Structural Models of Comorbidity among Common Mental Disorders: Connections to Chronic Pain

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Abstract
Patterns of comorbidity among common mental disorders can be understood from the perspective of a model that regards mood, anxiety and somatoform disorders as reactions within an internalizing spectrum of disorder, and substance use and attentional behavior disorders as elements within a separate, externalizing spectrum of disorder. In this approach, we examine the possibility of linking this model to somatic or chronic pain. Evidence from psychiatric and biological perspective provides a mechanistic framework that links chronic pain with internalizing disorders. Further research will provide a unified framework for understanding how new findings for disorders on connections between chronic pain and mood, anxiety, and related disorders and traits.

Introduction
Common mental disorders—those involving mood dysregulation, anxiety, substance misuse, and attentional behavior—are frequently comorbid [1-4]. Indeed comorbidity is often the rule, rather than the exception, in clinical practice [5, 6]. Nevertheless, patterns of comorbidity among common mental disorders are also systematic. Mental disorders involving depression and anxiety co-occur frequently enough that they can be conceptualized as elements within a broad spectrum of “internalizing” disorders. In addition, mental disorders involving substance misuse and attentional behavior can be conceptualized as elements within a broad spectrum of “externalizing” disorders, a spectrum distinct from the internalizing spectrum. Together, the internalizing and externalizing spectra form a model of comorbidity among common mental disorders.
that has now been replicated by a number of independent research groups [7–12]. This kind of model is referred to as a structural model because it points to the personality structures (the internalizing and externalizing spectra) that link various common mental disorders and help explain why common mental disorders show specific patterns of co-occurrence. Under this model, internalizing can be understood in a tendency to express distress internally, placing the person at odds with themselves, and is manifested as syndromes that involve problems like depression, somatization, and anxiety. Similarly, externalizing can be understood as a tendency to express distress outwardly, placing the person at odds with others and society, and is manifested in syndromes that involve problems like antisocial behavior, substance misuse, and impulsivity.

A heuristic guide to this model is presented in Figure 1. As shown, syndromes involving depression, somatization, and anxiety are linked together as elements within the broader internalizing grouping. Similarly, syndromes involving antisocial behavior, substance misuse, and impulsivity are linked together as elements within the externalizing grouping. In addition, the internalizing and externalizing groupings are linked at a higher level by the presence of distress in all common mental disorders. That is, the model states that all common forms of psychopathology involve distress, which can be internalized or externalized, and subsequently expressed as the specific syndromes listed at the bottom of Figure 1.

Emerging evidence suggests that this model organizes not only the observed, or phenotypic structure of common forms of psychopathology, but also underlying genetic risk for these syndromes [11]. That is, emerging evidence suggests that internalizing problems go together because they are linked by common genetic factors. Similarly, externalizing problems go together because they, too, are linked by common genetic factors—factors separate from those that link internalizing problems. The model therefore has high utility for organizing the search for genes that confer risk for the development of numerous common forms of psychopathology.

The goal of the current chapter is to extend this model to a new and relatively uncharted area at the interface between mental disorders and physical disorders: chronic pain. We begin with a review of literature pointing toward psychosocial and genetic mechanisms that may help to explain relationships between pain and other internalizing phenomena. We then turn to a discussion of some of our recent research linking somatic syndromes (including pain symptoms) within the internalizing spectrum of the internalizing-externalizing (IE) model. We conclude by discussing how the IE model could help organize research on psychosocial and genetic mechanisms that underlie the internalizing spectrum, including chronic pain.

**Psychotherapeutic Treatments for Depression and Chronic Pain**

Cognitive behavioral therapy (CBT) techniques were originally developed in the 1950s and 1960s, initially to be used in treating depressive disorders [1]. However, the effectiveness of CBT has also been demonstrated in individuals with chronic pain. Studies often show that CBT focused on pain-related symptomatology is effective in reducing both pain-related symptoms and depressive symptoms as evidenced by typical measures of these symptoms [14–16]. Benefits of CBT on pain-related symptoms have also been evidenced using an external criterion such as number of days of work missed following treatment [17]. These results have also been demonstrated in the use of CBT with children and adolescents [18]. In addition to CBT, behavioral techniques often used to treat depression and anxiety have been used as effective treatments for chronic pain [19]. Furthermore, even acute systemic activity has been found to aid both depression and pain [20].

