

Chronic pain and depression: Twin burdens of adaptation

Christina M. Van Puymbroeck, Ph.D.,

Alex J. Zautra, Ph.D.,

& Peter-Panagioti Harakas, MS.

Department of Psychology

Arizona State University

P.O. Box 871104

Tempe, Arizona 85287-1104

**In A. Steptoe (Ed.) Depression and Chronic Illness. Cambridge: Cambridge
University Press, in press.**

Introduction

It is estimated that chronic pain afflicts between 50 and 80 million people in the United States alone [1]. Adding to this burden of pain, feelings of depression frequently accompany the pain experience [2]. These depressive symptoms include feelings of sadness, loss of pleasure, and fatigue, and they range in severity from transient malaise to persistent and debilitating episodes. For many, it is common sense that negative feelings would follow painful experiences, but at the same time, a number of researchers have noted that depressed patients frequently report high levels of pain as well. Not only is pain a common somatic complaint in individuals suffering from depressive disorders [3], but according to some accounts more than 50% of clinically depressed patients report pain as a symptom [4]. Because all investigators do not use the same criteria to determine the presence of depression, the exact prevalence of depression among chronic pain patients is not easy to estimate [5]. Banks and Kerns [6] reviewed only studies that used standardized criteria to diagnose depressive disorders and estimated that at any given point 30-54% of clinic-based patients suffer from major depressive disorder (MDD), rates substantially higher than that of found in the general population [7], and higher than in outpatients of other medical conditions¹.

Thus, there appears to be a strong association between depressive symptoms and persistent pain, but the underlying causal mechanisms remain poorly understood. Nevertheless, our conceptualizations of both pain and depression are currently evolving at a rapid pace, offering the possibility of a full accounting of the complex relationships between depression, pain, illness, and immune functioning.

For centuries, pain had been understood as a sensation arising from underlying tissue damage. About fifty years ago, this bottom-up (stimulus-response) model of pain was challenged by Melzack and Wall's [9] gate control theory of pain, which emphasized a top-down, multidimensional conceptualization of pain. The gate control theory posited three dimensions of pain, a sensory-physiologic dimension, a motivational-affective dimension, and a cognitive-evaluative dimension. A number of psychosocial models of the pain-depression relationship followed in the footsteps of gate control theory and further emphasized the importance of psychological processes in the experience of chronic pain. Nonetheless, despite numerous studies conducted in this area over the past decades, the causal relationship between pain and depression remains controversial [10]. For this reason, we believe it is instructive to briefly review the historically dominant hypotheses formulated about the nature of the pain-depression relationship.

The Antecedent Hypothesis. The first proposed pathway for the relationship between depression and chronic pain is that depression is responsible for the onset or maintenance of pain in individuals who suffer from both sets of symptoms. This hypothesis, often termed 'the antecedent hypothesis' [2], posits that depression precedes pain. Early studies used psychogenic conceptualizations of pain to suggest that chronic pain was potentially a variant of depressive disorder [11], a form of "masked" depression characterized by continuous pain, denial of emotional and interpersonal difficulties, and an inability to tolerate success and happiness [12]. This research has been widely criticized on both methodological [13] and theoretical grounds [14]. Despite the repudiation of much of the early research, several recent studies still suggest that depression plays a significant role

in the etiology of chronic pain and often precedes the development of chronic pain [15-16].

The Consequence Hypothesis. On the other hand, the ‘consequence’ hypothesis views depression as secondary to chronic pain. According to this view, depressive symptoms follow the onset of pain. This reactive depression is often seen as the result of an incapacitating physical condition that arises from the sustained reduction in physical and social activities [17].

Common Pathogenesis. The common pathogenesis model assumes that depression and pain, although clearly distinct conditions, have a shared etiology. The proposed mechanisms include key neurotransmitters such as serotonin, norepinephrine, substance P, and corticotrophin releasing factor [CRF; 18]. In a similar fashion, other researchers have proposed that chronic inescapable stress might be the link between chronic pain and depression, and that the HPA axis might be specifically involved in the etiology of both [19]. Thus, depressive symptoms may manifest in chronic pain patients because of long-term stress activation of the HPA axis as a result of chronic pain.

