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Neuroimmune Function, Life Distress, Stress Management Skills and Physical Symptoms in Chronic Fatigue Syndrome

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UNIVERSITY OF MIAMI

NEUROIMMUNE FUNCTION, LIFE DISTRESS, STRESS MANAGEMENT SKILLS
AND PHYSICAL SYMPTOMS IN CHRONIC FATIGUE SYNDROME

By

Emily G. Lattie

A THESIS

Submitted to the Faculty
of the University of Miami
in partial fulfillment of the requirements for
the degree of Master of Science

Coral Gables, Florida

June 2012

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NEUROIMMUNE FUNCTION, LIFE DISTRESS, STRESS MANAGEMENT SKILLS
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Chronic Fatigue Syndrome (CFS) is a debilitating disorder with no clear etiology. Many, but not all, patients with CFS evidence signs of neuroimmune dysfunction prompting the suggestion that there exist subgroups of CFS patients with significant neuroimmune dysfunction while other subgroups of diagnosed patients may suffer from CFS-like symptoms due to other causes. Research has demonstrated that emotional distress responses impact CFS symptoms and that having adequate coping skills may predict less illness severity among individuals with CFS. However, no study to date has examined the influence of a comprehensive set of stress management skills on CFS symptoms nor has prior work evaluated if a relationship between stress management skills and CFS symptoms is mediated by lowered levels of emotional distress. Given the breadth of research literature linking neuroimmune dysfunction to emotional distress symptoms such as depression, and to physical symptoms such as fatigue, this study sought to examine a mediation model in which perceived stress management skills predict physical symptoms via lowered emotional distress. Moreover this study also sought to examine whether this model is most salient in individuals with a higher degree of neuroimmune dysfunction. In total, 117 individuals with CFS provided blood and saliva samples, as well as self-report measures of emotional distress, perceived stress

management skills (PSMS), and CFS symptoms including fatigue. Plasma interleukin-2 (IL-2), IL-5, IL-6, IL-12, and tumor necrosis factor-alpha (TNF- α), and diurnal salivary cortisol were analyzed. This study examined relations among perceived stress management skills, emotional distress, and physical symptoms in CFS patients who did and did not evidence neuroimmune abnormalities. Results indicated that higher levels of perceived stress management skills were related to lower levels of emotional distress, which related to lower levels of fatigue and a lower total symptom severity score. Greater levels of PSMS were also associated with lower circulating levels of IL-2 and a more negative diurnal cortisol slope. The indirect relationship between perceived stress management skills and fatigue via emotional distress was moderated by level of plasma IL-6, such that it was significant in participants with elevated levels of IL-6, but not significant in those participants with lower levels of IL-6. No other neuroendocrine or cytokine indicator functioned as a moderator of this relationship. In conclusion, the relationship between perceived stress management skills and fatigue via emotional distress was more pronounced in individuals with greater levels of the circulating pro-inflammatory cytokine IL-6. These findings support the need for research examining the impact of stress management interventions in subgroups of CFS patients showing neuroimmune dysfunction.

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CHAPTER 1: INTRODUCTION

Chronic Fatigue Syndrome (CFS) is a debilitating disorder characterized by severe, unexplained fatigue that is not alleviated by rest, as well as by at least 4 of the following 8 symptoms that did not predate the fatigue: unrefreshing sleep, sore throat, lymph node pain, muscle pain, multi joint pain, memory and concentration difficulties, severe headaches, and postexertional malaise (Fukuda et al., 1994). Nationwide prevalence of CFS has been estimated to be between 400,000 and 800,000 (Jason et al., 1999; Reyes et al., 2003). In the United States alone, disability due to CFS has been estimated to cost \$9.1 billion in lost productivity every year (Reynolds, Vernon, Bouchery, & Reeves, 2004). As this syndrome is a serious public health concern, research has been done in a variety of domains of the illness in attempts to better understand the mechanisms by which it operates. Much of the ongoing work focuses on biological mechanisms, namely endocrine and immune system dysfunction (Klimas & Koneru, 2007; Siegel et al., 2006; Tomoda et al., 2005; Torres-Harding et al., 2008) that may underlie the symptom expression and chronicity of this condition.

Endocrine Dysfunction

Although there is no clear diagnostic marker of Chronic Fatigue Syndrome, researchers have repeatedly found evidence of endocrine and immune system dysfunction in patients with CFS. Particular focus has been paid to cortisol, which is a glucocorticoid that is released as the end product of the hypothalamic-pituitary-adrenal (HPA) axis. In healthy populations, the diurnal pattern of cortisol output generally peaks in the morning and decreases throughout the day (Stone et al., 2001). Abnormal cortisol patterns indicate dysfunction within the endocrine system and dysfunction in this system can be

related to a variety of health outcomes. In a study of patients with metastatic breast cancer, those patients with an abnormal diurnal cortisol pattern, marked by a flatter negative slope or one that rose in the evening, had significantly earlier mortality than those patients with a normal cortisol pattern (Sephton et al., 2000). A flatter negative cortisol slope has also been associated with greater levels of fatigue in breast cancer survivors (Bower et al., 2005).

Within populations of individuals with CFS, a few common patterns in cortisol regulation have emerged. Research has suggested that patients diagnosed with CFS may evidence abnormalities in hypothalamic pituitary adrenal (HPA) axis functioning which are associated with hypocortisolemic pattern (Cleare et al., 2001; Demitrack & Crofford, 1998; ; Tak et al., 2011). In a study of individuals with CFS compared to individuals with unexplained fatigue and to healthy individuals, a flatter cortisol slope was observed in the CFS patients, marked by lower cortisol output in the morning and higher cortisol output in the evening (Nater et al., 2008). It has been noted that 20-25% of individuals with disorders such as CFS, post-traumatic stress disorder and fibromyalgia have low cortisol levels (Fries, 2005). Because these disorders may all be exacerbated by stress, Fries and colleagues theorized that hypocortisolism may be a protective effect resulting from a prolonged period of hyperactivity of the HPA axis, despite the fact that hypocortisolism has been associated with increased pain and fatigue. Additionally, Roberts and colleagues (2004) found a lower cortisol response to awakening in individuals with CFS compared to healthy controls, providing further support for the notion that CFS involves endocrine dysfunction.

Although there is a growing amount of consistency in findings regarding cortisol dysregulation in CFS, there is still much to be determined regarding the unique ways that low cortisol output and/or low cortisol variability relate to specific symptoms and outcomes in individuals with CFS. One of the primary concerns in interpreting this research is the fact that because there is not a universally agreed upon case definition of CFS, different populations are often used which can limit the generalizability of results. CFS is occasionally grouped in with other conditions (including irritable bowel syndrome, fibromyalgia, and functional dyspepsia) and given the title of Functional Somatic Syndrome (FSS). In a comparison of Japanese adults with FSS versus healthy controls, there were no differences seen in levels of morning salivary free cortisol. However, when relating cortisol level to participant reports of anxiety and depression, contrasting relationships were found for those participants with FSS and healthy controls. Those with FSS displayed negative relationships between cortisol level and depressive and anxious symptomatology, whereas healthy controls displayed a positive relationship between these variables. In a study done on adolescent females with severe fatigue compared to healthy adolescent females, no associations were found between fatigue severity and the cortisol awakening response (ter Wolbeek et al., 2007a). However, this study selected females with high levels of reported fatigue for at least one month for the CFS group, which does not follow any of the commonly used diagnostic criteria; therefore the results are unlikely to be generalizable to populations with a clear CFS diagnosis. In a study that selected CFS participants based on the US and UK definitions, there was not a significant relationship between cortisol output and fatigue, but there was a negative correlation between fatigue and ACTH output, indicating that there may be

neuroendocrine dysregulation relating to fatigue which cannot be observed through salivary cortisol measurement (Gaab et al., 2004).

While some research results appear promising in uncovering a unique link between cortisol dysfunction and CFS symptomatology, it is possible that researchers are not analyzing their data in a manner that reveals this potential relationship. In exploratory analyses by Torres-Harding and colleagues (2008), salivary cortisol was analyzed in terms of total mean cortisol, cortisol slope, and by clinical classification, judged by a physician as abnormal if the daily pattern varied much from the “normal” cortisol pattern of peaking in the morning and decreasing throughout the day. These cortisol values were then related to various symptoms associated with CFS such as fatigue, pain, and neurocognitive function. Although there were no significant relationships found for neurocognitive functioning, a significant relationship between fatigue and cortisol was only found when looking at abnormal clinical cortisol classification. Of additional note in this study was that higher pain severity related to a flatter cortisol slope as well as to an abnormal clinical classification of cortisol diurnal pattern. In another study by the same group of researchers, it was seen that participants with a cortisol output pattern classified as abnormal at baseline did not evidence CFS symptom improvement after being randomized to various non-pharmacologic interventions, whereas those with a normal cortisol pattern showed improvements on a number of measures after the intervention (Jason et al., 2008). Although the method of clinical classification would be difficult to replicate across other groups of researchers, the results of these studies provide additional insight into the relationship between cortisol and CFS symptomatology.

There is growing support for the notion that abnormal cortisol production may be a predictor of poorer response to cognitive behavior therapy (CBT). Upon delineating participants as “responders” or “non-responders” to a CBT protocol based on post-treatment rating by the therapist, it was seen that non-responders had significantly lower diurnal cortisol slope compared to responders and, when examining participants who were free of medications, the non-responders also had a significantly lower total urinary cortisol output over a 24 hour period (Roberts et al., 2010). These findings, in conjunction with those from Jason and colleagues (2008), suggest that dysregulated cortisol variability may play a significant role in the maintenance of CFS symptoms.

Immune Dysfunction

The immune and endocrine systems generally work in tandem. Glucocorticoids, such as cortisol, are known to down-regulate pro-inflammatory cytokine levels and cytokine receptor expression (Wiegers & Reul, 1998). Because of this connection, cytokine levels have also been seen to fluctuate when individuals are under stress, causing dysregulation of the immune response. In healthy individuals, it's been seen that cortisol responses to acute psychological stress have an inverse relationship with proinflammatory cytokines (Kunz-Ebrecht et al., 2003) and that acute mental stress appears to cause an increase in pro-inflammatory cytokines (Maes et al., 1998; Steptoe et al., 2001). In individuals with CFS, acute mental stress has been seen to decrease rather than increase the release of proinflammatory cytokines (Gaab et al., 2005). It should be noted that stress is not a one-dimensional concept and it appears that in healthy individuals chronic stress relates to impaired immune function (Cohen et al., 2002). One explanation for this acute versus chronic stress difference in immune response is a

glucocorticoid resistance model presented by Miller, Cohen and Ritchey (2002). This model asserts that chronic psychological stress impairs the ability of the immune system to respond to the anti-inflammatory signals of corticosteroids.

