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Effects of Telephone-Delivered Cognitive Behavioral Stress Management Intervention on Fatigue Interference and Neuroimmune Function in Chronic Fatigue Syndrome

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EFFECTS OF TELEPHONE-DELIVERED COGNITIVE BEHAVIORAL STRESS
MANAGEMENT INTERVENTION ON FATIGUE INTERFERENCE AND
NEUROIMMUNE FUNCTION IN CHRONIC FATIGUE SYNDROME

By

Daniel Lee Hall

A DISSERTATION

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MANAGEMENT INTERVENTION ON FATIGUE INTERFERENCE AND
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Effects of Telephone-Delivered
Cognitive Behavioral Stress
Management Intervention on Fatigue
Interference and Neuroimmune Function
in Chronic Fatigue Syndrome.

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The perceived impact of chronic fatigue on daily living (i.e., fatigue interference)

is particularly relevant for patients diagnosed with Chronic Fatigue Syndrome/Myalgic

Encephalomyelitis (CFS/ME), a medically unexplained illness associated with

neuroendocrine and immune abnormalities. Literature suggests that fatigue interference

is higher among women with CFS/ME than with other women facing chronic fatigue

concerns, such as cancer survivors. To date, these comparisons have been primarily

qualitative, limiting the ability to statistically control for related factors such as fatigue

severity. Furthermore, greater fatigue interference in CFS/ME may relate to a suppressed

cortisol awakening response (CAR) and heightened levels of the pro-inflammatory

cytokine interleukin-6 (IL-6), though these associations have not been tested before.

Finally, previous cognitive behavioral interventions including cognitive behavioral stress

management (CBSM) have been shown to be helpful for this population, leading to

improvements in psychological functioning and less dysregulated physiology. Given the

high degree of fatigue and debilitating symptoms in CFS/ME, the efficacy of a 10

session, telephone-delivered CBSM intervention on fatigue interference and

neuroimmune function over time was investigated.

In Study 1, previously collected data on fatigue interference and fatigue severity were examined among 95 women with CFS/ME and 67 fatigued breast cancer survivors approximately 5 years post treatment. Analyses controlled for age, race/ethnicity, education level, marital status, employment status, number of children, time since diagnosis, and fatigue severity. Women with CFS/ME were found to endorse higher fatigue interference scores, $p < .001$. Next, neuroimmune correlates to fatigue interference scores were assessed among the CFS/ME sample. Again controlling for relevant covariates, higher fatigue interference scores were associated with a more diminished CAR with respect to increase (CARi), $p = .02$. No relationships were observed between fatigue interference and the CAR with respect to ground (CARg) or IL-6 levels. Additionally, these relationships were not amplified in the presence of high depressed mood.

In Study 2, the effects of a 10-session, telephone-delivered cognitive behavioral stress management (CBSM) intervention on these variables were assessed. Participants included 93 women with CFS/ME from Study 1 who were randomized to either the CBSM ($n = 53$) or attention-matched control condition ($n = 40$). Results failed to identify intervention effects on changes in these variables from baseline (BL) to five months (5M) or nine months (9M) later. This may have been due to comparisons with a strong control condition, or to potential limitations in participants' engagement via telephone. Interestingly, the CARi, CARg, post-awakening cortisol, and IL-6 were observed to decrease significantly over time in both conditions ($ps < .05$). Mechanisms of change might include gains in self-efficacy due to mastery of skills in either CBSM or attention control conditions. Examination of potential lagged effects of CBSM on cortisol

and IL-6 levels warrants future investigation, as lowest levels of these biomarkers were at 9M. Future studies could also use videophone delivery of CBSM, which might bolster participant engagement in sessions and help to reach homebound or highly symptomatic CFS/ME patients. Emerging biomarkers of neuroimmune dysfunction in this population may yield insights into mechanisms underlying this elusive illness and help to identify new targets for psychosocial approaches to care.

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Chapter 1

Introduction

Overview. Fatigue is a common and potentially debilitating phenomenon. It is estimated that 15 to 25 percent of the general population is presently experiencing fatigue that will last between one and 30 days (Jason, Sunnquist, Brown, & Reed, 2015; Lewis & Wessely, 1992). Some individuals have prolonged fatigue lasting up to five months (8% prevalence) or chronic fatigue lasting six months or longer (4% prevalence) (Jason et al., 1999; Jason et al., 2015). In medical populations, *chronic fatigue* can impair one's quality of life resulting in functional losses, depressed mood, and neuroimmune changes (Antoni et al., 1994; Bower, Ganz, Aziz, & Fahey, 2002; Cella, White, Sharpe, & Chalder, 2013). The impact of fatigue is particularly relevant for patients diagnosed with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME), a medical disorder characterized primarily by severe, debilitating chronic fatigue with no established etiology (Fukuda et al., 1994).

CFS/ME is frequently associated with comorbidities that collectively result in decrements in social, occupational, emotional, and physical functioning (Cella et al., 2013). As will be discussed, the economic burden of CFS/ME for patients and society is substantial. Comorbid depression occurs in approximately 32% of CFS/ME patients, and the majority of patients evidence marked dysfunctions in nervous, endocrine, and immune system functioning (Cella et al., 2013; Fukuda et al., 1994; Klimas, Broderick, & Fletcher, 2012; Reeves et al., 2007). Jointly referred to as *neuroimmune function*, biomarkers of the neuroendocrine (i.e., cortisol levels) and immune (i.e., inflammation) systems and their dysregulation have been linked with CFS/ME illness burden (Fletcher,

Zeng, Barnes, Levis, & Klimas, 2009; Klimas et al., 2012; Klimas, Salvato, Morgan, & Fletcher, 1990).

Links between neuroimmune dysregulation in CFS/ME and psychological phenomena are less well established. Individuals with CFS/ME often report focusing on their fatigue, anticipating it being burdensome, and fearing that it will be worse in the future (Fry & Martin, 1996; Knoop, Prins, Moss-Morris, & Bleijenberg, 2010; Stahl, Rimes, & Chalder, 2013; Wiborg, Knoop, Prins, & Bleijenberg, 2011). Importantly, patients' beliefs of the psychosocial impact that fatigue has on their life, also known as *fatigue interference*, may impact their overall health. While to date no study has directly measured fatigue interference in CFS/ME, theoretically these perceptions may contribute to worsened physical health states through various pathways. As will be further discussed, fatigue interference can discourage patients from engaging in physical activity (White et al., 2011; Wiborg, Knoop, Stulemeijer, Prins, & Bleijenberg, 2010), lead to under-utilization of social support resources (Wiborg et al., 2011), or contribute to depressive mood states (Cella et al., 2013; Friedberg & Krupp, 1994; Petrie, Moss-Morris, & Weinman, 1995; Price, Mitchell, Tidy, & Hunot, 2008; Stahl et al., 2013; Traeger et al., 2011; White et al., 2011). Among patients with CFS/ME, no study has examined links between the perception of fatigue as highly interfering in one's daily activities and indicators of physiological functioning. In this dissertation, CFS/ME patients' fatigue interference levels will be measured and correlated with parameters of neuroimmune function as indices of physiological health.

Of clinical import, fatigue interference could be a suitable target for psychosocial interventions aiming to reduce the burden of this onerous illness. Among treatments

available for CFS/ME, cognitive behavioral therapy (CBT) is among the most efficacious at reducing illness burden and improving patients' mental and physical health (Castell, Kazantzis, & Moss‑Morris, 2011; Jason et al., 2007; Lopez et al., 2011; Roberts et al., 2010; Roberts, Papadopoulos, Wessely, Chalder, & Cleare, 2009; White et al., 2011). CBT also has the benefit of being more cost-effective than other interventions for CFS/ME, including support groups and pharmacological treatment (McCrone, Ridsdale, Darbishire, & Seed, 2004; Scheeres, Wensing, Bleijenberg, & Severens, 2008; Severens, Prins, Van der Wilt, Van der Meer, & Bleijenberg, 2004). Recently, a form of CBT called cognitive behavioral stress management (CBSM), which includes components targeting stress management, social support, and relaxation, was shown to improve quality of life among CFS/ME patients (Lopez et al., 2011). For reasons that will be discussed, CBSM may also be particularly helpful at reducing fatigue interference and neuroimmune dysfunction in this population.

The modality of psychosocial intervention delivery is another important consideration in this population, as patients' fatigue levels can impede their ability to attend in-person sessions (Wiborg, van der Werf, Prins, & Bleijenberg, 2010). Thus, telephone-delivered CBSM may be particularly suited to the needs of this population. This dissertation will report on the first randomized controlled trial to examine whether telephone-delivered CBSM can be a helpful tool for decreasing fatigue interference and neuroimmune dysfunction in CFS/ME.

Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. In 1988, Holmes et al. coined the term "chronic fatigue syndrome" to describe the symptom presentation of

patients formerly diagnosed with "chronic Epstein-Barr virus syndrome". Accumulating evidence suggested that links between positive Epstein-Barr virus serologic results and presenting symptoms were spurious, so the investigators opted for a term with no presumed etiology but rather a description of clustering symptoms (Holmes et al., 1988). Since then, numerous case definitions have emerged with the aim of establishing reliable diagnostic criteria, with some purporting the use of the term "Myalgic Encephalomyelitis" (ME; for recent review, see Brurberg, Fonhus, Larun, Flottorp, and Malterud, 2014). Recently, the Institute of Medicine called for a renaming of the illness to "Systemic Exertion Intolerance Disease". It includes a revised case definition that has already faced considerable backlash, prompting leading researchers to suggest continuing to use previous criteria while the consequences of the IOM's redefinition are empirically examined (Friedberg, 2015; Jason, Sunnquist, Kot, & Brown, 2015; Jason et al., 2015). Pragmatically, the term *Chronic Fatigue Syndrome/Myalgic Encephalomyelitis* (CFS/ME) has been adopted by researchers and will therefore be used throughout this dissertation.

As described earlier, CFS/ME is characterized in part by severe, unexplained fatigue not alleviated by rest for at least 6 months (Fukuda et al., 1994). CFS/ME patients must also experience at least 4 out of the following 8 symptoms, not predated by 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). The patient's difficulties with fatigue cannot be better explained by another medical condition, such as rheumatoid arthritis or hypothyroidism, or medical treatment, such as chemotherapy.

CFS/ME has prevalence in the United States as high as 2.54%, the majority of whom are females (Fukuda et al., 1994; Reeves et al., 2007). Due to loss in household and work productivity, the economic burden of CFS/ME in the United States is estimated to be between $9.1 Billion and $23.9 Billion annually in direct and indirect costs (Jason, Benton, Valentine, Johnson, & Torres-Harding, 2008; Lin et al., 2011; Reynolds, Vernon, Bouchery, & Reeves, 2004). Collectively, CFS/ME is an illness with severe and debilitating consequences for patients, their families, and society at large. To better understand potential targets for intervention, an overview of key physiological disruptions associated with this illness is provided below.

Neuroimmune Dysfunction in CFS/ME. The term "neuroimmune" refers jointly to neuroendocrine and immune systems in the body. Neuroendocrine regulation is largely determined by the hypothalamus-pituitary-adrenal cortical (HPA) axis, a psychoneuroendocrinological system known to activate in response to perceived stress or alarm (Fries, Dettenborn, & Kirschbaum, 2009; Kudielka, Schommer, Hellhammer, & Kirschbaum, 2004). The HPA axis is responsible for regulating secretion of cortisol, a hormone released by the adrenal cortex that is associated with a number of regulatory processes (e.g., learning, memory, emotion, metabolism, sleep, and reproductive behavior and physiology).

Cortisol regulates cellular activity through glucocorticoid receptors and mineralocorticoid receptors found in most cells (Buckley & Schatzberg, 2005). After binding to one of these receptor sites, the resulting complex translocates to the cell nucleus, modifies genetic expression to influence cellular activity, including the

breakdown of lipids and proteins by cells (Miller, Chen, & Cole, 2009). Cortisol has widespread influence in regulating important bodily processes. It is involved in multiple activities related to cognition, including learning, memory, and emotion (via its use in glucose transport and glucose utilization in the brain); appetite, metabolism, and reproductive behavior and physiology (decreasing both the release of growth hormone and insulin sensitivity); and inflammatory and immune responses (Sapolsky, Romero, & Munck, 2000). Cortisol also triggers the liver to produce additional glucose (Miller et al., 2009). In this role, cortisol can promote the release of additional energy for hours, as opposed to the immediate, short-lasting bursts of energy provided via the Sympatho-Adrenal-Medullary network (Denson, Spanovic, & Miller, 2009).

Due to its effects on energy metabolism and immune function, cortisol has been the subject of substantial investigation in the CFS/ME literature. In research settings, cortisol is typically sampled throughout the day to obtain information about diurnal patterns of secretion. Cortisol secretion follows a circadian pattern, peaking within 30 minutes after awakening and, generally, gradually decreasing throughout the day (Weitzman et al., 1971). Levels of cortisol upon awakening and soon thereafter (also known as the cortisol awakening response; CAR) are considered to reflect basal HPA axis activation and are commonly used as a proxy for overall HPA axis functioning (Chida & Steptoe, 2009; Fries et al., 2009).

In studies of adults with CFS/ME, findings consistently indicate a pattern of hypocortisolism, with an attenuated CAR and less total cortisol output throughout the day than healthy controls (Demitrack et al., 1991; Di Giorgio, Hudson, Jerjes, & Cleare, 2005; Hall et al., 2014; Hornig et al., 2015; Nater et al., 2008; Poteliakhoff, 1981;

Roberts, Wessely, Chalder, Papadopoulos, & Cleare, 2004; Tak et al., 2011). For example, after adjusting for awakening levels, Roberts and colleagues (2004) examined differences in the total amount of cortisol secreted by their CFS/ME sample (n = 56) over the first 30 minutes of awakening versus that of a healthy control sample (n = 35). The authors found that increases in total cortisol secretion among patients with CFS/ME were approximately half as large. In their meta-analysis of 82 studies measuring HPA axis activity in functional somatic disorders (i.e., CFS/ME, fibromyalgia, and irritable bowel syndrome), Tak and colleagues (2011) advise that studies prioritize measuring the CAR for two related reasons. First, hypocortisolism was most evident in morning levels of cortisol. The authors suggest that future studies should examine predictors and consequences of these low morning cortisol levels, as this trend characterized these populations' neuroendocrine functioning. Second, afternoon and evening cortisol levels tended to vary greatly among studies, which the authors suggest could be due to poor adherence to sampling schedules. Morning samples had better adherence to sampling protocols and therefore more reliable data.

Suppression of the CAR has been linked to CFS/ME patients' deficits in energy, concentration, metabolism, and recovery post-exertion (Hall et al., 2014; Heim, Ehlert, & Hellhammer, 2000; Hornig et al., 2015; Janssens et al., 2012; Nater et al., 2008; Powell, Liossi, Moss-Morris, & Schlotz, 2013; Roberts et al., 2004). One study by Nater and colleagues (2008) compared CARs of 75 CFS/ME patients with those of 110 healthy controls. Participants were medication-free, and age and sex-matched. The authors found an attenuated CAR, operationalized as the total output of cortisol from 6:30am to 8:00am with respect to increase from baseline, in CFS/ME patients versus their healthy

counterparts. Furthermore, lower CARs were associated with worse physical fatigue. Interestingly, both findings were only evidenced among female participants. Nater et al. concluded that a suppressed CAR is implicated as a key pathophysiological mechanism underlying CFS/ME in women. Recently, our research group has found that the total amount of cortisol released from awakening to 30 minutes post-awakening is negatively associated with post-exertional malaise severity, after controlling for participant age and sex (Hall et al., 2014). Not only is suppression of the CAR linked with poor health states in CFS/ME, but increased CAR levels can predict better outcomes. Nijhof and colleagues (2012, 2015) conducted an RCT that targeted, among other factors, the CAR in adolescents with CFS/ME. The intervention comprised of 20 internet-delivered cognitive behavioral therapy sessions lasting 6 months. Notably, remission of symptoms at the end of treatment was significantly related to increased levels of cortisol upon awakening; one standard deviation increase in the CAR from pre to post-intervention was associated with 93% higher odds of recovery.

Given these findings, why might suppression of the CAR influence physical health states in CFS/ME? Poor utilization of cortisol may impair energy metabolism throughout the CFS/ME patient's body, including musculoskeletal cells, organ tissues, and cells related to immune function (Morris & Maes, 2013; Powell et al., 2013; Stone et al., 2001). It may also result in weakened utilization of peripheral blood mononuclear cells (PBMCs) such as monocytes, immune cells which help fight infection and help repair diseased cells. Monocytes are often "called to action" by receiving cortisol signals on glucocorticoid receptors attached to their cell membranes (Quax et al., 2013; Sorenson & Jason, 2013). As previously described, this binding, and resulting translocation of a

glucocorticoid-receptor complex to the nucleus, triggers cellular responses. Recent findings suggest that glucocorticoid receptors on monocytes of CFS/ME patients have polymorphisms that effectively disrupt their ability to process signals from cortisol. Rajeevan and colleagues (2007) found polymorphisms in the glucocorticoid receptor gene (*NR3C1*) in CFS/ME patients when compared to patients with sub-clinical fatigue and non-fatigued controls. Thus hypocortisolism in CFS/ME may exacerbate already poor cortisol utilization by patients' PBMCs, and could therefore indicate a quieting of communication between the nervous and immune systems.

Indeed, overall, CFS/ME patients tend to exhibit a chronically activated and dysregulated immune system, marked in part by the elevated presence of inflammatory biomarkers (Bansal, Bradley, Bishop, Kiani-Alikhan, & Ford, 2012; Brenu et al., 2012; Brenu et al., 2011; Broderick et al., 2010). This finding is perhaps due to several diagnostic criteria for CFS/ME, including myalgia, arthralgia, tender lymph nodes, sore throat, and post-exertional malaise, being associated with high inflammatory states (Klimas et al., 1990). Recent evidence implicates high levels of inflammation as a key mechanism underlying poorer health states in CFS/ME (Anderson, Berk, & Maes, 2014; Fletcher et al., 2009; Maes, Twisk, Kubera, & Ringel, 2012; Morris & Maes, 2013). These findings are based on examinations of circulating levels of pro-inflammatory cytokines, which are assessed as an indirect measure of inflammation in the body.

