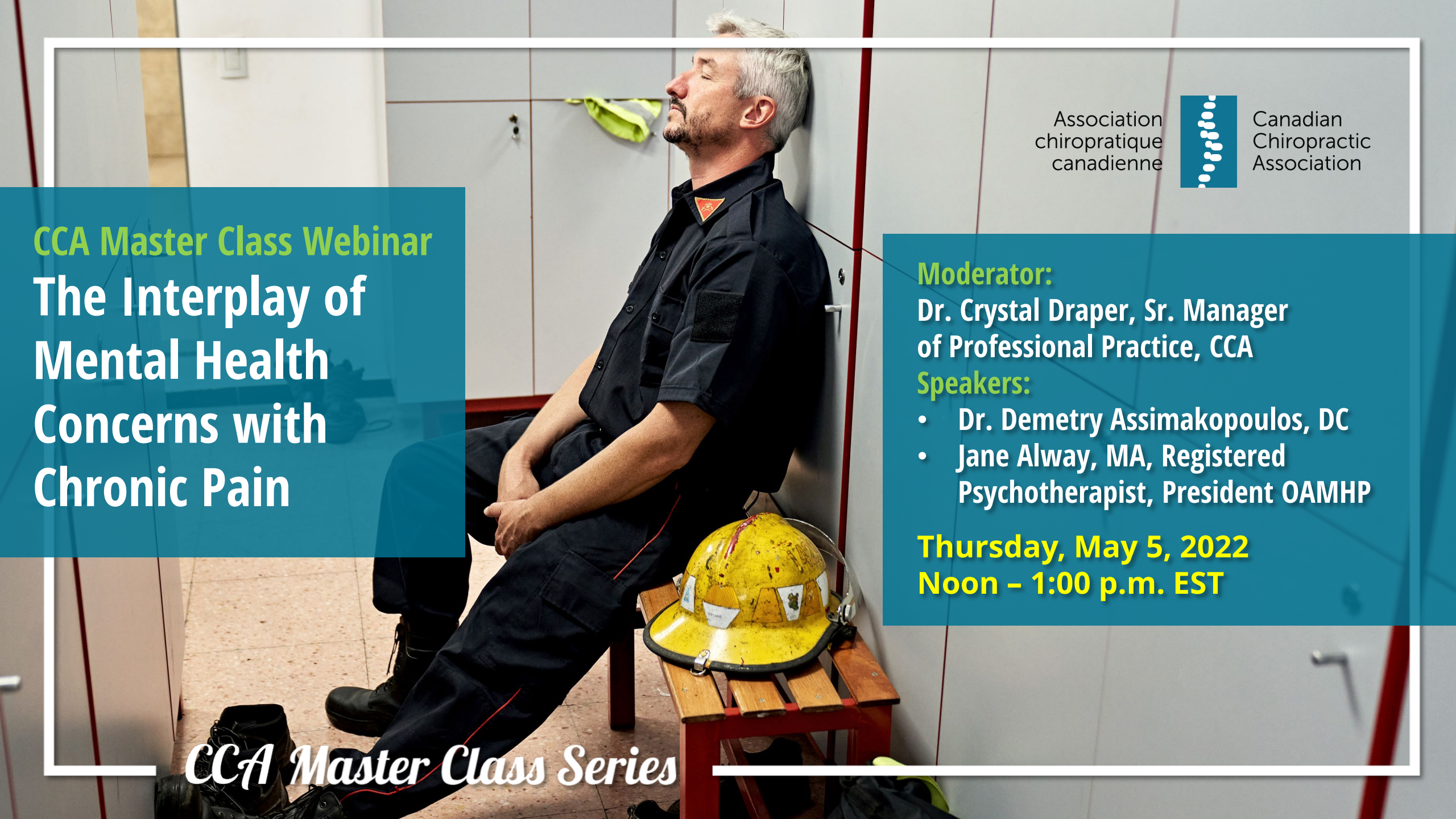


Association chiropratique canadienne

Canadian Chiropractic Association

CCA Master Class Webinar

The Interplay of Mental Health Concerns with Chronic Pain

Moderator:
Dr. Crystal Draper, Sr. Manager of Professional Practice, CCA

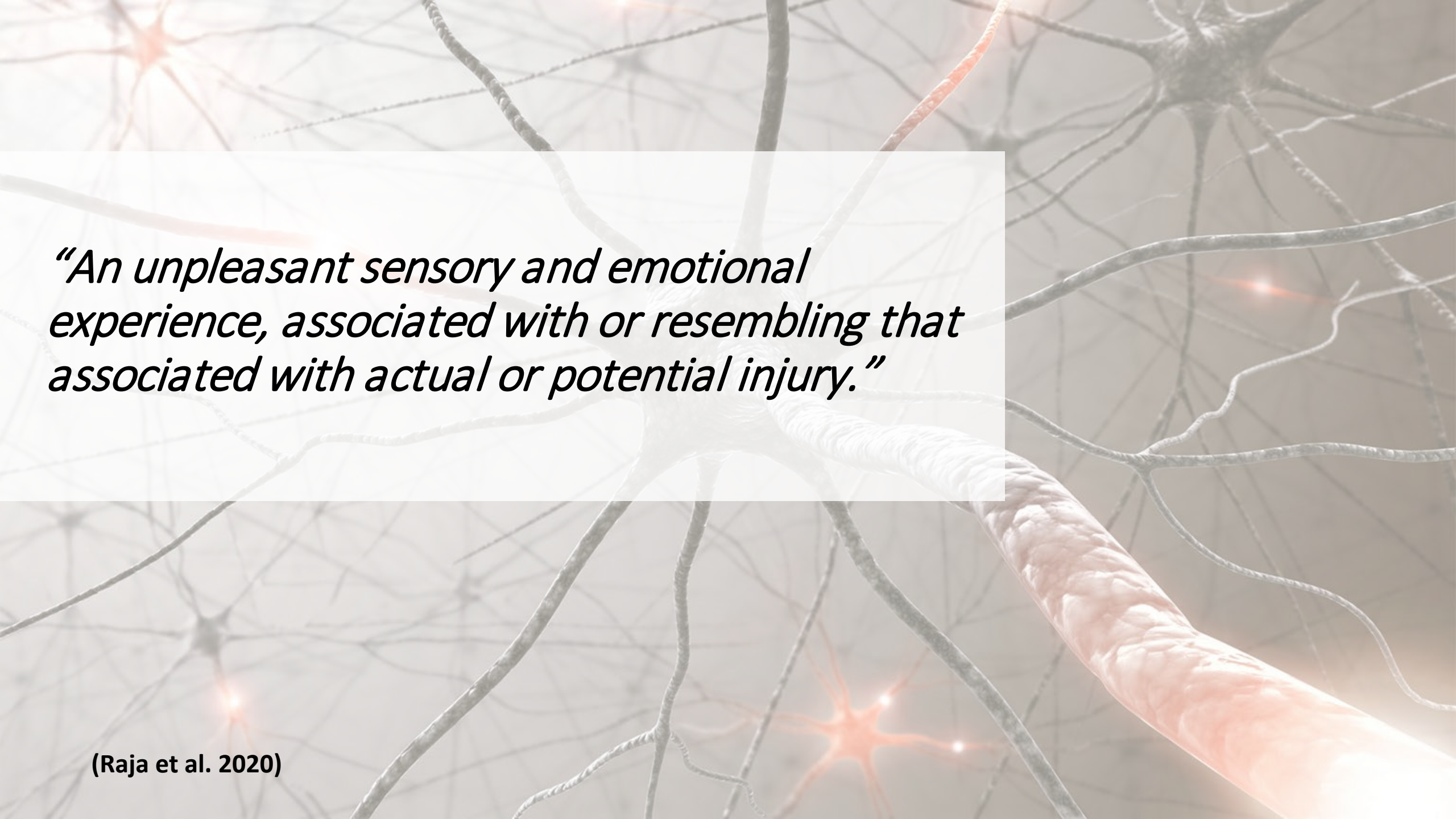
Speakers:

- Dr. Demetry Assimakopoulos, DC
- Jane Alway, MA, Registered Psychotherapist, President OAMHP

Thursday, May 5, 2022
Noon – 1:00 p.m. EST

CCA Master Class Series

What is Pain?



"An unpleasant sensory and emotional experience, associated with or resembling that associated with actual or potential injury."

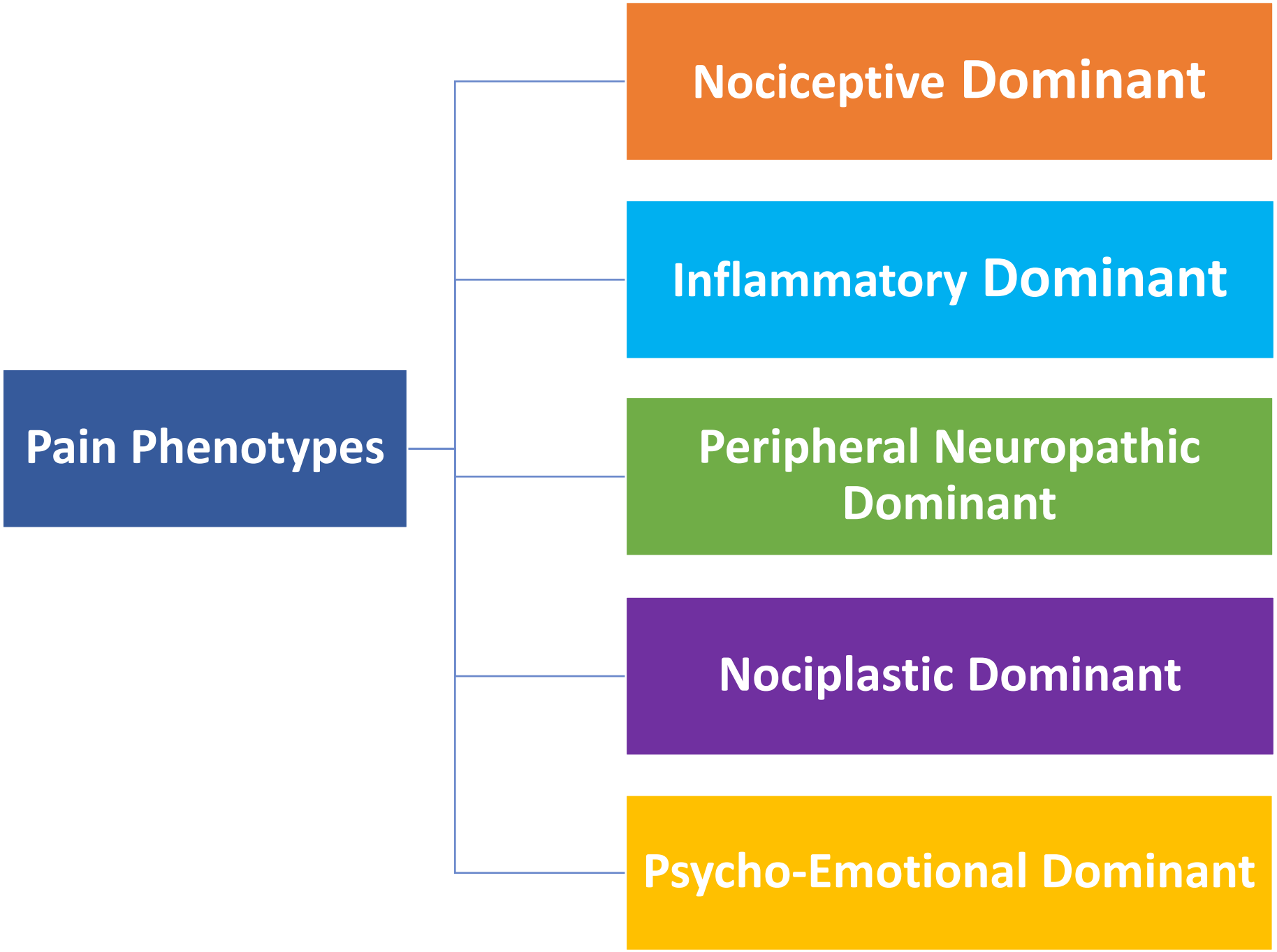
(Raja et al. 2020)

Definition of “Chronic Pain”

- **Old Definition:** Pain that persists past the normal healing time and lacks acute warning function of physiological nociception

- **New Definition:** Pain which lasts or recurs > 3-months (ICD-11)

(Nicholas et al, 2019)


Pain Phenotypes
Nociceptive Dominant
Inflammatory Dominant
Peripheral Neuropathic Dominant
Nociplastic Dominant
Psycho-Emotional Dominant

Psychoemotional Dominant Pain Phenotype

- Psychological = PRIMARY DETERMINANT OF HEALTH (trans-diagnostic)
- History of, or current, psychopathology (beyond threshold)
- History of trauma
  - Adverse Childhood Experiences, Adverse Life Experiences
- Maladaptive thoughts
  - Kinesiophobia, catastrophizing, perception of injustice
- Poor stress management, or lives in context of stressful environment which cannot be controlled
  - Improves while on vacation or when separated from stressor
- Inconsistent mechanical pattern
- MORE FEATURE YOU FIND → LIKELIHOOD

(Walton, 2018)

The Role of the Chiropractor

- Pain management of neuro-MSK conditions within our scope & skillset

- Gatekeeper for referral
  - Operate within your scope
  - Know enough about therapies outside of your scope to know when they are needed

- Mental health – talk → confirm symptom presence → refer with letter
  - Depression, anxiety, PTSD and sleep screening symptom checklists in resources
  - Yellow Flag Risk Form in resources
    - Outcome measure & conversation starter
    - Confirm with other questionnaires

Different Types of Mental Health Practitioners

Regulated Practitioners

- Registered Psychotherapists (ON, QC) & Counselling Therapists (NB, NS, PEI, and soon AB)*
  scope of practice is the same for all these practitioners
- Registered Social Workers
- Psychologists and Psychological Associates
- Occupational Therapists
- Nurses
- Nurse Practitioners
- Doctors/Medical Psychotherapists/Psychiatrists

Unregulated Practitioners

- Counsellors
  (e.g Addictions Counsellors)
- Counsellors located in YT, NT, NU, BC, SK, MB and NL

Scope of Practice

Communicating a DSM Diagnosis:

- Psychologists/many Psychological Associates
- Nurse Practitioners
- Doctors/Medical Psychotherapists/Psychiatrists

(Note that Psychometrists administer psychological tests and typically work under the supervision of a Psychologist or Psychological Associate. Psychometrists cannot communicate a diagnosis unless they also hold the title of one of the aforementioned practitioners.)

