Anxiety in Functional Pain Disorders

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Overview

Affective processes can interact with nociception and pain at a variety of levels—pain generation, pain modulation, and pain response. These relationships are found with pain regardless of its source, but there has been a special focus on the role of affective processes in functional pain disorders. This emphasis is due not only to a lack of good peripheral biological models for generation of symptoms in these disorders but also to empirical findings of increased comorbidity of functional syndromes with psychiatric disorders such as anxiety and depression. Anxiety is the negative affect most often identified as being linked with functional disorders, and this chapter will review the theory and evidence regarding the role of anxiety in the development, persistence, and treatment of functional syndromes.

How we approach such issues as the role of anxiety in functional pain disorders has shifted considerably with the development of affective neuroscience as a predominant paradigm for studying emotion. It is important to recognize that negative affect can be studied from multiple
points of view. Much of what we know about the phenomenology of negative affect, and specifically anxiety, comes from self-report data and behavioral observations collected in questionnaires, in clinical interviews, or during laboratory experiments. From these data we now recognize specific anxiety disorders, which are based on a cluster of persistent symptoms that lead to life interference (e.g., panic disorder and generalized anxiety disorder), as well as dimensional characteristics that are related to anxiety but are present to some extent in the entire population (e.g., trait anxiety, worry, and specific fears).

For the purposes of this chapter, we have taken a broad conceptualization of the anxiety construct. We believe that anxiety emanates from the activation of a highly evolved neural network of cortical, subcortical, and brainstem regions that promote survival through threat detection and avoidance, i.e., the aversive/defensive system [13,29,61,63]. Negative affective states are the phenomenological experiences that result from the activation of this network, and the feeling of anxiety is one label for these experiences.

It is important to identify and define a number of anxiety-related terms that have been used throughout the pain literature to provide the reader with a framework for understanding our review. State anxiety is a diffuse negative affect associated with arousal, apprehension, and hyper-vigilance that is directed at the potential for future harm. Trait anxiety is the general tendency to experience state anxiety, reflecting a stable, trait-like disposition [115]. Similarly, neuroticism is a stable personality trait associated with the propensity to experience negative affect [34]. Stress is a term that has several meanings; however, for the purposes of this chapter it will be used to refer to the negative emotional reaction associated with exposure to a real or imagined threat that is typically concomitant with fight-or-flight reactions [70]. Worry is used to refer to cognitive responses to real or imagined threat [43,78], and catastrophizing involves cognitive processes associated with magnification, rumination, and helplessness about negative events such as pain. Fear avoidance and related terms (e.g., kinesiophobia) refer to negative affect stemming from the negative consequences (e.g., pain) of movement and physical activity [107,127]. Therefore, many of these terms clearly have significant conceptual overlap in that they are psychological responses to threat.
Affective neuroscience has emphasized the importance of examining the central nervous system (CNS) or neurocognitive processes that generate phenomenological categories and dimensions. For example, somewhat separate circuits within the limbic system have now been identified that subserve anxiety and fear-like behaviors in both humans and other mammals [128].
The focus on building-block neurocognitive processes that underlie both symptoms and behaviors associated with anxiety leads naturally to an examination of commonalities and interrelationships between processes involved in anxiety and those involved in pain modulation. Fig. 1 illustrates a proposed model of this relationship. Several key elements of this model are described as follows.

1) On a descriptive level, anxiety-related processes may influence the development and persistence of somatic symptoms via multiple interrelated pathways. These processes include increasing arousal and defensive responses to somatic information; altering interoceptive sensitivity, and particularly pain sensitivity, via descending modulatory pathways; increasing vigilance to somatic symptoms; and interfering with normal cognitive and behavioral strategies for coping with injury and illness.

2) Symptom-specific anxiety can be distinguished from more general anxiety in that the cues for triggering the negative affect are primarily related to the experience of symptoms and the contexts in which they occur.

3) At the level of neurocircuitry, these interacting processes are hypothesized to involve cortico-limbic-pontine interactions, with primary roles for the activity of the lateral prefrontal cortex interacting with limbic and paralimbic structures of the medial prefrontal cortex, anterior cingulate, and amygdala. Also involved are brainstem structures that mediate the various physiological and motor responses in response to stress.

4) Anxiety can also significantly influence functional syndromes at the level of behavior; for example, fear of movement may be a powerful incentive to rest, which in turn may lead to greater pain and fear.

Each of these processes will be discussed in more detail below.