Expanding on work that Cohen's group has done on stress and viral infection in healthy individuals, and on work that Smith and colleagues (1999) performed which demonstrated that CFS patients were more susceptible to acute infections, Faulkner and Smith (2008) examined the relationship between psychological distress, mood and occurrence of upper respiratory tract infections in a group of participants diagnosed with CFS. They found that both one's reported stress and negative mood ratings in the past week predicted a greater likelihood of infection in the following week. In a recent study examining immune markers and psychosocial status of Turkish Chronic Fatigue Syndrome patients versus healthy control subjects, Nas and colleagues (2011) found that, compared to controls, participants with CFS reported significantly greater depression, fatigue, pain, disturbed sleep, and social isolation as well as problems with their physical abilities and emotional reactions. Participants with CFS also had significantly higher circulating levels of IL-6 and IL-2r. Furthermore, greater levels of IL-6 and IL-2r were related to greater reported sleep difficulties. Additionally, participants with CFS had significantly lower numbers of CD56 cells, a natural killer cell subset, and there was an inverse relationship between CD56 cell count and reported problems with emotional reactions. Prior work has theorized that several biological and psychological factors contribute to the maintenance of CFS symptoms (e.g., Patarca-Montero et al., 2001). These more recent studies suggest that the relationship between immune measures,

emotional distress and health complaints should be more closely examined in individuals with CFS.

Immune system dysfunction has long been observed in individuals with CFS, typically marked by either increased or decreased levels of pro-inflammatory cytokines compared to healthy controls. A good deal of work has focused on characterizing different cytokine levels in CFS patients, often with inconsistent results. Several central CFS symptoms, including pain in joints, sleepiness and fatigue, bear a strong resemblance to “sickness behavior” which can be induced by administration of pro-inflammatory cytokines (Dantzer & Kelley, 2007). Supporting the similarities to “sickness behavior,” some researchers have noted increased levels of interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α) in individuals with CFS (Gaab et al., 2005; Broderick et al., 2010). Contrary to these findings, Skowera and colleagues (2004) found increased levels of anti-inflammatory interleukin-4 (IL-4) producing cells in a sample of individuals with CFS. In ter Wolbeek’s research (2007b) on severely fatigued adolescents (not CFS diagnosed), increased levels of the anti-inflammatory cytokine interleukin-10 (IL-10) were found as well as decreased levels of the pro-inflammatory cytokines IL-6 and TNF- α . In a study that compared 14 individuals with CFS to 23 healthy controls, participants with CFS were seen to have significantly lower levels of Transforming Growth Factor- β 1 than controls, but no differences were seen in levels of IL-6, TNF- α , IL-10, IL-18, and interferon-gamma (IFN- γ) (Tomoda et al., 2005). In a recent study, Fletcher and colleagues (2009) measured 16 cytokines in peripheral blood plasma using a sensitive multiplex technology to simultaneously measure cytokine levels. Results from this study indicated increased

levels of IL-1 α , IL-1 β , IL-4, IL-5, IL-6, IL-12 and lymphotoxin-alpha (LT α), and decreased levels of IL-8, IL-13 and IL-15 in CFS patients compared to control subjects, and introduced the notion that IL-4, IL-5, IL-12 and LT α may be the best biomarkers to distinguish CFS patients from controls.

In a novel technique of analyzing cytokine co-expression networks based on pairwise mutual information patterns, Broderick and colleagues (2010) analyzed the cytokine network of a group of women with CFS versus a group of healthy women who served as control participants. The computed networks showed vast between-group differences and shed light on the relationships between different cytokines in people with CFS and healthy individuals. Particularly of note were a tight cluster of primarily Th1 cytokines in the CFS network and a weaker cluster of cytokines associated with innate immunity and/or a Th2 adaptive response. The second cluster, despite having a weak association, still demonstrated elevated levels of circulating IL-6 and IL-1 α , suggesting an inflammatory environment. Additionally, a strong relationship between IL-6 and IL-10 was noted, emphasizing the interaction between pro-inflammatory and anti-inflammatory cytokines.

Although a number of research groups have identified immune system dysfunction in individuals with CFS, the overarching nature of the dysfunction has not yet been determined. Given the heterogeneous nature of the illness population, many researchers have attempted to establish subgroups of individuals with CFS (Borish et al., 1998; Corradi et al., 2006; Hickie et al., 1995; Porter et al., 2010; Siegel et al., 2006). The idea that CFS patients may be separated into subgroups on the basis of the presence or absence of immunological abnormalities is not a new notion but it appears to demand

further exploration. In a study done by Siegel and colleagues (2006), participants with low natural killer cell activity reported more daytime dysfunction and cognitive impairment, as well as less vigor. It is plausible that establishing reliable CFS patient subgroups may help to clarify some of the inconsistent results for neuroendocrine and immune parameters noted in the field to date.

Stress, Coping, and CFS symptoms

A subset of work on neuroimmune mechanisms has provided evidence that stressors and perceived stress may exacerbate CFS symptoms via psychoneuroimmunological processes (Antoni & Weiss, 2003; Gaab et al, 2006; Nas et al., 2011). Lutgendorf and colleagues (1994) found evidence that distress responses to Hurricane Andrew were a strong predictor of the likelihood and severity of a subsequent symptom relapse in a prospective study of CFS patients. Faulkner and Smith (2008) demonstrated that self-reported ratings of psychological distress during the past week predicted a greater degree of physical fatigue during the following week. These findings suggest that there may be a relationship between emotional distress and physical symptoms in CFS.

The association between perceived stress and an individual's health outcomes may be impacted by the use of appropriate coping mechanisms that help people manage stress (Lazarus & Folkman, 1984; Folkman, Lazarus, Gruen, & DeLongis, 1986; DeLongis, Folkman, & Lazarus, 1988). For instance, in a study examining stress management skills, distress, and quality of life among patients with a variety of cancer diagnoses found that high levels of stress management skills are associated with less

distress and higher quality of life ratings (Faul et al., 2010). Similar findings have emerged with breast cancer (Antoni et al., 2006b) and prostate cancer (Penedo et al., 2004; Penedo et al., 2006) patients. Coping strategies and cognitive appraisals of stress could explain differences in health outcomes, but past research on this topic within samples of CFS patients has been mixed. Recent research has demonstrated that coping skills, such as seeking social support and problem solving, predicted less illness severity among individuals with CFS (Walker, Lindner, & Noonan, 2009). However, other work in CFS does not support such an association (Johnson, Gil-Rivas, & Schmalings, 2008). In an examination of CFS patients with and without major depressive disorder, Antoni and colleagues (1994) found that dysfunctional attitudes and distorted automatic thoughts, as well as the use of maladaptive coping strategies (e.g., mental disengagement, behavioral disengagement, and denial), were associated with a greater illness burden in CFS patients. In an examination of coping skills and length of illness, Brown, Brown and Jason (2010) found that CFS patients with a relatively longer illness duration utilized more adaptive coping strategies (such as positive reframing, acceptance and planning) compared to participants with a relatively shorter illness duration. However, there were no differences in physical impairment or symptom severity between these two groups. A possible explanation for the lack of differences could be that developing adaptive coping strategies prevented those with longer illness durations from getting worse. However, due to the cross-sectional nature of the study and the unpredictable nature of CFS, this alternative explanation cannot be examined. Although findings regarding coping and CFS symptoms are mixed, there is preliminary evidence indicating that the use of adaptive coping skills may have positive health outcomes among patients with CFS.

Furthermore, none of the research to date has specifically examined the influence of a broad set of stress management skills on specific CFS symptoms. Given the association between stress and CFS symptoms, the role of specific stress management skills in this relationship warrants further investigation and will be one of the areas of focus in the present study.

Maintenance and Exacerbation of CFS Symptoms

The etiology of CFS remains unknown despite findings of endocrine and immune abnormalities of varying degrees among CFS patients. In recent years, the medical research community has increased the focus on understanding processes underlying the maintenance and exacerbation of CFS symptoms. In 1998, Vercoulen and colleagues published an influential paper explaining a model of the persistence of fatigue in CFS. Vercoulen's model posited that when CFS patients attribute their complaints to a somatic cause, they tend to reduce their physical activity level, which may cause an increase in fatigue.

The Vercoulen model led researchers and health care providers to believe that by increasing activity levels of patients with CFS, they may be able to directly reduce sickness severity. Because CFS is often believed to exist as a result of both behavioral and psychological factors, cognitive-behavioral therapies have been developed as a treatment for CFS. Many researchers have placed exercise as the cornerstone of these interventions, and have designed cognitive-behavioral protocols aimed at changing participant attitudes toward exercise and increasing the amount of physical activity in which participants partake. However, in a meta-analysis of three randomized control

trials of this nature, increases in exercise were not found to be a mediator between the effect of cognitive-behavioral therapy and reductions in fatigue (Wibourg et al., 2010). Across the samples included in the meta-analysis, the mean mediation effect of physical activity only accounted for about 1% of the total treatment effect. In short, cognitive behavioral therapeutic protocols have been shown to reduce fatigue in individuals with CFS, but it does not appear that getting participants physically active causes this reduction in fatigue.

Previous evidence against the Vercoulen model was collected by Song and Jason (2005) when they applied the model to 5 fatigued groups (participants with Chronic Fatigue Syndrome, participants with chronic fatigue symptoms that were psychiatrically explained, participants with chronic fatigue symptoms that were medically unexplained, participants with chronic fatigue symptoms that were linked to substance misuse, and participants with idiopathic chronic fatigue). Song and Jason found that the model adequately represented chronic fatigue that was secondary to psychiatric conditions (including but not limited to melancholic depression), but it did not represent the sample of participants with CFS or any of the other fatigued groups. These findings emphasize the notion that the persistence of fatigue in CFS may be caused by factors other than somatic attributions, low levels of physical activity, and a high focus on bodily sensations.