Other researchers view the effects of stress as having an even more prominent role in explaining the pain-depression association. One of the theories developed to explain medically unexplained chronic pain such as found in fibromyalgia focuses on dysregulation of the human stress response as a result of central nervous system processes [20]. This view is consistent with research findings that stressors perceived as inescapable, unavoidable or unpredictable evoke strong biological reactions [21], and with findings from animal studies that early life-stressors may permanently biologically impact animals’ responses to stressors [22]. The proposed mechanisms involve

disturbances in CRH production, which affect the HPA axes by producing central effects on nociceptive processing, and leading to abnormalities in autonomic function [20].

Cognitive Behavioral Theories. The relationship of chronic pain and depression has often been explained within a cognitive-behavioral framework. Here, coping beliefs and behaviors are considered to play important roles in patients' adjustment. In this vein, thoughts that sustain the "illness role," or the beliefs that medications and solicitous responses from others are necessary, have been shown to covary with depression. One frequently discussed set of cognitions in pain patients is referred to as 'catastrophizing'. Patients who catastrophize expect the worse outcome and worry excessively about possible negative consequences of events in an effort to defend against pain exacerbations. These cognitions have been found to be associated with depression [23]. In the cognitive-behavioral mediation model of depression [24], the direct relationship between pain and depressed mood is influenced by cognitive appraisal variables such as perceived interference and lack of self-control. Rudy et al. referred to perceived interference as the extent to which patients feel pain affects their ability to participate in social, recreational, vocational, family, and domestic activities, and how much satisfaction they derive from such activities. The cognitive-behavioral mediation model challenged the notion of pain as a variant of depression and appeared to offer a parsimonious integration of earlier cognitive and behavioral theories on the relationship of pain and depression [25-28].

Psychoneuroimmunological Developments

A comprehensive review of current research provides strong evidence that depressive symptoms can also be conceived of as affective, behavioral and cognitive

responses to immune activation. Profound immune activation can occur due to internal (e.g. bacterial) or external (e.g. grief) stressors that activate the HPA axis. At the heart of this argument is the increasingly well-articulated relationship between proinflammatory cytokines and the symptoms of depression. In this view, depressive symptoms are seen as evolutionarily valuable responses: responses intended to conserve energy for survival in the face of an internal or external threat. Similarly, new neuroimaging studies have provided evidence that pain also is a homeostatic response predicated on the need to avoid further harm by energy conservation and withdrawal.

Taken together, we may surmise that depressed mood and chronic pain are distinct but related responses to underlying physiologic events driven by mechanisms that evolved because they promoted survival. When these responses are not properly regulated by countervailing homeostatic processes, however, they become self-propagating, pathological, and chronic.

Depression and the Immune System. Although the relationship between depressive symptoms and immune regulation is complex [29], accumulating evidence suggests that depressive symptoms are related to the action of several cytokines. Cytokines are signaling proteins that facilitate communication between immune cells and play a key function in the regulation of the immune response [30]. It is these cytokines that induce the functional changes in the brain characteristic of the non-specific symptoms of infection. These symptoms, termed ‘sickness behaviors’ [31], are comprised of behavioral (restlessness, reduced activity, hypersomnia, social withdrawal), cognitive (lack of concentration, loss of interest), and affective (depressed mood, anhedonia) components that match closely to the criteria for depression as defined by the DSM-IV-

TR [32]. These behaviors may be considered to be part of a homeostatic process used to conserve energy to fight infection [33], and represent a motivational state that promotes resistance to pathogens by resetting an organism's priorities [34].

