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Pain and Stress in a Systems Perspective:

Reciprocal Neural, Endocrine and Immune Interactions

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Abstract

This paper advances a psychophysiological systems view of pain in which physical injury, or wounding, generates a complex stress response that extends beyond the nervous system and contributes to the experience of pain. Through a common chemical language comprising neurotransmitters, peptides, endocannabinoids, cytokines and hormones, an ensemble of interdependent nervous, endocrine, and immune processes operates in concert to cope with the injury. These processes act as a single agent and comprise a supersystem. Acute pain in its multiple dimensions, and the related symptoms that commonly occur with it, are products of the supersystem. Chronic pain can develop as a result of unusual stress. Social stressors can compound the stress resulting from a wound or act alone to dysregulate the supersystem. When the supersystem suffers dysregulation, health, function and sense of well-being suffer. Some chronic pain conditions are the product of supersystem dysregulation. Individuals vary and are vulnerable to dysregulation and dysfunction in particular organ systems due to the unique interactions of genetic, epigenetic and environmental factors, as well as the past experiences that characterize each person.

Perspective—Acute tissue injury activates an ensemble of interdependent nervous, endocrine and immune processes that operate in concert and comprise a supersystem. Some chronic pain conditions result from supersystem dysregulation. Individuals vary and are vulnerable to dysregulation due to the unique interactions of genetic, epigenetic and environmental factors, and past experiences that characterize each person. This perspective can potentially assist clinicians in assessing and managing chronic pain patients.

Introduction

Despite parallel advances in neurophysiological and biopsychosocial models of pain, an integrated explanation for chronic pain still eludes us. Conventional understanding holds that acute pain is an unpleasant sensory and affective experience normally associated with injury. It arises from activation of the peripheral nervous system and emerges from complex higher level processing. Chronic pain, in contrast, relates poorly or not at all to a focus of injury and incurs a constellation of related miseries such as fatigue, sleep disturbance, impaired physical and mental function, and depression.

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This paper calls attention to an inconvenient and overlooked fact: any injurious event provokes autonomic, endocrine and immune processes as well as sensory signaling. These processes interact and collectively comprise a defensive biological response to injury. Because the interactions of sensory, autonomic, endocrine and immune responses to tissue injury are complex and adaptive, a systems approach can advance understanding and engage difficult questions such as how pain becomes chronic.

The organization of this paper is as follows. We begin by fitting a complex adaptive systems framework to acute tissue injury, or wounding, and review nervous, endocrine and immune responses to wounding within this framework. To set the stage for a systems model of pain, we review evidence for the cross-communication and feedback interdependence of nervous, endocrine and immune systems. On the basis of this, we postulate that the nervous-endocrine-immune ensemble constitutes a single overarching system, or supersystem, that responds as a whole to tissue trauma and contributes to the multidimensional subjective experience of pain. This leads to the hypothesis that supersystem dysregulation contributes significantly to chronic pain and related multi-symptom disorders. Finally, we discuss factors that make the individual patient uniquely susceptible to developing a particular pattern of chronic pain.

Fundamental Concepts

Systems Perspective

A human being is an open, living, adaptive system that pursues the dual objectives of adaptation to the environment and survival. The term system denotes a set of components constituting a whole within which each component interacts with or is related to at least one other component, and all components serve a common objective. Every system contains nested subsystems that function as component parts. Nervous, endocrine and immune systems are among the subsystems that comprise the body. These subsystems function interdependently.

All adaptive systems have three essential features. The first is *irritability*: the system is dynamic and responds to perturbations such as tissue injury by moving away from equilibrium to meet the challenge and returning toward equilibrium afterwards. Second, connections and interactions exist among the components of a system; this is its *connectivity*. Through connectivity patterns form and self-regulating feedback occurs. Consequently, the connectivity of a system is more important than the system components themselves. Third, adaptive systems have *plasticity*. They change selectively in response to alterations in the environment, and change is often nonlinear. System theorists describe nonlinear transitions as state or phase shifts. For example, the development of allodynia around a focus of injury is a central state shift in sensory processing. A key aspect of system nonlinearity is that small perturbations can produce large system changes while large perturbations often do not. Other features of adaptive systems include emergence, self-organization, and self-regulation.

Wounds

Pain fosters survival after wounding. A wound is disruption of normal anatomic structure and function¹¹⁴. Wounds result from pathologic processes that begin externally or internally, originating in accidental or intentional trauma or disease. They are normally acute, but may become chronic.

Acute wounds are those that repair themselves in an orderly and timely fashion. Injury disrupts local tissue environment, triggers inflammation, constricts blood vessels, promotes coagulation and stimulates immune response. Sympathetic responses at the wound restrict blood flow. Immediate vasoconstriction temporarily blanches the wound and reduces hemorrhage, fosters platelet aggregation, and keeps healing factors within the wound. Subsequently, a period of vasodilation produces the erythema, edema, and heat observed after tissue injury. C fibers

interact with wounds, by secreting pro-inflammatory peptides and signaling injury. Pro-inflammatory cytokines, neutrophils, macrophages, complement and acute phase proteins generate a systemic *acute phase reaction*^{34, 202} that protects against microbial invasion, and they sensitize the wounded area to protect and promote healing. Acute wound healing entails a series of interrelated cellular and molecular processes that first reestablish the immune barrier violated by traumatic injury and then repair or regenerate lost normal tissue architecture.

Chronic wounds are those that fail to repair themselves in an orderly and timely fashion and remain indefinitely¹¹⁴. The healing process is incomplete and disorganized. Familiar examples include chronic diabetic and pressure ulcers. Local wound environments depend upon myriad systemic factors, particularly those that influence tissue oxygenation such as peripheral venous hypertension. Psychophysiological, emotional arousal increases sympathetic activity systemically through autonomic and endocrine mechanisms, and this may disrupt normal wound healing processes by compromising blood flow. Like cutaneous wounds, musculoskeletal and visceral wounds may fail to heal after injury, persisting as a focus of chronically disorganized, locally inflamed processes that respond maladaptively to systemic changes at the nervous, endocrine and immune levels. Some chronic pain states reflect chronic wounds, but the key concept is persistence of chronic disorganization.

In many chronic cases, the local tissue environment appears to repair itself but sensory processes remain abnormal, creating chronic pain. One hypothesis for this type of chronic pain is failure of the central nervous system processes to “reset” sensitizing adjustments implemented during injury when peripheral tissue complete wound healing. This underscores a second key point: The impact of a wound extends beyond its local tissue environment to its interactions with higher order systems. Incomplete wound healing may involve altered relationships between local tissue and higher order systems.

Defense Response

This term has multiple meanings in the literature, all of which underscore its adaptive function. Here defense response refers to sensory detection and multi-subsystem, self-organizing arousal to tissue injury or threat of tissue injury. Related physiological changes facilitate fight, flight or freezing. Although the defense response can mean the psychophysiological response to wounding, the term incorporates the anticipation of wounding and appraisal of threat. The nervous system plays a strong role in defense by detecting threat in the external environment, cognition (anticipation, appraisal), signaling of incurred tissue injury, and through motor responses geared to escape or fighting. The endocrine system mounts a major physiological arousal response that maximizes the chances for survival; i.e., the stress response. The immune system detects microbial invasion and toxins¹⁶ and initiates complex inflammatory responses that protect against microbial threat and promote wound healing. Thus, the term defense response designates purposeful, coordinated activity in three interdependent subsystems.

Homeostasis, Allostasis and Stress

Homeostasis—Although the term homeostasis commonly connotes adjustment to achieve balance, McEwen asserts that homeostasis strictly applies to a limited set of systems concerned with maintaining the essentials of the internal milieu¹²⁷. The maintenance of homeostasis is the control of internal processes truly necessary for life such as thermoregulation, blood gases, acid base, fluid levels, metabolite levels, and blood pressure. McEwen’s strict distinction means that homeostasis does not contribute to adaptation; rather, adaptation protects homeostasis.

Failure to sustain *homeostasis* is fatal. Generic threats to homeostasis include environmental extremes, extreme physical exertion, depletion of essential resources, abnormal feedback

processes, aging and disease. Environmental perturbations can threaten homeostatic regulation at any time. The stress response exists to sustain homeostasis.

Allostasis and Stress—Three interdependent systems contribute to the preservation of homeostasis when injury occurs: neural, endocrine and immune⁷¹. Adaptive response involves substantial autonomic activity and the connectivity of humoral messenger substances that also serve as mediators and determinants of neural regulatory processes, particularly hormones, neurotransmitters, peptides, endocannabinoids and cytokines. The term for the physiological protective, coordinated, adaptive reaction in the service of homeostasis is *allostasis*^{111, 127}. Allostasis insures that the processes sustaining homeostasis stay within normal range.

Stress is the resource-intensive process of mounting allostatic responses to challenges that occur in the external or internal environment. A *stressor* is any event that elicits a *stress response*. It may be a physical or social event, an invading microorganism, or a signal of tissue trauma. Selye¹⁷⁹ first described this response as a syndrome produced by “diverse noxious agents.” He characterized the stress response as having three stages: alarm reaction, resistance, and if the stressor does not relent, exhaustion. The normal stress responses of everyday life consist of the alarm reaction, resistance and recovery. The primary features of stressors are intensity, duration and frequency. The impact of a stressor is the magnitude of the response it elicits. This impact involves cognitive mediation because it is a function of both the predictability and the controllability of the stressor.

Allostasis is the essence of the stress response because it mobilizes internal resources to meet the challenge that a stressor represents. Stressors may be multimodal and complex or unimodal and simple. When a stressor, such as tissue trauma, persists for a long period of time, or when repeated stressors occur in rapid succession, allostasis may burn resources faster than the body can replenish them. The cost to the body, or burden, of allostatic adjustment, whether in response to extreme acute challenges or to lesser challenges over an extended period of time, is *allostatic load*.

Three Systems Responding to Tissue Injury

The Nervous System

Progress in pain research and theory moves steadily from simple to more complex concepts. Early thinking in the previous century favored a sensory modality with the following cardinal processes: transduction, transmission, modulation, projection and realization. This position still dominates thinking outside of the interdisciplinary pain community. As Zhang and Huang (page 930) put it, “Pain is generally considered a purely neural phenomenon”²²⁸. One may argue in defense of this approach that the best way to engage a puzzle in the life sciences is to form the simplest acceptable representation of that puzzle and solve it. Unfortunately, pain stubbornly resists this Procrustean fit; clinical problems of acute and chronic pain do not easily conform to the purely neural model. The persistence of chronic pain as a major problem in medicine indicates that the purely neural model has largely failed to guide clinicians toward curative interventions.

We emphasize that tissue trauma initiates multiple processes that exert an extensive non-neural physiological impact. Such processes affect overall health, functional capability, and sense of well-being. Pain is the conscious end product of this multi-faceted impact. Although complex patterns of brain activation are a part of the process from which pain emerges,⁴ pain reflects much more than activation of thalamus, somatosensory cortex and various limbic structures. Two often overlooked features of pain are: 1) The subjective awareness of tissue trauma is inherently multimodal and typically includes integrated visual, kinesthetic and enteric sensory modalities as well as noxious signaling; and 2) Tissue trauma occurs against background of

overall bodily awareness that encompasses interdependent neural, endocrine and immune states.

