

The relationship between fibromyalgia, stress and depression

Fibromyalgia is noted for its association with both psychological stress and depression. However, the precise nature of these relationships remains contentious, as indicated by a large body of conflicting literature. Inconsistencies regarding the nature of stress in fibromyalgia are related to the poor characterization of biological stress systems in the different presentations of fibromyalgia. Similarly, conflicting literature regarding depression and fibromyalgia is likely due to the heterogeneous nature of both fibromyalgia and depression. Emerging evidence indicates that fibromyalgia and depression are both syndromes, which affects the way in which each disorder should be considered. In this review, the nature of stress and depression in the context of fibromyalgia will be discussed.

Angeline S Thiagarajah¹,
Emma K Guymer^{1,2}, Michelle
Leech^{1,2} & Geoffrey O
Littlejohn^{*,1,2}

¹Department of Medicine, Monash
University, Melbourne, Australia

²Department of Rheumatology, Monash
Health, Melbourne, Australia

*Author for correspondence:
geoff.littlejohn@monash.edu

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LEARNING OBJECTIVES

Upon completion of this activity, participants will be able to:

- Distinguish events that might promote fibromyalgia
- Analyze psychological traits associated with the diagnosis of fibromyalgia
- Assess the effects of stress, fibromyalgia, and depression on the hypothalamic–pituitary–adrenal axis
- Evaluate the relationship between depression and fibromyalgia



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CME author: *Charles P Vega, MD*, Associate Professor and Residency Director, Department of Family Medicine, University of California, Irvine, CA, USA.

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Authors & credentials:

Angeline S Thiagarajah, BMedSc (Hons), Department of Medicine, Monash University, Melbourne, Australia

Disclosure: Angeline S Thiagarajah has disclosed no relevant financial relationships.

Emma K Guymer, MBBS, FRACP, Department of Medicine, Monash University, Melbourne, Australia and Department of Rheumatology, Monash Health, Melbourne, Australia

Disclosure: Emma K Guymer has disclosed no relevant financial relationships.

Michelle Leech, MBBS, PhD, FRACP, Department of Medicine, Monash University, Melbourne, Australia and Department of Rheumatology, Monash Health, Melbourne, Australia

Disclosure: Michelle Leech has disclosed no relevant financial relationships.

Geoffrey O Littlejohn, MBBS (Hons), MD, MPH, FRACP, FRCP (Edin), Department of Medicine, Monash University, Melbourne, Australia and Department of Rheumatology, Monash Health, Melbourne, Australia

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Fibromyalgia is a common chronic pain syndrome, which affects 2–4% of people worldwide [1]. Women with fibromyalgia outnumber men by a ninefold factor [2]. Chronic widespread pain (CWP) is the cardinal symptom of fibromyalgia, and associated symptoms defining the phenotype include sleep disturbance, fatigue and cognitive dysfunction. Psychological experiences of anxiety and affective dysfunction are common [3].

Given the abundance of psychological phenomena contained within the associated symptoms of fibromyalgia it is expected that it is commonly associated with stress. The strength of this relationship is such that fibromyalgia has been described as a ‘stress-related illness’ [3]. However, in order to contextualize the importance of stress in the pathogenesis of fibromyalgia, the nature of stress must first be discussed.

What is stress?

Although the term ‘stress’ is ubiquitous in both clinical and lay vocabularies, the concept of stress is difficult to define. Broadly, stress may be conceptualized as any challenge that disrupts the body’s natural homeostatic mechanisms [4]. This challenge may come in the form of a physical stressor, or a psychological stressor.

Physical stressors, including infections and tissue damage, result in the activation of the locus coeruleus in the rostral pons [5]. The locus coeruleus, involved in the modulation of physiological stress responses, arousal and sleep, also projects to the hypothalamus, connecting it to the hypothalamic–pituitary–adrenal (HPA) axis [6].

The HPA axis is itself quintessentially associated with stress, and emotional stressors result in the direct activation of the HPA axis [5]. The function of the HPA axis and its effects on the hippocampus also involves memory and learning, key to adaptability in stressful situations [7,8]. The reciprocal connection between the HPA axis and the locus coeruleus means that activation of the physical stress response necessarily involves the emotional stress response, and vice versa [6].

Both the locus coeruleus and the HPA axis have additional bidirectional projections to the amygdala [6]. The amygdala is responsible for the processing of stimuli that may cause fear, which links it to the notion of stress [6]. Together, the locus coeruleus, HPA axis and the amygdala have a conceptually triangular relationship. This constitutes the body’s core mechanism for a response to stress which is in turn modulated by the prefrontal cortex (Figure 1) [6].