Evidence for the association between depressive symptoms and cytokines comes from both animal and human studies. Experimental studies have shown that the administration of proinflammatory cytokines to animals induces 'sickness behaviors' [35-36], whereas the administration of the respective cytokine antagonists reverses some of these depressive-like symptoms [37]. In humans, increased plasma concentrations of cytokines such as IL-6 have been observed in depressed patients [38-39], and proinflammatory cytokines have been associated with the development of feelings of distress, despair and hopelessness expressed by many cancer patients [30]. Furthermore, cytokines such as interferon- α (IFN- α) appear to be implicated in depressive states experienced by patients receiving cytokine therapy. For example, cancer and hepatitis patients who are administered purified or recombinant cytokines develop flu-like, neurovegetative symptoms, followed (after several weeks) by the onset of psychiatric disorders, depression being the most prevalent [40-42, 30]. Three of these symptoms have been identified as particularly destructive to the patient's quality of life: anhedonia (loss of pleasure), alternations in cognitions, and changes in responses to pain. The implication of cytokines in the expression of depressive symptoms appears so strong that some have proposed that these depressive effects of cytokines during cytokine therapy constitute the basis of a "cytokine-associated depressive syndrome" [43].

Depressive symptoms are also highly prevalent in chronic inflammation associated with autoimmune diseases such as systemic lupus erythematosus (SLE) and

multiple sclerosis [MS; 44-46]. To illustrate, MS associated depressive symptoms have been shown to correlate with tumor necrosis factor- α (TNF- α) and interferon- γ (IFN- γ) mRNA expression in patients during acute episodes [47]. Accordingly, a number of researchers now suggest that at least part of these symptoms are not mere reactions to the suffering caused by the specific medical condition, but may be associated with immune changes that precede the development of the clinical symptoms of the autoimmune disease [48-49].

Evolving Understanding of Pain. Early thinking about pain emphasized the specificity viewpoint- the idea that pain is a distinct sensation represented by specific elements in both the central and peripheral nervous systems. The current perspective is one of convergence, where pain is conceived as an integrated state caused by a pattern of convergent somatosensory activity (that arises from perceptions of sensory stimulation on or in the body) within the neuromatrix. This perspective is typified by Melzack and Wall's [5] "Gate Control Theory," which posits that both small and large diameter afferent nerve fibers converge on the primary somatosensory cortex via the somatosensory thalamus where they produce the feeling of pain through activation of wide-dynamic-range (WDR) cells [50-51].

However, new evidence obtained using functional neuroimaging techniques has provided a profoundly different picture of the neurological substrate of pain. Providing strong support for the early proponents of the specificity perspective, Craig has identified specific labeled lines, as well as convergent somatic activity in an organized, hierarchical system in the brain that serves the purpose of maintaining the body's homeostasis [52-53]. The system includes a spino-thalamo-cortical pathway which provides a neural

representation of the state of the body, and leads to a subjective meta-representation of feelings from the body that are associated with emotion (such as feelings of exhaustion or malaise, and the corresponding negative affect). These pathways are only present in a few primate species, and are developed to a high degree in humans. In this view, pain is a feeling from the body transmitted by lamina I neurons first to the homeostatic system in the spinal cord and hindbrain, and then on to the forebrain where they provide a cortical image of the afferent representation of interoception (or the perceived physiological state of the body). In the forebrain, these afferent signals also activate the limbic motor cortex, which motivates a behavioral response. In the case described above (exhaustion, malaise, and negative affect) the likely response is to shut down; in the case of pain, the likely response is withdrawal. Thus, pain is demonstrated to be a homeostatic emotion akin to temperature or itch, with a line-dedicated pathway that maps on to interoceptive systems in the forebrain and activates a motivational system. Simply put, the feeling of pain, like depression, is both a distinct sensation and a motivation.

