Neurobiology of depression, fibromyalgia and neuropathic pain

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1. ABSTRACT

This article synthesizes recent data suggesting that the high rates of comorbidity observed between major depression, fibromyalgia and neuropathic pain likely result from the fact that these disorders share multiple biological and environmental underpinnings. This perspective suggests that these biologically complex conditions result from similar genetic vulnerabilities interacting with environmental adversity. Shared genetic determinants

include poorly functional alleles regulating monoaminergic, glutamatergic, neurotrophic, opioid and inflammatory cytokine signaling. Chief among environmental risk factors are psychosocial stress and illness, both of which promote, in vulnerable individuals, relative resistance to glucocorticoids, increased sympathetic/decreased parasympathetic activity and increased production and release of proinflamnmatory mediators. Dysregulation of stress/inflammatory pathways promotes alterations in brain circuitry that modulates mood, pain and the stress response. Over time, these functional changes likely promote disruptions in neurotrophic support and disturbances of glia-neuronal communication. These changes, in turn, have been associated with the related processes of central sensitization in pain disorders and "kindling" in depression, both of which may account for the progressive and self-perpetuating nature of these disorders, especially when inadequately treated.

2. INTRODUCTION

Nowhere are the limitations of current psychiatric diagnostic schemas more apparent than at the interface of Major Depressive Disorder (MDD) and chronic pain. Indeed, one might emerge from a search through the DSM-IV-TR with the impression that depression and pain had little in common. Pain is not listed as a symptom of any mood disorder, and depressive and anxiety complaints are strikingly marginalized in the list of symptoms required to meet criteria for a chronic pain disorder. Unfortunately, several decades of research demonstrate that this officially sanctioned segregation of mood and pain maps poorly onto both clinical and neurobiological reality.

In reality, comorbidity between depression and pain appears to be more the rule than the exception, with a 30-60% co-occurrence rate reported in a recent review (1). Similarly high rates of comorbidity have been repeatedly observed between fibromyalgia (FM) and major depression, leading to many years of debate between researchers as to whether the conditions are most parsimoniously considered as separate illnesses with high comorbidity or as differential symptom presentations of a single underlying condition (2). Moreover, overwhelming evidence suggests that chronic pain and depression do more than co-occur—they also promote the development of each other, such that chronic pain is strong predictor of subsequently developing major depression, and vice versa. When comorbid, pain and depression also significantly complicate the treatment of each condition. For example, once treatment of depression is initiated, pain is a major obstacle to achieving remission (3, 4) and a significant risk factor for relapse (5). In a three-year longitudinal study by Geerlings et al. the presence of painful symptoms substantially reduced the chance of recovery in a group of elderly depressed patients (n=327). Significantly more patients with MDD alone attained recovery (47%), compared with only 9% of patients with MDD combined with painful symptoms (6). Finally, a higher level of pain may delay the onset of remission in the treatment of MDD (7), thereby decreasing the chances for an optimal outcome (8).

Given these findings, it should perhaps not be surprising that recent developments in fields as diverse as social neuroscience and psychoimmunology point to the fact that pain and depression co-exist symptomatically because they are driven by largely overlapping pathophysiological processes in the brain and body. This review will attempt to review current scientific understandings of these shared processes and to demonstrate how recent advances in our knowledge regarding the epidemiology, phenomenology and etiology of FM, chronic pain and major depression (MDD) provide important clues for how the clinician may best approach these challenging clinical issues. Indeed, we believe that gaining a better understanding of the shared neurobiological bases of MDD, FM and neuropathic pain (NeP) will provide the clinician with important tools for improving clinical decision making, and—by extension—patient outcomes.

3. EPIDEMIOLOGY AND COMORBIDITY OF MAJOR DEPRESSION, FIBROMYALGIA AND NEUROPATHIC PAIN

Although 10-12% of the population worldwide and in the US endorse chronic widespread pain, only about 2% (3.4% of women and 0.5% of men) of individuals meet the American College of Rheumatology (ACR) criteria for Fibromyalgia (FM). FM is characterized by chronic widespread pain (tenderness in at least 11 of 18 pre-defined points), lasting at least three months, typically accompanied by fatigue and sleep disturbance (9, 10). While no single etiology has been identified for the condition, a unifying hypothesis that continues to receive increasing scientific support suggests that FM is a consequence of sensitization of the central nervous system (9).

Neuropathic pain (NeP) is typically a consequence of a direct nerve injury or damage to neural tissue, resulting in abnormal sensory processing (11). Common features of NeP include hyperalgesia (augmented sensitivity to painful stimuli), allodynia (abnormal pain response to non-noxious stimuli) and paresthesias (11, 12). Shared clinical features, consistent with a role for central sensitization, have prompted authors such as Martinez-Lavin and others to suggest that FM and NeP share an overlapping pathophysiology (12, 13). Estimates suggest that various forms of NeP (diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, spinal cord injury, radiculopathy, etc.) afflict up to 26 million people worldwide, including approximately 1.5% of the US population (11, 12). Consistent with these estimates, a large survey of 6000 adults in the United Kingdom reported an 8% prevalence of chronic pain, most of which was of neuropathic origin. As with FM, women were significantly more likely than men to be affected (14).

Many patients suffering with either FM or NeP (or both) will also meet diagnostic criteria for major depressive disorder (MDD). Moreover, patients with FM are at significantly increased risk of subsequently developing MDD and related psychiatric conditions. For example, Arnold et al reported that patients with FM were

4.3 times more likely than healthy control subjects to develop MDD at some point in their lives and 4.7 times more likely to develop an anxiety disorder (15). Surprisingly, Weir et al. found that although women were much more likely to develop fibromyalgia in the first place, once FM had developed the risk of males and females subsequently developing MDD was comparable: with a risk ratio of 2.91 (95% CI 2.15-3.94) vs. 2.85 (95% CI 2.38-3.42) (16). Overall depression and anxiety are among the most common comorbidities of FM, with prevalence rates ranging in studies from 20-80% and 13-63.8%, respectively (17).

The high comorbidity between depression and pain is not restricted to subjects with FM, but is also relevant for patients suffering with NeP. For example, in an Austrian study that surveyed 7707 individuals (18), the prevalence of NeP was 3.3%, with two-thirds of the sample suffering from pain for longer than a year. Depression was reported in 34% of the sample, anxiety in 25% (18). The severity of pain tended to be enduring and associated with significant impairment of functioning.

4. CLINICAL RELEVANCE OF A NEUROBIOLOGICAL UNDERSTANDING OF MDD, FM and NeP

Relationships between MDD, FM and NeP are complex and intricate. Based on clinical and neurobiological similarities, some researches have even made a claim that FM and NeP may be variations of the same condition (13, 19). However, other researchers have pointed out that, unlike FM which is characterized exclusively by altered neural function, NeP has a discernable neuro-pathologic substrate, such as a lesion of the peripheral nerve or CNS (e.g. central pain due to brain tumor) (20). Diagnostic quandaries aside, it is increasingly apparent that, like MDD, conditions characterized by chronic pain share a common a progressive course that is reflected in cognitive alterations, as well as structural changes within the brain itself (21-27).

As noted above, a preponderance of current scientific evidence suggests that NeP and FM are characterized by central sensitization (28, 29). Relevant to its relationship with pain, MDD is widely considered to represent a "kindling" phenomenon. In the context of depression, kindling implies that each episode of depression makes subsequent depressive episodes more likely and less dependent upon an external impetus such as stress or sickness (30). Robert Post—who first proposed kindling as a construct for understanding the tendency of mood disorders to worsen over time—has recently suggested that kindling and sensitization may have similar neurobiological underpinnings, such as neuroplastic changes and alterations in gene expression (31). In this vein, some authors have gone so far as to posit "neuro-sensitization" as a common etiology for chronic pain, depression and anxiety disorders (i.e. PTSD) (32).

Consistent with the predictions of a sensitization model for pain and mood disorders, FM, NeP and MDD have many common features. All 3 conditions are either precipitated or aggravated by stress (19, 28, 30, 33-36). In addition to peripheral and central sensitization, FM and NeP are also characterized by altered limbic and cortical function and structure (28, 37, 38). The circuitry involved in modulating pain (typically altered in FM and NeP) has common elements with the circuits regulating stress response and mood (36, 39-43). Remarkably, fMRI studies have demonstrated that brain areas (i.e. dorsal anterior cingulate) central to experience of negative affect in response to physical pain also mediate distress in response to the "pain" of social exclusion (44). These findings strongly suggest that emotional and physical pain co-occur so often because they share the same central nervous system pathways (45). Consistent with this, similar functional and structural changes in amygdala and hippocampus have been described in MDD, FM and NeP (46-51). Dysfunction of these limbic formations is believed to contribute to perturbations in neuroendocrine, autonomic and immune functioning that may further contribute to the generation and/or worsening of mood and pain symptoms (28, 37, 42, 52). In this regard, increasing data demonstrate that excessive sympathetic activation, combined with elevated proinflammatory cytokine production and release, likely plays a role in the etiology of MDD, FM and NeP (19, 42, 53). Finally, at the cellular level all three conditions are associated with disturbed neuron-glia relationship, glutamatergic dysregulation and alterations in intracellular signaling cascades and neurotrophic trafficking (Figure 1) (54-61).

One clear clinical implication of the neurobiological links between depression and pain is that each set of symptoms worsens the other and/or makes the other more likely to develop. A second implication arises from the many empirical studies demonstrating that the core symptoms of pain disorders (i.e. pain, chronic fatigue, sleep disturbance and cognitive complaints) significantly complicate the treatment of MDD because these symptoms tend to be especially non-responsive to conventional treatments (4, 62-64). Conversely, both depression and anxiety are extremely common in FM and NeP (17, 18) and may intensify the experience of pain (43, 65). In summary, available evidence suggests that MDD and FM/NeP mutually amplify each other, thus contributing significantly to treatment resistance in both depressive and pain disorders. Consistent with this, timely treatment of MDD may optimize the chance of remission and decrease the chances of enduring structural changes (8, 21, 66-68). Full and sustained remission may also decrease the chance of future recurrences (69). In this regard, the comorbidity of MDD and pain may hinder an early and appropriate diagnosis of MDD (70, 71), thereby delaying treatment and subsequent benefits of remission. Consistent with this, resolution of painful symptoms doubled the remission rate in a recent study of depressed patients: 36.2% of the subjects who had >50% reduction of pain on a visual analogue scale (VAS) attained remission vs. only 17.8% of the individuals who had <50% reduction on the VAS (3).

5. GENETICS OF MDD, FM AND NEP

Given the high degree of overlap between MDD, FM and NeP in terms of symptom profiles, disease course
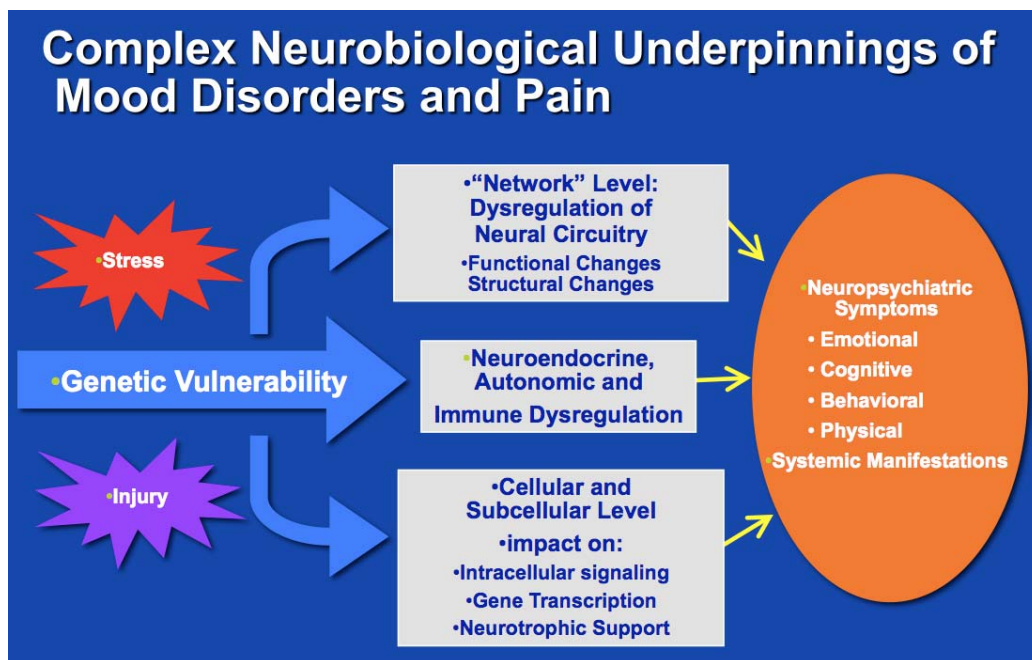
Figure 1. An integrated view of the shared neurobiological underpinnings of major depression (MDD), fibromyalgia (FM) and neuropathic pain (NeP) .

and underlying neurobiology, it should perhaps not come as a surprise that these conditions also appear to share a number of genetic determinants. Interestingly, many of these shared genes contribute to the structure and/or functioning of pathways in the brain and body that evolved to respond to danger signals from the internal and external environment, whether these signals arise from environmental threat (i.e. stress), tissue damage (i.e. pain) or infection (i.e. inflammation). One result of the tremendous complexity and interdependency of these systems is that MDD, FM and NeP are clearly genetically heterogeneous conditions to which multiple polymorphic genes contribute to various degrees and in various combinations. On the other hand, because CNS and peripheral danger pathways tend to respond in a coordinated and highly stereotyped manner to a variety of environmental threats (72), it should also come as no surprise that alterations in genes linked to very different physiological elements in this circuitry (i.e. neurotransmitters and inflammatory cytokines) are capable of producing similar abnormalities in emotional state and pain perception, reflecting what is often referred to as a "final common pathway" phenomenon. Nonetheless, even this level of analysis fails to do justice to the full complexity of genetic contributions to MDD, FM and NeP, as demonstrated by epistatic interactions in which two "bad" genes—rather than additively contributing to disease development—actually cancel each other out (73). Finally, even the notion that genes specifically exist for MDD, FM and NeP reifies these states of emotional distress and physical pain in a way that does violence to emerging scientific data demonstrating that risk factor genes do not cause these conditions, but rather predispose the brain and body to physiologically respond to internal and external environmental conditions in ways that lead to symptom production (74).

5.1. Genetics of MDD

Dozens of different genes have been implicated in the development of MDD. Among the many genes that have been identified as conferring vulnerability to the disorder, studies have most consistently supported a role for polymorphisms in genes that regulate the serotonin transporter promoter locus (5HTTPR), the serotonin 5HT2A receptor, catechol-O-methyl transferase (COMT), monoamine oxidase (MAO) and brain-derived neurotrophic factor (BDNF). More recently, genes regulating the synthesis and/or activity of CRF and glutamate receptors have also been implicated (75). An exciting development in the field of psychiatric genetics is the recognition that genes are more likely to code for "endophenotypic traits" that increase the risk of psychiatric morbidity, than they are to code directly for any specific psychiatric disorder (74). For mood and pain disorders, these endophenotypic factors center primarily on circuitry essential for affective function, cognition and threat appraisal, as well as for stress and immune system activity.

5.1.1. Genes involved in regulation of serotonergic function

As noted above, "depression genes" frequently do not contribute directly to the development of the disorder, but rather confer vulnerability to developing depression in response to environmental threat. For example, a study by Caspi et al. demonstrated that the inconsistently observed association between depression and the short allele of 5HTTPR was likely explained by the fact that the allele increased the likelihood of developing both depression and suicidal ideation in individuals exposed to life stressors, but not in individuals

spared environmental adversity (76). This finding has been replicated several times. For example, Kendler et al observed identical interactions between the 5HTTPR short variant ("s" allele), stressful life events and the risk of developing MDD. In addition they described a gender effect, such that women with the short 5HTTPR allele were especially likely to develop depression in response to stress (odds ratio of 7 compared to males with the long allele) (77).

The "s" allele of the 5HTTLPR gene has been associated with a number of alterations in brain function and morphology, including compromised functional and structural integrity of amygdala-ACC circuitry involved in regulation of emotional, behavioral and endocrine response to stress, as well as in processing the experience of pain (40, 41, 78-81). The short allele has also been linked to reduced anterior cingulate cortex (ACC), amygdala and hippocampal volumes (78). These structural changes, in turn, may result in aberrant connectivity between ACC and amygdala which is believed to interfere with emotional homeostasis and effective modulation of the stress response (78, 79, 82). Gotlib et al. have proposed relationships between the "s" 5HTT allele, responses to stress, HPA reactivity and susceptibility to MDD, given data that girls homozygous for the "s" allele reacted to stress with prolonged elevation of cortisol, compared to ones with "l" allele, indicating greater reactivity to stress and possible increased susceptibility towards depression (83).

