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Neuroendocrine and Immune Contributors to Fatigue

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Abstract

Central fatigue, a persistent and subjective sense of tiredness, generally correlates poorly with traditional markers of disease. It is frequently associated with psychosocial factors, such as depression, sleep disorder, anxiety, and coping style, which suggest that dysregulation of the body's stress systems may serve as an underlying mechanism in the maintenance of chronic fatigue (CF). This article addresses the endocrine, neural, and immune factors that contribute to fatigue and describes research regarding the role of these factors in chronic fatigue syndrome as a model for addressing the biology of CF. In general, hypoactivity of the hypothalamic-pituitary-adrenal axis, autonomic nervous system alterations characterized by sympathetic overactivity and low vagal tone, as well as immune abnormalities, may contribute to the expression of CF. Noninvasive methods for evaluating endocrine, neural, and immune function are also discussed. Simultaneous evaluation of neuroendocrine and immune systems with noninvasive techniques will help elucidate the underlying interactions of these systems, their role in disease susceptibility, and progression of stress-related disorders.

INTRODUCTION

Fatigue comes in various forms. Acute fatigue is a normal, protective mechanism in healthy individuals, is usually linked to a single cause, and is often relieved by rest or life-style change

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(ie, diet, exercise, rest, stress management). Rarely is it associated with long-term cognitive dysfunction, a state that most often returns to baseline after rest and recovery. However, chronic fatigue (CF) is considered maladaptive or pathologic, lasts 6 months or more, adversely affects physical and mental function, and may have multiple and unknown causes. Generally, no relief is gained from usual restorative measures aimed at relieving fatigue [1]. CF is especially apparent in individuals with chronic disease, such as autoimmune diseases (rheumatoid arthritis [RA], multiple sclerosis, systemic lupus erythematosus [SLE]), psychiatric disorders (major depressive disorder [MDD]); neurologic disorders, eg, stroke; cancer (during and after treatment); and idiopathic chronic multisymptom illnesses, eg, chronic fatigue syndrome [CFS] and fibromyalgia (reviewed in [2]). Peripheral fatigue is observed in chronic diseases associated with muscle wasting and inflammation or joint abnormalities, as often occurs in RA and SLE, myasthenia gravis, and cardiorespiratory diseases. Peripheral fatigue can be attributed to organ-system dysfunction and usually is not associated with cognitive loss.

Central fatigue generally correlates poorly with traditional markers of disease [2] and is frequently associated with other psychosocial factors, such as depression, sleep disorder, anxiety, and coping styles [3,4], which suggests that dysregulation of the body's stress systems may serve as an underlying mechanism of CF. Indeed, there appears to be an intricate interplay between the neural, endocrine, and immune systems in regulating the body's response to stress and the maintenance of homeostasis.

CROSS TALK AMONG NEURAL, ENDOCRINE, AND IMMUNE STRESS SYSTEMS

That the nervous and immune systems communicate with each other in a bidirectional manner is well established (reviewed in [5-12]). There are 2 main pathways by which psychogenic stress is relayed from the brain to the body: (1) via the hypothalamic-pituitary-adrenal (HPA) axis with the resultant release of glucocorticoids (cortisol in humans and primates; corticosterone in rodents) and (2) via the sympathetic nervous system (SNS), with the resultant release of catecholamines (noradrenaline and adrenaline). These neuroendocrine stress systems coordinate the response of many other physiologic systems to a stressor, including the immune and cardiovascular systems, as well as energy production and/or utilization and behavior, therefore, bringing the physiologic systems back to homeostasis [13].

However, maintenance of homeostasis during an immune challenge involves activation of the immune system, resolution of the challenge, and protection of the host against potentially detrimental inflammatory processes. Relevant to the latter, interleukins (IL) and/or cytokines (tumor necrosis factor [TNF]-α, IL-1, and IL-6 in particular) activate the same stress pathways to coordinate an appropriate immune response [5,6,12]. Cytokine receptors have been detected at all levels of the HPA axis, and, therefore, each level can serve as an integration point for immune and neuroendocrine signals [5]. In turn, glucocorticoids negatively feedback onto immune cells to suppress the further synthesis and release of innate proinflammatory molecules. Glucocorticoids also shape immunity by influencing immune cell trafficking to sites of inflammation and alter downstream adaptive immune responses by causing a shift from cellular (Th1 inflammatory) to humoral (Th2 anti-inflammatory) type immune responses [14,15]. Therefore, in contrast to the traditional view of glucocorticoids as immunosuppressant hormones, a more accurate view is that they are immunomodulatory hormones that stimulate as well as suppress immune function, depending on glucocorticoid concentration, type of immune response, immune compartment, and cell type. Glucocorticoids also play an important role in the regulation of the SNS. In addition to subserving permissive effects on relevant synthetic enzymes and receptors for catecholamines, endogenous glucocorticoids restrain SNS responses under resting conditions and after stress [16].