Pain, Depression and the Immune System

Equally important as the evidence that pain and depression are both motivational processes is the mounting evidence that pain too, can be a product of immune activation and subsequent inflammatory processes. Maier and colleagues [54] demonstrated that products of immune activation, such as cytokine IL- β , increase pain sensitivity. Another cytokine, TNF- α can also produce hyperalgesia. Watkins and Maier [55] suggest that hyperalgesia serves an adaptive function in that it discourages movement, conserves energy, and promotes wound healing.

Abramov and colleagues [56] propose that the immune system necessarily participates in nociception in a variety of diseases and likely has a role in the development of chronic pain syndromes. Animal studies in their laboratory demonstrate that immune activation leads to hyperalgesia, and more importantly, that in stress-sensitive animals, this hyperalgesia is significantly stronger and leads to increased vocalization. They suggest that the response of stress sensitive animals with activated immune systems is akin to the facilitation of emotional response components of pain in humans under conditions of immune stimulation.

In studies of patients with and without autoimmune disease, we have found that the presence of depression amplifies the relationship between disease activity and stress [57]. We found that stress leads to predictable increases in disease activity, for individuals with both RA (an autoimmune disease) and OA (non-immune related disease). However, only RA participants had increases in IL-6 during and after stress, and depression amplified this difference, with depressed RA participants showing the highest levels of immune activation in response to stress. This relationship was particularly strong for stressors of an interpersonal nature, which makes sense considering the survival value of maintaining intimate relationships among the chronically ill. Indeed, cross-sensitization between cytokines and stressors has been demonstrated in several studies, suggesting that cytokines might change brain circuitry, making it more responsive to stress [30]. In another study that supports the relationship between cytokines and stress sensitivity, Zautra and Smith [58] showed that depressive symptoms led to increases in perceived stress and pain for RA patients. However, for OA patients, who do not have the same level of circulating cytokines as RA patients, depression was

related only to pain, not stress. Depression was a risk factor for pain in both samples (RA and OA patients), but only in RA patients did depression predict stress-reactive pain.

The link between immune activation and pain has been further explored by Watkins, Maier and Goehler [59] who noted that peripheral events that induce hyperalgesia also activate immune cells, which in turn activate peripheral nerves that terminate in the brain or dorsal horn of the spinal cord. Experimental studies have shown that hyperalgesia can be elicited by direct administration of substances known to evoke the release of proinflammatory cytokines [60]. They concluded that pain facilitation is part of the larger set of adaptive sickness behaviors mediated by cytokines and that also serve the purpose of conserving energy for essential functions when the immune system signals to the brain that a threat is present.

The role and function of antidepressants. If depression and pain are processes induced by immune activation and dysregulation, then one would expect that antidepressant medications act, directly or indirectly, on the immune system, and not just the monoamine systems through which antidepressants have been long thought to exert their effects. Antidepressant medication would also be expected to cause a decrease in pain as the proinflammatory immune products are down-regulated. This in fact, appears to be the case. Capuron, Dantzer and colleagues point out that all antidepressant drugs, regardless of their pharmacological class, attenuate the behavioral and neuroendocrine effects of immune activation [30, 61-62]. In addition, it has been demonstrated that antidepressant treatment causes a shift in the balance between pro- and anti- inflammatory cytokine production in the brain [61].

Recently, Musselman and colleagues [63] demonstrated that paroxetine reduces the incidence of major depression by 34% in melanoma patients treated with interferon- α . Clomiprimine, imipramine, and citalopram were likewise shown to suppress the secretion of IL-2 by activated T lymphocytes, and of IL-1 β and TNF- α by stimulated monocytes [64]. Maes and colleagues [65] provided additional evidence for the immunoregulatory effects of tricyclic and SSRI antidepressants through the inhibition of IFN- γ and stimulation of an anti-proinflammatory cytokine, IL-10.

