the plain fact is that we do not have an adequate theory of how the brain works.

My analysis of phantom limb phenomena<sup>5,6</sup> 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 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*.<sup>5,6</sup> 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 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,<sup>7</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” which leaves an imprint on something else. In this sense, the neuromatrix “casts” its distinctive signature on all inputs (nerve impulse patterns) which 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 which 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 which 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.<sup>8</sup> 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 (vs. 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 which impresses a characteristic signature on all the inputs that converge on it and thereby produces the never-ending stream of feeling from the body.

The experience of the body-self involves multiple dimensions—sensory, affective, evaluative, postural, and many others.<sup>1,9</sup> 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 which contributes a distinct portion of the total neurosignature. To use a musical analogy once again, it is like the strings, timpani, woodwinds, and brasses of a symphony orchestra which each comprises a part of the whole; each makes its unique contribution yet is an integral part of a single symphony which 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<sup>7</sup> 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 is directed at three systems: (1) the neuromatrix that produces awareness of the output; (2) a neuromatrix involved in overt action patterns; and (3) the homeostatic system that maintains physiological equilibrium in the face of stress. 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) and homeostatic regulation.

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 due to 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.

### 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>10</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. 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 tumor necrosis factor, enter the bloodstream in 1 to 4 minutes 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: epinephrine 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.<sup>11,12</sup>

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 adrenocorticotropic 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 minutes after injury.

Cortisol, together with noradrenergic activation, sets the stage for response to life-threatening emergency. If the output of cortisol is prolonged, or 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 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% of adults who suffer from an autoimmune disease, two out of three are women. Pain diseases also show a sex difference, as Holdcroft and Berkley<sup>13</sup> have 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. 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<sup>12</sup> 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, all together, produce them. Sex-related hormones, genetic predispositions, 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.

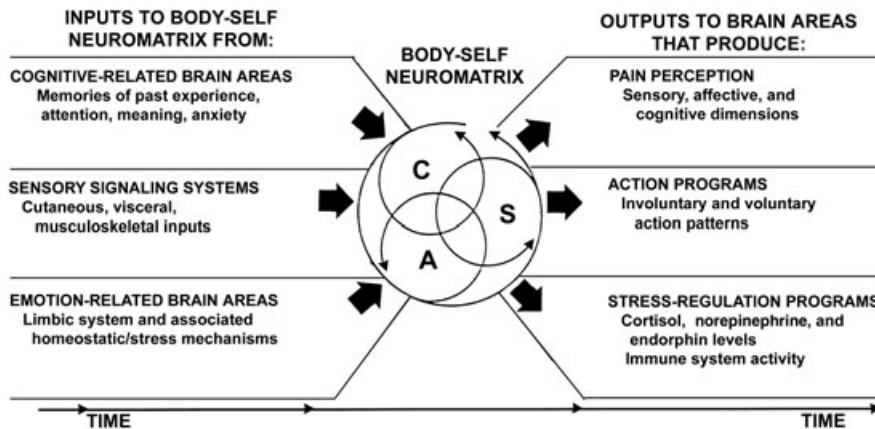
These speculations are supported by strong evidence. Chrousos and Gold have documented the effects of dysregulation of the cortisol system: effects on muscle and bone, to which they attribute fibromyalgia, rheumatoid arthritis, and chronic fatigue syndrome.<sup>11</sup> They propose

that they are caused by hypocortisolism, which could be due to depletion of cortisol as a result of prolonged stress. Indeed, Sapolsky 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. 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.

### 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, may produce neural "distress" patterns that contribute to the total neuromatrix pattern, and may also produce destruction of tissues that give rise to chronic pains. Each contribution to the neuromatrix output pattern may not by itself produce pain, but both outputs together may do so. The stress-regulation system, with its complex, delicately balanced interactions, is an integral part of the multiple contributions that give rise to chronic pain.



**Figure 1.** Factors that contribute to the patterns of activity generated by the body-self neuromatrix, which is comprised of sensory (S), affective (A), and cognitive (C) neuromodules. The output patterns from the neuromatrix produce the multiple dimensions of pain experience, as well as concurrent homeostatic and behavioral responses. From Melzack (2001), with permission.

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 produces the sensory, affective, and cognitive dimensions of pain experience and behavior.<sup>14</sup>

## IMPLICATIONS OF THE NEW CONCEPT

### Phantom Limb Pain

The new theory of brain function, proposed largely 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 study<sup>15</sup> 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.

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.

### Low Back Pain

Low back pain is one of the most common types of pain, yet it is poorly understood. It illustrates the complexity of interactions among different contributing factors and the need for multiple approaches to treat it.<sup>15</sup>

The only definite causes of low back pain are protruding discs and arthritis of vertebral joints. However, about 60 to 70% of patients who suffer severe low back pain show no evidence of disc disease, arthritis, or any other symptoms that can be considered the cause of the pain. Even when there are clear-cut physical and neurological signs of disc herniation (in which the disc pushes out of its space and presses against nerve roots), surgery produces complete relief of back pain and related sciatic pain in only about 60% of cases. The rate of success in different reports ranges from 50 to 95%, depending in part on the spatial distribution of the pain. Furthermore, patients with physical signs such as disc herniation in the lower spine are rarely helped by surgical procedures such as fusion of several vertebrae to provide structural support to the back.<sup>16</sup>

A variety of forms of physical therapy are more likely to help low back pain. The most effective is a regimen of exercises that develops the back muscles. Transcutaneous electrical nerve stimulation, ice massage, and acupuncture may also help some patients. Injections of anesthetics into trigger points may be effective as well. Still, despite all of these therapies, many patients continue to suffer severe, unrelenting pain.<sup>17</sup>

A high proportion of cases of chronic back pain may be due to more subtle causes. The perpetual stresses and strains on the vertebral column (at discs and adjacent structures called facet joints) produce an increase in small blood vessels and fibrous tissue in the area.<sup>18</sup> As a result, there is a release of substances that are known to produce inflammation and pain into local tissues and the blood stream; this whole stress cascade may be triggered repeatedly. The effect of stress-produced substances—such as cortisol and norepinephrine—at sites of minor lesions and inflammation could, if it occurs often and is prolonged, activate a neuromatrix program that anticipates increasingly severe damage and attempts to counteract it. The program to reduce strain and inflammation could include generating the neurosignature for pain—part of a neural program which presumably evolved to induce rest, the repair of injured tissues, and the restoration of homeostasis.