Role of Anxiety in Development of Functional Pain Disorders

It is likely that the development of one or multiple functional pain disorders involves a summation of several vulnerabilities, of which some may be
syndrome-specific and others are more common to functional pain disorders in general. It has been suggested that certain genetic predispositions and early life trauma may raise the probability of both functional pain disorders and anxiety-related conditions. Although a review of these literatures is beyond the scope of this chapter, it is relevant to note that there is some evidence that childhood abuse is most highly associated with panic disorder (as compared to other anxiety disorders or depression) [108]. In irritable bowel syndrome (IBS) it appears that vulnerability to anxiety (in the form of neuroticism) appears to be a primary pathway for translation of negative early experience into symptom generation [119] (see also Chapter 20 by Papp and Sobel; Chapter 6 by Chang and Drossman). Consistent with this conceptualization, a recent brain imaging study has shown that IBS patients with a history of abuse, compared to those without such a history, report more pain, greater mid-cingulate cortex activation (associated with affective experience of pain), and reduced activity of a region implicated in pain inhibition and arousal, the subgenual anterior cingulate cortex (ACC) [105].

The study of genetic vulnerability for functional pain disorders is in its infancy and is reviewed elsewhere in this volume (Chapter 20 by Papp and Sobel). So far, the results have shown intriguing relationships between genetic markers related to the serotonin and norepinephrine systems and the development and presentation of symptoms [23]. Many of these same markers have also been associated with anxiety and threat sensitivity [110]. Given the data suggesting a strong overlap of functional pain disorders with panic and generalized anxiety disorder (discussed below), it is interesting to note a recent report differentiating separate genetic vulnerabilities for panic versus generalized anxiety versus agoraphobia and other specific phobias [46]. It is likely that the relationships between genetic markers and both affective and pain symptoms are complex. For example, Diatchenko et al. [22] have recently reported a very strong association between haplotypes of the β2 adrenergic receptor (ADRB2) and the development of temporomandibular joint disorder (TMD) (see also Chapter 4 by Maixner). Individuals who carried one haplotype coding for high expression and one coding for low expression of ADRB2 displayed the most positive psychological functioning
and were about 10 times less likely to develop TMD than those without these haplotypes. However, of the anxiety measures used in this study, trait anxiety was negatively related to presence of one haplotype, current anxious mood was positively related to another, and several other measures were unrelated to the genetic markers. Overall, emerging but still preliminary data support the hypothesis that some of the common vulnerability between anxiety and functional pain disorders may be related both to overlapping genetic variables and to a history of trauma, and that these factors can be tied to specific CNS mechanisms of arousal and pain modulation.

**Comorbidity of Anxiety and Functional Pain Disorders**

A growing body of research demonstrates that functional somatic syndromes, including fibromyalgia syndrome (FM), irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), and chronic headache, are all associated with an increased prevalence of anxiety disorders as defined by the Diagnostic and Statistical Manual (DSM) criteria [1]. The data are not sufficient to pinpoint the degree of overlap with precision, but it appears that the combined rate of any anxiety disorder may be three or more times that of the general population and also greater than for clearly organic defined illnesses with similar symptom patterns such as gastrointestinal (GI) discomfort, pain, and fatigue. In clinic and especially tertiary care populations, the rates are even higher, with some findings of 60% or more of patients having a comorbid anxiety disorder. Examples of these studies are provided as follows.

*Fibromyalgia syndrome.* Epstein et al. [28] report a 17% rate of panic disorder, a 17% rate of simple phobia, and a 35% rate of any lifetime anxiety disorder in a clinic-based sample of FM patients. Arnold et al. [4] report a 28% rate for panic, a 21% rate for phobia, a 23% rate for post-traumatic stress disorder (PTSD), and a 60% rate for a lifetime diagnosis of anxiety. In agreement with these studies, a meta-analysis of five studies of FM also found panic disorder to be the most common of the comorbid anxiety diagnoses, with an odds ratio (OR) of 9.0 [4].
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**Irritable bowel syndrome.** Kumano [56], in a large Japanese population study, found that panic disorder (OR = 3.58) and agoraphobia (OR = 1.96) were significantly more prevalent in subjects with IBS compared to those without. Several other authors have also reported increased rates of panic disorder and several other anxiety disorders as well as depression in IBS [66,129] in population studies, and an even greater prevalence of anxiety was found in GI clinic samples (30–60%) [64]. One study has also reported a high rate (36%) of PTSD in clinic patients with IBS [47]. A meta-analysis also found that anxiety, but not depressive symptoms, was associated with consulting for abdominal symptoms [45].

**Chronic headache.** In a large population study (n > 60,000), Zwart et al. [141] report significantly higher rates of anxiety disorders in individuals with both nonmigraine headaches (7.8%; OR = 2.7) and migraine headaches (9.2%; OR = 3.2). In another population study, Lake et al. [59] reported an increased prevalence of anxiety in subjects with recurrent headache as well as greater anxiety with more frequent headache. There was no greater risk for anxiety in subjects with infrequent headache.

**Interstitial cystitis.** While there is very little information about interstitial cystitis (IC), Wu et al. [136], studying a large population of patients in a health maintenance organization (HMO), reported significantly increased rates for depression (relative risk [RR] = 2.8) and even greater rates for anxiety (RR = 4.5) in patients diagnosed with IC. Talati et. al. [118] also report a genetically linked clustering of panic and social anxiety disorder with several medical syndromes including IC.

