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Limbically Augmented Pain Syndrome (LAPS): Kindling, Corticolimbic Sensitization, and the Convergence of Affective and Sensory Symptoms in Chronic Pain Disorders

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ABSTRACT

There is abundant clinical evidence that depression occurs with high frequency among chronic pain patients. When compared with other serious medical disorders, the prevalence of depression in chronic pain appears high. The fundamental reason for this association is unknown. Theories have attempted to explain the link between pain and depression in terms of psychologic mechanisms. Other theories highlight shared neurobiologic substrates. However, a comprehensive theory integrating biologic and psychologic viewpoints remains elusive. In this article, we draw on research on neuroplastic processes in corticolimbic structures to model the linkage between the sensory and affective domains of pain. Our hypothesis is based on kindling experiments in animals that elucidate the complex neurobiologic mechanisms that transduce exteroceptive and interoceptive stimuli into "memory" at the cellular/synaptic level. This experimental model has found application in the affective disorders to explain how a person's history of exposure to psychologic trauma configures the neurobiologic substrate for later-amplified pathologic response. In applying kindling research to pain, we begin by reviewing the literature on nociception-induced neuroplasticity at the corticolimbic level. We suggest that kindling and related models of neuroplasticity can be used to describe ways in which exposure to a noxious stimulus may, under certain conditions, lead to a sensitized corticolimbic state. This sensitized state can be described in terms of the kindling properties of amplification, spontaneity, neuroanatomic spreading, and cross-sensitization. A case example illustrates how these properties offer a neurobiologic framework for understanding the sensory/affective/behavioral symptom complex seen in a subset of chronic pain patients. These patients are characterized by atypical and treatment-refractory pain complaints, in association with disturbances of mood, sleep, energy, libido, memory/concentration, behavior, and stress intolerance. We introduce the term "limbically augmented pain syndrome" to describe this symptom complex.

Key Words. Chronic pain; Depression; Kindling; Limbic system; Neuronal plasticity; Theory; Sensitization

Toward a Biopsychosocial Model of Chronic Pain Disorders

The neuroanatomy and neurophysiology of nociception in the peripheral nervous system and spinal cord have been explicated in exquisite detail. The Gate Control Theory proposed by Melzack and Wall in 1965 opened the door to understanding the role of the central nervous system (CNS) in the modulation of nociception, primarily at the spinal level [1]. Numerous other investigators subsequently expanded our knowledge of the bidirectional facilitatory and inhibitory processes responsible for hyperalgesia, allodynia, the pathologic involvement of the sympathetic nervous system in various pain states, and the persistence of pain after the reduction or cessation of activity in

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nociceptive afferents [2]. In addition, increasing attention has been directed to supraspinal structures and processes involved in the perception and modulation of nociception [3]. With the aid of techniques such as positron emission tomography, microdialysis, "knockout" models, and single neuron-recording techniques, remarkable inroads have been made in recent years to explore the brain, particularly the limbic system and somatosensory cortex, and its role in the experience of pain.

Although the response of acute pain to current treatments is reasonably satisfactory, the suffering of patients with chronic pain all too frequently yields little to analgesic therapies. Regardless of the body region involved or the pathophysiologic process implicated, a subset of patients with persistent benign pain tax our diagnostic schemata and fail to respond to therapeutic interventions directed at specific nociceptive generators. Furthermore, these patients commonly experience a diverse array of associated symptoms that include depression, behavioral dysfunction, and heightened sensitivity to internal and external stimuli, and are refractory to treatments that have proven efficacy for acute pain. What is responsible for this multifaceted symptom complex? What has gone awry with homeostatic control in these patients? How are advances in neurobiology applicable to this compelling clinical problem?

Remarkable advances have been made in recent years to elucidate the neuroplastic processes that transduce interoceptive and exteroceptive stimuli into cellular memory. Neuroplasticity has been studied utilizing models of kindling, partial kindling, long-term potentiation (LTP), long-term depression (LTD), behavioral sensitization, and time-dependent sensitization (TDS). In this study, we refer collectively to these related neurophysiologic processes by the term *kindling*. *Kindling* is used as a generic term that refers to a set of stimulus-induced neuroplastic mechanisms that modify neuronal membrane functions, intracellular messenger systems, synaptic activity, and the microscopic neuroanatomy of the CNS. Kindling (without italics) refers to a specific type of stimulus augmentation phenomenon that induces seizures and is described in more detail later. Post and Weiss [4], Racine et al. [5], Gilbert [6], and others have used *kindling* experiments in animal models to investigate the complex neurophysiology of sensitization and its effects on behavior. In these experiments, an organism's previous experience with a stimulus and the environmental context in which the stimulus occurs are among the determining factors of the augmented response. We suggest that *kindling* is a cogent model for nociception-induced neuroplastic changes that can develop in the limbic system and other supraspinal structures (i.e., corticolimbic sensitization) and can produce a clinical picture of persistent pain, affective dysregulation, and behavioral disturbance.

Clinical observations and neurobiologic evidence suggest that nociception/chronic pain disorders and emotion/affective disorders have important similarities in clinical phenomenology, pharmacologic treatments, and neuroanatomic loci and in their molecular substrates. *Kindling* mechanisms have been considered in the pathophysiology of migraine [7], trigeminal neuralgia [8] and other painful conditions [9]. *Kindling* also has been applied in recurrent depression [10,11], bipolar illness [4,12], post-traumatic stress disorder [13,14], multiple-chemical sensitivity syndrome [15,16], and drug addiction [17–19].

This study posits a hypothesis that integrates *kindling* research with theories about the relationship between pain and affect. Prevailing theories have largely attended to short-term, state-related aspects of this relationship. The enduring affective symptoms that afflict a substantial subgroup of chronic pain patients have not been well described at the neurobiologic level, notwithstanding the extensive clinical and epidemiologic literature that has documented these comorbidities. The concept of a limbically augmented pain syndrome (LAPS) is introduced as the clinical manifestation of corticolimbic sensitization induced by *kindling* mechanisms in supraspinal structures that subserve both nociceptive processing and affective regulation. The LAPS hypothesis, although framed with reference to the shared neurobiologic substrate of nociception and emotion, should not be construed as biologic reductionism. On the contrary, the psychologic and learning principles applicable at higher orders of behavioral analysis still apply. A wealth of chronic pain literature leaves no doubt as to the importance of these factors. The argument simply states that we now have a neurobiologic model to describe these principles at lower orders of analysis. This basis in neurobiology, which has not been well developed in prevailing theories of the psychology of chronic pain, offers fertile ground for refining our clinical impressions within a framework that lends itself to testable hypotheses.