Providing Treatment Via the Controlled Act of Psychotherapy:

- Registered Psychotherapists and Counselling Therapists
- Registered Social Workers
- Occupational Therapists
- Registered Nurses and Registered Practical Nurses
  (Note that in some settings a doctor's order may be required for RNs/RPNs to provide treatment.)

Providing Coping Skills/Life Skills/Promoting Activities of Daily Living/Assisting with Substance Use Concerns along with counselling and psychotherapeutic techniques:

- All those listed above in the Scope of Practice list along with counsellors

Controlled Act of Psychotherapy (versus Psychotherapy or Counselling):

Treating, by means of psychotherapy technique, delivered through a therapeutic relationship, an individual's serious disorder of thought, cognition, mood, emotional regulation, perception or memory that may seriously impair the individual's judgement, insight, behaviour, communication or social functioning.

Controlled Act of Communicating a Diagnosis:

Communicating to the individual or his or her personal representative a diagnosis identifying a disease or disorder as the cause of symptoms of the individual in circumstances in which it is reasonably foreseeable that the individual or his or her personal representative will rely on the diagnosis.

(Source: RHPA)

YELLOW FLAG RISK FORM

Name: _____ Date: _____ Primary Complaint:_____

1. Please indicate your usual level of pain during **the past week.**

No Pain **Worst pain possible**

0 1 2 3 4 5 6 7 8 9 10

2. Does pain, numbness, tingling, or weakness, extend into your leg (from back) &/or arm (from neck)?

None of the time **All of the time**

0 1 2 3 4 5 6 7 8 9 10

3. How would you rate **your general health**?

Poor **Excellent**

0 1 2 3 4 5 6 7 8 9 10

4. If you had to spend the rest of your life with your condition as it is right now. How would you feel about it?

Delighted **Terrible**

0 1 2 3 4 5 6 7 8 9 10

5. How anxious (eg. tense, uptight, irritable, fearful, difficulty in concentrating / relaxing) have you been feeling **during the past week**?

Not at all **Extremely anxious**

0 1 2 3 4 5 6 7 8 9 10

6. How much have you been able to control (ie. Reduce / help) your pain / complaint on your own during **the past week**?

I can reduce it **I can't reduce it at all**

0 1 2 3 4 5 6 7 8 9 10

7. Please indicate how depressed (eg. down in dumps, sad, downhearted, in low spirits, pessimistic feelings of hopelessness) have you been feeling in **the past week**.

Not depressed at all **Extremely depressed**

0 1 2 3 4 5 6 7 8 9 10

8. On a scale of 0-10, how certain are you that you will be doing normal activities or working in **six months**?

Very certain **Not certain at all**

0 1 2 3 4 5 6 7 8 9 10

9. I can do light work for an hour.

Completely agree **Completely disagree**

0 1 2 3 4 5 6 7 8 9 10

10. I can sleep at night.

Completely agree **Completely disagree**

0 1 2 3 4 5 6 7 8 9 10

11. An increase in pain is an indication that I should stop what I am doing until the pain decreases.

Completely disagree **Completely agree**

0 1 2 3 4 5 6 7 8 9 10

12. Physical activity makes my pain worse.

Completely disagree **Completely agree**

0 1 2 3 4 5 6 7 8 9 10

13. I should not do my normal activities including work, with my present pain.

Completely disagree **Completely agree**

0 1 2 3 4 5 6 7 8 9 10

The maximum score is 130, and can be stratified in the following way:
1. <50 low risk of psychosocial factors and pain-related disability
2. 51-64 moderate risk of psychosocial factors and pain-related disability
3. > 65 high risk for psychosocial factors and pain-related disability

Fear/escape C-sens dominant – 9, 11, 12, 13 - /40

Emotional/Affective and confidence in general health dominant – 3, 4, 5, 6, 7, 8 - /60

Peripheral dominant = 1, 2, 6, 10, 12 - /40

Post-Traumatic Symptoms		
Symptom	Yes	No
Uncontrollable thoughts about event		
Constant vivid recall of injury or shock - Flashbacks		
Dulled responses to others/ outside world.		
Sleep disturbance		
Nightmares		
Severe anxiety		

Sleep Symptoms		
Symptom	**Yes**	**No**
1. Do you have difficulty falling asleep, staying asleep or both?		
2. What keeps you awake • Pain? • Thoughts? • Nightmares?		
3. Do you feel rested when you wake up in the morning?		
4. How long have these symptoms been occurring?		
5. What happens to your pain when you do not sleep well?		
6. Do you snore?		
7. Have you every stopped breathing in the middle of the night?		
8. Does your partner ever tell you that you stop breathing in the middle of the night?		
9. Is your pain worse or better in the morning?		
10. Does your mood affect your sleep?		

DSM 5 – Depression Checklist		
Symptom	Yes	No
Feeling sad all or most of the time		
Diminished interest/pleasure in activities (anhedonia)		
Feelings of guilt, worthlessness, hopelessness, regret		
Energy deficit		
Concentration deficit		
Increased or decreased appetite		
Psychomotor retardation or agitation		
Suicidal ideation		
Increased/Decreased sleep compared to normal		

DSM 5 – Anxiety Checklist		
Symptom	Yes	No
Excessive worry		
Difficult to control worry		
Any number or greater of the following: • Restlessness • Easily fatigued • Irritability • Sleep disturbance		
Clinically significant distress or impairment in social, occupational or other areas of functioning		
Symptoms not secondary to substance (ie. Drugs, alcohol)		
Cannot be explained by anything else		

CCA Master Class: The Interplay of Mental Health Concerns with Chronic Pain

May 05, 2022

Dr. Demetry Assimakopoulos & Jane Alway

Support Tips for Suicidality Resources

If a patient reports having had suicidal thoughts:

1. Query if they are actively suicidal (they have the intention, a plan and a means to attempt suicide).

2. If they are actively suicidal, contact local crisis intervention services and/or arrange for the person to get to their local ER. If you are working within a collaborative setting that employs mental health practitioners who are available for immediate intervention, connecting the patient with these practitioners is also an option.

3. If the person is not actively suicidal, but has had suicidal thoughts or there has been a previous attempt, provide the patient with a list of local crisis/support lines and their hours of operation. Note that a list is important because some crisis/support lines may be overloaded and patients should, if at all possible, have a variety of options.

4. Encourage the patient to have this list and any Safety Plan readily available - crisis lines/safety plans are more likely to be used if readily accessible to the patient in a time of need.

5. Ask the patient if they are open to using the numbers on the list and, if they are hesitant, query and explore any hesitancy with the patient.

6. Safety Plan: Query if the patient has a safety plan in place. If a Safety Plan has been developed engage in collaborative care with the patient's mental health practitioner by ensuring that you both have access to the Safety Plan.

One national resource you could offer:

CRISIS SERVICES CANADA
Website (English): https://www.crisisservicescanada.ca/en/
Website (French): https://www.crisisservicescanada.ca/fr/
Phone (24/7/365): 1-833-456-4566 or 1-866-277-3553 in Quebec
Text (4 pm to midnight ET): 45645 (French Text support is currently unavailable)

Note that the website of Crisis Services Canada also provides a list of additional and provincially based talk/text services.

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Cost-Effective Mental Health Treatment Options

Insurance
Query if the patient has private/workplace insurance and, if so, what type(s) of practitioners they are covered for. Encourage the patient to check their insurance prior to sending a referral.

OHIP Covered
Some clinic and hospital-based programs provide treatment under OHIP.

NeuroNova Centre: Patient Courses & Personal Development and Patient Courses
The NeuroNova Centre offers a variety of Mindfulness-Based Chronic Pain Management courses. Some of these courses are covered under OHIP while others have a set fee for a course/program.

Family Services/Catholic Family Services/Jewish Family Services
These community-based agencies offer affordable professional therapy/counselling.

Canadian Mental Health Association (CMHA)
CMHA provides services via district offices across Canada. They also offer the Bounceback Program which is a free skill-building program for those over age 15 designed to help with low mood, mild to moderate depression and anxiety, stress or worry; this is delivered via phone coaching and online videos. They also offer Recovery Colleges to teach adults about mental health and well-being - courses are offered online.

Centre for Addiction and Mental Health (CAMH): 416-535-8501, option 2
This link provides centralized information, intake and scheduling for the majority of CAMH's services.

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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 function[114]. 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 indefinitely[114]. 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. Psychophysiologically, 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 toxins[16] and initiates complex inflammatory responses that protects 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 milieu[127]. 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 *homeostasi*s 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 immune[71]. 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 a*llostasis*[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. Selye[179] first described this response as a syndrome produced by "diverse nocuous 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 Aδ 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 chemotaxis[62] in the acute phase reaction[78]. Macrophages, lymphocytes, mast cells interact with SP, CGRP and NKA released from C fibers to create a chemical “soup” of proalgesic mediators[101]. 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 prostaglandins[169]. 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-1β and TNFα[153].

Dorsal Horn: The dorsal horn is a complex, multisynaptic structure with multiple functions[196]. 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 environments[115]. 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 cortex[37].

The spinal cord demonstrates plasticity by shifting bi-phasically between states of nociceptive inhibition and nociceptive facilitation[171]. Sandkuhler[177] 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 inhibition[52]. Vanegas and Schaible identified the periaqueductal gray and rostal ventromedial medulla as an efferent channel for nociceptive control and proposed that a shift from inhibitory to facilitatory influence might contribute to chronic pain[208].

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 signals[94]. 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 input[94].

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 horn[115] and continues in the basal ganglia[144], solitary nucleus[88], superior colliculus[190] and cortex [116], which contains multimodal neurons[66]. This process is selective and bi-directional in that cortex mediates multi-sensorial integration in deeper structures[95].

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. Craig[37] 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 cortices[4]. 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 colleagues [88] 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 Craig[37], 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 injury[119]. Frontal-PAG circuits play a role in pain modulation. Tracey and Mantyh[201] 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 PAG[24]. 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 processes[37]. Tracey and colleagues[200] 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 response[119]. 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 LC [6]. 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 behaviors[140]. In general, amygdala is the mechanism of conditioned fear[149, 175]. It communicates with hypothalamus via neural circuitry[227]. 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 Derijk[45] 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) axis [148]. 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 levels[60], including the LC[163]. 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 brain[118]. CRH-1[45] 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 CRH[163]. LC neurons increase firing rates in response to CRH, and this increases NE levels throughout the CNS[93].

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 ACTH[136] 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 peptides[44] 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. Kohl[110] 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 system[150].

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 wound[78]. 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, IL1-β, stimulates the release of SP from primary afferent neurons[91]. The neurogenic inflammatory response helps initiate the immune defense response and at the same time is in part a product of that response[62].

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 innervation[58] 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. Tracey[202] 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 INFα and INFγ; c) Tumor Necrosis Factors, including TNFα; 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 IL1-β, IL-2, IL-6, IL-8, IL-12, IFN-γ and TNFα. 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 IL1-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 astrocytes[226]. 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 issue[164]. Pro-inflammatory cytokines instigate the behavioral, neuroendocrine and neurochemical features of depressive disorders[3]. The therapeutic use of pro-inflammatory cytokines INFα and IL-2 for cancer treatment produces depression[32]; 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 injury[18]. 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

substances[134]. 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 body[133], 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 production[59]. In addition, NPY's receptors, Y1 and Y2, exist throughout the immune system. NPY stimulates lymphocyte proliferation[212], enhances leukocyte function[193], and modulates macrophage activity[42].

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 pain[82]. Microglia are immune cells closely related to macrophages that express the same surface markers[64]. Injury and other events that threaten homeostasis activate microglia. These immune cells contribute to hyperalgesia and alloydynia by releasing pro-inflammatory cytokines and chemokines, and they are probably involved in several neuropathic pain conditions[125].