While increased physical activity does not mediate the effect of CBT on reductions in fatigue in CFS patients (Wibourg et al., 2010), it is plausible that stress reduction, may mediate the relationship between CBT and fatigue reductions. Promising early results were found in a pilot study of cognitive behavioral stress management

(CBSM) therapy for individuals with CFS. Those who received CBSM had significantly greater decreases in levels of perceived stress and less severe CFS symptoms than those individuals who were part of a psychoeducational control group (Lopez et al., 2010). Participants in the CBSM group also demonstrated lower levels of mood disturbance and higher ratings on a quality of life measure compared to those participants in the control group. Biological factors, such as cortisol levels and circulating cytokines, were not analyzed in this study. Given the knowledge that stress and coping are related to endocrine and immune functioning, and that alterations in these stress, neuroendocrine and immune processes have been linked to increased fatigue symptomatology, there is a need for research that focuses on uncovering systematic connections between stress, coping, neuroendocrine and immune function, and CFS symptoms.

Proposed Study

This study examines the relationship between perceived stress management skills, emotional distress, fatigue, and immune and neuroendocrine indicators within a population of individuals diagnosed with CFS. First, it is hypothesized that lower perceived stress management skills and higher reports of emotional distress will relate both to lower reports of CFS symptoms and greater degrees of neuroimmune dysfunction. While there are several symptoms of CFS specified by the Fukuda (1994) diagnostic system, this study will examine participants' total symptom severity, as well as individual reports of fatigue, sleep difficulties, and post-exertional malaise because these symptoms have been seen as hallmark symptoms of CFS (Taylor, Jason & Curie, 2002; Morriss, Wearden & Battersby, 1997). Second, it is hypothesized that the relationship between higher perceived stress management skills and lower reports of CFS symptoms will be

mediated by lower levels of emotional distress. Third, it is hypothesized that the effects of perceived stress management skills on symptoms of CFS via emotional distress will be greatest among a subgroup of patients with a greater degree of neuroimmune dysfunction, indicated by greater levels of circulating IL-2, IL-5, IL-6, IL-12, and TNF- α , as well as by lower diurnal cortisol slope. Fourth it is hypothesized that the effects of perceived stress management skills on CFS symptoms via emotional distress will be greater among a subgroup of patients with a longer illness duration. A final goal of this study is to characterize the features of the neuroimmune and illness duration subgroups demonstrating the strongest moderating effects. The overarching goal of this study is to identify subgroups of CFS patients for whom stress management skills and emotional distress may have the greatest influence on symptomology, and who therefore might achieve the greatest benefits from stress management intervention. Specific aims and hypotheses for the study are as follows:

Specific Aim 1: To examine the relationship between perceived stress management skills and emotional distress.

Hypothesis 1: Lower levels of perceived stress management skills will be significantly associated with higher levels of emotional distress.

Specific Aim 2: To determine if perceived stress management skills and emotional distress are associated with CFS symptoms (characterized as fatigue, sleep difficulties, post-exertional malaise and total symptom severity).

Hypothesis 2a: Lower levels of perceived stress management skills will be significantly associated with greater CFS symptom severity.

Hypothesis 2b: Greater levels of emotional distress will be significantly associated with greater CFS symptom severity.

Specific Aim 3: To determine if perceived stress management skills and emotional distress are associated with neuroimmune dysfunction as indicated by greater levels of circulating IL-2, IL-5, IL-6, IL-12, and TNF- α , and a lower diurnal cortisol slope.

Hypothesis 3a: Lower levels of perceived stress management skills will be significantly associated with greater neuroimmune dysfunction (greater IL-2, IL-5, IL-6, IL-12, and TNF- α ; and lower diurnal cortisol slope).

Hypothesis 3b: Greater levels of emotional distress will be significantly associated with greater neuroimmune dysfunction (greater IL-2, IL-5, IL-6, IL-12, and TNF- α ; and lower diurnal cortisol slope).

Specific Aim 4: To determine if the relationships between perceived stress management skills and CFS symptoms are mediated by reports of emotional distress.

Hypothesis 4: The relationship between lower perceived stress management skills and greater CFS symptom severity will be mediated by greater emotional distress.

Specific Aim 5: To determine if the mediation effects between perceived stress management skills and CFS symptoms via emotional distress are moderated by levels of circulating IL-2, IL-5, IL-6, IL-12, TNF- α , cortisol slope, or illness duration.

Hypothesis 5a: The relationship between perceived stress management skills and CFS symptoms via emotional distress will be more pronounced in individuals with greater levels of circulating IL-2, IL-5, IL-6, IL-12, and TNF- α .

Hypothesis 5b: The relationship between perceived stress management skills and CFS symptoms via emotional distress will be more pronounced in individuals with more dysregulated HPA axis functioning, as indicated by lower diurnal cortisol slope.

Hypothesis 5c: The relationship between perceived stress management skills and CFS symptoms via emotional distress will be more pronounced in individuals with a longer illness duration.

Exploratory Aim: For variables found to serve as significant moderators, moderator-defined subgroups will be compared for difference in socio-demographic variables in order to learn more about individuals most likely to benefit from stress management interventions.

Hypothesis: Participants in subgroups defined by significant moderators will be compared for differences in socio-demographic variables, such as age, gender, ethnic identification, educational level, employment status and relationship status.

CHAPTER 2: METHOD

Participants

Data for this study was collected at baseline of an ongoing longitudinal study examining the efficacy of group-based, telephone-delivered cognitive behavioral stress management intervention for individuals with CFS. Physician referral was the primary source of participant recruitment. Additionally, recruitment efforts for this study included presentations at local CFS conferences, support groups and special events, as well as advertisements on relevant websites.

Inclusion/Exclusion Criteria

Eligibility requirements for this study included having a CFS diagnosis based on the Fukuda et al., 1994 definition, being between the ages of 21 and 75 years, and being fluent in English. Potential participants were excluded if they met DSM-IV criteria for a severe psychiatric disorder, substance abuse, if they were actively suicidal, or if they were of diminished cognitive capabilities as indicated by having made four or more errors on the Short Portable Mental Status Questionnaire (Pfeiffer, 1975). Participants were also excluded if they had been diagnosed with an illness or were receiving medical treatment that would explain chronic fatigue and/or modulate the immune system (e.g. Lyme disease, renal dialysis, corticosteroids).

Procedures

After enrollment in the study, research team members conducted a home visit. During this visit, a study staff member administered a battery of measures of psychosocial status and CFS symptoms. Participants were subsequently provided with 8

Salivette® tubes and were instructed to provide saliva samples on two consecutive weekdays within one week of the baseline interview. They were instructed to take a sample upon awakening, 30 minutes after awakening, at 4 pm, and at 9 pm on both days. While being trained on the collection protocol, participants were asked not to eat or drink prior to and between the first two samples each day, as well as to avoid eating a large meal an hour prior to the afternoon and evening samples. Participants were further advised to not exercise vigorously on sample collection days and to abstain from alcohol within 12 hours prior to sample collection. They were instructed to refrigerate the Salivette® tubes in order to preserve the integrity of the salivary cortisol. Within one week of the initial home visit, participants attended a blood draw appointment, during which they returned their saliva samples to the study staff. In order to provide flexibility while still avoiding extreme diurnal variations, peripheral venous blood samples were taken between 11am and 3pm. After completing the home visit, the saliva samples, and the blood draw, participants were compensated \$50.

Measures

Perceived Stress Scale (PSS)

This scale was used to measure participants' perceptions of life stress (Cohen, Kamarck, & Mermelstein, 1983). Participants were asked to indicate how often they felt or thought a certain way in the last week (0 = never to 4 = very often). Sample items include "How often have you been upset because something happened unexpectedly?" and "How often have you felt confident about your ability to handle your personal problems?" Items stated in a positive manner were reverse scored. Demonstrated internal consistency of this measure has been excellent ($\alpha = .84 - .86$ in past studies) and

it correlates well with a wide range of self-reports of stress (Cohen, Kamarck, & Mermelstein, 1983; Hewitt, Flett, & Mosher, 1992).

Center for Epidemiologic Studies Depression Scale (CES-D)

This scale was used to measure participants' depressive symptomatology present over the past week (Radloff, 1977). Sample items include "I felt like everything I did was an effort" and "I felt hopeful about the future." Participants were asked to indicate how often they felt this way (1 = rarely or none of the time, < 1 day, to 4 = most or all of the time, 5-7 days). Positively worded items were reverse scored. Internal consistency has been shown to be excellent ($\alpha = .85$ in the general population and $\alpha = .90$ in a patient sample) and discriminate validity has been good (Radloff, 1977)

Profile of Mood States (POMS)

The POMS was used to measure mood states over the prior week (McNair, Lorr, & Droppelman, 1971). Participants are asked to reflect on the past week and to indicate to what degree they have felt on 65 adjective scales relating to different moods. The responses are on a 5 point scale with 0 indicating "not at all" and 4 indicating "extremely." The POMS consists of 6 clearly defined factors: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment. This measure demonstrates excellent internal consistency for all of these factors ($\alpha > .85$) and has demonstrated good predictive and construct validity in several studies (McNair, Lorr, & Droppelman, 1971).

Emotional Distress

In order to assess the participants' level of recent emotional distress, a composite score was created using of the PSS (Cohen et al., 1983), CES-D (Radloff, 1977), and

POMS depression-dejection and anxiety-tension subscales (McNair, Lorr, & Droppelman, 1971). The construction of this composite score was based on the theory that feelings of perceived stress, depression, and anxiety contribute to one's total experience of emotional distress. A sum of the z-scores from the PSS, CES-D and POMS depression-dejection and tension-anxiety measures demonstrated excellent internal consistency (Cronbach's $\alpha = .89$) and comprised an emotional distress composite score.

Perceived Stress Management Skills

The Measure of Current Status (MOCS; Carver, 2006) was used to examine perceived stress management skills in the present sample. This measure asks participants to rate their ability to respond to the various challenges of daily life using a 5-point response scale with 1 indicating "I cannot do this at all" to 5 indicating "I can do this extremely well." Items on the MOCS are based on behaviors and personal characteristics that are generally associated with efficient stress management. Examples of these behaviors and characteristics in one's awareness of tension, relaxation skills, cognitive restructuring, coping skills, utilization of social support, as well as the appropriate expression of anger. Items from this measure include "It's easy for me to go to people in my life for help or support when I need it" and "I am able to use mental imagery to reduce any tension I experience." Similarly to how this measure has been used in a sample of men with prostate cancer, (Penedo et al., 2006), the present study uses a sum of all of the MOCS items in order to compose a total stress management skills score. This score had a high degree of internal consistency (Cronbach's $\alpha = .85$).