From Periphery to Brain: Bidirectional Processes

Transduction: The sensory organ for the detection of tissue trauma is the nociceptor, a primary afferent lacking specialized terminal structures that innervates skin, muscle, blood vessels, viscera, connective tissues and bone. The term nociceptor encompasses both the unmyelinated C fiber and the thinly myelinated, faster conducting A δ fiber^{30, 221}. Most nociceptors are C fibers, although not all C fibers are nociceptors. The nociceptive C fiber is more than a feature detector that responds preferentially to tissue injury; it participates actively in the wound by releasing Substance P (SP), Calcitonin Gene-Related Peptide (CGRP), Neurokinin A (NKA), other peptides and nitric oxide (NO), all of which contribute to the dynamic process of inflammation. In this way, nociceptor activation initiates neurogenic inflammatory processes that amplify responses to subsequent stimuli, whether noxious or innocuous.

At the periphery, the nervous system cooperates dynamically with the immune system to create inflammation and associated chemotaxis⁶² in the acute phase reaction⁷⁸. Macrophages, lymphocytes, mast cells interact with SP, CGRP and NKA released from C fibers to create a chemical “soup” of proalgesic mediators¹⁰¹. These substances induce vasodilation, extravasation of plasma proteins, and the release of further chemical mediators including K⁺, H⁺, bradykinin, histamine, serotonin, NO, Nerve Growth Factor (NGF), cytokines and the prostaglandins¹⁶⁹. Collectively, they sensitize normally high threshold nociceptors and awaken silent nociceptors so that they respond to normally innocuous stimulation. Sympathetic nerve terminals contribute to this sensitization by releasing norepinephrine and prostanoids. Increased NGF expression occurs in the presence of the pro-inflammatory cytokines IL-1 β and TNF α ¹⁵³.

Dorsal Horn: The dorsal horn is a complex, multisynaptic structure with multiple functions¹⁹⁶. It produces spinal reflexes, relays nociceptive messages to higher structures, and modulates to either inhibit or facilitate nociceptive transmission depending on information from higher structures or from the periphery. The integration of multi-modality sensory input begins at the dorsal horn, which contains multi-receptive neurons. These neurons receive and integrate information from multiple sensory modalities and interface with both external and internal environments¹¹⁵. This is the first step in the nervous system’s construction of a somesthetic image of the body. Further integration occurs in the medullary brain, particularly the solitary nucleus,⁸⁸ and cortex³⁷.

The spinal cord demonstrates plasticity by shifting bi-phasicly between states of nociceptive inhibition and nociceptive facilitation¹⁷¹. Sandkuhler¹⁷⁷ classified spinal nociceptive inhibitory mechanisms into three types: 1) supraspinal descending inhibition, 2) propriospinal, heterosegmental inhibition, and 3) segmental spinal inhibition. The short-range adaptive value of nociceptive inhibition is clear; pain must not impair flight or fight. Sustained inflammation may bring about time-dependent changes in dorsal horn function, favoring nociceptive facilitation where previously there was inhibition⁵². Vanegas and Schaible identified the periaqueductal gray and rostral ventromedial medulla as an efferent channel for nociceptive control and proposed that a shift from inhibitory to facilitatory influence might contribute to chronic pain²⁰⁸.

Dorsal horn facilitation results from wound inflammation or from intense or prolonged nociceptive input. It lowers pain threshold, amplifies nociceptive responses, and expands the receptive fields of nociceptive higher order neurons to incorporate non-injured areas near the wound and normally non-nociceptive sensory signals⁹⁴. A major mechanism is activation of N-methyl-D-aspartate (NMDA) receptors via glutamate, the main central nervous system

(CNS) excitatory neurotransmitter^{52, 135}. Normally, acute dorsal horn facilitation subsides with wound healing. Changes at the spinal cord level bring about changes in higher systems. For example, sensitization at the dorsal horn results in long-term potentiation at hippocampal and cortical levels, and this enhances responses to noxious input⁹⁴.

The CNS can shift from normal functioning to states of either facilitation or inhibition. Sensory thresholds change in response to prolonged noxious stimulation in two ways. First, hitherto non-noxious stimuli generate noxious signaling (e.g., mechanical allodynia) and second, stimuli that previously would have produced minimal pain become intensely painful (hyperalgesia).

Higher Structures: Pain, as aversive somatic awareness, involves integration of information from multiple sensory modalities that begins at the dorsal horn¹¹⁵ and continues in the basal ganglia¹⁴⁴, solitary nucleus⁸⁸, superior colliculus¹⁹⁰ and cortex¹¹⁶, which contains multimodal neurons⁶⁶. This process is selective and bi-directional in that cortex mediates multi-sensorial integration in deeper structures⁹⁵.

Unimodal studies of nociceptive transmission, projection and processing sketch a complex picture. Signals of tissue trauma reach higher CNS levels via the spinothalamic, spinohypothalamic, spinoreticular including the locus coeruleus (LC) and the solitary nucleus, spinopontoamygdaloid pathways, the periaqueductal gray (PAG) and the cerebellum^{157,29}. Thalamus projects to limbic areas including the insula and anterior cingulate. Craig³⁷ holds that anterior insula integrates emotional and motivational processes. Noradrenergic pathways from the LC project to these and further limbic structures. Accordingly, functional brain imaging studies of the human brain during the experience of pain reveal extensive limbic, prefrontal and somatosensory cortical activation. A meta-analysis of the literature described brain activity during pain as a network involving thalamus, primary and secondary somatosensory cortices, insula, anterior cingulate, and prefrontal cortices⁴. Thus, the brain engages in massive, distributed, parallel processing in response to noxious signaling.

The mechanisms of multimodal integration pose a fascinating challenge. For example, Hollis and colleagues⁸⁸ addressed how catecholaminergic neurons in the solitary nucleus integrate visceral and somatic sensory information when inflammation is present peripherally. Intense physiological arousal, pre-existing fatigue, dysphoria or nausea, and a systemic inflammatory response induced by pro-inflammatory cytokines^{2, 61} could all contribute sensory information to the brain's processing load during the construction of pain. Apart from Craig³⁷, few investigators have addressed the integration of information from multiple sensory modalities and central processes related to emotion and cognition in the formation and emergence of pain.

Descending modulation of noxious signaling operates principally at the dorsal horn. Through descending pathways, higher structures can facilitate or inhibit the pain experience. Frontal-amygdalar circuits may modulate the affective intensity of injury¹¹⁹. Frontal-PAG circuits play a role in pain modulation. Tracey and Mantyh²⁰¹ review top down influences in nociceptive modulation.

Higher Processes and Defense: Many functional brain imaging pain studies to date implicitly assume that pain results from a unimodal sensory process. The dynamic interaction of multiple brain subsystems generates a dynamic, coherent model of the body and the social self in the world. Research on the defense response sheds light on the integration of aversive conditions in general, including, but not limited to, noxious input. The main neural substrates are the medial hypothalamus, amygdala and dorsal PAG²⁴. These structures respond reliably but not exclusively to noxious signaling, interact with one another, and actively integrate cognitive, sensory and emotional processes. Some pain research has begun to address the issue of

integration in cognitive processes³⁷. Tracey and colleagues²⁰⁰ employed functional brain imaging to study subjects attending to or distracting themselves from, painful stimuli cued with colored lights. Distraction and pain reduction occurred in conjunction with PAG activation, linking cortical control and the PAG.

Frontal-amygdalar circuits are a well-studied aspect of the defense response¹¹⁹. Cognitive variables such as interpretation, attention and anticipation can influence amygdalar response through the frontal-amygdalar circuit. The amygdala, in turn, can influence the hypothalamo-pituitary-adrenocortical axis^{86, 130}, a major organ of the stress response. Frontal influences also affect patterns of activity at the LC⁶. Endogenous cognitive stimuli generated during anticipation or memory reconstruction can activate complex neural circuits that mobilize the stress response in the absence of tissue trauma. The central nucleus of amygdala projects to the PAG, which coordinates defensive behaviors¹⁴⁰. In general, amygdala is the mechanism of conditioned fear^{149, 175}. It communicates with hypothalamus via neural circuitry²²⁷. Other issues requiring scientific inquiry include how memory shapes expectancy, presumably involving frontal-amygdalar pathways, how these processes in turn influence physiological functioning through the central autonomic network^{10, 11, 197} and how other sensory modalities integrate with noxious signaling.

The Endocrine System

The Endocrine Stress Response—The stress literature tends to group all reactions to a stressor such as wounding under the single heading of stress response. However, DeKloet and Derijk⁴⁵ characterize the stress response as having two modes of operation, or states. The first state is immediate arousal in response to the stressor in order to enable adaptive behaviors and the second state is a slower process that promotes recovery, behavioral adaptation and return to normalcy. They describe these phases as the fast and slow responding modes. We designate the first state as *defensive arousal* and the second as *recovery*.

Defensive Arousal: The major mechanisms of the stress response at the level of the brain are the LC noradrenergic system, the hypothalamo-pituitary-adrenocortical (HPA) axis based in the hypothalamic periventricular nucleus (PVN)²⁰⁴, and the sympathoadrenomedullary (SAM) axis¹⁴⁸. The peripheral effectors of these mechanisms are the autonomic nervous system, the SAM circulating hormones, principally the catecholamines epinephrine (E) and norepinephrine (NE) together with the sympathetic co-transmitter neuropeptide Y (NPY)²³⁰, all of which originate in the chromaffin cells of the adrenal medulla. The stress response also involves hypothalamically-induced release of peptides derived from pro-opiomelanocortin (POMC) at the anterior pituitary. The POMC-related family of anterior pituitary hormones includes ACTH, β -lipotropin, β -melanocyte stimulating hormone and β -endorphin.

Corticotropin-releasing hormone (CRH), produced at the hypothalamic PVN initiates the stress response. CRH initiates and coordinates the stress response at many levels⁶⁰, including the LC¹⁶³. It is the key excitatory central neurotransmitter and regulator in the endocrine response to injury. Two receptors respond to CRH and CRH-related peptides, CRH-1 and CRH-2. These distribute widely in limbic brain¹¹⁸. CRH-1⁴⁵ is the key mechanism of the *defensive arousal* response. Figure 1 illustrates the HPA axis response to a stressor such as tissue injury.

Central Noradrenergic Mechanisms: Noxious signaling inevitably and reliably increases activity in the LC noradrenergic neurons, and LC excitation appears to be a consistent response to nociception^{192, 194}. The LC heightens vigilance, attention, and fear as well as facilitating general defensive reactions mediated through the sympathetic nervous system. Basically, any stimulus that threatens the biological, psychological or psychosocial integrity of the individual

increases the firing rate of the LC, and this in turn increases the release and turnover of NE in the brain areas having noradrenergic innervation. The LC exerts a powerful influence on cognitive processes such as attention and task performance^{6, 12}. In addition to directly receiving noxious signals during spinoreticular transmission, the LC also responds to CRH¹⁶³. LC neurons increase firing rates in response to CRH, and this increases NE levels throughout the CNS⁹³.

Adrenomedullary Mechanisms: The adrenal medulla, an endocrine organ, is a functional expression of the sympathetic nervous system that broadcasts excitatory messages by secreting substances into the blood stream. Acetylcholine (Ach) released from pre-ganglionic sympathetic nerves during the stress response triggers secretion of E, NE and NPY into systemic circulation. E and NE exert their effects by binding to adrenergic receptors on the surface of target cells, and they induce a general systemic arousal that mobilizes fight or flight behaviors. These catecholamines increase heart rate and breathing, tighten muscles, constrict blood vessels in parts of the body and initiate vasodilation in other parts such as muscle, brain, lung and heart. They increase blood supply to organs involved in fighting or fleeing but decrease flow in other areas.