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 glutamate[224]. 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 hyperalgesia[137]. Conversely, minocycline administered preemptively at the time of injury reverses hyperalgesia and allodynia[117]. 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 responses[74]. C fibers release it the wound along with SP, and mast cells appear to be the primary targets[33]. In caudal dorsal raphe nucleus, CRH induces the release of serotonin from neurons[80]. At central amygdala, CRH has an anxiogenic function[131] and is important for memory consolidation[172], but these effects are independent of its action at the HPA axis[143]. Psychogenic stressors can trigger the release of CRH at amygdala[130]. 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 adenolate 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 inflammation[213]. CGRP suppresses IL-2 production[215].

In addition to pro-inflammatory peptides, peripheral C-fibers release SOM, which enters systemic circulation and exerts anti-inflammatory and analgesic effects[154]. 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 exist[195], 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 microglia[46].

VIP and PACAP regulate both innate and adaptive immunity[67, 68]. Most lymphoid organs contain VIPergic nerve fibers located close to immune cells[112]. T cells, particularly Th2 cells, produce VIP. VIP and PACAP limit the cytotoxicity of CD4+ and CD8+ T cells, probably by inhibiting chemokine receptors[75]. 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 cytokine[156]. 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 macrophages[47]. 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 not[106]. When injected intradermally, PACAP is strongly anti-inflammatory, presumably modulating cytokine production[108].

Other peptides serving as messenger substances include orphanin FQ/nociceptin[132], 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 responses[181].

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 infection[126]. Il-1β upregulates tachykinin in the peripheral nervous system[99].

Tachykinins also exist in the immune system[113, 165] where they stimulate monocytes and macrophages[96], 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 TNFα from peripheral blood monocytes and in bone cells[73]. SP receptors also exist in blood vessels[165].

Cytokines as Messengers—Cytokines help coordinate the nervous and immune systems. Pro-inflammatory cytokines act at multiple levels of the neuraxis[54]. They bind to sensory afferent terminals of the vagus and glossopharyngeal nerves and thereby influence the solitary nucleus and other mesencepahlic noradrenergic sites[55, 124, 206]. IL-1 triggers cerebral NE metabolism and secretion[53] and influences activity in the LC[22]. Pro-inflammatory cytokines act at the PVN and at other levels of the HPA axis to release adrenal glucocorticoids[184, 206] and IL-1β stimulates CRH neurons[100]. 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-1β release in hypothalamus and hippocampus[89]. The ability of other, non-invasive stressors to increase IL1-β depends upon NE[20]. IL1-β activates the HPA axis, increases NE release at hypothalamus[223]. and stimulates LC activity[22].

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 IL1-β are releasing factors for opioid peptides[178]. Leukocytes secrete endogenous opioids in response to releasing factors such as CRH, NE and pro-inflammatory cytokines[168, 169]. Endogenous opioids supress 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 acid[38]. Nervous, blood and endothelial cells release endocannabinoids[160]. The endocannabinoid endogenous ligands anandamide (AEA) and 2-arachidonoylglycerol (2AG) bind to the G protein-coupled receptors CB1 and CB2[107]. Broadly, the endocannabinoids exert immune-suppressing effects. Anandamide inhibits the migration of CD8+ T lymphocytes[98]. Extended exposure to marijuana compromises immune function and may result in disturbance of the normal Th1/Th2 cytokine ratio[31]. Monocytes, helper T-cells, macrophages, and brain microglia all express cannabinoid receptors[214].

CB1 cannabinoid receptors and ligands occur principally in brain, immune and other peripheral tissues, while CB2 receptors and ligands occur primarily in immune cells[107]. 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 brainstem [255]. 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 mediators[186]. On the one hand, low AEA concentrations induce CB1 receptor-mediated inhibition of electrically-induced neuropeptide release from dorsal root ganglion neurons[176]. On the other hand, high

AEA concentrations evoke TRPV1 receptor-mediated neuropeptide release at central terminals of capsaicin-sensitive sensory neurons[199], which could potentially oppose peripheral CB-mediated inhibitory action. Cannabinoids may act solely through the TRPV1 receptor[151] 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 hormones[148]; 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 brain[204], the sympathetic components of the central autonomic network. From the pain perspective, the stress response has several key properties[86]. 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 amygdala[87] and the mesocorticolimbic dopaminergic system[204].

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 noxious[147]. AVP production is simultaneous and AVP interacts synergistically with CRH[204]. 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-endorphin[138]. 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 production[136]. 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 axis[146]. 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 expression[77].

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 cells[81]. 5-HT stimulates secretion and synthesis of CRH[92]. 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 effects[121]. 5-HT inhibits production of INFγ, 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 nucleus[80]. Dunn summarized the impact of IL-1 administration on the HPA axis[53]. 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 features[150]. 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 cells[122]. In general, catecholamines including dopamine tend to shift the cytokine balance in the Th2, or anti-inflammatory, direction[59]. 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 responses[210].

Corticotropin-Releasing Hormone—Centrally, CRH plays a major role in linking immune and endocrine function[100]. 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-1[17]. In addition, POMC-expressing neurons exist in hypothalamus, elsewhere in the CNS and in the skin[158]. Circulating corticosteroids and pro-inflammatory cytokines appear to control circadian rhythms of POMC expression[180].

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 cells[1]. CRH presence in inflammatory tissues may be the product of immune cells, peripheral nerves, or both[33]. 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 activation[27]. AEA intracerebral ventricular administration activates the HPA axis, increasing serum levels of ACTH and corticosterone in a dose-related manner[219], probably via the CB1 receptor and further hypothalamic PVN cannabinoid receptor binding[220].

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 axis[184]. Microglia are likely the primary central source of IL-1[20]. 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 axis[53].

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 medulla[13]. Glucocorticoids also inhibit Th1 cytokine production in a variety of systems while increasing the production of several Th2 cytokines[60].

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 Blalock[19] 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 acceleration[63]. 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 outputs[25] that are essential bi-stable state shifts. Abrupt,

non-liner 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 injury[94]. 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 neurons[85]. 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 agent[76]. 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 disappeared[128]. 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 damaging[44]. 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 production[60]. This is another form of protection against overshoot of positive-feedback-driven arousal responses[59].

Many writers[102] 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 axis[13] 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 interface[33]. Weber identified the same potential source of disease[218]. 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 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 neuropathy[182]. 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 example[9]. Among its many effects is control of POMC gene expression[162]. 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 dysregulation[109], peptide dysregulation[187], Th1/Th2 cytokine dysregulation[61, 209], endogenous opioid dysregulation[167] and dysregulation of the relationship between pain and blood pressure[28]. 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 hypogonadism[41].

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 regulation[39] and the relationship of cytokine regulation to the LC response[22]. 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 signal[128]. 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 colleagues[211] 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 11b-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 trauma[183]. 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 function[7]. 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 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 Mantyh[201] 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 populations[188]. 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 life[57]. 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 stress[45]. 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 way[159]. 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 responses[51]. 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 deprivation[35] 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 effect[33]. 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 diseases[60] 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 infection[70].

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 pain[198]. 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 colleagues[141] describe the joint influence of genes and environment as gene-environment, or G × E, interaction, which stands in contrast

to traditional assumptions of additive nature and nurture influences. The G × 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 sensitivity[49]; both synthesis and function of proteins affecting the plasticity of the CNS[69], tissue remodeling after injury[203] catecholamine metabolizing enzymes such as catechol-O-methyltransferase, or COMT[50], production of pro-inflammatory cytokines[14], tendency to high blood pressure and altered pain sensitivity[79]; thermal receptor sensitivity mediated via vanilloid receptors and opioid receptor subtypes[103], and the efficacy of opioid and other analgesic drugs[166, 173]. Pathogenic mutations may be responsible for congenital insensitivity to painful events[139]. In some cases, genetic factors influence individual differences only marginally[104], 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 ancestors[222]. 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 health[185]. They determine opioid μ-receptor expression[90] and influence the HPA axis aspects of the stress response[129]. Many investigators focus on the role of environment-driven maternal behavior as a determinant of subsequent gene expression. For example Zhang and colleagues[229], demonstrated that environmental adversity affected mothers in a way that enhanced the capacity for a heightened defense response in the offspring. This increases the probably 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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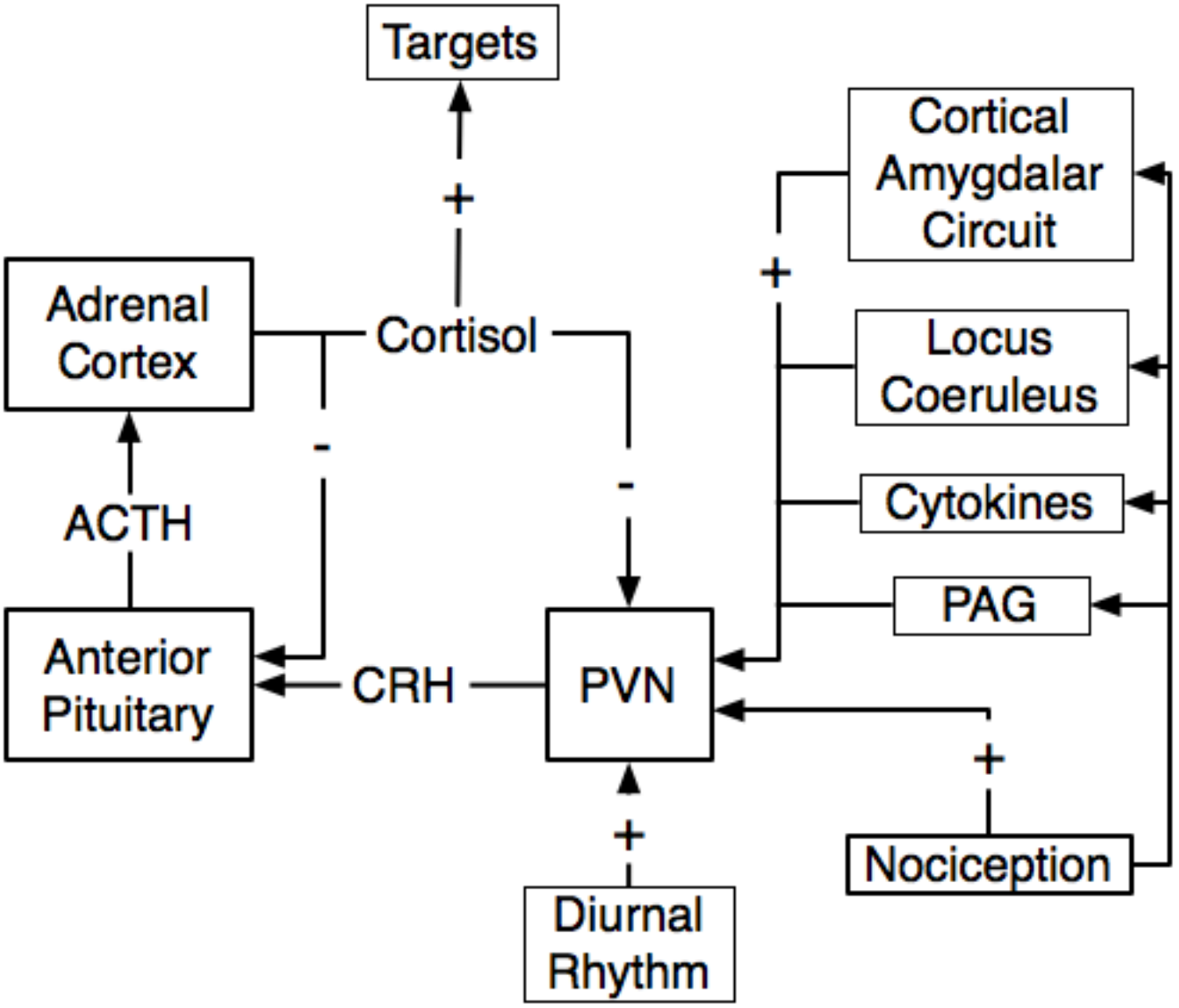

Figure 1. The Hypothalamo-Pituitary-Adrenocortical Axis Stress Response

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.