As a result of the persistence of low back pain despite all the available therapies, it is not surprising that psychological therapy, such as relaxation therapy, hypnotic suggestion, and behavior modification, has become an important approach to the problem. But no one therapy is more effective than the others. In fact, clinics often employ several procedures at the same time to get the best results. One study found that patients with several syndromes, but mostly low back pain, were helped by the use of multiple techniques that converge to relieve the pain—about 80% of patients reported marked to moderate improvement after treatment, and 50% claimed they were still improved 3 to 6 months later. Interestingly, most patients reported that the pain was unchanged but they were able to work, to live with their pain, and to lead more normal lives.<sup>19</sup>

### Fibromyalgia

Fibromyalgia affects 2% of the population, attacks more females than males (7:1), and reflects the complexity of most chronic pain syndromes.<sup>20</sup> The major features of fibromyalgia are multiple tender areas (“trigger points”) of the skin and muscles, “aching all over,” increased skin sensitivity to almost every kind of stim-

ulation, major sleep disturbances, and several indices of abnormal functioning of the whole stress-regulation system.

I believe that an understanding of fibromyalgia has eluded us because we have failed to recognize the role of stress mechanisms in addition to the obvious sensory manifestations which have dominated research and hypotheses about the nature of fibromyalgia. My interpretation of the available evidence is that the body-self neuromatrix’s response to stressful events fails to turn off when the stressor diminishes, so that the neuromatrix maintains a continuous state of alertness to threat. It is possible that this readiness for action produces fatigue in muscles, comparable to the fatigue felt by paraplegics in their phantom legs when they spontaneously make cycling movements. It is also possible that the prolonged tension maintained in particular sets of muscles produces the characteristic pattern of tender spots.

The abnormal neural program of prolonged, centrally maintained alertness may produce a generalized state of perceptual vigilance or “open sensory gates” to receive information for rapid response to threat. The persistent low-level stress (ie, the failure of the stress response to cease) would produce anomalous alpha waves during deep sleep, greater feelings of fatigue, higher generalized sensitivity to all sensory inputs, and a low-level, sustained output of the stress-regulation system, reflected in a depletion of circulating cortisol.

Goldenberg has described striking similarities between fibromyalgia and chronic fatigue syndrome, and notes that the frequent reports by patients in both groups that the onset of fibromyalgia or chronic fatigue syndrome was preceded by a flu-like or viral illness suggests an immune system abnormality.<sup>21</sup> I agree, but a large proportion of patients (about 45%) do not report a flu-like illness but instead report a preceding accident, surgical operation, or no apparent cause. This suggests that an abnormal, partially genetically determined mechanism fails to turn off the stress response to viral, psychological, or other types of threat to the body-self.

### Reflex Sympathetic Dystrophy

The neuromatrix theory of pain also has implications for understanding reflex sympathetic dystrophy, also known as complex regional pain syndromes,<sup>22</sup> which is characterized by severe, relentless pain and other symptoms after a sprain, a fall, or other injury. The pain and symptoms are usually out of proportion to the injury,

which is often minor. John Hannington-Kiff has observed that the early, mainly sympathetic symptoms—such as local changes in skin temperature and blood flow—are usually obvious about 3 to 6 weeks after the injury.<sup>23</sup> After this time, major dystrophic changes occur in the skin and nails, with muscle and joint stiffness, skin swelling, excessive heat and sweating, abnormal blood flow, skin color and sensitivity, and severe pain. It has long been assumed that reflex sympathetic dystrophy is primarily a disease caused by abnormal activity of the sympathetic nervous system. This may be true initially. However, it is possible that after a period of time, the pain and destructive signs of the skin are the result of dysregulation of the cortisol system rather than the noradrenergic system. This could explain the observation that anesthetic blocks of the sympathetic system may sometimes stop reflex sympathetic dystrophy if administered early in the disease but rarely do so if given after the signs are well under way.

At this stage, treatment with sympathetic blocks is rarely effective. The reason may be that the cortisol-regulation system may have superseded the sympathetic system and now dominates the stress response to the injury that initiated the cascade of events. For this reason, it is possible that psychological stress also contributes to the sequence of events. This does not mean that reflex sympathetic dystrophy is due to “psychogenic” causes. Rather, it may be a stress-related disease, in which all types of stress contribute to cumulative destructive effects.

These considerations suggest lines of therapy that differ from those now generally in use. Manipulation of the stress system may be more likely to produce pain relief for these people who suffer so terribly. Franklin Kozin<sup>24</sup> and his colleagues have achieved excellent results with many patients by using steroid injection therapy, and Kozin notes wistfully that “unlike the interruption of sympathetic pathways, no currently known theoretic mechanisms explain the efficacy of corticosteroids in reflex sympathetic dystrophy.” The powerful role of the stress system in chronic pain provides a plausible mechanism.

### CONCLUSIONS

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 addi-

tion 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 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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