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In addition to HPA axis-immune interactions, there is strong evidence for interactions between the immune system and the autonomic nervous system (ANS) (SNS and parasympathetic nervous system [PNS] pathways) and peripheral nerves. Whereas, circulating hormones, such as glucocorticoids, regulate immunity at a systemic level, neural pathways regulate immunity at a local and regional level. The SNS and peripheral nervous system innervate immune organs, where sympathetic influences can be both pro- and anti-inflammatory, depending on the type of adrenergic receptor to which the catecholamine binds [8,9]. Neuropeptides released from peripheral nerves, such as substance P, tend to be proinflammatory [7]. Locally released norepinephrine or circulating epinephrine also affect lymphocyte trafficking, proliferation, function, and cytokine production. With regard to the peripheral nervous system, both afferent and efferent parasympathetic activities have been shown to be immunomodulatory. Whereas, afferent vagal fibers express IL-1 receptors on paraganglia cells situated in parasympathetic ganglia [12], efferent vagal fibers have been shown to exert anti-inflammatory action via the release of acetylcholine [10,11]. Therefore, the vagus nerve also serves as a source of negative feedback on the immune system, with the brain being an integral relay station.

Dysregulation of any of these stress systems can lead to dysregulation of multiple physiological and behavioral systems, which leads to a maladaptive response to stress [13-17]. Indeed, dysregulation of neural-immune interactions is described in many stress-related disorders, including inflammatory, autoimmune, metabolic, and cardiovascular disease, as well as psychiatric and somatic disorders.

The capacity of proinflammatory cytokines to cause changes in behavior, including symptoms of fatigue, psychomotor retardation, anorexia, anhedonia, hyperalgesia, somnolence, lethargy, muscle aches, cognitive dysfunction, and depressed mood, has led to the suggestion that proinflammatory cytokines may contribute to the behavioral features of depression [18,19] as well as somatic disorders, such as CFS and fibromyalgia [20].

The first indication that inflammation may induce psychosomatic symptoms came from research about depression. There is a strong similarity between neurovegetative symptoms (anorexia, sleep disturbance, psychomotor retardation, fatigue, and pain) of depression and inflammation-induced sickness behavior [21]. Indeed, cytokine-based immunotherapy (interferon [IFN]-α) induces 2 distinct behavioral syndromes: a neurovegetative syndrome, which appears early, persists, and is minimally responsive to classical antidepressants; and a mood-cognitive syndrome, characterized by depressed mood, anxiety, and cognitive dysfunction, which appears later and is responsive to classic antidepressants (ie, selective serotonin reuptake inhibitors [SSRIs]) [22]. Moreover, differential clustering of mood-cognitive and neurovegetative syndromes is observed in patients with cancer. Indeed, cancer-related fatigue does not respond well to antidepressants, which suggests that it is not exclusively a mood or behavioral problem. [23]. Of note, cancer-related fatigue has also been associated with elevated inflammatory biomarkers and impaired HPA axis function [24,25].

It appears that these 2 categories of symptoms are mediated by different biological mechanisms. For example, dopaminergic pathways may play a more prominent role relative to other monoamine neurotransmitters (serotonin, norepinephrine) in the neurovegetative subset [3, 22]. In support of this notion, Meeusen et al [26] proposed a central fatigue hypothesis and suggested that an increase in the brain ratio of serotonin to dopamine is associated with feelings of tiredness and lethargy, which accelerates the onset of fatigue, whereas, increased dopamine levels favor improved performance through the maintenance of motivation and arousal.