Antidepressant medications are widely used in chronic and neuropathic pain conditions for their antinociceptive effects, even in the absence of depressive symptomatology [66]. Sawynok, Esser, & Reid [67] note that antidepressants exhibit analgesic properties in multiple systems, including inflammatory, nociceptive, and neuropathic test systems. Support for the analgesic qualities of tricyclic antidepressants comes from both human and animal models [68], and these medications are increasingly being used in the management of headaches, arthritis, cancer pain, and other types of chronic and neurogenic pain [69-70]. In a review of 59 randomized, placebo-controlled trials, Lynch [71] found that the data in support of the use of tricyclic antidepressant for analgesia was undisputed, but that studies of the newer antidepressant class of SSRIs yielded conflicting results.

Chronicity: The Role of Sensitization

Up to this point, we have outlined the evidence that both depression and pain are sickness behaviors, provoked by proinflammatory cytokines and comprising an adaptation designed to minimize harm and maximize recovery when a threat to the organism is perceived. However, both depression and pain symptoms may become

chronic through processes of sensitization which allow the symptoms to self-propagate, requiring less and less stimulation (perceived threat) to set them into motion.

Central sensitization is a well known and oft-studied mechanism whereby the neurochemical substrate that facilitates the sensation continues to fire in the absence of objective stimuli. Central pain sensitization occurs as low threshold afferents that normally do not transmit pain signals, become recruited through persistent central nervous system activation to transmit pain signals. This state of hyper-excitability includes the temporal summation of repetitive C fiber stimulation, amplification of the pain response, spinal neurons behaving as wide ranging dynamic cells, and the spread of pain sensitivity to non-injured areas [72-74]. Winkelstein [75] suggests that cytokines released upon initial insult (injury or inflammation induced) affect the electrophysiologic responses of pain and help to establish a continuous feedback loop. She found that not only are cytokines such as IL-1, IL-6 and TNF up-regulated in persistent pain, but that they induce the expression of multiple pain mediators, such as prostaglandins and substance P, which lead to further spinal sensitization. In addition, neuroinflammation occurs in which immune cells migrate from the periphery into the CNS, leading directly to central sensitization.

A review of the clinical presentation of depressive disorder suggests that central sensitization processes may underlie depressed affect as well as pain. Depression is persistent within episodes and typically recurrent throughout the life span. The DSM-IV Mood Disorders field trials found that the most frequent course was “recurrent, with antecedent dysthymia, without full interepisode recovery” [76]. Two related hypotheses

have been offered to account for the chronicity of the disorder, the kindling and scar hypotheses.

The scar hypothesis suggests that a depressive episode wears away personal resources, leaving in its wake a relatively more vulnerable psyche to protect against future depressions [77]. One area on which a scar is most evident is that of cognitive attributions. Children who have been depressed show a deterioration of attributional styles that does not remit, even when the depressive episode has ended [78].

The kindling hypothesis proposes that changes in information processing potentiates depressive processes so that where a stressor may have been present to evoke the first depressive episode, each new episode is more and more autonomous and less related to external stimuli [79]. Indeed, the neurochemical changes provoked by stressors are typically fairly short lived. However, these changes can be re-elicited by mild stressor conditions that would have only minor impact on their own [80]. In 2000, Joiner offered an integrative model in which he argued that depression is characterized by both erosive processes that corrode psychological resources, and self-propagating processes that serve to prolong or exacerbate symptoms and leave an individual more vulnerable to recurrences [77].

There is now evidence that cytokines too, provoke a sensitization response that can exert a proactive influence on the development of depression and other forms of psychopathology. Interleukin- 1β has been shown to elicit sensitization effects in animal studies, increasing the co-expression of stress hormones corticotrophin releasing hormone (CRH) and arginine vasopressin (AVP). Upon initial administration of IL- 1β , increased levels of CRH and AVP became evident after 4 days and peaked on day 11 (although the

phenotypic change was present for several weeks following administration). If the rats were subject to an additional stressor, in this case foot-shock, then the stress hormone levels were significantly enhanced, providing support for the hypothesis that peptide co-expression makes the HPA system more responsive to all sorts of challenges [81].

