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Named Series: Fatigue, Brain, Behavior, and Immunity

Fatigue, brain, behavior, and immunity: Summary of the 2012 Named Series on fatigue

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ABSTRACT

The focus on fatigue for the 2012 Named Series in brain, behavior, and immunity reflects the growing wave of research examining immune underpinnings of fatigue in healthy and clinical populations. Fatigue is prevalent in the general population and in patients with a variety of medical conditions. However, the etiology of fatigue remains elusive.

Psychoneuroimmunological approaches to fatigue have yielded important advances in our understanding of this complex symptom and are represented in the twelve articles included in the Named Series. These articles include animal and human models of fatigue and cross a variety of different medical conditions, including cancer, chronic fatigue syndrome, and diabetes. This review briefly summarizes the articles included in the series and highlights the themes that have emerged from this body of work.

The focus on fatigue for the 2012 Named Series in Brain, Behavior, and Immunity reflects the growing wave of research examining immune underpinnings of fatigue in healthy and clinical populations. Recent estimates indicate that up to 38% of community dwelling individuals and 42% of primary care patients experience significant fatigue (Fuhrer and Wessely, 1995; Pawlikowska et al., 1994; Ricci et al., 2007), and these rates are even higher among patients with inflammatory diseases such as rheumatoid arthritis (Wolfe et al., 1996) and multiple sclerosis (Heesen et al., 2006). Fatigue has a negative impact on emotional, social, and occupational functioning and causes serious disruption in overall quality of life. In the United States, workers with fatigue cost employers $136.4 billion annually in lost productivity (Ricci et al., 2007). Thus, fatigue is an important public health problem.

Psychoneuroimmunology has much to contribute to our understanding of fatigue. Basic research on neuro–immune interactions has demonstrated that peripheral pro-inflammatory cytokines can signal the central nervous system to initiate fatigue/reduced activity and other behavioral changes, collectively described as "sickness behavior" (Dantzer et al., 2008). Stimulated by these findings, investigators have become interested in the possibility that inflammatory signaling may contribute to fatigue experienced by patients with a variety of medical and psychiatric disorders as well as healthy individuals. The twelve articles included in the Fatigue Named Series reflect this translation of basic findings on inflammation and fatigue into clinical and applied settings. The series includes one animal model of fatigue and eleven studies focusing on humans. Five of these studies examined fatigue in cancer patients, three focused on chronic fatigue syndrome, one examined patients with type 1 and type 2 diabetes, one examined patients with acute infections, and one focused on a community sample. Together, these reports showcase the diverse contexts in which fatigue research is being conducted and highlight important new findings from this area of work. Here, we briefly review the articles included in the series and summarize the themes that emerged from this body of work. The range of factors considered as contributors to fatigue in the series is illustrated in Fig. 1.

York et al. examined the impact of low-dose ionizing radiation on mouse behavior and neuroimmunity as a model of radiation exposure that might occur during high-altitude commercial air flight, a nuclear reactor accident, or solar particle event (York et al., 2012). These investigators found that a single dose of gamma radiation led to increased expression of TNF-α in the hippocampus as early as 4 h post-irradiation. Reductions in locomotor activity (their behavioral measure of fatigue) were observed at 6 h post-irradiation. Examination of gene transcripts in whole blood showed increased expression of IL-1α at 6 h post irradiation and of IL-1β and IL-1RA at 8 h post irradiation; however, no changes in TNF expression in the blood were observed. Results from this study suggest that neuroimmune activation may underlie the early