Given the role of corticotropin-releasing hormone (CRH) in behavioral and HPA-axis activation, it has been hypothesized that defective central CRH synthesis and/or release may also contribute to symptoms of fatigue [27]. Indeed, abnormal central CRH pathways have

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been detected in various chronic disease states with a fatigue component, including SLE, multiple sclerosis, RA, fibromyalgia, and CFS [2,27]. Moreover, both psychogenic and immune stressors can induce similar neuroendocrine and neurotransmitter changes in the brain, therefore, sensitizing the brain to subsequent stressors, and, hence, inducing a state of increased stress vulnerability as seen in various psychiatric and psychosomatic disorders [28].

In the next section, we discuss how hypoactivity of the HPA axis, ANS alterations characterized by sympathetic over-activity and low vagal tone, as well as immune abnormalities, may play a role in CFS.

BIOLOGICAL CORRELATES OF FATIGUE: DYSREGULATION OF STRESS SYSTEMS EXEMPLIFIED BY CFS

A diagnosis of CFS requires that an individual displays severe CF for more than 6 months without a defined cause (with all other medical conditions being excluded), as well as the presence of 4 of the following 8 symptoms: myalgia, arthralgia, sore throat, tender nodes, cognitive difficulty, headache, postexertional malaise, or sleep disturbance [29]. (See Clauw later in this supplement.)

HPA Axis

A substantial body of research on the pathophysiology of CFS has focused on dysregulation of the neuroendocrine systems. The HPA axis is the key neuroendocrine system that adapts the organism to various challenges, including emotional, physical, chemical, and immune stressors. These stressors have been associated with risks for developing CF. The secretion of glucocorticoids from the adrenal cortex results in multiple metabolic, behavioral, and immune regulatory responses that help the organism adapt to such challenges. Dysregulation of these regulatory functions may be causally associated with symptoms of CFS. Thus, insufficient glucocorticoid signaling has been associated with increased immune activation and inflammatory responses, potentially promoting symptoms of fatigue, malaise, somnolence, myalgia, and arthralgia (reviewed in [13,17]).

Dysfunction of the HPA axis, characterized by lower than normal cortisol secretion, is one of the hallmark biological features of CFS, although the literature is somewhat inconsistent. Poteliakhoff [30] first described attenuated basal plasma cortisol levels in patients with CFS. After these initial observations, Demitrack et al [31] reported lower than normal cortisol excretion in patients with CFS. Results of several subsequent studies confirmed lower than normal cortisol levels in plasma or saliva [32-39], flattened cortisol diurnal secretion [38-40], and decreased urinary free cortisol secretion in patients with CFS [41-44].

However, results of a substantial number of studies failed to identify hypocortisolism in CFS (eg, reviewed in [45-46]). Similarly, results of an array of endocrine challenge studies revealed signs of hypocortisolism in CFS, including enhanced negative feedback inhibition of the pituitary [47-50] or mild adrenal insufficiency [31,51], although results are inconsistent [45, 46]. Results of a recent study found decreased glucocorticoid sensitivity of immune cells in persistently fatigued adolescent females [52], which suggests decreased cortisol signaling, consistent with the idea of a lack of cortisol effects contributing to CFS. However, in vitro studies on glucocorticoid sensitivity are also inconsistent [53]. Of note, glucocorticoid sensitivity was shown to be regulated in a tissue- and cell-specific manner (reviewed in [6]).

There may be important subgroups of patients with CFS, depending on etiologic pathways or clinical features. Heim et al [54], for example, demonstrated, in a population-based sample, that only those patients with CFS who reported childhood traumatic experiences exhibited low cortisol levels compared with well controls, whereas patients with CFS and without a history

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of severely stressful circumstances had normal cortisol levels. Thus, it is plausible that several of the neuroendocrine features of CFS covary with risk factors other than illness state and reflect a vulnerability to develop CFS in response to challenge [54]. Of note, hypocortisolism, as reported in patients with CFS, has been observed in animal models of early life stress (reviewed in [55]). Thus, CFS could be conceptualized as a disorder of adaptation that is promoted by developmental risk factors.

Some researchers have suggested that hypocortisolism in CFS might be a consequence of having the disorder, because low cortisol secretion has been associated with illness features, for example, inactivity [56]. In addition, the stress of symptoms themselves, such as fatigue, sleep and mood disturbances, and pain, can contribute to the further dysregulation of biological stress pathways, which lead to a positive feed-forward cascade. Whether or not hypocortisolism is a cause or a consequence of CFS remains to be evaluated in longitudinal studies. Perhaps it is both.