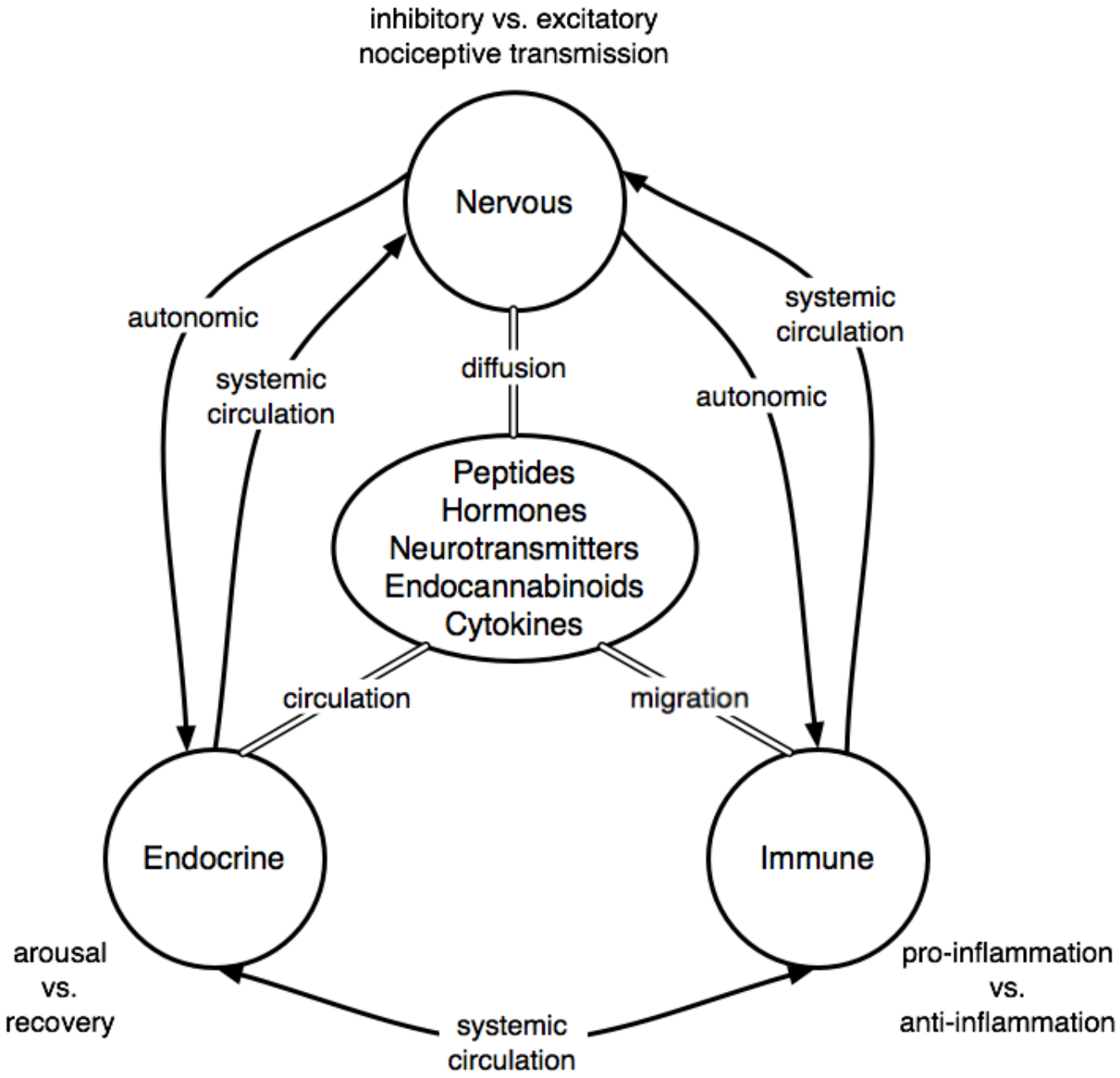

Figure 2. Connectivity

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.

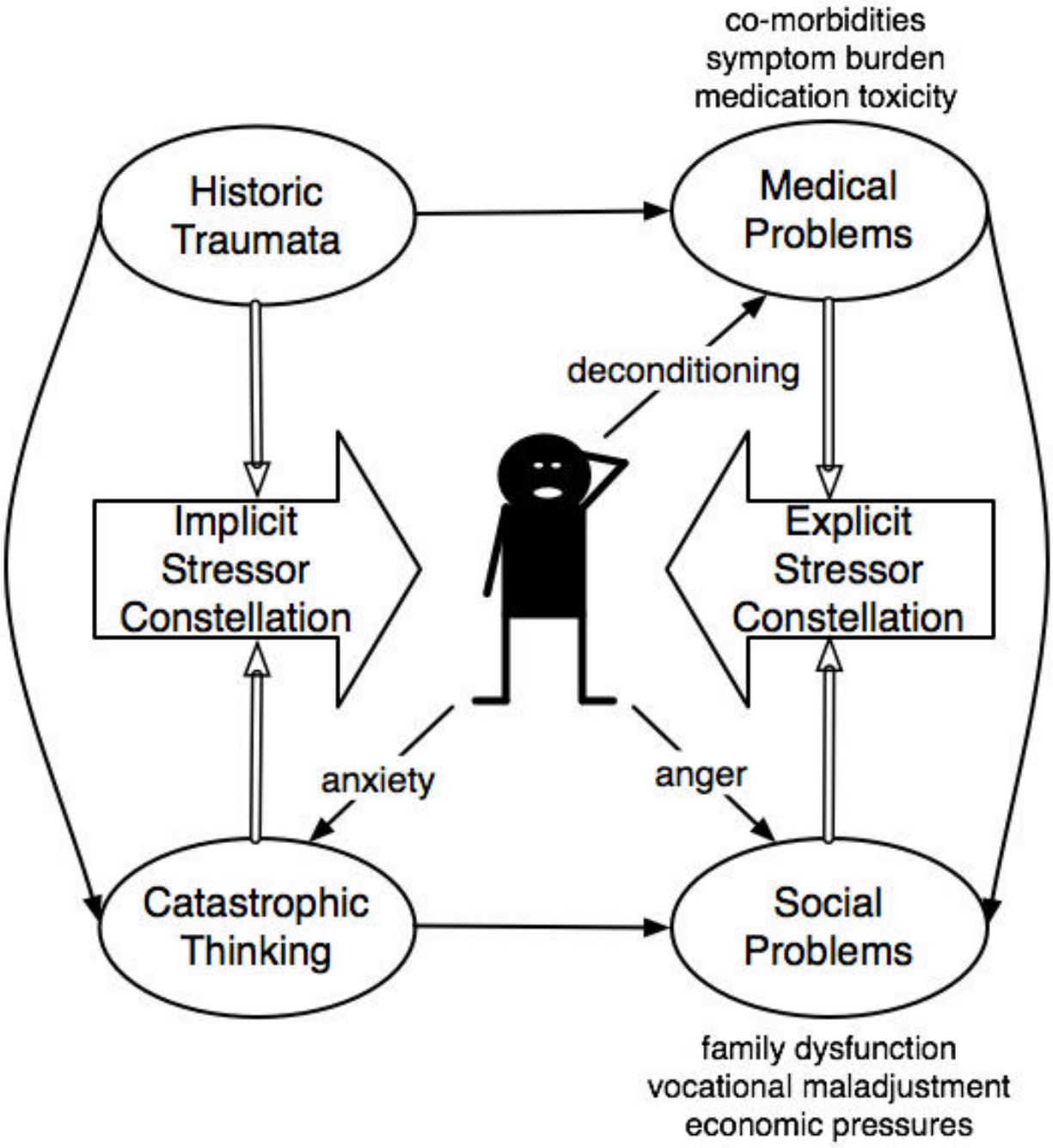

Figure 3. Stressors and the Chronic Pain Patient

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.

Topical Review

PAIN®

VIDEO

Pain management in people with severe mental illness: an agenda for progress

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1. Prevalence and impact of pain in people with severe mental illness

There is growing recognition that people with severe mental illness (SMI) have substantially poorer physical health and die 15 to 20 years prematurely, largely because of poor physical health.[30] Severe mental illness often refers to schizophrenia spectrum (psychosis), bipolar, and major depressive disorders, following World Health Organization (WHO) and World Psychiatric Association terminology.[21,39] The global prevalence of schizophrenia is 0.28% (95% uncertainty interval: 0.24-0.31),[16] of bipolar disorder is 0.7% (0.6-0.8),[28] and of major depression disorders is 4.4% (4.1-4.7).[27] Severe mental illness is associated with increased likelihood of physical health problems (eg, diabetes and HIV)[30] with a high burden of pain.[1,49]

Although the pain–depression relationship has been studied extensively, innovations are still needed to optimize pain management in people with comorbid major depression.[6,48] Pain management in people with bipolar and psychotic disorders is underresearched.[106,109] This review will highlight diagnostically specific challenges for pain management across major depression, bipolar disorder, and psychosis and discuss methodological approaches that may prove useful for improving pain management across them. This review does not capture other mental disorders that are often comorbid with and complicate pain management. These include anxiety,[3] posttraumatic stress,[32] substance use,[73] and personality disorders,[23,51] which are sometimes categorised with SMI when they cause severe functional impairment.[88] Given the brevity of this review, we have chosen the narrower SMI definition to begin to advance this discussion.

Depression and pain commonly co-occur, although estimates of pain prevalence in people with depression vary widely (15%-100%; mean 65%).[6] Pain prevalence is also high in people with bipolar disorder: 1 meta-analysis (k = 22) found that 29% of people with bipolar disorder (n = 171,352) reported pain, over double the risk of healthy controls (n = 12,342,577).[106] Some doubt arises from unvalidated pain assessments used by many studies in the review.[106]

The pain–psychosis association is complex. Meta-analyses of experimental studies show that adults with schizophrenia have elevated pain thresholds and tolerance, independent of antipsychotic medication.[110] However, a meta-analysis (k = 14) found that 35% of people with schizophrenia (n = 242,703) reported clinical pain, similar to age-matched and sex-matched controls without mental illness (n = 4,259,221).[109] Given the heightened cardiometabolic burden in psychosis[35] and the association between pain and cardiometabolic risk factors, such as obesity[37] and diabetes, this raises the possibility that pain may be underrecognized or underreported in this group.[109] Adding to this complexity, in 1 study of people with psychosis (n = 438), comorbid depressive symptoms were associated with clinically relevant pain.[107] Therefore, pain reporting may be diagnostically specific, with psychosis associated with underreporting and (comorbid) depression with increased reporting.

As in the general population, pain is associated with increased disability and poorer quality of life in people with SMI.[70,107] Importantly, both SMI and pain are associated with increased suicide risk.[34,89] However, pain is not routinely assessed and managed in this population,[107] and pain communication and assessment might be obscured by the nature of the SMI. Among people with psychosis, reduced self- and clinician-identification of pain may partially explain under or late recognition of conditions that commonly present with pain, such as appendicitis and cardiovascular disease; this may also partially explain the higher

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rates of late, inadequate, or absent treatment, adding to excess morbidity and mortality.[19,30,103,109] Routine assessment and management of pain and its causes needs to improve in this population. There is also urgency to find ways to identify acute time-sensitive conditions earlier if pain is not serving as an indicator.

2. Understanding pain and its treatment in people with severe mental illness: where is the evidence?

Understanding of biopsychosocial[26,67,117] influences on pain and related disability in people with SMI, particularly those with psychosis and bipolar disorder, is scarce and may be diagnostically specific. Research is needed to reconcile comparable rates of reported clinical pain in people with psychosis and healthy controls with mechanisms underpinning reduced experimental pain sensitivity.[109,110] Increased striatal dopamine[46] may contribute to pain underreporting in this population, given converse evidence of a negative association between striatal dopamine and pain in Parkinson disease.[92] By contrast, serotonin and norepinephrine depletion may account for the depression–pain link.[36] Of course, mechanisms explaining differences in pain reporting in SMI are likely multifactorial. Presently, research is lacking to understand whether and how positive symptoms (eg, delusions and hallucinations), negative symptoms (eg, poverty of speech), and thought disorder influence the meaning attributed to pain and related behavioral responses. One qualitative study of veterans with bipolar disorder and persistent pain described their sense of disconnecting from pain and overactivity during manic episodes, which increases pain.[114] However, investigation of variations in the experience, impact, and communication of pain associated with different SMI features (eg, negative symptoms or depressive comorbidities in schizophrenia and mania in bipolar disorder) is in its infancy.[107,110,114]

Understanding of pain treatments in people with SMI is also limited. Recommendations for managing persistent pain include exercise, psychological therapy, and analgesic optimisation (where indicated).[77,78] However, to increase sample homogeneity, people with SMI are often excluded from randomized controlled trials (RCTs) of pain treatments. Evidence is thus needed to understand the applicability of existing pain treatments to this population.