Interleukin-6 (IL-6) is consistently implicated in models of neuroimmune dysregulation in CFS/ME patients (Arnett & Clark, 2012; Morris & Maes, 2013; Patarca-Montero, Antoni, Fletcher, & Klimas, 2001). IL-6 is a pro-inflammatory cytokine that influences innate and adaptive immune processes. It aids in the synthesis of acute phase

proteins, and helps to grow B-lymphocytes, which produce antibodies to aid immune function (Heinrich et al., 2003). Relative to healthy individuals, CFS/ME patients have been shown to exhibit elevated basal concentrations of plasma IL-6 (Chao et al., 1991; Fletcher et al., 2009; Gaab et al., 2005; Hornig et al., 2015; Klimas et al., 2012; Klimas et al., 1990; Nas et al., 2010). Additional support for the relevance of IL-6 as a neuroimmune biomarker in CFS/ME comes from research on the effects of acute laboratory administrations of IL-6. It has been demonstrated that the administration of exogenous pro-inflammatory cytokines, including IL-6, can induce acute cytokine mediated sickness behavior similar in presentation to CFS/ME (Arnett & Clark, 2012; Dantzer & Kelley, 2007). This is particularly true when administering IL-6 to patients with hypocortisolism, producing CFS/ME related symptoms, including fatigue, fever, and body aches within minutes (Papanicolaou, Tsigos, Oldfield, & Chrousos, 1996).

IL-6 levels in circulation are also a marker of illness burden in CFS/ME. Greater IL-6 levels are linked with greater general fatigue, physical-specific fatigue, as well as post-exertional malaise (Cohen, Kamarck, & Mermelstein, 1983; Hornig et al., 2015; Lattie et al., 2012). However, findings linking IL-6 to CFS/ME symptoms are somewhat mixed. Several null findings have been reported regarding differences between CFS/ME and healthy samples in basal IL-6 perturbations (Nakamura et al., 2013; Stringer et al., 2013). One study has even reported that patients with CFS/ME had lower plasma IL-6 levels than did healthy controls (Gaab et al., 2005). This inconsistency may reflect variability of illness durations within study participants. Recently, Hornig and colleagues (2015) observed that CFS/ME patients of illness duration more than three years had lower plasma IL-6 concentrations compared with patients of shorter illness duration as

well as healthy controls. In their study, there were no differences between IL-6 levels in patients with shorter illness duration and healthy controls.

Overall, there is preliminary yet mixed evidence that IL-6 may be a key biomarker of systemic inflammation and illness burden in CFS/ME. Rather than simply associating IL-6 with illness duration cross-sectionally, future studies of IL-6 in CFS/ME would benefit from longitudinal designs that track variations in IL-6 and symptomatology over time (Fischer et al., 2014). Such investigations would be of enormous benefit to better our understanding of factors associated with variability in IL-6 levels in this population.

Psychological Factors and Neuroimmune Dysfunction in CFS/ME. A growing body of literature has explored whether psychological factors relate to neuroimmune dysfunction in CFS/ME. Evidence, primarily from observational studies, suggests that CFS/ME patients' ability to cope with the impact of chronic fatigue on daily living is associated with their levels of cortisol secretion. For instance, early life adversity is highly prevalent in CFS/ME (Heim et al., 2009; Kempke et al., 2013), and has been associated with hypocortisolism in adult patients (Heim et al., 2009). Furthermore, CFS/ME symptom severity is known to worsen in response to extreme stress (Lutgendorf et al., 1995) and to improve with greater perceived stress management skills and stress management intervention (Lattie et al., 2012; Lopez et al., 2011); this relationship may be mediated by the CAR (Hall et al., 2014). Interestingly, elevated concerns about fatigue are related to CAR suppression (Chida & Steptoe, 2009; Clauw & Chrousos, 1997; Nater et al., 2008; Papadopoulos & Cleare, 2012; Pruessner, Hellhammer, & Kirschbaum, 1999; Roberts et al., 2009; Torres‐Harding et al., 2008). For example, Roberts and colleagues (2009) found that fatigue-related interference in social functioning is related to

a lower CAR in CFS/ME. Overall, this literature is consistent with conceptualizations of CFS/ME as a psychologically-influenced disorder, with strong associations between physical symptoms and concerns about persistent fatigue, exhaustion, and burnout (Antoni & Weiss, 2003; Heim et al., 2000; Lattie et al., 2012; Poteliakhoff, 1998; Torres-Harding et al., 2008).

In addition to perceptions of fatigue and its psychosocial impact, researchers have also examined whether depressed mood influences the CAR in CFS/ME. Rates of comorbid depression are staggeringly high, with a current prevalence of 32% to 51% and a lifetime prevalence of 78% to 87% (Cella et al., 2013; Prins, Bleijenberg, & Rouweler, 2005). These estimates were obtained through population-based studies using well-validated self-report measures of depression (with and without fatigue-related items) and structured clinical interviews. However, links between depression and CAR levels have been mixed, yielding null results (Nater et al., 2008; Roberts et al., 2009; Roberts et al., 2004) or implicating depressive symptoms as a moderator of factors related to hypocortisolism in CFS/ME (Tak et al., 2011). The potential influence of depressed mood on the CAR in CFS/ME thus warrants further examination.

Over the past 20 years, elevated fatigue-related concerns have also been linked with more pronounced inflammatory indicators in CFS/ME (Cannon et al., 1999; Carpenter et al., 2010; Gaab et al., 2005; Gupta, Aggarwal, & Starr, 1999; LeMay, Vander, & Kluger, 1990; Maes et al., 1999; Maier & Watkins, 1998; Voorhees et al., 2013). In particular, IL-6 concentrations in plasma and serum of CFS/ME patients are positively correlated with the presence of fatigue and fatigue-related concerns (Arnold et al., 2002; Bansal et al., 2012; Fletcher et al., 2009; Gaab et al., 2005; Lattie et al., 2012; Nas et al., 2010;

Patarca-Montero et al., 2001). Notably, these findings appear to be independent of acute physical exertion (Cannon et al., 1999; Gupta et al., 1999) and depressive symptoms (Dowlati et al., 2010; Howren, Lamkin, & Suls, 2009; Voorhees et al., 2013; Zorrilla et al., 2001), factors that are related to higher IL-6 levels. However, the findings to date are correlational and may be recursive; distress can impair immune functioning, and worsened health can be a source of distress. In their 2001 review of cytokine dysregulation in CFS/ME, Patarca-Montero et al. (2001) emphasize that investigations of top-down factors (e.g., fatigue-related perceptions and mood disturbance) influencing immune responses are particularly helpful, in part because they can help identify modifiable targets for psychosocial interventions. For this reason, examinations of IL-6 concentrations before and after a psychosocial intervention would be tremendously valuable, in particular those targeting fatigue and CFS/ME patients' perceptions of its impact.

    <u>Fatigue Interference in CFS/ME.</u> Literature reviewed thus far suggests that patients' perceptions of fatigue and its impact may relate to neuroimmune dysfunction in CFS/ME. According to biopsychosocial conceptualizations of the maintenance of CFS/ME symptoms, the subjective impact of fatigue on one's life may be due to, or exacerbated by, patients having maladaptive cognitions related to symptom focusing, anticipation of burden, and beliefs about fatigue (Friedberg & Krupp, 1994; Fry & Martin, 1996; Knoop et al., 2010; Wiborg et al., 2011). As will be discussed, the tendency to focus on and have catastrophic and negative thoughts about fatigue and its consequences may potentially be harmful for CFS/ME patients.

Negative, catastrophic, and defeatist perceptions of fatigue can impact CFS/ME patients in multiple ways. Recent neuroimaging findings indicate that appraisals of fatigue as threatening and demanding are related to increased emotional distress through two processes. Compared to healthy controls, CFS/ME patients viewing fatigue-inducing videos in an fMRI showed greater blood oxygen level dependent (BOLD) responses of the posterior cingulate cortex (a brain region implicated in emotion processing and retrieval emotionally-relevant memories) as well as deactivation of dorsolateral and dorsomedial prefrontal regions that downregulate dysregulated mood (Caseras et al., 2008). Interestingly, heightened neural responses in these areas were also related to patients' reports of fatigue-related fears and worries. These findings suggest that, at the neural level, perceptions about fatigue-related stimuli are emotionally salient for this population. Furthermore, negative perceptions about the impact of fatigue may discourage CFS/ME patients from engaging in physical activity (White et al., 2011; Wiborg, Knoop, et al., 2010), impair their performance in neuropsychological tasks (Smith & Sullivan, 2003), limit their ability to utilize sources of social support that could reduce illness burden (Wiborg et al., 2011), and result in emotional distress (Friedberg & Krupp, 1994; Song & Jason, 2005). Of note, negative fatigue-related cognitions among patients, such as focusing on fatigue and predicting a worsening of fatigue have been found to mediate effects of several psychosocial interventions on CFS/ME fatigue and illness burden, whereas objectively measured physical activity level has not (Knoop et al., 2010; Stahl et al., 2013; Wiborg, Knoop, et al., 2010). In their review of cognitive processes involved in the perpetuation of CFS/ME, Knoop and colleagues (2010) conclude that perceiving fatigue as "something negative and aversive" and "difficult to

influence," as well as "the tendency to underestimate one's own performance and ability to perform," are signature cognitive processes related to distress states and poorer health.