ANS

A number of studies examined the involvement of the ANS in the pathophysiology of CFS. The rationale for these studies is based on the observation that several symptoms of CFS, namely fatigue, dizziness, diminished concentration, tremulousness, and nausea, could be explained by autonomic dysfunction. In addition to the neuroendocrine system, the ANS is another key regulation system that adapts the organism to challenge. Thus, autonomic dysregulation could further trigger symptoms of CFS in response to challenges that disturb homeostasis.

Initial studies found an increased prevalence of neurally mediated hypotension and orthostatic intolerance in patients with CFS, measured by using a prolonged standing or a head-up tilt table test [57-64]. However, results of several studies failed to find differences between CFS and control groups regarding dysautonomia [65-68].

Another line of research in the study of ANS alterations in CFS has focused on cardiovascular autonomic measures. Results of most studies found increased heart rate measures in CFS, both at rest and in response to challenge [65,69-74]. Increased heart rate and/or reduced heart rate variability (HRV) is in accordance with other studies that reported low vagal tone [69,75-77] or general sympathetic overactivity [62,78-80], although inconsistent results exist (reviewed in [46]). Whether or not there are subgroups with CFS and altered autonomic function based on etiologic factors or illness features is unknown. Sympathetic overactivation, in concert with low glucocorticoid signaling, may contribute to an overactive immune system, particularly in response to challenge, which may lead to symptoms of CFS.

Immune System

Many findings suggest that infectious agents (viral and bacterial infections) and immunologic dysfunction (eg, inappropriate production of pro- and anti-inflammatory cytokines) may play a role in the pathophysiology of at least some cases of patients with CFS (reviewed in [81-83]). Indeed, persistent postinfection fatigue has been well documented [84]. Results of early studies showed that many individuals with CFS had evidence of enhanced antibody responses to Epstein-Barr virus (EBV). However, subsequent reports showed that many patients with CFS lacked evidence of EBV reactivity, although they displayed elevated antibody titers to a number of other viral agents. Interestingly, acute viral infection studies found that initial infection severity was the single best predictor of persistent fatigue [85]. Taken together, results of these studies suggest that, although some cases of CFS may be triggered by an infectious agent, the chronic symptoms of this syndrome are unlikely to be caused by an active infection.

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Results of other studies indicated signs of immune disturbance in patients with CFS, especially in the form of elevated proinflammatory cytokine levels [86,87], such as IL-6 and TNFα in serum and cerebrospinal fluid [88,89]. Consistent with these findings, increased in vitro inflammatory cytokine release has been reported in stimulated peripheral blood mononuclear cells of patients with CFS [90]. Other indices of cytokine-mediated immune alterations that have been reported in patients with CFS include increased levels of auto-antibodies, decreased natural killer cell activity, high levels of type 2 cytokine–producing cells, activated T lymphocytes, CD19+ B cells, neopterin (a marker of activated cell-mediated immunity), and activated complement [91-94]. In addition, alterations in the expression of genes involved in immunity have been detected [95]. However, despite multiple indications of immune system activation in CFS, the best-replicated immunologic findings in this disorder are suppression of several immune functions, especially natural killer cell activity and mitogen-induced lymphocyte proliferation [94-96]. Nonetheless, these multiple findings need to be interpreted in light of a meta-analysis [81] that found no evidence for clear immune abnormalities in CFS.

Interestingly, results of a recent and robustly designed study by Raison et al [97] showed that fatigue not only in its severe and chronic form, as in CFS, but also in its milder forms, is associated with increased inflammation, as indexed by elevated plasma C-reactive protein levels and white blood cell count, even after adjusting for depressive status. This study further supports the notion that the symptom of fatigue, rather than a diagnosis of CFS itself, may be what is clinically associated with inflammation. In addition, childhood traumatic experiences appear to be an important risk factor for a hypocortisolemic profile in CFS [54], and adults with a history of childhood trauma exhibit elevated markers of inflammation, even in the absence of depression [98]. Moreover, patients with depression and childhood trauma show even higher levels of inflammation than with either risk factor alone [98,99]. Whether immune status is different in patients with CFS, with or without a history of childhood trauma, remains to be determined.