Chronic stress has been associated with both HPA axis hyperactivity and HPA axis hypoactivity [12]. There are various theories as to the reasons for this discrepancy, one being that HPA axis activity depends on a person’s response to stress. A meta-analysis associated HPA axis hyperactivity with subjective distress responses, whereas HPA axis hypoactivity was more closely associated with stressed people who went on to develop post-traumatic stress disorder [12]. Alternatively, the association of stress and HPA axis hypoactivity in conditions such as fibromyalgia or rheumatoid arthritis has been used to explain the variation in studies regarding the nature of the HPA axis in chronic stress states [12,13]. Although the reason for the different associa-

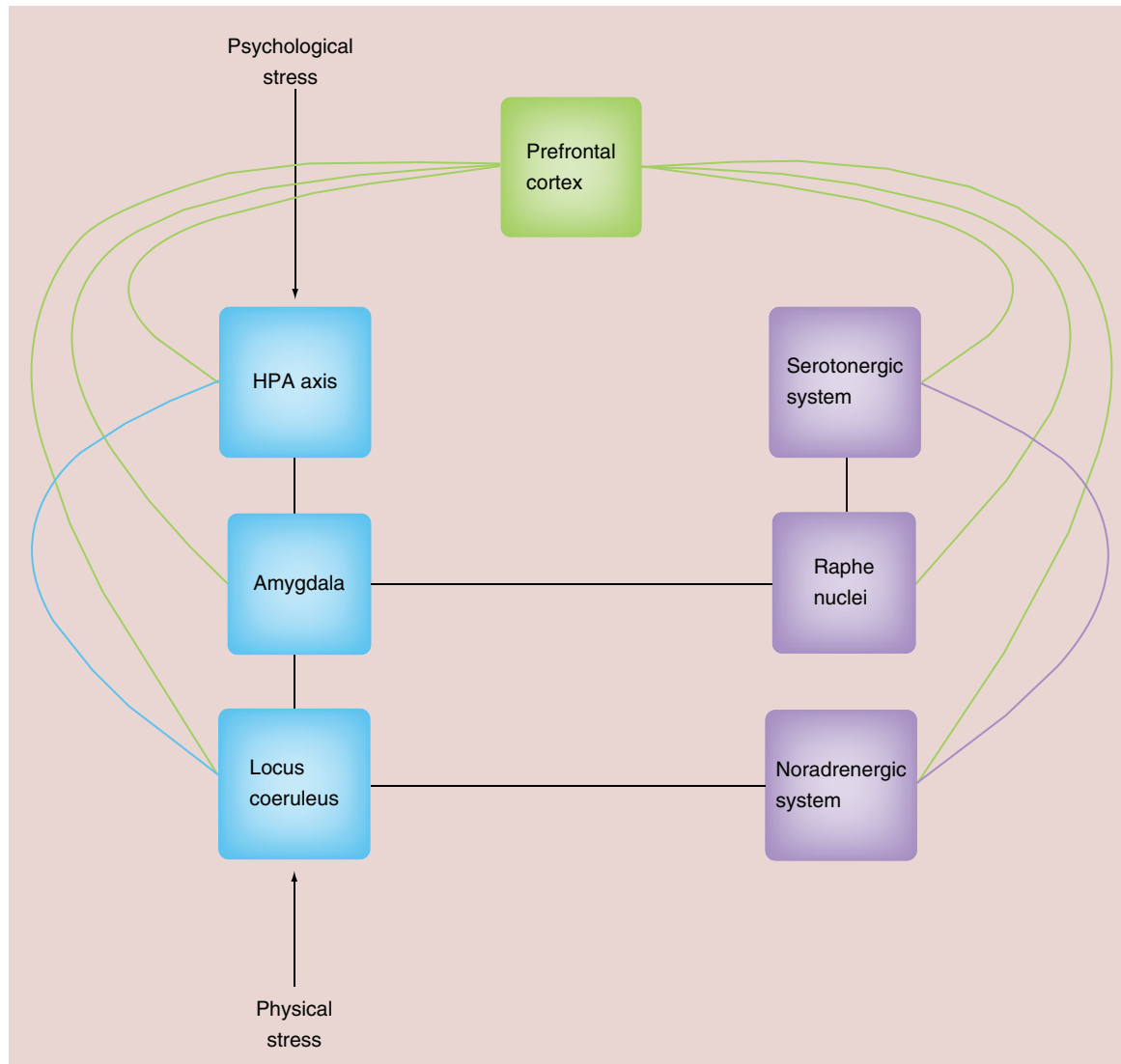


Figure 1. Biological systems and neurological regions related to stress and pain in fibromyalgia. Connections between elements in this model are bidirectional. HPA: Hypothalamic–pituitary–adrenal. Data taken from [6,9–11].

tions of the HPA axis with stress remains debatable, it is clear that chronic stress can be viewed a heterogeneous construct, as it may be associated with either HPA axis hyperactivity or HPA axis hypoactivity.

How does stress relate to pain & fibromyalgia?

The stress–response system outlined above does not exist in isolation from other neural mechanisms. As a noradrenergic neuron cluster, the locus coeruleus is associated with the function of noradrenergic pain control pathways, which in turn are associated with descending serotonergic pain pathways [9,10]. The additional association of the amygdala with the raphe nuclei in the brainstem further connects the stress systems to the pathways associated with pain, as the raphe

nuclei are associated with serotonergic pain pathways [11]. Again, this system is influenced by its connections to the prefrontal cortex, suggesting higher-level neural control over these systems (Figure 1) [11].

All of these biological systems and neurological regions have been associated with fibromyalgia. Various elements of the HPA axis have been observed to be abnormal in fibromyalgia (Table 1) [14–16].

The inconsistent association of the HPA axis with fibromyalgia presents a similar picture to the varied relationship between stress and the HPA axis, and again, could reflect the heterogeneous nature of fibromyalgia. However, many studies concur that HPA axis hypoactivity is present in fibromyalgia, and this is consistent with studies of other stress systems in fibromyalgia. A reduction in HPA axis activity would lead to

Table 1. The hypothalamic–pituitary–adrenal axis has been observed to be dysfunctional at many levels of the system in fibromyalgia.