The only broad-based meta-analysis of anxiety and depression across functional syndromes [45] found that both anxiety and depression were consistency higher in the four disorders studied—IBS, FM, CFS, and functional dyspepsia. The effect sizes for the association of anxiety with these syndromes were of moderate magnitude but highly significant statistically when compared with healthy persons and control patients with medical disorders of known organic pathology. There were some differences in the relationships, however. For example, IBS had a stronger association with anxiety than did FM. Although there were insufficient data for most of the syndromes, the analysis of IBS also showed that consulting behavior and severity of somatization were significantly related to levels of anxiety.
Taken together, the studies to date indicate a substantially greater rate of lifetime anxiety disorders in patients with many of the functional disorders. However, it is not clear whether specific disorders in the anxiety spectrum are more closely associated with some or all of the syndromes. This type of analysis is complicated by extensive overlap among the anxiety disorders and by the focus of many studies on a limited set of disorders. The very limited data do, however, suggest that panic disorder and generalized anxiety disorder are the types of anxiety most consistently associated with IBS and FM. These findings may indicate a stronger overlap of mechanisms involved in these disorders with those of functional pain disorders.

**Symptom-Specific Anxiety**

Although the comorbidity studies described above point to increased general anxiety and other negative moods in patients with functional syndromes, growing evidence indicates that symptom-specific anxiety and fears may be even more relevant for understanding the relationship between negative affect and symptom development and persistence in these disorders. *Symptom-specific anxiety* can be defined as the cognitive, affective, and behavioral response stemming from fear of specific somatic (or visceral) sensations, symptoms, and the context in which these sensations and symptoms occur [5,58]. Examples of symptom-related contexts for a visceral sensation might include situations involving food and eating such as restaurants or parties or locations in which bathroom facilities are unknown. For a chronic pain condition, symptom-related contexts might include situations associated with movement or physical strain, such as a long stairway, an airport, or a long car ride. Symptom-specific anxiety includes hypervigilance to—and fear, worry, and avoidance of—relevant sensations and contexts. Symptom-specific anxiety may perpetuate symptoms through alterations in autonomic and pain facilitation, as well as through cognitive mechanisms [52,72]. Symptom-specific anxiety is thought to be associated with beliefs of poor symptom control and high illness impact and may, therefore, also be a critical element in the severe decrements in quality of life found in most functional syndrome patients [58].
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Models of symptom-specific anxiety have been proposed for certain anxiety disorders [93,94] and more recently for chronic somatic pain [6,35] and functional GI disorders [58]. Anxiety sensitivity has been postulated as a constitutional predisposition characterized by hypersensitivity to anxiety-related somatic sensations (autonomic arousal) based upon beliefs that these sensations have harmful somatic, psychological, or social consequences [91,120]. Anxiety sensitivity can be distinguished from trait anxiety [92] in that it represents a specific tendency to respond fearfully to the interoceptive sensations of anxiety rather than the predisposition to respond anxiously to a wide range of stressors that characterizes trait anxiety. In a study of 8-year-old twins, Eley et al. [27] found a significant relationship between anxiety sensitivity and both panic symptoms and the ability to detect heartbeats (a measure of somatic vigilance). Genetic analysis suggested some common genetic vulnerability for these variables, although environmental influences appeared to be substantial.

Expansion of the anxiety sensitivity construct into multiple overlapping symptom-specific fears is partially an outgrowing of factor analytic research. For example, a recent factor analysis of a comprehensive measure of anxiety sensitivity revealed four specific somatic mechanisms or domains in addition to a single higher-order factor (general anxiety sensitivity trait) [120]. These domains corresponded to: (1) fear of respiratory symptoms, (2) fear of cardiovascular symptoms, (3) fear of cognitive dyscontrol, and (4) fear of GI symptoms. Overall, recent findings in the area of symptom-related anxiety support a common underlying vulnerability related to hypersensitivity to interoceptive information and threat, as well as specific content-related biases based on experience or other more specific vulnerabilities. In either case, clinical data suggest that symptom-specific anxiety is a powerful mediator of symptom severity, coping, and quality of life in patients with functional pain disorders.

Experimental Evidence for the Relationship between Negative Affect and Pain Processing

To understand the potential role of negative affect on functional pain, it is important to first characterize the experimental evidence in healthy
individuals. These data suggest that the relationship between negative affect and pain is nonmonotonic, such that the intensity of the emotional experience (typically assessed by level of arousal) determines the modulatory outcome (see Fig. 2) [99]. Specifically, negative emotions that are low to moderate in intensity (e.g., anxiety or apprehension) enhance pain, whereas very intense negative emotions (e.g., fear or panic) inhibit pain. Importantly, this effect is not simply due to arousal alone, because the relationship between positive affect intensity and pain is not nonmonotonic [99].