**Potential Mechanisms Underlying Psychotherapeutic Treatments**

A related line of research has sought to identify common underlying mechanisms in depression and chronic pain that may explain why some treatments are effective for both. Some studies have identified similarities in cognitive processes between depressive and chronic pain individuals. For example, information-processing biases such as selective attention to negative stimuli, selective recall of mood congruent stimuli and interpretation of ambiguity as
negative have all been related to both depression and chronic pain [21, 22]. Categorizing has also been related to increased levels of both depressive and pain-related symptoms [27-29].

Some common outcome variables have been investigated as they relate to effective treatment for both depression and chronic pain. In particular, changes in coping and self-efficacy appear to be an important measure of improvement in both depressive and pain-related symptoms following treatment [27, 28]. In this literature, coping is typically considered a cognitive variable related to the perceived use of effective strategies to deal with pain or depression symptoms. Problem-solving self-efficacy, as an individual's perception of their ability to problem-solve, has been identified as an important cognitive process involved in coping, and higher self-efficacy has been found to result in lower levels of pain and depression following treatment [29]. Similarly, perceived control has been linked with coping efficacy in both pain and depression [20, 30].

Kramer and Turner [21, p. 30] provide a review of cognitive and behavioral frameworks that aim to explain the depression-pain association. They discuss an operant behavioral perspective (disorder results as a response to the environment), a more general behavioral perspective (pain becomes associated with depression-related activities, activities are reduced to avoid pain, cycle of pain and depression results), and a cognitive perspective (disorder results from 'catastrophic' misinterpretations of cognitive processes). Research exploring the applications of these perspectives in the realm of pain-depression relationships, i.e., in targeting populations suffering from the comorbidity of chronic pain and depression, is lacking. Most of the emphasis on understanding applications of these theories has been in the depression literature [31], although the pain literature has become more active in this area recently.

Symptoms such as the ones reviewed above have always been effective in treating both chronic pain and depression and researchers have begun identifying similar underlying mechanisms that may explain the joint effectiveness of these treatments. However, most research to date that has included measures of both depression and chronic pain has investigated the effects of treatment for a particular population of chronic pain patients and measured changes in depression as well. It is less common for the selected sample to consist of patients with comorbid pain and depression, with the aim of understanding effectiveness of treatments for this comorbid condition, or extending the sampling scheme to patients with extensive and complex interlinking comorbidities (e.g., anxiety, depression, and pain). Thus, while some of the work in this area has begun to explore the complex mechanisms underlying the effects of treatment for pain and depression, it is important for future research to test theories of treatment for complex patterns of interlinking comorbidity that are frequently seen in clinical settings.

Psychopharmacological Treatments That Work for Depression and Chronic Pain

An influx of research over the last 15 years has provided compelling evidence that antidepressants can be used as an effective treatment for chronic pain. Tricyclics are a particular class of antidepressants that were hypothesized to be effective in treating pain. In support of this hypothesis, studies have generally found that tricyclic antidepressant pain symptoms [32, 33] and are effective in treating both pain and depressive symptoms [35]. Other antidepressants have also been studied in relation to pain, and some have been shown to have positive effects on pain symptoms [36-38] and on both pain and depressive symptoms [39, 40].

Hudson and Pope [41] reviewed the evidence on effectiveness of antidepressant treatments for a large class of disorders. Specifically, they identified major depressive disorder, bipolar, obsessive-compulsive disorder, panic disorder, attention deficit/hyperactivity disorder, comorbidity, migraine, and remitting, partial syndrome as a related class of disorders based on studies showing effective use of antidepressant treatments for them. Posttraumatic stress disorder and cyclical facial pain met the criteria to be classified in this grouping. Hudson and Pope termed this class of disorders that responded to antidepressants the "effectiveness spectrum disorder", based on the idea that response to treatment can be used to identify a similar nosology among disorders. Hudson et al. [42] also recently presented a family study demonstrating significant coaggregation of major depressive disorder with other forms of affective spectrum disorders, expanded to also include dystymic disorder, Guillain-Barré, general anxiety disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, and social phobia.

While most research in this area has looked at the impact of treatments for depression on symptoms of chronic pain, a recent study investigated the reverse relationship. Substance P, one of the best-understood neuropeptides, has been extensively studied in relation to pain. It has been widely established that substance P antagonists are helpful in alleviating pain [43]. Recently, evidence such as having similar enzymes of distribution in the CNS, led one group of researchers to posit that substances P may be linked to, or interact with, serotonin and noradrenaline pathways [44]. A randomized, double-blind, placebo-controlled study demonstrated that efficacy in the treatment

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of depressive symptoms with a substance P antagonist, supporting the theory that substance P plays a role in regulating depression as well as pain [44].