Element of HPA axis	Abnormalities observed in fibromyalgia
ACTH	Hyperactive ACTH response to CRH
Cortisol	Hypercortisolemia: high basal total plasma cortisol
	Hypocortisolemia: low basal total plasma cortisol, low 24 h urinary-free cortisol levels and low peak serum cortisol levels
GC receptors	GC feedback resistance
ACTH: Adrenocorticotrophic hormone; CRH: Corticotrophin-releasing hormone; GC: Glucocorticoid; HPA: Hypothalamic–pituitary–adrenal Data taken from [14–16].	

a reduction in amygdala function, and this is reflected in an observed reduction of grey matter volume in the amygdala of patients with fibromyalgia [6,17].

A reduction in HPA axis activity would also lead to decreased activity of the locus coeruleus, which would lead to decreased activity of the serotonergic and noradrenergic pain modulation systems [6]. Decreased serotonergic and noradrenergic activity is consistently demonstrated in fibromyalgia, and forms the scientific basis for the use of serotonin–noradrenaline reuptake inhibitors in the treatment of fibromyalgia [3].

What stimulates the stress system in fibromyalgia?

As illustrated in **Figure 1**, both physical stressors and psychological stressors play a role in the modulation of stress and pain. These stressors are able to feed into this cyclic model of pain and stress perpetuation, increasing the severity of fibromyalgia [18]. Importantly, both types of stressors are associated with the pathogenesis of fibromyalgia.

Trauma can act as a significant physical stressor, and is related to the onset of fibromyalgia. Fibromyalgia has been linked to motor vehicle accidents, as well as surgery, both of which have the capacity to induce severe physical stress [3,19]. Unsurprisingly, trauma is also associated with psychological stress, which would feed back into the HPA axis, and further perpetuate the individual's experience of stress (**Figure 1**) [20].

Infectious diseases are also frequently cited as physical stressors, and certain pathogens have been implicated as potential triggers of fibromyalgia. The observation of significantly higher *Helicobacter pylori* IgG levels in the serum of patients with fibromyalgia compared with controls has led to the suggestion that *H. pylori* infection may be associated with the development of fibromyalgia [21]. Additionally, exposure to pathogens such as Epstein–Barr virus and parvovirus is also associated with the development of CWP [3].

Infection with *Borrelia burgdorferi*, otherwise referred to as 'Lyme disease', may be associated with symptoms of

fibromyalgia [22]. The nature of this relationship is more complicated than that of fibromyalgia and other pathogens, as chronic Lyme disease may present with 'fibromyalgia-like' symptoms [23]. Therefore, debate exists as to whether the experience of CWP in association with Lyme disease can rightly be termed as 'fibromyalgia'. However, it is clear that many infectious pathogens have the capacity to induce chronic muscle pain and other features of fibromyalgia which is consistent with the theory that physical stressors may trigger fibromyalgia.

In a similar fashion to the experience of trauma, infectious physical stressors may also simultaneously result in psychological stress, resulting in sickness behavior [24]. In particular, proinflammatory cytokines released by the host in response to an infectious pathogen may induce peripheral pain sensitization, as well as having a positive feedback effect on the HPA axis, meaning that infections may affect multiple aspects of the stress response system (**Figure 1**) [25,26].

Chronic physical stressors may also impact people with fibromyalgia. Fibromyalgia commonly co-occurs with a number of physical conditions, including rheumatoid arthritis and systemic lupus erythematosus [19]. These diseases are both associated with significant physical and psychological stress, which further compounds the potential stressors that may affect people with fibromyalgia [27,28].

Aside from the indirect psychological stressors associated with fibromyalgia, as noted above, fibromyalgia is also associated with direct psychological stressors. Of importance, a meta-analysis of 18 studies found that the experience of fibromyalgia is significantly associated with a past history of physical or sexual abuse, two triggers highly associated with psychological stress [29].

Another study looking at workplace stress, defined as having a large workload, low decision latitude or a history of workplace bullying, also found that occupational stress was associated with fibromyalgia [30]. There are also relationships between fibromyalgia and other stressors, including financial difficulties and illness or death of a close relative [31].

Although all of these stressors have been significantly associated with fibromyalgia, it is clear that the experience of one or more of these stressors is not a sufficient cause of fibromyalgia. As noted by van Houdenhove *et al.*, it is possible to experience any combination of these stressors, which may take the form of longer-term predisposing and perpetuating stressors, or precipitating stressors, which may be more acute [32]. Importantly, it is also possible to experience these stressors without developing fibromyalgia, which suggests that other factors modulate the perception of stress in fibromyalgia.

Why does stress lead to fibromyalgia in some patients?

The perception of stress is different in patients with fibromyalgia compared with controls. A study of patients with fibromyalgia found that patients were more likely to report life events that they found to be stressful, compared with controls [33,34]. Importantly, this seemed to be related to the fact that fibromyalgia patients were more likely to rate mild stressors more severely than controls. This suggests that stressors are perceptually augmented in people with fibromyalgia, which may increase the pathogenic role of stressors in such patients.

Conceptually, the relationship of stress to fibromyalgia may be understood by examining the diathesis–stress model of disease. The diathesis–stress theory of disease describes a psychological model by which people with particular vulnerabilities respond differently to stress compared with people without such vulnerabilities (Figure 2) [35,36].

According to this theory, patients with particular tendencies would be more resistant to stress, and would be able to self-regulate their mood and cognitions in response to the changes associated with stress. However, patients with other tendencies would not be able to cope with a challenge to their environment, and would become vulnerable to disorders such as depression [35].

