3 The Functional Neuroanatomy of Pain Perception

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Summary

Pain is usually a source of warning and protection; this is not the case for chronic pain. The experience of pain is a form of consciousness consisting of integrated physical and psychological neural inputs. It typically originates with the spinal transmission of noxious sensory stimuli arising from damaged tissues; this level of processing is termed nociception. Signals are conveyed from the spinal cord to supraspinal networks that include the brainstem, subcortical, and cortical regions. This processing network is termed the pain neuromatrix. It is the supraspinal network that transforms the sensation of nociception into the complex and uniquely individual experience that is pain. Pain modulation (inhibitory or facilitatory) is emerging as an important clinical target for pharmacologic and non-pharmacologic interventions. This chapter outlines the neuroanatomical and physiological mechanisms underlying the experience of acute (physiological) and chronic (pathological) pain. It also highlights the theoretical role of CAM techniques in pain modulation. Finally, in order to provide an integrative view of pain perception, the dimensions of the pain experience are presented and contrasted, including the discriminative, cognitive, and affective elements.

Key Words: acute pain, chronic pain, nociception, pain modulation, neuroplasticity, anti-nociception, pain neuromatrix, pain dimensions, CAM

1. INTRODUCTION

Pain is a conscious multidimensional experience that typically arises from threat or actual damage to tissue *(1)*. The language of pain can be confusing, as a variety of terms

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may be employed in its description (Table 1). Acute pain, however, may be readily contrasted with chronic pain. Acute pain usually occurs with tissue injury or disease. The value of acute pain perception arising from tissue damage in muscles, ligaments, or nerves is obvious; it is a warning of imminent danger. Chronic pain, however, typically

Table 1

Pain Classification

Pain	An unpleasant sensory and emotional experience that is associated with actual or potential tissue damage, or described in terms of such damage (IASP). Pain may be modulated by affect and cognitive factors such as attention.
Acute pain (nociceptive pain)	Acute pain is a symptom with a recognizable cause, which will continue until tissue damage is repaired, usually within a time period of several months. An ankle sprain would be an example of a disorder producing acute pain. This is physiological pain and serves an important adaptive function.
Chronic pain	This is pain that persists beyond the expected time course of tissue healing. Chronic pain may also be recurrent, as with rheumatoid arthritis. It often occurs in the absence of identifiable tissue damage and may be termed non-nociceptive pain. In this case, there is no biological value; the pain is pathological.
Neuropathic pain (central pain)	This is a pain arising in association with damage or dysfunction within the peripheral or central nervous system. Unfortunately this type of pain is often difficult to treat and may become a source of chronic pain. Diabetic neuropathy is an example of neuropathic pain.
Deafferentation pain	The reduction or loss of afferent input into the central nervous system will trigger pain. This pain condition may arise in association with peripheral or central nervous system pathology.
Somatic pain	The presence of injury or disease in skin or musculature causes somatic pain. The sensation from deep musculature is felt as aching or throbbing and more burning or stinging if superficial. A torn quadriceps muscle would trigger somatic pain.
Visceral pain	This pain is diffuse, poorly localized, and felt as cramping or pressure. It is produced by nociceptive responses within internal organs, which are diseased or injured. Visceral pain could be the result of malignant infiltration of the liver.

has no survival value; it is itself a disorder of the anatomy and function of the central nervous system. There are then two major categories of pain: acute pain, which is physiologic and nociceptive, and chronic pain that is the result of persistent nociceptive input or neuropathic pain (lesions or dysfunction of the peripheral or central nervous system). Persistent or chronic pain may also arise from a continuous nociceptive tissue injury and inflammation, such as inflammatory arthritis or malignant disease. Central pain is a form of chronic neuropathic pain arising from a lesion anywhere within the central nervous system, but usually involving the spinothalamic tract in the spinal cord or brain. It is among the most difficult pain syndromes to treat. Multiple causes of tissue injury can lead to the state of chronic pain, wherein pain and dysfunction characteristically persist beyond the expected healing period of injured tissue.

Pain perception emerges as a unified mental state consisting of several interactive biological influences, including genetic, molecular, synaptic, anatomic, physiologic, and psychosocial inputs, which usually arise in association with nociceptive generators. Pain perception is not just a sensation, but an integrated state composed of mental activity that evokes emotion, memory, attention, expectation, motor activity, autonomic responses, and an awareness of the extent of physically injured or diseased anatomy. It is this multilevel neural integration, involving nociception, input modulation, and neuroplasticity, that gives rise to the uniquely individual perception associated with the pain experience. Pain states in general are compelling personal experiences that are imposed onto both the somatic and psychosocial domains of our being with a potentially devastating impact.

The potential benefit of pain research lies in reducing the enormity of humanity's burden of pain. Chronic pain in particular appears to represent a model for the study of mind–body interactions and because of the dearth of effective treatments within traditional medical models, opens the door for the research of complementary and alternative medicine (CAM) strategies. Some important pain related research questions might include—*(1)* How do we maintain balance and homeostasis in nervous system function while encountering the myriad of mental and physical stressors arising from our external and internal environment during states of pain? *(2)* Which clinical interventions promote change in the injured brain or spinal cord by using sensory or motor conditioning inputs that trigger beneficial neuroplasticity? *(3)* How much of a role will CAM or integrative techniques such as acupuncture or manual therapy play in pain management, either acute or chronic?

The study of pain neurobiology also promises to elevate our understanding of how the body and mind interact in health and disease. The study of pain consciousness promises to provide important insights into the mind–body problem. Increasing evidence demonstrates that psychosocial factors (stress, anticipation, coping, beliefs) are better predictors of prognosis for recovery, especially in chronic pain, than the patient's specific disease and the extent of pathophysiology *(2)*.

It is the conscious awareness of tissue injury that typically results in the perception of pain. The presence of threat or actual damage to tissue initiates a signaling cascade of coded neural activity in the periphery that is transmitted to spinal and supraspinal sites. This evoked neural activity, which arises in association with inflammatory, thermal or mechanical tissue damage, is known as nociception, and evokes the accompanying pain perception. The magnitude of pain perception is not necessarily proportional to the extent of tissue injury or damage. Nociceptive processing (tissue damage) may occur independently of the perception of pain and the inverse is also true; pain may

be perceived in the absence of peripheral or central damage-induced nociception. This latter circumstance, known as non-nociceptive pain, is common in chronic pain states such as psychogenic pain.