Psychological and exercise-based treatments are often combined to reduce pain-related distress and disability. Meta-analyses of RCTs show that cognitive-behavioral therapy for pain produces small- to medium-sized improvements in disability and mood compared with treatment as usual.[118] However, little is known about the efficacy of psychologically informed interdisciplinary pain management for people with SMI because they are often excluded from trials. Of 75 trials in the 2020 Cochrane review of psychological therapies for pain,[118] 60% explicitly excluded people with SMI (**Table 1**). Psychosis or schizophrenia was the most common exclusion (35% of studies), followed by any serious psychiatric disorder (23%). Of the remaining trials, only 1 reported the sample proportion with comorbid SMI, so we know very little about the efficacy of psychological treatments for pain in this population. This is echoed in clinical practice. For example, an audit from a large pain clinic in England indicated complex mental health needs (eg, severe depression) as one of the most common exclusion reasons from interdisciplinary treatment or short-term individual psychological therapy for pain.[58]

Pharmacological management of pain in SMI is complicated by the potential for harmful side effects and interactions with psychotropic medications and the underlying mental health condition.[50,65,85] Antidepressants, including serotonin–norepinephrine reuptake inhibitors, are effective for pain management in the absence of depression[113] and of course may improve comorbid depression[64]; however, unopposed antidepressants may destabilise mood in bipolar disorder. Collaborative pharmacological and psychological care for comorbid pain and major depression is promising, but scarce.[2]

The potential benefits and harms of other analgesics need careful consideration for people with SMI, as in the general population. In particular, people with major depression and bipolar disorder (but not schizophrenia[84]) are more likely than age- and sex-matched controls without mental illness to receive long-term opioids and experience adverse effects. Research is needed to determine whether these findings persist after reduced opioid prescribing in many countries. Cannabis and cannabinoids are increasingly discussed for pain despite evidence that cannabis use is associated with an increased risk of psychosis and increased risk of relapse and rehospitalization among people with psychosis.[43,72,99] Guidelines advise against antipsychotics, gabapentinoids, benzodiazepines, and ketamine for chronic primary pain,[78] but when used for psychiatric comorbidities,[8,98,100] they may help comorbid pain. Recent advances in drugs targeting sleep disturbance[53,56] and transcranial magnetic stimulation[62] may prove fruitful for comorbid pain and SMI. There is a particular evidence gap for analgesics in people with bipolar disorder and psychosis, and research is thus needed. Medication optimisation for pain and SMI must occur alongside an interdisciplinary approach.[78]

3. Psychological and exercise-based interventions for severe mental illness in the wider context: synergies with pain management

For decades, pharmacological interventions were the main treatment offered for SMI. However, evidence for psychological treatments in psychosis, bipolar disorder, and severe depression has increased significantly. There has also been a growing focus on exercise-based interventions in this population.

3.1. Cognitive-behavioral treatments

Cognitive-behavioral therapy for psychosis, bipolar disorder, and depression uses cognitive and behavioral strategies to reduce distress and illness-related disabilities, facilitate adaptive coping, and support recovery goals. Individualised formulations of problem development, maintenance, and exacerbation are a central feature. Cognitive-behavioral therapy has efficacy for improving symptoms of psychosis, bipolar disorder, and severe depression.[20,83,101,115] There is clear overlap in the use of cognitive-behavioral therapy for these disorders and evidence-based cognitive-behavioral methods for pain, including facilitating use of adaptive strategies to manage distressing thoughts and feelings and engage in personally meaningful activities in the presence of difficulties.[47,118] This overlap can facilitate integration of cognitive-behavioral treatments for pain and SMI.

3.2. Family and carer interventions

Many people with SMI are closely supported by "informal" carers, primarily close relatives, whose support is key in determining outcomes.[79] For those with family contact, family interventions

Table 1

Severe mental illness exclusion criteria listed in randomized controlled trials included in the most recent Cochrane review of psychological therapies for chronic pain.

SMI exclusion criteria	Frequency (%) of trials reporting the exclusion*
Psychosis/schizophrenia†	26 (34.7%)
Any serious psychiatric or psychological disorder†	17 (22.7%)
Suicide risk	10 (13.3%)
Bipolar disorder†	7 (9.3%)
Severe/significant depression	6 (8.0%)
Any serious Diagnostic and Statistical Manual axis II disorder	5 (6.7%)
Any mental disorder (nature/severity not specified)	4 (5.3%)
Any serious Diagnostic and Statistical Manual axis I disorder	3 (4.0%)

Note: 45 of the 75 (60%) trials in the 2020 Cochrane review of psychological treatments for chronic pain[118] explicitly excluded people for at least one of the reasons listed above. Exclusion criteria of the primary studies were reviewed by the authors of the current topical review.

* % was computed from the total number of trials (n = 75). The mental health exclusion criteria are not mutually exclusive, and studies often reported multiple mental health exclusions, including for other mental health problems not classed as SMI.

† Some studies described the presence of these disorders without further qualification, whereas others qualified exclusion if the disorder was "poorly controlled or untreated."

SMI, severe mental illness.

are associated with reduced relapse and hospitalisation in people with psychosis and bipolar disorder.[12,18,87,90] Family members often identify physical health problems and facilitate timely receipt of assessments and interventions.[82] Therefore, family members are key in advocating for and supporting people with SMI to manage pain and its causes. It is also important to consider how certain caregiver behaviours and communication patterns, such as invalidating or overly solicitous responses toward pain expression may affect distress and disability in people with SMI and pain.[14]

Importantly, caregiving can adversely affect carer well-being. Carers of people with psychosis are less likely to continue caregiving when in poor health, hence the importance of identifying factors that adversely affect their health.[82] Common mental disorders, sleep difficulties, and isolation are common in SMI carers.[60,102] In addition, reports of pain may be elevated in carers of people with psychosis compared with noncarer peers, although the mechanisms underpinning this are unclear.[40] Understanding how pain is experienced, communicated, and managed in SMI carers is important to develop tailored interventions. For example, delivering cognitive-behavioural approaches for pain jointly for people with SMI and their carers may enable both individuals to develop more adaptive responses to pain and create a healthier caregiving relationship. The need for a joint cognitive-behavioural approach has been discussed for couples affected by pain, but there is limited evidence to date.[13]

3.3. Exercise-based treatments

Persistent pain and SMI are, individually, associated with low physical activity.[105,112] As it does in the general population, persistent pain also influences the ability of people with SMI to be active.[108,111] Thus, despite the plethora of benefits of physical activity for physical health, pain, and mental health seen in meta-analyses of RCTs in persistent pain[33] and SMI populations,[112] both disorders are associated with underactivity.

Little is known about specific levels and benefits of physical activity for individuals with persistent pain and SMI. Exercise-based treatments hold great promise to improve health, well-being, and social connections in this group, as in the general population.[86] Specifically, recent European[112] and World Psychiatric Association guidelines identify that physical activity (including aerobic and resistance training) can reduce the risk for SMI onset and improve mental health symptoms, cognition, quality of life, and cardiorespiratory fitness in people with SMI.[31] However, data on the impact of physical activity for pain in SMI are unclear, despite the positive effects noted in persistent pain generally.[33,97]

People with persistent pain and SMI experience a range of barriers to physical activity, including low mood and motivation, fatigue, isolation, lack of support, stigma, financial constraints, and service fragmentation.[29,71] The multitude of barriers to and any facilitators of physical activity in people with SMI and persistent pain need to be better understood. This could help to develop or repurpose models of increased movement in this population. Historically, access to physical activity has been low, but the recent focus on improving the physical health, particularly metabolic health, of those with SMI has seen an increase,[59,71,93] although effects are not well evaluated, particularly in the context of pain in this population.

4. Opportunities to improve integration of care for pain and severe mental illness

There is recognition of the need to better integrate physical and mental health services, with notable innovations to this end.[5,55,76] At present, however, treatments for pain and SMI often occur in isolation within separate services and serially, despite clear synergies. Research is needed to understand how to optimise treatment integration and how to best adapt existing pain management pathways so that they are used by and work well for people with SMI. Opportunities to improve integration of care are briefly outlined.

4.1. Improving pain recognition and assessment

Identifying people with SMI who have or are at risk of experiencing pain is essential.[109] Research should explore differences in pain communication between people with psychosis, bipolar disorder, and severe depression and healthcare professionals' sensitivity to that communication and how this might vary depending on patient racial and ethnic minority status. The latter point is particularly important as people from racial and ethnic minority groups are disproportionately diagnosed with SMI (eg,

schizophrenia)[80] and conditions where pain constitutes a primary component (eg, sickle cell) and experience higher healthcare inequalities.[45,80] Pain assessment exclusively based on self-report may be challenging for people with psychosis who are less likely to self-identify pain and, depending on service setting, might be more inclined to underplay difficulties due to concerns of receiving additional services/treatments. Therefore, nonverbal assessment of pain behaviour is important.[41,42] In addition, families or close friends can provide vital information given their critical caregiving role and should thus be included in the pain assessment process where possible. Nonverbal assessments of pain behaviours, such as facial expressions (eg, grimacing), body movements (eg, guarding), and interpersonal changes (eg, not wanting to be touched), are well-validated in other populations where self-report is problematic, such as dementia.[42] Research is needed to determine the utility of these tools in people with psychosis.

Reports of severe pain in people with SMI may contribute to inappropriate medical management of pain, such as long-term opioid prescribing.[84] Severe pain may prompt use of invasive treatments, which must be carefully considered because, for example, people with psychosis and bipolar disorder have an increased risk of infection and readmission after surgery for painful conditions compared with those without mental illness.[52] Aggressive pain treatment may lead to underrecognition and treatment of SMI. Therefore, early detection of SMI in people with severe pain is also imperative to enable provision of appropriate treatment and reduce the risk of iatrogenic harm.

Despite increasing awareness and willingness to discuss mental health, SMI continues to be highly stigmatised,[74] which may further impede pain recognition. Healthcare professionals underestimate pain in the presence of perceived "psychosocial" problems,[22] making discounting of pain in people with SMI particularly likely. Indeed, there is evidence that they experience diagnostic overshadowing for physical health care.[30] In addition to limiting treatment access, pain-related invalidation, stigma, and discrimination exacerbate distress.[94–96] Investigation is needed to understand the impact of intersecting experiences of stigma and discrimination in people with SMI and pain and how to address these. At the structural level,[104] for example, service planning and funding that enable integration of treatments for pain and SMI may reduce stigma and discrimination experienced when fragmented services exclude people.[71] At the interpersonal level, role plays developed with people with lived experience may be useful for training to improve clinicians' communication with people with pain and SMI so that interactions are empathic and respectful.[25,104] At the individual level, psychological interventions may help people respond effectively to the personal impacts of stigma and discrimination, although effects may be modest in the absence of intervention at the other levels.[96,104]

4.2. Stakeholder involvement

Meaningful involvement of people with lived experience of SMI and pain will be crucial[7,11,81,91] to improve existing pain management pathways and develop integrated treatments. Involvement of a range of stakeholders is also needed, including carers, mental health and pain management clinicians from primary to tertiary care, healthcare commissioners, policymakers, and third sector organisations. Stakeholder involvement can include, for example, Priority Setting Partnerships, which can be modelled after exemplary work in paediatric pain.[9] Stakeholders can provide crucial input to shape pain assessment and intervention tailoring, identify meaningful treatment targets, optimize pathways into treatment, and enhance clinician training. Drawing again from work in paediatric pain,[15] stakeholders can shape dissemination and implementation of knowledge about research and best practice.

4.3. Treating and evaluating the individual

To rapidly advance the understanding of pain management in people with SMI, innovations in treatment evaluation are needed. RCTs are the gold standard for evaluating interventions but require highly selected samples, protocol-adherent treatment delivery, and group-based analysis.[75] This limits their potential to inform flexible treatment delivery that addresses the context and complexity of individuals in practice.[116]

Single-case experimental designs (SCEDs) are well suited to advance development of integrated treatments in a manner that appreciates the heterogeneity of diagnostically specific challenges relating to pain and SMI. SCEDs are a rigorous alternative to RCTs that can enable personalized care.[17,61,63,68,116] In SCEDs, the individual is their own control through intensive, repeated measurement during baseline and treatment phases.[68,75] Multiple SCEDs can be undertaken informing multiple treatment approaches with heterogeneous participants using fewer resources than would a single RCT with a homogenous sample.[68,75] The frequency of assessments in SCEDs provides greater opportunity than that in RCTs to evaluate treatment mechanisms necessary to improve effectiveness.[10]

Single-case experimental designs are not without limitations. The baseline phase can be demanding and is not feasible when urgent treatment is needed, such as for active suicidality.[54] The generalizability of SCEDs has been questioned, but replication across patients and settings allows generalizability to be tested.[54] Although RCTs offer many advantages, SCEDs are highlighted here as a lesser used methodology with underexplored possibilities for developing and evaluating treatments in people with pain and SMI.

4.4. Implementation science

Implementation science holds promise to ensure that research into new models of care has a real-world impact. Implementation science is "the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and hence, to improve the quality and effectiveness of health services and care"[24](p. 1). Implementation frameworks draw on behavioral and social science and identify individual-level (eg, clinician knowledge, motivation, and professional role/identity) and structural-level (eg, resources, organizational culture, and policy) factors that influence intervention uptake.[4,15,44,57,66] The number and complexity of available theories can present a challenge for implementation research, particularly where empirical findings are underused in refining theory.[57]

Nonetheless, implementation theories may help identify barriers to and facilitators of integrating existing and novel treatments for pain and SMI in practice. For example, quantitative and qualitative methods can investigate knowledge, skill, and perceptions about professional roles for pain/SMI treatment among clinicians in pain and mental health services. This could inform novel training and supervision models, which could be developed using implementation principles to ensure uptake, scalability, and sustainability.[38] In addition, linking existing data sets of, for example, referral patterns and treatment outcomes from primary to tertiary care can provide insights into opportunities for integration across the system. There are emerging local examples of how rapid communication between mental and physical health services can improve outcomes for people with SMI.[69]

As an example of bringing different methods together, data set linkages may identify repeat referrals of patients between pain and mental health services. Interviews with mental health clinicians may reveal a need for training in pain management, whereas interviews with pain clinicians may reveal perceptions that the format (eg, group-based) or duration (eg, number of sessions) of commissioned treatment is unsuitable for people with pain and SMI. Together, these data could argue for more collaboration and mutual training between pain and mental health clinicians and coproduction with service users to better deliver holistic pain management within their services. Surveys of service funders could identify key targets (eg, reduced referrals and improved patient satisfaction) that would allow this model to be sustainably funded.