![Fig. 2. Hypothesized relationship between negative affect and pain modulation in healthy persons. Negative affect with low to moderate intensity (arousal) enhances pain, whereas negative affect with high arousal inhibits pain. This figure also synthesizes ideas related to differences in emotional intensity and threat imminence. In particular, greater threat imminence (greater spatial or temporal proximity of a threatening stimulus or event) is associated with greater negative emotional intensity. Threat that is imminent and severe is likely to lead to intense negative affect (e.g., fear) that will inhibit pain processes. In contrast, threat that is less imminent (less proximal) will result in negative affect with less emotional intensity (e.g., anxiety). Therefore, threat that is not imminent and is less severe or unpredictable will lead to moderately intense negative affect that will facilitate pain processes. For persons with functional pain disorders, this relationship could be altered in several ways such that negative affect has a greater propensity to enhance pain (e.g., inhibitory processes are depleted, predictable threat enhances pain, and negative affect is generally exacerbated).]

This nonmonotonic relationship of negative affect and pain is likely to have evolved as a means to promote survival during potential or immediate threat (conditions that would elicit negative affect). In situations
associated with low to moderate threat (in which less intense negative affect would predominate), it is adaptive to promote environmental scanning, vigilance, and sensory intake as a means to improve threat detection [77,130]. In this situation, threat is more unpredictable, and hyperalgesia (enhanced pain) would be adaptive because it promotes detection of somatic threats and recuperation from tissue damage that might have been incurred during a time of high threat. However, when threat is present, imminent, and predictable (situations in which intense negative affect would predominate), pain and its associated reflexes and behaviors might interfere with active defense (fight-or-flight) [29,111]. In this latter situation, hypoalgesia (reduced pain) is adaptive.

Support for the relationship between negative affect and pain stems from research using various research methodologies. In preclinical studies, a large body of research has shown that acute and chronic stress leads to alterations in nociceptive sensitivity. Both analgesia and hyperalgesia have been demonstrated in studies of somatic pain, depending on the nature of the stress, the animal strain, and the behavioral indications of pain [54,67]. Studies of visceral sensitivity have shown long-lasting stress-induced hyperalgesia, suggesting potentially differential mechanisms for somatic and visceral pain modulation [12]. For example, Cornwall and Donderi [16] induced anxiety using a stressful interview or by providing a warning of an upcoming pressure pain test, compared to a no-anxiety condition. Findings suggested that both anxiety manipulations enhanced ratings of the pressure stimulus, with subjective stress showing a positive correlation with pain. In other studies, anxiety has been induced by verbal threat of electric shock and was found to reduce heat pain thresholds (causing hyperalgesia) [42,97]. Similar hyperalgesic effects occurred when instructions were given to generate anxiety about the same shock that was used to test pain [131]. Dougher and colleagues used emotionally charged statements to evoke negative affect, but also manipulated the focus of the emotion. They had participants read statements that produced general anxiety (e.g., walking down a dark alley), pain-specific anxiety (e.g., slamming a finger in a car door), or pain-task-specific anxiety (e.g., describing a device that produces extremely painful sensations) and found that only pain-specific anxiety reliably enhanced pain.
Evidence has shown that the repetitive application of a noxious stimulus leads to successively larger pain responses (temporal summation), an effect believed to be related to central sensitization. Robinson and colleagues [106] demonstrated that state anxiety during testing was positively correlated with temporal summation, suggesting that anxiety may engage mechanisms to enhance CNS pain processing. This effect was replicated by Granot and colleagues [38], and research by Edwards and colleagues [26] suggests that pain catastrophizing may have a similar facilitatory effect.

Ploghaus and colleagues [86] presented a neutral cue prior to the onset of a constant-intensity stimulus. However, in some trials the cue was followed by a stimulus of greater intensity. Thus, the cue came to elicit anxiety about the potential stronger stimulus. These authors found hyperalgesia to the constant-intensity stimulus, an effect that correlated with activation in the hippocampal formation as measured by functional magnetic resonance imaging.

As noted in the study by Ploghaus and colleagues, when a neutral cue (a conditioned stimulus) is paired with an aversive stimulus (an unconditioned stimulus), the conditioned stimulus comes to elicit negative affect—a procedure referred to as fear conditioning. In a variant of the fear conditioning paradigm, Williams and Rhudy [135] paired an unconditioned stimulus (a mild shock) with a conditioned stimulus consisting of a facial expression of fear. Later, the fear expression was presented to induce moderately intense negative affect (anticipatory anxiety) during pain testing. The investigators found that the fear expression reduced pain thresholds (causing hyperalgesia), despite the fact the fear expression had no influence on pain before being paired with shock.