Although this model is generally employed to describe psychiatric disorders, this idea could extend to consider any condition, as many physical disease processes require more than one vulnerability factor before they become pathogenic [37]. Fibromyalgia is one such disorder, where many predisposing factors may constitute a vulnerability trait in people, rendering them at risk of developing the disorder [38].

Certain genes have been associated with an increased risk of experiencing fibromyalgia. Smith *et al.* observed that several genes, including *RGS4*, are associated with fibromyalgia. The association of *RGS4* with fibromyalgia is particularly important, due to the localisation

of *RGS4* in the locus coeruleus [39]. Not only does this link a genetic anomaly into the stress system, dysfunction of *RGS4* in the locus coeruleus has also been associated with a down-regulation of μ -opioid receptor function [40]. This finding, therefore, may partially explain the inefficiency of opioid analgesia in fibromyalgia, and may suggest that fibromyalgia patients with locus coeruleus dysfunction are particularly unlikely to benefit from opioid therapy.

This study additionally observed that single nucleotide polymorphisms occur at a different rate in patients with fibromyalgia when compared with controls [39]. Theoretically, it is possible that the observation of different single nucleotide polymorphism profiles in patients with fibromyalgia is an epigenetic effect, rather than a contributing factor, to the pathogenesis of the disease. However, the familial clustering of fibromyalgia, especially in monozygotic twins compared with dizygotic twins, suggests that genetic risk plays a role in developing a susceptibility to fibromyalgia [41].

Another gene associated with fibromyalgia is *COMT*, which is involved in the metabolism of catecholamines, and is associated with a number of functional polymorphisms [42]. In particular, the val158met polymorphism of the *COMT* gene is less active than its original counterpart, and is associated with psychological distress in fibromyalgia, as well as being associated with a higher sensitivity to pain [43,44]. This is another link between stress and pain, which is particularly important due to the effects of *COMT* on catecholamines, which connects *COMT* to the stress and pain model as outlined in Figure 1.

Other significant risk factors associated with the development of fibromyalgia are related to personality psychology. We have previously shown that neuroticism, a personality trait associated with an increased risk of negative emotional states, modulates the experience of stress in people with fibromyalgia [45]. Patients with fibromyalgia are also more likely to have high levels of maladaptive perfectionism, which is also associated with depression [46]. Hysteria, a personality parameter associated with denial and ‘anxiety-related complaints’ has also been shown to be increased to pathological levels in patients with fibromyalgia [47]. The increased reporting of ‘anxiety-related complaints’ in such people is conceptually similar to the finding that patients with fibromyalgia are more likely to evaluate moderately uncomfortable situations as highly stressful, as noted above.

Coping mechanisms, which are required to process stressful stimuli, are also different in patients with fibromyalgia compared with those without fibromyalgia. For example, patients with fibromyalgia are less capable of modulating their experience of pain with

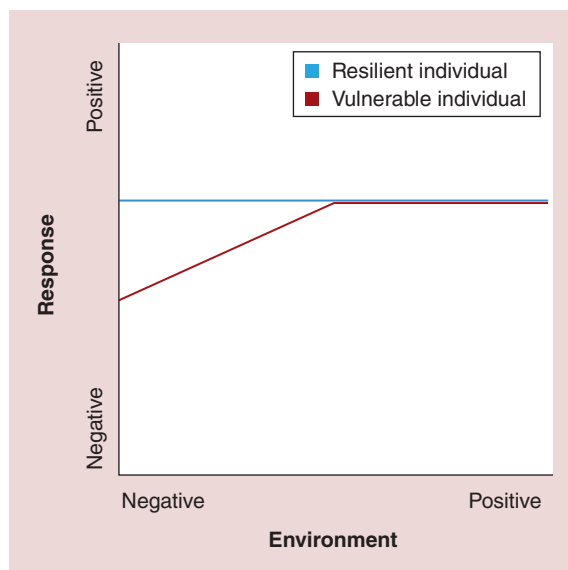


Figure 2. The diathesis–stress model of disease. People who are resilient to stressors are resistant to changes in their external responses to challenges. Conversely, people who are vulnerable to stressors experience a deterioration in their responses to external challenges when confronted with a negative environment. Data taken from [36].

a positive affect compared with healthy controls, and also have lower total levels of positive affect [48,49]. Moreover, a small study has reported an increase in catastrophizing behavior in fibromyalgia patients compared with controls [50]. In concert, these findings show that patients with fibromyalgia have impaired natural coping mechanisms, alongside additional maladaptive coping strategies, increasing their risk of negative responses to stressors.

Importantly, psychological traits differ within cohorts of fibromyalgia patients. A study of temperament and character revealed three clusters of characteristics in fibromyalgia patients: ‘cautious’, associated with high harm avoidance, low self-directedness, uncertainty and shyness, ‘curious’, associated with low anxiety and curiosity, and ‘divergent’, associated with high harm avoidance, low self-directedness, social intolerance and disorganisation [51]. Not only does this reinforce the psychological heterogeneity of fibromyalgia, but also, the particular association of the ‘divergent’ cluster with chronic stress in this study suggests that stress is differentially associated with psychological fibromyalgia phenotypes.