It is worth examining whether these types of perceptions describe the *severity* of fatigue or the *interference* in one's daily functioning stemming from the fatigue.   In CFS/ME, neither the severity nor interference alone may fully characterize fatigue's impact on quality of life and psychological distress (Chambers, Bagnall, Hempel, & Forbes, 2006). To date, no study has specifically examined the differential influence of perceived fatigue severity versus fatigue interference on indicators of mental and physical health among CFS/ME patients. However, evidence from the breast cancer literature suggests that patients' wellbeing is more intimately tied to fatigue interference than fatigue severity (Traeger et al., 2011). Traeger and colleagues (2011) note that greater fatigue interference may indicate that a patient has more difficulty managing fatigue-related symptoms, which could reflect concurrent unmet psychosocial needs. It may also suggest that a patient perceives their fatigue to be overly deleterious given their fatigue severity, which could be a function of maladaptive cognitions related to fatigue. Importantly, patients with heightened fatigue interference would theoretically benefit from psychosocial interventions that offer patients resources, coping skills, cognitive restructuring techniques, and social support.

Levels of fatigue interference have yet to be examined in CFS/ME. However, preliminary evidence suggests that CFS/ME patients may have greater fatigue interference than other fatigued medical populations. Comparison studies between fatigued cancer patients and CFS/ME patients indicate that while both groups report similar fatigue severity, CFS/ME patients report greater decrements in physical quality of

life, including more functional impairment, less physical activity, and less self-efficacy about instrumental care (Bennett, Goldstein, Friedlander, Hickie, & Lloyd, 2007; Servaes, Prins, Verhagen, & Bleijenberg, 2002). These findings suggest that CFS/ME patients may be disadvantaged relative to other fatigued medical patients, in part due to greater perceived interference from fatigue.

To gain a preliminary understanding of whether levels of fatigue interference among CFS/ME patients are higher or similar to those of other fatigued medical populations, one could compare scores of fatigue interference between two samples: women with CFS/ME and fatigued breast cancer survivors. This latter sample is ideal for comparison with CFS/ME patients for three reasons. First, breast cancer survivors five years post-treatment frequently endorse high levels of fatigue (Bower et al., 2000; Hall, Mishel, & Germino, 2014; Stasi, Abriani, Beccaglia, Terzoli, & Amadori, 2003; Von Ah, Kang, & Carpenter, 2008). Additionally, sufficient time has likely passed so that their experiences of fatigue and/or depression are not secondary to acute psychological or physiological sequelae of diagnosis and treatment (Bower, 2005; Von Ah et al., 2008). Relatedly, by five years after treatment, breast cancer patients have dealt with persisting symptoms chronically, making them a suitable comparison group for patients with CFS/ME.

Factors potentially impacting fatigue interference in CFS/ME could also be examined. Depressive symptoms could represent one such factor, as they commonly co-occur with fatigue and could make coping with fatigue more difficult (Anderson et al., 2014; Dansie et al., 2012; Friedberg & Krupp, 1994). Among cancer patients with elevated fatigue, greater fatigue interference has been associated with depressive

symptoms measured via self-reported measures and structured clinical interviews (Traeger et al., 2011). Thus it is plausible that fatigue interference in CFS/ME could be worsened by concurrent depressive symptoms, though this association remains untested. Relatedly, an investigation of fatigue interference could also statistically control for fatigue severity. This methodological consideration is similar to the approach taken by Traeger et al. (2011), and would strengthen conclusions about the presence and impact of fatigue interference.

Cognitive Behavioral Stress Management and Fatigue Interference in CFS/ME. After relationships among fatigue interference and neuroimmune processes are established among CFS/ME patients, a logical next step would be to assess the efficacy of interventions in improving these processes. Interventions utilizing cognitive behavior therapy have demonstrated the greatest efficacy in improving mental and physical wellbeing in CFS/ME patients (Castell et al., 2011; Jason et al., 2007; Prins et al., 2001; Roberts et al., 2010; Roberts et al., 2009; White et al., 2011). These interventions aim to identify and change maladaptive cognitions and coping strategies, as well as increase social support and use of relaxation strategies. Cognitive behavioral stress management (CBSM) intervention could be one appropriate treatment, as it has been shown to improve quality of life in CFS/ME (Lopez et al., 2011). In other medical populations, CBSM has improved perceived stress management skills, emotional distress, dysregulated cortisol output, and cellular immune functioning (Antoni et al., 1991; Antoni et al., 2000; Antoni et al., 2001; Antoni et al., 2012; Lutgendorf et al., 1998; Penedo et al., 2004; Penedo et al., 2006; Stagl et al., 2015).

For several reasons, CBSM may also have the potential to reduce a CFS/ME patient's fatigue interference. First, CBSM asks patients to identify their maladaptive cognitions, several of which (generalization, catastrophizing, and magnification) are associated with symptom magnification (Fry & Martin, 1996; Knoop et al., 2010). Among CFS/ME patients, these maladaptive cognitions tend to focus on fatigue (Antoni et al., 1994; Cella et al., 2013; Friedberg & Krupp, 1994; Lopez et al., 2011; Petrie et al., 1995; Price et al., 2008; Stahl et al., 2013; White et al., 2011). After identifying these cognitions in CBSM, patients engage in thought replacement strategies to introduce appraisals that are more rational and balanced (Antoni, 2003; Jason, Fennell, & Taylor, 2003; Wiborg et al., 2011). In this capacity, CBSM may alter patients' appraisals of the interference fatigue has on their daily functioning. Research has found that "focusing on fatigue" mediates the effects of cognitive behavior therapy on both fatigue severity and overall illness impact in daily functioning in CFS/ME, although results are most prominent with latter (Wiborg et al., 2011). These results demonstrate the malleability of perceived fatigue interference in response to interventions targeting maladaptive cognitions.

Second, CBSM may reduce fatigue interference by encouraging patients to increase their social support. CBSM has patients brainstorm strategies for increasing emotional, informational, and tangible support to ease day-to-day functioning and also teaches assertiveness and anger management skills, which may act to preserve and better utilize available social support resources. Increased social support may reduce ratings of fatigue interference by increasing patients' capacity to get their needs met by soliciting help effectively from family, friends, and peers.

Third, CBSM encourages patients to use relaxation techniques such as deep breathing, progressive muscle relaxation, special place imagery, and mindfulness relaxation. These strategies may make coping with fatigue more tolerable for patients by cuing them in to nascent states of stress early on, prompting individuals to alter cognitions that may exacerbate distress states (Friedberg & Krupp, 1994; Lopez et al., 2011; Vargas et al., 2014), and have also been shown to improve dysregulated HPA axis functioning in other chronic illness populations (Cruess et al., 2000; Pawlow & Jones, 2002; Phillips et al., 2008). Increased use of these techniques could thus potentially dampen the perceived impact of fatigue on one's daily life.

Therefore, examination of CBSM's efficacy in reducing fatigue interference in CFS/ME patients is warranted. Recently, CBSM has been found to decrease fatigue interference, but not severity, among breast cancer patients (Vargas et al., 2014). These results suggest that CBSM-related reductions in fatigue interference are independent of levels of fatigue severity, though this remains to be tested in a sample of CFS/ME patients. Determining the impact of CBSM on CFS/ME patients' fatigue interference levels could yield information critical to the refinement of future psychosocial interventions with this population, targeting patients whose fatigue appraisals place them at risk for poorer neuroimmune functioning.

Telephone-Delivery of Cognitive Behavioral Stress Management. For patients with CFS/ME, physical mobility can be a barrier to receiving psychosocial intervention. For both homebound and non-homebound patients, debilitating levels of fatigue characteristic of this population can limit CFS/ME patients from seeking regular psychosocial support

(Wiborg, van der Werf, et al., 2010). Homebound CFS/ME patients may also have higher fatigue levels and perceived impairment than their non-homebound counterparts (Wiborg, van der Werf, et al., 2010).

Recent advances in telehealthcare have allowed researchers and clinicians to provide patients with psychosocial resources in lieu of face-to-face intervention (Schulz et al., 2009). These approaches include the use of telephone-based technologies to deliver interventions. Telephone-administered cognitive behavioral therapy has been shown to have less attrition than face-to-face cognitive behavioral therapy, and comparable post-treatment improvements in depressed mood (Mohr et al., 2012). To date, no study has evaluated whether telephone-delivered CBSM in CFS/ME patients improves patient outcomes, including fatigue interference and neuroimmune function.

Implications of Dissertation. This project will advance the field in six important ways. First, fatigue interference has never been calculated in a sample of CFS/ME patients. This project will be the first to assess and quantify fatigue interference levels in CFS/ME patients. Additionally, as a preliminary evaluation of whether elevated fatigue interference differentiates CFS/ME patients from other fatigued medical patients, scores will be compared between CFS/ME patients and fatigued cancer survivors.