Administration of TNF- α has also been shown to elicit sickness behaviors at a much lower dosage than is typically required to evoke such behaviors if the second administration follows the first by 14-28 days. This sensitization has a specific timeframe in which it can occur; sensitization was not evident when the second TNF- dosage was within 7 days of the first [82]. Typically, psychological stressors have been considered “processive,” as they involve the cognitive processing of a situation and require higher cortical functioning. Recently, the category of stressor has broadened to include “systemic” or metabolic insults, such as viruses and bacterial infections, which may evoke many of the same neurochemical changes as the processive stressors. Interestingly, sensitization occurs when the initial and subsequent stressors are the same (i.e. instances of loss) and when the stressors are of different classes (i.e. initial stressor = loss; second stressor = virus). Thus cross-sensitization can occur between stressors and cytokine challenges [80]. In fact, when systemic stressors occur on a backdrop of processive stress, a synergistic effect may occur.

Thus, the following picture emerges. When a stressor occurs in sufficient strength whether it is a psychosocial or physiological threat, the organism mounts a vigorous defense through the immune system, leading to high levels of circulating cytokines which can evoke both depressive symptoms and pain as part of the array of sickness behaviors designed to protect and defend the individual. In this view, the frequent co-morbidity of

depression and pain arises because each symptom is a manifestation of the same homeostatic drive to conserve energy for survival. This cascade of events may be highly adaptive following an acute stressor but may become chronic and maladaptive. Central sensitization processes may sustain and reinstate these sickness behaviors in a positive feedback loop that over time can give rise to depression and pain even without a precipitating threat.

Resilience

If pain and depressive symptoms both originate as processes of adaptation that are vulnerable to becoming chronic and debilitating when dysregulated, it behooves us to consider what can be done to support and restore the self-regulation of such processes. What do the aforementioned relationships suggest about potential models of resilience, and relatedly, methods of prevention and intervention? Two pathways seem particularly critical to the discussion of resilience in the face of most types of pathology: the preservation of homeostatic boundaries and restoration of equilibrium. The first pathway, preservation, can be thought of as a mechanism of primary prevention: How can we *preserve* the self-regulation of these systems in order to facilitate a response to threat of sufficient intensity and length to ward off the danger while retaining the necessary homeostatic elements that bring our physiology and psychology back to its baseline state? In particular, how do we sustain the fine distinctions individuals must make, particularly once the context itself has become the cue for arousal? For instance, a child growing up in an abusive environment shows resilience when, having few other options, she can transport herself out of the situation through fantasy and daydreaming. However, when this child grows up, it may no longer be adaptive to resort to fantasy in the face of

conflict. Here, her nervous and immune systems are forced to make clear distinctions between past and present threats, between her generalized learned fear of conflict and actual danger to the self. Charney [83] makes the suggestion that resilience may in fact be characterized by an ability to avoid overgeneralizing conditioned stimuli to the larger context, having reversible storage of emotional memories, and being able to facilitate extinction of learned responses. Psychophysiological flexibility built on complexity and a capacity for variability in responding may hold the key.

The question of how to facilitate the extinction of learned responses leads us directly to the second pathway, restorative processes that allow a system to return to normal functioning after a period of heightened responsiveness, sensitization, and maladaptation. McEwen and Stellar [84] identify allostatic load as the cumulative impact that substantially raises health risk due to chronic dysregulations in multiple systems. Considering how to reduce allostatic load is a preventative intervention as well, but at a different stage of adaptation. Here we need to identify the ingredients of recovery, as well as the mechanisms for their appropriate utilization.