Of course, genes such as the "s" 5HTTPR allele don't exist in isolation but interact in myriad ways with other genes—a process known as epistasis. For example, the combination of the 5HTTPR "s" allele with a functionally less competent allele of the 5HT1A receptor gene has been associated with exaggerated amygdala reactivity in medicated MDD patients (84).

5.1.2. The role of genes regulating neurotrophic factors
The activity of genes known to modulate neurotrophic factors, cellular resilience, neuroplasticity and neurogenesis may be compromised in MDD patients (85, 86). For example, the val66met allele confers reduced BDNF functioning and has been associated with structural brain changes common in MDD, including reduced gray matter volume in dorsolateral prefrontal cortex (DLPFC), lateral-orbital prefrontal cortex (LOPFC) and hippocampus (87, 88). Dwivedi et al reported altered genetic expression of BDNF in hippocampus and PFC of depressed suicide subjects, further supporting the relevance of neurotrophic factors in MDD (89).

5.1.3. The Role of genetic epistasis in MDD
Epistasis has been reported with the 5HTTPR gene and a variant of the gene for BDNF known as val66met. In a seminal study, Kaufman et al. reported that the "s" allele of 5HTTPR and the "met" variant of the val66met BDNF allele increase the risk of developing depression in an additive fashion in the context of environmental adversity early in life (90). On the other hand, a very different epistatic interaction between the "s"

allele of the 5HTTPR and the "met" variant of the val66met BDNF was recently reported by Pezawas and colleagues. In a volumetric MRI study of 111 healthy, non-depressed, individuals, researchers found that—contrary to expectations—the met BDNF allele (which increases depression risk) provided protection to circuitry linking amygdala and rostral ACC (rACC). As noted above, this circuitry, which is involved in emotional modulation and stress responses, tends to function sub-optimally and be reduced in volume in 5HTTPR "s" carriers. However, these abnormalities are significantly muted in 5HTTPR "s" carriers who also carry the met BDNF allele, because this allele made amygdala-rACC circuitry relatively insensitive to 5HT signaling, thereby protecting these individuals from loss of rACC gray matter volume (73). This finding may have significant clinical implications, given that rACC also plays a role in pain signaling and predicts treatment response to antidepressants (91).

Similarly, studies have reported that 5HTT, COMT, and MAOA polymorphisms and gender have a convergent effect on the HPA-axis response to psychological stress and endocrine challenges (92). Individuals with less functional 5HTT, COMT and MAOA alleles had blunted baseline ACTH and cortisol responses to DEX/CRH challenge, reflective of potential susceptibility towards MDD. This study also implies that monoamines play an important role in neuroendocrine homeostasis and maintenance of health (92).

5.1.4. Polymorphism of genes regulating MAO
Polymorphisms in the MAOA gene have been shown to interact with maltreatment with adverse impact on children's mental health. Depressed MAO-H (higher activity) carriers, tend to have compromised amygdala-prefrontal connectivity and greater illness severity (93).

5.1.5. COMT gene polymorphisms
The COMT Val108/158 Met genotype has a significant impact on hippocampal and prefrontal gray matter volume (94). Beyond structural differences, Met 158 COMT allele has been associated with increased limbic reactivity to unpleasant stimuli and altered connectivity between amygdala and PFC (95).

5.1.6. Polymorphisms in genes involved in regulating the inflammatory response
Polymorphisms in inflammation-related genes have been reported to confer susceptibility to major depression and to effect antidepressant response (96, 97). Inflammatory reactions are an integral component of the stress response. Interestingly, proinflammatory cytokines have a profound impact on mood, HPA axis regulation, monoamine signaling, as well as regulation of neurotrophic factors and pain modulation (42, 53).

In summary, genes regulating monoamine receptors, transporters and enzymes involved in their metabolism, all seem to contribute to vulnerability towards MDD (98). These genes combined with ones regulating corticosteroid, neurotrophic and inflammatory signaling influence structural integrity and functional connectivity in

areas involved in generating adaptation to stress (86, 99, 100). Consistent with this, a recent review suggested that genes associated with depression may act in unison by accelerating sensitization to stress (101).

5.2. Genetics of nociception and FM

Significant data suggest that FM is genetically related to a wide range of conditions subsumed under the rubric of "affective spectrum disorders" (ASD), including depressive and anxiety disorders, premenstrual dysphoric disorder, attention deficit hyperactivity disorder (ADHD), FM, irritable bowel syndrome (IBS) as well as migraine and cataplexy conditions. For example, a recent family study concluded that patients with FM were twice as likely to have at least one of these other conditions, compared with individuals without FM (OR 2.0, 95% CI 1.2-3.2, p = 0.004) (102). A recent study has refined our understanding of genetic links between mood and pain/somatic disorders by suggesting intriguing patterns of genetic overlap and environmental specificity for these conditions. Specifically, in a large twin study of the relationship between two psychiatric disorders (MDD and generalized anxiety disorder [GAD]) and somatic syndromes such as FM, chronic fatigue, IBS and recurrent headache, multivariate analyses suggested the influence of two factors: one, most likely genetic, shared between somatic disorders, MDD and GAD and a second one, more specific to somatic conditions, that was more environmentally based. Thus, these conditions are a product of interaction of genes, some shared, some more specific to individual conditions, and environmental factors (103).

It is not surprising that genetic studies of nociception are in their infancy given the genetic heterogeneity of pain disorders, as well as the complexity of relevant gene/environment interactions (104). Nonetheless, a number of genes known to modulate human nociception have emerged as potential risk factors for impaired pain processing, including genes coding for opioid receptors, transient receptor potential cation channels (TRPV1), fatty acid amino hydrolase (FAAH) and GTP cyclohydrolase 1 (104, 105). Genes implicated in mood disorders have also been identified as risk factors for FM and related pain states. These genes include 5HTTPR, the 5HT2A receptor, COMT and the dopamine D4 receptor, as well the proinflammatory cytokines IL-1 and IL-6 (105-110). Although not found by all studies (107), the association between FM and the "s" allele of 5HTTLPR is particularly interesting given its association with a wide range of conditions that are either risk factors for—or frequent concomitants to—FM, including anxiety, neuroticism (best conceptualized as a tendency towards excessive emotional reactivity to stressful stimuli), MDD, Bipolar Disorder, Psychosis and even ADHD (111-114). Given the significant role played by stress in the initiation of chronic pain and fatigue states, it is interesting that the "s" 5HTTLPR allele has also been shown to affect stress responses and to be a risk factor for the development of depression and fatigue in response to chronic inflammatory exposure during interferon-alpha treatment for hepatitis C (115). In addition to potentially conferring

a risk for FM development, genetically-linked alterations of 5HTTLPR density in FM patients may be associated with symptom severity (108).

Other genes implicated in mood and anxiety disorders that may also contribute to chronic pain states, include COMT, as well as the 5HT2A and D4 dopamine receptors. Zubieta et al reported an association between a common val158met polymorphism of COMT (catechol-O-methyl-transferase, an enzyme involved in catecholamine metabolism) and sensory and affective pain ratings (116). Met homozygous carriers showed a diminished mu-opioid receptor response to pain, and a stronger subjective experience of pain when compared to heterozygous subjects. Other studies have found that this COMT polymorphism may play a role in the stress response, the trait of novelty seeking, cognition, MDD, schizophrenia, anxiety disorders and ADHD (92, 117, 118). The 5HT2A receptor gene is also a candidate for involvement in FM, given a recent study reporting that carriers of the T/T allele, while under-represented in the FM population, had significantly higher pain scores than FM carriers of the C/C allele or healthy controls (119). Interestingly, a separate study noted that the same T/T allele, in the presence of high maternal nurturance, was associated with lower depressive symptoms than the C/C genotype, consistent with the notion that "vulnerability" genes may have been maintained in the human gene pool because they are "opportunity" genes given the proper environmental exposure (120). Finally, some reports have established a connection between a gene coding for the D4 dopamine receptor and a vulnerability towards FM (119, 121). Other studies link the D4 receptor gene to a personality trait called "novelty seeking" and to ADHD (118, 119).

In conclusion, genetic studies of depression, pain and FM have noted alterations in genes regulating (likely in a convergent manner) monoamine and inflammatory signaling (92, 115, 119). It is tempting to speculate that shared genetic vulnerabilities towards depression and pain states may be reflected in dysregulation of circuitry involved in modulating stress responses, pain and emotional states.

6. FUNCTIONAL AND STRUCTURAL ALTERATIONS IN CENTRAL NERVOUS SYSTEM CIRCUITRY INVOLVED IN REGULATION OF EMOTION AND PAIN

Because emotional reality appears to be actively construed, rather than just passively experienced (122), a person's world literally changes with changes in brain functioning. In the case of depression, these changes warp reality into a frightening or empty realm that calls forth a depth of emotional pain that often defies verbal description (123).This emotional pain frequently engenders an equally disabling experience of physical pain, even when no peripheral source for such pain can be identified. Conversely, anyone who has long struggled with chronic physical pain knows that the dark emergence of emotional despair commonly compounds the physical

ache with a sense of affective terror. Given the numerous links between depression and pain conditions such as FM or NeP outlined thus far, it should come as no surprise that the different disorders also resemble each other in terms of abnormalities in CNS structure and function. It is to these abnormalities that we now turn.

6.1. Structural and functional brain changes in depression

6.1.1. Abnormalities in prefrontal cortex (PFC)

Prefrontal cortical (PFC) abnormalities are a common finding in MDD. However, because different subregions of the PFC have profoundly different functional roles, a more detailed description of these areas and their activities is required to gain a sense of how this brain region contributes to MDD. In this discussion we will focus on three subregions most often implicated in MDD: ventromedial prefrontal cortex (VMPFC), lateral orbital prefrontal cortex (LOPFC) and dorsolateral prefrontal cortex (DLPFC).

VMPFC tends to demonstrate increased activity in MDD (26, 124). VMPFC has rich reciprocal connections with limbic formations and the hypothalamus (125-127). VMPFC not only serves as a major recipient of limbic projections, but also modulates amygdala and hippocampal activity through complex feedback connections (126, 128). VMPFC also plays a key role in regulating appetitive drives and pain responses (129). Increased VMPFC activity in MDD patients has been associated with melancholy ruminations and intensity of negative affect (130, 131). These observations suggest that this prefrontal subregion, together with anterior cingulate cortex (ACC) and limbic areas, is a component of an integrated network involved in processing emotionally relevant information for the purpose of guiding behavior and orchestrating adaptive autonomic and endocrine responses (130). Given the key regulatory role of VMPFC, it is intriguing that several authors have found significant VMPFC volume reduction (up to 32%) in MDD patients compared to healthy controls (132, 133).

Lateral orbital prefrontal cortex (LOPFC) seems to be involved in suppressing maladaptive and perseverative emotional responses. LOPFC may also have a major role in volitional regulation of emotion and cognitive reappraisal (122, 134). LOPFC activity is enhanced in depression (26), most likely in a compensatory role to modulate excessive limbic activity. Lacerda et al have found a significant reduction in LOPFC gray matter volume of MDD patients compared with healthy subjects (133). Medial dorsal PFC (MDPFC), associated with automatic emotional and attentional control and self-appraisal (134, 135), also suffers a greater gray matter decline over time in MDD patients compared to healthy controls (20).

Dorsolateral prefrontal cortex (DLPFC) is a primary component of an executive function network in the brain that also includes dorsal ACC (dACC) and parts of the parietal cortex (130, 314, 136). DLPFC tends to have a "top-down" regulatory influence over limbic structures (134, 137) (Figure 2). Decreased activity in DLPFC in MDD may contribute to the compromised working memory, impaired sustained attention and executive dysfunction seen in the disorder (137). In addition to functional abnormalities in MDD, a recent three-year prospective study reported significantly greater DLPFC gray matter decline in un-remitted MDD patients compared to control subjects and to subjects with MDD who attained remission (21).

6.1.2. Abnormalities in anterior cingulate cortex (ACC)

The anterior cingulate cortex (ACC) is probably the brain area most often implicated in the pathophysiology of MDD, with most studies emphasizing the subgenual ACC (sgACC) as being especially relevant. The sgACC has a role in assessing the salience of emotional and motivational information and making necessary adjustments in behavior. It is also involved in modulation of sympathetic and neuroendocrine responses. Functional imaging studies suggest increased metabolism in this area in depressed patients (when corrected for reduced volume) (138). Structural studies have noted significantly decreased volume of sgACC in MDD subjects. For example, Drevets et al. noted that sgACC had 48% lesser volume in individuals with familial depression than in healthy controls (130). These alterations likely contribute to disturbances of motivation, limbic regulation (especially amygdala), and neuroendocrine function, all of which are commonly seen in patients with MDD (48, 80, 138). Although more anterior areas of the ACC have been a primary focus of research, more dorsal areas of the ACC have received increasing attention for their potential role in MDD. For example, in a study of patients with MDD, Chen and colleagues reported that reduced gray matter volume of dorsal ACC and DLPFC were correlated with increased symptom severity in MDD patients (91). This report resonates with the work of Matthews et al. who noted reciprocal connectivity between supragenual ACC and amygdala in unmedicated depressed patients (48). In summary, recent research lends credence to the hypothesis that these "executive network" areas have a role in "top-down" modulation of limbic areas and that when this modulation fails, depression is likely to ensue (134, 139). Finally, several lines of evidence suggest that ACC abnormalities are associated with treatment response. Mayberg et al. has noted that activity in sgACC normalizes in patients who respond to either an active antidepressant or placebo (137), and diminished function and volume of pre-genual ACC has also been associated with a delayed antidepressant treatment response (91).

6.1.3. Hippocampal changes

The hippocampus is a key limbic area located at the "crossroads" of circuitry that regulates the stress response by providing inhibitory feedback to the HPA axis, in addition to its role in mood modulation and memory formation (68, 125). However, its central location may render the hippocampus vulnerable to functional dysregulation that accompanies extreme stress and mood disorders (125). Reflecting this vulnerability, alterations in hippocampal volume are among the most common imaging findings in
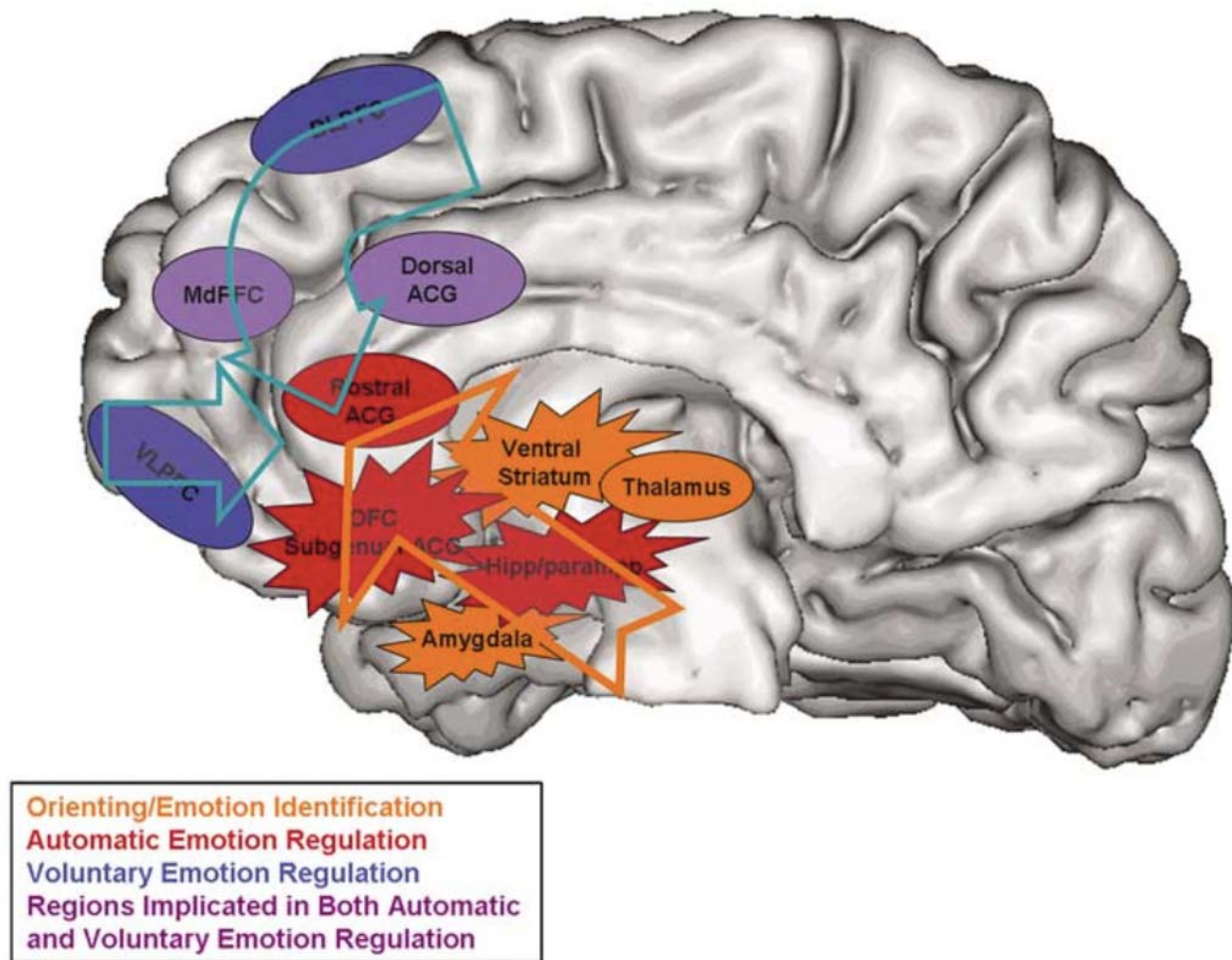
Orienting/Emotion Identification
Automatic Emotion Regulation
Voluntary Emotion Regulation
**Regions Implicated in Both Automatic
and Voluntary Emotion Regulation**

Figure 2. Cortical and subcortical areas involved in voluntary and automatic regulation of mood and the stress response. Reprinted with permission from (134).