How can nociception arising from inflammatory or mechanical tissue injury occur without triggering pain perception? The pain system (like other neural systems) is arranged in a hierarchy of cortical, subcortical, and spinal neural networks that process nociceptive input to generate pain perception. Higher-order cognitive and affective pain modulatory neural networks may fire with sufficient intensity and duration in a variety of settings, i.e., sports competition, religious ritual, and combat environments, to produce significant antinociceptive or analgesic effects. This descending inhibitory influence is possible, as pain perception is the interaction of multiple excitatory and inhibitory spinal and supra-spinal processing nodes throughout the central nervous system (CNS). An extensive CNS network thus modulates the nociceptive input at the spinal cord and medullary dorsal horn (trigeminal) with both facilitatory and descending inhibitory (antinociceptive) pathways. The net output of these opposing networks and the influence of other pain-processing factors will determine the intensity and color of the pain perception. What about pain perception in the absence of tissue injury and nociception? Since the pain system is bi-valent, it may serve to amplify and even generate pain perception so under some circumstances pain perception can become independent of the presence of tissue damage.

As a result, the cortex plays a critical role in both the amplification and suppression of pain. These effects appear to be mediated by the endogenous opioid system. The role of the cortex in pain processing is a familiar experience to the marathon athlete who is able to suppress pain perception by triggering inhibitory cognitive and affective neural pathways activated by rigorous exercise. However, the role of the cortex in pain processing was not a historically accepted view in neuroscience. Only since the latter years of the 20th century has this view become established *(3)*. The role of the cerebral cortex in pain perception evaded scientific recognition until the early 1990s. It was the introduction of powerful anatomical and functional neuroimaging techniques such as PET and fMRI that identified cortical activity in pain studies. Prior to this period, the 20th-century view by Head and later Penfield was dominant *(4,5)*. In their view, the cerebral cortex played a limited role in the production of pain; the thalamus was believed to be the primary site of pain activation. Their view was supported by evidence that during neurosurgical ablation in the somatosensory cortex, patients failed to demonstrate any change in pain perception. In addition, they also observed little change in pain intensity in patients who had sustained trauma to the somatosensory cortex. Today, we know from functional neuroimaging studies that supraspinal pain processing occurs in a widespread, hierarchically distributed network of cortical, subcortical, and brainstem processing nodes. This network has been termed the pain neuromatrix *(6)*. The pain experience then is not encoded in a discretely localized area of the brain, such as the thalamus, as posited by Head, Penfield and others (see Chapter 4).

The neural hierarchy of spinal and supraspinal neuroanatomy is an important prerequisite for understanding nociception and pain perception. The functioning of spinal and supraspinal anatomic networks gives rise to the perception of pain regardless of whether it is acute or chronic. Neuroanatomy of the spinal pathway includes the nociceptor or primary afferent nerve, dorsal root ganglion (DRG), dorsal horn of the spinal cord, and ascending and descending tracts. The ascending and descending spinal

pathways connect nociceptive traffic between the spinal cord and brain and also play a critical role in the function of nociceptive modulation, which is convergent upon the dorsal horn (see Chapter 2).

Supraspinal neuroanatomy and its functions are related to higher-order nociceptive processing, the generation of pain perception and its bivalent modulation. The complexity of supraspinal pain processing is daunting and many questions remain unanswered in this complex and challenging frontier of pain research. What is the role of placebo or nocebo in healing encounters? How does the frontal cortex enhance the chronicity of pain? Can placebo induction become a therapeutic intervention? Do CAM practices somehow enhance or optimize the placebo response to pain? How can a patient's belief translate into pathophysiological or healing states? Although still under investigation, the supraspinal neuroanatomical components of the pain neuromatrix appear to include an extensive array with elements arising in the brainstem, cerebellum, thalamus, basal ganglia, subcortical and cortical regions. This chapter will focus on the spinal and supraspinal anatomy and function related to pain and its perception.

2. NOCICEPTOR

The perception of acute pain originates in the context of threatened or actual damage to visceral or peripheral tissue, including nerve fibers. Following tissue damage, peripheral and spinal neural pathways are synaptically activated and signals are then supraspinally transmitted throughout the pain system.

The most peripheral aspect of the pain system consists of nerves with specialized receptors known as nociceptors; they are associated with mostly small unmyelinated or thinly myelinated afferent nerve fibers. Their cell bodies are located in the dorsal root ganglion. Nociceptors are the gatekeepers of noxious afferent information, translating tissue damage and inflammation into nerve impulses. These impulses are transmitted through the spinal nerves and their trigeminal equivalent into the spinal and medullary dorsal horn respectively. Peripheral tissue damage arising from trauma or inflammation, including nerve injury, normally triggers the release of numerous nociceptive provoking or algesic agents. This inflammatory "soup" sensitizes local nociceptors, an event known as peripheral sensitization, which enhances peripheral neural input. There is an expanding array of algesics, including biochemical, neurotrophic, and cytokine agents (Table 2) *(7)*. Peripherally, sensitized nociceptors may alter their function and begin to demonstrate spontaneous firing, lowered thresholds of depolarization, and increased responses to noxious stimuli. Clinically, the change in sensitization of the peripheral nociceptor can lead to heightened responses to painful sensation known as hyperalgesia. This enhanced state of afferent barrage may then trigger abnormal functional and structural changes in the spinal and supraspinal pathways, a state known as central sensitization. This state can initiate allodynia, the experience of pain linked to normally non-painful sensation. Both peripheral and central sensitization phenomena are important as they contribute (along with neuroplastic mechanisms) to the transformation of acute pain to persistent and chronic pain.

Peripheral nociceptive signaling has additional routes. As mentioned above, another important afferent pathway mediating nociception is the trigeminal sensory nucleus (nucleus caudalis). It receives nociceptive peripheral afferents from the head and is analogous in function to the dorsal root ganglion. The trigeminal nociceptive pathway is activated with episodes of facial pain and during headache syndromes. There is also

Table 2

Inflammatory Pain Mediators

Bradykinin
Prostaglandin
H+
Adenosine
Serotonin
Nitric oxide
Noradrenaline
Growth factors
Chemokines
Cytokines
Bradykinin
Prostaglandin

evidence of nociceptive functioning in the afferents of cranial nerve X, i.e., the vagus nerve *(8)*. Autonomic responses such as elevated blood pressure and tachycardia occur during the perception of pain. In addition, both excitatory and inhibitory effects on spinal nociceptive processing, depending on the intensity of the stimulus, have been reported with vagal afferents *(9)*. These effects are probably mediated through bulbospinal pathways. Electrical stimulation of the vagus has been reported to reduce pain *(10)*. Vagal stimulation is also proposed as a mechanism of action for several CAM techniques such as acupuncture, and manual therapy *(11,12)*.