Similarly, a study of personality characteristics in the NEO Five-Factor inventory identified two subgroups of fibromyalgia patients according to psychological parameters [52]. ‘Cluster 1’ was associated with high levels of neuroticism, and low extraversion, defined as the ability to be gratified by external factors, whereas ‘Cluster 2’ was not associated with these characteris-

tics. Again, the two groups were separated by their risk of psychological distress, as ‘Cluster 1’ was shown to be more closely associated with anxiety and depression.

This understanding of vulnerability factors contextualizes a diathesis–stress model of fibromyalgia (Figure 3).

The vulnerability factors contribute towards the perpetuation of the pathological response to a stressor, leading to the symptoms of chronic stress in association with fibromyalgia. The symptoms of fibromyalgia and stress would then contribute to the prolongation of symptoms, as the pain from fibromyalgia could continue to be a source of physical stress feeding into the locus coeruleus, and chronic stress symptoms could feed back into the HPA axis (Figure 1). As chronic stress is often considered a model of depression, it is important to note at this stage that this model of long-term stress in fibromyalgia is associated with depression, which would perpetuate the cycle of psychological stress and HPA axis dysfunction [53]. Chronic issues that perpetuate the cycle of stress and pain in fibromyalgia include deconditioning and sleep disturbance, which are common experiences in fibromyalgia, as well as biochemical feedback loops, such as the peroxynitrite cycle, which involves increasing synthesis of nitric oxide or superoxide in response to stressors in fibromyalgia [54,55].

However, although chronic stress and depression are related by HPA axis dysfunction, chronic stress is not identical to depression, as there are slight biological differences between the two. For example, the presence of ghrelin may protect against the depressive symptoms associated with chronic stress [56]. Therefore, to completely understand the relationship between stress and fibromyalgia, it is necessary to characterize the relationship between depression and fibromyalgia.

Are depression & fibromyalgia related?

Depression is a common comorbidity in patients with fibromyalgia; patients with fibromyalgia have a 30% likelihood of having comorbid major depression at diagnosis, and a 74% lifetime risk of depression [57]. There are several similarities between the two disorders; psychological stressors may trigger episodes of either condition, and there are several symptoms common to both disorders (Figure 4) [3,58–60].

Certain personality traits associated with the development of fibromyalgia are also associated with depression. For example, depressed patients often exhibit high harm avoidance and low self-directedness, in a similar pattern to certain groups of fibromyalgia patients [61]. Similarly, neuroticism, which is a common observation in patients with fibromyalgia, also lends susceptibility to the development of depression [62].

Additionally, psychotherapy is employed in the management of both disorders. A study of mindfulness-based stress reduction in fibromyalgia found that the technique increased participants' ability to cope with the symptoms of fibromyalgia, as well as improving quality of life and decreasing pain severity [63]. The importance of this finding was reinforced by the retention of these improvements upon 3-year follow-up of participants. The fact that stress reduction techniques are often employed in fibromyalgia management is important, as it further underscores the pathological role of the stress system in fibromyalgia. However, it also further solidifies the relationship between fibromyalgia and depression, as depression may also be effectively managed with mindfulness-based stress reduction [64].

Finally, antidepressants are also used in the management of both conditions. Tricyclic antidepressants and serotonin–noradrenaline reuptake inhibitors have been shown to effectively reduce symptoms in both fibromyalgia and depression, suggesting at least one shared pathophysiological pathway between the two disorders [65,66].

Although the relationship between depression and fibromyalgia is consistently proven, the temporality of this association remains contentious. There are three primary models that seek to elucidate the relationship between depression and diseases involving chronic pain, such as fibromyalgia. These models are the 'antecedent' hypothesis, the 'consequence' hypothesis, and the 'scar' hypothesis (Figure 5) [67].

The 'antecedent' model suggests that depression predisposes a patient to fibromyalgia, and the 'consequence' model suggests that depression is triggered by fibromyalgia. The 'scar' hypothesis, combined with theoretical input by Magni *et al.*, suggests that some people are predisposed to both depression and pain via a similar pathogenic pathway [67,68].

There is substantial evidence that depression may either precede or succeed fibromyalgia, thus diminishing the validity of the mutually exclusive 'antecedent' and 'consequence' hypotheses [67]. Additionally, a twin study by Kato *et al.* indicated that an unknown genetic trait predisposes to both major depressive disorder and CWP, which is a characteristic of fibromyalgia [69].

The pathophysiological model of CWP set out by Kato *et al.*, derived from a study of 31,318 twins, suggests that there are two traits that predispose to CWP (L1 and L2) [69] (Figure 6).

Kato *et al.* noted that the first trait was associated with affective processing of pain, and the second was associated with sensory processing of pain. The former trait was strongly correlated with depression, whereas the latter was not linked to depression (Figure 6) [69].

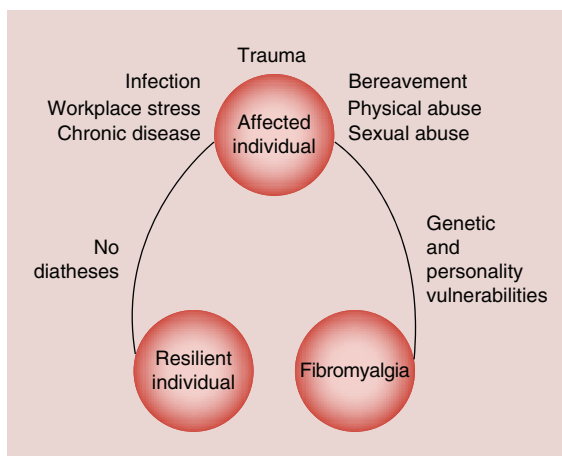


Figure 3. Stressors affect an individual, who may then develop fibromyalgia if genetic or personality vulnerabilities (diatheses) are present.