MDD patients (68). Recent data strongly suggest that physiological abnormalities, inherent to depression, may actually lead to reductions in hippocampal volume. Indeed, Frodl et al found a significant decline over a three-year period in hippocampal gray matter volume in MDD patients compared to healthy controls (21). Successful treatment appeared to have a protective effect, given that remitted patients had a significantly greater hippocampal density than non-remitted ones (21). Consistent with this, one post hoc analysis (68) has found a significant increase in hippocampal volume (21%, p=0.004) after 6-7 months of antidepressant treatment in a small subset of patients with atypical depression. Similarly, Sheline et al found an inverse relationship between the days of untreated depression and hippocampal volume (140), and Colla and colleagues noted a negative correlation between duration of depression and hippocampal volume, corrected for age and intracranial volume (141). The potential importance of restoration of hippocampal structure and function for successful treatment of depression was further highlighted by a study conducted by Block et al (142). Using magnetic resonance spectroscopy (MRS), these

investigators found a significant association between hippocampal increases in N-acetylaspartate (NAA) (a marker of neuronal density, function and myelination) and choline compounds (Cho) (a marker of membrane integrity and metabolism) and treatment response. These authors also reported reduced glutamine (Gln) in depressed subjects. Glutamate (Glu), a major excitatory neurotransmitter is metabolized into Gln, after being taken up by astrocytes. Gln has major significance for maintenance of Glu/GABA balance in neuron-glia signaling. This is the first study providing evidence that successful treatment with two different antidepressants, a predominantly noradrenergic and a predominantly serotonergic one, may lead to functional and structural restoration of hippocampal neurons and astroglia (142).

6.1.4. Amygdala alterations

As with other relevant brain regions, neuroimaging studies suggest that functional abnormalities of the amygdala may contribute to depressive symptom development and that pathophysiological processes inherent to depression may, in turn, damage this extremely important brain structure.

Functional neuroimaging studies have, for the most part, found increased activity in the amygdala of depressed individuals (143). Because the amygdala plays an important role in rapidly assessing and assigning emotional value to surprising and ambiguous stimuli, it is not surprising that patients with MDD respond to angry and fearful faces with increased amygdala activity, even when these faces are presented below the level of conscious awareness (143-145). It is intriguing to consider that this type of amygdala over-activity may translate into the increased anxiety and emotional misattribution, both of which are commonly observed in patients with MDD (146, 147). Because the amygdala and other limbic structures have significant bidirectional connections with the hypothalamus, it is also not surprising that sympathetic and neuroendocrine dysregulation are a frequent concomitant of mood disorders (125, 128). Structural neuroimaging studies of the amygdala suggest that this brain region is negatively impacted by physiological processes inherent to depression. The same prospective study that recently reported an association between ongoing depression and loss of brain volume in DLPFC and hippocampus also noted a decline in amygdala gray matter (esp. left) over time in MDD patients, relative to control subjects (21).

6.1.5. Insular abnormalities

Insular cortex has emerged in recent years as another limbic structure of tremendous relevance to the regulation of both affect and pain. Insula has rich connections with other limbic (e.g., amygdala and hippocampus) and paralimbic cortical areas (ACC and LOPFC). Because of this, it is widely considered to be a primary target of thalamo-cortical projections. As such, the insula plays an essential role in sensory-affective integration that creates a bodily sense of self. The anterior insula is also involved in modulating the influence of sensory and emotional distractors (148-150). Consistent with these roles and interconnections, altered activation of insula in MDD subjects has been described in several studies (26, 150, 151). In general, MDD patients appear to have decreased activity of insula, which tends to improve with antidepressant treatment (26, 150). Neuroimaging studies, utilizing labeling of 5HT2 receptors, have also found evidence of altered sertononergic transmission in insula in MDD subjects (148).

6.1.6. Abnormalities in sub-cortical areas

Functional and structural changes have been noted in basal ganglia and thalamus of patients with mood disorders (152). Functional studies have noted increased thalamic activity in depressed individuals. Thalamic hyper-metabolism is associated with increased activity in sgACC and decreased metabolic activity in dACC (153), both of which have been observed in MDD. Some, but not all, studies have found alterations in cerebellar function in patients with MDD (26, 152). This is of particular interest because the vermis of the cerebellum has been implicated in generating automatic emotional responses—including empathy—to facial expressions (154-156).

6.1.7. Abnormalities in connections between brain regions in MDD

Several studies have found altered connectivity between limbic and paralimbic prefrontal areas in MDD (144, 157-159). Combined with studies that have found white matter abnormalities in patients with MDD (158), these studies point to a compromise in the integrity of fronto-subcortical and prefrontal-limbic circuits in the disorder (48, 157, 159). Additional involvement of fronto-cerebellar-thalamic circuitry is likely (151). Therefore, cumulative evidence suggests that disruption of circuitry that provides cognitive-emotional integration and control of stress responses may be responsible for complex manifestations of MDD. In summary, structural and functional studies support an organic basis for the emotional, cognitive and neuroendocrine symptomatology of MDD (128, 138, 158). Unfortunately, current research indicates that cognitive impairments in MDD tend to be persistent, non-specific and progressive, with a greater number of episodes being associated with increasing cognitive burden (160, 161).

6.2. The role of the peripheral and central nervous system in FM and chronic pain
6.2.1. Abnormalities in peripheral nerves and spinal cord pathways

Pain pathways implicated in NeP and FM have peripheral and central components—in this section we trace how pain signals originate in the periphery and reach the brain

Pain signals are detected by peripheral nociceptive nerve endings and conveyed to neurons located in dorsal root ganglia (DRG). From the DRG pain information is conducted by lightly myelinated A-delta and un-myelinated slow C-fibers to secondary sensory neurons localized in the dorsal column of the spinal cord. Aside from functional alterations in nerve membranes and endocellular signaling (discussed elsewhere), peripheral sensitization may occur as a result of alterations in synaptic connectivity resulting from sprouting of sympathetic axons within DRG (which may further augment pain transmission), ectopic discharges and ephaptic (direct electrical transfer of signal) communication. Central sensitization in NeP may in part be mediated by collateral sprouting (whereby non-nociceptive A-beta fibers form new connections with nociceptive neurons in the dorsal horn), as well as damage to inhibitory GABA inter-neurons (29, 162, 163).

Damage to these initial components of pain processing circuitry (e.g. nerve injury) is the primary cause of altered pain signaling in NeP. On the other hand, there are fewer data to support an important role for abnormalities in peripheral or spinal cord pain signaling in FM. Nonetheless, some evidence does indicate potential peripheral contributions to the disorder. For example, Salemi et al. have performed skin biopsies in 53 FM patients and found mononuclear and fibroblast-like cells adjacent to nociceptive neuronal fibers that stained positive for inflammatory cytokines, suggesting a role for neurogenic inflammation in the etiology of the FM (164).

Other authors have found evidence of changes in Schwann cell morphology in the skin (165) and altered blood flow in the muscles of FM patients (166, 167).

6.2.2. The role of supraspinal structures in pain

After synaptic processing in the dorsal horn of the spinal cord, pain signals are propagated via spinothalamic (paleo-spinothalamic) and spinoparabrachial (neo-spinothalamic) tracts to higher CNS pain centers. Spinothalamic signals are relayed through thalamus to somatosensory cortices I and II (SI and SII) and associated areas, including insula, ACC and posterior cingulate cortex (PCC). ACC, in turn, has close bidirectional connections with amygdala and hippocampus. Spinoparabrachial fibers convey information to the parabrachial nucleus in the brainstem and then on to amygdala, hippocampus and hypothalamus. Ascending pain signals and information from supraspinal pain circuitry are integrated in the mesencephalic periaqueductal gray area (PAG), which also has a pivotal role in regulating descending pain pathways (163, 168). DLPFC and LOPFC appear to initiate the descending pain modulatory sequence, explaining how attention and anticipation may influence the intensity of pain. These prefrontal areas, richly innervated by dopamine fibers, can trigger opioid release in PAG, substantially reducing the intensity of experienced pain (descending pain modulatory system will be discussed in more detail, later in the text (38, 169).

Imaging studies have consistently identified several brain areas as having a major role in pain processing, including primary and secondary somatosensory cortices (S1 and S2), thalamus, insula, ACC and PFC. Together these brain areas are commonly referred to as the "pain matrix" (170) and many studies indicate that function is disrupted in this matrix in the context of chronic pain states, including FM and NeP. For example, Bailiki et al. utilized fMRI to study chronic back pain patients. These authors reported an association between the intensity of spontaneous pain and activation of medial PFC (mPFC) (49), an area known to have a role in automatic emotional regulation (134). On the other hand, in this population, duration of pain was most strongly associated with increased activity in the insula (49). A second fMRI study noted a greater activation in DLPFC and ACC in response to non-painful stimuli in patients with FM relative to control subjects, a finding likely to reflect alterations in processes central to the cognitive and emotional aspects of pain, such as attention and anticipation (171). In response to an equivalent pressure stimulus, patients with FM have been shown to demonstrate increased activity in several areas of the CNS pain matrix when compared to normal control subjects, including S2, insula, posterior cingulate cortex (PCC), ACC, superior temporal gyrus and inferior parietal lobule (172). Moreover, mild pressure applied to subjects with FM elicited subjective pain and cerebral responses similar to the responses seen in normal subjects when twice as much pressure was applied (172).

fMRI studies like these provide objective evidence of altered cerebral processing of painful stimuli in FM patients. More recently, abnormalities in some of the same brain regions have also been observed using magnetic resonance spectroscopy (MRS). For example, Petrou et al. noted altered choline compounds (markers of membrane metabolism and myelination) in DLPFC of FM patients compared to healthy controls (173) Alterations in choline significantly correlated with subjective pain intensity. Another MRS study found evidence of increased glutamatergic activity in the insula of FM patients that correlated with measures of clinical pain (174). In an earlier study, the same group described decreased mu-opiate receptor binding potential in the cingulate cortex, amygdala and nucleus accumbens of FM individuals compared to controls, a finding that may explain why opiate medications are often ineffectual in reducing FM pain (50).

Temporal summation of "second pain" (TSSP) is one of the landmark clinical features of FM. TSSP results from repetitive stimulation of C-fibers and is believed to reflect a summation mechanisms in dorsal horn neurons (i.e., "windup"), therefore it is a basic substrate for widespread central sensitization in FM (175). Consistent with this, Staud et al found that TSSP correlated with elevated activity in S1, S2, thalamus, insula and ACC in FM subjects relative to healthy controls (176). It appears that enhanced pain sensitivity in the context of FM may arise more from altered activity of the entire "pain matrix", rather than from individual components.

6.2.3. Descending pain modulation in chronic pain disorders

Imaging studies have consistently suggested that both FM and NeP are characterized by dysregulation of pain processing circuitry involving ACC and insula. These two formations appear to have a significant role in regulating descending pain modulatory pathways that include PAG and rostro-ventral medulla (RVM) (177-179). Insular cortex appears to exert regulatory control over descending _inhibitory_ tracts that project from the RVM to the dorsal horn of the spinal cord via the dorsolateral funiculi (DLF). ACC has a principal role in modulating descending pain _facilitatory_ pathways, which project from RVM via the ventrolateral funiculi (VLF) to the dorsal columns. NE, 5HT and Ach are the principal neurotransmitters in _inhibitory_ descending pathways (177). Primary neurotransmitters in _facilitatory_ descending pain pathways include glutamate, 5HT, neurotensin, cholecystokinins and BDNF (177, 178, 180). Dysregulation of descending pain pathways, as a result of inadequate activity in the inhibitory pathway, excessive activity in the facilitatory pathway or both, has been proposed as an important etiological factor for the secondary hyperalgesia/ allodynia often observed in FM and NeP (178, 180, 181).

6.2.4 Structural brain changes in FM and NeP

In addition to functional differences, several studies have found significant structural changes in the brains of FM patients. Kuchinad et al. reported

significantly reduced gray matter density in the cingulate cortex, insula, mPFC and the para-hippocampal lobe of FM patients when compared to a control group (24). As with depression, the physiological changes that accompany FM may themselves damage brain structures over time, given that in this study duration of illness correlated with greater gray matter changes, such that each year of disease had an impact equivalent to 9.5 times the loss due to normal aging. Changes in these areas appear to contribute to the compromised pain regulation, emotional modulation, stress responsivity and cognitive functioning, often described in FM patients (24). For example, Luerding et al. reported that neurocognitive deficits in FM patients correlated with reduced gray matter volume in DLPFC and ACC (areas typically associated with executive function), additionally pain scores were noted to be negatively correlated with gray matter volume in mPFC (25). A recent MRS study noted lower NAA levels in hippocampus of FM patients compared to controls. NAA levels are commonly considered to be a marker of neuronal and axonal integrity and function. Hippocampal alterations may be associated with impaired pain regulation, cognition, sleep and neuroendocrine function in FM (47).

Fewer neuroimaging studies have been conducted in neuropathic pain than in either depression or FM. Nonetheless, fMRI studies of neuropathic pain have implicated brain areas known to be functionally abnormal in FM and chronic non-neuropathic pain, including PFC, thalamus, insula and ACC (38, 41). Apkarian et al. utilized volumetric MRI to assess gray matter changes in a group of chronic back pain (CBP) sufferers, the majority of who had neuropathic pain (22). The investigators found significantly reduced gray matter volume in DLPFC and thalamus of CBP patients when compared to controls. Moreover, decreased gray matter density in DLPFC was correlated with pain intensity, duration and negative affective characteristics in this population. Disturbingly, the magnitude of gray matter reduction in CBP patients was equivalent to 10-20 years of normal aging. Wiech et al. have reviewed the evidence that establishes a supporting role for DLPFC and dorsal ACC in volitional pain control via activation of descending pain modulatory pathways (182). Considering the well-established role of DLPFC in top-down regulation of limbic and paralimbic prefrontal areas, it is conceivable that morphological changes in DLPFC may contribute to the compromised emotional and pain modulation apparent in NeP patients (22). Prefrontal structures, through processes of attention, expectation and reappraisal, also appear to play an important role in the cognitive modulation of pain (182).