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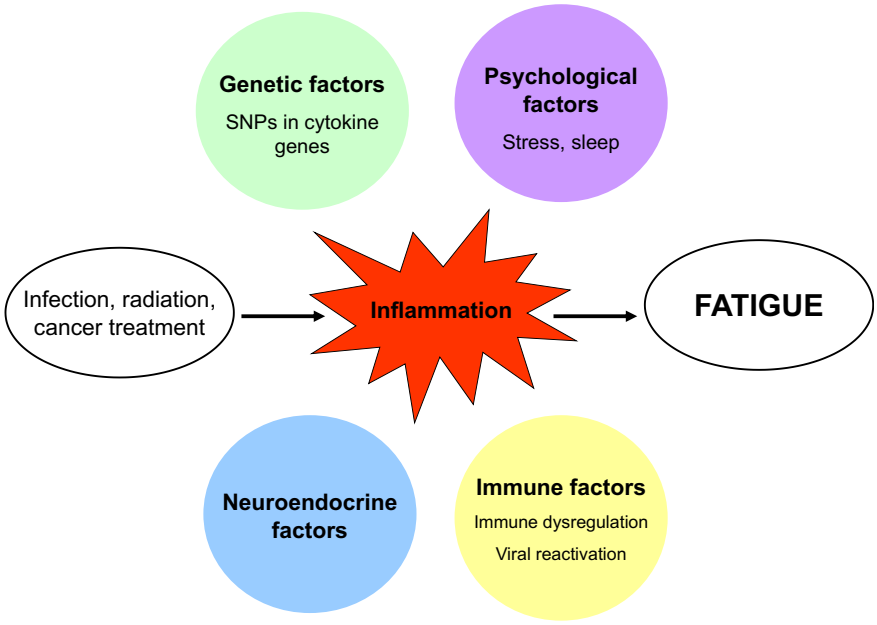

Fig. 1. This figure illustrates the range of factors considered by articles in the Named Series as potential contributors to fatigue. The basic model proposes that inflammation underlies symptoms of fatigue in various contexts. The trigger for inflammatory processes varies by context but may include acute infection, exposure to low dose ionizing radiation, and cancer/cancer treatments. Other factors that may influence inflammation, fatigue, and/or their association are indicated in circles and include genetic, psychological, neuroendocrine, and immune-related processes. Integrated models that span across these systems are important for advancing our understanding of this complex symptom.

emergence of fatigue-like symptoms following low-dose radiation exposure, although the mechanisms through which radiation triggers this response are not clear.

Cancer-related fatigue has emerged as a prominent model of inflammation-related fatigue, reflecting the high prevalence of this symptom in cancer patients and survivors and growing evidence that immune alterations may contribute to fatigue in this context (Bower and Lamkin, 2012). Cancer is also a compelling model because there is an identifiable trigger for the onset or worsening of fatigue symptoms, specifically the initiation of cancer treatment. The study by Wang et al. provides a nice example of this approach (Wang et al., 2012). These investigators assessed fatigue and other symptoms in 103 patients (38 women, 65 men) undergoing chemoradiation therapy for locally advanced colorectal or esophageal cancer. Participants provided blood samples and reported symptoms weekly during the 6 week course of treatment and over a 7 week follow-up. Fatigue increased during treatment, as did serum levels of the soluble TNF receptor type I (sTNF-RI) and IL-6. Moreover, sTNF-RI was correlated with fatigue severity controlling for potential confounds, including age, sex, BMI, and disease-related factors. These results support a role for over-expressed TNF in the development of fatigue during this intensive treatment, consistent with findings from other cancer patients (Bower et al., 2011; Wang et al., 2010).

Fatigue typically co-occurs with other behavioral symptoms in the context of cancer, including sleep disturbance. However, despite compelling evidence for bidirectional interactions between inflammatory processes and sleep in non-cancer populations (Irwin, 2002), few studies have examined associations among fatigue, sleep, and inflammation in cancer patients. Two of the studies in the Named Series probed these relationships using longitudinal study designs. Clevenger et al. examined the association between sleep disturbance, fatigue, and plasma IL-6 in 136 women with ovarian cancer prior to surgery and again at 1 year post-diagnosis among those who were disease-free and had completed their adjuvant treatment (n = 63) (Clevenger et al., 2012). At pre-surgery, higher levels of IL-6 were associated with fatigue and sleep disturbance, and there was some evidence that sleep disturbance partially mediated the association between IL-6 and fatigue. In addition, changes in IL-6 from pre-surgery to 1 year were positively correlated with changes in fatigue and in sleep disturbance.