Dennis Charney [83] offers one framework for the psychobiological mechanisms of resilience and vulnerability in which he identifies 11 potential mediators of the psychobiological response to extreme stress. Each one of these 11 mediators offers the possibility of a treatment target either alone or in functional interactions. Charney suggests that the psychobiological profile of a resilient individual is characterized by high relative levels of DHEA, neuropeptide Y, galanin, testosterone, and 5-HT_{1a} and benzodiazepine receptor function; and low relative levels of HPA axis activation, CRH, and locus coeruleus-norepinephrine activity. Based on the mounting evidence that there

may be an endophenotype for resistance to hopelessness and anhedonia in the face of stress, he suggest the potential utility of a wide array of biochemical agents, including psychostimulants, dopamine reuptake inhibitors, dopamine receptor agonists, and NMDA receptor antagonists to treat the symptoms of anhedonia and hopelessness in the face of traumatic stress for individuals' with a more vulnerable endophenotype. Future research will continue to elucidate how the restoration of balance in the hormonal and endocrine systems can alleviate the negative consequences of stress related systemic activation.

Emotion Complexity

Work in emotional regulation is another promising avenue for interventions to support and restore homeostatic functioning. At its foundation this work derives from an understanding of emotions as complex motivational systems of approach and avoidance that govern cognition and behavior. Unlike Charney [83], here the emphasis is on cognitive and affective systems of regulation, not the associated physiological substrates. Positive emotions and negative emotions, for example, have been shown to behave as independent affect systems rather than as opposite ends of a single affective continuum [85-87].

This distinction between affective states has important ramifications for regulation of the stress response. Zautra [88] has reviewed a number of studies showing that positive emotions play an important role in promoting resilience in the face of a variety of stress-producing and negative experiences. One well-established consequence of pain is an increase in negative affect during the pain event [89-90] that over time (in the condition of chronic pain) leads to stable elevations in negative affect [91]. Positive emotions can play a pivotal role in undoing these negative affective states and improving

health risks associated with negative affect. They appear to serve a restorative function in the face of stress [88].

Research in our laboratory with arthritis patients has led to the development of a dynamic affect model [DA model; 87, 92-93] that may help guide further research in this area. The model predicts changes in affective complexity as a function of stress. While positive and negative affects are independent factors under ordinary circumstances, under conditions of pain and stress affective space is compressed toward a more bipolar state. The uncertainty inherent in stressors provokes this simplification of complex emotional systems because of increased demand on information processing to resolve the uncertainty and reduce threat. In times when uncertainty is high, such as under conditions of stress or pain, the additional demands of maintaining a complex emotional framework would tax the system's capacity, leading to a simpler "black versus white" structure of affective experience. This collapse to a one-dimensional affective system is evident in the increasingly inverse relationship between positive and negative affects during times of stress [88]. The consequences for people in chronic pain (and by extension for those who suffer from long-term depression) are considerable. With worsening pain, affective complexity is compromised leading the individual to adopt increasingly simple representations of their emotional states, and less flexibility in response to challenge. Since it is stressful circumstances that lead to this representational simplification, in these instances, negative affect crowds out positive affect. Mood clarity is one factor that the DA model predicts will support the maintenance of independent systems even under stress, and indeed, our data bear this out. Arthritis patients with greater mood clarity retained more independence in their ratings of positive and negative mood states [87].

Furthermore, the presence of positive affect diminished the extent of the strong positive relationship between negative affect and pain [94]. The DA model lends itself to testable hypotheses regarding interventions intended to increase the ability to maintain emotional complexity, and enhance opportunities for positive affect during times of stress. In our view, facilitating the retention of the independent affective structure through interventions focused on emotional regulation among people who are ill, in pain, or otherwise under chronic stress will lead to greater flexibility in coping responses and better functional outcomes.