6.3. Implications of the CNS overlap of depression and pain

A striking feature of neuroimaging studies, reviewed thus far, is the significant overlap in brain areas that are functionally and/or structurally abnormal in MDD, FM and NeP. These brain areas include DLPFC, mPFC, LOPFC, insula, ACC, amygdala, hippocampus and thalamus. As would be expected from this overlap, symptoms of pain and depression also ramify each other

in ways that cause depression and pain conditions to worsen each other in a feed-forward circuit. For example, multiple lines of evidence (i.e. electrophysiological, biochemical, and imaging) are indicative of compromised function and structure of the amygdala in chronic pain (43). Depressive and anxious feelings, as well as chronic stress, may enhance amygdala responsivity to pain (43). Rainville et al. have demonstrated that negative emotions, a defining feature of MDD, enhance the perception of pain and associated autonomic responses to painful stimuli (65). The very similar functional and morphological alterations of DLPFC in MDD and chronic pain (21, 22, 26), may conspire to disrupt the "top-down" regulation of depression and pain, eventually impacting the function of descending pain pathways (while at the same time compromising cognition, and therefore, coping abilities) (182).

Ventral striatum/ nucleus accumbens (N.Acc.) is a critical component of both stress/pain response and reward/analgesic systems (183-185). N.Acc. receives cognitive information from the PFC, emotionally relevant signals from amygdala, and contextual information from hippocampus (183). It is richly innervated with dopaminergic and opiate fibers (183, 184, 186). Feedback fibers from N.Acc have a key role in modulating VTA dopaminergic output, and therefore play an important role in maintaining the balance between meso-cortical and meso-limbic dopaminergic activity (183). Neuroimaging evidence suggests that N.Acc/VTA regulation may be disrupted in MDD and chronic pain states (187, 188). Excessive activation of amygdala/sgACC/vmPFC in chronic stress, pain and depression may interrupt VTA dopaminergic transmission leading to impaired reward perception, cognitive dysfunction, decreased interest in novelty, compromised pain regulation and possibly, vulnerability towards substance abuse (184-188).

In summary, MDD, pain and chronic stress synergistically activate limbic circuitry, mutually amplifying the distress signal, while simultaneously degrading the regulatory influence of prefrontal cortical structures.

Depressed patients activate DLPFC and VLPFC in response to pain in a significantly greater manner than healthy controls, which may be interpreted as a compensatory attempt to suppress negative emotions (189). Consistent with this view, Graff- Guerrero et al. reported decreased cerebral blood flow (CBF) in areas associated with emotional response to pain, such as amygdala, hippocampus, insula, ACC and PCC after antidepressant treatment. Changes in CBF coincided with increased experimental pain threshold and tolerance (190). Depressed patients may also have an impaired ability to modulate pain due to heightened emotional reactivity. For example, Strigo at al. noted increased activation of insula, dACC, and amygdala in MDD subjects anticipating pain compared to controls (191). Depressed patients also had decreased activation of rACC and PAG, implicating compromised functioning in descending pain modulatory pathways. Greater activation of amygdala in this study

was associated with increased levels of perceived helplessness, indicating a possible bidirectional relationship between depression and pain (191). Changes in ACC function and structure have been noted in MDD, FM and NeP (21, 24, 41, 91). Some authors have proposed that altered ACC function may result in increased activity of facilitatory descending pathways (179, 192). Similarly, changes in insula in MDD and FM may negatively impact inhibitory descending pathways (24, 26, 177, 181).

In summary, when viewed as a continuum MDD, FM and NeP overlap significantly in terms of associated brain changes. When viewed as separate diagnostic conditions they clearly exist in complicated bidirectional relationships with each other, such that depression may give rise to altered pain processing and alterations in pain processing may promote affective states conducive to the development of depression. Shared patterns of dysregulation in circuitry involved in modulating emotion, pain and the stress response, especially as manifested by excessive activation of amygdala and compromised hippocampal function and structure in MDD and FM, may also have neuroendocrine, autonomic and immune repercussions, to which we turn next.

7. NEUROENDOCRINE, AUTONOMIC AND IMMUNE DYSREGULATION IN MDD, FM AND NEP

A central thesis of this article is that disorders of mood and pain share so many commonalities in symptoms and disease course precisely because these conditions are characterized by similar patterns of dysregulation in the activity and structure of brain regions and circuits that play a primary role in sensing, evaluating and responding to danger, whether the danger be from the external (e.g. a predator or social threat) or internal (e.g. infection, tissue damage) environment. This perspective provides clarity to the otherwise rather remarkable finding that disorders as diagnostically diverse as major depression, post-traumatic stress disorder, FM and chronic fatigue syndrome share similar abnormalities in neuroendocrine, autonomic and immune function. At the most basic level, we would suggest that these brain-body commonalities reflect the fact that many conditions currently parsed into separate DSM diagnoses can be understood as states of CNS and peripheral danger system hyperactivity. Moreover, even the patterns of hyperactivity observed across these multifarious conditions are strikingly stereotyped and have as their primary features insufficient glucocorticoid signaling, increased sympathetic and/or reduced parasympathetic tone and activation of innate immune inflammatory pathways (42). Increasing evidence suggests that these patterns of stress—immune system derangement not only purvey a heightened risk for the development of medical illness, but may also provide physiological feedback to the brain that promotes the development of both depression and chronic pain. In this section we will attempt to enlarge upon the role of danger system dysregulation in depression and pain by describing and comparing abnormalities in the HPA axis, autonomic nervous system and inflammatory response system in major depression, FM, NeP and other conditions of chronic pain and distress.

7.1. Abnormalities of the HPA axis in depression and pain

7.1.1. HPA abnormalities in depression

Hyperactivity of the HPA axis (with resultant hypercortisolism) is one of the most replicated physiological abnormalities seen in patients with major depression (193). Many studies suggest that this hyperactivity commences with overproduction of corticotropin releasing hormone (CRH) (the primary secretagogue for the HPA axis), which is released from the paraventricular nucleus (PVN) of the hypothalamus, whenever higher brain areas (or signals arising in the body) indicate potential threat to the organism (194). Findings indicative of CRH over production in MDD include 1.) elevated cerebrospinal fluid (CSF) concentrations of CRH; 2.) increased CRH mRNA and protein in the PVN (postmortem samples); 3.) blunted ACTH response to CRH challenge (likely reflecting ACTH receptor downregulation secondary to increased CRH), and 4.) downregulation of CRH receptors in the frontal cortex of suicide victims (many of whom were presumably depressed) (195-200). Reflecting the fact that CRH drives production of adrenocorticotropin (ACTH) and the subsequent release of glucocorticoids (i.e. cortisol in primates, corticosterone in rodents) from the adrenal glands, MDD is also frequently associated with hypercortisolemia. Evidence for this in MDD includes 1) increased number of cortisol and ACTH secretory pulses across the circadian cycle resulting in elevated concentrations of cortisol in the peripheral circulation, urine and CNS; 2) an exaggerated cortisol response to adrenocorticotropin (ACTH); and 3) enlargement of pituitary and adrenal glands, suggestive of hypertrophy secondary to HPA overdrive.(201-205)

The notion that MDD is characterized by insufficient glucocorticoid signaling seems at first blush to be directly contradicted by the multiple findings indicative of increased—rather than decreased—HPA axis activity in the disorder. However, the signaling strength of any hormonal system depends not just on hormone levels, but also on how effectively the signal "gets through", which is also dependent upon receptor sensitivity, as well as ancillary factors such as binding proteins (206). And in the context of MDD, many years of data demonstrate that glucocorticoid receptors (GR) have reduced activity, leading to a relative failure in cortisol signaling, even in the context of increased cortisol levels (207, 208). Indeed, a strong association exists between increased cortisol blood levels and decreased GR sensitivity in MDD (209), suggesting that rather than being indicative of excessive glucocorticoid tone, the hypercortisolism of depression is more often a reflection of relative GR resistance and hence inadequate glucocorticoid signaling.

In addition to being a primary mediator of the stress response, cortisol is also the body's primary anti-stress and anti-inflammatory molecule, so one would

expect that insufficient glucocorticoid signaling would lead to an inability of neuroendocrine stress pathways to terminate activity and to a release of inflammatory processes from regulatory control (206). Both abnormalities are seen in MDD and strongly argue for the fact that glucocorticoid signaling is insufficient in the disorder. Rates of impaired glucocorticoid responsiveness in the HPA axis (as a result of the axis being insensitive to cortisol-mediated inhibitory feedback control) vary from approximately 25 to 80% (201), depending on depressive symptomatology (highest rates are found for melancholic, or endogenous, subtypes) (210), age (older subjects are more likely to exhibit glucocorticoid resistance) and the technique used for assessment (the DEX-CRH stimulation test is more sensitive than the traditional dexamethasone suppression test [DST]).(201, 211) Of note, both the DST and the DEX-CRH test have been shown to powerfully predict clinical response and relapse (212-215). And in the case of the DEX-CRH test, there is evidence that impaired glucocorticoid responsiveness represents a genetically-based risk factor for the development of depression (216). Complimenting *in vivo* findings, *in vitro* studies have demonstrated that peripheral immune cells from patients with major depression exhibit decreased sensitivity to the well-known immunosuppressive effects of glucocorticoids (207). Whereas normal subjects show a marked inhibition of *in vitro* natural killer (NK) cell activity, lymphocyte proliferation or cytokine production following glucocorticoid (usually DEX) exposure, patients with major depression, especially DST non-suppressors, consistently show an attenuated inhibitory response (217-220).

7.1.2. HPA abnormalities in FM and chronic pain

Although not entirely consistent, most studies report that conditions of chronic pain, fatigue and other somatic symptoms (i.e. FM, chronic fatigue syndrome [CFS]) are characterized not by the hypercortisolism of depression but by decreased cortisol production and release, both at baseline and in response to a variety of stressors (206, 221). Interestingly, depressive conditions characterized by atypical symptoms (i.e. increased sleep, increase appetite and profound lethargy) also appear to be associated with reduced HPA axis activity (blunted cerebrospinal CRH) (222), perhaps reflecting the fact that pain and exhaustion feature prominently in this type of depressive presentation. As with MDD, the pressing question revolves around whether decreased cortisol production and release leads to glucocorticoid insufficiency in conditions of chronic pain and fatigue or whether changes in glucocorticoid receptor activity compensate (or even over-compensate) for the reduced levels of hormone. The relevance of this question is highlighted by the fact that the idea of glucocorticoid receptor supersensitivity in FM, CFS (and PTSD) has gained significant currency in recent years based on studies showing increased sensitivity to feedback inhibition of both the HPA axis and the immune system in these frequently comorbid conditions (223, 224). However, although not as widely considered, a significant number of studies support the opposite conclusion—that (as with MDD) FM, chronic widespread pain (CWP) and CFS are conditions of reduced glucocorticoid sensitivity (225). The potential pathophysiological relevance of this

reduced sensitivity is highlighted by findings that high levels of cortisol following the DST (i.e. glucocorticoid resistance) strongly predicted the future development of CWP over a 15-month period in a group of 267 at-risk individuals based on a somatasizing personality style (226). Also suggesting that reduced glucocorticoid sensitivity may contribute to symptom development are findings from a trial of a multidisciplinary intervention in FM. The investigators found that symptomatic improvement over a 3-week period was associated with increased mRNA expression for the active form of the glucocorticoid receptor (which would be expected to enhance glucocorticoid signaling) (227).

To resolve whether the end products of the HPA axis (i.e. glucocorticoids) contribute to depression, fatigue and pain primarily through overactivity or under-activity (i.e. insufficient signaling), several lines of evidence can be marshaled based on known effects of glucocorticoids on a variety of relevant physiological and behavioral endpoints. Because glucocorticoids exert profound anti-inflammatory effects in the brain and body, one would expect evidence for reduced inflammatory activity in MDD, FM and CFS if these conditions were states of excessive glucocorticoid activity. As will be reviewed in some detail below, the opposite appears to be the case as evidence for increased inflammation in these conditions mounts. Similarly, if increased glucocorticoid signaling contributes to symptom development in these disorders, one would expect that adding exogenous corticosteroids would worsen symptoms. In fact, quite the opposite appears to be the case, given studies showing that hydrocortisone, although not widely used due to risk for adverse events, demonstrates antidepressant efficacy and improves symptoms in patients with CFS and PTSD, both of which are frequently comorbid with FM (228-231). If cortisol routinely contributed to the high rate of FM development that occurs after motor vehicle accidents, one would expect high levels of the hormone to predict subsequent symptom development, but in fact the opposite appears to be the case, with several studies showing that reduced cortisol responses to motor vehicle accidents strongly predicts subsequent PTSD, which is, in turn, a significant risk factor for the development of FM-type symptoms. Consistent with a protective effect for cortisol, patients who receive stress doses of hydrocortisone as part of their treatment while in a medical intensive care unit (ICU) have reduced rates of ICU-related PTSD symptoms (232), and subjects administered cortisol or prednisone prior to exposure to standardized laboratory stressors report less distress and less fatigue (233, 234). Finally, the administration of hydrocortisone to aging veterans with PTSD was shown to enhance both episodic and working memory (235).

Less controversial than whether glucocorticoid signaling is excessive or impaired in the context of pain and depression is the consistent finding that the diurnal rhythm of the HPA axis is flattened in MDD, anxiety and conditions associated with fatigue and pain, such as FM and CFS.(236-238) In healthy individuals, cortisol production peaks around wake time and then falls thereafter (excepting "blips" of increased cortisol in response to

meals) until the early morning hours when it commences its climb toward wake-time (239). In a variety of conditions linked to stress, pain and emotional misery, this pattern is disrupted, such that cortisol levels are lower around wakening, show more disorganized variability during the day and do not fall sufficiently in the evening. Such flattening is an ominous development indeed, given that it predicts the following: subsequent development of chronic widespread pain in medically healthy individuals (226), development of fatigue and depression in patients receiving interferon (IFN)-alpha (240) and increased mortality in patients with cancer (241). In animal models, flattening of the cortisol rhythm impairs the production and release of BDNF and impairs neurogenesis in brain regions in which such neurogenic processes are tightly linked to antidepressant response (242, 243). Behavioral interventions that improve pain symptoms in FM patients also steepen the cortisol slope.(227).

7.2. Autonomic nervous system abnormalities in depression and pain

Given the known role of glucocorticoids in modulating autonomic nervous system (ANS) activity (206), if the hypercortisolism of depression and the hypocortisolism of FM, CWP and CFS were really functionally different, one would expect to find these disorders reliably associated with very different types of ANS abnormalities. In fact, the opposite is the case. Although inconsistencies in the data exist, the majority of available evidence suggests that depressive and pain disorders are characterized by a common ANS signature comprised of increased SNS signaling and diminished parasympathetic (or cholinergic) tone.

Evidence supporting increased SNS/decreased parasympathetic tone in MDD includes increased heart rate at rest and in response to stress, increased blood pressure, increased systemic vascular resistance, increased whole body sympathetic activity based on measures of postganglionic norepinephrine (NE) release and NE clearance, reduced overall heart rate variability (HRV), reduced high frequency HRV (a measure of parasympathetic tone), impaired autonomic information flow (AIF) on 24-h ambulatory electrocardiograms, impaired baroreflex, higher ventricular repolarization time and increased incidence of multiple firing within a sympathetic burst based on single-unit muscle sympathetic nerve analysis (244-254), Conversely, although not entirely consistent, data suggest that various forms of treatment, including repeated transcranial magnetic stimulation, ECT, antidepressants and psychotherapy correct sympathetic/parasympathetic imbalances by attenuating SNS activity and/or increasing vagal tone (255-260). Epidemiologic studies link intake of omega-3 fatty acid with a reduced depression risk and improved heart rate variability (261). Interestingly, a recent study suggests that applying biofeedback to directly induce these ANS changes improves depressive symptoms, strongly suggesting that ANS activity may be as much a cause of depressive symptomatology as a result (262).

As with MDD, disturbances in SNS/parasympathetic balance have been frequently reported in FM and highly comorbid conditions such as PTSD and CFS and may contribute to disease pathology by perpetuating neuroimmune dysregulation and facilitating neurogenic inflammation (42, 263). In one of the rare studies in men with FM, Cohen et al. conducted power spectral analysis of HRV and found that orthostatic intolerance in FM patients may result from sympathetic hyperactivity and concomitant reduced parasympathetic tone (264). Several other authors have identified sympathetic overactivity as a component of the stress response that both precipitates and perpetuates FM and NeP symptoms such as fatigue, sleep disturbance, anxiety, depression, vasomotor instability and gastrointestinal complaints (19, 265). In an intricately designed, controlled, study, Torpy et al. observed excessive sympathetic and HPA activity in FM patients after an IL-6 injection, supporting the notion that FM may, at least in part, be disorder of the stress system dysregulation (266). A number of studies report increased heart rate in FM (267). HRV is also reduced and shows abnormalities in circadian patterning (268-270), although the association between reduced HRV and FM may be stronger in women than men (271). One study noted that FM patients show enhanced SNS and reduced parasympathetic activity when recumbent, but fail to adequately activate SNS activity or withdraw vagal tone upon standing (272). This lack of reactivity has also been documented in response to psychological stressors (224). Of note, biofeedback training that enhanced HRV (i.e. reduced SNS activity and increased vagal tone) significantly improved pain and other symptoms in patients with FM (262), suggesting that—as with MDD—ANS abnormalities may actually contribute to symptom development and might be an effective target for intervention in FM. Similar patterns of ANS disturbance have been reported in conditions that are highly comorbid with FM, such as CFS and PTSD (236, 273, 274).