The LAPS profile

An estimated 30% to 50% of clinic-based chronic pain patients suffer from major depressive disorder [20]. When other affective spectrum disorders are included (e.g., anxiety disorders, subacute depression), estimates of psychiatric comorbidity are con-

siderably higher [21]. There can be little question that the causes of emotional disturbance in chronic pain are multiple and the forms that emotional disturbance may take are diverse and run the gamut of severity. However, the LAPS construct outlined in this study refers specifically to the distal end of the spectrum of chronic pain patients who have psychiatric comorbidity—patients whose history, clinical presentation, and treatment course reveal a complex linkage between the sensory and affective domains of their illness.

One difficulty in describing the LAPS construct is that there are, as yet, no pathognomonic markers of this putative syndrome. Functional neuroimaging and other new techniques may eventually identify the presence of corticolimbic sensitization. Lacking such markers, we must proceed by describing the clinical features of these patients and then check the goodness-of-fit of this hypothesis. The distinguishing features of LAPS, as we conceptualize it, include (in the prototypic case) alterations in pain perception that are chronic, often atypical, and resistant to analgesic treatments in association with disturbances of mood, sleep, energy, libido, memory/concentration, behavior, and stress intolerance. The recognition of this cluster of symptoms is far from new. Such patients tend to gravitate to pain clinics and have been written about extensively [22–24]. It is the etiologic interpretation of this symptom complex that has been debated, not that there is a subpopulation of such patients [25]. The illustrative case history below helps to identify the subgroup of chronic pain patients of interest to this discussion.

Case history

A 42-year-old woman entered a multidisciplinary pain clinic with a 3-year history of right lower extremity pain that began as a soft-tissue injury to the foot. Over several months after the initial injury, symptoms of a complex regional pain syndrome (CRPS) began to emerge and included features of allodynia, hyperalgesia, and skin and temperature changes. She complained of a severe, burning, dysesthetic pain, with swelling and weakness in the affected extremity and described generalized activity intolerance and frequent pain flares with and without identifiable triggers. Her medical history included juvenile-onset migraine, with chronic daily headache during much of the last 5 years. Psychiatric history was positive for at least 3 previous episodes of major depression with intercurrent dysthymia. Her developmental history was traumatic, primarily because of a depressed, alcoholic, and abusive father. Various treatments had been tried, including physical therapy, nonsteroidal anti-inflammatory drugs, sympathetic blockade, opioid analgesics, α-adrenergic antagonists, gabapentin, cognitive-behavioral therapy, and tricyclic and serotonergic antidepressants. Her response to treatment had been evanescent at best; nothing provided sustained relief. Over the course of her illness, she had complaints of dysphoria, anhedonia, memory and concentration disturbance, severe insomnia, fatigue, and loss of initiative, which often coincided with flares of pain. Her pain complaints have spread to the opposite leg and right hand and arm.

Pain Pathways, Pain Sensation, and Affect

Medial and lateral pain systems

There is a well-established rationale for dividing the pain system into two distinct processing networks: (1) the lateral pain system (involved in localization and sensory discrimination of painful stimuli), and (2) the medial pain system (involved in affective-motivational responses to painful stimuli) [26–28]. The lateral and medial pain systems are defined, in part, on the basis of the divergence of spinothalamic projections in the thalamus. Spinothalamic projections in the lateral system synapse in the ventral posterolateral and ventral posteromedial thalamic nuclei. Thalamocortical projections then carry nociceptor-derived information to primary and secondary somatosensory cortices [29]. Supraspinal neurons within the lateral pain system are nearly always contralateral to the stimulus and are somatotopically organized [26].

The medial pain system, which is of principal interest for the LAPS hypothesis, encompasses spinoreticular and spinothalamic projections to various brainstem nuclei (including the periaqueductal gray matter, the locus ceruleus, and the raphe nuclei) and to medial thalamic nuclei (including the parafascicular and centrolateral nuclei) [26]. Thalamic and extrathalamic pathways then carry nociceptor-derived signals to limbic and paralimbic regions and continue rostrally through projections to prefrontal and motor cortices. Giesler et al. [30], using electrophysiologic tracing methods in rats, have demonstrated direct and indirect (polysynaptic) nociceptor-responsive projections to key limbic and basal ganglia structures, including the hypothalamus, central nucleus of the amygdala, nucleus accumbens, infralimbic cortex, ventral pallidum, and globus pallidus. According to Vogt et al. [26], receptive fields of the neurons of the medial system tend to be large and may include one side of the body or the entire body surface and may be both ipsilateral and contralateral. The medial pain system has limited somatotopic organization. Definitional issues and the com-

plicated reciprocal innervations among cerebral structures blur a precise anatomic and functional separation of the lateral and medial systems [31]. Nevertheless, this dichotomy is relevant because it appears that medial pain pathways provide emotional coloration to painful stimuli, thereby regulating the strength of arousal and response behaviors [32].

The Relationship between the Sensory-Discriminative and Affective-Motivational Dimensions of Pain

The functional relationship between the sensory-discriminative (lateral) and affective-motivational (medial) dimensions of pain is multifaceted and is of central importance to the LAPS hypothesis. Price and Harkins [33] addressed this issue by proposing a 2-stage model of pain affect (Figure 1). They identified a first component (primary pain affect) that is linked directly to the sensory-discriminative dimension of pain. A painful sensory event gives rise simultaneously to an awareness that has the affective valence "unpleasant," which at times can be unbearably intense. This unpleasant affect is generated in medial pain pathways that include limbic and paralimbic structures, which provide the aversive emotional coloration [26,34]. Associated with this affect is a complex cascade of interrelated neuroendocrine and autonomic processes that mediate the stress response and catalyze fearfulness, vigilance, and avoidance behaviors [35–37]. The second component (secondary pain affect) in the 2-stage model involves affective/cognitive responses that are triggered by the composite (primary) unpleasant sensory event. The second stage incorporates the attributions and meanings associated with the pain experience. Through feedback mechanisms, secondary pain affect recalibrates the primary unpleasant affect, which continues in an iterative fashion. The neuroanatomic circuits of secondary pain affect are widely distributed throughout the brain and have not been well characterized. The location of this integrative activity is thought to include polymodal association cortices and paralimbic regions (i.e., cingulate and parahippocampal gyri). Rainville et al. [38] identified the anterior cingulate gyrus as a cortical locus in which pain affect is recorded. These cerebral regions are in a downstream position to receive processed nociceptive input from primary and secondary somatosensory cortices and to integrate it with other sensory modalities and higher-level cognition [39]. In these brain regions, thoughts, feelings, and mnemonic associations triggered by pain merge seamlessly with sensation itself, thus forming a conscious awareness of the multifaceted state of pain.