Studies discussed thus far evoked negative affect by the presentation, or anticipation of, a painful stimulus; however, others have used non-painful stimuli. Rhudy and Meagher [98] presented startling noise bursts to evoke negative affect. When the noises elicited negative affect and low arousal, hyperalgesia was produced, but when the noises elicited negative affect with high arousal, hypalgesia ensued. Zelman and colleagues [139] had participants read emotionally charged statements unrelated to pain to produce sadness and found that negative affect reduced cold pressor tolerance (i.e., caused hyperalgesia). Other studies have used mental imagery,
although rarely to induce negative emotions. Using personal negative imagery, Smith and Wolpin [113] found that cold pressor pain tolerance was decreased and that the effect was correlated with the vividness of the imagery. In three studies, Rainville and colleagues [90] used hypnotic suggestion to induce negative affect (anger, fear, sadness) and found that changes in negative affect were associated with changes in pain unpleasantness and pain-related heart rate responses.

In an innovative study, Villemure and colleagues [126] examined the influence of computer-delivered pleasant and unpleasant odors and found that, relative to pleasant odors, unpleasant odors increased negative mood and anxiety and enhanced pain unpleasantness. Further, odor-evoked mood was correlated with pain unpleasantness ratings. Unfortunately, this study did not include a neutral control condition to determine whether pleasant odors decreased, or unpleasant odors increased, pain unpleasantness. Indeed, when others included a control condition, evidence was mixed. One study found that pleasant odors reduced pain [89], whereas another found that unpleasant odors enhanced pain [69].

A problem with any experiment that manipulates emotion is the difficulty in standardizing the procedures so that emotion can be reliably manipulated across participants, laboratories, and studies. A recent technological advancement in this area was the development of the International Affective Picture System (IAPS) [60]. The IAPS is a normed set of emotionally charged visual stimuli that evoke reliable subjective and psychophysiological emotional responses in healthy participants [14] and engage corticolimbic systems [32,39,84]. Research has shown that unpleasant images from the IAPS (e.g., mutilated bodies, attack scenes, snakes, and spiders) reliably enhance pain threshold, pain tolerance, and pain ratings of noxious stimuli [21,76,80,137].

More recently, researchers have used the IAPS to determine whether physiological correlates of pain are modulated in the same manner as the subjective experience. This issue is important, given that the relationship between negative affect and pain could be due, at least in part, to experimental demands or report bias without any changes in nociceptive processing. In a series of studies, Rhudy and colleagues [102–104] assessed the influence of threatening images from the IAPS on the
nociceptive flexion reflex (NFR). The NFR is a spinal reflex that promotes withdrawal from a noxious stimulus; it is dependent on the activation of Aδ-fiber nociceptors [109]. The threshold for eliciting the reflex correlates significantly with pain threshold, and the magnitude of the reflex covaries with subjective pain [109,112]. Thus, researchers have used the NFR as a physiological correlate of spinal nociception. Rhudy et al. [102–104] found that threatening images facilitated pain and increased the NFR, suggesting that emotion enhances nociceptive processing by activating descending brain-to-spinal cord circuitry. Given that pictures do not represent an immediate threat, the variation in emotional intensity elicited by pictures only elicits negative affect with low to moderate arousal (see Fig. 2). Nonetheless, the degree of nociceptive facilitation appeared to depend on the amount of arousal the pictures elicited, with greater facilitation resulting from greater emotional intensity [104].

It is also interesting to note that the ability of negative affect to engage descending facilitatory processes may depend on the predictability of the noxious stimulus. Rhudy and colleagues [103] manipulated whether the noxious shocks presented during emotional picture-viewing were predictable: half of participants received a cue (a light) just before each shock was delivered (predictable), whereas the other half received no cue (unpredictable). In both groups, unpleasant pictures facilitated pain report. However, the NFR was not modulated by unpleasant pictures when the noxious shock was predictable. This finding suggests that descending modulation was disengaged at the same time that supraspinal modulatory mechanisms that alter pain report remained intact.

In other studies, IAPS stimuli were found to modulate additional physiological responses to noxious stimuli, such as skin conductance response [96,104], heart rate acceleration [96,104], and eye blink magnitude [134]. Moreover, Kenntner-Mabialia and Pauli [51] demonstrated that pain-evoked somatosensory potentials were enhanced by unpleasant pictures. Taken together, studies of negative affect of low to moderate intensity suggest that hyperalgesia is observed and that this effect can involve descending circuits that modulate ascending nociception at spinal levels, especially when the noxious stimulus is unpredictable (and thus more anxiety provoking).
Relatively few studies have examined the influence of intense negative emotions on pain, primarily due to the difficulty of doing so in an ethical and safe manner. Nonetheless, a few well-controlled studies have been successful. Pitman and colleagues [85] exposed war veterans suffering from PTSD and a control group to a combat-related video. The video elicited highly arousing negative affect and hypoalgesia in the PTSD group, an effect that was opioid mediated. Janssen and Arntz [48] presented live spiders to arachnophobics to elicit intense negative affect. In this study, the manipulation also resulted in an opioid-mediated hypoalgesia, although it is unclear whether phobic stimuli reliably elicit hypoalgesia [c.f. 49].