7.3. Inflammatory signaling in mood and pain disorders

Interestingly, abnormalities in HPA axis and ANS functioning frequently observed in both mood and pain disorders have in common a proclivity for activating the same peripheral innate immune inflammatory pathways that are activated in response to pathogen invasion and/or tissue trauma (206). Several studies link glucocorticoid resistance with increased inflammation (220, 275). An even larger literature demonstrates a tie between SNS activation and/or parasympathetic withdrawal and enhanced inflammatory tone (248, 275-283). Not surprisingly, therefore, a rapidly increasing literature indicates that mood and pain disorders are associated with increased inflammation.

When compared to non-depressed individuals, as a group patients with major depression exhibit all of the cardinal features of inflammation, including elevations in inflammatory cytokines and their soluble receptors in peripheral blood and cerebrospinal fluid (CSF), as well as elevations in blood concentrations of acute phase proteins, chemokines, adhesion molecules and inflammatory

mediators such as prostaglandins (284-304). Associations between depression and increased proinflammatory cytokines and/or c-reactive protein (CRP) have been apparent across the adult life span, whether comparisons are made between clinically depressed patients and matched controls (284, 285, 288) or whether they derive from large population-based studies (289, 291, 305-310). Recent investigations have reported positive correlations between levels of various inflammatory mediators and depressive symptom severity (284, 285, 304, 305, 309, 311-315); however, the association between immune activation and depression appears to be robust enough to be detectable in the context of mild depressive symptoms that do not meet criteria for major depression (314). Indeed, even single depression-related symptoms—such as fatigue, insomnia, fear and anger/hostility—appear to increase the likelihood of inflammatory activation in otherwise healthy individuals (314, 316-321). Inflammation has generally been assessed at a single time point; however, a recent study found that IL-6 production was abnormal across the entire circadian cycle in patients with major depression (284). Although most studies have focused on cytokine production/release, emerging data indicate that depression may also be associated with activation of "downstream" inflammatory second messenger signaling pathways, such as the NF-kappa-B pathway (208). Although recent research has focused primarily on cytokines which mediate the innate immune response, including IL-1, tumor necrosis factor (TNF)-alpha, and IL-6, findings of increased markers of T cell activation (e.g. soluble IL-2 receptor) in depressed patients raises the specter that both acquired (e.g. T and B cell) and innate (e.g. macrophage) immune responses may participate in inflammation in depression (322).

Perturbation of neuroimmune control has also repeatedly been cited as a shared feature of conditions such as FM, NeP and CFS that are characterized by pain, fatigue, sleep disturbances and cognitive complaints (53, 164, 323, 324). Although results have not always been consistent, several authors have reported elevations of TNF-alpha, IL-8 and IL-6 in FM (324-326). The inflammatory cytokine IL-8 is released by the pain promoting peptide substance P, modulates HPA axis activity and is involved in the induction of sympathetically mediated pain (324-327). Consistent with these effects, elevation of IL-8 appears to be one of the more consistent findings in FM (325, 326, 328). Moreover, several studies found associations between blood levels of IL-8 and subjective pain ratings in FM (325, 328). In addition to elevations in proinflammatory activity, data suggest that chronic pain conditions may also be characterized by reductions in anti-inflammatory activity. For example, chronic widespread pain has been shown to be associated with reduced gene expression and blood protein levels of the anti-inflammatory cytokines IL-4 and IL-10 (329). Elevations in inflammatory activity may be a widespread phenomenon in FM, given a recent study that reported TNF-alpha, IL-1 and IL-6 in the skin of a majority of FM patients but in none of the controls (164). Elevations in peripheral levels of the chemokine MCP-1, which is known to activate microglia in the CNS,

have also recently been reported in FM and chronic pelvic pain (330, 331). Although microglial activation in the CNS of humans with chronic pain has not been directly demonstrated, it is intriguing that several studies find elevations in proinflammatory cytokines in the cerebrospinal fluid of patients with chronic pain (332, 333). In further support of the important role of immune factors in etiopathogenesis of disorders characterized by chronic pain and fatigue, researchers at the Centers for Disease Control and Prevention have recently reported that subjects with CFS or with CFS symptoms such as fatigue and pain, had significantly higher levels of plasma CRP than did well controls (334). This study utilized a large population-based sample and found correlations with unwellness symptoms such as pain, fatigue and sleep disturbance even after adjustment for multiple potential confounding factors such as age, sex, race, body mass index and depressive symptom status. In this study, increased CRP was associated with increased physical, but not emotional symptoms, highlighting the especially close link between somatic symptoms and inflammatory activity.

In summary, altered neuroimmune, neuroendocrine and autonomic regulation may interact to perpetuate states of pain and depression (53, 335-337). Peripheral mediators of an aberrant stress response (cortisol, NE, proinflammatory cytokines) may not only be responsible for many of the clinical symptoms of MDD, FM and NeP, but may also have a role in perpetuating disturbed homeostasis in cortico-limbic circuitry, therefore maintaining a vicious cycle (42, 53, 335-337) (Figure 3). In this sense MDD, FM and NeP may be seen as composed not just of psychosomatic components (i.e. brain driving bodily dysregulation), but also of somato-psychic components (i.e. bodily processes promoting CNS dysregulation). On a deeper level, one may even question the utility of such causal dichotomies between mind/brain and body.

8. NEUROTRANSMITTERS IMPLICATED IN MDD, FM AND NEP

8.1.1. Glutamate and GABA in MDD
Multiple lines of evidence implicate aberrant glutamate (Glu) and GABA transmission in the etiopathogenesis of MDD, NeP and FM. As the principal excitatory neurotransmitter in the circuitry linking limbic and cortical areas, Glu is virtually ubiquitous in the brain. Cortical glutamatergic projections have a principal role in modulating activity in the source neuronal regions for norepinephrine (locus ceruleus [LC]), serotonin (nuclei raphe [NR]) and dopamine (substantia nigra [SN] and ventral tegmental area [VTA]) (338, 339). Glutamatergic neurotransmission relies on several classes of receptors. Ionotropic receptors include N-methyl-D-aspartate (NMDA-R), alpha-amino-3-hydroxyl-5 methyl-4-isoxazole-propionate (AMPA-R) and kainite receptors (KR). In order for NMDA-R to be activated, neural membranes must also express AMPA-R. NMDA –R "uncoupled" from AMPA-R are also referred to as "silent NMDA" receptors (340). Increased neural activity leads to
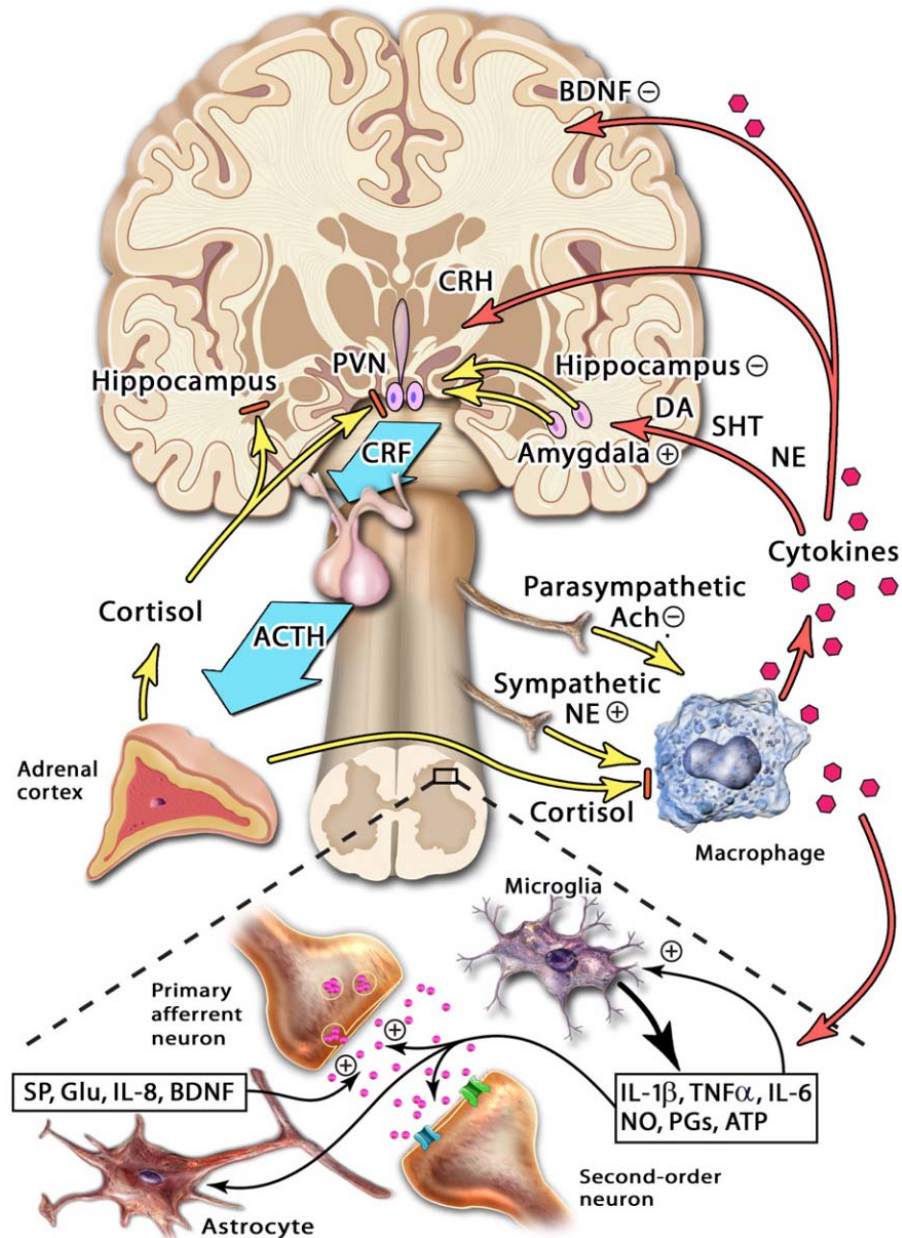
Figure 3. Mood disorders, fibromyalgia (FM) and neuropathic pain (NeP) may have shared systemic consequences. Compromised homeostatic function of prefrontal cortical-limbic circuitry in MDD, FM and NeP appears to disrupt autonomic, neuroendocrine and neuroimmune regulation. Stress, pain and depression lead to excessive and untimely release of corticotropin-releasing hormone (CRH), adenocorticotropic hormone (ACTH) and glucocorticoids. Sympathetic over-activity, combined with diminished parasympathetic tone, contributes to immune activation and release of proinflammatory cytokines (e.g. TNF-alpha, IL-1, IL-6) from macrophages and other immune cells. Inflammatory cytokines further interfere with monoaminergic and neurotrophic signaling. They may also down-regulate central glucocorticoid receptor sensitivity, leading to further disruption of feedback control of the hypothalamic-pituitary-adrenal (HPA) axis and the immune system. In depression and pain states, disturbances of serotonin (5HT), norepinephrine (NE) and dopamine (DA) transmission may impair regulatory feedback loops that turn off the stress response, with a resultant compromise in the function of descending pain modulatory pathways. Elevated mediators of the inflammatory response, combined with excessive sympathetic tone may further impact dorsal column processing of pain signals by contributing to activation of microglia and astroglia. Activated microglia exchange signals with astrocytes and nociceptive neurons, amplifying pain-related transmission of glutamate (Glu), substance P (SP), adenosine triphosphate (ATP), brain-derived neurotrophic factor (BDNF), pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF-alpha, nitrogen oxide (NO) and prostaglandins (PGs). PVN= Paraventricular nucleus of hypothalamus; IL = interleukin; TNF-alpha = Tumor necrosis factor-alpha; Ach=acetyl choline

repeated activation of synaptic NMDA-R, promoting synthesis of brain derived neurotrophic factor (BDNF). Binding of BDNF to tyrosine kinase-B (TrkB) receptors facilitates synaptic delivery of AMPA-R, thereby mediating neural plasticity and long-term potentiation (LTP), which are key mechanisms for translating experience into enduring modification of synaptic transmission (340, 341). Additionally, BDNF modulates dendritic arborization and synaptic spine density and morphology, contributing to a micro- feed-forward circuit that allows the brain to "re-wire" itself in response to increased neural activity (341). Conversely, Glu binding to extra-synaptic NMDA-Rs, has an opposite effect and suppresses BDNF synthesis (338). Glu also binds to three different classes of pre-synaptic and post-synaptic metabotropic receptors (mGlu-Rs), which have a role in modulating neurotransmitter release and post-synaptic activation of AMPA-Rs and NMDA-Rs(342).

Early studies that examined serum and plasma glutamate levels in MDD subjects had equivocal findings (338). More recently, MRS studies have noted decreased Glx (a measure combining glutamate, homocarnosine, GABA and glutamine spectroscopic signatures) in ACC and amygdala of depressed adults, children and elderly patients. In one of these studies, this alteration normalized with successful ECT treatment (see (338) and (343) for a review). A significantly higher Glu/GABA ratio was reported in the occipital cortex of depressed individuals compared to controls. Additional reports indicate changes in the NMDA receptor glycine binding site in depressed suicide victims and NMDA subunits in LC of depressed subjects (338). Altered function of glutamatergic fibers originating from vmPFC and projecting to sympathetic and parasympathetic brainstem centers has been described in MDD patients (344). This abnormality may provide a link between emotional dysregulation and excessive stress reactivity, repeatedly noted in depressed individuals (344). Open label studies of lamotrigine and rizulole (both inhibitors of glutamate release), as well as a controlled randomized trial of ketamine (an NMDA antagonist) in treatment resistant depressed patients provide preliminary evidence of efficacy of glutamatergic modulators in the treatment of MDD (345).

Several studies have reported that MDD is associated with reduced plasma GABA levels (see (346) for a review), as well as decreased GABA neurons in lateral orbital PFC (LOPFC) and DLPFC (347). This is a particularly interesting finding, given the previously described role of DLPFC and LOPFC in cognition, voluntary regulation of emotion and suppression of maladaptive affect. Some preliminary data suggest that altered cortical GABA and Glu concentrations may not only differentiate MDD patients from controls but also differentiate depressive subtypes from each other (melancholy and atypical) (348). A recent MRS study found reductions in GABA levels in dmPFC, DLPFC and ACC in MDD. It should be noted that these are the same brain areas in which patho-histological studies established alterations in glial density in MDD patients compared to healthy controls (349). Finally, several preclinical and

clinical studies noted that antidepressants and ECT improve GABA deficits (350, 351).

8.1.2. Monoamine Neurotransmitters in MDD

Despite decades of elaboration, the "monoamine hypothesis" of depression remains beset with controversies. Prompted by the evident treatment efficacy of medications that modulate 5HT, dopamine (DA) and norepinephrine (NE), it has long been held that insufficient monoamine signaling may play a cardinal role in the etiopathogenesis of MDD (352, 353). In support of this hypothesis, researches have noted alterations of NE and 5HT receptor density in cortical and limbic formations of depressed patients (353). In a PET imaging study comparing dopamine type-1 receptor (D1) binding potential (BP) in MDD patients vs. healthy subjects, researchers found significantly reduced D1 BP in the depressed group. This reduction in D1 BP correlated negatively with illness duration and anhedonia ratings (354). We have already provided evidence implicating genes that code for 5HTT, COMT, MAO and monoamine receptors in perpetuating vulnerability towards depression. Meyer et al. have reported elevated levels of MAO-A in the brains of depressed patients. Since MAO-A is a primary monoamine-lowering enzyme in the nerve cells, its excessive activity may contribute to a disturbance of monoamine signaling in MDD (355). Changes in platelet 5HT and NE receptor density have also been noted in depressed and suicidal patients (353). Patho-histological studies have reported a decrease in the number of NE neurons in LC of depressed patients whose death was unrelated to suicide when compared to matched controls (356). The same authors also noted a decrease in the number of 5HT neurons in dorsal nuclei raphe of depressed patients compared to healthy controls (356). Neuromelanine-sensitive MRI imaging has revealed an attenuated signal in LC of depressed patients (357). On the other hand, research assessing NE and 5HT metabolites in the CSF has yielded inconsistent results. Levels of 5-hydroxyindoleacetic acid (5-HIAA) have been reported to be lower in depressed patients and especially low in victims of violent suicide (353). However, because MDD is a biologically heterogeneous syndrome, it is not surprising that there are differing reports on the levels of monoamine biomarkers. For example, 3-methoxy-4-hydroxyphenylglycol (MHPG), a major NE metabolite, was found to be elevated in plasma of agitated and anxious depressed patients, while depressed individuals with psychomotor retardation were found to have lower MHPG and homovanillic acid (HVA) (a primary dopamine metabolite) levels than healthy controls. Patients with psychotic depression had elevated plasma levels of HVA. (358). Another study, using catheters placed in the internal jugular vein noted reduced NE and DA release in the brains of patients suffering from refractory depression relative to healthy volunteers (359). In contrast, using a similar technique, brain 5HT turnover was found to be elevated in depressed patients when compared to healthy subjects (360).