Gracely [40] has modified the 2-stage model of Price and Harkins [33] by suggesting another layer: pain-unrelated affect. This refers to the general affective state of the person apart from the pain experience. Gracely also developed the concept of the "affective processor" that functions as an amplifier of affective outflow, analogous to a gain control mechanism. In Gracely's view, gain control is calibrated by emotional and cognitive factors such as anxiety, "catastrophizing," or, conversely, hypnotic suggestion. Gain control is considered to be a factor in all 3 forms of pain affect: (1) primary pain affect ("unpleasantness"), (2) secondary pain affect, and (3) pain-unrelated affect. It is in these gain control mechanisms that neuroplastic processes such as *kindling* would exert their influence. *Kindling* is, in effect, a form of gain control. Through encoding at the level of gene expression, *kindling* induces a lasting set of changes in responsivity to particular types of stimuli [41]. Unlike primary pain affect, which is a universal and immediate response to activation of peripheral nociceptors, *kindling*-induced changes in gain control mechanisms are acquired over time in a subset of persons as a function of a complex set of stimulus variables in interaction with hereditary vulnerabilities [11]. Thus, the *kindling* hypothesis of corticolimbic sensitization can provide a neurobiologic explanation for the clinical observation that patients with a history of emotional trauma and/or illness are at greater risk for developing the complex pain syndrome that we term LAPS [42].

Gracely's model identifies gain control mechanisms in the affective-motivational (i.e., medial) dimension of pain. The symptom complex of LAPS, however, also encompasses perturbations in the sensory-discriminative (i.e., lateral) dimension of pain in addition to disturbances of pain affect. We and many other authors have noted that patients with the LAPS constellation of symptoms tend to report atypical sensory phenomena that defy both conventional neuroanatomic distribution patterns and the expected relationship to peripheral nociceptive generators [43,44]. On this clinical evidence, it would seem reasonable to assume that supraspinal neuroplastic changes would encompass gain mechanisms within sensory-discriminative pathways. There also is substantial experimental support for this view based on research in both animals and humans [45–47]. Therefore, in Figure 1 we have included a gain mechanism within the sensory pain pathway that projects from the ventral poster-

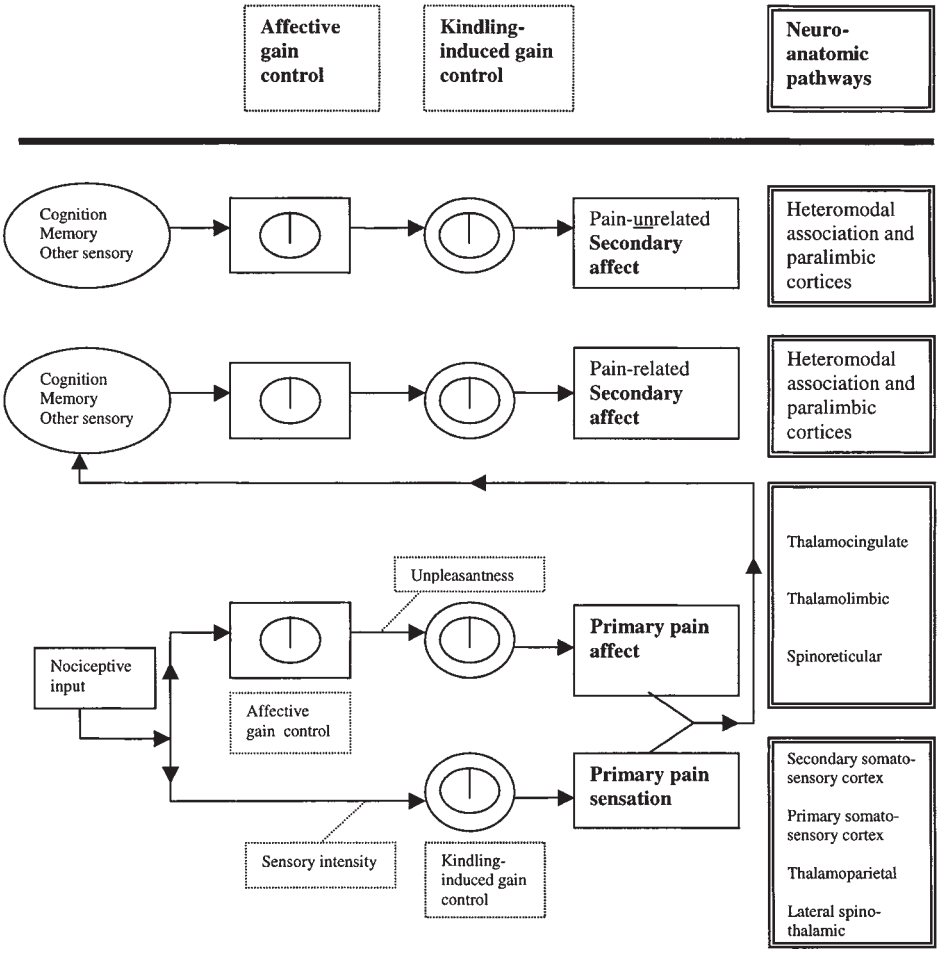

Figure 1 Gain control mechanisms in affective and sensory pathways. Primary pain affect (unpleasantness) is derived from the output of an affective gain control mechanism that receives input from ascending nociceptive afferents. Primary level affective gain control is calibrated by descending modulatory fibers and is influenced by secondary level affect and cognitions. *Kindling*-induced gain control is an acquired state that results from exposure to certain temporal patterns of stimulation and may amplify the intensity of both primary level affect and primary level sensation. The composite sensory and affective output at the primary level then ascends through higher level corticolimbic regions where it undergoes integration with cognitive, mnemonic, and non-nociceptive sensory information to produce secondary pain-related affect. Secondary level (heteromodal) integration may include two additional layers of gain control: affective gain control and *kindling*-induced gain control. A third form of affect, pain-unrelated secondary affect, also includes both forms of gain control and reflects the general emotional state of the individual. (Modified from Gracely [40]. By permission of the American Pain Society.)

olateral and ventral posteromedial thalamic nuclei to primary and secondary somatosensory cortices.

Nociception, Neuroplasticity, and *Kindling*

Kindling *Models of Neuroplasticity*

In 1949, Hebb [48] proposed that the efficiency of communication between a presynaptic and a postsynaptic neuron would increase if both cells fired at the same time. The kindling phenomenon itself was described initially by Goddard et al. [49], who used repeated subthreshold electrical stimulation of the amygdala to induce seizure activity in rats. Limbic structures are particularly susceptible to kindling and related sensitization mechanisms, although other brain structures can also be kindled [6]. Neocortical and limbic sites show different behavioral manifestations of kindling, but not all involve ictal discharge. These include persistent memory disturbance, impaired passive avoidance learning, disturbances of conditioned emotional responses, and explosive defensive reactions to mild provocation [6]. Subsequent research has shown that kindling can also be induced by (1) various pharmacologic agents, including stimulants such as cocaine and amphetamine; (2) endogenous opioid peptides such as β-endorphin and

enkephalin; (3) local anesthetics such as lidocaine, cholinergic agonists, γ-aminobutyric acid antagonists, corticotropin-releasing hormone; and (4) pesticides (see Racine et al. [5] for a review).