**Putative Mechanisms Underlying Psychopharmacological Treatments**

The documented high levels of cooccurrence between depression and chronic pain have led some researchers to speculate that there is a common neurochemical association to account for the pain-depression relationship. Specifically, researchers have posited a serotonin noradrenergic hypothesis to explain this connection [45]. It has been well-established in the literature that serotonin and noradrenaline play a role in depression [46, 47], and in the experience of pain [48]. In addition, endorphins in CNS have been shown to have a pain-modulating function and play a role in psychiatric disorders such as depression [32].

One model that has been proposed is the relationship between serotonergic and noradrenergic systems and the experience of pain. This model suggests that the serotonergic and noradrenergic systems play a role in regulating pain perception. Specifically, the model posits that the noradrenergic system plays a role in the modulation of pain perception, while the serotonergic system plays a role in the modulation of emotional response to pain.

**Quantitative Genetic Studies of Pain and Negative Emotions**

Phenotypic studies are important as they demonstrate extensive relationships between pain and depressive symptoms. However, it is important to note that these studies require careful interpretation and consideration of potential confounding factors. Overall, the evidence supports the idea that pain and negative emotions are related, but further investigation is needed to understand the specific mechanisms involved.

**Summary**

The use of antidepressants for chronic pain has received increasing attention over the last decade. In general, studies have shown antidepressants to be effective in treating chronic pain and in some studies, in treating both pain-related and depressive symptoms. The tricyclic antidepressants have been the most widely studied, and different types of antidepressants that are effective in treating pain may provide further information regarding the underlying neurochemical pathways. In addition, substance P is a neuropeptide associated with pain, and more recent work has found substance P antagonists to produce an antidepressant effect. Hypotheses of similar neurochemical pathways for pain and depression have primarily focused on the neurotransmitters serotonin and norepinephrine, which have been linked to both pain and depression. The use of antidepressants for pain and depression is likely to continue to grow in the future, and these findings provide important information to support this approach.

**Structured Model**

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associated with depression, such as anxiety and neuroticism. In research by Kijima et al. [34], for example, recently investigated genetic and environmental relationships between back-neck pain and symptoms of depression and anxiety. The authors demonstrated that both pain and symptoms of depression and anxiety were more prevalent in individuals with genetic factors acting on both, whereas the correlation was attributed to environmental factors not shared between relatives. Overall, these results suggest that, in the back-neck pain and depression association, the majority of that correlation is due to genetic factors acting on both, the remainder of the association is due to environmental factors largely specific to each individual.

Examination of other forms of pain, such as pain associated with premenstrual symptoms, supports the importance of genetic factors in relationships between depression and pain. Silber et al. [35], for example, demonstrated that concurrence between premenstrual symptoms and symptoms of anxiety, depression, and neuroticism can largely be attributed to genetic factors common to both sets of traits. Todor et al. [36], similarly, reported a genetic correlation of 0.70 between premenstrual symptoms and illness major depression, and a genetic correlation of 0.62 between premenstrual symptoms and neuroticism.

Molecular Genetic Studies of Pain and Negative Emotions

Evidence for genetic relationships between pain, depression, and other forms of negative emotion indicates that these phenomena share common molecular genetic substrates. Identifying these substrates—the peculiar genes and genetic systems involved in associations between pain and depression—is essential to understanding the etiology of both. Emerging evidence is revealing a number of neuromodulatory systems involved in various forms of negative emotion, suggesting candidate substrates of interrelating phenomena.

Much of the existing knowledge about genes mediating the association between pain and depression is derived from findings that systems known to be involved in pain are also involved in depression. For example, there are findings that the neuropeptide neuropeptide (i.e., substance P, tachykinins) is involved in the etiology of pain and depression. Numerous studies have established the role of neuropeptide in nociception; emerging evidence suggests that it plays an important role in the expression of negative emotions such as anxiety and depression as well. In this context, studies on example, have demonstrated that neuropeptide is expressed in brain regions associated with regulation of negative emotion, such as the amygdala and dorsal raphe nuclei [44, 57, 58]. Also, as noted earlier, neuropeptide antagonists show potent antidepressant effects in animals as well as in humans [44]. Various studies are beginning to elucidate the genetic mechanisms by which neuropeptide regulates depression and other negative emotions. Such a neuropeptide, neuropeptide is directly encoded by the TRPV1 gene, which in humans is located on the long arm of chromosome 17 in the 2q21-q22 region. TAC1 encodes a neuropeptide precursor, preproenkephalin, which is spliced to form neuropeptide. Neuropeptide activity is also influenced by expression of the neuropeptide receptor gene TACR1, which is located on the short arm of chromosome 2 in the 2p12 region.