Monoamine transporters also seem to be influenced by the disease process. For example, the dopamine transporter (DAT) has a 15% lower binding potential in depressed patients compared to controls (361),

and 5HT transporter (5-HTT) binding potential (which can be considered as a marker of 5-HTT density) tends to be elevated during a depressive episode, especially a more severe one (362). Pharmacologic strategies that deplete monoamines suggest that the therapeutic effect of antidepressants may be selectively reversed by depleting the monoamine affected by that particular antidepressant (363).

However, a converging body of evidence brings into question simplistic interpretations of the "monoamine theory". If monoamines are the primary abnormality in MDD, it is hard to understand why in the STAR*D trial 50% of the patients failed to respond to the first line SSRI treatment, 65% did not achieve remission and more than a half of those who did still had two or more residual symptoms (364). While in vivo preclinical evidence describes prompt LC activation following SSRI application (365), clinical studies have shown that it may take as long as five to eight weeks until optimal antidepressant response is attained (366). Mayberg et al. evaluated SSRI responses utilizing PET imaging. These investigators found no difference between responders and non-responders following a week of antidepressant treatment. Rather, the pattern of activity associated with depression was reversed only after six weeks of treatment, suggesting an adaptation to chronic antidepressant administration as the basis of therapeutic effect (137). Wong et al. measured CSF NE and plasma cortisol levels in a group of patients suffering from melancholic MDD. Samples obtained around the clock showed that depressed patients had significantly higher levels of NE and cortisol than healthy subjects. NE and cortisol levels were strongly correlated to each other (200). A variety of antidepressant medications and ECT have been reported to suppress the activity of tyrosine hydroxylase (TH), a key enzyme regulating NE synthesis (367), while remarkably consistent evidence shows reductions in CSF levels of MHPG (the main NE metabolite) in depressed patients taking antidepressants (331). Imaging studies have uncovered insufficient activity and reduced volume of vmPFC in depressed individuals (26, 124, 132, 137, 344). Because vmPFC plays a key role in regulating amygdala activity and sympathetic/parasympathetic balance, it is not surprising that depressed patients tend to exhibit excessive sympathetic activation in response to stressful stimuli (221, 344). A recent preclinical study demonstrated a significant reduction in LC electrophysiological activity following 14 days of treatment with a diverse group of antidepressants, including desipramine (a predominantly noradrenergic TCA), paroxetine and citalopram (SSRIs) and mirtazepine, an alpha-2 antagonist (331).

Barton et al. recently reported elevated 5HT turnover in unmedicated MDD patients. Marked reduction in brain 5HT turnover, accompanied by clinical improvement, ensued after twelve weeks of SSRI treatment (360), suggesting a relatively insufficient 5HT transmission in MDD.

Strong evidence suggests that monoamines also regulate each other through complex interactions. For example, dopaminergic input tends to up-regulate serotonergic and down-regulate noradrenergic activity. Elevated serotonergic activity has a mostly inhibitory effect on NE and DA, while increases in NE tend to suppress DA but can modulate 5HT transmission in either direction (368, 369). Complex cross talk between dopaminergic and noradrenergic systems appears to take place in VTA, LC and dorsal hippocampus (370). Extracellular DA in the prefrontal cortex originates not only from dopamine but also from NE terminals (371). Furthermore, not only do monoamines influence each other via complex interactions but GABA and Glu tend to have a bidirectional regulatory influence on monoamines (351, 372-375). In summary, extant evidence supports the view of a complex dysregulation of interrelated neurotransmitter systems and distributed brain networks involved in regulation of mood, cognition and the stress response, rather than a simple deficit of monoamine signaling (122, 376).

8.1.3. Endogenous Opioids and other peptide neurotransmitters in MDD

The role of the peptide neurotransmitters galanin and substance-P (SP) and endogenous opiates in the pathophysiology of MDD has been a focus of recent research (377-379). Galanin coexists in serotonergic DNR neurons and noradrenergic LC neurons. Galanin receptors are located in PFC, amygdala, hippocampus, hypothalamus and the brainstem nuclei LC and DNR (379). Galanin receptor modulators are showing early promise in preclinical and clinical studies as antidepressant, anxiolytic and neurogenesis-promoting agents (379).

A recent review emphasized the pivotal role of SP in communicating peripheral inflammation and stress response to the brain. SP appears to occupy a key position in bidirectional communication between the brain and the body (377). Additionally, SP fibers and the main neurokinin-1 receptor (NK-1), are well represented in the prefrontal cortical and limbic areas, involved in the regulation of mood, anxiety and stress response (380). Recent studies have demonstrated that emotional stress results in SP efflux in amygdala and septal areas (380). A preclinical study indicates that stress-induced release of SP in LC, facilitates neurotransmission via NE projections to mPFC, thus relaying the stress signal to this area (380). SP also modulates the firing rate of serotonergic DNR neurons and dopaminergic VTA neurons, as has been demonstrated in studies utilizing systemic administration of NK-1 receptor antagonists (381).

Kennedy et al. utilized PET imaging to assess endogenous opioid transmission in female MDD patients. These authors reported a reduction in mu-opioid binding in ACC, ventral basal ganglia, hypothalamus and amygdala of MDD patients compared to healthy subjects (378). Supporting data in depressed patients, demonstrate perturbation of opioid transmission in the aforementioned areas involved in emotional and neuroendocrine regulation.

8.2.1. Glutamate and GABA in pain disorders

Glutamate is the principal neurotransmitter in both ascending and descending pathways involved in inhibiting and facilitating pain transmission in the CNS, including the dorsal column, thalamo-cortical and cortico-limbic circuitry involved in pain processing (174, 177, 180, 382, 386). Excessive Glu transmission leads to conjoined activation of AMPA and NMDA receptors all along the neuroaxis involved in pain perception and modulation, which tends to promote increased synthesis of neurotrophic factors (177, 180, 382). Such an enhancement of neurotrophic signaling has been associated with enduring neuroplastic changes, which are—in turn—the substrate for long-term potentiation (LTP) and "central sensitization" (177, 180, 382). Additionally, activation of metabotropic Glu receptors (mGluR) has been implicated in both peripheral and central pain sensitization (387).

Based on concomitant increases in Glu, nerve growth factor (NGF) and BDNF in the CSF of FM patients, investigators have recently hypothesized that increased Glu neurotransmission may facilitate NGF and BDNF synthesis in pain relevant pathways, which in turn may promote the expression of NMDA receptors in neural membranes, effectively closing a positive feed-forward circuit that enhances pain signaling (388). Temporal summation of second pain (TSSP) and "windup", also believed to reflect a summation process characteristic of dorsal horn neurons, are cardinal manifestations of central sensitization in FM. Repeated release of Glu and SP from C-fiber terminals, followed by excessive NMDA activation, appears to be the neural substrate for these phenomena (175). For example, a study that measured the concentration of excitatory amino acids in CSF of FM patients reported a relationship between elevated Glu and examination-based measures of pain intensity in FM patients, including the tender point index (TPI) (389). Harris et al, using fMRI imaging to study the effect of a non-pharmacologic treatment in a group of FM patients demonstrated a relationship between changes in Glu levels in insula and improvements in multiple pain domains (174). Thus, alterations in Glu transmission at both cortical and dorsal column levels may play an important role in the etiology of FM. Consistent with this, alterations in spinal glutamatergic signaling and subsequent NMDA activation, as well as excessive limbic NMDA mediated transmission, has also been documented in preclinical models of neuropathic pain (11, 390-392).

Elevated glutamatergic transmission in NeP may, in part, be attributable to upregulation of the alpha-2-delta subunit of voltage-gated calcium channels. A group of authors reported a 17-fold increase in alpha-2-delta subunit in dorsal root ganglia of animals subjected to an experimental model of neuropathic pain (393). Such increased expression of alpha-2-delta subunits may produce an excessive influx of calcium into the nerve cells, resulting in augmented release of excitatory amino acids and SP, with a resultant amplification of pain (394).

GABA has an important modulatory role in pain transmission, from interneurons in dorsal column to complex cerebral circuitry involved in pain processing and regulation of descending pain pathways (168, 395). Alterations in peripheral benzodiazepine receptors (PBR) on platelets (396) and monocytes (291) have been reported in FM patients relative to healthy controls. For example, upregulation of PBRs, a proxy indicator of GABA-ergic function, correlated with severity of FM symptoms (396). Insular dysfunction associated with GABA, DA and opiate neurotransmission has been documented in both clinical and preclinical models of FM (397). Moreover, extensive preclinical studies support a role for GABA in the mediation of neuropathic pain (395). Similarly, dysfunction of dorsal horn GABA interneurons due to injury may play a key role in NeP pathogenesis (163, 398). Directly supporting a role for GABA in the development of chronic pain, preclinical models suggest that early GABA administration to spinal cord may prevent subsequent development of neuropathic pain (395). Consistent with these data, pharmacologic manipulation of GABA-A receptors successfully prevented NeP and alleviated pain in a preclinical model involving sciatic nerve crush injury (399). On the other hand, inadequate GABA-opiate system regulation in PAG may result in compromised function of the descending pain pathway in models of NeP (162, 395).

8.2.3. Monoaminergic neurotransmitters in pain disorders

Monoaminergic nuclei in mesencephalon and brainstem have rich projections that innervate cortical, limbic and thalamic areas involved in regulating mood, stress responses and pain processing (see previous text). Additionally, serotonergic and noradrenergic brainstem nuclei provide innervation for descending pain-modulating tracts (180),(177), (400). Several authors have reported decreased CSF levels of the monoamine metabolites (5-HIAA, MHPG and HVA) in FM patients relative to healthy controls (401, 402). Serotonergic abnormalities in FM are of particular importance given the role played by 5HT in regulating SP transmission, another mediator heavily implicated in pain regulation (402). Serum concentrations of 5HT were found to be lower, while 5-HT receptor density on circulating platelets was higher, in FM patients compared to controls (401, 403). *In vivo* microanalytical studies have reported elevated levels of 5-HT, NE, SP, TNF-alpha and IL-1 in skeletal muscle of myofascial pain sufferers (404). FM patients were also noted to have lower plasma levels of tryptophan, which is the metabolic substrate for 5HT (405). Although not all the studies support serotonergic involvement in FM, alterations in 5HT signaling may contribute to the HPA axis and sleep dysregulation commonly observed in studies of FM (9. 405). In the context of NeP, 5-HT appears to have a dual role, participating in antinociceptive descending modulation (400, 406) on the one hand, and contributing to signaling in facilitatory descending fibers, on the other. Moreover, together with NE, 5HT participates in sensitizing peripheral C-fiber axons in preclinical models of NeP (407).

We have previously described elevated sympathetic tone in FM and NeP, and recent studies have confirmed that sympathetic manipulation enhances pain sensitivity in a subgroup of heat sensitive NeP patients (408). Decreased CSF concentrations of MHPG and HVA (primary metabolites of NE and DA) in FM patients may be related to compromised neurotransmission in inhibitory descending pathways (401, 402). A recent study utilizing PET imaging assessed dopaminergic function in FM patients (409). Unlike healthy controls, FM patients were not able to mount a release of DA in basal ganglia in response to painful stimulation. While the amount of released DA correlated with pain intensity in normal controls, no such relationship was noted in FM patients (262). Because DA has a role in motivation and cognition, it is intriguing to speculate that it may mediate at least some psychiatric symptoms that are common in the context of FM (39). Finally, monoamines may play a synergistic role in modulating NeP, given a recent preclinical study that found that combined 5-HT and NE uptake inhibition conferred greater analgesic benefits than uptake inhibition of a single monoamine. Interestingly the addition of DA uptake inhibition further ameliorated NeP pain in this animal model (410).

8.2.4. Endogenous opioids in chronic pain

The dopaminergic system is closely linked to the opioidergic system, which is probably the best established antinociceptive pathway in the CNS (38). Opioid release in cortical and limbic areas involved in emotional processing and the stress response appears to regulate pain-associated cognition, effectively attenuating emotive aspects of pain and sadness (411, 412). Sustained pain reflexively activates the endogenous opioid system in ACC, PFC, insula, thalamus and hypothalamus (413). Cognitive modulation of pain, mediated by ACC and DLPFC activity, is conveyed by mu-opioid receptors (414). The coupling of rACC and PAG opioid analgesic systems may have a crucial role in placebo anesthesia and alteration of pain perception by change in expectation (413). Subcortical opioid circuits are more involved in modulating the sensory component of pain. Moreover, activation of the endogenous opioid system in conditions of stress and danger may modulate affective and sensory components of pain independently (411). The hyperalgesic effect of psychological distress appears to be suppressed by endogenous opioid release, particularly in women (411). Activation of descending pain inhibitory tracts leads to opioid release in the dorsal horn of the spinal column, where a hyperpolarizing analgesic effect is mediated by mu-, delta- and kappa- opioid receptors (400). Glu acting through NMDA receptors, and SP acting through NK-1 activation, both modulate endogenous opioids, which in turn have an inhibitory influence on NE release (400).

Evidence suggests altered opioid signaling in FM and NeP (12, 405). A recent PET imaging study has revealed decreased availability of mu-opioid receptors in nucleus accumbens, dACC and amygdala of FM patients relative to healthy controls (50). A significant relationship was also detected between depression and mu-opioid receptor availability in amygdala of FM patients compared to controls (50). Reduced mu-opioid receptor availability correlated with affective pain ratings, possibly explaining the reduced efficacy of exogenous opiates in FM patients and elevated CSF and plasma levels of endogenous opioids in this population (50, 405). Preliminary evidence provides an intriguing view of the role that glial cells may play in the modulation of pain. In preclinical models, morphine promoted release of Glu and inflammatory mediators from astrocytes, leading to paradoxical increase in pain transmission. Nonetheless, the role of this mechanism in the clinical setting remains to be determined (415).

Preclinical models of NeP suggest an intriguing dissociation between supraspinal and spinal opioid nociceptive systems. In an animal model of NeP, an intrathecal injection of morphine had a significantly reduced analgesic effect, whereas supraspinal administration had a potent antinociceptive effect (386). Additionally, pain-facilitating neurons that originate from rostral ventromedial medulla (RVM) and are typically modulated by the opioid system seem to be sensitized after nerve injury in preclinical models of NeP. This sensitization likely contributes to allodynia and hyperalgesia in NeP (416).

8.2.5. Contributions of SP to conditions of chronic pain

Much like opioid and monoamine projections, the substance-P (SP) system is present in several cortical and limbic regions involved in the stress response and the regulation of emotion and pain (380, 417). In preclinical models, both chronic pain and chronic stress have been associated with down-regulation of SP NK-1 receptors and BDNF synthesis in hippocampus, suggesting similarities in mechanisms underlying chronic pain and depression (417). Activation of nociceptive fibers leads to a concomitant release of glutamate and SP in dorsal horn synapses (9, 418). NK-1 receptors are expressed by lamina-I dorsal horn neurons which project to brainstem and thalamus, modulating descending inhibitory and facilitatory pathways (418). It is no surprise that altered SP transmission and subsequent dorsal horn neuron sensitization has been implicated in the etiopathogenesis of both FM and NeP (9, 419, 420). SP release seems to be promoted by elevations of proinflammatory mediators and reduced by administration of dexamethasone in preclinical models of NeP (421). C-fibers are also capable of retrograde release of SP into the injured tissue, which then contributes to "neurogenic inflammation" mediated by proinflammatory substances, especially IL-8 (168, 326). This reiterative loop may amplify and perpetuate chronic pain. Several authors have reported elevations of SP in CSF of FM patients relative to healthy controls, often associated with a reduction of monoamine metabolites and endogenous opiates (401, 422-425). However, elevated levels of SP in the CSF do not appear to be specific to FM. Given its association with other painful conditions, it may be better considered as a biological marker of chronic pain than as a marker of any particular diagnostic condition (37).