Recovery—The *recovery* phase commences before the defensive arousal, or alarm, phase, ends to protect against arousal overshoot. The defensive state is catabolic and, if the allostatic response is too strong or goes on too long, it can deplete neurotransmitters and/or dysregulate system functions. The purposes of the recovery response are first to regulate the intensity of the alarm reaction and second, when it is safe to stop defense, to terminate allostasis, minimize the costs of allostatic load, and bring the body back to normalcy.

CRH synthesis and release occur in response to a stressor such as tissue injury and also in response to levels of circulating cortisol (CORT) and the diurnal rhythm. The neurons of the median eminence secrete CRH into the hypophyseal portal circulation, and this carries it to the anterior pituitary where it binds to CRH receptors on corticotropes. This generates POMC synthesis and release of ACTH¹³⁶ into systemic circulation. Circulating ACTH stimulates production of CORT at adrenal cortex with release into systemic circulation. Circulating CORT, in turn, provides a negative feedback signal to the PVN and the anterior pituitary. See Figure 1.

The mechanism for recovery is CRH-2 receptor expression. This receptor responds to the CRH family of peptides⁴⁴ including the urocortins. The anterior pituitary initiates production of adrenocortical glucocorticoids (GCs), including CORT, that bind to glucocorticoid receptors (GRs). The primary agent and classical marker for stress recovery in human is CORT. It normally functions in concert with the catecholamines and CRH. GR activation promotes energy storage and termination of inflammation to prepare for future emergency. Although the recovery process is inherently protective, prolonged CORT can cause substantial damage^{44, 45, 60}.

The Immune System

The Immune Defense Response and Inflammation—Just as the nervous system is the primary agent for detecting and defending against threat arising in the external environment, the immune system is the primary agent of defense for the internal environment. Kohl¹¹⁰ described it as “a network of complex danger sensors and transmitters.” This interactive network of lymphoid organs, cells, humoral factors, and cytokines works interdependently with the nervous and endocrine systems to protect homeostasis. Parkin and Cohen provide a detailed overview of the immune system¹⁵⁰.

The immune system detects an injury event in at least three ways: 1) through blood-borne immune messengers originating at the wound; 2) through nociceptor-induced sympathetic activation and subsequent stimulation of immune tissues, and 3) through SAM and HPA endocrine signaling. Immune messaging begins with the acute phase reaction at the wound⁷⁸. Local macrophages, neutrophils, and granulocytes produce and release into intracellular space and circulation the pro-inflammatory cytokines IL-1, IL-6, IL-8 and TNF- α . This alerts and activates other immune tissues and cells that have a complex systemic impact. The acute phase reaction to injury is the immune counterpart to nociception in the nervous system, as it encompasses transduction, transmission and effector responses.

The immune and nervous systems interact cooperatively at the wound. Tissue injury releases the immunostimulatory neuropeptides SP and NKA. These activate T cells and cause them to increase production of the pro-inflammatory cytokine IFN- γ ¹¹³. In addition, another pro-inflammatory cytokine, IL-1- β , stimulates the release of SP from primary afferent neurons⁹¹. The neurogenic inflammatory response helps initiate the immune defense response and at the same time is in part a product of that response⁶².

Immune-nervous system interaction is feedback-dependent. Sympathetic outflow following injury can directly modulate many aspects of immune activity and provide feedback. This can occur because all lymphoid organs have sympathetic nervous system innervation⁵⁸ and because many immune cells express adrenoceptors^{105, 210}.

Inflammation assists the immune system in defense against the microbial invasion that normally accompanies any breach of the skin. If microorganisms reach the blood stream, sepsis occurs. The inflammatory process creates a barrier against the invading microorganisms, activates various cells including macrophages and lymphocytes that find and destroy invaders, and sensitizes the wound, thereby minimizing the risk of further injury. Redness, pain, heat and swelling are its cardinal signs. Inflammation reduces function and increases pain by sensitizing nociceptors. Tracey²⁰² described the “inflammatory reflex” as an Ach-mediated process by which the nervous system recognizes the presence of, and exerts influence upon, peripheral inflammation. Through vagal and glossopharyngeal bidirectional nerves, the nervous system modulates circulating cytokine levels. The key point is that certain nervous structures sense the activities of the immune system.

Cytokines and Inflammation—Although a wide variety of cell types produce cytokines in response to an immune stimulus, classical description holds that their principal origin is leukocytes. They exert powerful effects on many tissues and one another, but cytokines are also major signaling compounds that recruit many cell types in response to injury. They bind specifically to cell surface receptors to achieve their effects, and exogenous antagonists can block their effects. Cytokines act upon: 1) The cells that secrete them, autocrine mode; 2) Nearby cells, paracrine mode, and 3) Distant cells, endocrine mode. Chemokines are chemotactic cytokines that attract specific types of immune cells, mainly leukocytes, to an area of injury. Broadly, cytokines group into four families based on their receptor types: a) Hematopoietins, including IL-1 to IL-7 and the Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) group; b) Interferons including INF α and INF γ ; c) Tumor Necrosis Factors, including TNF α ; and d) Chemokines, including IL-8. For a basic review, see Elenkov and colleagues and Gosain and Garnelli^{61, 72}. Cytokines can act synergistically or antagonistically in many dimensions.

Soon after formation, helper T cells differentiate into two types in response to existing cytokines and then secrete their own cytokines with one of two profiles: Th1, pro-inflammatory; and Th2, anti-inflammatory. Most cytokines classify readily as either Th1 or Th2 according to the influence they exert. For example, IL-4 stimulates Th2 activity and

suppresses Th1 activity, so it is anti-inflammatory. IL-12, on the other hand, promotes pro-inflammatory activity and is therefore Th1. Pro-inflammatory cytokines include IL-1- β , IL-2, IL-6, IL-8, IL-12, IFN- γ and TNF α . Anti-inflammatory cytokines include IL-4, IL-10, insulin-like growth factor 1 (IGF-10), and IL-13. Some investigators characterize an individual's immune response profile using a *Th1/Th2 ratio*.

The Sickness Response—Fever and sickness with pain is an immune systemic response^{61, 191, 216, 217, 225}. This *sickness response* is cytokine-mediated and depends on the CNS. Macrophages and other cells release pro-inflammatory cytokines including IL-1- β , IL-6, IL-8, IL-12, IFN- γ and TNF- α in response to injury. These substances act on the vagus and glossopharyngeal nerves, hypothalamus and elsewhere to trigger a cascade of unpleasant, activity-limiting symptoms^{174, 226}.

The sickness response, a system-wide change in mode of operation triggered by cytokines, is a vivid and dysphoric subjective experience characterized by fever, malaise, fatigue, difficulty concentrating, excessive sleep, decreased appetite and libido, stimulation of the HPA axis, and hyperalgesia. The sickness-related hyperalgesia may reflect the contributions of spinal cord microglia and astrocytes²²⁶. Functionally, this state is adaptive; it minimizes risk by limiting normal behavior and social interactions and forcing recuperation.

Depression may be another complex immune response. Mounting evidence supports the hypothesis that cytokines are causal mechanisms of depression, even though specifics are still at issue¹⁶⁴. Pro-inflammatory cytokines instigate the behavioral, neuroendocrine and neurochemical features of depressive disorders³. The therapeutic use of pro-inflammatory cytokines INF α and IL-2 for cancer treatment produces depression³²; more specifically, hyperactivity and dysregulation in the HPA axis, which are common features of severe depression. The sickness response and depression overlap in that many of the behavioral and sensory manifestations of sickness are also manifestations of a depressive disorder.

Immune Complexity—Immune organs such as bone marrow, thymus, spleen, lymph nodes, and various cells are widely distributed, highly varied, and they lack a focus of central control. Yet, they function with extraordinary coordination as a single adaptive system^{32, 83, 150}. The immune system has a clear sensory function, in that it detects what the nervous system cannot: microbial invasion, toxins, tumors, and cell injury¹⁸. It evaluates, (e.g., self versus not-self), makes decisions (e.g., cell trafficking), takes action (e.g., the inflammatory response, cell trafficking), and it learns from past experience (adaptive immunity and conditioning). These properties approximate sentience, cognition and behavior as we know them in the nervous system.

Connectivity

The literature makes a strong case for the communication and interdependence of nervous, endocrine and immune systems, but nearly all of the studies and reviews focus on two systems rather than all three. To generate a comprehensive perspective, we follow the pair-wise threads of inquiry to marshal evidence for our contention that the three systems operate and respond to stressors interdependently.

Nervous System - Immune System Connectivity

Autonomic Mechanisms—Because all lymphoid organs, including bone marrow, have autonomic innervation^{58, 133, 191, 210}, events that activate the central autonomic network affect the immune system. When sympathetic nervous system arousal occurs, sympathetic axon terminals innervating lymphoid tissues release E, NE and NPY. Lymphocytes, macrophages and other immune cells bearing functional adrenoceptors respond to the released

substances¹³⁴. The release of SAM catecholamines into the systemic circulation exerts a similar effect. Through activation of circulating leukocytes and other immune cells and immune tissues at various locations throughout the body¹³³, catecholamine secretion modulates all aspects of immune responses, such as initiative, proliferative and effector phases, and it can alter lymphocyte proliferation, cell trafficking, antibody secretion, and cytokine production⁵⁹. In addition, NPY's receptors, Y1 and Y2, exist throughout the immune system. NPY stimulates lymphocyte proliferation²¹², enhances leukocyte function¹⁹³, and modulates macrophage activity⁴².

Glial Cells—Microglia, oligodendrocytes and astrocytes reside within the CNS and contribute to inflammation and peripheral injury-induced pain^{217, 225}, including the spread of pain⁸². Microglia are immune cells closely related to macrophages that express the same surface markers⁶⁴. Injury and other events that threaten homeostasis activate microglia. These immune cells contribute to hyperalgesia and allodynia by releasing pro-inflammatory cytokines and chemokines, and they are probably involved in several neuropathic pain conditions¹²⁵.

The astrocyte, a non-migratory subtype of glial cell, diversely supports CNS function. Through its direct contact with blood capillary networks, it provides vasomodulation of localized blood flow, metabolic support (e.g., glucose delivery), and control of the blood brain barrier function on micro and macro levels. Subpopulations of astrocytes surround neurons and their synaptic connections, thereby influencing pre-synaptic neurotransmitter release through modulation of synaptic cleft calcium concentration and membrane polarization. In controlling local environments, they functionally organize regional synaptic connections. In addition, they provide the important function of neurotransmitter uptake, thus protecting against glutamate neurotoxicity, which is implicated in several central pathological states.

Microglia and astrocytes play key roles in positive feedback circuits (described below) involving cytokines and glutamate²²⁴. Activators and inhibitors can exacerbate or block the influences of microglia and astrocytes on nociception. Fractalkine, naturally expressed on the surface of neurons, can activate microglia to produce allodynia and hyperalgesia¹³⁷. Conversely, minocycline administered preemptively at the time of injury reverses hyperalgesia and allodynia¹¹⁷. The relationship of acute hyperalgesia and allodynia to microglial activation, and the unfolding vision of microglial activation as mechanisms in chronic neuropathic pain exemplify of the interdependence of nervous and immune systems.

Peptides—Multiple peptides link the activities of the nervous and immune systems^{152, 195, 207}. CRH is a prominent shared peptide produced at hypothalamic PVN and also at extra-hypothalamic sites. CRH functions as a neurotransmitter as well as a hormone. CRH and its family of neuropeptides, including the urocortins, contribute to peripheral inflammatory responses⁷⁴. C fibers release it the wound along with SP, and mast cells appear to be the primary targets³³. In caudal dorsal raphe nucleus, CRH induces the release of serotonin from neurons⁸⁰. At central amygdala, CRH has an anxiogenic function¹³¹ and is important for memory consolidation¹⁷², but these effects are independent of its action at the HPA axis¹⁴³. Psychogenic stressors can trigger the release of CRH at amygdala¹³⁰. Thus, CRH is clearly pleiotropic, exerting both pro- and anti-inflammatory effects, depending upon its location and role.