Second, links between fatigue interference and neuroimmune profiles have yet to be examined in persons with CFS/ME. This project will aim to relate fatigue interference to the cortisol awakening response (CAR) as well as proinflammatory cytokine interleukin-6 (IL-6) levels. Third, whether depressive symptoms exacerbate the influence of fatigue interference on neuroimmune functioning is unknown. Literature has been cited suggesting that depressive symptoms could suppress the CAR and raise levels of IL-6,

and may co-exist with elevated fatigue interference. Whether concurrent depressive symptoms exacerbate the proposed negative impact of fatigue interference on neuroimmune function will therefore be examined.

Fourth, the role of CBSM in influencing fatigue interference is not established. This project will examine the efficacy of a telephone-delivered CBSM intervention in reducing patients' fatigue interference levels post-intervention (5 months post-baseline) and again 9 months post-baseline. Fifth, the longitudinal effects of changes in fatigue interference on changes in neuroimmune profiles during CBSM are unknown. The influence of CBSM changes on CAR and IL-6 levels over time will be assessed, and the mediating role of fatigue interference in these changes will be examined. Sixth, whether specific skills targeted by CBSM intervention covary with changes in fatigue interference is unknown. Changes in fatigue interference over time will be examined as a function of changes in participants' self-perceived skills in relaxation, stress awareness, assertiveness, and coping/cognitive restructuring over time. The current proposal will be the first to report on these six critical gaps in our knowledge.

Specific Aims and Hypotheses.

Study 1: Baseline Associations.

Aim 1: Assess and quantify levels of fatigue interference in female CFS/ME patients and demonstrate whether female CFS/ME patients have greater fatigue interference than do fatigued breast cancer survivors, an illness group known to report elevated fatigue interference.

Hypothesis 1: CFS/ME female patients' fatigue interference scores will be higher than those of fatigued female breast cancer survivors.

Aim 2: Relate fatigue interference to neuroimmune profiles in female CFS/ME patients.

Hypothesis 2.1: Greater fatigue interference scores will be associated with lower levels of the cortisol awakening response (CAR).

Hypothesis 2.2: Greater fatigue interference scores will be associated with higher levels of plasma concentration of interleukin-6 (IL-6).

Aim 3: Demonstrate whether depressed mood in female CFS/ME patients moderates fatigue interference's relation with neuroimmune profiles.

Hypothesis 3.1: Greater levels of depressed mood will strengthen the association observed in Hypothesis 2.1. The negative association between fatigue interference scores and the CAR will be significantly stronger among patients with greater levels of depressed mood.

Hypothesis 3.2: Greater levels of depressed mood will strengthen the association observed in Hypothesis 2.2. The positive association between fatigue interference scores and IL-6 levels will be significantly stronger among patients with greater levels of depressed mood.

Study 2: CBSM Intervention Effects

Aim 4: Test the effects of CBSM intervention on changes in fatigue interference in female CFS/ME patients. As a supplement, examine whether fatigue severity and depressed mood are also influenced by CBSM intervention.

Hypothesis 4.1: Participants in the CBSM intervention will evidence greater decreases in fatigue interference from **baseline** to **5-months** and **9-months** than participants in the attention control condition.

Aim 5: Test the effects of CBSM intervention on changes in neuroimmune profiles across two time intervals in female CFS/ME patients.

Hypothesis 5.1: Participants in the CBSM intervention will evidence greater increases in the CAR from **baseline** to **5-months** and **9-months** than participants in the attention control condition.

Hypothesis 5.2: Participants in the CBSM intervention will evidence greater decreases in the plasma concentration levels of interleukin-6 (IL-6) from **baseline** to **5-months** and **9-months** than participants in the attention control condition.

Exploratory Aim A: Assess whether effects of CBSM intervention on changes in neuroimmune profiles observed in Aim 5 are partially mediated by changes in fatigue interference.

Hypothesis 6.1: Decreases in fatigue interference from baseline to 5-months and 9-months will serve as an intermediary to the relationships observed in Hypothesis 5.1. The greater increases in CAR levels from baseline to 5-months and 9-months in the CBSM (vs. attention control) condition will be partially mediated by decreases in fatigue interference from baseline to 5-months.

Hypothesis 6.2: Decreases in fatigue interference from baseline to 5-months and 9-months will serve as an intermediary to the relations observed in Hypothesis 5.2. The greater decreases in IL-6 levels from baseline to 5-months

and 9-months in the CBSM (vs. attention control) condition will be partially

mediated by decreases in fatigue interference from baseline to 5-months.

Exploratory Aim B: Assess the extent to which changes in specific skills targeted by

CBSM intervention covary with changes in fatigue interference observed in Aim 4.

Participants' current self-perceived skills in relaxation, stress awareness, assertiveness,

and coping/cognitive restructuring will be examined.

Hypothesis 7.1: Increases in these self-perceived skills from baseline to 5-months

will correspond with decreases in fatigue interference from baseline to 5-months.

Hypothesis 7.2: Increases in these self-perceived skills from 5-months to 9-months

will correspond with decreases in fatigue interference from 5-months to 9-months.

Exploratory Aim C: In the absence of significant group-by-time omnibus interaction

effects in Aims 4 and 5, examine potential correlates of significant omnibus time effects.

Factors to be considered include session attendance, illness duration, baseline

psychosocial factors (depression, anxiety, and perceived stress), and symptom frequency

and duration.

Chapter 2

Study 1 Methods

　　Participants. CFS/ME patients and breast cancer survivors were recruited

separately for longitudinal studies of stress management and psychosocial processes in

these populations (NIH 5R01NS055672 and NCI 1R01CA064710, M. Antoni). Details

of recruitment for these studies have been reported elsewhere (Lattie et al., 2012; Stagl et

al., 2015). Participants in Study 1 were women who provided data for these two trials.

　　Both samples were recruited via physician referral, support groups, special events

including conferences. Recruitment of the CFS/ME sample also utilized advertisements

on CFS-related websites. The majority of potential participants screened lived in South

Florida and were referred by local physicians.

　　Several criteria were used to determine eligibility to participate. Participants with

CFS/ME were required to have a physician-determined CFS diagnosis according to the

Centers for Disease Control and Prevention (CDC) criteria (Fukuda et al., 1994). Breast

cancer survivors were required to have undergone surgery for non-metastatic stage 0–IIIb

breast cancer at least five years prior to data collection as verified by their clinician. For

the present study, breast cancer survivors could not be included if a cancer recurrence or

prior CFS/ME diagnosis was indicated. Exclusion criteria for both CFS/ME and breast

cancer survivors included prior cancer (i.e., prior to the breast cancer), lack of fluency in

English, and prior treatment for a serious psychiatric disorder (e.g., psychosis,

suicidality). A brief screening tool (First, Spitzer, Gibbon, & Williams, 2002) was used

to assess the presence of current potential psychiatric exclusions, including: meeting DSM-IV-TR criteria for schizophrenia, bipolar disorder, or substance abuse; having a history of psychiatric hospitalization(s); or being actively suicidal.

To ensure comprehension of study questionnaires and intervention material, potential participants were excluded for cognitive impairment if they made four or more errors on the Short Portable Mental Status Questionnaire (Pfeiffer, 1975). Participants could also be excluded for having comorbid autoimmune illness or a medical condition that could alter neuroimmune function, such as thyroid disease, cancer, AIDS, rheumatoid arthritis, or lupus. Additionally, participants could also be excluded for taking medications that could modulate immune and neuroendocrine functioning, such as use of corticosteroids. Eligible participants were also required to live within the study area, have an active home telephone line, and be between the ages of 21 and 75 years.

From the original sample of 117 patients with CFS/ME, data for female participants were retained, resulting in a final sample of 95 women with CFS/ME. The breast cancer study sample consisted of 67 women who consented to participate in a follow-up study examining five-year survivorship experiences.

Procedures. Eligible participants signed a written, informed consent for participation in the study during a home visit by a member of the study staff. At this visit, both medical samples completed a psychosocial and symptom questionnaire battery. In addition, women with CFS/ME were provided salivette tubes, instructions for completing the saliva collection protocol (see Study 1, Measures), and an appointment for a blood draw. Saliva and blood collection occurred within one week of the questionnaire

battery assessment. All blood draws occurred between 11:00am and 3:00pm.

Compensation for all participants was $50 and was provided upon completion of the full

assessment.

    <u>Measures.</u>

    Salivary Cortisol. Salivary cortisol was obtained from the CFS/ME sample.

Corticosteroid binding globulin levels, which may fluctuate within an individual, mediate

differences in unbound and total (unbound and bound) cortisol levels within individuals;

however, this is not a factor when measuring salivary cortisol since only the unbound

levels are obtained (Foley & Kirschbaum, 2010). Moreover, unbound (free) cortisol

levels among plasma, serum, and saliva are highly correlated ($r > .90$; Foley &

Kirschbaum, 2010). For this reason, in addition to being a less intrusive sampling

method, salivary cortisol is a good outcome for investigation of HPA activity.