Fatigue

Fatigue severity across the prior week was assessed using the Fatigue Symptom Inventory severity subscale (FSI; Hann et al., 1998) and the POMS fatigue-inertia subscale (McNair, Lorr, & Droppelman, 1971). The FSI severity scale consists of 4 items on an 11-point scale where 0 indicates “not at all fatigued” and 10 indicates “as fatigued as I could be.” Sample items on this scale include “rate your level of fatigue on average in the last week” and “rate your level of fatigue right now.” The fatigue-inertia subscale of the POMS is composed of adjectives rated along a 5-point scale with 0 indicating “not at all” and 4 indicating “extremely.” Sample items for the fatigue-inertia subscale include “worn out” and “fatigued.” The fatigue composite score was created by adding both the z-score of the severity subscale of the FSI and the z-score of POMS fatigue-inertia subscale. This composite score demonstrated good internal consistency ($\alpha = .75$).

CDC Symptom Inventory for assessment of Chronic Fatigue Syndrome

The CDC Symptom Inventory (Wagner et al., 2005) was used to measure the presence of CFS symptoms in participants’ lives over the past month. Participants were asked to rate the frequency (1 = a little of the time to 5 = all of the time) and severity (1 = very mild to 5 = very severe) of 19 CFS-related symptoms. The symptoms surveyed include the 8 case definition symptoms as defined by Fukuda et al. (1994) as well as other common symptoms, including sleeping problems, stomach or abdominal pain, sensitivity to light, and depression. For the purposes of the present study, the total symptom severity score and the post-exertional malaise score will be used. This measure

has demonstrated excellent internal consistency among the case definition symptoms ($\alpha = .82$) and among the other symptoms ($\alpha = .74$) and has been shown to be a reliable measure of CFS symptoms (Wagner et al., 2005).

Pittsburgh Sleep Quality Index

Sleep disturbance was measured using the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a 19 item measure that generates a global sleep score as well as seven subscale scores: duration of sleep, sleep disturbance, sleep latency, daytime dysfunction, sleep efficiency, sleep quality and use of sleeping medications. For the purposes of the present study, the global score was examined. This measure has repeatedly demonstrated good internal consistency ($\alpha = .77-.83$) and good reliability (Buysse et al., 1989; Backhaus et al., 2002).

Salivary Cortisol

Participants provided 8 samples of salivary cortisol over a two day period to ensure reliability of cortisol measurements (Kraemer et al., 2006). Saliva samples were frozen at -20°C prior to being assayed in batches. On the day that the cortisol assay took place, saliva samples were thawed, vortexed and centrifuged at 1500 RPM for 15 minutes. Then, they were assayed using the Salimetrics high sensitivity ELISA kit (State College, PA). To control for daily fluctuations in cortisol production, values from each time point (awakening, 30 minutes post-awakening, 4 pm and 9 pm) were averaged between the two days of collection. The mean values for each time point were then used in the computation of the slope of the regression line fitted through the cortisol data time points using procedures outlined by Sephton and colleagues (2000).

Plasma Cytokines

Circulating cytokines, IL-2, IL-5, IL-6, IL-12, and TNF- α , were measured from blood plasma using the Q-Plex™ Human Cytokine – Screen, an ELISA-based test produced by Quansys Biosciences (Logan, Utah). Within 4 hours of the blood draw, blood was centrifuged and plasma was stored at -20°C prior to assays being run in batches. The Q-Plex™ Human Cytokine – Screen method uses distinct capture antibodies in a 96-well plate in a defined array and has previously been described by Fletcher and colleagues (2009). Each plasma sample was run in duplicate for reliability purposes, and images were taken of the 96-well plate using the the Quansys Imager, driven by an 8.4 megapixel Canon 20D digital SLR camera. After images were taken, the plates were analyzed using Quansys software. This multiplex method has compared favorably with both single plex ELISA assays, as well as other multiplex methods (Chiswick et al., 2012; Trune et al., 2011).

Control Variables

Demographic variables, including age, gender, years of education, and ethnicity, as well as alcohol and tobacco use were measured as part of a paper and pencil, self-report assessment. Based on past research regarding the impact of these factors on cortisol and cytokines (Kirschbaum et al., 1999; O'Connor et al., 2009), these variables will be assessed as potential covariates for immune and endocrine outcome variables. Consistent with prior literature, the same demographic variables will be analyzed as potential covariates of emotional distress and CFS symptom reports (Torres-Harding et al., 2008; Faul et al., 2010; Jason et al., 1999).

Statistical Analyses

Preliminary Analyses

All variables in the study were tested for internal consistency and normality. Variables with non-normal distributions, defined as having a skew index of 3.0 or greater and a kurtosis index of 8.0 or greater, were logarithmically transformed. Data for all variables were examined for outliers, and any scores greater than three standard deviations from the mean were winsorized. Undetectable cytokine levels were substituted with the lowest detectable limit value for each cytokine. Correlations and one-way analyses of variance (ANOVAS) were run between the study outcome variables and demographic variables (e.g. age, gender, years of education, ethnicity, smoking status) in order to assess for covariance. All demographic variables that are related to outcome variables at a $p < .10$ level were included as control variables in all analyses including those specific outcome variables.

Primary Analyses

Specific Aim 1:

To examine if lower levels of perceived stress management skills were associated with higher levels of emotional distress, a hierarchical linear regression analysis was conducted. All covariates of emotional distress were entered into the first block, and the MOCS total score was entered into the second block. A negative and significant ($p < .05$)

beta coefficient for the MOCS total score indicates that low levels of perceived stress management skills are associated with higher levels of emotional distress.

Specific Aim 2:

Hierarchical linear regression analyses were conducted to examine if perceived stress management skills and emotional distress are associated with CFS symptoms. Four separate analyses were conducted with each symptom of interest (fatigue, sleep difficulties, post-exertional malaise and total symptom severity) serving as the dependent variable and with the MOCS total score serving as the independent variable. An additional four analyses were conducted, examining each symptom of interest as the dependent variable and with emotional distress serving as the independent variable. All covariates of CFS symptoms were entered into the first block, and the MOCS total score or the emotional distress score were entered into the second block. A significant ($p < .05$) beta coefficient for the independent variable (MOCS total score or the emotional distress score) indicates that the independent variable is associated with the dependent variable.

Specific Aim 3:

Hierarchical linear regression analyses were conducted to examine if perceived stress management skills and emotional distress are associated with indicators of neuroimmune dysfunction. Six separate analyses were conducted with each indicator of potential biological dysfunction (IL-2, IL-5, IL-6, IL-12, TNF- α and diurnal cortisol slope) serving as the dependent variable and with the MOCS total score serving as the independent variable. An additional six analyses were conducted, examining each indicator of potential neuroimmune dysfunction as the dependent variable and with

emotional distress serving as the independent variable. All covariates of cytokine and cortisol variables were entered into the first block, and the MOCS total score or the emotional distress score was entered into the second block. A significant ($p < .05$) beta coefficient for the independent variable (MOCS total score or the emotional distress score) indicates that the independent variable is associated with the dependent variable.

Specific Aim 4:

To examine if the relationships between perceived stress management skills (PSMS) and CFS symptoms are mediated by emotional distress, linear regression analyses were utilized. Perceived stress management skills were entered as the independent variable, emotional distress was entered as the mediator, and all significant outcomes found in Specific Aim 2 of the present study (fatigue, sleep difficulties, post-exertional malaise and total symptom severity) were entered as dependent variables in separate analyses. All relevant covariates used in Specific Aims 1 and 2 were included in these mediation models. Following the criteria presented by Baron & Kenny (1986), full mediation was indicated if the addition of the mediator (emotional distress) to the regression of CFS symptoms on PSMS resulted in a non-significant relationship between CFS symptoms and PSMS. If the relationship between CFS symptoms and PSMS remained significant after adding emotional distress to the model, then the possibility of partial mediation was further investigated. The bootstrapping method, which does not assume normality and does not require a direct significant relationship between the independent and dependent variables, has become an increasingly popular method for testing mediation in recent years (Preacher & Hayes, 2008). Bootstrapping was used to check for partial mediation, or indirect effects, in the present study. Bootstrapping is

based on resampling with replacement and for each resample, an indirect effect is calculated, resulting in the calculation of a confidence interval. If the confidence interval does not contain zero, it is assumed that the indirect effect is different than zero and partial mediation is indicated.

Specific Aim 5:

To examine if any indirect effects between perceived stress management skills and CFS symptoms vary as a function of levels of circulating IL-2, IL-5, IL-6, IL-12, TNF- α , diurnal cortisol slope, or illness duration, tests of conditional indirect effects, or, moderated mediation analyses, were conducted. Specifically, the hypothesis that the relationship between perceived stress management skills and emotional distress will vary by the level of circulating IL-2, IL-5, IL-6, IL-12, TNF- α , cortisol diurnal slope, and/or illness duration was tested on all significant findings from specific aim 3. Conditional indirect effects were tested using methods outlined by Preacher, Rucker & Hayes (2007), in which an interaction term was created using the independent variable (perceived stress management skills) and the proposed moderating variable (IL-2, IL-5, IL-6, IL-12, TNF- α , diurnal cortisol slope and illness duration). The product of the regression coefficient from the interaction term to the mediator (emotional distress) and the regression coefficient from the mediator to the dependent variable (fatigue) was examined for statistical significance in order to determine if different indirect effects exist for different conditional values of IL-2, IL-5, IL-6, IL-12, TNF- α , diurnal cortisol slope and/or illness duration. A p-value < .05 indicates that conditional indirect effects exist. The nature of the conditional indirect effects was tested at the mean as well as one standard deviation above and below the mean of the moderating variable. In order to confirm the

significance of these effects, bootstrapping was used. When bootstrapped confidence intervals do not contain zero, then the indirect effect at the tested level of the moderator is considered to be significantly different from zero and mediation is indicated at that level of the proposed moderator. In order to establish subgroups in which the mediation model is most salient, moderator-defined tertile subgroups were created and the indirect effect were tested in each subgroup using bootstrapping.