3. PERIPHERAL NERVE

Nerve cell fibers have long processes known as peripheral nerves. The constituents of the peripheral nerve include sensory, motor, and autonomic fibers. Nociceptive neural activity arising from tissue damage and inflammation in the periphery is initially transmitted to the dorsal horn of the spinal cord along variable-sized primary afferent nerve (PAN) fibers. These cell bodies are located in the dorsal root ganglion or the trigeminal ganglion. A central axon projection of the PAN synapses in the spinal or medullary dorsal horn. Fiber types of PAN mediating nociception include the A-delta and unmyelinated C-fibers. A-delta fibers conduct cold and localized nociceptive stimuli while C-fibers conduct poorly localized mechanical and heat stimuli. The size of the afferent fiber is clinically relevant because small fibers conduct an excitatory effect resulting in nociception, while the large diameter fibers (A-alpha, A-beta) arising from proprioceptors and muscle spindles have an inhibitory or gating effect on spinal cord nociceptive transmission, reducing nociceptive barrage *(13)*.

Following tissue injury, primary afferent nerve fibers convey coded noxious peripheral and visceral stimuli to the spinal cord dorsal horn, and then, in parallel pathways, to distributed supraspinal sites including the brainstem, cerebellum and multiple sites in the cortical and subcortical pain neuromatrix. As a result of the processing in this neuromatrix, a sensory stimulus arising in the primary afferent nerve undergoes transformation into a conscious state of pain perception.

4. SPINAL CORD

Nociception at the level of the spinal cord is important because of its critical role in states of pathological pain. A powerful pain modulatory mechanism originates in a network of supraspinal centers thought to be located in the cortex and brainstem. Through descending pathways, excitatory or inhibitory control is exerted on the afferent neural transmission within the dorsal horn neurons of the spinal cord.

Neurons of the spinal cord are organized into ten (I–X) gray matter layers, or laminae, first described by Rexed *(14)*. The substantia gelatinosa (lamina II) is an important node in the network of pain modulation since it is capable of blocking input from nociceptors segmentally (gating) and also through the supraspinal influence of the descending inhibitory pathways arising in the cortex and brainstem. Lamina II maintains a high concentration of opiate receptors responsible for analgesic effects. Inputs to the dorsal horn include several cell types including low threshold mechanoreceptors, low threshold thermoceptors, and nociceptive specific neurons. Wide dynamic range (WDR) neurons are second-order neurons that encode a wide range of stimuli from innocuous to noxious (low and high threshold) and have been implicated in the development of chronic pain. Neurochemicals modulating dorsal horn nociception include excitatory and inhibitory agents released by the terminals of the primary afferents, interneurons, and descending axons originating from a number of supraspinal sites *(15)*. Neurotransmitters such as glutamate and substance P mediate the synaptic transmission between nociceptors and dorsal horn neurons. Gamma-amino butyric acid (GABA) is released by interneurons and can modulate locally the response of the second-order neuron to the primary afferent barrage. Long-lasting nociceptive input from peripheral nerve injury or other damaged tissues may elicit windup and central sensitization in the dorsal horn (see Chapter 2). Peripheral sensitization of the nociceptors may be one factor that can lead to a sustained activation of the WDR and contribute to the heightened responsiveness of the second-order neuron called wind-up. This response is mediated by activation of N-methyl-D-aspartate (NMDA) receptors *(7)*. If sustained for a long enough period of time, a resultant increase in neuronal excitability throughout the spinal and supraspinal networks can occur known as central sensitization. A model for the maintenance of central sensitization is a form of increase in synaptic activity known as long-term potentiation (LTP). Its counterpart is reduced synaptic activity and known as long term depression (LTD). These mechanisms are thought to underlie the activities of learning and memory in the hippocampus and might also explain the transformation of acute to chronic pain *(16,17)*. This prolonged state of excitation may induce activity-dependent neuroplastic changes that impair the supraspinal modulation of pain. Excessive excitation may then increase the signal gain throughout the pain system elevating the risk for chronic pain (Fig. 1) *(15)*. When nociception is persistent, in addition to central sensitization, another mechanism promoting chronic pain has been recently identified based on a pathologic neuroimmune response. The response includes glial activation, pro-inflammatory cytokine release and increased release of pain mediators *(7,15)*. These factors also enhance neural sensitivity and increase the likelihood of chronic pain. In another recent study, chronic pain processing was reported to promote astrogliosis in the cingulate cortex associated with dysfunction of the cortical delta-opioid receptors *(18)*.

The gate control theory was a breakthrough concept in pain research *(13)*. It suggested that the pain experience was not a passive, static mechanism, but a dynamic

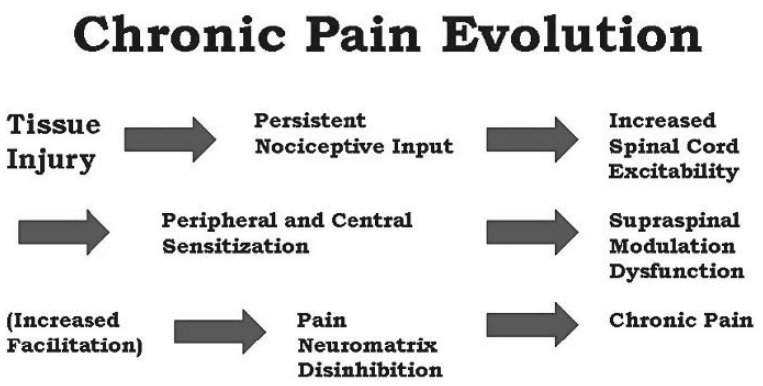

Fig. 1. Chronic pain evolution.

one, wherein afferent nociceptive signaling could be modified and influenced by neurons in the CNS acting as inhibitory or excitatory gates with both a segmental (spinal) and a central influence. Their theory described dorsal horn transmission cells as the convergence site of signals from a variety of peripheral afferent fibers (Fig. 2). Transmission cells project nociceptive signals into the supraspinal centers. The gate was a reference to either inhibition or facilitation of nociceptive signals by large and small fibers, respectively, within the substantia gelatinosa of the dorsal horn. Large diameter fibers act segmentally, and along with the supraspinal descending pathways, block nociceptive signaling in small diameter fibers. This gating mechanism serves as a potential model for the peripheral and central action of several CAM techniques. These techniques include therapies that trigger rhythmic afferent neural discharges in large-diameter mechanoreceptor fibers such as acupuncture, manual therapy, massage, exercise and transcutaneous electrical nerve stimulation (TENS).