Negative affect-induced hypoalgesia is not limited to clinical samples, however. For example, Janssen and Arntz [50] have shown that a parachute jump can induce an opioid-mediated hypoalgesia. Rhudy and Meagher [95,97,100,101] have shown that an intense, negative affect-producing shock results in elevated heat pain thresholds, and Willer [133] has shown that a neutral stimulus previously paired with a very intense shock of 70 mA inhibits spinal nociception (as assessed from the NFR).

To summarize, the influence of negative affect on pain can be facilitatory or inhibitory. While this complexity led to some initial confusion in the literature, it appears the direction of modulation is dependent on the intensity of the negative emotion that is elicited [99]. Negative affect of low to moderate intensity that stems from unpredictable, future threat (e.g., anxiety) results in hyperalgesia. In contrast, intense negative affect that stems from a present, immediate, predictable threat (e.g., fear) results in hypoalgesia.

**Experimental Evidence for the Relationship between Negative Affect and Pain in Functional Pain Disorders**

Numerous correlational studies have identified a relationship between negative affect and functional pain disorders [19,41,43,58,116,124]. However, there are relatively few experimental studies. Emotion-induction paradigms, combined with well-controlled experimental pain procedures, have the capacity to provide significant insight into pathophysiological
mechanisms of chronic pain syndromes [25,81,104]. Sensitization or
dysregulation of threat detection circuitry may lead to a lower threshold
to experience negative emotions, more prolonged negative emotions, or
exacerbated levels of negative emotions in patients with functional pain
syndromes [73]. These mechanisms may result in a greater propensity
toward negative affect-induced hyperalgesia. In addition, these patients
may have depleted resources for engaging pain inhibitory mechanisms
[62,114,132]. Thus, intense, highly arousing negative emotions may not
elicit hypoalgesia, as noted in healthy individuals. If any or all of these
circumstances are true, the net result would be enhanced pain sensitivity
in these populations.

Evidence suggests that negative emotions and stress can exacer-
bate clinical pain. Davis and colleagues [18] studied experimentally induced
negative affect on clinical pain in persons with FM or osteoarthritis. Half
of the participants were first primed using sad imagery, while the other
half were not. All participants were then asked to recall a stressful inter-
personal conflict. Results suggested that FM patients who were primed
reported enhanced pain during the stress recall manipulation. This en-
hanced pain also persisted during a subsequent recovery period, but only
in the primed FM group. Gannon and colleagues [31] exposed headache
patients and controls to a stressful mental arithmetic task. Over 68% of
participants who suffered from frequent migraine or tension headaches
developed a headache during this stressful procedure. However, only 25%
of participants with infrequent headaches developed a headache. Monto-
aya and colleagues [81] used pleasant and unpleasant pictures from the
IAPS to manipulate affect in patients with FM or musculoskeletal pain
without fibromyalgia. They found that unpleasant pictures enhanced FM
pain relative to pleasant pictures and a no-picture baseline condition. This
effect was not noted in the musculoskeletal pain group.

A few studies have experimentally induced emotion and pain in
patients with functional pain disorders. Bach and colleagues [7] induced
stress through anticipation of a public speaking task in IBS patients and
controls before the participants were exposed to rectal distension. These
authors found an abnormal physiological stress response in patients (in-
creased heart rate reactivity), but the stress manipulation did not alter
discomfort thresholds to distension for either group. Posserud and colleagues [88] tested pain and discomfort thresholds from rectal distension in IBS patients and controls after mental stress (induced by the Stroop test and mental arithmetic). Their results also suggested abnormal stress responses in IBS patients (greater subjective stress, higher corticotropin-releasing hormone and adrenocorticotropic hormone [ACTH] levels, and lower epinephrine and norepinephrine levels). Discomfort thresholds decreased in controls during and after stress, but only after stress in patients. Distension pain thresholds decreased (i.e., hyperalgesia occurred) in patients after stress. However, it is important to note that no controls experienced pain from the distension in this study; therefore, it is difficult to interpret these data. Dickhaus and colleagues [24] exposed IBS patients and controls to noise stress (conflicting music) or relaxing sounds (ocean waves) and examined the effect on pain due to rectal distension. Results suggested that IBS patients had slightly stronger negative emotional responses to the stressor, although there were no group differences in stress-related neuroendocrine responses (norepinephrine, ACTH, cortisol, and prolactin levels). Nonetheless, noise stress enhanced distension-related pain relative to relaxing noise only in IBS patients.