Exploratory Aim:

In order to characterize the tertile subgroups of a significant moderating variable, ANOVAs and chi-square analyses were run to examine potential differences in socio-demographic variables, such as age, gender, ethnic identification, educational level, employment status and relationship status, between the groups. To reduce Type I error, a p value of .01 rather than .05 was used to indicate statistical significance between groups.

CHAPTER 3: RESULTS

Preliminary Analyses

Sample Description

Of the 161 individuals screened for the study, 134 individuals were eligible. Participants were excluded for not having a CFS diagnosis ($n = 6$), living out of study area ($n = 11$), being older than 75 years of age ($n = 1$), not speaking English ($n = 1$), not having a working phone line ($n = 3$), and for having an exclusionary medical condition ($n = 5$). Of the 134 eligible individuals, 10 indicated that they were not interested in participating, 7 were lost to follow-up prior to participating, and 2 were excluded for not having a working telephone line. The final sample consisted of 117 individuals, including 97 women and 20 men. The average age of this sample was 50.7 years of age ($SD = 11.5$), and the majority (79.5%) were non-Hispanic White. The remaining 20.5% of the sample identified as Hispanic (15.4%), African American (2.6%), Asian (0.9%) and biracial (1.7%). Participants were generally highly educated, with 87.2% of the sample having had attended at least some college. Approximately 42.7% of participants were married, 22.2% were single, 19.9% were divorced or separated, 5.1% were widowed, 9.4% were in a monogamous relationship and one participant (0.9%) identified her relationship status as “other.” At the time of assessment, the majority of participants were not working, as indicated by being either on disability (40.2%), unemployed (13.7%), or retired (10.3%). The remainder of participants worked full-time (17.1%), worked part-time (9.4%), performed volunteer work (0.9%), attended school (1.7%), or had an alternate employment status, such as serving as a freelancer or consultant (6.8%). The demographic characterization of the present sample is found in Table 1 and the

descriptive statistics for the self-report and biological variables are found in Tables 2 and 3.

Analysis of Covariates

Demographic variables were assessed as potential covariates in the study models. All potential covariates (age, gender, years of education, ethnicity and smoking status) were assessed using one-way analyses of variance or bivariate correlation analyses. Relationships were deemed significant at a $p < .10$ level and significant demographic variables were included as covariates in the relevant analyses. Age was significantly related to IL-2 level ($r = -.235$, $p = .012$). Gender was significantly related to IL-5 ($F[1, 114] = 2.802$, $p = .097$), emotional distress ($F[1, 116] = 3.488$, $p = .064$), PSQI score ($F[1, 117] = 13.865$, $p < .001$) and total symptom severity ($F[1, 113] = 4.163$, $p = .044$), such that IL-5 was higher in men, while the emotional distress scores, PSQI scores, and total symptom severity scores were higher in women. Ethnicity was significantly related to emotional distress scores such that Non-Hispanic Whites had lower emotional distress scores than minority groups ($F[1, 116] = 4.015$, $p = .047$). Smoking status was significantly related to IL-6 level ($F[1, 114] = 4.480$, $p = .037$), MOCS total score ($F[1, 115] = 4.058$, $p = .046$), and post-exertional malaise score ($F[1, 117] = 4.050$, $p = .047$), such that IL-6 and self-report scores were higher in smokers compared to non-smokers.

Primary Analyses

Specific Aim 1:

In order to examine the relationship between perceived stress management skills and emotional distress, a hierarchical linear regression analysis was conducted. After controlling for gender and ethnicity, the MOCS total score was significantly related to

emotional distress ($\beta = -.452, p < .001$), indicating that low levels of perceived stress management skills are associated with higher levels of emotional distress.

Specific Aim 2:

The second set of analyses was conducted to examine if perceived stress management skills and emotional distress are associated with CFS symptoms (fatigue, sleep difficulties, post-exertional malaise and total symptom severity). All analyses controlled for relevant demographic variables. The first four models tested relationships with perceived stress management skills. The first of these models examined the relationship between perceived stress management skills and fatigue. This model was significant ($\beta = -.353, p < .001$), indicating that low levels of perceived stress management skills are related to higher levels of fatigue. The next model demonstrated a similar inverse relationship between perceived stress management skills and sleep difficulties ($\beta = -.189, p = .035$). As seen in Table 4, there were not significant relationships between perceived stress management skills and post-exertional malaise or between perceived stress management skills and total symptom severity.

The second four models tested relationships with emotional distress. Emotional distress had a significant, positive relationship with fatigue ($\beta = .544, p < .001$), sleep difficulties ($\beta = .247, p = .006$) and total symptom severity ($\beta = .261, p = .005$). As seen in Table 4, there was not a significant relationship observed between emotional distress and post-exertional malaise scores, therefore post-exertional malaise was excluded as an outcome variable for further analyses. These results indicate that high levels of emotional distress correspond with higher levels of fatigue, greater reports of sleep difficulties, and a greater severity of CFS symptoms.

Specific Aim 3:

The third set of analyses was conducted to examine if perceived stress management skills and emotional distress are associated with indicators of neuroimmune dysfunction (IL-2, IL-5, IL-6, IL-12, TNF- α and diurnal cortisol slope). The first six models tested the relationships with emotional distress. As indicated in Table 5, none of the indicators of neuroimmune dysfunction were related to emotional distress (all p 's > .05). The next six models tested relationships with perceived stress management skills. Perceived stress management skills were significantly related to IL-2 ($\beta = .197$, $p = .040$), indicating that individuals reporting high levels of perceived stress management skills also had lower levels of IL-2. A significant relationship was also observed between perceived stress management skills and diurnal cortisol slope ($\beta = -.207$, $p = .028$) indicating that higher levels of perceived stress management skills related to a more pronounced diurnal slope.

Specific Aim 4:

A fourth set of analyses was conducted to examine if the relationships between perceived stress management skills (PSMS) and CFS symptoms are mediated by emotional distress. Fatigue, sleep difficulties and total symptom severity were examined as outcome variables in three separate mediation models based on the significant relationships established in Specific Aims 1 and 2.

Emotional Distress Mediating the Relationship between PSMS and Fatigue

The first mediation model examined fatigue as the outcome variable. The first three steps of Baron and Kenny's (1986) mediation method were met in Specific Aims 1 and 2, such that perceived stress management skills were significantly related to fatigue,

perceived stress management skills were significantly related to emotional distress, and emotional distress was significantly related to fatigue. To examine step 4 of Baron and Kenny's method, emotional distress was added to the regression model of fatigue on perceived stress management skills. As seen in Figure 1, this resulted in the relationship between perceived stress management skills and fatigue to become non-significant, which indicated mediation. Bootstrapping results were examined to confirm the statistical significance of the indirect effect of perceived stress management skills on fatigue via emotional distress. Based on 1000 bootstrap resamples, the 95% confidence interval was -.0774 to -.0236. Because this interval did not contain zero, the indirect effect is further supported.

Emotional Distress Mediating the Relationship between PSMS and Sleep Difficulties

The second mediation model examined sleep difficulties as the outcome variable. Again, the first three steps of Baron and Kenny's (1986) mediation method were met in Specific Aims 1 and 2, such that perceived stress management skills were significantly related to sleep difficulties, perceived stress management skills were significantly related to emotional distress, and emotional distress was significantly related to sleep difficulties. To examine step 4 of Baron and Kenny's method, emotional distress was added to the regression model of sleep difficulties on perceived stress management skills. As seen in Figure 2, this resulted in the relationship between perceived stress management skills and sleep difficulties to become non-significant, and the relationship between emotional distress and sleep difficulties to become marginally significant ($p = .053$). Because the relationship between emotional distress and sleep difficulties did not remain significant, the mediation hypothesis was not supported using the Baron and Kenny (1986) criteria.

However, the Baron and Kenny method of assessing mediation based on a formal p-value assumes a normal sampling distribution of the indirect effect. The Baron and Kenny method has drawn criticism as this assumption of normality is often violated. In order to further probe for an indirect effect, bootstrapping was utilized based on 1000 resamples. The 95% confidence interval for this indirect effect was -.0855 - .0002. Because this confidence interval contained zero, the hypothesis that the indirect effect is significantly different from zero is not supported, and this mediation model was dropped from further analyses.

Emotional Distress Mediating the Relationship between PSMS and Total Symptom Severity

The third mediation model, seen in Figure 3, examined the CFS total symptom severity score as the outcome variable. Specific Aim 1 demonstrated a significant relationship between PSMS and emotional distress, and Specific Aim 2 demonstrated a significant relationship between emotional distress and total symptom severity, but failed to show a significant relationship between PSMS and total symptom severity. Based on the Baron and Kenny (1986) steps, mediation is unable to be established. However, bootstrapping, which does not assume normality and is recommended for small to moderate size samples, was used to examine the indirect effect of PSMS on CFS total symptom severity score via emotional distress. Based on 1000 bootstrap resamples, there is a significant indirect effect of PSMS on CFS total symptom severity scores (95% confidence interval = -.4586 to -.0647). Because this interval did not contain zero, there is statistical support for an indirect effect of perceived stress management skills on total symptom severity scores via emotional distress.

Specific Aim 5:

A fifth set of analyses was conducted to examine if the indirect effect between perceived stress management skills and fatigue or total symptom severity via emotional distress varied as a function of levels of pro-inflammatory cytokines, diurnal cortisol slope, or illness duration. Conditional indirect effects were tested using methods outlined Preacher, Rucker & Hayes (2007) on the significant models from Specific Aim 4 in order to determine if these models are more salient in some subgroups of participants with a higher degree of neuroimmune dysfunction and/or a longer illness duration. In order to examine these models, an interaction term was created using the independent variable (perceived stress management skills) and the proposed moderating variable (IL-2, IL-5, IL-6, IL-12, TNF- α , diurnal cortisol slope and illness duration). The regression coefficient from the interaction term to the mediator (emotional distress) and the regression coefficient from the mediator to the dependent variable (fatigue or total symptom severity) were examined for statistical significance in order to determine if different indirect effects exist for different conditional values of IL-2, IL-5, IL-6, IL-12, TNF- α , diurnal cortisol slope and/or illness duration. No significant moderation effects were found for the mediation model that examined total symptom severity as a dependent variable (all p 's > .05). Similarly no significant moderation effects were found for IL-2, IL-5, IL-12, TNF- α , diurnal cortisol slope or illness duration (all p 's > .05) for the mediation model that examined fatigue as the dependent variable. This indicates that the mediation model was unconditional, or, did not vary, in accordance with participants'

level of IL-2, IL-5, IL-12, or TNF- α , with participants' degree of diurnal cortisol slope, or with the length of participants' illness.