Glu and SP have a synergistic pro-nociceptive effect. Proinflammatory cytokines enhance the release of both transmitters, and are in turn, themselves stimulated by SP. IL-8, whose release is facilitated by SP, promotes sympathetic pain (326, 400). Pro-nociceptive effects of SP are opposed by endogenous opiates and galanin, a peptide over-expressed in sensory neurons following peripheral nerve damage that is also known to promote a sustained inhibitory effect on dorsal horn synapses (400).

Only selected neurotransmitters and mediators of pain have been addressed in this article. A more exhaustive review of substances involved in pain modulation is beyond the scope of this review. In summary, there is a remarkable similarity and overlap in how multiple neurotransmitter systems, utilizing glutamate, GABA, monoamines, endogenous opioids and SP, through complex supraspinal and spinal interactions, modulate the stress response, emotions and pain.

9. CELLULAR, SUBCELLULAR AND NEUROTROPHIC CHANGES IN MDD, FM AND NeP

9.1. An overview of glial architecture and function

Accumulating evidence suggests that MDD may be associated with significant CNS cellular pathology, especially in glia cells. The human nervous system has approximately 100 billion neurons and one trillion glia cells (426). Traditionally, glia cells have been cast as a passive supportive matrix for neurons (426). However, in dramatic contrast to prior assumptions, contemporary research has established astroglia and oligodendroglia as full-fledged neuronal partners in neurotransmission (54). Indeed, brain architecture is defined by astrocytes. Each protoplasmic astrocyte occupies its own territory, covering all the neural elements within its domain (427). Each human astrocyte contacts and encapsulates approximately two million synapses (427). In addition to managing the content of the synaptic cleft, astroglia may have a role in synchronizing the activity of all neurons within their domains (428). Brain connectivity is effectively shaped by astroglia through regulation of synaptogenesis, synaptic strength and plasticity (427). Almost all classes of serotonin, norepinephrine, dopamine, cholinergic, GABA, glutamate, neurotrophin and cytokine receptors are expressed on glial cell membranes (54, 55, 428). Additionally, astroglial membranes express monoamine (5HTT, NAT, DAT) and glutamate transporters. Evidence suggests that neurotrophic factors, such as brain-derived and glia-derived neurotrophic factors (BDNF and GDNF), as well as cytokines (i.e. TNF-alpha) are synthesized within glia cells (54, 55). However, unlike neurons, which release neurotransmitters in response to action potentials, glia cells discharge the content of Glu vesicles in response to graded increases in cytoplasmic Ca++. Astroglia also have a role in regulating neuronal energy supply. Cerebral perfusion is significantly influenced by astroglia. On one end astroglial extensions "sense" synaptic activity, on the other end their distal processes, or "feet", modulate vascular tone and capillary permeability (429, 430).

Moreover, at times of peak neuronal activity glia cells release lactate in response to increased energy needs.

Recent research suggests that in addition to myelinating axons, Schwann cells and oligodendroglia are instrumental in the long term maintenance of axonal functional integrity, with this role being independent of myelin formation (431). Neurotrophic factors, including BDNF that are generated and released by oligodendroglia have a significant role in axonal resilience and recovery (432). Loss of glial support appears to promote axonal degeneration and local inflammation (431). Oligodendroglia appear to have a dominant role in human white matter Glu clearance. An altered ability to remove Glu, likely mediated by TNF-alpha, may be the underpinning of Glu excitotoxicity (433).

Astrocytes and oligodendrocytes most likely have a common glial precursor, with local microenvironments during development determining the eventual fate of the cell (434). On the other hand, microglia are the only cell population in the brain of mesodermal origin (435). Microglia have a complex role in the CNS. They act as resident macrophages, constantly screening the CNS environment. Depending on circumstances, microglia perform a variety of functions, including the apparently opposite functions of neuroprotection and perpetuation of cellular damage, as well as the support of oligodendrogliagenesis (436). Microglia may be conceived as the principal CNS recipients of peripheral stress signals . Under usual circumstances, microglia have a protective role; however, in pathologic conditions these cells amplify and perpetuate stress signals, contributing to oligodendroglial and neuronal damage (437, 438). Like astrocytes and oligodendroglia, microglia are endowed with a wide variety of receptors, including those for chemokines, cytokines, GABA, glutamate, Ach, NE, dopamine, SP and opioids. They are capable of synthesizing and releasing prostaglandins, proinflammatory cytokines, oxygen- and nitrogen-reactive species (ROS and NRS), neurotrophic factors, Glu and quinolinic acid (439).

9.2. Contributions of glial pathology to MDD

Glial cell pathology has been reported in the sgACC, DLPFC, orbitofrontal cortex and the amygdala of unmedicated MDD patients (54, 440, 441)) It appears that both astroglia and oligodendroglia may be affected. Uranova et al. describe a prominent 19% reduction in oligodendroglia in the DLPFC (BA 9) of MDD patients (441). Having in mind the crucial role that DLPFC plays in executive function and "top-down" limbic regulation, the implications of this finding are striking, because it may provide a neurobiological substrate for both the emotional dysregulation and cognitive dysfunction commonly observed in MDD. Hamidi et al. have described reductions in oligodendroglia density in amygdala of MDD patients (442). Genetic factors may contribute to these oligodendroglia abnormalities, given a recent transcriptional profiling study of MDD subjects that has identified aberrant expression of 17 genes related to oligodendroglia function (443). Rajkowsa et al. have noted

a significant reduction of glia density in DLPFC and OPFC of MDD subjects (444). Further supporting glial involvement in mood disorders (445), Stockmeier et al. observed a significant decrease in glial density in the dentate gyrus of the hippocampus in MDD subjects (446). Additionally, age dependant decrements in the astroglial markers were reported in a group of MDD subjects (447).

A study using immunohistochemistry assessed microglia density in DLPFC, ACC, mediodorsal thalamus and hippocampus of depressed patients. The authors suggest that significant microgliosis (i.e. increased number of microglia) in depressed patients who committed suicide relative to healthy controls, might be a marker of pre-suicidal stress. Proinflammatory mediators released from microglia may have altered 5HT and NE transmission and contributed to suicidality (448).

In contradistinction to widespread glial abnormalities, neuronal changes appear to be subtler and more discrete in MDD. For example, some authors have noted decreased pyramidal somal size in hippocampus (446), ACC (449), DLPFC (BA 9) and OPFC (BA 47) in postmortem studies of MDD patients (440). The distribution of this cellular pathology overlaps remarkably with findings from structural and functional imaging studies. Si et al. investigated the influence of age and MDD on packing density of glial fibrillary acedic protein (GFAP)-positive astrocytes in DLPFC. Individuals afflicted with MDD had a much steeper correlation between reduction of GFAP levels and age relative to healthy controls, suggesting a synergy between the aging process and disease state in reducing glia density in DLPFC (286).

Microglia-Astroglia-Oligodendroglia-Neuron "units" may be conceptualized as neural microsystems that interface with peripheral macrosystems, including autonomic, immune and endocrine signals, providing an ongoing integration of these peripheral regulatory systems with cerebral activity. We have previously described circumstances leading to neuroendocrine, autonomic and neuroimmune dysregulation in MDD, with concomitant elevations of proinflammatory cytokines, catecholamines and circulating corticosteroids (sections 7.1-7.3). Peripheral mediators of the inflammatory response propagate their influence on the brain via several pathways, including 1.) afferent neural fibers (i.e. vagal nerve); 2.) stimulation of immune cells in circumventricular organs (e.g. area postrema, eminentia mediana, pineal gland), leading to release of proinflammatory cytokines; and 3.) induction of blood-brain barrier (BBB) cells (ependymal, endothelial and choroid plexus cells), which respond by releasing IL-1, IL-6, TNF-alpha, prostaglandins, NO and MCP-1. Limited evidence suggests that transport of proinflammatory cytokines across BBB may also be possible. (450),(451).

Microglia are the chief recipients of inflammatory signals conveyed from the periphery. Activated microglia respond by releasing additional amounts of IL-1, IL-6, TNF-alpha, PGs, NO and H2O2, which in turn induce astroglia to release more of these inflammatory mediators. This positive feedback loop amplifies cytokine signals from the periphery (55, 429, 437, 448, 452, 453), Multiple effects are likely to result from this feed-forward proinflammatory, pro-oxidant activity. For example, oligodendroglia are likely to suffer oxidative damage due to overexposure to reactive oxygen and nitrogen species (ROS and RNS). TNF-alpha released by microglia and astrocytes in the context of diminished neurotrophic support has a direct toxic impact on oligodendroglia, consequently contributing to demyelination. Because oligodendroglia also play a role in Glu uptake, their damage may add to excessive accumulation of this neurotoxic transmitter (455), (433),(456).

Proinflammatory cytokines (e.g. IL-1, IL-6, TNF-alpha) and prostaglandins (e.g. PGE-2) synergistically induce indoleamine 2,3- dioxygenase (IDO), an enzyme that converts tryptophan to kynurenine, thereby diminishing its availability for 5-HT and melatonin synthesis (56, 457). Proinflammatory cytokines, such as IL-1and TNF-alpha, may also compromise serotonergic neurotransmission by increasing reuptake of the neurotransmitter from the synaptic cleft (90). For example, mRNA expression for these cytokines was associated with elevated 5HT transporter activity in MDD patients (458).

In addition to reducing serotonin availability, IDO may contribute to depression directly as a result of the production of kynurenine and its downstream metabolites. For example, the downstream metabolite quinolinic acid (QUIN) is a potent NMDA agonist and stimulator of Glu release. While the complete enzymatic pathway for QUIN production is only present in microglia, activation of IDO in astrocytes may aid in the conversion of tryptophan into kynurenic acid (KA), a compound known to down-regulate dopaminergic transmission and NMDA activity (56, 459-461). Whether KA is more likely to protect against depression via its inhibitory effects on NMDA transmission or to promote depression via its ability to down-regulate dopamine signaling is an important, and unanswered, question.

Astrocytes have recently been found to be a source of GABA in the CNS and may be important modulators of GABA activity in hippocampus (462). In the context of MDD, a shift in the microglia/astroglia balance, favoring microglial activity, may lead to excessive Glu transmission relative to GABA output (56, 459, 462); a dominance of T-helper-1 (Th-1) signaling (mostly proinflammatory) over Th-2 activity (predominantly associated with release of the anti-inflammatory cytokines IL-4 and IL-10); and inadequate neurotrophic support for oligodendroglia, contributing to demyelination (456, 459).

Astrocytes contain serine racemase, an enzyme responsible for the conversion of L-serine to D-serine (463). Compromised astrocytic function in MDD may therefore lead to altered D-serine release. D-serine is an endogenous ligand of the glycine receptor and therefore a co-modulator of NMDA function and synaptic plasticity (463). Astroglial coverage of the synapse determines the extent of D-serine available to synaptic NMDA receptors.

If astrocytic processes retract from the synapse, the amount of D-serine is reduced, resulting in long term depression of synaptic function (430). Conversely, excessive astrocytic release of D-serine and consequent NMDA over-stimulation may be toxic to neurons (429). In support of this view, a recent study has reported that elevation of plasma L-serine and Glu in depressed patients was directly associated with symptom severity, possibly hinting at astrocytic insufficiency of converting L-serine to D-serine (464) (Figure 4).

The disturbance in sympathetic/parasympathetic balance associated with MDD may have significant repercussions on glia-neuron communication. Parasympathetic activity has a stabilizing effect on microglia activity, while sympathetic input can play a dual role, either inhibiting or activating microglia (439). In stressful situations it appears that sympathetic discharge induces microglial release of proinflammatory cytokines (465). Consistent with this, a recent study that reported increased nuclear factor- kappa B (NF-kappa B) activity in human volunteers after stress also observed that NF-kappa B responses to stress in animals was obviated by alpha-1 receptor blockade (277). NF-kappa B plays a pivotal role in catecholamine-induced synthesis of proinflammatory cytokines (466). Proinflammatory cytokines and glucocorticoids have opposing effects on NF-kappa-B regulation (208). Under usual circumstances glucocorticoids have an immunosuppressant effect. MDD and sustained stress are accompanied by insufficiency of glucocorticoid signaling and glucocorticoid receptor (GR) resistance (42. 206). Glucocorticoid resistance, in turn, may be associated with a "permissive state", leading to an augmented inflammatory response (42, 206). However, in the context of aberrant stress responses, glucocorticoids have also been reported to increase NMDA activation in microglia and neurons (467, 468). Regardless, it appears that stress-MDD-HPA-sympathetic-inflammatory dysregulation may be a self-perpetuated vicious cycle with the potential to negatively impact glia-neuron signaling.

Proinflammatory cytokines have been reported to induce nitric oxide synthase (NOS), a pivotal enzyme regulating nitrogen oxide (NO) synthesis. NOS induction following exposure to inflammatory cytokines has been reported in microglial, astrocytic and neuronal preparations (469-471). NMDA signaling is also associated with increased release of NO. A recent postmortem study reported elevated NOS in hippocampal neurons of depressed patients (471). Additionally, Xiong et al. reported a suppressant effect of NO on BDNF synthesis (472).

Neural injury caused by proinflammatory cytokines may in part be attributable to induction of cyclooxygenase (COX) and ensuing prostaglandin (PG) synthesis and release (473). Direct PG injection into rodent dorsal hippocampus was sufficient to impair memory and reduce post-conditioning BDNF levels (473). Other consequences of COX-2 activation include NMDA and QUIN mediated neurodegeneration (474, 475) and induction of NOS with ensuing accumulation of NO (476). Finally, preclinical studies suggest that age-related increases in hippocampal IL-1, TNF-alpha and PGE-2 can be prevented by a selective COX-2 inhibitor (477).

Multiple signaling pathways have a convergent influence on neurotrophic factor synthesis. We have already suggested that altered microglia-astroglia-neuron communication may lead to increased NO and prostaglandin production which may, in turn, have a negative impact on neurotrophic signaling. Preclinical data also demonstrate that a loss of diurnal rhythm of corticosterone secretion impairs BDNF function (242). Altered astroglia function in MDD may have significant ramifications on neurotrophic signaling. Stimulated astroglia release Glu almost exclusively into the extrasynaptic space where it binds to extrasynaptic NMDA receptors (430). Unlike activation of synaptic NMDA receptors, which promote BDNF release, activation of extrasynaptic NMDA receptors powerfully suppress BDNF synthesis through a CREB-dependent mechanism (478). Glia-derived neurotrophic factor (GDNF) is an important regulator of neuronal health and cognitive function. A recent study reported decreased serum levels of GDNF in depressed patients compared to healthy controls. Moreover, eight weeks of antidepressant treatment was associated with a significant elevation of serum GDNF in depressed patients (479). Juric et al. demonstrated a significant increase in BDNF in astroglial cultures treated with NE, DA and 5HT, establishing an important relationship between monoaminergic neuronal activity and astroglial neurotrophic support (480).

In summary, disturbed neuron-glia relationships in MDD may result in diminished neurotrophic support (BDNF and GDNF), altered energy supply and oxidative regulation, massive releases of glutamate accompanied by compromised uptake, accumulation of ROS and RNS, all of which may jointly contribute to neurotoxicity (56, 452, 481).