It is likely that L2 involves the abnormal function of pain modulators, such as a diminished diffuse noxious inhibitory control effect, which has been observed in patients with CWP and is not altered in depression [70]. As noted previously, patients with fibromyalgia have a 74% lifetime risk of depression. Therefore, it is possible that biological aberrations in these pain modulation systems are primarily responsible for the remaining 26% of patients who never experience depression.

With regards to L1, Kato *et al.* hypothesized that this system could be related to abnormal serotonergic gene function, which could be a vulnerability trait for both depression and fibromyalgia [69].

However, another related biologic factor linking depression and fibromyalgia is HPA axis dysfunction. As noted above, HPA dysfunction is frequently recorded in fibromyalgia and stress and fibromyalgia are often inextricably linked. These patterns are similarly observed in depression, which is also often associated with HPA axis dysfunction [6].

As per chronic stress and fibromyalgia, the precise nature of the HPA axis aberration in depression remains controversial, with some studies reporting HPA axis hyperactivity in depression and other studies observing HPA axis hypoactivity [6].

Relationship between the HPA axis & depression

HPA axis hyperactivity in depressed patients has been observed as hypercortisolemia and as diminished feedback inhibition on dexamethasone suppression tests [71–73]. Additionally, one study by van Rossum *et al.* found that polymorphisms of the glucocorticoid receptor (GR) resulting in HPA axis hyperactivity induce susceptibility to depression [74]. These findings com-

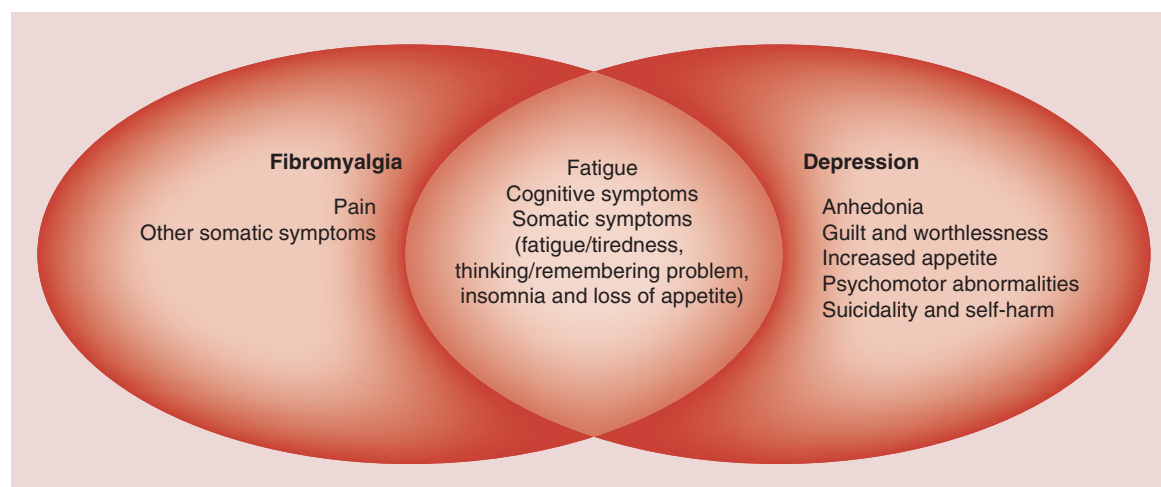


Figure 4. Several symptoms are common to the diagnoses of fibromyalgia, as outlined by the ACR, and depression, as outlined by the Diagnostic and Statistical Manual of Diseases.

Data taken from [59,60].

bine to suggest that depression is characterized by over-activity of the HPA axis.

However, the same study by van Rossum *et al.* similarly found that different GR polymorphisms resulting in HPA axis hypoactivity also induce susceptibility to depression [74]. Additionally, depressed patients have been observed to be deficient of corticotrophin-releasing hormone, and depression is a symptom of Addison's disease, which is a syndrome that is characterized by an underproduction of corticosteroids [6,75–76]. These findings suggest that depression is related to HPA axis underactivity, which contradicts the findings in the previous paragraph.

A meta-analysis of studies regarding the HPA axis in depression concluded that depression is associated with HPA axis hyperactivity, although the extent to

which this occurs depends on the associated depression subtype [77]. Hypercortisolemia and abnormal non-suppression of adrenocorticotrophic hormone and corticotrophin-releasing hormone are all consistent with HPA axis hyperactivity, and have been associated with melancholic depression [78,79]. Increased plasma cortisol and adrenocorticotrophic hormone levels have also been observed in psychotic depression, a subtype of depression that is particularly notable for its response to mifepristone (GR antagonist) therapy [80,81].

On the other hand, Gold and Chrousos have demonstrated HPA axis hypoactivity in atypical depression, and have additionally modelled an underactive HPA axis in seasonal affective disorder [6]. Clearly, the various subtypes of depression are differentially associated with the HPA axis, and certain depression phenotypes align to certain derangements of the stress system. This pattern is similar to the heterogeneous relationship observed between the HPA axis and fibromyalgia.