In the standard induction model, electrical kindling of the amygdala progresses through 3 distinct phases, as reviewed by Post and Silberstein [7]. The development phase is characterized by progressive amplification of focal afterdischarge activity in response to subthreshold electrical stimulation, culminating in a generalized seizure. The completed phase is defined by reliable elicitation of seizures from each stimulation. In the spontaneous phase, seizures occur in the absence of exogenous stimulation. Once kindled to spontaneity, an animal may remain in a permanent state of increased susceptibility to seizures. In the early phase of kindling, epileptic discharges are confined to the stimulated region. However, in later stages neuroanatomic spreading occurs and results in the propagation of seizure activity to other limbic and cortical regions apart from the stimulated focus [5,6,49]. Neuroanatomic spreading may, at times, follow a mirroring pattern in the opposite hemisphere [7]. Kindled limbic structures may also display an evolution of epileptic excitability so that seizures may be triggered by alternate (nonelectrical) forms of stimulation. This phenomenon is termed cross-sensitization and has been demonstrated to occur among electrical, chemical, and other environmental stimuli [50].

Once kindled, the organism is susceptible to seizures from otherwise nonconvulsive drugs such as morphine [51]. Of particular interest for this discussion is evidence that inherently nonconvulsive stimuli such as physical handling of the animal may trigger seizures in the kindled animal [52,53]. This indicates that cross-sensitization extends to psychosocial stressors. As we discuss below, this finding provides a neurobiologic framework for conceptualizing the linkage between psychosocial stressors and chronic pain.

Kindling, partial kindling, LTP, LTD, behavioral sensitization, and TDS are related but not identical mechanisms of neuroplasticity [5,54–57]. An animal can become either kindled or sensitized with cocaine, for example, depending on the particular dosage and timing schedule used in the protocol [15,58]. In contrast to kindling, behavioral sensitization, TDS, and LTP do not have convulsive end points, although they do produce a range of measurable neurophysiologic and behavioral alterations. For this reason, behavioral sensitization, TDS, and LTP are viewed as models of neuroplasticity that have greater applicability in nonconvulsive conditions [59]. All these models share the premise that a neurobiologic mechanism or set of mechanisms that occur preferentially within the limbic system serve as an amplifier for biologic reactivity to repetitive/low-intensity stimuli.

Behavioral sensitization can be produced by repeated exposure to environmental stimuli or a chemical agent such as a psychomotor stimulant. As noted by Weiss and Post [60], these behavioral phenomena are observed with repeated exposure to a stimulus: (1) shorter latency and increased magnitude of response (sensitization); (2) effects are dose-related and persist for weeks or months; (3) intermittent stimulus administration facilitates sensitization and continuous administration inhibits it; (4) genetic factors may influence sensitization; (5) sensitization is highly context-dependent and conditionable; and (6) cross-sensitization occurs between various stimuli. TDS can be considered a subtype of behavioral sensitization [61]. It is characterized by the fact that it can be induced following a 1-time exposure to a stimulus (and for this reason has been used as a model for post-traumatic stress disorder), provided enough time has passed between the initial exposure and subsequent re-presentation of the stimulus. In fact, in all these *kindling* models, the elapsed time is critical to the induction process [62].

Supraspinal nociception-induced neuroplasticity

The CNS is never static; it is continually adapting in response to changing internal and external environments. With regard to nociception, clinical and experimental evidence support an understanding of pain as a dynamic process in which the qualities of afferent input to the CNS configure the sensitivity of central sensory operations. It appears that some form of sensitization in response to noxious stimulation can occur at multiple levels in the neuraxis. The mechanisms of neuroplasticity that underlie changes in first- and second-order afferents have been characterized by Dubner and Ruda [63], Willis and Westlund [64], Woolf and Chong [65] and others. The interested reader is also referred to Coderre et al. [2] for further discussion of these complex molecular and cellular processes.

There are parallels between neuroplastic changes that occur in the spinal cord in response to nociception (i.e., windup and central sensitization) and neuroplastic changes in supraspinal structures that are modeled by *kindling* (i.e., corticolimbic sensitization). In the *kindling* model, corticolimbic sensitization is an acquired state that is configured by the person's previous experience of pain and affective distress. The similarities among neuroplastic processes at different levels of the CNS—and across species—are underscored by the fact that windup,

central (spinal) sensitization, and corticolimbic sensitization share molecular mechanisms, including mediation by the N-methyl-D-aspartate (NMDA) receptor [66]. LeDoux [67] addressed this point by stating that "[d]ifferent forms of (plasticity) are not necessarily distinguishable at the level of molecular events, but instead obtain their unique properties by way of the circuits of which they are a part."

There is abundant evidence that nociception-induced neuroplasticity occurs within third-order corticolimbic neurons. At this level of the CNS, however, the processes involved appear exponentially more complex, as suggested by recent research demonstrating region-specific forms of plasticity [68] and plasticity that is influenced by priming effects ("metaplasticity") [69]. In animal experiments, nociception-induced plasticity has been demonstrated in somatosensory cortex [70], thalamus [71], trigeminal brainstem neurons [72], and the limbic system [73]. The research of Vaccarino and Melzack [73] is of particular interest because it identifies specific structures in the limbic system that show memory-like mechanisms of plasticity as a result of previous exposure to a noxious stimulus. Vaccarino and Melzack [73] concluded:

> Sensory stimuli act on neural systems which are continually changing and modified by past experiences, and the behavioural output is, in part, dependent upon the memory of these prior events . . . . Long-term potentiation (LTP) has been well documented in the hippocampus and provides a possible mechanism for producing such long-lasting synaptic modifications (page 268)