Other prominent neuropeptides are SP, CGRP, somatostatin (SOM), vasoactive intestinal peptide (VIP) and its close relative, pituitary adenylate cyclase activating peptide (PACAP). T lymphocytes express receptors for all of these peptides, which play a role in immune regulation as well as pain. C-fibers innervating the various lymphoid organs release some of

these peptides^{113, 195}. SP and CGRP, released from peripheral C-nociceptor terminals, participate in neurogenic inflammation²¹³. CGRP suppresses IL-2 production²¹⁵.

In addition to pro-inflammatory peptides, peripheral C-fibers release SOM, which enters systemic circulation and exerts anti-inflammatory and analgesic effects¹⁵⁴. SOM inhibits hormone release in the anterior pituitary and inhibits T cell proliferation. It also down-regulates lymphocyte proliferation, immunoglobulin production, and the release of pro-inflammatory cytokines. A SOM - SP immunoregulatory circuit may exist¹⁹⁵, perhaps as part of a deeply nested, feedback control system.

VIP and PACAP are structurally related members of the secretin-glucagon-VIP family that perform multiple actions within the nervous and immune systems^{48, 67}. They act on the same receptors and share many biological activities. VPAC1 and VPAC2 receptors bind both VIP and PACAP with equal affinity but VPAC1 binds PACAP with a much higher affinity than VIP. VIP and PACAP exert an anti-inflammatory influence in the periphery^{48, 67}. Centrally, they inhibit chemokines in activated microglia⁴⁶.

VIP and PACAP regulate both innate and adaptive immunity^{67, 68}. Most lymphoid organs contain VIPergic nerve fibers located close to immune cells¹¹². T cells, particularly Th2 cells, produce VIP. VIP and PACAP limit the cytotoxicity of CD4+ and CD8+ T cells, probably by inhibiting chemokine receptors⁷⁵. These peptides directly inhibit macrophage pro-inflammatory cytokine production as well as production of pro-inflammatory cytokines and chemokines from microglia and dendritic cells. Broadly, they promote Th2 anti-inflammatory responses and reduce pro-inflammatory Th1 type responses. Pozo and Delgado contend that VIP qualifies for classification as a Th2, or anti-inflammatory cytokine¹⁵⁶. It groups with IL-10 as an -inflammatory cytokine because it mediates and regulates both neural and immune functions.

PACAP modulates many macrophage functions such as migration, adherence, phagocytosis as well as synthesis and release of IL-6 in resting macrophages⁴⁷. It inhibits IL-6 release in stimulated macrophages but enhances its secretion in unstimulated macrophages. PACAP exerts an effect on neutrophil inflammation even though VIP does not¹⁰⁶. When injected intradermally, PACAP is strongly anti-inflammatory, presumably modulating cytokine production¹⁰⁸.

Other peptides serving as messenger substances include orphanin FQ/nociceptin¹³², an endogenous ligand of the human opioid receptor-like, ORL1, (hereafter termed nociceptin receptor (Noci-R). Noci-R is also present and functional in human leukocytes and neutrophils^{5,65}. Nociceptin and its receptor recruit leukocytes to inflammatory sites in support of host defense and the generation of appropriate immune responses¹⁸¹.

Tachykinins are neuropeptides synthesized in neurons and released from nerve terminals. SP and NKA are the products of nociceptive afferents characterized by sensitivity to capsaicin. They are released during axon reflex and by exposure to conditions such as low pH, bradykinin, capsaicin, prostaglandins, and leukotrienes. There are three types of tachykinin receptors: NK1, NK2 and NK3. These receptors interact preferentially with SP, NKA and neurokinin B (NKB) respectively^{123, 128}. SP exists throughout the CNS, in both neuronal and glial cells. In the CNS, SP can initiate and augment the immune responses of glial cells following trauma or infection¹²⁶. IL-1 β upregulates tachykinin in the peripheral nervous system⁹⁹.

Tachykinins also exist in the immune system^{113, 165} where they stimulate monocytes and macrophages⁹⁶, degranulate mast cells, and cause adherence and chemotaxis of human neutrophils and eosinophils. They also modulate the chemotaxis, proliferation and activation

of lymphocytes. SP stimulates the release of cytokines such as IL-1, IL-6 and TNF α from peripheral blood monocytes and in bone cells⁷³. SP receptors also exist in blood vessels¹⁶⁵.

Cytokines as Messengers—Cytokines help coordinate the nervous and immune systems. Pro-inflammatory cytokines act at multiple levels of the neuraxis⁵⁴. They bind to sensory afferent terminals of the vagus and glossopharyngeal nerves and thereby influence the solitary nucleus and other mesencephalic noradrenergic sites^{55, 124, 206}. IL-1 triggers cerebral NE metabolism and secretion⁵³ and influences activity in the LC²². Pro-inflammatory cytokines act at the PVN and at other levels of the HPA axis to release adrenal glucocorticoids^{184, 206} and IL-1 β stimulates CRH neurons¹⁰⁰. Pro-inflammatory cytokines promote further cytokine synthesis within the CNS at microglia. They appear to play important but as yet unspecified roles in positive and negative feedback loops that influence processes jointly involving endocrine and immune responses to stressors.

Neural Detection of Cytokines—The sensory vagus and glossopharyngeal nerves have paraganglia that detect immune products and are sensitive to immune system signaling^{174, 217}. They detect peripheral pro-inflammatory cytokine release. Conversely, direct electrical stimulation of the vagus nerve induces IL-1 β release in hypothalamus and hippocampus⁸⁹. The ability of other, non-invasive stressors to increase IL-1 β depends upon NE²⁰. IL-1 β activates the HPA axis, increases NE release at hypothalamus²²³, and stimulates LC activity²².

Endogenous Opioids—The immune system is a source of endogenous opioid peptides, and tissue trauma enhances production of opioid peptides within immune cells located in inflamed tissue. CRH and IL-1 β are releasing factors for opioid peptides¹⁷⁸. Leukocytes secrete endogenous opioids in response to releasing factors such as CRH, NE and pro-inflammatory cytokines^{168, 169}. Endogenous opioids suppress peripheral C terminal excitability and inflammatory mediator release, thus contributing anti-inflammatory effects in peripheral nociceptor activation.

Endocannabinoids—Endocannabinoids constitute a lipid signaling system derived from arachidonic acid³⁸. Nervous, blood and endothelial cells release endocannabinoids¹⁶⁰. The endocannabinoid endogenous ligands anandamide (AEA) and 2-arachidonoylglycerol (2AG) bind to the G protein-coupled receptors CB1 and CB2¹⁰⁷. Broadly, the endocannabinoids exert immune-suppressing effects. Anandamide inhibits the migration of CD8+ T lymphocytes⁹⁸. Extended exposure to marijuana compromises immune function and may result in disturbance of the normal Th1/Th2 cytokine ratio³¹. Monocytes, helper T-cells, macrophages, and brain microglia all express cannabinoid receptors²¹⁴.

CB1 cannabinoid receptors and ligands occur principally in brain, immune and other peripheral tissues, while CB2 receptors and ligands occur primarily in immune cells¹⁰⁷. As a general rule, cannabinoids appear to have anxiolytic, neuroprotective, and anti-inflammatory properties^{36, 151}. However, in addition to binding to CB1 and CB2, AEA binds to the vanilloid receptor TRPV1 (transient receptor potential cation channel, subfamily V, member 1; formerly termed vanilloid receptor 1, VR1). Peripheral nociceptor terminals express and encode TRPV1 in response to multimodal stimuli related to tissue trauma. TRPV1 receptors exist on C nociceptive terminals and also reside on the central endings of primary sensory neurons in the dorsal aspect of the spinal cord and brainstem²⁵⁵. Through its dual agonist effects on TRPV1 and cannabinoid membrane receptors, AEA plays an important role in chemical nociception and in modulating peripheral hyperalgesic mechanisms^{84, 120, 186, 199}. Cannabinoid effects depend on concentration and also on the presence of inflammatory mediators¹⁸⁶. On the one hand, low AEA concentrations induce CB1 receptor-mediated inhibition of electrically-induced neuropeptide release from dorsal root ganglion neurons¹⁷⁶. On the other hand, high

AEA concentrations evoke TRPV1 receptor-mediated neuropeptide release at central terminals of capsaicin-sensitive sensory neurons¹⁹⁹, which could potentially oppose peripheral CB-mediated inhibitory action. Cannabinoids may act solely through the TRPV1 receptor¹⁵¹ or through simultaneous binding of TRPV1 and cannabinoid receptors. They exert modulatory effects, extending from organ systems to cellular levels.

Nervous System - Endocrine System Connectivity

The nervous and endocrine systems cooperate in the stress response. Neural structures initiate hormonal responses and provide the mechanisms of feedback-controlled regulation. Moreover, CRH, E, NE, β -endorphin and other substances assume the role of neurotransmitter in the nervous system and the role of hormone in the endocrine system. As hormonal messengers, these substances affect nervous structures at multiple levels of the neuraxis. Consequently, the literature often refers to the neuroendocrine stress response.

Acute Stress Response Mechanisms—Wounding triggers a neuroendocrine reaction with three aspects: 1) sympathomedullary release of NE, E and NPY as hormones¹⁴⁸; 2) CRH activation of the HPA axis including the production of mineralocorticoids and glucocorticoids^{44, 161}, and 3) activation of LC and the noradrenergic limbic brain²⁰⁴, the sympathetic components of the central autonomic network. From the pain perspective, the stress response has several key properties⁸⁶. First, noxious signaling is among its triggers. Second, the overall reaction to the stressor includes both anticipatory and reactive responses. Third, these responses occur in multiple, hierarchically organized, or nested, neurocircuitries. Furthermore, the stress response is not limited to the HPA axis but invariably involves multiple limbic brain areas including the amygdala⁸⁷ and the mesocorticolimbic dopaminergic system²⁰⁴.

When a stressor occurs, the hypothalamic PVN receives and integrates neural input from diverse sources that include sensory input, the limbic brain and the frontal cortex. Serotonin (5-HT), Ach and NE are among the most important neurotransmitters involved in neurogenic stimulation of CRH production^{15, 44} and arginine-vasopressin (AVP) production. Periventricular NE is the most salient neurotransmitter in HPA axis activation when the stressor is noxious¹⁴⁷. AVP production is simultaneous and AVP interacts synergistically with CRH²⁰⁴. Through the median eminence of the hypothalamus, CRH and AVP enter hypophyseal portal circulation, which extends to the anterior pituitary gland. There, CRH induces POMC, a precursor polypeptide that cleaves to form ACTH, α -melanocyte stimulating hormone (α -MSH) and β -endorphin¹³⁸. ACTH enters systemic circulation and activates CORT secretion at adrenal cortex. Central detection of circulating CORT completes the negative feedback loop (see Figure 1) and constrains ACTH and CORT production¹³⁶. These processes normally follow a diurnal rhythm as pulsations. In response to a stressor, the frequency of rhythmic secretory episodes increases.