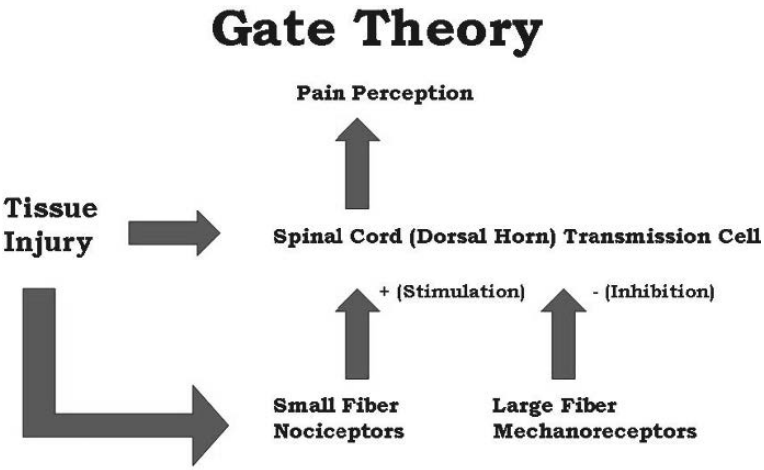

Fig. 2. Gate theory.

5. ASCENDING PATHWAYS

The anterolateral column of the spinal cord plays an important role in the ascending transmission and processing of nociceptive signaling (Figure 3). The spinothalamic tract (STT) is regarded as the most important ascending pathway for nociceptive transmission in humans. Lesions that block the anterolateral quadrant of the spinal cord result in the contralateral loss of pain and temperature and may result in ipsilateral loss of discriminative touch below the segmental level of the lesion. Such a lesion also blocks the spinoreticular, spinomesencephalic, and spinohypothalamic tracts that provide connections to the medulla, brainstem, and hypothalamus. STT cells originate in laminae I, III, IV, V, and to a lesser extent IX and X. Most cross within one or two segments and pass through the central white commissure to the opposite ventrolateral funiculus and ascend rostrally as the lateral STT. Deeper dorsal horn neurons give rise to the ascending anterior STT *(15)*.

There is an analogous pathway for the nociceptors originating in the face arising from the three divisions of the trigeminal nerve. The trigeminothalamic tract (TTT) originates from cells in the subnucleus caudalis. Second-order neurons of the STT and TTT arise from the dorsal horn of the spinal cord, (or brainstem), and ascend supraspinally to synapse in several ventral thalamic nuclei. In addition to the STT and TTT tracts, additional ascending nociceptive pathways arise in the dorsal horn that project to a variety of targets including the brainstem reticular formation, mesencephalic periaqueductal gray, thalamus, hypothalamus, amygdala, and indirectly to the frontal cortex. Third order neurons originating from the thalamus project in a wide distribution to cortical and subcortical targets as nociceptive signals are integrated throughout the supraspinal pain system *(15)*.

Inhibition of the STT in the dorsal horn can be triggered by the activation of noxious stimuli delivered to areas that are remote from the site of tissue damage. This inhibitory mechanism is known as the diffuse noxious inhibitory control system (DNIC) and is associated with activity in nociceptive neurons that recruits supraspinal inhibitory pathways *(19)*. This type of nociceptive inhibition may also be considered a tenable

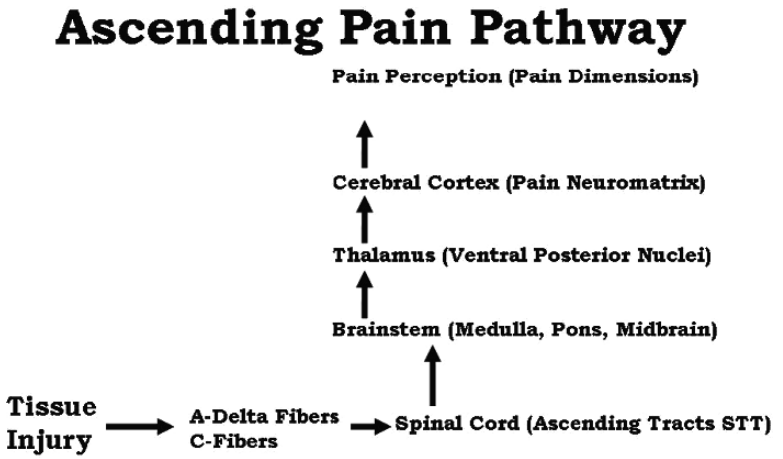

Fig. 3. Ascending pain pathway.

mechanism explaining the analgesic effects underlying counterirritant CAM techniques including TENS, acupuncture, and manual therapy.

Another major afferent spinal system, which extends to the brainstem, is the dorsal spinal (posterior) columns. Neurons in this pathway synapse in the dorsal column nuclei of the medulla oblongata. The dorsal column carries fibers activated by innocuous touch, proprioception and visceral nociception. As already mentioned, this system may also play an important role in pain modulation by activating inhibitory interneurons in the dorsal horn *(15,20)*.

6. DESCENDING PATHWAYS

Multiple neuroanatomic levels are known to be associated with the descending pain inhibitory system (Figure 4). They include the cortex, diencephalon, limbic system, mesencephalic periaqueductal gray (PAG), rostroventral medulla (RVM), and nucleus raphe magnus (NRM), and dorsal horn. The arrival of ascending spinal nociceptive synapses in the mesencephalon triggers inhibitory substrates in the PAG. These signals are then relayed to the nucleus raphe magnus (NRM) and then send descending fibers to the dorsal horn where modulation of nociception occurs. This descending influence on nociception can be either inhibitory or facilitatory. The dorsal horn receives NRM terminals in laminae I, II, and V with the capability of inhibiting nociceptive neurons of the STT, spinoreticular and spinomesencephalic tracts. Inhibition in lamina II (substantia gelatinosa) occurs following the release of 5-HT (serotonin) and norepinephrine from the descending inhibitory fibers. The inhibition of substance P is blocked by either inhibitory interneurons and/or opioid release *(7,15)*.