However, conditional indirect effects were seen when IL-6 was examined as a moderating variable on the relationship between PSMS and fatigue via emotional distress. Both the relationship between the interaction of IL-6 and perceived stress management skills and fatigue ($r = -.14$, $p = .009$) and the relationship between emotional distress and fatigue ($r = .22$, $p < .001$) were significant, indicating that the indirect effect of perceived stress management skills on fatigue via emotional distress was significant. In examining the conditional indirect effects at specific values of the moderator, it is seen that at one standard deviation below the mean of IL-6, the relationship between perceived stress management skills and fatigue via emotional distress is not significant ($z = -1.10$, $p = .273$) whereas the indirect effect model is significant at the sample's mean level of IL-6 ($z = -3.39$, $p = .0007$) and at one standard deviation above the mean level of IL-6 ($z = -3.42$, $p = .0006$). The significance of the conditional indirect effects was further supported through an examination of bootstrapped confidence intervals. The confidence interval for the indirect effect at one standard deviation below the mean of IL-6 was $-.0405$ to $.0079$. Because this interval contains zero, the indirect effect is not significantly different from zero, which indicates that in individuals within this sample with lower levels of IL-6, the effect of perceived stress management skills on fatigue via emotional distress is not statistically significant. The confidence intervals for the indirect effect at the mean level of IL-6 ($-.0655$ to $-.0162$) and at one standard deviation above the mean level of IL-6 ($-.1074$ to $-.0286$) both did not contain zero. These results support the

hypothesis that the mediation model would be more salient in individuals with a higher level of neuroimmune dysfunction, as indicated by higher levels of IL-6.

To examine the presence of the indirect effect in distinct subgroups of individuals with different degrees neuroimmune dysfunction, the mediation model was rerun in tertiles based on participants' IL-6 level. Using bootstrapping, the mediation model remained significant for participants in the high IL-6 subgroup as indicated by a 95% confidence interval of -.1139 to -.0050, but was not significant for participants in the low (95% confidence interval: -.0774 to .0075) or in the medium IL-6 group (95% confidence interval: -.0737 to .0151). A visual depiction of the relationships between perceived stress management skills and fatigue in the high IL-6 group compared to the same relationship in the low IL-6 group can be seen in Figure 4.

Exploratory Aim:

A final set of analyses was conducted to examine the socio-demographic characteristics of the moderator-defined subgroups in order to learn more about individuals most likely to benefit from stress management interventions. Because IL-6 was the only significant moderator found in Specific Aim 5, subgroups based on IL-6 were examined in this final set of analyses. Based on level of IL-6, participants were divided into tertiles to denote low, medium, and high levels of IL-6 relative to the rest of the sample. A one-way analysis of variance (ANOVA) was conducted to analyze differences in age (the sole continuous socio-demographic variable) between IL-6 subgroups, and no significant differences were found $F(2, 113) = .393, p = .676$.

Chi-square analyses were conducted to assess differences between IL-6 subgroups in the remaining categorical socio-demographic variables. There were no significant

differences in gender, $\chi^2(2, N = 114) = .194, p = .907$. Although the sample contained only 20 men, they were evenly distributed across groups with 7 in low tertile, 6 in middle tertile, and 7 in the high tertile. Women were similarly distributed across groups with 30 in the lowest tertile, 33 in the middle tertile, and 31 in the highest tertile. Similarly, there were no significant differences across IL-6 subgroups in regards to ethnic group $\chi^2(8, N = 114) = 6.043, p = .642$, relationship status $\chi^2(12, N = 114) = 7.933, p = .790$, smoking status $\chi^2(2, N = 114) = 3.271, p = .195$, or employment status $\chi^2(14, N = 114) = 20.216, p = .123$. However, upon closer inspection of the data points, there appeared to be some trends in the employment status data. Individuals who were employed full time more frequently fell into the low tertile ($n = 7$) or middle tertile ($n = 9$) than into the high tertile ($n = 3$), whereas those who were on disability demonstrated an opposite pattern with 18 participants falling into the high tertile, 15 in the middle tertile, and 13 in the low tertile. The breakdown of retired participants more closely mirrors that pattern of those who were employed, with 6 retired participants falling into the low IL-6 tertile group, 6 into the middle tertile group, and zero retired participants into the high tertile group.

CHAPTER 4: DISCUSSION

The present study aimed to evaluate whether having greater perceived stress management skills related to less chronic fatigue syndrome (CFS) symptoms via the influence of stress management skills on emotional distress levels in a sample of men and women diagnosed with CFS. Results of this study indicate that higher levels of perceived stress management skills relate to lower levels of emotional distress. This finding is novel to the CFS literature and is consistent with prior research in other clinical disease (e.g., cancer) populations, which has routinely linked greater perceived stress management skills with less distress and a higher quality of life (Faul et al., 2010; Antoni et al., 2006; Penedo et al., 2004; Penedo et al., 2006). Significant indirect relationships were found between greater perceived stress management skills and lower fatigue severity and between greater perceived stress management skills and lower total symptom severity via lower levels of emotional distress. These findings are in accordance with previous research that has revealed links between emotional distress and later CFS symptom exacerbations (Faulkner & Smith, 2008; Lutgendorf et al., 1995) and between coping mechanisms and CFS symptoms (Walker, 2009; Antoni et al., 1994). This study adds to the body of knowledge regarding emotional distress, coping and CFS symptoms by indicating that stress-reducing coping strategies (including relaxation, cognitive reappraisals, and interpersonal communication skills) may mitigate the severity of CFS symptoms by reducing individuals' emotional distress levels.

There was no significant relationship found between post-exertional malaise and emotional distress. This may have been a measurement issue, as the post-exertional malaise score was created by multiplying the reported frequency of post-exertional

malaise by the reported severity of post-exertional malaise using a single item from the CDC Symptom Inventory (Wagner et al., 2005). This was used because there is not a gold standard measure of post-exertional malaise in CFS research. However, the development and use of a more descriptive measure may serve to better illuminate a potential relationship between emotional distress and post-exertional malaise.

Additionally, although there were significant relationships between emotional distress and sleep difficulties and between perceived stress management skills and sleep difficulties, there was not a significant indirect effect of perceived stress management skills on sleep difficulties via emotional distress. This indicates that emotional distress is not a mediator in the relationship between perceived stress management skills and sleep difficulties. While emotional distress is often linked to sleep disturbances (Ford & Cooper-Patrick, 2001; Neckelmann et al., 2007) and some evidence suggests that stress management programs may improve sleep (Willert et al., 2010), there has not been prior research examining the influence of a comprehensive set of stress management skills on an individual's total sleep difficulties. Results of this study extend the line of research by indicating that perceived stress management skills and emotional distress independently relate to sleep difficulties in individuals with CFS. These findings provide a platform from which to conduct further investigation, perhaps examining these distress relationships in the context of individuals with and without a clinically significant mood disorders which exhibit pervasive sleep difficulties such as major depression and generalized anxiety disorder.

Neuroimmune Dysfunction

Another aim of the present study was to examine if perceived stress management skills and emotional distress were associated with indicators of neuroimmune dysfunction. A significant relationship was noted between perceived stress management skills and diurnal cortisol slope and between perceived stress management skills and IL-2 level. Greater perceived stress management skills were related both to a lower level of circulating plasma IL-2 and to a greater di-urnal cortisol slope. This may indicate that participants with greater perceived stress management skills have a less dysfunctional immune profile since past research has demonstrated elevated IL-2 levels in CFS patients (Patarca et al., 1994) and that greater levels of IL-2 could indicate greater inflammatory activity (Smith, 1988). However, since consistent associations between perceived stress management skills and other pro-inflammatory cytokines were not revealed in the present analyses, this isolated finding should be cautiously interpreted.

The association between greater perceived stress management skills and a more sharply pitched negative diurnal cortisol slope indicates that individuals with a greater ability to manage stress demonstrated better hypothalamic pituitary adrenal (HPA) axis regulation (Sephton et al., 2000; Stone et al., 2001). A sign of HPA axis dysfunction, dysregulated cortisol production, has been widely observed in the CFS literature. Compared to healthy controls, CFS patients have been seen to have low overall levels of cortisol (hypocortisolism), a decreased awakening response, and a flatter diurnal cortisol slope (Demitrack & Crofford, 1998; Heim et al., 2009; Nater et al., 2008; Roberts et al., 2004). While there was not a significant relationship between fatigue and participants' degree of diurnal cortisol slope, this was not surprising as research regarding a

relationship between cortisol levels and fatigue within CFS has been inconsistent. Some researchers have revealed a link between HPA dysfunction and fatigue using less conventional measurement methods (Gaab et al., 2004; Torres-Harding et al., 2008) but significant relationships have not been noted using standard methods of measuring cortisol dysfunction (Rubin et al., 2005; ter Wolbeek et al., 2007). While one could theorize that HPA axis dysfunction, observed as cortisol dysregulation, is more relevant in the development of CFS than it is in the continued maintenance of CFS symptoms (Heim, Ehlert & Hellhammer, 1999), it is also possible that there is some stress management-dependent aspect regarding alterations in the endocrine and immune systems that were simply not revealed in the present analyses due to their cross-sectional nature. These relationships should be further explored in using longitudinal data collected at multiple intervals in order to examine the potential time-dependent nature of these processes.