    Participants were asked to complete a saliva collection protocol over two

consecutive weekdays. On each of the collection days, participants were asked to take a

sample immediately upon awakening, 30 minutes after awakening, at 4:00pm, and at

9:00pm. Samples were collected in salivettes using a cotton swab (Sarstedt,

Rommelsdorf, Germany). Participants were asked to self-report the time of sampling on

the label of each salivette. To maximize the integrity of the samples, participants were

instructed to abstain from eating or drinking before and between the first two samples

each day, and to avoid eating a large meal an hour before the afternoon and evening

samples. Participants were also asked to avoid alcohol for at least 12 hours prior to

sample collection and to avoid vigorous exercise on sample collection days. Following

the collection of samples, participants were instructed to freeze the salivette tubes in their home freezers in order to keep the salivary cortisol stable until samples were retrieved by a study staff member.

Study staff then stored samples in a secure freezer at -20 degrees Celsius until assayed. When enough samples were collected to conduct an assay, a batch of saliva samples were thawed, vortexed, and centrifuged at 1500 rpm for 15 minutes prior to being assayed using the Salimetrics high sensitivity ELISA kit (State College, PA).

Cytokine Interleukin-6. Blood was obtained from the CFS/ME sample. Blood samples were centrifuged within four hours of collection. After it was separated, plasma was stored in a secure location at -20 degrees Celsius until assayed. Among 16 cytokines, plasma concentrations of the proinflammatory cytokine interleukin-6 (IL-6) were measured using the Q-Plex™ Human Cytokine – Screen, an ELISA-based test produced by Quansys Biosciences (Logan, Utah) were used for the present study. The test uses distinct capture antibodies in a 96-well plate in a defined array (Fletcher et al., 2009), with images of the plate taken by the Quansys Imager, a device that uses an 8.4 megapixel Canon 20D digital SLR camera. After imaging, Quansys software was used to convert the plates into raw data.

Fatigue Interference and Fatigue Severity. Both the CFS/ME and breast cancer samples completed the Fatigue Symptom Inventory (FSI), a self-report measure of fatigue-related beliefs and experiences that was developed and validated with breast cancer patients (Hann et al., 1998). The FSI consists of two subscales: one measuring fatigue interference and the other measuring fatigue severity. The fatigue interference subscale consists of 7 Likert-type items measured on 11-point scales (0=No Interference;

10=Extreme Interference) that assess the degree to which fatigue during the past week was appraised to interfere with "general level of activity", "ability to bathe and dress", "normal work activity (includes both work outside the home and housework)", "ability to concentrate", "relations with other people", "enjoyment of life", and "mood". The fatigue severity subscale consists of 4 Likert-type items measured on 11-point scales (0=Not at all fatigued; 10=As fatigued as I could be) that assess current fatigue level in addition to most, least, and average fatigue levels during the past week. Each subscale is summed then divided by number of items to create a mean subscale score.

The CFS/ME sample was administered the range of response options (0 to 10) used in the original test development research. However, the breast cancer survivors were presented with response options from 1 (not at all fatigued/no interference) to 9 (as fatigued as I could be/extreme interference). In order to make meaningful comparisons between these samples, a transformation was performed to the breast cancer survivor sample's FSI data to convert item scores from a scale of 1 to 9 to the correct scale of 0 to 10 by conducting a linear conversion. For the breast cancer sample's data, each item was first recoded by subtracting a value of 1 from each response. This set the breast cancer FSI data to the same starting place as in the CFS/ME FSI data (i.e., 0 = not at all fatigued/no interference). Next, these items were multiplied by a factor of 1.25, transforming the data to the correct range of response options (0 to 10). Post-transformation, the resultant Severity and Interference subscale scores among the breast cancer sample had the same internal reliability (Cronbach alphas) as pre-transformation.

Examination of the frequency of responses pre- and post-transformation confirmed that the same individuals who previously answered an item with a 1 or 9 correspondingly had a response of 0 or 10.

Cronbach alphas for fatigue interference and fatigue severity within the CFS/ME sample were .86 and .79, respectively. Within the breast cancer survivor sample, Cronbach alphas were .93 for fatigue interference and .77 for fatigue severity. Overall, internal consistency was acceptable to good among both samples across these subscales. In the combined sample, fatigue severity was positively correlated with fatigue interference ($r = .76, p < .001$).

Depressed Mood. Participants completed the Center for Epidemiologic Studies Depression Scale (CES-D) as a measure of depressive symptoms during the past week (Radloff, 1977). The CES-D measures depressive symptoms by asking participants to rate 20 items such as ''I felt that I could not shake off the sad feelings even with help'' on a 4-point scale, from 0 (rarely or none of the time, <1 day) to 3 (most or all of the time, 5–7 days). Items are then summed to create a total score. Internal consistency has been shown to be excellent (α's= .85-.90) (Radloff, 1977). Cronbach αs for CES-D total scores in both samples were acceptable (0.91 in CFS/ME patients and 0.89 in breast cancer survivors).

Due to the potential overlap of fatigue-related and depressive symptoms, an important methodological consideration was to isolate depressed mood items from those on the CES-D associated with vigor, energy, and concentration-related difficulties, as has been done previously (Hertzog, Van Alstine, Usala, Hultsch, & Dixon, 1990; Radloff, 1977). A depressed mood score was calculated by summing the subset of 7 items that

describe mood disturbance and not somatic symptoms. Cronbach α's for CES-D depressed mood scores were satisfactory (0.91 in CFS/ME patients and 0.85 in breast cancer survivors).

Potential Control Variables. Participants reported their age, alcohol use, smoking status, race/ethnicity, marital status, number of children, years of formal education, and employment status. Prior literature suggests that these factors may influence cortisol and IL-6 levels (Fries et al., 2009; O'Connor et al., 2009) and should therefore be examined as potential covariates.

Statistical Analysis Plan for Study 1.

Preliminary Analyses. Analyses were conducted using SPSS version 22.0 (IBM). All variables were examined for outliers and normality of distributions. Outliers, defined as scores greater than 3 standard deviations from the mean, were winsorized. Extreme values in cortisol and IL-6 data were replaced with ±3 standard deviation values previously reported for women with CFS/ME (Fletcher et al., 2009; Nater et al., 2008; Roberts et al., 2004) prior to winsorization. Non-normal distributions, as indicated by large skew (≥ 3.0) and/or large kurtosis (≥ 8.0), were logarithmically transformed. Lower limits of detection were substituted for undetectable IL-6 and cortisol values when analyzing neuroimmune data among the CFS/ME sample.

Demographic and medical variables were analyzed for group differences between the CFS/ME and breast cancer samples using an independent-samples t-test (for continuous data) and Pearson Chi-Square test (for categorical data). Covariates for hypothesis testing were determined by correlating age, alcohol use, smoking status, race/ethnicity, marital status, number of children, years of formal education, and

employment status data with the study outcome variables. Any potential covariates related to an outcome variable ($p < .10$) were used as a covariate in analyses of that outcome.

Missing value patterns for each variable were closely examined to ascertain whether data for each variable were likely missing at random (MAR) or missing not at random. There were patterns of scatter for missing data across all variables, cases, and values, suggesting that data was MAR or missing completely at random (Rubin, 1976). When data is missing in this way, multiple imputation is considered to be an appropriate and advantageous way to preserve computational power and limit bias (Rubin, 2004). This approach minimizes potential bias in hypothesis testing by imputing values missing values multiple times, effectively creating multiple imputed datasets. These datasets are run simultaneously, and pooled results are generated by statistical software.

In the present study, 21 imputational datasets were created using fully conditional specification with SPSS version 22.0 (IBM). To enhance the precision of estimates of missing values, auxiliary variables were included in the imputational model that could potentially account for patterns of missingness (Rubin, 2004).

Adherence to Cortisol Timing Protocol. As cortisol levels naturally fluctuate throughout the day, timing of cortisol sampling is a critical methodological consideration. Participant adherence to saliva collection timing protocols can influence results of CAR analyses (Broderick, Arnold, Kudielka, & Kirschbaum, 2004; Kudielka, Broderick, & Kirschbaum, 2003). Therefore, adherence was assessed using patients' self-reported collection times. Samples were deemed ''adherent'' in accordance with previously established standards if a second sample was obtained between 15 and 45 minutes after

the awakening sample (Hall et al., 2011). If a participant was adherent to the cortisol collection protocol on both Days 1 and 2, CARs for both days were computed then averaged together. If a participant was adherent on only one day, only that day's cortisol values were retained for calculating the CAR.

Calculation of Cortisol Awakening Response. Cortisol awakening response (CAR) values were computed for each participant using values obtained from adherent samples. Consistent with recommendations from Powell et al. (2013), the CAR was operationalized using two area under the curve (AUC) computations: the AUC with respect to the ground (CARg) and the AUC with respect to increase from baseline (CARi). A commonly used parameter for modeling total cortisol secretion, CARg is a measure of overall cortisol output during a specified timeframe. It is less subject to measurement error associated with variability in the awakening measurement than other CAR measures, and has been positively related to emotional distress (Chida & Steptoe, 2009). In the present study, CARg was used to reflect total cortisol output from awakening to approximately 30 minutes post-awakening. In addition to CARg, CARi can also yield important information about morning output relative to one's baseline (Powell et al., 2013). It is a proxy for the change in cortisol secretion during a specified timeframe, and can indicate the degree to which cortisol levels increase, decrease, or stay stagnant. In the current study, CARi was used to reflect the change in cortisol levels from awakening to approximately 30 minutes post-awakening.