Cells in the NRM and RVM change their firing rates in response to modulatory inputs from higher cortical centers. Some cells are described as "off ," leading to descending inhibition (anti-nociceptive), while others are "on," causing descending facilitation (pro-nociception), with neutral cells also present *(21)*. Thus, the descending pain modulatory system maintains opposing influences, anti-nociception or pain

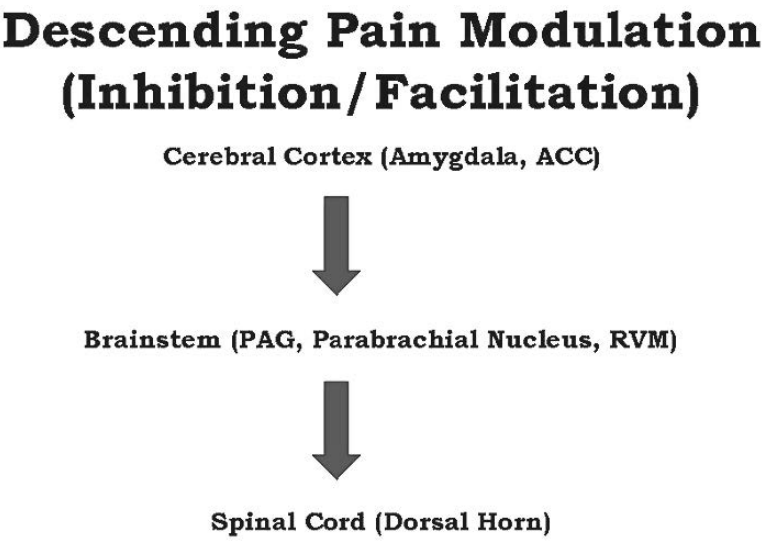

Fig. 4. Descending pain modulation (inhibition/facilitation).

inhibitory, and a pro-nociceptive or a pain facilitatory system. The neural architecture provides for both an ascending nociceptive and descending inhibitory or facilitatory pathway; a balance is normally maintained that provides an appropriate response level to nociceptive input. However, dysfunction arising from an increased duration of nociceptive input, failure of descending inhibition or an enhanced facilitatory tone, or all of these factors may be important in the evolution of chronic pain disorders *(22–24)*. The final balance of these pathways significantly influences the amplitude and character of the individual pain experience.

Descending modulatory pain processing is found at multiple levels of the neuraxis *(25)*. Recently, it was reported that the frontal cortex and brainstem interact to play important roles in descending pain modulation *(26)*. One mechanism for the placebo response is thought to involve the descending inhibitory pathways originating from the prefrontal and anterior cingulate cortices *(27)*. Using a thermal pain model, functional neuroimaging revealed that cortical sites can modulate afferent nociceptive input likely through the activation of the endogenous opioid network located in the brainstem. Activation of the descending inhibitory pathway appears to be operational in CAM techniques such as acupuncture and possibly in manual therapy *(28,29)*. While there are preliminary reports on spinal functional neuroimaging, until these techniques mature, the imaging evaluation of spinal cord pain processing and the study of the descending modulatory system will require more limited and invasive techniques *(30)*. Functional neuroimaging data is minimal in the descending inhibitory pathways. Some functional neuroimaging work in the brainstem, however, is underway *(31–34)*.

It is probable that a variety of mechanisms modulate nociceptive transmission at almost every synaptic relay site in the neuraxis. Modulation is accomplished by dynamic interaction between numerous neurotransmitters, their receptors and the neural inputs from the periphery, spinal interneurons and the brainstem's descending inhibitory and facilitatory control systems. This endogenous system of analgesia has been termed the anti-nociceptive system *(35)*. To summarize, three principles of endogenous anti-nociception have been identified: *(1)* supraspinal descending inhibition, where depressed discharge rates of nociceptive spinal dorsal horn neurons are detected during stimulation in the mesencephalic periaqueductal gray (PAG) or medullary nucleus raphe magnus. Higher-order descending supraspinal interactions are likely involved with this type of anti-nociception, which under certain circumstances can actually lead to pro-nociception or descending facilitation. *(2)* Propriospinal, heterosegmental inhibition resulting from the heterosegmental interneurons that are activated by a noxious conditioning stimulation. This is the DNIC mechanism *(19)*. Only A-delta or C fibers can trigger the DNIC. Convergent, but not nociceptive, neurons are impacted in the dorsal horn by DNIC. Higher-order descending input may also have an influence. In particular, stress may be a natural trigger for the activation of the endogenous pain inhibitory systems. Stress-induced analgesia (SIA) occurs following threat, restraint, rotation, and forced swim in animals. In humans, athletic competition, sexual stimulation, and combat exposure have been shown to elicit the SIA response. What role the endogenous opioids play in SIA, however, is still unclear, since the response to naloxone (an opioid antagonist) blockade is frequently quite variable. Some forms of SIA, elicited by continuous afferent input, probably act to diminish nociceptive transmission. The CAM techniques of acupuncture, manual therapy, and even rigorous aerobic exercise may utilize these mechanisms to provide pain relief. Given this analgesic effect, these techniques could decrease nociceptive sensitization in the dorsal

horn and thus diminish the risk of chronic pain *(36)*. *(3)* Long-term depression (LTD) of synaptic transmission in spinal cord dorsal horn nociceptors can be induced by low-frequency stimulation of primary afferent A-delta-fibers. The role of inputs from the higher descending pathways if any is still unclear in this segmental type of gating.

7. SUPRASPINAL NEUROANATOMY

It is now clear that no single cortical or subcortical area exclusively processes nociceptive input. Instead, human functional neuroimaging studies show that multiple supraspinal targets are activated in a distributed sensory, motor, affective, and cognitive pain network. This integrated network also provides the basis for evoked states, including anxiety, expectancy, and fear that may accompany pain processing. The supraspinal component of the pain system is where the physiology of nociception is transformed into the psychology of pain.

Although some neuroimaging evidence distinguishes acute from chronic pain, there is much overlap. Chronic pain, however, is typically characterized by neuroplastic mechanisms that sustain activation of brain regions associated with emotional and cognitive evaluation *(37,38)*. Unfortunately, there is minimal functional neuroimaging evidence identifying impaired neural circuitry underlying states such as pathological pain. This is certainly an important objective for future research. Attempts have been made to classify the extensive array of neuroanatomical substrates in the supraspinal pain system in order to provide models for experimental study. Melzack coined the widely utilized term *pain neuromatrix* to describe the cortical and subcortical neural network involved in the multidimensional pain experienced by phantom limb patients (Table 3) *(6)*. He also coined the term *neurosignature* to express the influence of neuroplastic modulation in the pain neuromatrix, recognizing the dynamics of synaptic connections that become altered as the pain experience varies over time.