It is important to note, at this stage, that another explanation for the inconsistent relationship of the HPA axis with fibromyalgia and depression has been postulated by van Houdenhove *et al.* In this hypothesis, a 'switch' occurs in the pathogenesis of fibromyalgia and depression, shifting from HPA axis hyperactivity in the earlier stages of the disease, to HPA axis hypoactivity in the later stages of the disease [82]. Although this hypothesis is different to our presented hypothesis of different HPA axis abnormalities aligning with different depressive subtypes, the two theories are not mutually exclusive. It is theoretically possible for depression and fibromyalgia to develop from one subtype to another, depending on the balance of biochemical anomalies present in the patient. Similarly, the fact that not all patients evidence a 'switch' from

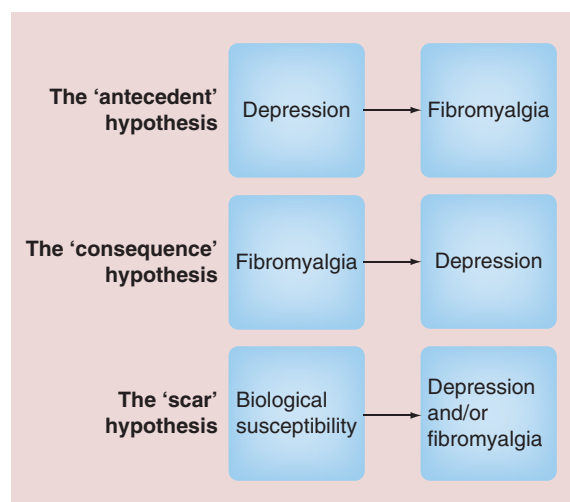


Figure 5. Models describing hypothetical relationships between depression and fibromyalgia.

Data taken from [67].

HPA axis hyperactivity to hypoactivity suggests the existence of multiple subtypes, within the two syndromes.

Does depression fit into our understanding of stress & fibromyalgia?

As detailed above, an underactive HPA axis may be associated with fibromyalgia, depression and chronic stress. In accordance with the model of stress outlined in this review, an underactive HPA axis would result in reduced activity of the locus coeruleus noradrenergic system and the amygdala, and disinhibition of the prefrontal cortex [6]. Anhedonia, a key symptom of depression, is associated with underactivity of the amygdala, and overactivity of the prefrontal cortex, which lends consistency to the depression in this model of stress and pain [83].

Importantly, two studies have found that depressive symptoms in fibromyalgia patients are particularly associated with reduced cortisol release [84,85]. This suggests that hypocortisolaemia, and therefore, an underactive HPA axis, is common when both conditions co-occur.

Moreover, the pathophysiological model developed by Kato *et al.* outlined previously associated depression and fibromyalgia with generalized anxiety disorder, irritable bowel syndrome, and chronic fatigue, suggesting that they were all related by an unknown pathophysiological abnormality [69]. All of these conditions have been associated with stress and HPA axis hypofunction, further emphasising the connection between depression, fibromyalgia and HPA axis hypofunction [86,87]. Importantly, chronic fatigue syndrome is strikingly similar to both fibromyalgia and depression, including a shared propensity towards HPA axis hypoactivity, abnormal serotonergic gene function, and abnormal personality traits, including high harm avoidance and neuroticism [69,87–89]. Although full discussion of this relationship is beyond the scope of this review, it is an important consideration in the management of functional somatic syndromes.

Significantly, a study by Ross *et al.* evaluated the depressive subtypes of fibromyalgia patients with depression, and found that atypical depression was more common than melancholic depression amongst patients with fibromyalgia [90]. As noted above, both atypical depression and fibromyalgia are connected by their shared association with HPA axis hypoactivity, which could explain the reason why atypical depression was reported more frequently in fibromyalgia. This finding is important, as it illustrates the significance of drawing relationships between fibromyalgia, stress and depression, as the biological model may help to explain phenotypic observations of the diseases.

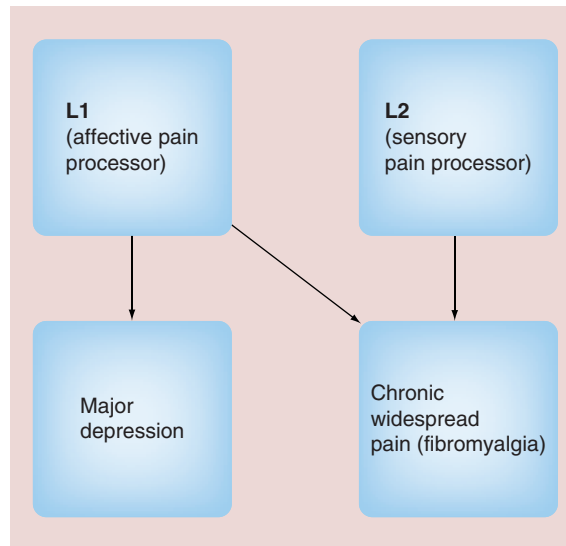


Figure 6. A shared trait vulnerability may lend susceptibility to both depression and fibromyalgia.

Data taken from [68].

It may be tempting, at this stage, to theorize that fibromyalgia may be related to any disease associated with psychosocial stress through dysfunction of the HPA axis. However, a study of the HPA axis in psychopathology found that GR dysfunction was much more marked in major depressive disorder, compared with bipolar mania, post-traumatic stress disorder, panic and schizophrenia. This suggests that HPA axis dysfunction in depression is not just an epiphenomenon due to the experience of psychological stress, but rather, that HPA axis aberrances form part of the pathophysiology of the disease [91].