Neuroplastic changes have been reported in the somatosensory thalamus of patients with denervation injuries. These neuronal changes include high rates of spontaneous firing, abnormal bursting activity, and evoked responses to stimulation of body areas that normally do not activate these thalamic neurons [2]. Plasticity in the cortical homunculus has been demonstrated in human phantom limb pain and central pain syndromes [46,47]. Flor et al. [74] found a strong positive relationship between the amount of somatosensory cortical reorganization that occurred after unilateral amputation and the intensity of phantom pain. They proposed that remodeling of the functional architecture of the cortex after damage to the nervous system could serve as an adaptive compensatory mechanism by restoring activity in a zone deprived of afferent input. They also suggested that phantom limb pain might represent dysfunction in this compensatory mechanism, possibly related to a lasting hyperexcitability of nociceptive pathways induced by previous pain. Coderre et al. [2], in a review of neuroplasticity in pathologic pain, concluded from numerous case reports that past pain may be reactivated years after the original injury, in some cases by a peripheral trigger that provides the required input to activate neural structures subserving the memory trace. Birbaumer et al. [75] compared the amplitude of pain-evoked potentials in chronic pain patients to nonpain controls using electroencephalographic and magnetoencephalographic mapping of the centroparietal region. Controls demonstrated a graded increase in wave amplitude according to whether the stimulus was below or above pain threshold. In contrast, pain patients showed similarly high-wave amplitudes with both stimulus conditions. This result and related findings [76] were interpreted to reflect widespread and probably permanent changes in responsiveness in primary somatosensory cortex. Melzack [77] has proposed an overarching construct that he has termed the "neuromatrix" and has described how disruptions in the integrity of the neuromatrix can account for symptoms such as phantom limb pain.

Electrical stimulation of subthalamic, thalamic, and capsular regions has been shown to reproduce pain in patients with neuropathic conditions [78,79]. Lenz and colleagues [80] have proposed that deep brain stimulation in a region of the somatosensory thalamus reproduces pain with strong affective loading only in patients who had previously experienced such affectively charged pain. Stimulation of the same brain region in patients without a history of affectively charged pain evoked a sensory pain experience that was apparently free of emotional coloration. Lenz et al. [80] proposed that the pathways mediating sensory-limbic memory project from the nucleus ventralis caudalis to secondary somatosensory and insular cortices and then engage limbic structures (i.e., hippocampus and amygdala), which confer emotional coloration. This report, based on a series of three patients, is relevant to the *kindling* model for several reasons. It underscores a fundamental premise of the *kindling* model: that a person's previous pain history configures the substrate for later pain experiences. It also suggests that learned associations linking substantially separate sensory and affective pathways are formed in such a way as to be reproduced as an ensemble (i.e., a composite of sensation, affect, and cognition) by stimulation of a single brain region.

It is now well established in syndromes such as thalamic pain, phantom limb, and deafferentation pain that pathologic changes in sensory processing occur not only at the spinal level but also in supraspinal structures [81]. This recognition has been facilitated by functional neuroimaging research, which has identified a fairly consistent pattern of alterations in regional cerebral blood flow (rCBF) in

the anterior cingulate cortex, insula, thalamus, primary and secondary somatosensory cortices, and prefrontal cortex [28,82–84]. A similar pattern of rCBF disturbance is observed in patients with major depressive illness without pain [85–87].

The Effects of Pain, Stress, and *Kindling* on Gene Transcription in Corticolimbic Structures

The measurement of the proto-oncogene c-*fos* and other immediate early genes and transcription factors serves as a marker for activity within nociceptive pathways [88]. In general, the expression of c-*fos* and related transcriptional factors can be understood as one element in a complex neurobiologic cascade whose end point is the transduction of internal and external stimuli into cellular "memory" [89]. Although the mechanisms of transduction are not well understood, especially with regard to when and how neuronal modifications become permanent memory traces, the mapping of c-*fos* is useful in this discussion as additional evidence that numerous limbic and paralimbic structures are engaged in nociceptive processing.

Nociception-induced c-*fos* immunoreactivity has been observed in rats in these limbic and interconnected cortical and brainstem regions: (1) cingulate, retrosplenial, insular, perirhinal, and entorhinal cortices; (2) periaqueductal gray matter; (3) locus ceruleus; (4) several thalamic nuclei; (5) lateral septal area; (6) dorsomedial hypothalamus; and (7) amygdala [88–91]. The correlation between the number of cells expressing c-*fos* and pain behavior is strong [92]. Furthermore, it is of particular interest that many of these same regions show c-*fos* expression in response to stressors other than nociception. For example, Matsuda et al. [93] have shown that rats exposed to species-specific intermale aggression on a chronic but not acute basis showed lasting c-*fos* expression in cingulate cortex, hippocampus, hypothalamus, septal nuclei, amygdaloid complex, central gray matter, and raphe nuclei. This suggests that both pain and social stress may selectively engage some of the same corticolimbic pathways and induce similar gene transcription factors.

Kindling induces c-*fos* expression in many of the same limbic regions where it is also induced by nociception and social stress [94–96]. In addition to c-*fos* expression, with *kindling* there are also effects on neuropeptides, including somatostatin, thyrotropin-releasing hormone, enkephalin, corticotropin-releasing hormone, and a long-term decrease in dynorphin [88]. The full significance of these overlapping neuroanatomic and neurochemical findings awaits further study. However, current evidence raises provocative questions about shared mechanisms and pathways for pain, psychosocial stress, and *kindling*. This is the neurobiologic foundation of the LAPS hypothesis presented in this article.

Kindling and Illness

Kindling *as a model for human neurobehavioral syndromes*

Kindling, behavioral sensitization, and related models of neuroplasticity have had considerable theoretical and clinical appeal for investigators struggling to comprehend the complex biopsychosocial interactions that underlie various human neurobehavioral syndromes. Among the conditions to which these models have been applied are major depression [10,11], bipolar disorder [4,12], post-traumatic stress disorder [13,14], panic disorder [97], multiple-chemical sensitivity syndrome [15,16], epilepsy [50,97], and the addictive disorders [18,19]. The appeal of *kindling* models has to do with several conceptual and practical issues. First, *kindling* offers a neurobiologic model for investigating the mechanisms and pathways that mediate the relationship between the organism and its environment. Second, *kindling* can be studied in laboratory animals, with the ability to control environmental contingencies while investigating neurobiologic substrates through techniques such as labeling of c-*fos* [90]. Third, it has been used to study neuropharmacology, specifically issues such as drug efficacy and tolerance, in relation to the spatiotemporal cascade of intracellular messenger systems. This has proven especially useful in developing alternative pharmacologic treatments for bipolar disorder [98,99]. Fourth, there is both theoretical and experimental support for the idea that the mechanisms underlying neuroplasticity evolve from certain basic neurophysiologic building blocks and, as such, may be independent of location in the CNS and even the animal species being studied [54,57]. In this regard, Kandel [100] has noted that the plasticity of neurons is derived from the properties of specific proteins such as the NMDA receptor and adenylyl cyclase, which are common to neurons throughout the CNS. Kandel has proposed that there is a "molecular alphabet" for learning, whereby simpler forms of plasticity represent elements of more complex forms. It is on this basis that we draw parallels between nociception-induced sensitization at the spinal level and sensitization in corticolimbic pain pathways.