Treede has proposed a supraspinal neuroanatomical classification consisting of two functional subsystems within the pain neuromatrix, the lateral and medial (Figure 5) *(39)*. The lateral pain system consists of inputs from the spinal Rexed lamina I (additional inputs from lamina V) projection fibers, lateral thalamic nuclei and the

Table 3

Pain Neuromatrix

Somatosensory cortex (S-1, S-2)
Supplementary motor cortex
Insula
Anterior Cingulate Cortex
Prefrontal cortex
Posterior parietal
Striatum
Thalamus
Cerebellum
Periaqueductal gray
Hypothalamus
Amygdala

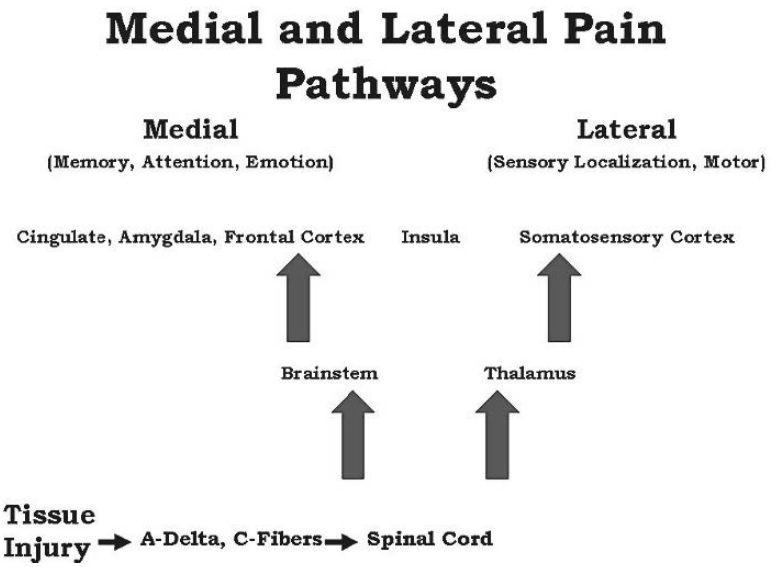

Fig. 5. Medial lateral pain pathways.

primary and secondary somatosensory cortices. The lateral subsystem subserves the sensory-discriminative function of pain. The medial pain system consists of both Rexed laminae I and V projection fibers, the medial thalamic nuclei, and the ACC. The medial pain system is involved with the emotional and motivational aspects of pain. Although the insula is clearly involved in pain processing, it is not associated with either the medial or lateral subsystems of pain processing, but is identified as an intermediate region *(3)*.

It has been reported that the medial pain system is more susceptible to exogenous and endogenous opioid neuromodulation than the so-called lateral pain system *(40)*. This finding has direct clinical relevance. A reduction in opioid receptor-binding capacity has been demonstrated in neurons within central neuropathic pain patients *(41)*. The areas of the pain matrix involved included the dorsolateral prefrontal cortex, anterior cingulate, and insula, along with the thalamus. The reduction in opioid receptor-binding capacity may have resulted in a state of disinhibited nociceptor activity within some of the structures associated with the medial nociceptive system. Persistence of such an abnormal state could contribute to the development of neuropathic pain.

The definition of supraspinal (cortical and subcortical) targets and their underlying neurotransmitter systems triggered by CAM techniques is still a topic of intense ongoing functional neuroimaging and clinical investigation. The antinociceptive effects of acupuncture appear to be related to effects arising from the endogenous opioid network. The analgesic quality of opioids has been recognized throughout history. The discovery in modern times of the opioid receptor *(42)* and the endogenous opioid ligand, enkephalin, served as a major catalyst in the understanding of pain and its modulation *(43)*. A few years later, the endogenous opioid neuromodulatory system was identified as the mechanism underlying the nonspecific effects of placebo analgesia *(44)*. However, the relative contribution, of the specific and nonspecific effects arising from the opioid network in CAM techniques awaits additional investigation. Other neurotransmitters, such as serotonin, norepinephrine, and dopamine, are also likely to

play an antinociceptive role. Disorders of the endogenous opioid network are becoming more recognized. There is recent evidence indicating that sustained pain can be the result of altered endogenous opioid regulation or abnormal opioid receptor regulation or both *(45)*.

8. BRAINSTEM

The role of the brainstem in selective pain modulation became recognized following the technique of stimulation-produced analgesia. This technique utilized intracranial electrical stimulation of the mesencephalic periaqueductal gray (PAG) *(46)*. Pain modulation induced in the dorsal horn by the brainstem was an important advance in the understanding of pain modulation by the endogenous opioid system. Today, the regions of the PAG and RVM are recognized as a circuit known to provide bi-directional influence (inhibitory and facilitatory) for the regulation of the endogenous descending pain modulatory system. Nociceptive activation in brainstem centers also triggers concomitant physiological processes involving spinal sensory modulation, autonomic and motor circuits in an effort to maintain homeostasis *(47)*.

9. THALAMUS

The thalamus is located in the diencephalon. Until the advent of functional neuroimaging, it was considered to be the highest level of pain processing, since the cortex was felt to play a limited, if any, role in nociceptive processing. Nociceptive projection pathways in the spinothalamic and trigeminothalamic tracts ascend from the spinal cord to the thalamus. Synapses are eventually formed with many supraspinal targets, including the brainstem reticular formation, hypothalamus, basal ganglia, amygdala, limbic system, and the thalamic nuclei. The thalamus transmits afferent input to the cortex and is divided into several distinct nuclei that are linked to the cortex through bidirectional tracts. The thalamus can be divided into medial and lateral components. The medial thalamus includes the medial and intralaminar nuclei, which receive input from the spinal cord and reticular system. With selected areas of the cortex, they make up the medial pain subsystem. The lateral or ventrobasal thalamus receives somatotopically organized receptive fields and projects to the primary somatosensory (S-1) and secondary somatosensory (S-2) cortex to provide discrimination of the spatial and temporal characteristics of painful stimuli. Thalamic nuclei have widespread cortical efferents projecting to frontal, parietal and limbic regions throughout the cortical and subcortical pain system *(36)*.

Until recently, deep brain thalamic stimulation was a technique utilized in neuropathic pain patients who were refractory to conservative treatment *(48,49)*. Thalamic stimulation of the sensory nuclei was shown to produce analgesia and reduce some, but not all, types of neuropathic pain. Today, deep brain stimulation for chronic central neuropathic pain has largely been replaced by motor cortex stimulation (MCS). Motor cortex stimulation is effective because it increases regional cerebral blood flow in the ipsilateral ventrolateral thalamus. It is in this area that corticothalamic connections from the motor and premotor areas are concentrated *(49)*. Pain relief following MCS also correlated with an increase of blood flow in the cingulate gyrus suggesting that MCS stimulation reduced the affective component experienced in chronic neuropathic pain.