Conclusion: implications of the relationship between fibromyalgia, stress & depression

Understanding the relationship between fibromyalgia, stress and depression has important clinical and scientific consequences. Importantly, the knowledge that fibromyalgia and depression are syndromes leads to the understanding that categorising the two disorders into clinical subtypes may reveal specific associations between them. This observation remains true in reverse; forming a clinical phenotype based on the presence of shared biological stress pathways between fibromyalgia and depression may lead to better clinical management of the co-morbid conditions.

Characterizing the role of the stress system in fibromyalgia may lead to a more targeted approach to treatment. Gabapentin, an $\alpha 2\delta$ ligand used to manage pain in fibromyalgia, is known to act on the locus coeruleus, and a mouse study indicates that it can alleviate neuropathic pain by increasing noradrenergic activity in descending pain pathways [92,93]. As such, the identifi-

cation of a fibromyalgia disease phenotype corresponding with diminished locus coeruleus activity may assist in identifying appropriate clinical guidelines for the use of Gabapentin.

Tricyclic antidepressants (TCAs), used to treat both fibromyalgia and depression, are known to increase GR activity [94,95]. Again, the identification of a fibromyalgia–depression phenotype associated with abnormal HPA axis function may help guide the clinician in the use of TCAs in the management of fibromyalgia. It should be noted, however, that these studies regarding the effect of TCAs on GRs were conducted in rodents. As such, further research is required to determine an adequate dosing regimen to induce a clinically significant increase of GR activity in fibromyalgia.

Importantly, it is important to note that pain induced by activation of stress responses, as outlined in this review, is a separate pathophysiological process to pain pathways that are unrelated to depression and stress. An example of such a pathway is the diffuse noxious inhibitory control pathway, dysfunction of which, as noted above, has no relationship to depression, but is highly related to fibromyalgia. This is clinically relevant, as it provides a distinction between depressed patients who may have locus coeruleus associated pain, and fibromyalgia patients, who may have a combination of locus coeruleus-associated pain alongside pain caused by other pathophysiological pathways. This distinction is helpful for clinicians, as it may help guide treatment of two illnesses that frequently have overlapping symptoms.

Significantly, this distinction is also helpful for patients with fibromyalgia. The understanding of the relationship between fibromyalgia and depression elucidates one of the causes of pain in patients with a chronic pain condition associated with stress. It has been reported that patients with chronic musculoskeletal pain feel stigmatized when the origin of that pain is unknown [96,97]. In particular, fibromyalgia patients frequently believe that they are stigmatized by medical professionals, especially if physicians view their disease as a form of depression, rather than a clinical phenomenon in its own right [98]. Therefore, this distinction between pain associated with stress, depression and fibromyalgia, and pain uniquely associated with fibromyalgia, may assist in alleviating feelings of inadequacy in patients with fibromyalgia.

Future perspective

As noted previously, further work delineating fibromyalgia phenotypes that correspond to biological aberrations in the human stress system may assist in the appropriate management of fibromyalgia patients. In particular, the association of certain fibromyalgia phenotypes with biological systems known to be risk factors for depression may assist in pre-emptive management and appropriate education of patients. The importance of recognising fibromyalgia, stress and depression as heterogeneous constructs may shape future studies, allowing for more accurate scientific research into the phenomena.

Executive summary

- ‘Stress’ describes any factor that poses a challenge to homeostasis.
- Stress and pain modulation systems are centrally connected.
- Many stressful triggers are associated with fibromyalgia.
- The pathogenesis of fibromyalgia may be conceptualized by a diathesis–stress model.
- Fibromyalgia often co-occurs with depression.
- Fibromyalgia, stress and depression may all be associated with a hypoactive hypothalamic–pituitary–adrenal axis.
- The variable association of fibromyalgia, stress and depression with each other and hypothalamic–pituitary–adrenal axis abnormalities reflects the heterogeneous nature of the phenomena.
- Approaching fibromyalgia as a heterogeneous syndrome may help to better characterize relationships between fibromyalgia, stress and depression, and may inform more targeted clinical management.

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The relationship between fibromyalgia, stress and depression

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					
1. Which of the following stressful events may promote fibromyalgia?					
☐ A Motor vehicle crash					
☐ B Chronic disease such as rheumatoid arthritis					
☐ C History of sexual abuse					
☐ D All of the above					
2. Which of the following psychological traits is most associated with fibromyalgia?					
☐ A Borderline personality					
☐ B Schizoid personality					
☐ C Neuroticism					
☐ D Malingering					
3. Which of the following statements regarding the effects of stress, depression, and fibromyalgia on the hypothalamic–pituitary–adrenal (HPA) axis is most accurate?					
☐ A Depression in and of itself usually suppresses the HPA axis					
☐ B Chronic stress has been associated with HPA hyperactivity and hypoactivity					
☐ C Comorbid fibromyalgia enhances the hypercortisolemia common in depression					
☐ D Fibromyalgia has no intrinsic effect on HPA function					
4. Which of the following statements regarding the relationship between fibromyalgia and depression is most accurate?					
☐ A Depression coexists with fibromyalgia in 30% of fibromyalgia cases					
☐ B Low harm avoidance and high self-directedness characterize both fibromyalgia and depression					
☐ C Research clearly demonstrates that depression invariably follows the diagnosis of fibromyalgia but does not precede it					
☐ D Antidepressants may alleviate depression but not fibromyalgia					