In summary, chronic (pathologic) fatigue can be attributed to hypoactivity of the HPA axis; ANS alterations characterized by sympathetic overactivity and low vagal tone; and immune abnormalities, including reduced cellular responses and enhanced inflammation and humoral responses. CFS is an exemplar, but not the only example, of fatigue conditions, with these associations. Disparate findings among various studies may be because of (1) differences in methodology, recruitment, and analysis; (2) comorbidities, including depression and/or other chronic diseases; (3) lack of an epidemiologically comparable control group; and (4) biological changes not present in all cases of a heterogeneous disorder, such as CFS, but rather related to particular symptoms or risk factors of the disorder. The latter indicates the importance of grouping by symptom subtypes rather than an arbitrarily defined disorder. Indeed, different symptom categories of CFS may be mediated by different biological mechanisms, as seen in cytokine-induced depressive symptomatology [22]. To help elucidate a “molecular signature” for clinical sub-types within a heterogeneous disorder, noninvasive methods for evaluating neural, endocrine, and immune function are available without causing further pain or distress, which could confound outcome measures of interest.

NONINVASIVE METHODOLOGIES TO EVALUATE STRESS SYSTEMS

Measurement of hormones, cytokines, and neuroactive substances has frequently posed a problem for clinicians and investigators because of the need to perform invasive tests, such as drawing blood. Noninvasive and ambulatory methodologies of neural, endocrine, and immune biomarker collection can overcome several limitations intrinsic to invasive methods, reducing the stress triggered by collection of samples and allowing a wider application to community-based settings. Collection of sweat and saliva and measurement of HRV are noninvasive methods that can be applied to evaluate neuroimmune interactions. Ultimately, simultaneous

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evaluation of neural and immune systems with noninvasive techniques will help elucidate the underlying interactions of these systems and their role in disease susceptibility and progression of stress-related disorders.

HPA Axis: Salivary Cortisol

Because (1) the HPA axis is a self-regulated dynamic feedback system and (2) cortisol is secreted in a pulsatile fashion, single time-point measures of cortisol cannot be used to accurately interpret HPA axis function. An adequate assessment of HPA axis function requires multiple serial sampling (to test basal activity and circadian profiles) or dynamic testing by using pharmacologic or psychologic challenges (to test reactivity and/or feedback sensitivity). More recently, the salivary cortisol response to awakening has received considerable scientific attention and has been shown to be sensitive to detect HPA axis dysregulation related to stress and disease, including CFS [39,100]. When collected in the context of such sampling protocols, cortisol can be reliably measured in saliva as an index of HPA axis function [101].

The majority of circulating cortisol is bound to corticosteroid-binding globulin, which inactivates the biological actions of cortisol. Only the free fraction of cortisol is biologically active and can bind to glucocorticoid receptors to influence gene expression and protein synthesis. In saliva, only the free fraction of cortisol can be measured. Free cortisol measures in saliva reliably reflect the amount of free cortisol circulating in the blood stream [101]. In studies that focus on the actions of cortisol in target systems, it is advantageous to measure the free and biologically active fraction of cortisol. However, for studies that focus on assessment of total cortisol output of the adrenal gland or ratios of bound versus unbound cortisol and corticosteroid-binding globulin activity, blood measures are necessary. These differences must be considered when interpreting data from salivary cortisol studies.

ANS: Salivary *α*-Amylase and Heart Rate Variability

Because the transfer of norepinephrine from blood to saliva takes approximately 1 hour [102], which is too long for accurate assessment of stress-induced changes, salivary *α*-amylase (sAA), a digestive enzyme, has become an emerging biomarker for stress as an indicator of SNS activity. Both the sympathetic and parasympathetic branches of the ANS innervate the salivary glands, where SNS stimulation increases protein secretion and PNS stimulation increases salivary flow rate [103]. sAA has repeatedly been found to increase in response to physical stress or exercise, as well as psychological stress, and also correlates with plasma norepinephrine responses to those same stressors, although to a lesser extent to psychosocial stress (reviewed in [104]). sAA concentration can also serve as an index for pathologic dys-regulation of the ANS in specific clinical and subclinical conditions, such as anxiety and somatic disorders [104]. One important caveat of measuring sAA is that, in the presence of stress and SNS activation, the PNS is inhibited, which leads to reduced salivary flow rate, and hence, decreased saliva production. Therefore, stress-induced increases in sAA could be confounded with parallel decreases in salivary volume, thereby increasing sAA concentration.