10. CEREBRAL CORTEX

The primary somatosensory cortex consists of Brodmann subdivisions 1, 2, 3a, and 3b. Neurons in S-1 are somatotopically organized with each area of the body distinctly, but dynamically, represented by a homunculus. The map size on the cortical surface correlates with the peripheral density of somatosensory receptors in the various body regions. S-1 plays a role in the detection and discrimination of noxious stimuli. It is, however, variably activated by noxious input during functional neuroimaging studies *(3)*. The secondary somatosensory cortex (S-2) displays another complete somatotopic map in the parietal lobe. It is located on the superior bank of the Sylvian fissure. Both S-1 and S-2 receive thalamic sensory input and participate in the integration of innocuous and noxious mechanical, thermal, and electrical stimuli. The somatosensory cortices are responsible for encoding the sensory discriminative aspects of pain that include temporal, spatial and the intensity characteristics *(36)*.

The CNS is known to adapt to peripheral and central injury during development as well as throughout adult life *(50)*. Alteration in sensory inputs following stroke, nerve injury (deafferentation), phantom pain, or other highly relevant sensory input, such as chronic pain, appear to modify the functional and structural organization of cortical somatosensory somatotopic maps *(51–53)*. These altered representations, or states of cortical and subcortical neuroplastic reorganization, are capable of promoting adaptive, as well as maladaptive, clinical outcomes. The latter may result in lowered pain thresholds, lowered pain tolerance and the development of phantom pain. The underlying dynamic mechanisms involve both short and long-term neuroplastic changes. Preliminary work indicates that interventions that alter peripheral input by utilizing a correlated conditioning afferent stimulus may trigger beneficial sensorimotor reorganization and improve clinical outcomes in chronic pain *(54,55)*.

The anterior cingulate cortex (ACC) a component of the limbic system is related to many pain processing functions including anticipation, anxiety, attention and the distress of pain *(56)*. The ACC has extensive connections with the autonomic system and is also widely connected to relevant regions of the descending pain modulation system. In a study of affective modulation, Rainville used PET to measure the modulation of the ACC under hypnotic suggestion *(57)*. The level of pain unpleasantness, an affective function, was positively correlated with pain-evoked activity in the ACC. More recently, Petrovic described the shared relationship between the opioid analgesia and placebo neural networks. This study also revealed a positive ACC covariation with the pons *(27)*. The ACC as a higher cognitive center is implicated in the placebo analgesic response, and may serve as the trigger for descending modulation of pain.

The insula is located in the parietal lobe within the Sylvian fissure and consists of an anterior and posterior component; it is commonly involved in supraspinal pain processing. The anterior portion has been identified by fMRI to be related to pain attention, while the posterior is associated with sensory discrimination *(39,58)*. The insula receives thalamocortical projections and has extensive reciprocal corticocortical connections. The insula occupies an intermediate position between the lateral and medial subsystems in the supraspinal pain system *(39,59)*. The insula receives lateral system nociceptive input ascending from the spinal cord Rexed lamina I. It also receives medial thalamic input. The insula projects fibers to the amygdala, the lateral hypothalamus and important sites in the brainstem such as the nucleus tractus solitarius,

parabrachial nucleus and ventral lateral medulla. The connectivity of this network supports the view that the insula plays a role in the affective processing of pain. In addition to processing nociceptive input, the insula also processes visceral sensory and motor activity *(59)*. The insula is frequently activated by noxious stimuli during functional neuroimaging studies *(3)*.

The medial orbitofrontal cortex (mOFC) maintains reciprocal connections with the thalamic nuclei involved in nociceptive processing and reciprocally connected with the somatosensory cortex (S–1). The mOFC is activated by noxious stimulation from mechanical, visceral or thermal (cold) stimuli. Along with other sites in the cortex, there is evidence that the orbitofrontal cortex is involved with pain modulation *(36,60)*.

Other sites, thought to be important in supraspinal pain processing, include the cerebellum, hypothalamus, and basal ganglia. A brief discussion of their influence in pain processing follows. Recent animal and human neuroimaging studies have shown that the cerebellum has a role in pain related processing *(61)*. Cerebellar activation in pain studies is apparently related to awareness and escape behaviors but may also play a pain modulatory role. The hypothalamus integrates and regulates the autonomic nervous system and neuroendocrine responses to painful stimuli. Dysfunctional regulation in the hypothalamus is a source of stress. It also organizes visceral and somatic reaction patterns triggered by tissue damage and pain. The hypothalamus is connected to limbic forebrain structures (cingulate, hippocampus, amygdala and septal region). It receives ascending input through the dorsal longitudinal fasciculus formed by fibers from the PAG, segmental nucleus (midbrain) and visceral, motor and autonomic centers in the caudal medulla, nucleus tractus solitarius (NTS), and vagus. A reticulohypothalamic connection allows for the brainstem influence on the hypothalamus and the limbic forebrain *(36)*.

The basal ganglia are interconnected nuclei, including the caudate, putamen, globus pallidus, and substantia nigra. The subthalamic nucleus, nucleus accumbens, claustrum, and amygdala are associated nuclei. Nociceptive information reaches the basal ganglia and associated nuclei from the cerebral cortex, posterior thalamus, amygdala, parabrachial nucleus, and dorsal raphe nucleus. Basal ganglia and associated nuclei appear to play a role in the cognitive, affective-motivational, and evaluative-discriminative dimensions of pain. They also participate in evoked motor responses, and there is evidence for pain modulation in the basal ganglia *(36)*. Abundant opiate receptors are present in the amygdala, suggesting an important role in pain processing related to states of negative emotion and affect. The central nucleus of the amygdala receives afferent input from the hypothalamus and thalamus and has been termed the nociceptive amygdala because of its participation in pain modulation *(62)*. Environmental and affective contexts allow the amygdala to play a role in either facilitatory or inhibitory pain behavior.

Characterizing pathological neural activity in multiple cortical, subcortical, and spinal pathways across distributed neural networks defines a major research objective in pain research. The complexity of pain processing is daunting and most research has been historically based on clinical, behavioral, electrophysiological, and animal models. Modern functional neuroimaging techniques have made dramatic contributions in the identification of the main components of the cortical and subcortical pain neuromatrix in human experimental and clinical pain trials. Eventually, the brainstem and spinal cord pain circuitry will also be displayed using imaging techniques. An imaging perspective of the entire pain system would provide the first integrative view of pain

pathophysiology. As the integrated anatomy and function of the spinal and supraspinal pain circuitry is revealed, new treatment models will evolve which promise to more precisely target the underlying pathophysiology of acute and chronic pain.

11. DIMENSIONS OF PAIN PERCEPTION

Pain perception is a complex conscious phenomena resulting from the integration of neural activity arising in multiple peripheral and CNS networks which process nociceptive activity. An integrative model of the pain experience must incorporate the multidimensional anatomic and physiological levels of organization arising from genetic, biochemical, histological, neurophysiological, autonomic, psychological, and behavioral inputs (Figure 6). These multidimensional anatomic and physiological levels of pain physiology constitute the various targets of CAM interventions in previous and ongoing research.