There are reciprocal connections between central CRH and LC noradrenergic neurons^{93, 147, 204}. The noradrenergic LC system is not only involved in alarm reactions, but also plays a key role in maintaining waking/vigilance and in many higher order cognitive processes^{6, 12}. LC noradrenergic projections extend widely throughout the limbic brain and can excite the amygdala, which is involved in negative emotion and defense responses. In the periphery, postganglionic sympathetic neurons are noradrenergic, although CRH, NPY and SOM co-localize in noradrenergic vasoconstrictive neurons.

The SAM endocrine response to a stressor involves the release of E, NE and NPY from the adrenomedullary chromaffin cells into systemic circulation. The ratio of E to NE in plasma is 4:1 in humans, and the major source of circulating NE is not adrenomedullary secretion but release from sympathetic efferent endings. Circulating catecholamines increase blood pressure

and heart rate, dilate pupils, and increase skin conductance, thereby initiating arousal for the fight or flight response.

Peptides and Serotonin—Peptides link the endocrine and nervous systems. VIP and PACAP help regulate the HPA axis¹⁴⁶. The hypothalamus contains both peptides. The pituitary gland synthesizes VIP but not PACAP, although the adrenal gland expresses both. Both peptides increase pituitary ACTH secretion. VIP from the pituitary elicits hypothalamic release of CRH, and PACAP by directly stimulating pituitary corticotropes and by activating CRH gene expression⁷⁷.

The indoleamine neurotransmitter 5-HT also links nervous and endocrine stress response systems. The hypothalamic PVN has dense serotonergic innervation, and 5-HT-containing axons innervate hypothalamic CRH-containing cells⁸¹. 5-HT stimulates secretion and synthesis of CRH⁹². Conversely, CRH has multiple and complex effects on serotonergic neurons, as do glucocorticoids. 5-HT reuptake inhibition in rats significantly increased ACTH secretion five fold, CRH messenger ribonucleic acid (mRNA) expression in the PVN by 64% and POMC mRNA expression in the anterior pituitary lobe by 17%⁹⁷. 5-HT appears to increase synthesis of CRH in the PVN and POMC in the anterior pituitary lobe. High 5-HT has negative immunoregulatory effects¹²¹. 5-HT inhibits production of INF γ , a pro-inflammatory cytokine, even though augmented CRH during stress generally tends to increase certain other pro-inflammatory cytokines such as IL-1, IL-2, and IL-6. CRH increases 5-HT activity in the caudal dorsal raphe nucleus⁸⁰. Dunn summarized the impact of IL-1 administration on the HPA axis⁵³. Among the effects was an increase in 5-HT metabolism.

Immune System - Endocrine System Connectivity

Mechanisms—The immune system distributes widely throughout the body, involves a variety of organs and cells, and has both innate and acquired features¹⁵⁰. The endocrine system uses systemic circulation to evoke system-wide messaging and feedback. Therefore, the immune - endocrine interface has many facets. Reciprocal interactions involve the hypothalamus, pituitary gland, adrenal cortex, adrenal medulla, as well as multiple immune cells, which have adrenoceptors and receptors for various peptides. They also release peptides and cytokines.

During stress, the immune and endocrine systems also interact at the periphery. For example, stress-activated circulating E and NE bind to the β_2 adrenoceptors expressed on mononuclear phagocytic cells^{33, 59} and dendritic antigen-presenting cells¹²². In general, catecholamines including dopamine tend to shift the cytokine balance in the Th2, or anti-inflammatory, direction⁵⁹. Similarly, glucocorticoids produced by HPA axis activation suppress pro-inflammatory, or Th1, cytokine production. These hormones appear to protect against overshoot in the pro-inflammatory response to a stressor such as tissue damage. Together, the stress-induced, circulating catecholamines and glucocorticoids are the major integrative and regulatory influences on immune responses²¹⁰.

Corticotropin-Releasing Hormone—Centrally, CRH plays a major role in linking immune and endocrine function¹⁰⁰. CRH originating at the PVN initiates the stress response at the HPA axis through ACTH secretion, leading to CORT release from adrenal cortex and catecholamine release from adrenal medulla, in addition to activating central noradrenergic structures such as the LC^{93, 147, 204}.

Central CRH activates the anterior pituitary, a part of the endocrine system, and causes expression of the POMC pro-hormone, which undergoes extensive cleavage to yield a range of biologically active peptides. Among them are ACTH, the melanocyte-stimulating hormones α -, β - and γ -MSH, β -endorphin, as well as β - and γ -lipoprotein. α -MSH antagonizes the pro-

inflammatory cytokine IL-1¹⁷. In addition, POMC-expressing neurons exist in hypothalamus, elsewhere in the CNS and in the skin¹⁵⁸. Circulating corticosteroids and pro-inflammatory cytokines appear to control circadian rhythms of POMC expression¹⁸⁰.

As a hormone and neuropeptide acting in the periphery, CRH is behaviorally anxiogenic and exerts pro-inflammatory effects on immune cells by enhancing the release of pro-inflammatory cytokines from macrophages and other immune cells¹. CRH presence in inflammatory tissues may be the product of immune cells, peripheral nerves, or both³³. As with SP and CGRP, peripheral nerves release this neuropeptide in response to tissue damage. CRH is chemically similar to urocortin, also a peptide, and both are over-expressed in inflammation. CRH and urocortin stimulate production of pro-inflammatory cytokines by immune cells. The mast cell is a major target of peripheral CRH release.

On the other hand, CRH contributes to anti-inflammatory processes by inducing POMC synthesis at the peripheral and central interfaces of the endocrine and immune systems. In the periphery, tissue injury increases opioid receptor expression in dorsal root ganglion neurons. Inflammatory processes induce releasing factors, among them CRH, cytokines and NE, that cause leukocytes to secrete endogenous opioids that bind to receptors on peripheral nerve terminals and reduce their excitability^{168, 169}. CRH also fosters opioid receptor expression on sensory neuron terminals in the wound. Opioid receptor-expressing leukocytes and macrophages responding to chemokines migrate to the inflammatory environment. Thus, CRH participates in the control of local inflammation by acting as a releasing factor for endogenous opioids.

Endocannabinoids—Although classic descriptions of endocannabinoids focus on interactions of nervous and immune systems, these substances also play a role in endocrine function. Cannabinoid administration affects multiple hormone systems including gonadal steroids, growth hormone, prolactin, thyroid hormone and HPA axis activation²⁷. AEA intracerebral ventricular administration activates the HPA axis, increasing serum levels of ACTH and corticosterone in a dose-related manner²¹⁹, probably via the CB1 receptor and further hypothalamic PVN cannabinoid receptor binding²²⁰.

Cytokines—Finally, the immune system exerts a powerful effect on the endocrine stress system through cytokines, which act at the hypothalamus and pituitary. Cytokine receptors, including the pro-inflammatory cytokines IL-1 and IL-6, exist at all levels of the HPA axis¹⁸⁴. Microglia are likely the primary central source of IL-1²⁰. In addition, IL-6 produced at a peripheral site of injury/inflammation reaches the hypothalamus through systemic circulation^{55, 170}. IL-1 activates the LC and thereby the noradrenergic limbic brain^{22, 53}. Increased 5-HT metabolism accompanies IL-1 stimulation of the HPA axis⁵³.

Negative feedback processes limit cytokine HPA axis activation. The HPA axis produces adrenal glucocorticoid, which suppresses the effects of immune cell cytokines at the anterior pituitary and adrenal medulla¹³. Glucocorticoids also inhibit Th1 cytokine production in a variety of systems while increasing the production of several Th2 cytokines⁶⁰.

The Single System Vision: Supersystem

Our literature review indicates that wounding activates processes in nervous, endocrine and immune domains, that these processes operate in an interdependent and integrated manner rather than as distributed physiological processes, and that their highly orchestrated agency in defending against threat employs self-regulation and self-direction. In light of this, we put forward a *supersystem* model: The neural-endocrine-immune ensemble is an agent that operates as an overarching system, within which each individual system functions as a

subsystem. A corollary is that the supersystem nests with a larger system that we characterize as the whole person, or individual. Figure 2 characterizes the supersystem, emphasizing connectivity. It depicts a dynamic process of constant message interchange within the autonomic nervous system and through systemic circulation.

Our model proposes that the supersystem governs the adaptive response to wounding and the generation of the related phenomenal pain state. It rests on three falsifiable hypotheses, namely that the supersystem: 1) Demonstrates connectivity; 2) Employs cross-subsystem information feedback loops for self-regulation; and 3) Demonstrates agency when perturbed by injury. Below, we clarify the concepts behind these hypotheses.

Connectivity: A Common Chemical Language

Our review reveals what Blalock¹⁹ and others had already detected, albeit with a more limited focus: a system of shared ligands and receptors comprises a “chemical language” that makes possible a complex, coherent response to a stressor at all levels of human physiology^{16, 195}. The major elements of this language are neurotransmitters, peptides, endocannabinoids, cytokines and hormones. Some versatile proteins, such as CRH, play several of these roles across systems and at multiple levels. This language makes possible self-organizing, adaptive responses. One can test the role of any given substance in connectivity.

Whether a “language” substance exerts an excitatory versus inhibitory, or pro- versus anti-inflammatory, effect is not always straightforward because it depends upon system context: many are pleiotropic. The impact of these messenger substances does not reduce merely to discrete actions they exert in a specific physiological locus. At the systems level, they deliver information that makes continuous coordination possible, participate in negative or positive feedback loops that move a system towards or away from equilibrium, and make possible the processes that comprise allostasis during stress. They allow the system to negotiate its environment, adapt in real time, mount emergency responses, and recover from those responses.

Feedback Loops

Feedback means that information about the output of a system passes back to the input and thereby dynamically controls the level of the output. System self-regulation and self-organization depend upon feedback, as does self-direction. Feedback-dependent regulatory processes and stress responses cross the nervous, endocrine and immune system boundaries and thereby contribute to overall system regulation. For example, cross-subsystem feedback loops play key roles in the interdependence of endocrine and immune systems^{13, 170}. Glucocorticoid products of the HPA axis modulate the basal operations of cytokine-producing immune cells. Cytokines, in turn, influence the activity of the HPA axis. Thus, the products of one subsystem provide messenger substances that provide feedback for another subsystem.

Feedback loops can be negative or positive. Negative feedback permits stability while positive feedback allows the organism to mount emergency responses. The regulatory processes of homeostasis and allostasis are feedback dependent. Negative feedback insures system stability and maintains homeostasis. Feedback is positive when a variable changes and the system responds by changing that variable even more in the same direction, generating escalation and rapid acceleration⁶³. This process abandons stability for instability. From an adaptation point of view, positive feedback loop capability is essential for meeting acute threat with defensive arousal.

Positive feedback loop activation plays a prominent role in pain. It allows systems to convert graded inputs to decisive all-or-none outputs²⁵ that are essential bi-stable state shifts. Abrupt,

non-linear shifts to facilitative modes of noxious signaling within the nervous system typically result from positive feedback loop activation, inducing hyperalgesia and allodynia. It characterizes the interdependence of peripheral and dorsal horn sensitization processes and, as we noted above, dorsal horn sensitization generates hippocampal and cortical potentiation that enhances responses to injury⁹⁴. Positive feedback can also occur with inhibitory circuits, resulting in hypoalgesia or analgesia.

Each mode of operation has adaptive value as a short-range response in certain types of injurious events. Sustained periods of positive feedback have the potential for destructive consequences. For example, excessive noxious input to the dorsal horn can increase glutamate to excitotoxic levels and thereby destroy inhibitory inter-neurons. Such damage becomes evident as the formation of dark neurons⁸⁵. This suggests that the perseveration of inflammatory noxious signaling can cause dorsal horn pathology.