To conclude, there is an urgent need to advance research and practice to improve pain management in people with SMI. This work should draw on synergies in the existing evidence for managing pain and SMI. Meaningful involvement of people with lived experience is essential to advance this agenda.

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Supplemental video content

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Perspective

From Fear to Safety: A Roadmap to Recovery From Musculoskeletal Pain

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Abstract

Contemporary conceptualizations of pain emphasize its protective function. The meaning assigned to pain drives cognitive, emotional, and behavioral responses. When pain is threatening and a person lacks control over their pain experience, it can become distressing, self-perpetuating, and disabling. Although the pathway to disability is well established, the pathway to recovery is less researched and understood. This Perspective draws on recent data on the lived experience of people with pain-related fear to discuss both fear and safety-learning processes and their implications for recovery for people living with pain. Recovery is here defined as achievement of control over pain as well as improvement in functional capacity and quality of life. Based on the common-sense model, this Perspective proposes a framework utilizing Cognitive Functional Therapy to promote safety learning. A process is described in which experiential learning combined with "sense making" disrupts a person's unhelpful cognitive representation and behavioral and emotional response to pain, leading them on a journey to recovery. This framework incorporates principles of inhibitory processing that are fundamental to pain-related fear and safety learning.

Keywords: Fear of Movement, Musculoskeletal Pain, Recovery, Rehabilitation

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Background

Chronic musculoskeletal pain is now a leading cause of disability worldwide, with the disability burden predicted to grow exponentially in the next 2 decades, placing unsustainable strain on health systems.[1]

Once serious pathology has been excluded, a person's musculoskeletal pain experience is influenced by a varying interplay of multidimensional factors, including, physical, pathoanatomical, lifestyle, psychological, social, culture, past history, sensory, comorbid health, genetics, sex, and life stage.[2–5] The dynamic interplay and the relative contribution from each factor is variable, interrelated, and fluctuates temporally, making chronic pain a unique experience to each individual.[4] These interactions influence tissue sensitivity and continually shape a person's interpretation of their pain experience.[2,5,6]

Contemporary conceptualizations of pain emphasize its protective function.[2,5,7] The meaning assigned to pain is potentially a powerful cognitive contributor to the need for protection and therefore influences both the pain itself and the person's individual experience and response to pain. For instance, a recent trial randomized patients to receive threatening and non-threatening information from MRI reports. Compared with those who received non-threatening information, patients randomized to threatening information were more likely to perceive a need for interventions that carry greater risk and lower benefit such as opioids, injection, and surgery, while also reporting worse pain intensity, disability, pain cognitions, mental health, and self-efficacy.[8] This highlights how both threatening and safety messages can influence a person's pain experience and trajectory in the health system.[9] The meaning of pain also influences emotional (ie, pain-related fear) and behavioral responses (ie, protection and avoidance).[4] Thus, pain-related fear can be defined as a cognitive and emotional response to an evaluation that the body is in danger and needs protecting.[10]

Pain-related fear, psychological distress, and self-efficacy have all been shown to mediate the relationship between pain and disability.[11] High levels of pain-related fear predict increased disability and poorer outcomes in people with chronic musculoskeletal pain.[12,13] Pain-related fear is modifiable,[12] and targeting protective (eg, slow and guarded task performance) and avoidance (eg, not performing a task) behavior may be an opportunity to reduce disability and the burden of chronic musculoskeletal pain.[14]

In this paper, we draw on recent data on the lived experience of people with pain-related fear to discuss both fear and safety-learning processes and their implications for the management of musculoskeletal pain. There is now compelling evidence that management of chronic musculoskeletal pain should integrate biological, psychological, and social perspectives.[15–19] However, there is a lack of clear directions for clinicians, particularly physical therapists, on how to implement psychologically informed approaches into practice.[20–24] The paper aims to provide physical therapists with a clinical framework that describes how Cognitive Functional Therapy (CFT) [25] can be implemented through the lens of the common-sense model[26,27] to promote safety learning in people with musculoskeletal pain. CFT is an exposure-based physical therapy-led approach[25] that was developed to reduce disability in people with chronic musculoskeletal pain. Because chronic musculoskeletal pain across different body regions shares common biopsychosocial risk profiles for pain and disability, we consider this framework applicable across a range of musculoskeletal pain conditions.[15,28]

To illustrate the utility of this framework, we present a case study where CFT is used to guide a person with disabling back pain and high pain-related fear on a journey to recovery. Recovery is here defined as a person developing control over pain, confident engagement with valued activities, and quality of life.[29]

Fear Learning

Societal Beliefs About the Body and Pain

In Western society, people of all ages, both with pain and without pain in geographically diverse settings, commonly hold unhelpful beliefs about the body and pain.[30–33] The body is often perceived as fragile and vulnerable to harm, and the experience of pain is interpreted as threatening and often understood as a sign of structural damage. As such, there is a perception that the painful body part always needs to be protected and "fixed."[30–33] There are examples of this in people suffering from pain in the back,[30,34] knee,[35] and hip.[36] Our own clinical studies have demonstrated that people with and without back pain, as well as physical therapists who manage people with back pain, show an implicit (non-conscious) bias about the vulnerability of the back even when they explicitly report otherwise.[37–39] This suggests that as a society, we are biased towards information that supports fear beliefs about the body and pain.[40]

Lived Experience of Pain-Related Fear

A body of qualitative work[31,34,41,42] exploring the lives of people living with chronic pain and high fear provides compelling evidence that pain-related fear can be understood as a common-sense response to a threatening pain experience described as severe, uncontrollable, and unpredictable. For example, when a person believes that performing a painful activity will hurt and/or cause harm to their body, avoiding or modifying that activity is common sense. Although avoidance may reduce fear and or pain in the short term, it also prevents the person from having positive learning experiences that would disconfirm their expectations and beliefs. Failed attempts to gain control over the pain experience and its impact can reinforce fear learning and result in increased disability in the long term.[26,27] Qualitative[26,27] and experimental[43,44] data highlighted several factors that can reinforce pain-related fear and behaviors, including diagnostic uncertainty, threatening radiological reports coupled with negative advice (explicit or implicit) received from clinicians during health care encounters, conflicting advice from different clinicians, and societal beliefs about the structural vulnerability of the body. For some, threatening social contexts such as abusive relationships, bullying, stressful life events, and negative health care encounters promote a salient learning experience and may also play a role in facilitating fear learning.[45]

Pain-related Fear, Protection, and Avoidance of Movement

A large proportion of people with chronic back pain believe that a wrong movement could result in serious negative consequences to their back.[46] This belief potentially increases pain expectation, pain experience, and fear, shaping people's behavior[34,47] towards activity avoidance, protective muscle

guarding, and restricted movement.[48,49] It has been proposed (but not yet empirically established) that overprotective motor responses can be pro-nociceptive, leading to abnormal stress on sensitized spinal structures and, in turn, increased pain intensity and pain persistence[50,51] Other studies highlight the role of cognitions and emotions as potential mechanisms that may underlie co-occurrence of pain and fear and modulate a person's pain experience.[52–54]

Generalization of Fear, Protection, and Avoidance

The inability to distinguish what is safe from what is dangerous has been proposed as a core mechanism in the generalization of protective responses that lead to disability.[14,55] This can result in pain being triggered by more functionally dissimilar stimuli,[11] meaning that people are more likely to disengage from a wider range of movements and activities. For example, when the original painful trigger is associated with bending and lifting, this may result in generalization of fear, avoidance, and pain to similar (eg, vacuuming, putting on shoes) and dissimilar (eg, walking, washing dishes) movements and activities.[11] This generalization of fear and avoidance reduces the opportunities to challenge and disconfirm a person's feared expectations, reinforcing fear as a driver of unhelpful behavior and perpetuating disability.[10,34] This sustained perceived lack of safety may play a role in the maintenance of pain-related fear.[55]

Models of Fear Avoidance in Musculoskeletal Pain

The Fear Avoidance Model

A prevailing model explaining the pathway to disability associated with chronic musculoskeletal pain is the fear avoidance model.[10,14,56] The model describes how a threatening pain experience can lead to an unhelpful cycle of catastrophic thoughts, pain-related fear, avoidance of movement and activity, and subsequent disability and depressed mood, which in turn heightens the pain experience.[10,56] Although the fear avoidance model proposes the return to normal activity in the absence of catastrophizing leads to recovery,[10,56] the pathway to recovery is less researched and understood.

The Common-Sense Model and Fear Learning

Sense-making is the process by which an individual makes sense of their pain and what it means now and moving forward. Insights from qualitative research suggest that "sense-making" processes, beyond pain catastrophizing, play a role in pain-related fear learning and disability.[31,34] Sense-making is at the heart of the common-sense model.[57] Bunzli et al proposed the utility of the common-sense model as a framework to assist health care professionals to understand the sense-making processes involved in the fear avoidance cycle and how these processes can be targeted to facilitate fear reduction in people with chronic musculoskeletal pain (see safety learning section).[27] The model describes a dynamic process that constitutes a person's "cognitive representation" of their pain condition, which is formed by memory structures of their normal functioning self, past experiences of pain, treatments, lifestyle, and social activities. This is updated based on new information that is heard (eg, media, family, encounters with health care professionals), observed (eg, vicarious experience from friends, family, work colleagues), and felt (eg, bodily sensations, a perceived painful sensation). Once a person experiences pain, their cognitive representation helps them make sense of pain based on 5 dimensions: identity (What is this pain?), cause (What caused this pain?), consequences (What are the consequences of having this pain?), timeline (For how long will this pain last?), and cure/controllability (Can this pain be cured or controlled?).[57] How a person makes sense of their pain will influence how they respond to it from both a behavioral and emotional perspective.[26,27] The dynamic process that includes a person's understanding and their behavioral and emotional responses is here defined as "learning schema."

For example, when a person with back pain believes that "spinal flexion will cause pain," the action taken is to avoid and guard against flexion, and therefore the predicted outcome is that pain is avoided. If this occurs, it appears that there is coherence between prediction and outcome even though the coherence actually relates to an opposing prediction and its outcome. Nonetheless, the original cognitive representation (that flexion will cause pain) is reinforced by inference, and the behavior is maintained (ie, the experience does not promote learning). If the prediction then becomes "avoiding flexion prevents pain" but this does not occur (ie, pain is experienced despite avoidance of flexion), there is incoherence between prediction and outcome and learning occurs sensibly toward the notion that the cognitive representation does not work and things are even worse than they first appeared. A person's inability to predict what makes their pain worse and the lack of control over their pain experience results in an inability to make sense of pain, which is in turn self-perpetuating, distressing and disabling, and reinforces fear learning (fear learning schema).[10,27,52]

Safety Learning

Extinction research highlights the importance of learning of a new experience of safety as the primary underlying mechanism in fear reduction.[58] Fear reduction is related to people's ability to form new safety memories that compete with old fear memories, thus regulating their emotional and behavioral response to the source of their fear.[7,59] This concept is grounded in the inhibitory learning theory from the field of anxiety management, which proposes a shift from models that use cognitive restructuring and fear habituation (ie, exposure until fear reduces) as an index of corrective learning, towards developing safe associations (ie, new experience of safety).[59–61] Inhibitory learning strategies have been proposed to maximize learning of new safe memories.[59,60] Figure 1 provides a summary of the information presented in this section, outlining "how to" principles for clinicians to promote safety learning in clinical practice.

Common-Sense Model and Safety Learning

The common-sense model can also assist clinicians to understand the sense-making processes involved in safety learning in people with chronic musculoskeletal pain.[27] Take the same person with back pain who is fearful, guarded, and avoidant of lumbar flexion. If they are reassured that "spinal flexion is safe" and they experience that flexing their back in a graded and relaxed manner does not result in an increase in back pain (or indeed a reduction in pain), there is incoherence between prediction and outcome; subsequently, learning occurs.