Subgroup analyses

The study also examined whether the association between perceived stress management skills and fatigue via emotional distress varied in accordance with participants' levels of circulating cytokines, degree of diurnal cortisol slope, and/or participants' illness duration. It was hypothesized that the indirect relationship between perceived stress management skills and CFS symptoms via emotional distress would be most pronounced in individuals with a longer illness duration and the greatest degree of neuroimmune dysfunction, as indicated by elevated levels of circulating IL-2, IL-5, IL-6, IL-12, TNF- α , and a reduced diurnal cortisol slope. Although there is preliminary research indicating that individuals with a longer illness duration utilize more adaptive

coping methods than those with a shorter illness duration, there were no moderating effects found regarding individual's length of illness (Brown, Brown, & Jason, 2010). Individuals' level of IL-6 was found to moderate the indirect relationship between perceived stress management skills and fatigue severity via emotional distress. The indirect relationship existed in those participants with elevated levels of IL-6, but not in participants with lower levels of IL-6 relative to the rest of the sample. Elevations of IL-6 in samples of CFS patients have been one of the most well-documented neuroimmune abnormalities noted in the literature (Broderick et al., 2010; Carlo-Stella et al., 2006; Gaab et al., 2005). Fitting with prior research, the present sample demonstrated high levels of IL-6 overall (mean IL-6 level = 11.5 pg/ml). Therefore, those with relatively lower IL-6 levels within the sample were viewed as having closer to normal IL-6 levels relative to those observed in the general population (Nater, 2008; Robinson et al., 2010). These results demonstrate that the relationship between perceived stress management skills and fatigue via emotional distress is indeed most salient in individuals with a higher degree of neuroimmune dysfunction as indicated by greater elevation of circulating plasma IL-6. This paves the way for future research regarding the creation of distress-sensitive subgroups of CFS patients. Future research may also examine the effect of an IL-6 antagonist, tocilizumab (Actemra; Genentech, Inc), on individuals' perceived stress management skills, emotional distress, and CFS symptoms. Tocilizumab has been seen to block IL-6 from binding to IL-6 receptors, thus inhibiting the inflammatory response (Smolen et al., 2008; Schiff et al., 2011). Exploring associations in this manner could help researchers determining the temporality and causality of the relationships presented in this study.

It should be noted that the indirect effect of perceived stress management skills on fatigue was not conditional for other indicators of neuroimmune dysfunction (IL-2, IL-5, IL-12, TNF- α , degree of diurnal cortisol slope). Although the indirect effect of perceived stress management skills on fatigue was not conditionally linked to cortisol levels, future research should test this model using longitudinal data in an attempt to provide additional support for the theory that cortisol levels are linked with one's ability to respond to psychosocial intervention (Jason et al., 2008; Roberts et al., 2010). Based on the results of this study, and on the consistently observed relationship between IL-6 and health status indicators (Collado-Hidalgo, et al., 2006; Dantzer & Kelley, 2007, Davis et al., 2008; Lutgendorf et al., 1999; Thomas et al., 2011; Vollmet-Conna et al., 2004), IL-6 may be an ideal biomarker for identifying a subgroup of CFS patients who are particularly sensitive to the impact of emotional distress on the severity of their CFS symptoms.

However, participants with elevated IL-6 levels may differ systematically from CFS patients demonstrating other neuroimmune abnormalities. Analyses were conducted for the exploratory aim of this study examining the socio-demographic characteristics of the IL-6 tertile subgroups in order to learn more about individuals most likely to benefit from stress management interventions. No significant findings emerged in these analyses. This lack of significant findings lend to the potential value of IL-6 as a biomarker for identifying individuals with a propensity for distress-sensitive symptoms. However, these results may have been limited by the fact that the sample was fairly homogenous in regards to socio-demographic characteristics (see Table 1). Due to the breadth of research surrounding inflammation and race/ethnicity, it may appear notable that there was the lack of significant differences among subgroups regarding

race/ethnicity. Although prior studies examining ethnic and racial differences in circulating cytokines primarily have found differences between African Americans and Caucasian/Anglo Americans (Kiecolt-Glaser et al., 2003; Mills et al., 2007; Walston et al., 2007) the present sample includes just three African American participants, compared to 92 Caucasian participants.

We did not find significant differences in frequency of health behaviors such as smoking in the IL-6 defined subgroups. However, few participants endorsed smoking in the prior 90 days ($n = 15$). Upon a closer inspection of the data points, it appeared that there was a trend for smokers to fall into the high IL-6 group. Of those 15 participants who endorsed smoking, 8 fell into the high IL-6 subgroup, while only 4 fell into the low IL-6 subgroup. This is consistent with the literature surrounding tobacco use and inflammation, which typically indicates that smokers express higher levels of circulating IL-6 (Bermudez et al. 2002; Mendall et al., 1997). Beyond demographic and health behavior characteristics examined, it is possible that participants with elevated IL-6 levels have co-morbid medical conditions that could account for IL-6 elevations, however, information regarding medical comorbidities was not available for the study sample.

Limitations

There are several limitations to this study that may limit the generalizability of these findings. These methodological limitations include the use of the Fukuda et al. (1994) diagnostic system in selecting participants with CFS, the high degree of education within the sample, the use of a cross-sectional design, the lack of data for some potential covariates, the assessment of immune parameters at a single time point, and the use of primarily self-report measures of perceived stress management skills, distress, and CFS

symptoms. The Fukuda et al. (1994) diagnostic system has been the standard criteria in the United States for almost two decades, and while it has been viewed as a fairly rigorous method, particularly compared to the criteria developed by Reeves and colleagues (2005), some researchers have questioned the specificity of the system (Jason et al., 2004). Recently, an expanded international case definition of myalgic encephalomyelitis (ME) was established which has more stringent criteria and aims to select a more homogenous patient population with a common underlying pathophysiology (Carruthers et al., 2011). However, the number of participants in the current study who meet the new international case definition is unknown. Future work may benefit from including these diagnostic criteria,

In examining the socio-demographic information of the participants, 86.8% of the sample was seen to have at least some college education, resulting in a highly educated sample and 79.5% of the sample identified as non-Hispanic White. While this degree of education and the high proportion of non-Hispanic White participants is not uncommon in research samples of CFS patients, (Jason et al., 2007; Servaes et al., 2000), it is possible that the findings may not generalize to a less educated sample or to a more ethnically diverse sample.

Additionally, there are a few limitations in regards to the measurement and analysis of both the immune and the endocrine parameters in the current study. Circulating plasma cytokines were measured from a single blood draw, which occurred sometime between 11 AM and 3 PM. This blood draw time window was chosen in order to limit potential variations due to diurnal changes in circulating cytokines, however, the existence of variations within this time frame is still within the realm of possibility. The

literature of diurnal variations of IL-6 has been fairly mixed with some researchers indicating that IL-6 levels tend to fluctuate throughout the day (Alesci et al., 2005; Bonda et al., 2010) while others have found it to be generally stable (Haack et al., 2002; Bollinger et al., 2010). While significant gender differences were not noted in IL-6 levels within the present study, further research may analyze women and men in isolation. Researchers often examine men and women in separate samples due to the intricate relationship between androgens and cytokine production (Bebo et al., 1999; Bouman, Heineman, & Faas, 2005; Fletcher et al., 2009). Further research examining males and females separately could determine if the relationships noted in the present study are equivalent between men and women with CFS. Additionally, information regarding participants' body mass index (BMI) was not available, therefore BMI was unable to be examined as a potential covariate. Relationships observed between BMI and cortisol variability have been inconsistent, with some studies failing to find a relationship (Bower et al., 2005; Farag et al., 2008) while other research indicates that individuals with a high BMI have a flatter cortisol slope (Daniel et al., 2006). However, high BMI has been repeatedly linked to high levels of circulating pro-inflammatory cytokines, including IL-6, so the results of this study may be interpreted as preliminary findings that demand replication (Himmerich et al., 2006; Panagiotakos, et al., 2005).

Finally, the fact that all symptom reports and psychological measures were based on self-reported data at the same time point does not allow one to determine whether actual stress management skills predated the theorized fluctuations in distress and CFS symptoms. Because it is possible that one's level of current illness severity could affect both one's perceptions of stress management skills and of emotional distress, or that

one's current level of emotional distress could affect one's perceptions of present stress management skills and of illness severity, the longitudinal effect of changes in stress management skills should be explored in order to better illuminate the relationships between these skills, emotional distress, and CFS symptom reports. Additionally, the temporality of the relationship between circulating IL-6 levels and changes in perceived stress management skills, emotional distress and CFS symptoms should be examined in order to further elucidate the model.

There are also limitations in the accurate assessment of emotional symptoms in CFS, due to the complex nature of the illness. Some test items that have been shown to be reliable indicators of emotional distress in healthy populations may be reflective of illness severity in population of individuals with CFS, as the illness consists of a constellation of physical and cognitive symptoms that may be included on established measures of anxiety and depression similar to those used in the present study. Due to this potential overlap of physical and emotional symptom assessment, there is a need for the development of emotional distress measures that do not include CFS symptoms.

Conclusions

The present study examined relationships between perceived stress management skills, emotional distress, and CFS symptoms reports, and further placed these relationships into the context of neuroimmune dysfunction. These findings provide basic support for the theory that individuals with CFS who are confident in their stress management abilities will demonstrate lower levels of emotional distress and will endorse a lower level of symptom severity. Additionally, these associations appear to be most notable in a subgroup of individuals with a high degree of neuroimmune

dysfunction, as evidenced by high levels of circulating IL-6. Together, these findings indicate that stress management interventions may be appropriate for individuals with CFS, particularly those with high levels of IL-6, as increasing patients' stress management skills may in turn reduce emotional distress and reduce symptom severity. However, further work may be warranted utilizing cytokine network analyses in order to determine if particular patterns of inflammatory cytokine activity, perhaps including IL-6, can more astutely identify a distress-sensitive subgroup (Broderick et al., 2010).

Cognitive-behavioral therapies (CBT) have been commonly used as a psychosocial component to CFS treatment and have previously been seen to reduce fatigue (Knoop et al., 2008; Prins et al., 2001; Stulemeijer et al., 2005; White et al., 2011). However, past CBT interventions have primarily focused on cognitive restructuring to change individuals' illness beliefs surrounding activity with an increase in physical activity as a primary treatment goal. Results of a recent meta-analysis demonstrate that physical activity did not mediate the effects of CBT on reductions of fatigue (Wibourg et al., 2010). This study provides theoretical support for a more cogent explanation regarding the relationship between CBT and fatigue reductions such that a reduction in emotional distress is often achieved through participation in CBT. A pilot study of group-based cognitive-behavioral stress management (CBSM) for patients with CFS exhibited an ability to reduce stress, as well as decrease symptom severity, while improving self-reported quality of life (Lopez et al., 2011). CBSM has been an effective method of lowering emotional distress and improving quality of life, as well as health indicators in a wide range of medical populations including individuals with HIV and various cancer diagnoses (Antoni et al., 2000; Antoni et al., 2006a, Antoni et al., 2009,

Cruess et al., 2000; McGregor et al., 2004; Penedo et al., 2007). Due both to the initial benefits found using CBSM in a CFS patient population and to the broad benefits noted in other medical populations, further research is warranted regarding the use of a CBSM intervention in a CFS patient population. There appears to be a potential ability of such an intervention to increase stress management skills, lower emotional distress reports and reduce physical symptom severity. Results from the present study suggest that the effects of a CBSM intervention may be greatest in individuals with high levels of IL-6; therefore future research should examine this possibility.