The CARg and CARi were calculated using the following formulae from Pruessner et al. (2003), adapted for this dissertation and simplified as follows:

$CARg = [(m_2 + m_1)*(\text{time difference between morning samples})] / 2$

CARi = [(m_2 - m_1)/2]*(time difference between morning samples)

Here, m_1 denotes the awakening cortisol value, and m_2 denotes the cortisol value from approximately 30 minutes post-awakening. The time difference between morning samples was calculated from self-reported times of participant saliva collection.

Upon examination of the CARi values, it was observed that 14.8% of scores were negative. Negative values for the CARi are non-intuitive – they suggest that instead of a morning "rise", there was a morning "dip" from awakening – and likely reflect participant non-adherence to the saliva collection protocol (Breslau, Davis, & Schultz, 2003; Fischer et al., 2014). In one study, Kupper and colleagues (2014) observed negative CARi values among 11% of their sample of healthy twins. Ambulatory vertical accelerometer readings confirmed that these individuals woke up on average 40 minutes prior to the times they had self-reported awakening. In the present study, no available demographic or medical data were associated with having a negative CARi. Thus, for these cases, CARi values were imputed to limit introducing methodological error into interpretation of CARi findings and preserve the integrity of CARi analyses.

Calculation of Diurnal Cortisol Change. For descriptive purposes, an index of diurnal change in cortisol was computed for each participant. Evening cortisol levels obtained at approximately 9:00pm were subtracted from awakening cortisol levels. These change scores reflect the magnitude of the difference from awakening to evening levels; negative scores reflect lower cortisol in the evening than in the morning.

Primary Analyses.

Study 1, Aim 1. The breast cancer subjects' Fatigue Symptom Inventory scores were obtained from a database from an ongoing trial conducted at the University of

Miami (PI: Michael H. Antoni, National Cancer Institute 1R01CA064710). Permission for use of this data for the current analysis was granted. For this aim, three analyses of covariance (ANCOVAs) were run. Controlling for covariates, these models examined group differences in fatigue interference, fatigue severity, as well as fatigue interference controlling for fatigue severity.

Study 1, Aim 2. To assess whether fatigue interference scores controlling for severity are associated with CARg, CARi, or levels of IL-6 among women with CFS/ME, three separate hierarchical linear regressions were run with fatigue interference as the independent variable and either CARg, CARi, or IL-6 level as the dependent variable. In all models, Step 1 included any covariates identified in preliminary analyses. Step 2 included the fatigue severity scores. Step 3 included fatigue interference scores.

Study 1, Aim 3. To ascertain whether levels of depressive symptoms moderate the associations tested in Aim 2, three hierarchical linear regressions were conducted. CARg, CARi, or IL-6 levels were used as the dependent variable. In all models, Step 1 included any covariates identified in preliminary analyses. Step 2 included fatigue severity scores. Step 3 included mean-centered fatigue interference scores and mean-centered depressed mood scores. Step 4 included an interaction term created by multiplying the Step 3 variables.

Chapter 3

Study 1 Results

Preliminary Analyses. All participants provided demographic data detailing age, race/ethnicity, marital status, number of children, years of formal education, and employment status. Categorical variables (education, race/ethnicity, marital status, and employment) were dichotomized as follows: completed college (yes/no); self-identified as non-Hispanic White (yes/no); married or in a committed partnership (yes/no); and employed full-time (yes/no). These data are summarized in Table 1.

Women in both samples were predominantly non-Hispanic white (77% among CFS/ME patients and 72% among fatigued breast cancer survivors). Both samples were on average in their early-to-mid 50's, although the CFS/ME sample tended to be several years younger. Additionally, women in both samples were on average more than five years since their illness diagnosis. A larger percentage of the breast cancer survivor sample had completed college (81% versus 44% in CFS/ME sample), were married or partnered (61% versus 43% in CFS/ME sample), and worked full-time (69% versus 18% in CFS/ME sample).

In addition, CFS/ME participants provided data regarding present smoking habits and alcohol intake. Most women identified as non-smokers ($n = 84$, 88.42%) and reported having consumed less than two alcoholic beverages during the prior week (M = 1.52 beverages, SD = 3.13, range = 0 to 18).

Study 1, Aim 1 Results: Fatigue Interference Comparison. To gain insight into whether patients with CFS/ME have similar or greater difficulties with fatigue interference than other fatigued medical populations, a preliminary comparison was

conducted using a convenience sample of data from fatigued breast cancer survivors.

Three ANCOVA models were conducted controlling for age, race/ethnicity, education

level, marital status, employment status, number of children, and time since diagnosis.

These models predicted participants' scores on fatigue interference, fatigue severity, or

fatigue interference controlling for fatigue severity.

As indicated in Table 2, CFS/ME patients (M= 7.03, SD = 1.90) had significantly

higher fatigue interference scores than did fatigued breast cancer survivors (M = 2.62, SD

= 2.11), $F(1,150) = 115.36$, $p < .001$. The partial η2 was .44, indicating a large effect

size. Additionally, CFS/ME patients (M= 6.83, SD = 1.35) had significantly higher

fatigue severity scores compared with breast cancer survivors (M = 4.65, SD = 1.53),

$F(1,150) = 40.08$, $p < .001$, partial η2 = .21 (large effect).

After controlling for fatigue severity scores, CFS/ME patients still had higher

fatigue interference scores, $F(1,149) = 59.02$, $p < .001$. The partial η2 was .28, indicating

a large effect.

Study 1, Aim 2 Results: Fatigue Interference and Neuroimmune Profiles in

CFS/ME.

Preliminary Analyses. Table 2 describes cortisol and IL-6 levels for the CFS/ME

sample. Cortisol-related variables include the CARi and CARg. For descriptive

purposes, cortisol levels at four times (awakening, post-awakening, afternoon, and

evening) and diurnal change (evening minus awakening levels) are summarized as well.

Adherence to Cortisol Timing Protocol. On Day 1, 93 participants (97.9%)

provided morning saliva samples that were adherent to the timing protocol. On Day 2, 92

participants (96.8%) were adherent. No participant was nonadherent on both Days 1 and

2. Therefore, all 95 participants were able to be included in analyses of cortisol data. On average, the timing difference between awakening and post-awakening samples was 31.42 minutes (SD = 2.35 minutes), with a range of 25.00 minutes to 40.00 minutes.

Primary Analyses. Associations between fatigue interference scores and CARi, CARg, and IL-6 were examined while controlling for the influence of fatigue severity and any associated covariates. Results are summarized in Table 3. As hypothesized, fatigue interference scores were significantly negatively associated with CARi values, standardized Beta = -.28 (small effect), $t(95)$ = -2.31, p = .02. Each standard deviation increase in fatigue interference was associated with a 0.28 standard deviation decrease in the CARi. Contrary to hypotheses, neither CARg nor IL-6 concentrations were significantly related to fatigue interference scores, standardized Betas .04 and .05 (small effect), $ps \geq .67$.

Study 1, Aim 3 Results: Moderating Role of Depressed Mood. It was hypothesized that higher levels of depressed mood would strengthen associations demonstrated in Aim 2. Analyses testing the moderating role of depression in these models failed to support these hypotheses. As seen in Table 4, for all three models, the interaction term was non-significant, standardized Betas -.02 to 11(small effect), $ps \geq .12$.

Summary of Study 1 Findings. In summary, women with CFS/ME endorsed greater levels of fatigue interference, fatigue severity, and fatigue interference controlling for severity than did fatigued breast cancer survivors (Aim 1). Within the CFS/ME sample, greater fatigue interference controlling for severity was associated with lower CARi values (Aim 2), but was not related to CARg or IL-6 levels. Support for depressed mood moderating these relationships (Aim 3) was not observed.

Chapter 4

Study 2 Methods

    <u>Assessments</u>. All Study 1 participants diagnosed with CFS/ME (n=95) were enrolled in a randomized controlled trial examining longitudinal effects of stress management and psychosocial processes (NIH 5R01NS055672, M. Antoni). Recruitment, eligibility, and informed consent procedures were as described in Study 1. Following the baseline assessment (BL), participants completed two additional assessments during the remainder of the study. The second assessment took place five months (5M) after baseline, to allow sufficient time for the participant to complete the 10-week intervention or control condition (described below). A third and final assessment was obtained nine months (9M) after baseline. For each assessment, participants were compensated $50 as a token of appreciation.

    <u>Randomization</u>. Randomization of group assignment occurred immediately after a participant completed the baseline assessment. Participants were randomized to either the CBSM or an attention control condition using a 1:1 randomization ratio. Computer software was used to generate random whole numbers ranging from 0 to 8. Integers 0, 2, 4, and 6 were assigned to CBSM, and integers 1, 3, 5, and 7 were assigned to attention control. The process was repeated until a balanced sample was obtained. Index cards were labeled with the group assignments in order of appearance in the list of random numbers and placed in enumerated envelopes. Upon completion of a baseline assessment, a participant's deidentified study identification number would be paired with the next unopened envelope organized in ascending order.