Expectancy violation is at the heart of inhibitory learning (or safety learning), meaning that new safe memories

Safety learning - 'How to' principles[a]

- **Screen** for contributing factors to pain using a multidimensional screening tool (eg, short form Orebro,[66] STarT Back Screening Tool[85]; STarT Musculoskeletal Screening tool[86]). Individual items can be used to guide and acts as prompts in the interview.
- **Interview** to enquire about patients' concerns, worries, fears and goals (use items on Orebro to guide and prompt)
  - Listen to the patient's story, considering multiple factors that can influence the person's experience, including but not limited to past pain and healthcare encounter experiences, past trauma, general health, lifestyle, social context, physical activity, etc.
  - Use the common-sense model framework to enquire about the five domains of their representation (identity, cause, consequences, timeline, control/curability), behavioral responses and emotional responses.
  - Identify the most feared, avoided, painful functionally meaningful task for the person
  - Explore person's expectations, goals and values.
- **Examine** using behavioral experiments (in addition to a thorough exam) to determine behavioral and emotional responses to pain; and to determine a person's sensory profile – sensitivity to touch, posture, movement and load.
  - Identify the feared task
  - Observe the task and enquire about the experience
  - Facilitate body relaxation, reduce safety-seeking behaviors teach body awareness/control
  - Reassure
  - Expose in a new way and enquire about the experience
  - Grade up exposure based on emotional and pain response
  - Violate the expectation where possible
  - The experience of moving without (an increase in) pain and without damaging consequences is likely to facilitate a new understanding and development of perceived control over the experience. A new experience that creates a new safe memory.
  - Effective strategies to control pain and manage flare ups.
- **Expose with control** – repeated exposure in new way – linked to goals, valued and essential activities
  - Repetition over time establishes coherency and reinforces safety learning
- **Make sense of pain** - Sense-making process including an explanation/conversation to reframe a person's experience and meaning of pain, using a new safe experience to create a new representation that is coherent and makes sense. Dispel myths where the patient is open. Provide relevant resources, patient stories.
- **Integrate** new representation and response (behavioral and emotional) to daily life, reinforcing safety learning, promoting generalization and facilitating the achievement of independence.
- **Provide** a clear exacerbation plan that provides the person with strategies that help the person achieve a better experience by themselves.
- **Refer** to (and facilitate) co-care as /if needed.

Figure 1. Key principles to promote safety learning in clinical practice (once serious and specific pathology has been screened). [a]These principles are described in detail elsewhere.[67,25]

(eg, "flexing my spine is safe") are developed and compete with the original fear memory (eg, "flexing my spine causes pain").[59] The development of a strategy that effectively controls the pain experience combined with an explanation that helps a person make sense of their pain challenges the original fear schema,[4] which is sensibly updated towards an experience that is deemed safe (safety learning schema). The repetition of an experience of safety integrated to the person's life is thought to reduce pain-related fear, disability, and distress.[26,27]

Utilizing CFT to Implement Safety Learning

We propose a framework that considers the person's journey into pain and disability but focuses on the process of change in which safety learning can lead to recovery. This framework enables clinicians to capture the patient's story, identify targets for recovery, and assist patients to acquire a new understanding through an alternative experience of safety. The experiential learning and sense-making process outlined in this framework aims to equip patients with

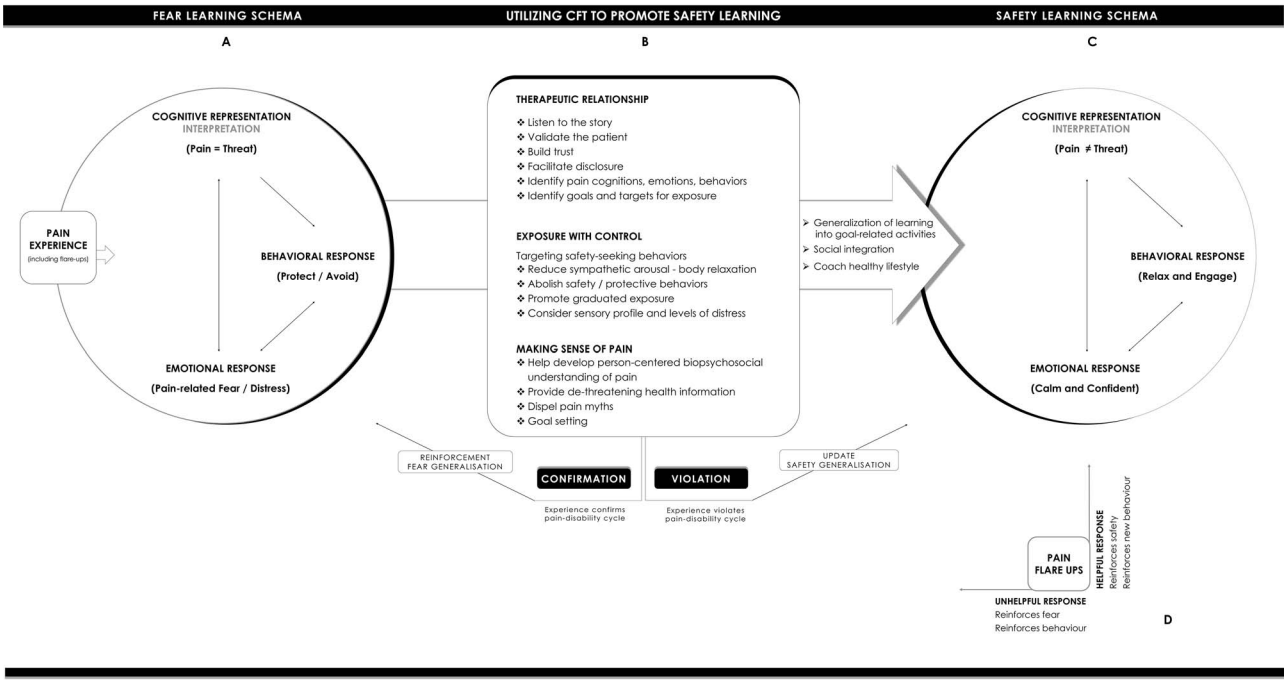

Figure 2. Schematic illustration of the proposed clinical framework. (A) Person's common-sense response to a pain experience interpreted as threatening (fear schema). (B) Core elements of Cognitive Functional Therapy as a vehicle to promote safety learning. The experience may confirm or violate the original schema. Confirmation of pain as a threatening experience (ie, learning does not occur) leads to the reinforcement of the person's fear response. Violation of pain as a threatening experience (ie, learning of safety occurs) can powerfully disconfirm fear-avoidance beliefs while reinforcing that valued activities can be safely confronted when performed without safety behaviors and reduced pain vigilance. This leads to an update of the person's response that promotes generalization of safety. (C) Person's common-sense response to an experience interpreted as safe (Safety schema). (D) Response to a pain flare, which may reinforce fear or safety learning. This is a crucial learning opportunity that influences a person's process to recovery.

effective strategies to independently control pain and prevent flare-ups in pain intensity and/or control the impact of pain in their lives and emotional responses to pain. The combination of a new cognitive representation and an effective set of strategies enables patients to problem solve the best course of action in any given context so they can confidently engage in valued life activities.[25,27,31] This framework endorses best-practice recommendations,[15] providing clinicians with a clear roadmap of how to implement exposure to promote change clinically.

Not all patients in pain are fearful. Acknowledging that avoidance can also occur as a commonsense response to an unhelpful pain representation based on what they have been told or experienced; we propose that our framework may also be helpful in patients who report low levels of fear.

The proposed clinical framework is schematically illustrated in Figure 2. It displays a pathway to recovery from pain-related fear using CFT as a vehicle to promote safety learning.

The Therapeutic Relationship

For patients in pain, the use of a communication style that is open, non-judgmental, reflective, and provides validation of the person's emotions, beliefs, and experiences is paramount to safety learning.[62] This communication style decreases arousal, facilitates disclosure, and encourages problem-solving.[63,64] Communication practices that foster a strong, trusting therapeutic alliance create an environment of reduced distress that sets the stage for safety learning and behavioral change.[63,65] The use of a screening questionnaire prior to the interview provides the clinician with a perspective on the person's pain and disability levels, cognitions, and emotions, providing opportunity for targeted exploration of their concerns within the interview[66] (Fig. 1 provides examples of screening tools).

Clinicians are encouraged to use the common-sense model to explore the patient's pain representation, emotions. and behavioral responses to pain. Patients can be prompted to reflect on experiences that led to their understanding of pain and how this impacts their behavior.[27,67] Insight into the person's feared, avoided, and pain-provoking activities that are aligned to their goals provides clear targets for exposure.[25,67] This approach encourages greater partnership in clinical encounters.[63,68]

Exposure

Behavioral exposure specifically targets pain-related fear and avoidance by gradually exposing the person to the tasks they fear or avoid while challenging unhelpful cognitions and disconfirming threat expectations (ie, task performance without the occurrence of the expected catastrophic outcome).[69] Traditionally, exposure therapy targets erroneous harm beliefs (eg, "lifting will damage my disc") rather than pain itself.[69] However, the basis of avoidance and the cognitive representation of pain vary between people (ie, fear of damage, fear of pain, fear of the consequences of being in pain, or a common-sense response to what they have been told or experienced).[27] For patients who avoid lifting because they fear an increase in pain and its consequences, exposure to repeated lifting when it leads to an increase in pain and distress may inadvertently reinforce fear learning.

In contrast, exposure with control is a process of behavioral change that explicitly targets the pain experience itself

(where possible), using pain as a hypothesis for testing during behavioral experiments (eg, "lifting will increase my pain"). Behavioral experiments during exposure provide an experience in which learned associations between threatening tasks and increased pain or harm may be corrected (ie, that new "safety" associations are formed). This strategy derives from the premise that the mismatch between expectancy and experience is helpful for new learning[60] (see Tab. 1; and row 3 in Suppl. Tab. 1 for an example illustrated by the case study). Whereas for some patients the goal is to experience less pain during task performance, for others, it may be engaging with the feared and avoided tasks without damage. In this process, sympathetic responses and safety-seeking behaviors that occur during the performance of painful, feared, or avoided functional tasks are explicitly targeted and controlled to create a discrepancy between the patient's expected and actual pain responses (ie, prior patient expectation: "I expect my pain will get worse with repeated bending"; behavioral experiment: patient experience "When I relax, breathe and bend my back without protecting it, my pain does not get worse—it in fact reduces"). This includes promotion of body relaxation prior to exposure, reduction of protective behaviors, facilitation of body awareness, and control that enables the person to experience the performance of functional activities in non-protective way.[25,70,71] For instance, lifting in a relaxed manner and modifying how the person physically performs the task without unhelpful protective responses (ie, breath holding, bracing, avoidance of spinal flexion) may result in a positive experience that promotes safety learning.[25,70] A recent case series demonstrated that for the people in whom improvements in pain were related to changes in movement, they adopted a new behavior considered "less protective" (ie, greater range and speed of movement and more relaxed back muscles).[70] In another case series, people with high pain-related fear reengaged with previously feared and avoided activities after undergoing a 12-week CFT intervention.[71] Exposure that promotes "control" of emotional and behavioral responses to pain provides a potential pathway to return a person to their valued activities without pain escalation and associated distress.[25]

Safety learning is consolidated by asking patients to reflect on what they learned regarding the non-occurrence of the feared event, discrepancies between what was predicted and what occurred, and the degree of "surprise" from the exposure practice.[60] The experience and this reflection process challenge the person's implicit and explicit beliefs.[4] This process is repeated for reinforcement of the new experience, and exposure is progressed to further disconfirm unhelpful beliefs. The new learned strategies are immediately integrated into daily activities to build self-efficacy and promote generalization across contexts and activities.

When pain control is not achievable during this process, the focus is placed away from pain and toward non-protection and reassurance that the activity is safe while undergoing the process of graded exposure to personally relevant functional and lifestyle goals. In these cases, the journey towards living is the experiment itself.[25,72]

Exposure can be very challenging for the patient as well as the clinician who needs to support the patient along the journey. To guide their patient to engage in painful, feared, and/or avoided movements and activities, clinicians need to be confident they have adequately screened for specific and underlying pathology and that they will not "harm" the patient in this process. They also need to be skilled to manage potential emotional responses, because exposure can elicit strong emotional responses, anxiety, and occasionally panic in a patient. An awareness of the clinician's own pain and movement/activity beliefs, as well as specific training, appears to be important when implementing this approach. This reflects a process of exposure training for both the clinician and the patient.[24,25,67,73]

Making Sense of Pain

The process of making sense of pain is reflective and uses a persons' own story combined with their experiences during behavioral exposure to gain a new understanding of their pain and build self-efficacy to achieve their goals.[25] The common-sense model can be used to explain this process.[27] Qualitative[31] and clinical[71] data of people with disabling back pain undergoing CFT found that clinical improvement was attributed to a person's ability to make sense of their pain experience in a non-threatening way and their ability to gain control over the pain experience and/or the effects of pain in their life. This was achieved through developing a new and coherent cognitive representation of pain that guides effective behavior.