Tables

Table 1. Demographic characteristics of the study sample.

	M	SD
Age	50.71	11.49
	N	%
Gender		
Female	97	83
Male	20	17
Ethnic Identification		
Caucasian (non-Hispanic)	92	79.5
African American	3	2.6
Hispanic	18	15.4
Asian/Asian American	1	0.9
Biracial	2	1.7
Relationship Status		
Single	26	22.2
Married or Equivalent Relationship	50	42.7
Separated	2	1.7
Divorced	21	17.9
Widowed	6	5.1
In a monogamous relationship	11	9.4
Other	1	0.9
Employment status		
Full-Time	20	17.1
Part-Time	11	9.4
Student	2	1.7
On Disability	47	40.2
Retired	12	10.3
Unemployed	16	13.7
Volunteer worker	1	0.9
Other	8	6.8
Education level		
< 8th grade	1	0.9
High school or GED	13	11.1
Trade school	1	0.9
Some college	37	31.6
College graduate	40	34.2
Graduate degree	25	21.4

Table 2. Descriptive statistics of self-report variables.

	Mean	SD	Range
FSI Intensity	26.74	5.27	14 - 38
POMS Fatigue-Inertia	26.37	5.07	14 - 35
POMS Vigor-Activity	15.25	4.31	8 - 25
Fatigue Composite	0	2.44	-6.15 - 5.32
Post-Exertional Malaise	13.59	7.68	0 - 25
PSQI Total	13.30	3.33	6 - 20
CDC Total Symptom Severity	43.99	14.48	13 - 83
CDC Total Symptom Frequency	45.48	14.82	14-83
PSS	30.96	8.97	10 - 56
CES-D	24.93	12.53	2 - 57
POMS Depression-Dejection	33.23	13.91	15 - 70
POMS Anxiety-Tension	17.98	7.71	4 - 38
Emotional Distress Composite	0	3.52	-6.13 - 8.70
Perceived Stress Management Skills	42	8.75	21 - 63

Table 3. Descriptive statistics of biological variables.

	Mean	SD	Range
IL-2	7.37	8.39	0 - 37.65
IL-5	6.59	8.42	.10 - 34.19
IL-6	11.49	19.12	.80 - 94.55
IL-12	9.94	16.23	.04 - 75.68
TNF- α	25.26	45.43	0 - 215.31
Cortisol slope	-.12	.15	-1.19 - .37

Table 4. Regression results for the influence of perceived stress management skills (PSMS) and emotional distress on CFS symptoms.

Independent variable	Dependent Variable	Beta	p-value
PSMS	Fatigue	-.353	< .001
PSMS	Sleep difficulties	-.189	0.035
PSMS	Post-exertional malaise	-.088	0.356
PSMS	Total symptom severity	-.056	0.554
Emotional Distress	Fatigue	0.544	< .001
Emotional Distress	Sleep difficulties	0.247	0.006
Emotional Distress	Post-exertional malaise	0.128	0.166
Emotional Distress	Total symptom severity	0.261	0.005

Note: Analyses including sleep difficulties and total symptom severity controlled for gender. Smoking status was included as a covariate in analyses including post-exertional malaise.

Table 5. Regression results for the influence of perceived stress management skills (PSMS) and emotional distress on biological indicators of neuroimmune dysfunction.

Independent variable	Dependent Variable	Beta	p-value
PSMS	IL-2	-.197	0.040
PSMS	IL-5	-.022	0.820
PSMS	IL-6	0.022	0.820
PSMS	IL-12	-.055	0.565
PSMS	TNF- α	-.059	0.535
PSMS	Cortisol slope	-.207	0.028
Emotional Distress	IL-2	-.080	0.404
Emotional Distress	IL-5	0.084	0.379
Emotional Distress	IL-6	0.078	0.404
Emotional Distress	IL-12	-.031	0.742
Emotional Distress	TNF- α	0.036	0.705
Emotional Distress	Cortisol slope	0.110	0.246

Note: Age was included as a covariate in analyses including IL-2, gender was included as a covariate in analyses including IL-5, and smoking status was included as a covariate in analyses including IL-6.

Figures

Figure 1. Regression coefficients for the relationship between Perceived Stress Management Skills and Fatigue as mediated by Emotional Distress. The values outside of parentheses are the simple regression coefficients and the values in parentheses are the regression coefficients for the full mediation model * $p < .05$, ** $p < .01$.

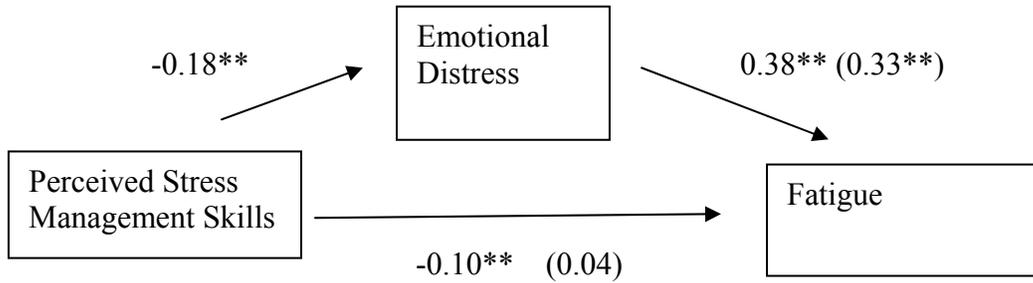


Figure 2. Regression coefficients for the relationship between Perceived Stress Management Skills and Sleep Difficulties as mediated by Emotional Distress. The values outside of parentheses are the simple regression coefficients and the values in parentheses are the regression coefficients for the full mediation model * $p < .05$, ** $p < .01$.

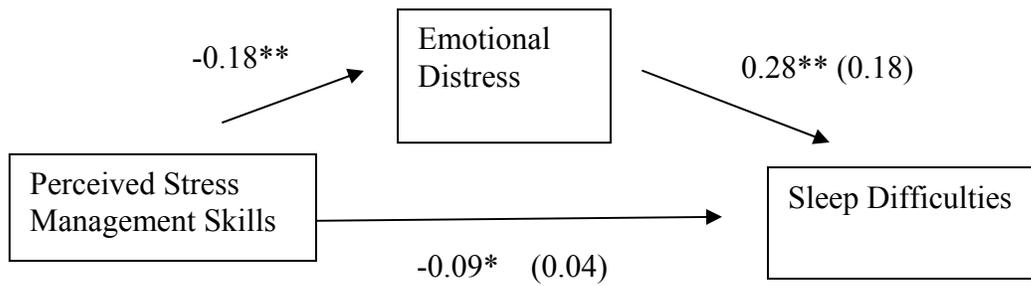


Figure 3. Regression coefficients for the relationship between Perceived Stress Management Skills and Total Symptom Severity as mediated by Emotional Distress. The values outside of parentheses are the simple regression coefficients and the values in parentheses are the regression coefficients for the full mediation model * $p < .05$.

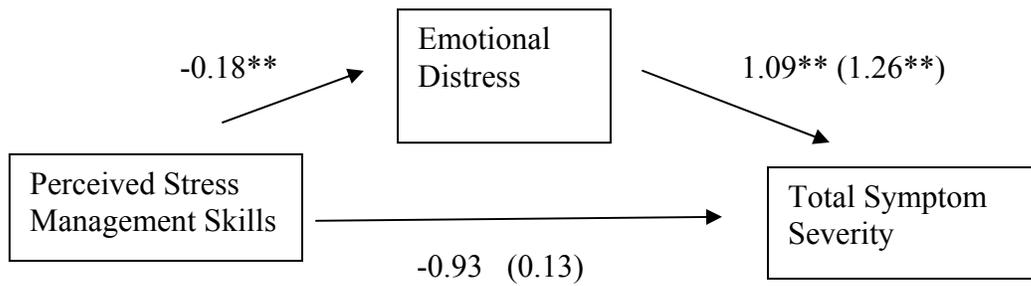
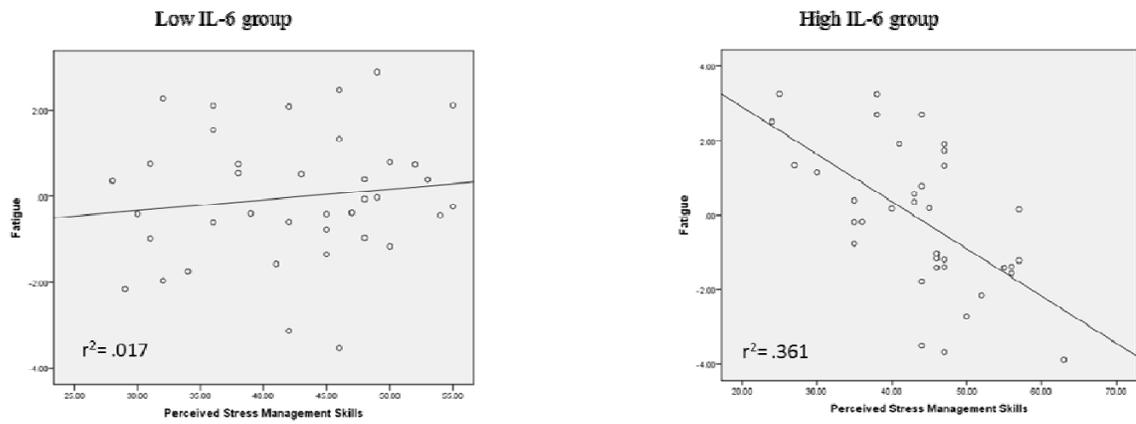


Figure 4. The relationship between perceived stress management skills and fatigue in participants within the low IL-6 tertile group and in participants within the high IL-6 tertile group.



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