Evaluation of the ANS can also be performed noninvasively through measurement of HRV. The heart is under tonic control by parasympathetic influences. Heart rate is characterized by beat-to-beat variability, which also implicates vagal dominance, because the sympathetic influence on the heart is too slow to produce rapid beat-to-beat variability. HRV is a term that describes variations of both instantaneous heart rate and the interval between consecutives beats. A prominent circadian variation in HRV, with significant increases during the night and decreases during the day, is observed in healthy individuals. Results of previous studies showed that this increase in nighttime HRV is blunted by acute stress and that decreased HRV is associated with increased overnight urinary cortisol and increased proinflammatory cytokines

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and acute-phase proteins [105]. Decreased HRV, indicative of reduced parasympathetic-vagal tone, is an independent risk factor for morbidity and mortality.

Neural and Immune Biomarker Profiles: Cutaneous Sweat Patch

Another noninvasive and nonstressful approach to evaluating neural and immune systems is through collection of sweat via a 24-hour cutaneous sweat patch. In our initial validation studies, we showed that immune biomarkers, such as proinflammatory cytokines, in sweat were tightly correlated with plasma levels in healthy women [106]. In addition, we have shown that a population of women with MDD in remission exhibited elevated sweat levels of proinflammatory cytokines, sympathetic neuropeptides (neuropeptide-Y), and pain-related neuropeptides (substance P, calcitonin gene–related peptide) but decreased parasympathetic (vasoactive intestinal peptide) neuropeptide levels relative to controls, which strongly correlated with plasma levels [107]. This pattern is consistent with a shift in MDD from parasympathetic to sympathetic tone and an underlying proinflammatory state that could account for enhanced susceptibility to conditions known to be comorbidly expressed with MDD, including cardiovascular disease, osteoporosis and diabetes. Moreover, biomarker levels strongly correlated with symptoms of depression and anxiety, which indicate functional significance of these biomarker profiles. A similar biomarker profile was reported in pain- and fatigue-related syndromes [2].

Ultimately, these noninvasive methodologies could provide a “molecular signature” for clinical subtypes within a heterogeneous disorder to be used for (1) diagnostic and prognostic purposes; (2) earlier intervention in asymptomatic conditions; (3) optimization of individualized treatment regimens; (4) patient monitoring in remote areas and in large-scale epidemiologic settings; (5) monitoring patients in whom invasive methodologies are unfeasible, especially vulnerable populations, including pregnant women, infants, children, and the elderly; and (6) to shed light on mechanisms that underlie individual vulnerability or resiliency to develop stress-related diseases and/or disorders.

CONCLUSION

In summary, CF states have been shown to be attributable to a dysregulation of stress systems, including hypoactivity of the HPA axis, ANS alterations characterized by sympathetic overactivity and low vagal tone, and immune abnormalities, such as reduced cellular responses and enhanced inflammation and humoral responses. Hypocortisolemia may develop through reduced synthesis or depletion of HPA-axis hormones, receptor downregulation, and/or increased negative feedback sensitivity [108]. Fries et al [108] proposed that the phenomenon of hypocortisolism may occur after a prolonged period of hyperactivity of the HPA axis because of chronic or traumatic stress, in which this “switch“ may prevent possible deleterious effects of excessive glucocorticoid exposure. CFS and related pain and fatigue disorders may then be interpreted as a maladaptive overadjustment, in which the HPA axis is then functioning at an alternate, more stress-sensitive steady state [109]. Interestingly, the consequences of insufficient glucocorticoid signaling, including hyperactive SNS activation and enhanced inflammation, result in similar deleterious effects to that of hyperactive glucocorticoid signaling, such as altered metabolic, cardiovascular, immune, neurologic, and behavioral functions [17], including the potentiation of fatigue and related symptoms. Given the complex nature of fatigue, with its many physiologic and behavioral risk factors and correlates, the most effective therapeutic strategy may require multimodal action. The simultaneous evaluation of a large array of neural, endocrine, and immune biomarkers, when using noninvasive methodologies, may help inform the design of more effective pharmacologic therapeutic interventions to be used along with nonpharmacologic interventions, such as cognitive-behavioral therapy. It may also inform clinicians of mechanisms by which these interventions

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act and how successful they are in altering the neuroendocrinologic and immunoregulatory aspects of fatigue.

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