9.3. Neuron-Glia Interactions in chronic pain

As with MDD, alterations in neuron-glia relationships may be of fundamental importance in the etiopathogenesis of chronic pain conditions (482-484). In the case of NeP, preclinical models are the primary source of information about the cascade of interactions between spinal glia cells and neurons, and the role of these interactions in the development of NeP-associated symptoms, such as allodynia and hyperalgesia. Microglia have been reported to respond to a range of pathologic conditions conducive to development of NeP, such as ischemia, infection and mechanical damage. These responses include morphological transformation, proliferation and migration to the site of the injury (398). In pathologic circumstances, a repetitive barrage of synaptic firing by nociceptive A-delta and C-fibers induces increased responsiveness of the dorsal horn pain-projecting neurons, a phenomenon also known as "central sensitization" (482). In this context, an intricate co-release pattern of glutamate, SP, calcitonin gene-related peptide (CGRP), fractalkine, BDNF and ATP ensues (163, 330, 482, 484). BDNF signaling, mediated by TrkB receptors, perpetuates the release of glutamate, CGRP and SP, and stimulates noradrenergic fiber sprouting following nerve injury, thus adding to the development of pathologic pain (485, 486). Both astrocytes and microglia release D-serine
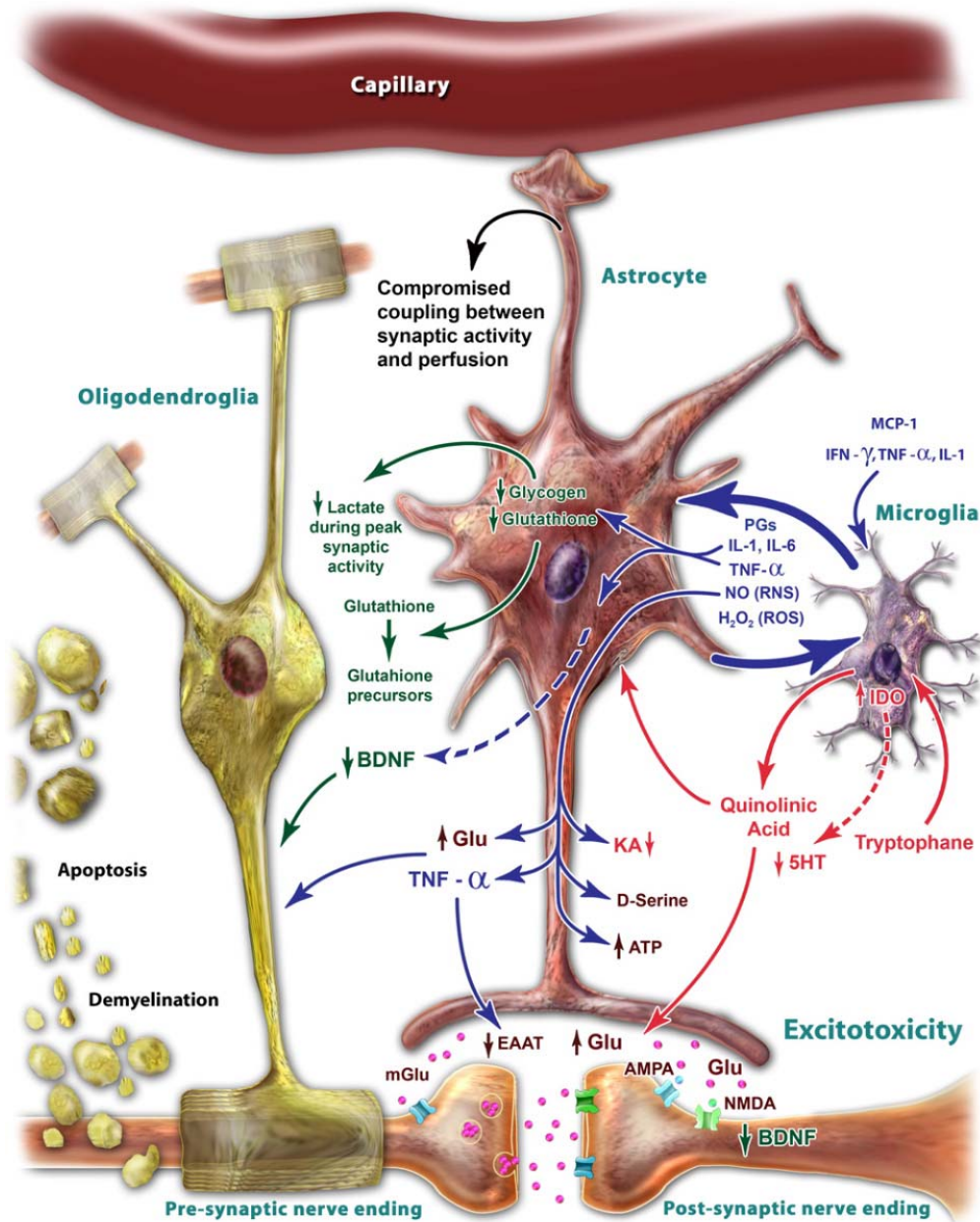
Figure 4. Microglia are the primary recipients of peripheral inflammatory signals as they reach the brain. Activated microglia initiate an inflammatory cascade by releasing cytokines, chemokines, prostaglandins and reactive nitrogen and oxygen species (RNS and ROS, respectively). Bi-directional exchanges between microglia and astroglia amplify inflammatory signals within the central nervous system (CNS). Cytokines including interleukin (IL)-1, IL-6, tumor necrosis (TNF)-alpha and interferon (IFN)-gamma induce indoleamine 2,3 dioxygenase (IDO), the enzyme responsible for degrading tryptophan, the primary precursor of serotonin (5-HT), into kynurenine, which is eventually metabolized into quinolinic acid (QUIN), a potent NMDA agonist and stimulator of glutamate (Glu) release. Multiple astrocytic functions are compromised due to the excessive exposure to cytokines, prostaglandins, QUIN and RNS/ROS, ultimately leading to downregulation of glutamate transporters, impaired glutamate reuptake, excessive glutamate release and compromised synthesis and release of neurotrophic factors. Oligodendroglia suffer damage due to toxic overexposure to cytokines such as TNF-alpha, and diminished neurotrophic support, both of which promote apoptosis and demyelination. Copious amounts of glutamate are released from astrocytes in the vicinity of extrasynaptic NMDA receptors, whose activation leads to inhibition of BDNF synthesis. Excessive NMDA activation, caused by QUIN and D-serine, is compounded by diminished glutamate reuptake by astrocytes and oligodendroglia. NMDA-mediated excitotoxicity, combined with a consequent decline in neurotrophic support, and an increase in oxidative stress, synergistically disrupts neural plasticity and induces apoptosis.

in response to peripheral inflammation, further up-regulating NMDA mediated transmission (487). Glutamate mediated NMDA receptor activation combined with voltage-gated Ca $^{2+}$ currents (VGCCs) cumulatively alter intracellular signaling (482). The subsequent activation of mitogen-activated protein kinase-1 (MAPK-1) pathways (e.g. extracellular signal-regulated kinase [ERK], p38, c-Jun N-terminal kinase [JNK]) and NF-kappa B pathways in spinal glia and neurons plays an important role in development of NeP (482-484). Neuronal ERK further sensitizes AMPA and NMDA receptors, thus augmenting excitatory neurotransmission (482). Enhanced purinergic transmission, mediated by ATP binding to P2X3 receptors, neurokinin-1 (NK-1) receptor activation by SP, glutamate binding to mGlu receptors and BDNF release cumulatively augment nociceptive transmission (482). Synaptic glutamate transporters, including glutamate transporter-1 (GLT-1) and glutamate-aspartate transporter (GLAST) (both principal regulators of synaptic glutamate) become dysregulated following prolonged and excessive exposure to glutamate (482). Under usual circumstances, GABA released by inhibitory neurons modulates glutamatergic transmission in the dorsal horn synapse (488). Following peripheral nerve injury, ATP stimulates BDNF release via P2X4 receptors in microglia (488). Interestingly, microglia are not the only source of BDNF, as oligodendroglia and astrocytes have also been found to release neurotrophins following spinal cord injury (489). BDNF signaling through Trk-B receptors reduces the levels of anion transporter KCC2, ultimately resulting in increased intracellular Cl $^-$ concentrations (488). In these pathological circumstances, GABA activation paradoxically leads to Cl $^-$ efflux, further depolarizing the dorsal horn neuron (488). Thus, BDNF has a role in perpetuating "central sensitization" by both facilitating excitatory transmission and by interfering with inhibitory regulation (488, 490).

Activation of MAPK and NF-kappa-B in microglia and astrocytes ultimately leads to increased synthesis and eventual release of proinflammatory factors, such as IL-1, IL-6, IL-18, TNF-alpha, PGE-2 and NO (482-484). Recent research suggests that the dorsal root ganglia (DRG) nociceptive neurons also express IL-1, possibly contributing to the inflammatory response seen in pathologic pain states (491). Release of proinflammatory mediators leads to a self-perpetuating activation of glia cells and excessive stimulation of dorsal horn neurons, producing sensory abnormalities typically associated with nerve injury (483, 484). Additionally, proinflammatory mediators may directly impact axons or become transported in a retrograde fashion to the cell bodies in dorsal root ganglia, where they alter gene expression in the primary nociceptive neurons, producing "neurogenic inflammation" and contributing to "peripheral sensitization" (163, 168, 492).

Altered neuron-glia interactions have recently been implicated in the genesis of "mirror pain", whereby pain is propagated to the side contra-lateral to the site of pathology (323). Hypothetically, robust glia activation on one side, due to pathological pain processes, can trigger gap-junction propagation of calcium waves that will activate glia on the contra-lateral side, leading to a release of pain mediators in an otherwise unaffected area (323). New data suggest that glia may also interfere with opioid analgesia in pathologic pain states (415). In response to morphine, glia cells release neuroexcitatory substances that oppose its analgesic effect (415). It appears that microglial activation is necessary for the initiation of pathological pain, while astroglia have a major role in propagation and maintenance of pain states (493, 494). Consistent with this view, administration of minocycline (an inhibitor of microglial activation) prevented the development of neuropathic pain, but failed to suppress acute pain or already entrenched pathologic pain (495, 496). Accumulating preclinical evidence suggests that disturbed neuron-glia relationships in the context of NeP may extend to the supraspinal regions (497-499). For example, a sciatic nerve ligation model of chronic pain produced a significant astrocyte activation in the cingulate gyrus (497). Similarly, a recent report indicated that spinal cord injury induced microglial activation and ensuing release of proinflammatory cytokines in remote locations, such as "below-level" spinal cord (i.e. below the level of injury) and the thalamus (500). Pain induced by peripheral inflammation was associated with elevated BDNF in PAG and subsequent NMDA-mediated descending pain facilitation, via RVM (rostral ventromedial medulla), suggesting a potential role for the supraspinal inflammation-neurotrophic factor-glutamate interactions in persistent pain (498). In a separate study, the same group of authors reported elevations of IL-1 and TNF-alpha in RVM, resulting in excessive NMDA activation and allodynia following chronic constriction injury, a preclinical model of neuropathic pain. Injection of the microglial and astroglial inhibitors abolished hyperalgesia and allodynia, providing further proof of supraspinal astrocyte and microglia involvement in perpetuating the descending pain facilitation (499).

Evidence supporting the neuron-glia pathology in the genesis of FM is modest at best. Kim et al. conducted an electron microscopic assessment of the skin biopsy samples from fibromyalgia patients and compared them with healthy controls (165). In 9/13 of FM patients unmyelinated Schwann cells were "ballooned", whereas none of the control samples displayed this type of pathology. Also, in most of the FM patients, axons were localized in the periphery of the unmyelinated Schwann cell sheets (165). This preliminary finding suggests that altered glia morphology and function may play a role in FM. Despite the paucity of hard evidence, some authors have posited that dysregulated neuron-glia relationships may play a role in FM, based on similarities in biochemical markers between NeP, other chronic pain states and FM (60, 420). In summary, multiple lines of evidence implicate disturbances in neuron-glia relationships with concomitant disruption in the regulation of glutamatergic, neurotrophic and inflammatory signaling as principal mediators of chronic pain states, including NeP, and perhaps FM. Some authors have even characterized chronic pain as a "gliopathy" (501).

10. CONCLUSION

Multiple lines of evidence suggest that the co-occurrence of depression and pain is more the rule than the exception. For example, recent studies demonstrate that 30-60% of depressed patients also suffer from a painful condition (1), and at least an equal percentage of people with chronic pain also meet criteria for a mood disorder diagnosis. (502-506). Of course, pain is one of many syndromes/symptoms that co-occur regularly with MDD. For example, there is also a considerable overlap between MDD and anxiety disorders (507, 508). Some authors have gone so far as to suggest that they are dual manifestations of the same underlying patho-physiological condition (354, 509). Manchikanti et al. even reported a "dose-response" relationship amongst pain, and depression and anxiety. In this study, 14% of the control group experienced GAD and 4% experienced MDD. Among the patients who experienced chronic pain involving one bodily region, the prevalence of GAD and MDD was 30% and 20%, respectively. If patients experienced pain in two or more regions, the prevalence of GAD and MDD rose to 54% and 32% (504). Given this overlap, it is no surprise that the presence of pain is a major predictor of depression and anxiety.

It is becoming increasingly clear that relationships between MDD, anxiety and pain run even deeper than the surface similarities shared by these conditions. For example, although not completely consistent, studies point to a shared genetic underpinning for these disorders, especially in relation to genes involved in the regulation of monoaminergic and peptide transmission, inflammatory response, diurnal rhythm and neurotrophic signaling. All of these are important modulators of pain, emotional tone and the stress response. Stress, in turn, is a major precipitant, perpetuant and an aggravating factor in all three conditions. Consistent with this, brain circuitry involved in the regulation of mood and the stress response overlaps to a significant degree with components of the "pain matrix", involved in emotional and cognitive aspects of pain processing.

From an evolutionary perspective, it is apparent that both negative emotions and physical pain have a tremendous survival value, given that both provide a clear signal that current conditions are a threat to an organism's goals and/or survival. Thus, it is not surprising, that, both peripheral and CNS depression and pain pathways overlap significantly, nor that these pathways are built into the warp and woof of the mammalian stress and immune response systems. While important differences exist in the processing of physical pain, emotional pain and stress responses at the level of pain sensory areas (e.g. thalamus, SI and SII), striking similarities are apparent in the involvement of limbic and paralimbic prefrontal cortical areas (amygdala, hippocampus, insula, ACC, vmPFC), as well as more "cognitive" and integrative brain areas, such as rACC, dACC dmPFC and DLPFC. Moreover, pain and depressed mood appear to have an overlapping capacity to engage autonomic, neuroendocrine and neuroimmune components of the stress response. MDD, FM and NeP are all associated with altered sympathetic/parasympathetic balance, neuroendocrine disturbances, characterized by insufficient HPA regulation and altered immune function. In turn, these peripheral responses signal back to the neural structures to further drive the CNS danger pathway activation, leading to a maladaptive feedforward circuit, which increasingly appears to be implicated in the production and maintenance of symptoms.

Microglia seem to be the principal recipients of bodily distress/pain signals. Differences in the micro-environments in the dorsal column of the spinal cord and brain areas involved in processing of pain in MDD, NeP and FM may be reflected in the different patterns of interaction between microglia, astroglia and neurons, in these respective conditions. Excessive firing of nociceptive neurons in the context of NeP and FM tends to be associated with increased release of substance-P, IL-8 (which promotes sympathetic pain), IL-18, fractalkine and CGRP, in addition to chemokines produced by macrophage and mononuclear cells (324, 482-484, 492), none of which are part of the usual spinal cord cellular milieu in MDD. Nonetheless, excessive excitatory glutamatergic transmission and compromised GABA mediated inhibition appear to be common features of depression and pain disorders. Dysregulation in monoamine, substance P, galanin and opiate signaling also characterizes both pain syndromes and MDD. On the other hand, depression and pain disorders have been reported to have different patterns of abnormality in the production of neurotrophic factors. MDD is characterized by the reduction of the serum BDNF levels, while serum BDNF levels tend to be increased in FM. . Nonetheless, pain, stress and depression have a similar, if not synergistic, impact on neurotrophic signaling in hippocampus, with all three conditions being associated with reduced BDNF synthesis. This finding is of particular interest, given that hippocampus represents a veritable "intersection" of pathways involved in emotional regulation, memory and coordination of the stress response.

MDD, NeP and FM are all associated with neuroplastic changes in the CNS. In pathologic pain states, facilitation of pain signaling, presumably based on neuroplastic changes in pain pathways, is often designated as the "central sensitization". Similarly, the recurrent and most likely progressive nature of MDD is often ascribed to "kindling", which—like central sensitization—reflects neuroplastic changes. Given this, MDD, NeP and FM may all be characterized by adaptive processes gone awry as a result of complex interactions between genetic vulnerabilities and environmental factors. In this scenario, persistent aberrant processing of emotional, painful and stressful signals eventually becomes "ossified", presumably due to ensuing neuroplastic changes. In some regards, depression, FM and NeP share dysfunctional psychosomatic and somatopsychic communication. It should be no surprise, then, that overlapping pathology gives rise to similar phenomenological manifestations. If we assume that shared biological underpinnings give rise to the clinical symptoms of MDD, NeP and FM, it is clear that

a full understanding of this "synergy" has critical treatment implications.

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