At least three definable neural states or dimensions contribute to the perceptual components of pain: discrimination, affect and cognition (Table 4). "Discrimination" refers to the anatomic localization of the nociceptive activity, that is, "Where is the pain and what tissue is involved?" In order to answer this question, the brain is required to refer interoceptively to its somatosensory somatotopic surface maps, to access an awareness of the site of injury. Unfortunately, it appears that the primary somatosensory somatotopy undergo maladaptive neuroplastic changes that may promote chronic pain states, as seen in phantom pain. The other question addressed by pain discrimination is "How much pain is present?" The intensity of pain often signals its biological significance. "Is it trivial or a threat to survival?" The discriminative dimension may often dominate the clinical encounter because the patient may be entirely focused on the personal interpretation of pain and its intensity.

Another dimension of pain perception is described as the "affective"; it may lie in parallel with the sensory or discriminative dimension *(63)*. Affective refers to the experience of emotional distress, unpleasantness and the evoked accompanying motivational responses to cope with the pain stimulus. Autonomic responses are a frequent concomitant of affective pain experience because the limbic system processes

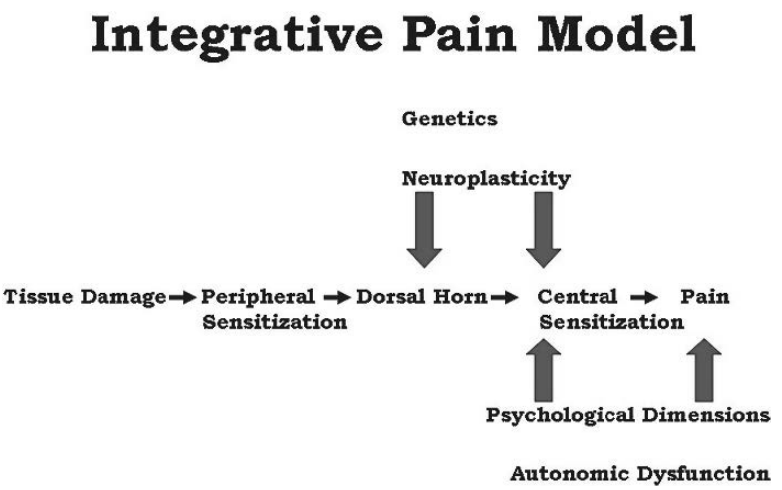

Fig. 6. Integrative pain model.

Table 4

Dimensions of Pain

Sensory-discriminative
Affective-motivational
Cognitive-evaluative
Motor
Autonomic

both affective and autonomic functions *(64)*. Patients in pain are often fearful that their pain will persist and even incapacitate them. The experience of pain then, is a perceived threat accompanied by a negative emotion. Suffering refers to the negative meaning and perceived threat directed at the integrity of one's self *(65)*. In the face of such a threat, there is typically an accompanying sense of helplessness and often exhaustion of the biological and psychosocial resources necessary for coping.

As chronic pain is a chronic stress, chronic pain patients often have disturbances of the hypothalamic–pituitary–adrenal (HPA) axis, with abnormal cortisol levels. In addition, chronic pain patients display an increased incidence of depression and anxiety. These stress-related disorders are frequently accompanied by disturbances in the limbic system including the regions of the hippocampus, amygdala and HPA axis *(66)*.

The "cognitive dimension" of pain perception includes the allocation of attentional resources to pain experience. Turning attention towards or away from a painful stimulus is known to modulate its perceived intensity. Pain can frequently captivate and dominate our attention to the extent that its persistence becomes anticipated or expected. This heightened degree of attentional allocation is termed *catastrophizing*. It may fuel persistent or chronic pain states, because attention amplifies some supraspinal pain circuitry and influences pain perception as described in a recent study *(67)*. The results suggested that catastrophizing influenced pain perception by increasing attention to and anticipation of pain, as well as heightening emotional responses to pain. The antithesis of attention is distraction, which is known to have analgesic effects. The processing capacity of the CNS is finite, so that the analgesic effects of distraction may occur when attentional resources for "distracting" stimuli are prioritized over those associated with nociceptive processing. Cognitive processing also includes the important role of previous pain experiences, as these episodic memories may color pain perception. Clinicians who learn to interact with chronic pain patients across all of the pain dimensions are more likely to increase the probability of a successful healing encounter, as cognitive and affective factors are a dominating influence.

The cognitive dimension of pain experience is known to include a learned component. The underlying mechanism remains under active investigation, but it is likely to include the mechanism of Hebbian neuroplasticity, the mode of CNS processing that provides long-term memory storage of highly relevant information *(16)*. This process may involve the induction of long-term potentiation or depression. The formation of a pain memory may be a maladaptive form of neuroplasticity or learning. In a use-dependent manner, persistent excitation, disinhibition or central sensitization occurring in the pain neuromatrix may provoke and sustain pain memories

formed through neuroplastic mechanisms. One (or more) of these mechanisms is likely involved in the transformation of acute to chronic pain *(68)*.

Functional neuroimaging literature supports a model of neuroplasticity in chronic pain in humans wherein cortical somatotopy that underlies the maladaptive neuroplasticity of chronic pain, (central sensitization?) can be therapeutically modified by modulating patterns of sensory input. Some degree of clinical improvement in chronic pain has been reported *(55,69)*. Conditioning afferent inputs may be modulating neural plasticity, improving behavioral performance, and improving learning and functional recovery in disorders including stroke *(70)*. This approach offers promise as a new tool in neurorehabilitation.

There is good reason for optimism in pain research, as much has been learned over the last 50 years. However, difficult questions remain unanswered, not the least of which is the mechanism operating over the transformation of acute to chronic pain. At present, we have no integrated view of the dynamics of the entire pain system; advances in functional neuroimaging will help remedy this shortcoming by simultaneously imaging the brain, brainstem and spinal cord during states of pain. Insights into the complex mechanism of pain neuroplasticity will be a vital link in understanding acute and chronic pain, as it appears to generate and maintain the perception of pain. There are multiple mechanisms underlying placebo analgesia, clarification of their role could enhance the use of placebo as a therapy. Increased understanding of CNS nociceptive processing and pain perception will continue to evolve, buoyed by the significant contributions from breakthroughs in modern research techniques ranging from neuroanatomy, functional neuroimaging and neurorehabilitation. One day, when these and other questions are answered, many will benefit from the advances in knowledge and scholarship acquired through basic and clinical pain research.

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