Negative and positive feedback processes can go awry within the nervous, endocrine and immune systems and dysregulate normal processes. Negative feedback may fail when an endogenous messenger substance providing the feedback disappears, occurs in excess, or becomes confounded by exogenous products such as medications or substances of abuse that resemble them in chemical structure. In some cases, negative feedback fails when an extraneous influence alters the set point. For example, the presence of opioid medications in a male pain patient dysregulates the hypothalamo-pituitary-gonadal axis and results in hypogonadism^{21, 40, 41}. Positive feedback processes can also malfunction. Positive feedback probably contributes to migraine headache, allodynia, severe idiopathic abdominal pain, non-cardiac chest pain and a variety of multi-symptom disorders.

Agency

An *agent* is an individual, self-organizing system operating purposefully within its environment in the service of adaptation. The concept of *agent* equates with the individual when the focus of study is on the interaction of an organism with its environment, especially its social environment. Agent-Based Complex Systems directly identify the individual in the world as an agent⁷⁶. However, agency exists within nested subsystems whenever an element exhibits some degree of autonomy. For example, dendritic cells serve as “professional antigen-presenting agents.” They appear in peripheral organs such as skin where they encounter and capture antigens. They then migrate to the T cell areas of lymphoid tissues and present the processed antigens in order to elicit antigen-specific T cell responses. Whatever the level of inquiry, agents are semi-autonomous units that evolve over time and help to maximize adaptation.

We postulate that the supersystem is an agent for meeting the challenge of wounding, engaging the threat it represents at both the external and internal environments, and resolving the wound by healing. The supersystem, as an agent, maximizes adaptation by representing the wound in consciousness as pain. The dynamic, multi-dimensional, unpleasant pain experience with its affective and sickness dimensions is the product of the supersystem, not just the nervous system.

Put practically, the agency hypothesis states that wounding induces correlated nervous, endocrine and immune changes. These correlations define relational variables, or outcomes if interventions exist. Relational variables determine on the one hand wound healing and on the other hand the various subjective aspects of the pain experience such as pain intensity, unpleasantness, affect, quality, interference with normal function, sickness and rate of change. Multivariate statistical methods can evaluate the agency hypothesis by modeling correlations.

Dysfunction During Stress: Acute Responses Become Chronic Disorders

We have emphasized that the individual patient is a system, but every system exists within a larger, encapsulating system that influences it. The psychosocial system surrounding the individual patient a potential source of stressors that demand allostatic response above and beyond that elicited by injury. Figure 3 illustrates the biopsychosocial interactions of the individual with his/her environment and the various contributions of psychosocial factors to allostatic load. In the presence of psychosocial stressors, wound-induced acute stress responses can fail to resolve properly, leading to chronic disorders. This can happen in three ways.

Failed Arousal-to-Recovery Transition

Pain clinicians sometimes see pain patients who report surviving a horrific accident or event that left them traumatized. A single trauma of sufficient magnitude can produce a stress response that does not resolve properly. McEwen described other allostatic load scenarios that might lead to system malfunction: 1) unremitting or chronic stressors; 2) inability to adjust to a stressor of modest duration and demand; and 3) not hearing the “all clear” in which the stress response persists after the stressor has disappeared¹²⁸. These concepts, collectively, describe an arousal or fast response phase that fails to give way to a recovery or slow response phase.

Dysfunctional Recovery

The recovery process in the HPA axis invokes the inverted “U” principle: CORT insufficiency and CORT excess are both damaging⁴⁴. Too little CORT means prolonged anabolism. Moreover, positive feedback arousal processes can go unchecked and conversion to the recovery state may not occur. Conversely, too much CORT over time has negative catabolic consequences. Hypercortisolism is a marker of severe depression. In both cases, loss of normal diurnal variation in CORT pulsing indicates dysregulation. Thus, a dysfunctional endocrine recovery process is a mechanism for long-term endocrine dysregulation.

The boundaries of endocrine dysregulation extend to the immune subsystem. GCs profoundly affect cytokine responses. Evidence indicates that GCs inhibit Th1 cytokine production while at the same time promoting Th2 cytokines production⁶⁰. This is another form of protection against overshoot of positive-feedback-driven arousal responses⁵⁹.

Many writers¹⁰² characterize the immune system as operating in either Th1 dominant (pro-inflammatory) or Th2 dominant (anti-inflammatory). These modes roughly parallel the stress response arousal and recovery phases. This is more than a parallel concept. Evidence indicates that pro-inflammatory cytokines activate the HPA axis¹³ and thereby elicit MR and GC responses whereas VIP, PACAP and certain other peptides support Th2 processes^{47, 68}.

Dysfunctional Sub-system Interface

The interface between systems can become dysfunctional, impairing intersystem coordination. For example, Calcagni and Elenkov, in reviewing both endocrine and immune system response patterns during stress, raised the possibility of dysregulation in the neuroendocrine - immune interface³³. Weber identified the same potential source of disease²¹⁸. By extension, one could explore potential dysfunction in the nervous-immune interface or the nervous-endocrine interface as causal mechanisms for chronic pain states.

Supersystem Dysregulation in Chronic Pain

Dysregulation

Dysregulation is prolonged dysfunction in the ability of a system to recover its normal relationship to other systems and its normal level of operation following perturbation. This

concept applies to any level of system focus, whether it is the HPA axis or the adjustment of an individual to a social environment. An extensive literature addresses the relationships of trauma and prolonged stress with dysregulation of the HPA axis, the central noradrenergic system, and the SAM axis^{44, 145}. The supersystem model proposes that pain becomes a chronic and disabling condition as a result of regulatory problems developing over time within the supersystem; dysfunction arising in one subsystem is likely to lead to dysfunction in the others because they operate interdependently within the supersystem. Prolonged dysregulation can cause irreversible organ pathology, and this in turn can generate noxious signaling, as in rheumatoid arthritis and other auto-immune disorders. Dysregulation may manifest in at least four ways in chronic pain patients. These manifestations are not mutually exclusive.

Biorhythm Disturbance

First, in a temporal frame of reference, dysregulation refers to deviation from or loss of normal biological rhythms. Humans eat, sleep, and work according to circadian rhythms, and social activity patterns reflect these rhythms. Rhythm is a fundamental feature of homeostasis, as temperature regulation demonstrates. Subsystems also operate according to rhythms. Hormones pulse at certain times, and the resting heart beats in rhythm. Dysregulation of temporal processes may play a role in peripheral neuropathy¹⁸². The concept of cross-system rhythm is still poorly defined, but some substances participating in connectivity appear to coordinate biological rhythms at multiple systems levels. The hormone melatonin is one example⁹. Among its many effects is control of POMC gene expression¹⁶². The relationship of temporal rhythm dysregulation to chronic pain is largely unexplored, apart from the documentation of sleep disturbances. Inquiry into multi-rhythm dysregulation at multiple system levels in chronic pain patients could prove informative.

Feedback Dysfunction

Messenger substances play multiple roles, including feedback messaging. Subsystems like the HPA axis depend upon negative feedback to terminate recovery from stress processes. Subsystems also limit lower level positive feedback loops that make possible emergency responses, thus protecting against overshoot. Positive feedback processes are not self-limiting by definition and without such control they continue until either a state shift occurs or the system self-destructs. Allodynia is a familiar example of positive feedback in chronic pain, as is panic attack in emotional regulation. Within the immune system, positive and negative feedback play a central role in T cell discrimination of self from non-self ligands^{142, 189}. This process, too, is subject to dysregulation with negative health consequences manifesting as auto-immune disorders.

The literature identifies many examples of disturbed feedback-dependent regulatory processes in stressed patients. For example, patients may develop HPA axis dysregulation^{51, 86}, autonomic dysregulation¹⁰⁹, peptide dysregulation¹⁸⁷, Th1/Th2 cytokine dysregulation^{61, 209}, endogenous opioid dysregulation¹⁶⁷ and dysregulation of the relationship between pain and blood pressure²⁸. Basically, a subsystem regulated by negative feedback breaks down in one way or another, for example, through depletion of a key neurotransmitter or peptide. In other words, the allostatic load causes dysregulation.

Feedback mechanisms may also falter under the opposite condition of resource excess. The medical introduction of substances that resemble biological messengers may interfere with normal allostasis and produce iatrogenic disorder. Opioid medications provide a strong example, as they resemble beta endorphin and other endogenous opioids. The hypothalamo-pituitary-gonadal axis responds to such products as though they were endogenous signals and the result is often hypogonadism⁴¹.

Disturbed Intersubsystem Coordination

We have offered evidence that N, E and I subsystems are interdependent and coordinate their responding to a stressor such as tissue injury. The connectivity essential for cross-subsystem coordination may falter or break down. Examples include the reciprocal relationship of cytokines with HPA axis regulation^{33, 53, 170, 209}, the relationship of cytokine regulation to autonomic regulation³⁹ and the relationship of cytokine regulation to the LC response²². We propose that dysregulation in one subsystem will tend to disrupt another, leading eventually to supersystem dysfunction.

Incomplete Recovery

Dysregulation could occur if a system alters its set point in response to a stressor and then fails to readjust to the normal level after the stress has passed. This corresponds McEwen's metaphor of failure to hear the all clear signal¹²⁸. This explanatory model nicely describes the hypervigilance and hyper-reactivity of post-traumatic stress disorder (PTSD)⁸.

Set points are often straightforward to define. For example, Vogeser and colleagues²¹¹ studied major surgery as a stressor and chose the cortisol:cortisone ratio as a marker of HPA axis activity and as a stress-sensitive indicator of the overall set-point shift in the breakdown of cortisone to produce CORT, namely 11 β -hydroxysteroid dehydrogenase activity. Surgery caused a shift in this set point that later returned to presurgical levels. Cardiac variability, MR/GR ratio and Th1/Th2 ratio represent other potential system set point indicators that may exhibit pathological shifts in chronic pain. The auditory startle response, which indicates excessive autonomic response activation to startling stimuli, may be a marker of past trauma¹⁸³. Traumatic life events can permanently alter the set point of an individual's feedback-dependent HPA axis^{26, 43}.

Indices of Dysregulation

Psychological concepts of trait and state are useful for describing how dysregulation manifests. A *trait* is a relatively enduring predisposition to respond in certain ways when perturbed. It gauges the adaptive capability of an individual challenged by a stressor. A *state* is a transitory condition of the system, typically following perturbation. During chronic pain, dysregulation is likely to alter traits and this alteration may manifest as abnormal state responses to perturbation. For example, a person with normal trait anxiety may undergo a traumatic event and afterwards become highly anxious in response to small problems and shows abnormal startle responses. This is high state anxiety. By analogy, the trait-state distinction applies to neural, endocrine and immune subsystems. Below, are some examples of ways to quantify subsystem dysregulation. One can either quantify traits directly or infer them from challenge-induced changes in states.

Autonomic Dysregulation

Cardiac variability, sometimes called vagal tone, provides a trait measure for the autonomic nervous system. It indexes behavioral, cognitive and emotional function⁷. Basically, cardiac variability reflects the balance of sympathetic and parasympathetic influence in autonomic function as evident in cardiac activity. The vagus nerve is bidirectional. Vagal afferent fibers from the heart project to the solitary nucleus. Efferent fibers from the brainstem terminate on the sinoatrial node, the cardiac pacemaker. Sympathetic activation accelerates heart rate and parasympathetic activation decelerates heart rate.