Liu et al. examined relationships among fatigue, subjective and objective markers of sleep disturbance, and three inflammatory markers (IL-6, CRP, and IL-1RA) in 54 women undergoing chemotherapy for stage I–III breast cancer (Liu et al., 2012). There was an increase in IL-6 during chemotherapy that was positively associated with changes in fatigue and in subjective (though not objective) sleep disturbance. The association between IL-6 and fatigue remained significant controlling for sleep disturbance, suggesting that sleep does not mediate this relationship. Together, results from these studies support a role for inflammation in the emergence of cancer-related fatigue and are among the first to demonstrate a link between inflammation and subjective sleep problems in cancer patients. These studies are also notable for their examination of the complex interactions between fatigue, sleep, and inflammation, and specifically whether sleep disturbance mediates the association between inflammation and fatigue in this context.

In addition to research on cancer-related fatigue, the Named Series also highlighted emerging research on fatigue in another common disease, diabetes. Although fatigue is a common complaint in diabetes, affecting up to 60% of patients (Fritschi and Quinn, 2010), the etiology of fatigue in this context has not been determined. The study by Lasselin et al. is one of the first to examine the association between inflammation and fatigue in diabetic patients (Lasselin et al., 2012). These investigators examined symptoms of fatigue and inflammatory markers (CRP, IL-6, TNF-α, and neopterin) in 20 type 2 and 20 type 1 diabetic patients (8 women, 32 men). Patients with type 2 diabetes had higher levels of fatigue and inflammatory markers than patients with type 1 diabetes, and several of these markers (IL-6, CRP, and neopterin) were positively correlated with fatigue in type 2 diabetic patients. These findings offer preliminary evidence that low-grade inflammation may contribute to diabetes-related fatigue, similar to what has been shown in cancer.

The studies described thus far have primarily focused on documenting an association between circulating inflammatory markers and fatigue. Several of the papers included in the Named Series have broadened this focus to consider other factors that may influence inflammatory processes and fatigue, including genetic factors. Jim et al. examined the association between SNPs in three proinflammatory cytokine genes and symptoms of fatigue in 53 men with prostate cancer undergoing androgen deprivation therapy (Jim et al., 2012). Results showed that patients with variant alleles of *IL6*-174 and *TNFA* -308 were at greater risk for fatigue during treatment, extending findings of earlier studies conducted with cancer patients undergoing radiation therapy (Miaskowski et al., 2010; Aouizerat et al., 2009) and cancer survivors (Collado-Hidalgo et al., 2008; Rausch et al., 2010).

Piraino et al. (2012) took a somewhat different approach to investigate the association between cytokine genes, fatigue, and other dimensions of the acute sickness response among 296 individuals (145 women, 151 men) acutely infected with Epstein Barr Virus (EBV), Ross River Virus (RRV), or Q fever. Symptom domains were empirically derived from self-report symptom data and included fatigue, pain, neurocognitive difficulties, and mood disturbance. Results showed unique genetic correlates of fatigue and the other symptom domains. Specifically, in analyses controlling for age, sex, and type of infection, *IFNγ* + 874 was associated with increased fatigue, whereas *IL10*-592 and *IL6*-174 were associated with mood disturbance. Together, these studies support a role for inflammation-related genes in the etiology of fatigue in various contexts, and suggest that different dimensions of the behavioral response to sickness may have different genetic correlates.

Psychosocial and behavioral factors may also influence inflammatory processes and fatigue. Early life stress has emerged as a risk factor for inflammation in later life (Miller et al., 2011), as well as the development of fatigue (Heim et al., 2006), although few studies have examined the possibility that inflammation may mediate the stress–fatigue relationship. A study conducted by Cho et al. tested this hypothesis in a community sample of 2716 White and African–American individuals aged 33–45 (1484 women, 1232 men) (Cho et al., 2012). Results showed that retrospective reports of early life stress were associated with elevated fatigue at baseline and over a 5-year follow-up. However, this longitudinal association did not appear to be mediated by IL-6 or CRP in covariate adjusted models, suggesting that other pathways may play a more central role.