It must be kept in mind that kindling is a nonhomologous model for all the conditions cited above (with the possible exception of epilepsy). The end

point of seizure does not correspond to mood swings, drug craving, or chronic pain. The amplification of the pain experience in LAPS is more closely modeled by behavioral sensitization, where the end point is not seizure but increased behavioral response to the same stimulus. It has been demonstrated that trains of nociceptive stimuli induce neuroplastic changes at the corticolimbic level, but it is an open question whether *kindling* and related models are responsible for the pathophysiology and associated psychopathology of certain chronic pain disorders. In a general sense, the significance of *kindling* mechanisms as a model for human neurobehavioral syndromes is not a 1-to-1 correspondence with animal models. Rather, its significance is as a window on the mechanisms of neuroplasticity at molecular and behavioral levels. *Kindling* research delineates a set of properties that help organize our thinking about the neurobiologic substrate of complex human behaviors [60]. To this end, we have included the diagram from Post and Silberstein [7] about how transient stimuli initiate an intracellular cascade, thereby creating a lasting neuronal "memory" (Figure 2).

Kindling *and clinical pain disorders*

Post and Silberstein [7] have used *kindling* to model syndrome evolution in a subgroup of headache patients with comorbid affective illness, who experience migraine transformation and drug tolerance. In applying this model, the authors highlight clinical evidence of comorbidity among patients with migraine and affective illness and, despite obvious differences in symptoms, identify points of overlap in terms of the paroxysmal nature of the disorders and shared drug treatments (e.g., anticonvulsants, antidepressants). Two points are of particular interest: first, there is evidence that patients with migraine and affective illness show increased vulnerability to stress; and second, both disorders tend to progress from infrequent, discrete episodes to more frequent recurrences and even constancy (i.e., transformed migraine and intercurrent dysthymia).

Pagni [8] has hypothesized that trigeminal neural-

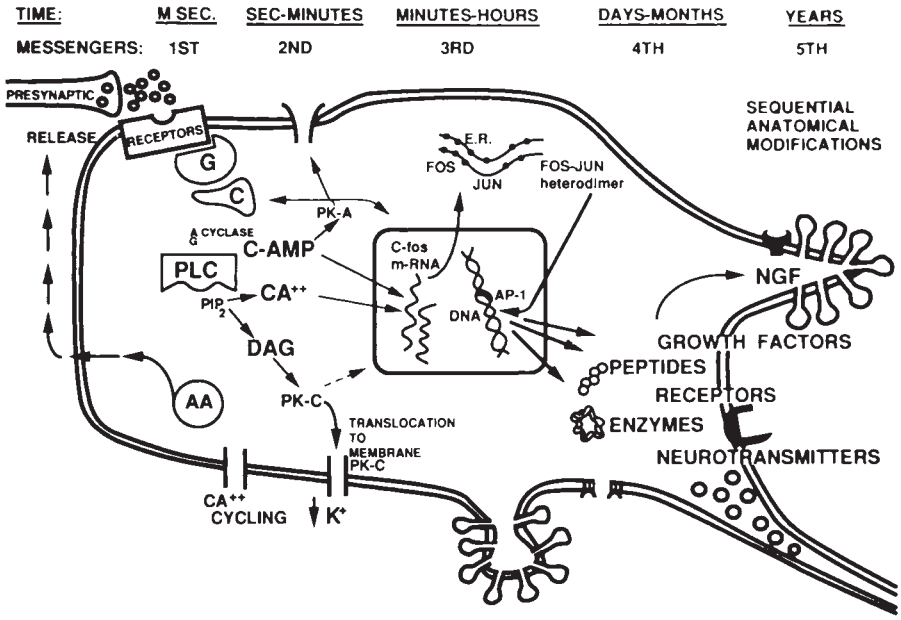

Figure 2 The schematic illustrates how transient synaptic events induced by external or internal stimuli can exert longer-lasting effects on neuronal excitability and microstructure of the brain via a cascade of effects involving alterations in gene transcription. The evolution of the neuronal "memory trace" occurs over a time course starting with microseconds for changes to occur within the first messenger system (i.e., neurotransmitters activating receptors), to seconds, minutes, and hours for immediate early genes (i.e., c-*fos* and c-*jun*) to bind to DNA to further alter transcription of late effector genes. In turn, late-effector genes can initiate a sequence of anatomical modifications that may take months or years to transpire (denoted as 4th and 5th messenger systems), which result in a state of enduring neuronal excitability that we have termed "corticolimbic sensitization." PLC, phospholipase C; PIP_2, phosphatidyl inositol 4,5-biphosphate; AA, arachidonic acid; DAG, diacylglycerol; PK-C, protein kinase C; AP-1, activator protein 1 [binding site on DNA]; ER, endoplasmic reticulum; PK-A, protein kinase A; NGF, nerve growth factor. (Reproduced with permission from Advanstar Communications, Inc., as reprinted from *Neurology*, October 1994, vol. 44, number 10, supplement 7, page S41. *Neurology* is a registered trademark of the American Academy of Neurology.)

gia may be a form of kindled sensory reflex epilepsy. He proposed that chronic root or nerve damage

> . . . provokes an exaggerated afferent barrage owing to ectopic generation of impulses with repetitive firing at the site of chronic injury . . . . Bombardment over long periods of time by such exaggerated barrage might promote modifications of the excitability and activity of the trigeminal nucleus cells just as chronic subthreshold stimuli applied to a discrete area of cortical or subcortical gray matter provokes epileptiform activity (Goddard's epileptic 'kindling') [49, pages 189, 190].

Sramka et al. [9] reported a single case of a patient with phantom pain in a traumatically amputated hand. Therapeutic deep brain stimulation in the area of the central medialis and dorsal medialis nuclei of the thalamus precipitated "mild jerks" that progressed over time to generalized seizures. This complication was compared to the kindling phenomenon described by Goddard.

Post and Silberstein [7] proposed that the excitatory amino acid–mediated cascade giving rise to chronic neuropathic pain has features also found in the progression of neurobiologic events in *kindling*. The clinical end points of windup and central (spinal) sensitization are noted to share NMDA receptor–mediated mechanisms with *kindling*, and both processes can be interrupted by NMDA antagonists [66]. The authors point out that there are other homologies involving neurotransmitters, receptors, and gene products that support *kindling* as a heuristic model [7].