Estimation of cardiac variability derives from respiratory sinus arrhythmia; that is, changes in heart rate during the respiratory cycle. During exhalation, vagal efferent activity modulates this rate and causes deceleration. Inhalation increases heart rate. Statistical indices of

instantaneous heart rate variability based on the R-to-R wave interval estimate cardiac variability. Such estimates are stress sensitive, and some investigators postulate that early trauma may permanently diminish cardiac variability, leaving the individual less resilient to future stressors^{23, 155}. High cardiac variability, or vagal tone, may be an indirect marker of an individual's ability to respond effectively to a stressor and recover efficiently from it.

Sensory Dysregulation

Tracey and Mantyh²⁰¹ postulate that chronic pain patients may have dysfunction in either the facilitatory system or the inhibitory system for nociceptive modulation. One can assess these processes by looking at windup and diffuse noxious inhibitory control (DNIC). Windup, or temporal summation, occurs when a subject undergoes a series of identical noxious stimuli. Tracking the pain rating across trials reveals increased pain or sensitization. This process may be abnormal in some chronic pain populations¹⁸⁸. When the activation of one noxious stimulus causes a diminished response to a second noxious stimulus, DNIC exists. In the laboratory, one measures the response to a phasic stimulus at baseline, applies a tonic stimulus such as the cold pressor test, and then measures the response to the phasic stimulus again. The response to the phasic stimulus should diminish following the tonic stimulus. This is independent of segment (hence diffuse) and not being naloxone reversible in most reports it is probably independent of the HPA axis. DNIC is a laboratory predictor of clinical pain and quality of life⁵⁷. Whether windup and DNIC are true opposing processes is uncertain but worth exploration.

Endocrine Dysregulation

Potential trait measures exist for the HPA axis. DeKloet and Derijk postulated that MR and GR mediated stress responses counterbalance: MR responses contribute to immediate arousal and coping whereas GR responses attenuate emergency reactions and assist recovery from stress⁴⁵. Normally, an individual possesses a characteristic MR/GR balance that is largely genetically determined.

Some approaches to diagnosing dysregulation involve challenging the HPA axis and looking for abnormal state responses to the challenges. The dexamethasone suppression test gauges HPA axis response in this way¹⁵⁹. Dexamethasone is an exogenous steroid that provides negative feedback to the pituitary to suppress the secretion of ACTH. It does not cross the blood-brain barrier. Excessive CORT response to dexamethasone occurs in up to half of all severely depressed patients, indicating axis dysregulation. Alternatively, the CRH challenge involves the infusion of CRH and measurement of subsequent ACTH and cortisol responses⁵¹. It, too, can gauge HPA axis dysregulation.

Detection of biorhythm dysregulation necessitates examination of diurnal or other chronological variation in hormones. This typically requires multiple samples within a single day and examination of the resulting profile against a normal profile. CORT, for example, normally peaks shortly after arising, and then blood levels decline and are very low late in the day and evening. Any other pattern indicates dysregulation. In contrast, opponent process dysregulation indicators derive from a ratio of opposing processes like the Th1/Th2 ratio. For this, there are many possibilities.

In looking at the negative impact of sleep deprivation³⁵ Copinschi examined both types of dysregulation. Sleep deprived subjects had increased cortisol levels in the late afternoon and evening. Examination of two brain-gut axis hormones related to appetite, ghrelin and leptin, also revealed dysregulation. Ghrelin increases appetite while leptin decreases it. With sleep deprivation, the ghrelin-to-leptin ratio shifted in the direction of higher ghrelin and lower leptin; this correlated strongly with increased hunger.

Immune Dysregulation

For the immune subsystem, Th1/Th2 balance has become a focus of attention in cytokine research^{60, 102}. The general view holds that stress is immunosuppressive. However, it is becoming clear that glucocorticoids and catecholamines support inflammation locally in certain conditions; that is, they promote Th1 cytokine production. And yet, systemically these substances potentiate Th2 production while inhibiting Th1 production, thereby exerting an anti-inflammatory effect³³. Because cytokine activity depends heavily upon stress hormones, such localized targeting of pro-inflammatory processes could be advantageous in promoting increased blood flow and cell trafficking to injured tissue. Th1/Th2 balance varies with the stress response. Regardless of whether that response is hyperactive or hypoactive, it may alter the course of immune-related disease. The Th1/Th2 ratio is skewed in several common diseases⁶⁰ and it is a useful parameter from a psychosomatic perspective. For example, Glaser and colleagues examined Th1/Th2 balance in chronically stressed caregivers of demented patients and found a shift in the Th2 direction, suggesting vulnerability to infection⁷⁰.

Individual Differences and Diathesis

Inheritable individual differences in stress response/recovery stem from two causal mechanisms: genetic and epigenetic. Non-inheritable, environmentally determined individual differences derive from previous life experiences including learning, culture and experience of trauma and the interactions of such experiences with genetic and epigenetic factors. Collectively, these influences interact to determine an individual's unique vulnerability for developing chronic pain. A severe stressor, a cascade of stressors, or continued self-generated stress-inducing thoughts can impose a heavy allostatic load that eventually causes dysregulation in one or another subsystem. Just as a metal link chain subjected to tension will break at the weakest link, a person with high, increasing allostatic load will experience dysregulation in the most vulnerable organ system. Genetic and epigenetic factors interact with environmental factors to determine which organ system is most vulnerable.

Diathesis

Diathesis refers to the vulnerability of an individual experiencing stress to a pathological consequence such as organ pathology or system dysregulation. With tissue trauma, each individual carries a unique risk of developing a chronic pain condition. For example, 22-67% of patients who undergo a thoracotomy develop chronic pain¹⁹⁸. The diathesis for each thoracotomy patient is a function of genetic factors, epigenetic factors, and an ensemble of other factors such as comorbidity, familial factors, psychological status and social support.

The stress diathesis model is not new in the chronic pain field, and psychologists in particular have called attention to individual differences in vulnerability to developing disabling chronic pain^{56, 205}. To date, pain stress-diathesis has not extended beyond a psychological view of nervous system function that lacks a physiological explanatory framework. We suggest that stress diathesis is an essential construct for the development of individualized pain medicine. The supersystem concept provides a framework for studying chronic pain at the individual level.

Genetics

Genes determine both the morphology of an organism and the processes by which it adapts to its environment, including its capacity to mount a defense response. One clinically important function of genetic profiling is to determine who is at risk under stress for pathology, such as disabling chronic pain. Another is to determine who can and cannot benefit from a given type of pharmacotherapy and at what dose. Moffit and colleagues¹⁴¹ describe the joint influence of genes and environment as gene-environment, or $G \times E$, interaction, which stands in contrast

to traditional assumptions of additive nature and nurture influences. The $G \times E$ interaction defines individual differences in risk for a given pathology during sustained or severe stress.

Genetic contributions to individual differences include the interactions of environment with individual genes, combinations of genes, gene mutations, allelic variants, and functional polymorphisms. Genetic factors may affect individual differences in pain sensitivity⁴⁹; both synthesis and function of proteins affecting the plasticity of the CNS⁶⁹, tissue remodeling after injury²⁰³ catecholamine metabolizing enzymes such as catechol-O-methyltransferase, or COMT⁵⁰, production of pro-inflammatory cytokines¹⁴, tendency to high blood pressure and altered pain sensitivity⁷⁹; thermal receptor sensitivity mediated via vanilloid receptors and opioid receptor subtypes¹⁰³, and the efficacy of opioid and other analgesic drugs^{166, 173}. Pathogenic mutations may be responsible for congenital insensitivity to painful events¹³⁹. In some cases, genetic factors influence individual differences only marginally¹⁰⁴, while in rare conditions such as congenital insensitivity, their effects are great.

Epigenetics

Epigenetics has many definitions, but the basic concept is that heritable traits exist, including transgenerational traits, that do not stem from changes to the underlying DNA structure and are potentially reversible. Epigenetic influences may reflect environmental pressure on an individual or on an individual's ancestors²²². Such changes in gene expression occur through the methylation of DNA, the post-translational modifications of histone proteins, and RNA-based silencing. Epigenetic factors can exert heritable influence on both disease and health¹⁸⁵. They determine opioid μ -receptor expression⁹⁰ and influence the HPA axis aspects of the stress response¹²⁹. Many investigators focus on the role of environment-driven maternal behavior as a determinant of subsequent gene expression. For example Zhang and colleagues²²⁹, demonstrated that environmental adversity affected mothers in a way that enhanced the capacity for a heightened defense response in the offspring. This increases the probability of offspring survival to sexual maturity but at the cost of multiple pathologies in later life. Epigenetic influences not only stem from the environment; like genetic influences they may interact with the environment. Unlike genetic influences, they are unstable and may alter with environmental change including in principle therapeutic intervention.

Conclusion

A human being is a complex adaptive system coping with a social and physical environment but possessing nested subsystems. Wounding generates an allostatic response that involves an ensemble of interdependent nervous, endocrine and immune processes. We hypothesize that these processes comprise a supersystem. Acute pain in its multiple dimensions, and related symptoms, are products of the supersystem.

The social system that encompasses the individual can also be a source of stressors. Social stressors can compound the allostatic load of a wound or act alone to dysregulate the supersystem. When the supersystem suffers dysregulation, health, function and sense of well-being suffer. We propose that some chronic pain conditions and related multi-symptom disorders stem from supersystem dysregulation. Individuals vary and are vulnerable to dysregulation and dysfunction in particular organ systems due to the unique interactions of genetic, epigenetic and environmental factors, and past experiences that characterize each person.

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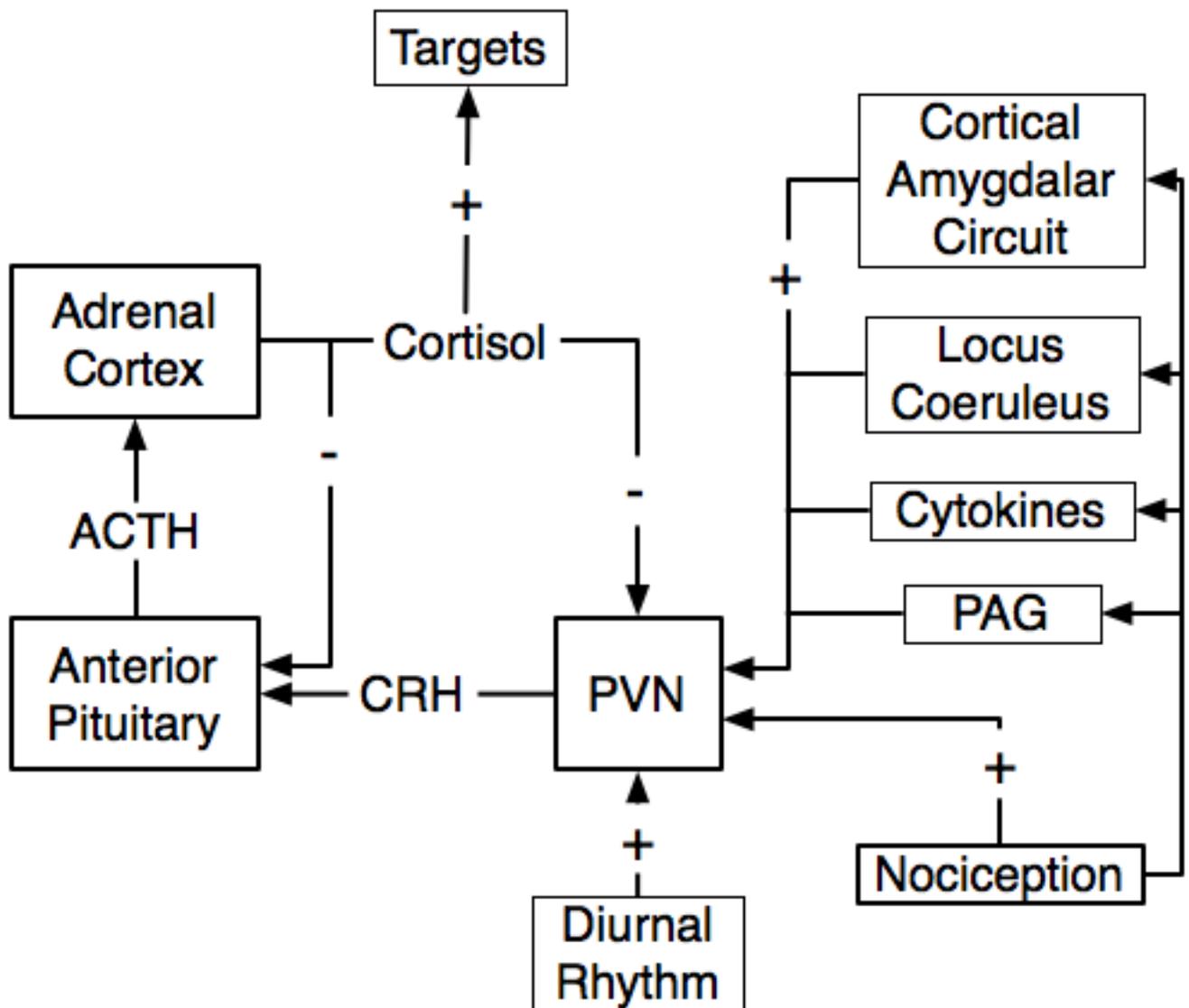