Knockout studies in mice have demonstrated the role of TAC1 expression in depression and anxiety. Consistent with previous research on neuropeptide and pain, TAC1 knockout mice demonstrated decreased nociception [39]. However, TAC1 knockout mice also express lower levels of depressive behavior than heterozygotes or wild-type mice. For example, TAC1 knockout mouse evidence decreased immobility in behavioral despair paradigms such as forced-swimming and tail suspension tests, and show decreased markers of depression in physiological paradigms [60]. TAC1 knockout mice express lower levels of anxiety in various paradigms as well. For example, TAC1 knockout mice are more active in the central area of an open field, spend more time in open maze compartments, show decreased latency to approaching food in a novel environment, and spend more time interacting socially with unfamiliar mice [60].

Knockout studies of the TACR1 gene have also demonstrated the role of neuropeptide signaling in regulation of negative emotion. Mice lacking the neuropeptide receptor gene show decreased levels of anxiety relative to heterozygotes and wild-type mice in a variety of paradigms. TACR1 knockout mice spend more time in open arms of an elevated plus-maze, show decreased latency to approaching food in a novel environment, and in pups, show decreased frequency of vocalizations when separated from their mother [38].

Overall, these studies demonstrate the role of neuropeptide in the regulation of negative emotion. The mechanisms by which neuropeptides and neuropeptide receptor gene expression regulate negative emotion are still well understood, however. There is some indication that neuropeptide systems interact with a negative emotion, but this is not established. For example, disruption of the TACR1 gene appears to increase firing of autonomic neurons in the dorsal raphe nuclei [58], and in neuropeptide antagonists have been used to decrease autonomic responses in a manner similar to that observed with sustained antidepressant use [61]. However, neuropeptide antagonists appear to not significantly influence autonomic functioning [44], and there is some indication that TACR1 disruption influences...
The role of pain in promoting and maintaining chronic pain is well established. Pain is a complex experience that involves both sensory and affective components. It is regulated by a network of neural circuits that are sensitive to both peripheral and central stimuli. Pain can be acute or chronic, and it can be classified as nociceptive (due to tissue damage) or neuropathic (due to nerve damage).

Recent evidence suggests that pain is not just a sensory experience, but also an emotional one. Chronic pain can lead to mood disturbances, anxiety, and depression, which can further exacerbate pain. This pain-mood interaction is bidirectional, with psychological factors influencing pain perception and physical factors influencing mood and behavior.

Conclusions: The relationship between pain and mood is complex and multifaceted. Future research should focus on understanding the mechanisms underlying this relationship and developing effective interventions to improve pain management.

References:
search for general mechanisms linking internalizing phenomena seen in children, and the inclusion of children within the model also seems warranted by our recent research in this area [10].

Some additional features of the EI model should also be emphasized, and one ability to organize research linking intimate disorder and chronic pain. Importantly, the model is dimensional and hierarchical in nature. What this means is that syndromes within the spectrum are viewed as varying continuously along within and between persons, and are organized at continuously varying levels of connection among syndromes. These features of the model are discussed in more detail by Krueger and Patrick [67], who also discuss statistical models that can be used to apply these features to empirical data. Thus, specific psychopathological and pathophysiologic features can be conceptually and statistically linked to single syndromes, multiple syndromes, or the broad and overarching interacting factors linking all syndromes within the spectrum. As a specific example, consider osteoarthritis. Research reviewed above suggests that this neuropathy may play a very general role within the interlocking spectrum: the most acute inflammatory pathophysiology may be intrinsically linked to the overarching interrelated factors. Within the context of this more general genetic risk for internalizing problems, specific patterns of coping and cognitive styles could help to explain why the behavioral geneticists for internalizing problems is expressed as specific persons as depression, anxiety, chronic pain, and so on, at specific times. To focus forward to these kinds of empirical extensions of the ideas presented herein.

References