To date, only one study has examined the effects of picture-evoked emotions on experimental pain in persons with functional pain disorders. Arnold and colleagues [2] presented pain-related, unpleasant, neutral, and pleasant IAPS pictures to participants with FM, back pain, and somatoform disorder, and healthy controls. During picture-viewing, they tested pressure pain applied to the finger. They found that all groups showed a similar pattern of modulation, with unpleasant and pain-related pictures enhancing pain relative to neutral pictures. Pain-related pictures showed the greatest facilitatory effects.

In a recent imaging study, Berman and colleagues [9] examined the effect of a cue that predicted the onset of rectal distension in IBS patients and controls. Although the study design did not allow the authors to examine the influence of the cue on distension-related pain, it did provide a means of examining brain activation patterns associated with pain and pain expectation. Results suggested that the cue elicited greater negative affect (stress, anxiety, and anger) in patients. Moreover, the cue
deactivated brain regions associated with nociceptive modulation (insula, ACC, amygdala, and dorsal brainstem) in controls to a greater extent than in patients (especially the insula and brainstem). Interestingly, anticipatory decreases in the brainstem were correlated with self-reported negative affect, suggesting that emotion may influence the activation of these regions involved with descending modulation.

To summarize, there appears to be a linkage between enhanced negative affect and functional pain disorders. However, there is a relative paucity of experimental studies examining the relationship between negative affect and enhanced pain in these populations. Nonetheless, there is some suggestion that emotion and stress reactivity may be dysregulated in some persons with functional pain disorders and that this dysregulation could contribute to enhanced pain. Clearly, additional well-controlled experimental research is needed.

**Neurobiology of Anxiety and Functional Pain Disorders**

Studies of the neurobiology of pain have identified structures and networks that may be important for the altered attention, affective response, and pain modulation seen in functional pain disorders. Although many of these aspects are discussed elsewhere in this volume, we will briefly review several that may directly play a role in the interplay of negative affect and functional pain symptoms. These involve corticolimbic interactions as well as brainstem areas involved in pain modulation, autonomic regulation, and peripheral manifestations of the defensive response (see Fig. 1).

A variety of corticocortical and corticolimbic interactions have been identified as playing a role in the response to both emotional and painful stimuli. Differential activation of subregions of the cingulate gyrus can be elicited by a wide variety of experimental stimuli, including somatic and visceral pain and emotional stimuli [11,37,74]. Areas of the dorsal cingulate cortex, especially an area toward the middle of the cingulate cortex, together with the insular cortex and the thalamus, respond to a wide range of painful and nonpainful, interoceptive, and exteroceptive stimuli and inform the brain about the homeostatic state of the organism. This group of
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structures has recently been labeled the “homeostatic afferent processing network” [74]. The most rostral aspect of the dorsal cingulate (subgenual ACC) and the adjacent medial prefrontal cortex have been implicated in negative feedback regulation of the amygdala and in arousal [68,87]. The same brain regions, which are rich in μ-opioid receptors, have also been implicated in the regulation of endogenous pain inhibition circuits [140]. Thus, the subgenual ACC/medial prefrontal cortex play important roles in the regulation both of emotional arousal and of pain perception [122].

It is therefore likely that altered activity in these same networks may be involved in the altered CNS responses associated with both chronic anxiety and functional pain disorders. A common finding across a variety of functional pain populations is an increased response in the mid-cingulate cortex to painful stimulation when compared to controls without pain disorders and in some cases when compared to patients with similar symptoms but with a clear peripheral organic cause [16,33,37,71,125]. In FM, activation in the dorsal ACC has been associated with greater catastrophizing [36]. Of perhaps even more relevance for the overlap of anxiety and pain mechanisms is the finding of altered relationships between cognitive control areas of the lateral prefrontal cortex and limbic structures such as the medial prefrontal cortex and amygdala in both anxiety and functional pain disorders [8,71]. Thus, it may be that a commonality across affective and functional pain disorders is primarily rooted in ineffective neurocognitive control, leading to increased or sustained arousal responses, especially when the individual is confronted with a salient affective stimulus.

The primary circuit by which supraspinal centers can alter afferent nociception involves the periaqueductal gray (PAG), and its projections to the rostral ventromedial medulla (RVM) and dorsolateral pons/tegmentum [30,33]. This circuit has been implicated in both descending inhibition and facilitation of nociception [30,121]. The PAG-RVM circuit receives input from higher brain centers including the hypothalamus, cortex (e.g., anterior cingulate), and amygdala [30,40,79], and it is through these extensive connections that cognitive, affective, and autonomic factors are believed to modulate nociception [30]. For example, ACC projections to the PAG-RVM are implicated in reductions in pain due to placebo
Additionally, the amygdala is known to play an important role in fear and anxiety [20] and in conditioned fear reactions [44,53], and animal research has suggested that connections between the amygdala and PAG-RVM are involved in affective modulation of nociception [17,44,53,75]. Interestingly, evidence suggests that if the amygdala were to become sensitized, this condition could promote the initiation and/or maintenance of chronic pain in the absence of a peripheral organic cause [82].