The *Kindling* Model of LAPS

The conscious experience of pain

The nexus of cerebral circuitry that gives rise to consciousness of pain—or for that matter, consciousness of any kind—is the subject of much conjecture. Consciousness has been described as an "emergent phenomenon," because it has characteristics that are qualitatively different than those of its constituent parts [101]. Consciousness does not seem to lend itself to localization within any particular cerebral region. Yet it seems safe to assume that consciousness represents some form of superordinate neuropsychologic phenomenon that is based largely in the heteromodal association cortices and paralimbic regions of the frontal, parietal, and temporal lobes [102,103]. With regard to nociception, these regions are the recipients of extensively processed input from lower-level circuits that transmit the sensory data of the pain experience. In the absence of pathologic sensitization, it is in these cortical and paralimbic areas that sensation is merged with other modalities (i.e., affect and cognition) without losing its veridical relationship to an external noxious stimulus. Thus, the conscious experience of pain can have specific sensory features (i.e., quality, intensity, duration, and location) that identify the stimulus, which are accompanied by an unpleasant affective valence (i.e., primary pain affect). Together, these can trigger a mnemonic template that carries with it another affective charge (i.e., secondary pain affect), all at the same time that a person is in the throes of emotionally charged life events such as bereavement, divorce, or litigation (i.e., pain-unrelated affect). Such a seamless set of awarenesses seems to be the essence of consciousness.

Kindling *properties and LAPS*

Kindling provides a model for a process whereby mental events such as sensations, emotions, ideas, associations, suggestion, and reinforcements can influence corticolimbic structures mediating both the somatic and psychologic aspects of pain. The *kindling* properties of amplification, spontaneity, neuroanatomic spreading, and cross-sensitization modify functioning of neural circuits. We will now summarize these properties and their relevance to the sensitized pain state we identify as LAPS.

Amplification. Kindling mechanisms amplify the response to a stimulus based on qualitative, quantitative, and temporal aspects of previous exposure to relevant stimulation. In the standard model of kindling, continued subthreshold stimulation eventually produces a quantum-like increase in response (i.e., the development of seizures). With behavioral sensitization, continued exposure to a stimulus results in a gradual and progressive increase in response (i.e., behavioral hyper-reactivity). *Kindling*-induced amplification at the corticolimbic level is a mechanism that can account for the disproportionate severity of pain in LAPS in relation to peripheral afferent activity.

Spontaneity. Spontaneity refers to the emergence of autonomous (kindled) seizure activity in the absence of stimulation [5]. In the putative syndrome of LAPS, spontaneity explains the evolution of a chronic pain disorder to a centrally driven state that is autonomous from peripheral nociceptive triggers (or absence thereof).

Neuroanatomic spreading. After kindling has been initiated in a limbic structure, lowered seizure thresholds may then develop in adjacent cerebral regions, a recruitment process identified as "neuroanatomic

spreading" [6]. Neuroanatomic spreading helps explain the accretion of symptoms in LAPS, such as the expansion of sensory symptoms beyond dermatomal/myotomal distributions and the development of non-nociceptive symptoms of limbic dysfunction (i.e., disturbances of affect, attention, volition, libido).

Cross-sensitization. After a kindled state is established in an animal, stimuli of novel types may acquire the capacity to induce seizures, a process referred to as "cross-sensitization" [104]. Electrical stimuli may cross-sensitize with chemical stimuli (e.g., endorphins, amphetamine) or environmental stimuli (e.g., handling stress) [52], each of which may then act as a trigger for the end point of seizure. Cross-sensitization is a mechanism by which psychologic stresses (long recognized as playing a pivotal part in the phenomenology of chronic pain disorders) may gain direct access to the circuitry underlying nociception, and vice versa.

These *kindling* properties collectively have the effect of diminishing the organism's ability to perceive accurately the qualities of a peripheral stimulus. Amplification at the spinal level transmits a message to cerebral regions that includes not only information about the activity of peripheral nociceptors, but also additional information contributed by sensitized spinal circuitry. Furthermore, if the amplified message also encounters sensitized supraspinal circuits, the resulting signal to noise ratio (the ratio of the veridical peripheral signal to the centrally driven perception) is proportionately diminished. With spontaneous activity in secondary and tertiary afferent pathways (spontaneity), the organism experiences pain that is exclusively the product of spinal and/or supraspinal processes. Through cross-sensitization, life events that are mental rather than physical can distort the processing of sensory (nociceptive) information, and, conversely, noxious sensory inputs can produce effects in the emotional/cognitive/behavioral domain. The research of Lenz et al. [80], cited previously, provides support for this. Their report provides another illustration that the interwoven neural circuitry of pain and affect is configured by the history of the organism's exposure to both somatic and psychologic stimuli. The *kindling* properties of neuroanatomic spreading and cross-sensitization facilitate linkages among lateral diencephalic and limbic structures, alloying the nociceptive signal with input from affective, other sensory, autonomic, and cognitive/mnemonic categories of information. Thus, the message received at the highest levels, which forms the basis for the conscious experience of pain, is multifaceted and encumbered by distortions that are mediated by sensitization in interconnected neural structures.

Polymodal allodynia and corticolimbic sensitization

Clinical observations suggest that patients with the constellation of symptoms we call LAPS demonstrate a generalized stress hypersensitivity combined with pathologic melding of sensory and affective symptoms. We propose the term "polymodal allodynia" to describe this sensitized state, which is characterized by hyper-reactivity to a broad range of stressors, both physical and psychologic. Polymodal allodynia implies that non-nociceptive stimuli such as physical exertion or a noisy job site may trigger the sensory/behavioral composite of affectively charged pain. This would explain the phenomena of (physical) activity intolerance and vulnerability to psychosocial stressors commonly observed in the LAPS subset of chronic pain patients. In parallel with the kindled animal that may develop seizures as the stereotyped response to diverse types of stimuli, the LAPS constellation of symptoms may be the analogous human behavioral end point in the aftermath of corticolimbic sensitization. Corticolimbic sensitization, as it is used here, refers to the full expression of *kindling* properties in supraspinal structures. The term connotes a sensitized cerebral condition characterized by amplified responses to stimuli, spontaneity (autonomy) of centrally driven processes, the recruitment of additional features through neuroanatomic spreading, and pathologic responsiveness to novel/non-nociceptive stimuli (cross-sensitization).

Exquisite sensitivity to a diverse array of stressors has presented major obstacles to the successful treatment of the patient described in the case history. Each stressful event in her life, whether a disagreement with her spouse, doing too much work in her garden, or worrying about a new swelling sensation in the affected limb is accompanied by a generalized flare in her sensory/affective/behavioral symptom complex. Cerebral processes are known to influence the experience of pain through descending modulatory effects in the dorsal horn of the spinal cord (gate control) [64] and through psychophysiologic reactions such as increased muscle tension [105]. These spinal and psychophysical factors, in concert with supraspinal mechanisms, presumably all contribute to the severity, chronicity, and refractoriness to conventional analgesic treatment of this prototypical patient.