Based on the common-sense model, a coherent representation includes diagnostic certainty from a biopsychosocial perspective (identity) that can explain a person's symptoms in a meaningful way (cause), replacing erroneous beliefs about pain and its damaging or disabling effects (consequences) and provides strategies for controlling symptoms and emotions in a manner that re-engages them with living (timeline and control).[27] The development of a new cognitive representation is an interactive learning process that is achieved via reflecting on the person's own narrative, experience, self-reflection, and education. This process disconfirms previously held unhelpful beliefs and allows a person to reconceptualize and understand their pain symptoms and emotional and behavioral responses to pain in a new way through a biopsychosocial lens, with the aim to gain self-efficacy.[25]

The Journey to Recovery

The experience of "safety" is key for the recovery of a person who is protective and/or avoidant. The pathway by which a person recovers is unique for each person. This was previously illustrated in Caneiro et al.[71] Although for some this process can occur in a few weeks, for others it may take longer (3–6 months).[25] A study investigating how changes in pain-related fear unfolded over the course of a 12-week CFT intervention demonstrated that changes in pain intensity, pain controllability, and pain-related fear were associated with changes in disability. The factors that changed, and the rate and pattern of change, differed for each person, highlighting individual variability in the process of change.[71] A qualitative study found that people with chronic back pain who gained control over pain by modifying the way they move reported an ability to self-manage pain and flare-ups while engaging in valued goals.[27] Among those who did not achieve pain control, some reported poorer outcomes at follow-up, whereas others reported that accepting the unpredictability and uncontrollability of pain or adopting a new and more positive mindset about the causes and consequences of pain enabled them to control their worry and engage in valued activities.[27] This suggests the likelihood of multiple individual

Table 1. Qualitative Reports Based on the CSM Before and After an Exposure-Based Approach[a][[ImEquation#]][[ImEquation#]]

CSM Constructs		Baseline (8 wk Pretreatment)	Management (12 wk)	Follow-Up (6 mo)
Representation	Identity	Tissue damage (ie, muscles, ligaments, disc, and nerves)	An individualized, exposure-based behavioral approach (Cognitive Functional Therapy) [25] including the following key components: The story: an interview centered in the person's narrative to explore their story and experiences of pain. This sets the scene for targeted behavioral experiments and exposure. Exposure with "control": a process of behavioral change through experiential learning following a "graded exposure" model designed to violate expectations of pain and damage via guided behavioral experiments. The movements and activities that she feared and avoided were explored and revealed breath-holding, muscle guarding, and avoidance of flexion of the lumbar spine during sitting, bending, and lifting. Behavioral experiments revealed that visualization of bending and lifting increased pain and muscle tension. Slow diaphragmatic breathing and relaxation of spine posture in sitting reduced pain. Graduated exposure to lumbar flexion with control (ie, relaxed spinal flexion) led to less pain than she expected. This positive experience confronted her beliefs about bending, pain, and damage, allowing her to experience pain control during feared and provocative tasks. Repeated exposure to relaxed bending and lifting was gradually progressed (from 0 kg to 15 kg) over 12 wk reinforcing that these movements were safe. The strategies learned were integrated with daily activities to reinforce safety learning and promote generalization. Making sense of pain: reconceptualization of pain via self-reflection, behavioral learning, and personalized education linked to her story. Explained how negative beliefs, distress, poor sleep, fear, worry, lack of confidence, activity avoidance, and protective muscle guarding set up a vicious cycle that sensitizes the spinal structures that lead to pain and disability. The positive experience during guided behavioral experiments reinforced that her back was structurally sound, that pain does not equal harm, and that relaxed movement is healthy and safe. Generalization: integration of strategies in her daily life enabled self-learning and self-discovery during the rehabilitation that guided subsequent progression across different sessions in a goal-orientated manner. Lifestyle change: behavioral modification addressing unhelpful lifestyle factors, including: (1) advice to improve sleep hygiene (7 h/night, regular sleep time, breathing techniques to relax); (2) encouragement to gradually reengage in family activities including walking, bike riding, and beach walking. She was advised to perform these activities on a time contingent manner rather than contingent on pain; (3) perform body and mind relaxation strategies daily. Flare–up plan: that equipped her with effective strategies to independently prevent or manage pain flare-ups, unhelpful responses to pain, and/or control the impact of pain in her life, which allowed her to engage in valued life activities. Treatment dose: 8 sessions over 12 wk. The initial session was 1 h and the follow ups were 30–45 min. This patient was seen on a weekly basis for the first 3 sessions and then progressed to 1 session every 2–3 wk. An individualized self-management program was provided that included behavioral strategies, progressive functional exercises, and lifestyle changes tailored to personal goals.	"The fear of doing things that would make me sore, and the tension that comes with it . . . and me disengaging from family, work and all that I wanted to do . . . . it was a vicious cycle really."

(*Continued*)

Table 1. Continued

CSM Constructs		Baseline (8 wk Pretreatment)	Management (12 wk)	Follow-Up (6 mo)
	Cause	"A car accident 23 years ago made my back weak, and then having kids made it worse."	"The fact that I avoided doing a lot of things and moving because I was fearful of making it worse is the reason why I got worse."	
	Consequences	"The pain is worsening (. . .) It affects my life every day. I'm not able to do things that I like . . . things like gardening . . . what normal people do."	"A big thing for me has been having the physical therapist alongside me, guiding me. Another big thing was having a positive experience."	
	Control/curability	"There's not much I can do to control it (. . .) Avoidance is my control."	"Definitely much more control than I had before. I still get occasional periods of pain, but they are a lot more manageable. I do things differently, more relaxed, breathing and using my legs and that reduces the pain."	
	Timeline	"That's just how it is, and I have to learn to accept it."	"Definitely improving, and it's kind of surprised me as well, because coming down off the Opioids was very hard."	
Behavioral response	Action	"Just anything that involves bending, just puts that thought in my mind. 'Can I or can I not?' And the majority of the time I'll just avoid."	"There was a process of teaching me how to move differently (in a relaxed manner). This gave me a sense of control over my pain, my life really."	
	Appraisal	"Nothing that I have done so far, chiropractor, physical therapist, massage, Pilates, injections, has been effective—only avoidance is effective."	"This process gave me confidence I can do most things. Now, I have strategies and a plan, and they work."	
Coherency		"There is a lot of conflicting advice . . . . I follow it, but I don't get better . . . .it is confusing really."	"A lot of it now, feels like it's common sense, but it was actually quite empowering for me to learn."	
Emotional response	Emotion	"It's upsetting, it makes you feel useless, not being able to do what other people can do (. . .) It is frightening."	"I'm not fearful of bending and lifting. I know I can change it and that makes me feel in control, empowered."	

[a]CSM = common-sense model.

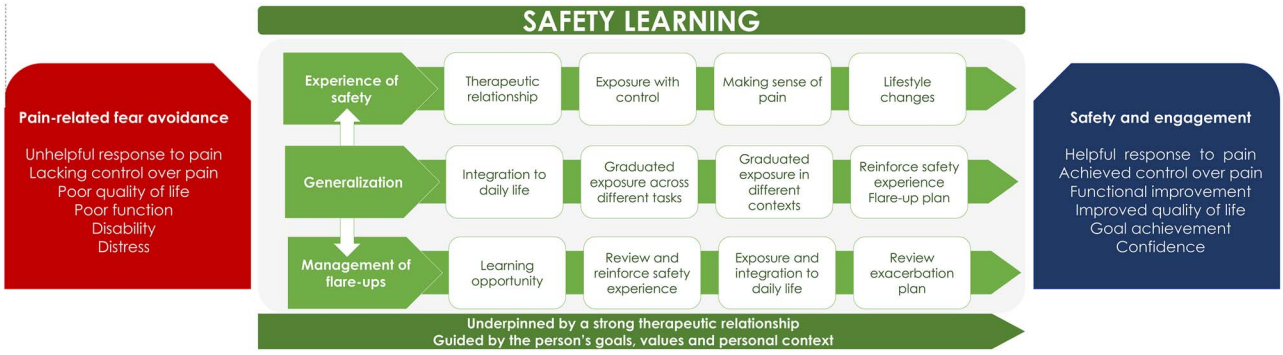

Figure 3. Roadmap to recovery.

pathways to reducing disability related to chronic pain in people with pain-related fear.

Booster sessions may be necessary for when/if pain again becomes uncontrollable, distressing, and/or disabling. During pain flares, the old cognitive representation can resurge strongly, often re-activating unhelpful behavioral and emotional responses. In the study by Caneiro et al, all participants experienced pain flare-ups of variable intensities and duration that provided opportunities to reinforce safety learning.[71] Providing patients with an individualized management plan for pain flare-ups with the potential to re-engage with care is important (see "flare-up plan" in Tab. 1).

The following clinical case illustrates the processes of fear learning and disability, and safety learning as a roadmap to recovery (Fig. 3).

Case Study

Patient's Story

A 45-year-old woman had a 23-year history of (non-specific) back pain. A mother of 2, she is married and works part-time from home. She has seen several health care professionals, including general practitioners, chiropractors, massage therapists, physical therapists, spinal surgeons, and pain physicians. She manages her pain with rest, heat packs, massage, light stretches, non-steroidal anti-inflammatories, gabapentin, several spinal injections, and opioids (including Oxycodone for many years). Her goals are to be able to participate in her family activities and be healthier, fitter, and stronger. Key contributing factors for this patient's presentation are unhelpful damage beliefs, high pain-related fear (of pain/flare-ups and damage), high pain catastrophizing, guarded movement and avoidance behavior, poor sleep, activity avoidance, low physical conditioning, and hyperalgesia to touch and movement. Table 1 outlines this patient's cognitive representation of her pain and her behavioral and emotional responses to pain before and after a CFT intervention (key elements of the intervention are outlined in the table). Supplementary Table 1 outlines how inhibitory learning strategies can be integrated to the management of musculoskeletal pain conditions, using the case patient in this paper as an example.

Challenges and Implications for Clinical Practice

Despite the promotion and awareness of a biopsychosocial approach to pain, a biomedical model commonly underpins current education and practice.[74] Health system models can limit access to best practice, where health funding frequently offers reimbursements for imaging, medication, and surgery (when not indicated by guidelines), but not for person-centered physical and psychological interventions.[75,76] The biomedical model of care provides a fertile context for fear learning, which can lead a person to believe their body is fragile and damaged and needs protection.[3]

The beliefs of both clinicians and patients that pain is associated with damage (in the absence of trauma or indicators of serious/specific pathology), that scans identify the source of pain, and that symptoms occur as a consequence of structural and biomechanical abnormalities are pervasive.[9,34,77,78] This commonly leads to the view that targeting the structure or body "abnormalities" will fix pain, which in turn often leads to overmedicalization, unnecessary and potentially unhelpful tests, and limited effectiveness of interventions for most chronic musculoskeletal pain conditions.[3] Threatening advice to patients such as "let pain guide you," "your pain is due to wear and tear," "if it hurts avoid it," "engage your core when you move," and "lift with a straight back" suggest vulnerability of the body and reinforces an unhelpful cognitive representation that can lead to or reinforce avoidance/protective behaviors.[77–79] In this way, physical therapists have the capacity to influence patients into fear or safety learning.

There is a need for change in how we communicate about the body and pain to people with and without pain to reduce fear learning, promote safety messages, and minimize or prevent the impact of pain in people's lives.[67,80] To promote safety learning, it is imperative to disseminate messages broadly in society that instill positive perceptions about the body and pain, that build confidence in the body in its capacity to heal and adapt, and that encourage the adoption of healthy behaviors, including movement and physical activity, as safe and helpful.[43,44,75] Having a unified narrative among family members, friends, carers, workplace colleagues, and advisors is critical because they play an important role in a person's journey to recovery. In contrast, conflicting advice, unhelpful carers, social stress, mental health, and co-morbidities can be obstacles for recovery.[76] This highlights the importance of co-care and communication with community services to support a person's path to recovery.

Clinical pathways that align with evidence and clinical practice guidelines are optimal, but not always delivered.[15] To facilitate safety learning in patients with pain who are fearful and/or avoidant, clinicians require excellent communication skills that are reflective, validating, and empowering.[25,62,76] Clinicians also need to be specifically trained and mentored to achieve competency to perform exposure with control,[25] and changes to physical therapy curriculum are needed to

upskill clinicians on the understanding and delivery of person-centered care.

Public health initiatives are needed to change the pervasive societal belief that the body (the back,[30,34] the knee,[35] and the hip[36]) is vulnerable.[67] Community outreach initiatives such as the Pain Revolution (https://www.painrevolution.org/), the painHEALTH (https://painhealth.csse.uwa.edu.au/), the joint pain website (https://www.myjointpain.org.au/), and Empowered Beyond Pain podcast (https://open.spotify.com/show/3ogpeLlDGLRLiHofEWvCje) aim to provide credible sources of information for clinicians as well as the general public to bridge the gap between science and practice upskilling society in the understanding of pain.

Evidence for Application of This Framework

There is emerging evidence of the effectiveness of exposure-based interventions for people with chronic musculoskeletal pain, utilizing principles outlined in this paper.[81,82,83] Physical therapists who were trained in this framework reported increased confidence and competence in managing the biopsychosocial dimensions of pain.[24,73] A large trial is currently underway to test the effectiveness of this approach against usual care in people with chronic back pain.[84] This framework is aligned with best-practice recommendations to manage musculoskeletal pain irrespective of body region.[15,16,19,28] Further research is needed to assess the efficacy of this approach in other musculoskeletal pain conditions.

Summary

The clinically useful framework we propose posits that experiential learning combined with sense-making enables people with musculoskeletal pain to gain control over pain and its impact by disrupting unhelpful cognitive representations and behavioral and emotional responses to pain, leading them on a journey to recovery. This clinical framework endorses best-practice recommendations. Although low back pain was used as an example in this paper, we consider that this framework is applicable across a range of musculoskeletal pain conditions.

Author Contributions

Concept/idea/research design: JP Caneiro, A. Smith, S. Bunzli, S. Linton, G. L. Moseley, P. O'Sullivan
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