Clinical Implications of Anxiety in Functional Pain Disorders

Assessment

The discussion above suggests several important areas of assessment related to anxiety that should be part of routine care for patients with functional pain disorders. These areas include general anxiety symptoms, symptom-specific anxiety, and history of trauma. Although these topics can be assessed relatively well during a clinical history, there are several advantages to using a validated self-report instrument. First, accurate assessment of anxiety requires an active questioning process regarding specific symptoms and their impact, which may be difficult in very brief primary care visits. Second, scales provide a better measure of the relative severity of the anxiety based on both general and functional pain norms. Fortunately, well-validated and brief instruments are available for these anxiety constructs. For anxiety symptoms, the Hospital Anxiety and Depression scales were specifically designed for use in a general medical context; this instrument is brief, with 11 items for the anxiety scale. Scales for symptom-specific anxiety in musculoskeletal pain and FM include the Tampa Scale for Kinesiophobia and the Fear-Avoidance Beliefs Questionnaire [117]. The Visceral Sensitivity Index is the only scale developed and validated specifically for anxiety related to visceral pain [57]. The Anxiety Sensitivity Index, although more targeted at panic symptoms, has been widely used in multiple pain disorders including headache [83]. Diagnosis of anxiety disorders is made using the DSM-IV categories and typically
is beyond the scope of a general medical visit. However, familiarity with the most important disorders that may affect patient care, including panic disorder, generalized anxiety disorder, and PTSD, would be worthwhile for practitioners treating functional pain disorders [1].

**Treatment**

Many of the most widely used treatments for functional pain disorders act on overlapping mechanisms involved in pain and negative affect or anxiety. They include psychopharmacological treatments using antidepressants, anticonvulsants, and anti-anxiety medications; psychological therapies including cognitive behavioral therapy; and lifestyle interventions such as exercise programs. Most of these treatments have shown some efficacy, especially for global improvement measures; and these data are reviewed in the “Treatment” section of this volume. An important question relevant to the topic of this chapter regards whether improvements in mood and improvements in functional pain symptoms change in parallel, are independent, or if positive change in one results in secondary changes in the other. To date there has been little direct study of these questions. However, some recent research has shown that symptomatic improvements from both pharmacological and psychological therapies do not depend on changes in mood (e.g., [3,55]). Also, while several of the primary hypothesized methods of action of both psychological and pharmacological treatment involve anxiety-related mechanisms [65], there is good evidence that the presence of anxiety or depression is not a prerequisite for the efficacy of either type of treatment and that symptoms can be improved without working through major changes in general mood.

**Future Research Directions**

More well-controlled experimental research is needed that examines the relationship between negative affect and pain processing in patients with functional pain disorders. If true, the hypothesis that there is a non-monotonic relationship between negative affect and pain modulation has a number of important implications. First, it is important to consider individual differences in emotional responsiveness to different stimuli and...
stressors. When the effects of a stressor or emotionally-charged stimulus are examined, some patients may react with hyperalgesia whereas others will respond with hypoalgesia. If so, there would be a zero net influence on pain at the group level. This consideration leads to a second suggestion—that measures should be taken to assess the physiological and subjective indices of emotion. Individual differences in emotional reactivity may determine how pain is modulated. Third, measures that assess the degree and quality of emotional intensity should be used. In particular, differences in arousal (affective intensity) may help determine the degree of threat experienced by the individual (anxiety versus fear), but also the direction of negative affect-induced pain modulation (hyperalgesia versus hypoalgesia). Fourth, it is important to keep in mind that the predictability of the noxious event may affect the mechanisms by which negative affect modulates pain. As noted by Rhudy and colleagues [103], descending facilitation of spinal nociception can be disengaged when the noxious stimulus is predictable. This finding has important implications for clinical treatments that address the sense of unpredictability and lack of control experienced by patients with functional pain disorders. And finally, although we have focused specifically on the role of negative affective states, it is important to simultaneously examine the role of positive affect. For example, deficits in positive affect may be associated with symptom exacerbation during periods of stress and negative emotion [138].

It is also important to use experimental designs that provide a means of disentangling the direction of the negative emotion-pain relationship. One suggestion is to experimentally manipulate emotion using within-subject designs. However, this issue can also be addressed in treatment studies by making sure to assess various forms of negative affect and functional pain symptoms longitudinally. Another issue involves more careful study of the relationship between symptom-specific fear or anxiety and more general anxiety. While these two constructs may share primary mechanisms, symptom-specific fear or anxiety is likely to be the negative affect that is more influential in clinical situations, but it is often overlooked as a predictor and outcome measure in studies. Finally, more use of functional brain imaging and other measures of CNS activity (such as startle responses, brain electrical responses, and nociceptive reflexes) as
both biomarkers and mechanistic tools will be extremely useful to test the neurocognitive mechanisms that underlie the relationship between negative affect and functional pain disorders.

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