Negative emotions also have adaptive significance, as they narrow the thought-action repertoire in response to threat, allowing for a rapid corrective response. However, positive emotions are necessary to rebound from negative experiences and return to a more regulated state. In a study demonstrating the relationship between physiological and psychological resilience, Tugade and Frederickson [95] found that positive emotions and cognitive appraisals contributed to the ability of resilient individuals to regulate their cardiovascular reactivity quickly in response to negative emotional arousal. Furthermore, they found that resilience can be taught to individuals who show greater stress reactivity for a longer duration than people who return to homeostatic functioning more easily after a threat. They suggest that an intervention that promotes positive appraisal styles might prove especially useful for building resilience. This is particularly important in light of a recent study that provided evidence that people who are dysphoric demonstrate a reduced ability to use mood-incongruent recall to repair sad moods, even when instructed to do so [96]. Indeed, it has been shown that people who report higher daily positive mood have more responsive immune systems than those that report lower positive mood [97], and

that people who are able to regain and maintain positive emotional states are less likely to show symptoms of ill health or use medical services during stressful periods [98].

As predicted by the dynamic model of affect [87], the ability to focus inward and identify complex emotions has been shown to increase the ability to regulate mood [99]. Likewise, greater emotional knowledge, in particular the ability to discriminate among negative emotions, was associated with larger repertoires of emotional regulation strategies in a recent experience-sampling study [100].

Cognitive-behavioral therapies (CBT) are commonly used in pain management programs to assist patients in changing maladaptive ways of thinking and feeling in response to pain and illness. These therapies encompass a variety of techniques, including biofeedback, autogenic training, relaxation training, cognitive restructuring, distraction, and activity pacing. An extensive literature on the use of CBT for RA has confirmed its utility for increasing adaptive pain coping responses and self-efficacy expectations [101,102] as well as reducing inflammatory processes [101] and joint pain and swelling [103]. However, a comprehensive review of studies of CBT for RA has demonstrated one area of weakness in particular, CBT has not been shown to reduce depression in pain patients [104]. In fact, in a well-controlled study by Bradley et al. [101], while pain and disease indices improved as a result of CBT, depression worsened. The current focus on pain management in these CBT programs limits their effectiveness by relative inattention to deficits in positive affect resources that appear critical to enhancing physical and psychological functioning in pain patients, and sustaining health and well-being over the long term. On-going clinical trial research in our laboratory is currently testing the

hypothesis that adding an emotion regulation emphasis to traditional CBT for pain management will improve a wide array of outcomes, including both pain and depression.

To summarize, resilience in the face of negative events allows the system to respond flexibly and restore homeostasis promptly following activation. Traditional pain management protocols targeting pain exclusively show little effect on improving depression. Including depression as an additional therapeutic target in pain management programs may foster resilience by preserving emotional complexity and maintaining independently functioning positive and negative affective systems. This allows positive emotions to restore balance after negative emotional experiences.

Conclusion

Depression and pain can be conceived of as two different, but closely related sets of symptoms that covary with immune activation in response to harm or threat of harm. When these processes become dysregulated, the physiological, cognitive, and emotional changes engendered by neuro-endocrine immune activation can become chronic and systemic, leading to the maintenance of alarm responses long after their utility has ended. Overactivation of the HPA axis and monoamine systems as a result of these alarm responses are particularly implicated in the etiology of syndromes of both chronic pain and depression and may maintain these conditions after the immune system itself has been quieted.

The mounting evidence for the implication of multiple systems in the experience of and recovery from depression and pain provides a wide array of intervention possibilities. Depression, pain, and immune responses to a perceived threat may initiate elevations in one another, potentially leading to the dysregulation in multiple systems.

Targets for intervention are diverse, including physiological, and also cognitive and emotional regulation. Furthermore, a consideration for the interconnectivity of the systems in the human body urges the adoption of a multifaceted approach to restoration of homeostasis. Emotional complexity is one such approach that has shown promise in regulating cognitive, affective, and behavioral manifestations of allostatic load.

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¹ In an effort to compare rates of depressive symptomatology across different pain conditions, Hawley and Wolfe [8] reported the results of a longitudinal study of 6,153 pain patients: depression scores among various chronic pain groups, such as rheumatoid arthritis, osteoarthritis, and low back pain were not significantly different, except for fibromyalgia patients, whose depression scores were elevated in comparison with other chronic pain conditions.