Whereas childhood stress may influence the development of fatigue in later life, the ability to effectively manage stress may buffer against fatigue symptoms. This hypothesis was investigated by Lattie et al. (2012) in a sample of 117 individuals with chronic fatigue syndrome enrolled in a stress management intervention (97 female, 20 male). At the baseline assessment (prior to treatment), higher perceived stress management skills were associated with lower levels of fatigue, consistent with predictions. Higher stress management skills were also associated with steeper diurnal cortisol slope and lower levels of IL-2, controlling for age and sex, although not with inflammation-related markers (IL-1β, IL-6, TNF-α, IL-10). The authors also hypothesized that the association between stress management skills and fatigue would be mediated by emotional distress, and moderated by neuroimmune dysregulation. Indeed, analyses showed that the association between stress management and fatigue was mediated by distress, suggesting that stress management may lower fatigue by reducing emotional distress. Further, the association between stress management skills and fatigue was strongest among those with elevated levels of IL-6, though not other neuroimmune markers. These findings suggest that there may be subgroups of CFS patients who are more susceptible to the beneficial effects of stress management.

Inflammation occurs within a broader biological context that includes other components of the immune system as well as the neuroendocrine system. The complex interplay of these systems is addressed in two review articles in the Named Series focusing on chronic fatigue syndrome. The article by Bansal et al. provides a detailed and comprehensive review of immune alterations that have been observed in patients with CFS, including cytokine dysregulation, alterations in the cellular immune system, and viral infection (Bansal et al., 2012). These authors propose an integrated model in which severe or prolonged infection leads to dysfunction in the cellular immune system, prompting the reactivation of preexisting chronic viruses or new viral infection, which then drives inflammation and symptoms of fatigue. The authors further propose a positive feedback loop whereby fatigue promotes alterations in mood, sleep, and activity, perpetuating dysregulation in immune and inflammatory processes. Of note, the importance of latent herpesviruses for fatigue is nicely illustrated in the empirical article by Fagundes et al., in which antibodies to CMV were positively correlated with symptoms of fatigue in 158 women recently diagnosed with breast cancer (Fagundes et al., 2012).

In their review of biomarkers for fatigue, Klimas et al. also propose a more integrated, transdisciplinary approach to understanding this symptom (Klimas et al., 2012). These authors provide a selected overview of recent studies that have examined neural, endocrine, and immune processes associated with fatigue, focusing on chronic fatigue syndrome but also including cancer, autoimmune, and inflammatory diseases. Based on this review, the authors argue that an integrative, network-based approach that spans across biological systems and across levels of intracellular signaling and metabolic function is required to understand the complex pathophysiology of this system. They provide some interesting examples of this approach that use novel measures and methods of analysis to characterize relationships within and across systems in patients with chronic fatigue syndrome and cancer-related fatigue.

Overall, the articles included in the Named Series represent a number of important advances in research on fatigue. These include increased methodological sophistication, as indicated by the use of longitudinal study designs, careful selection of biomarkers, inclusion of important covariates, and use of more sophisticated analytic approaches and validated measures of fatigue (e.g., Fatigue Symptom Inventory and Profile of Mood States) and sleep (e.g., Pittsburgh Sleep Quality Index). In addition, these papers demonstrate increased conceptual sophistication in their consideration of genetic, immune, neuroendocrine, psychological, and behavioral factors that may influence inflammatory processes and fatigue. Of note, very few studies in the series included more than one of these factors, and there are a number of important systems that were not represented, including the autonomic nervous system and endocrine factors other than the HPA axis. The development and evaluation of comprehensive models that integrate across these systems is critical for advancing research on fatigue and elucidating the complex processes that initiate and sustain this disabling symptom.

The series also highlights current "hot spots" for fatigue research, particularly cancer-related fatigue, and suggests new avenues for this research, including diabetes. Other important issues considered by articles in the series include the dynamic interplay of fatigue, sleep, and inflammation; the role of early life stress and stress management in fatigue onset and persistence; the identification of subtypes of fatigue and distinctions between symptom domains; and the genetic underpinnings of fatigue. We hope that the series serves as a springboard for innovative, rigorous research on fatigue and its association with the brain, behavior, and immunity.

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