Clinical correlates regarding affective disorders

Identifying what constitutes corticolimbic sensitization in the affective domain is perhaps more problematic than in the sensory domain, in part be-

cause a peripheral or spinal analogue does not exist in the affective domain. There is no mood-related equivalent of a receptive field or a dermatome. Nevertheless, Post et al. [106] and other investigators who have used *kindling* to model affective illness in humans have noted several characteristics of recurrent affective illness that suggest some form of sensitization does occur. They do so, however, with the caveat that, given our present state of knowledge, the only scientifically supportable use for *kindling* is as a model for organizing our thinking about how corticolimbic sensitization might evolve in affective illness. There is no proof that the etiology of recurrent affective illness is linked to *kindling* mechanisms per se [55].

In patients who have recurrent affective illness—major depression, bipolar disorder, post-traumatic stress disorder—the clinical features indicative of sensitization can be conceptualized within an endogenous versus reactive framework. Although this dichotomy has been criticized as being oversimplified, it nevertheless is useful insofar as it identifies a trend toward autonomy of the underlying disease process from environmental precipitants [106]. Since the time of Kraeplin, it has been noted that in the early stages of illness, patients with bipolar disorder seem to experience mood swings that can be linked causally to identifiable external stressors. With the passage of time, however, cycling becomes more frequent and the connection to external stressors becomes less evident. A heightened sensitivity to even minor traumatic events ensues. At the end stage of illness, cycling of mood may occur many times a day without apparent external triggers. Certainly not all patients suffer such an inexorable decline, particularly with psychopharmacologic treatment. Nevertheless, there is a subgroup of patients whose symptoms tend to break through previously effective medication regimens, and in these patients a syndrome of cyclicity and resistance to medication develops.

Complexity and chance

Caring for patients with chronic pain disorders is fraught with complexity. Their distress is multifaceted. There is quite obviously a variable and idiosyncratic relationship between nociceptive events in the periphery and the experience of pain. Clearly, time does not heal all wounds. Any model that would advance our understanding of chronic pain disorders must address this complexity because unidimensional theories of causation of biopsychosocial illnesses invariably lead to oversimplifications.

The value of *kindling* as a model for LAPS lies precisely in its complexity. This complexity is evident in the growing body of animal research that is pertinent to the neurobiology of chronic pain states in humans. For example, c-*fos*–labeling techniques have shown that the same limbic pathways that are activated by nociception may also be activated by psychosocial stressors and by *kindling* processes [93,96]. In another example involving an animal model of learned helplessness, it is possible to discern how environmental contingencies (i.e., the absence of an escape from a noxious stressor) sensitize the hippocampus to increased release of norepinephrine on subsequent presentation of a less intense stimulus [107]. Some forms of neuroplasticity (e.g., behavioral sensitization) illustrate one-trial learning and a dose-dependent relationship between the stimulus and an amplified behavioral response, whereas other forms (e.g., kindling) reflect an abrupt quantum-like alteration in behavior when a stimulus threshold is crossed. The present knowledge of neuroplasticity offers an often bewildering wealth of data regarding the ways in which the environment induces activity-dependent learning at the neuron/synapse. Although daunting, such complexity only increases the appeal of the *kindling* model as a window on the human experience of pain.

Painful illnesses/injuries and stressful life events are ubiquitous. Yet, it is apparent that only a small percentage of the population progresses to the clinical end point of LAPS. Evidently homeostatic mechanisms most often result in the failure of both painful tissue damage and stressful life events to induce enduring sensitization. These clinical observations are supported by evidence from animal experiments that suggests a concatenation of stimulatory events must fall within fairly narrow parameters for kindling to develop. In one example, if electrical stimulation of the amygdala varies significantly from the optimal frequency of once daily at the requisite amplitude, then either kindling does not evolve or inhibition (LTD) is registered [108,109]. This result underscores the point that various amplitudes and frequencies of stimulation may lead to either sensitization or inhibition, and a resulting element of chance is introduced [108]. The development of LAPS, therefore, would seem to be related in part to random events that determine the pattern of noxious stimulation encountered by the person. It is also likely that heredity and gender have some role in creating a diathesis to corticolimbic sensitization [110,111]. Both factors have been shown to influence kindling susceptibility [15,60]. Even in presumed high-risk populations (i.e., persons with a history of recurrent affective illness and/or painful

medical conditions), the relatively infrequent occurrence of LAPS suggests that physical and psychologic trauma usually induce neurobiologic events that ultimately produce a net quenching effect [109]. In mentioning the case history above, we do not intend that LAPS should be construed as referring to a single diagnostic entity such as CRPS [112] or to an invariant type of pathophysiology or preexisting psychopathology. When the vagaries of the environment and the neurobiology of the person interact to configure behavioral outcomes, myriad permutations are possible, as must be the case in the development of the sensitized pain state we identify as LAPS.

Conclusions

The high degree of comorbidity between chronic pain and depressive spectrum disorders has garnered much attention from clinicians, researchers, and theorists over the past several decades. The clinical imperatives of this comorbidity are the basis for the multidisciplinary model that is used in many chronic pain clinics today. Prevailing theories have explained the linkage between the affective, cognitive, and sensory dimensions of pain in several ways: (1) gating mechanisms in the dorsal horn [1] (2) cognitive- and behavioral-mediating factors [113]; (3) psychophysiologic mechanisms such as muscle tension [105]; and (4) shared neurobiologic substrates [32]. The *kindling* model proposes an additional avenue for this linkage through neuroplastic changes, acquired in the course of life experience, that under certain circumstances may lead to a state of corticolimbic sensitization. This avenue has particular relevance for understanding the depressive and behavioral comorbidities that characterize a subgroup of patients with chronic pain. To contribute to the discussion of these issues, we have introduced for heuristic purposes the construct of LAPS.

An understanding of neuroplasticity is key to unraveling the dynamic interactions between mind and body. *Kindling* research offers the most lucid window available on this extraordinarily complex issue. The *kindling* model of corticolimbic sensitization allows us to describe in neurobiologic terms the mechanisms of cellular/synaptic memory that register the ebb and flow of experience. It is in the interplay between cellular/synaptic events and whole organism behavior that *kindling* theory has its true heuristic value. The *kindling* properties of amplification, spontaneity, neuroanatomic spreading, and cross-sensitization offer an intriguing bridge between the realms of "bio" and "psychosocial." Whether *kindling*-related mechanisms per se are operative in the human cerebrum in certain chronic pain states remains to be proven. If they are not, however, *kindling* theory and the putative LAPS syndrome help organize our thinking about complex chronic pain disorders within a framework where variables are defined by neurobiology rather than metapsychology.

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