Figure 1. The Hypothalamo-Pituitary-Adrenocortical Axis Stress Response

Nociceptive signaling acts directly upon the hypothalamic PVN, but also upon the PAG, the LC, the cortico-amygdalar circuit, and also triggers release of pro-inflammatory cytokines from various immune cells and the adrenal medulla. All of these activate the PVN, which normally responds to diurnal rhythm and associated circulating cortisol levels. Stressor-induced activation of the PVN releases CRH from the median eminence into portal circulation. This stimulates the anterior pituitary and causes the release of ACTH into systemic circulation. ACTH provokes cortisol release at the adrenal cortex. Cortisol has widespread effects on a wide array of target organs. Because this is a negative feedback system, cortisol provides feedback to both the PVN and the anterior pituitary, thus controlling axis activity. PVN: periventricular nucleus of hypothalamus; PAG: periaqueductal gray; ACTH: adrenocorticotropic hormone, or corticotropin; CRH: corticotropin-releasing hormone.

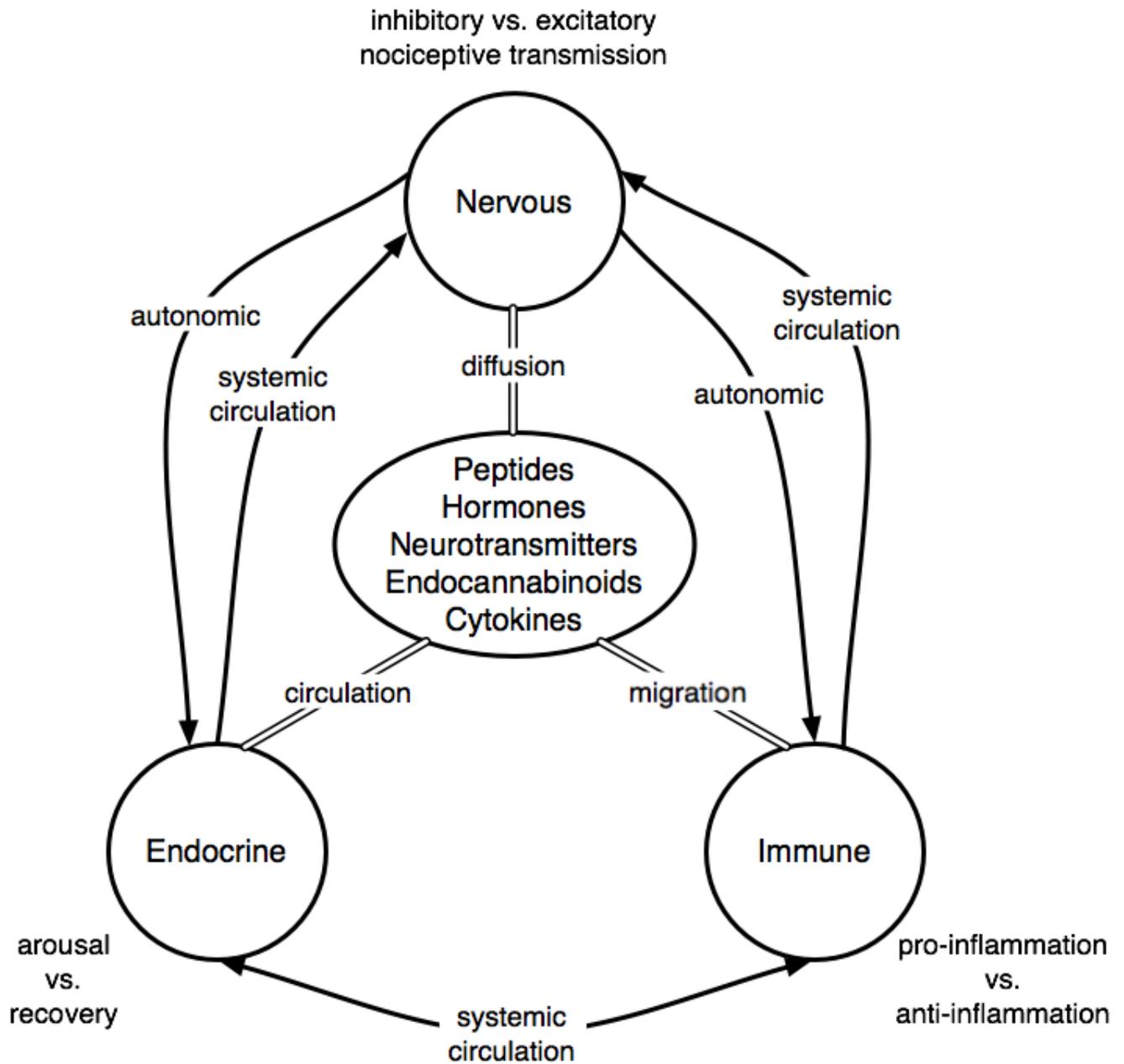


Figure 2. Connectivity

Nervous, endocrine and immune subsystems communicate dynamically using the language of common chemical substances, as indicated in the center of the figure. The major language elements are peptides, hormones, neurotransmitters, endocannabinoids and cytokines. These substances are pleiotropic in that they exert different effects depending upon context (e.g., phase and location). Circulation, diffusion and migration are some of the processes of information transmission. Systemic circulation and autonomic nervous system activity are other vehicles of information transmission. Because the nervous, endocrine and immune systems have constant reciprocal communication, they tend to react to a stressor in a highly orchestrated manner, as a single unit.

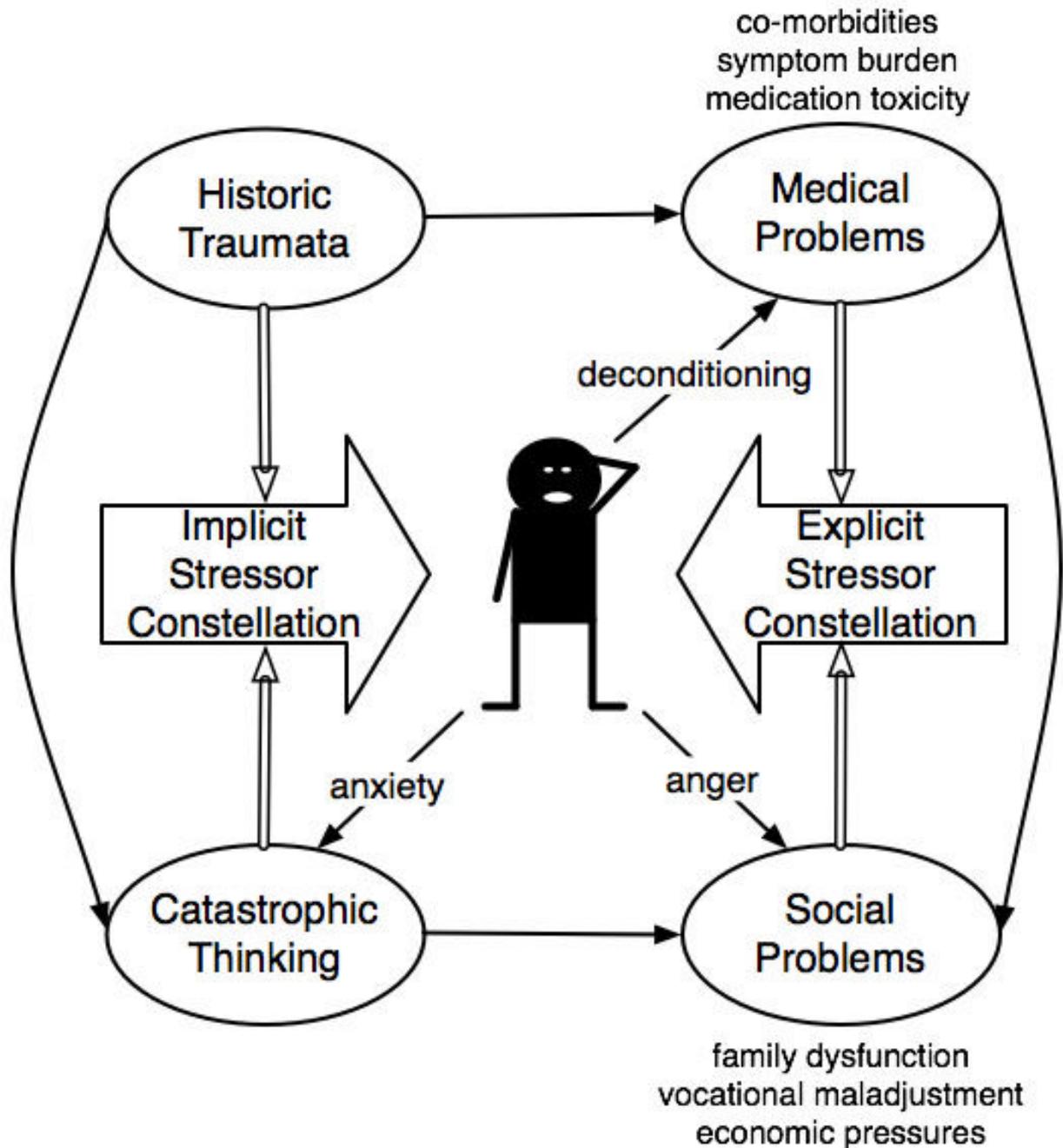


Figure 3. Stressors and the Chronic Pain Patient

A typical chronic pain patient has medical problems related to one or more historic events. These problems limit vocational options and normal social interactions, with resulting financial problems, social isolation and family distress. These processes comprise the explicit stressor constellation. Past history and memories of the patient, together with negative thinking, comprise the implicit stressor constellation. Catastrophic thinking is the tendency to frame every problem with a worst-case scenario. Patients tend to engage in it because of anxiety about their explicit problems. The negative thinking becomes its own stressor. Moreover, it makes relationships with people offering social and medical support difficult. Often, social problems and a sense of being a victim generate anger, which complicates vocational and family

relationships and exacerbates the explicit stressor constellation. Measures of social conflict processes characterize patient social interactions as the interactions of a subsystem within the larger system that surrounds it.