CBSM Intervention. The CBSM condition consisted of a CFS adapted 10-week manualized intervention protocol based on prior CBSM trials (Antoni, Ironson, & Schneiderman, 2007; Lopez et al., 2011; Penedo, Antoni, & Schneiderman, 2008). The intervention was delivered to groups of 3-6 participants via weekly telephone conference call sessions lasting between 60-90 minutes per session. Group sessions were facilitated by a Master's level clinician. Sessions began with a 10-20 minute period of relaxation, followed by a didactic portion. The relaxation component consisted of relaxation training in diaphragmatic breathing, progressive muscle relaxation, guided imagery, and mindfulness meditation. Participants were instructed in the technique then led in the relaxation practice. The didactic portion of sessions focused on cognitive-behavioral stress management techniques, including: identifying sources of stress and stress appraisals, cognitive distortion identification (i.e., identifying and labeling thoughts that are irrational and maladaptive, such as overgeneralizations, "should" statements, and all-or-nothing thinking), cognitive restructuring (i.e., replacing cognitive distortions with more balanced, rational thoughts), assertiveness and anger management training, increasing quality of life, and identifying sources of social support. The use of these coping strategies effectively was emphasized based on the principles of coping effectiveness training (Chesney, Chambers, Taylor, Johnson, & Folkman, 2003), which teaches patients to match coping skills with stressor types.

Sessions also allowed for discussion among group members regarding relaxation skills and/or cognitive-behavioral stress management topics. Where appropriate, role-plays and brainstorming activities were also conducted. In addition to the encouragement

of daily relaxation practice, participants were given weekly homework assignments to develop competencies in the stress management technique discussed that week.

Attention Control Condition. The attention control condition consisted of a 10-week, manualized protocol to deliver health promotion information on the topics of nutrition, communication with physicians, and sleep hygiene. Sessions were led by a Master's level clinician and delivered to individual participants via weekly telephone conference call sessions lasting between 60-90 minutes per session. Five sessions focused on dietary guidelines based on the New Food Pyramid and New American Plate, in addition to tips for making healthy eating choices (American Institute for Cancer, 2004; United States Department of Agriculture, 2005). Two sessions discussed the importance of patient-physician communication, including tips for sharing with and receiving information from one's physician. An additional two sessions then focused on physiological changes during sleep and strategies for improving sleep quality. Finally, the last session was an overview of all prior material. Sessions were primarily didactic, and discussion about that week's topic was encouraged. Each session had in-session exercises meant to reinforce that day's educational material.

Measures.

Salivary Cortisol and Cytokine Interleukin-6. Participants provided salivary cortisol and plasma IL-6 samples at all three timepoints using methods described in Study 1.

Fatigue Interference and Fatigue Severity. Participants completed the Fatigue Symptom Inventory, which has been previously described, at all three timepoints. Internal consistency was adequate for the fatigue interference subscale across all three

timepoints (BL α = .86; 5M α = .90; 9M α = .87). Similarly, internal consistency was adequate for the fatigue severity subscale throughout the study (BL α = .79; 5M α = .83; 9M α = .87).

Depressed Mood. Participants completed the Center for Epidemiologic Studies Depression Scale (CES-D) as a measure of depressive symptoms, which was described in Study 1. Participants provided responses at all three timepoints. Depressed mood was again calculated from a subset of 7 items not describing somatic symptoms. Reliabilities for CES-D total scores across the study were good (BL α = .91; 5M α = .89; 9M α = .87), as were scores of depressed mood only (BL α = .91; 5M α = .85; 9M α = .86).

Perceived Stress Management Skills. Participants completed the Measure of Current Status (MOCS) (Carver, 2006) as a measure of perceived stress management skills, which are targeted by the CBSM intervention, as well as non-specific group processes and perceptions. Participants provided responses at all three timepoints. The MOCS contains two sections: Part A asks participants to rate their ability to respond to various challenges of daily life, and Part B assesses non-specific processes (e.g., bonding). For the current study, only responses from Part A were used, specifically for Exploratory Aim B on changes with fatigue interference over time. Part A contains 13 items that fall into one of 4 subscales measuring participants' current self-perceived skills in relaxation (e.g., "I am able to use muscle relaxation techniques to reduce any tension I experience"), stress awareness (e.g., "I can easily recognize situations that make me feel stressed or upset"), assertiveness (e.g., "It's easy for me to go to people in my life for help or support when I need it), and coping/cognitive restructuring (e.g., "I can easily stop and re-examine my thoughts to gain a new perspective"). Participants rate items on a 5-point

Likert type scale, from 0 (I cannot do this at all) to 4 (I can do this extremely well). Items within each subscale are summed then divided by total number of subscale items to create an average score. Internal consistency for the subscales of relaxation, stress awareness, assertiveness, and coping/cognitive restructuring have been shown to be adequate (α's = .71, .77, .86, and .89, respectively) (Carver, 2006).

Anxiety and Perceived Stress. The Profile of Mood States (POMS) anxiety-tension subscale (McNair, Lorr, & Droppleman, 1992) and the Perceived Stress Scale (PSS)(Cohen et al., 1983) were administered at baseline as measures of anxiety and perceived stress, respectively. Scores were for use in Exploratory Aim C on moderating variables. Cronbach alphas for these scales were good (POMS anxiety-tension subscale α = .90; PSS α = .87).

Potential Control Variables. Participants reported their age, alcohol use, smoking status, race/ethnicity, marital status, number of children, years of formal education, and employment status. These factors were examined as potential covariates when analyzing Study 2 hypotheses.

Statistical Analysis Plan for Study 2.

Preliminary Analyses. All analyses were conducted using SPSS version 22.0 (IBM). All variables were examined for outliers and normality of distributions. Where applicable, outliers and non-normal data were addressed using methods described in Study 1.

Demographic and medical variables were examined as potential covariates, determined by correlating age, alcohol use, smoking status, race/ethnicity, marital status,

number of children, years of formal education, and employment status data with the study outcome variables. Potential covariates related to an outcome variable ($p < .10$) were used as a covariate in analyses of that outcome.

Recently, a panel of leading biostatisticians published recommendations for the treatment of missing data in clinical trials in *The New England Journal of Medicine* (Little et al., 2012). The authors purported using multiple imputation to avoid biases associated with complete-case analysis (i.e., achieved through listwise deletion). Thus, missing data in Study 2 was addressed using multiple imputation methods as described in Study 1.

Unless stated otherwise, all analyses reported henceforth are based on intention-to-treat. Intention-to-treat analyses measure data on all participants and include that data in analyses regardless of attrition or incompleteness of data (Schünemann et al., 2011). Using an intention-to-treat analysis in trials with imputed outcome data is both recommended and common, accounting for 78% of studies included in Cochrane meta-analyses of mental health trials (Spineli, Pandis, & Salanti, 2015)

Adherence to Cortisol Timing Protocol. Adherence was assessed by examining participants' self-reports of sampling times using methods described in Study 1.

Baseline timepoint. On Day 1, 91 participants (98%) provided morning saliva samples that were adherent to the timing protocol. On Day 2, 90 participants (97%) were adherent. No participant was nonadherent on both Days 1 and 2. Therefore, all 93 participants were able to be included in analyses of cortisol data. On average, the timing difference between awakening and post-awakening samples was 31.30 minutes (SD = 2.32 minutes), with a range of 25.00 minutes to 40.00 minutes.

5-month timepoint. On Day 1, 92 participants (99%) provided morning saliva samples that were adherent to the timing protocol. On Day 2, 89 participants (96%) were adherent. No participant was nonadherent on both Days 1 and 2. Therefore, all 93 participants were able to be included in analyses of cortisol data. On average, the timing difference between awakening and post-awakening samples was 31.44 minutes (SD = 2.88 minutes), with a range of 25.50 minutes to 43.00 minutes.

9-month timepoint. On Day 1, 91 participants (98%) provided morning saliva samples that were adherent to the timing protocol. On Day 2, 93 participants (100%) were adherent. As no participant was nonadherent on both Days 1 and 2, all 93 participants were able to be included in analyses of cortisol data. On average, the timing difference between awakening and post-awakening samples was 31.00 minutes (SD = 2.48 minutes), with a range of 26.50 minutes to 42.50 minutes.

Calculation of Cortisol Awakening Response and Diurnal Cortisol Change. The CARi, CARg, and diurnal change scores were computed as described in Study 1. A minority of participants had negative CARi values on both days of an assessment timepoint (*n* = 12 at BL; *n* = 8 at 5M; *n* = 8 at 9M). Four participants had negative CARi values at two timepoints, while none had such values at all three timepoints. No demographic or medical data were significantly associated with having a negative CARi (*ps* > .10). Following the rationale provided in Study 1, cortisol data for these cases were subsequently imputed in order to bolster the integrity of cortisol analyses.

Primary Analyses.

Study 2, Aim 4. To assess whether CBSM intervention influences fatigue interference and fatigue severity in CFS/ME patients, two 2x3 repeated-measures

analyses of covariance (ANCOVAs) were run. Both analyses had the group assignment (CBSM vs. attention control condition) as the between-subjects factor, and three levels of the timepoint (BL, 5M, and 9M) as the within-subjects factor. The first model included fatigue severity as the dependent variable and the following covariates: ethnicity, marital/partnered status, employment status, age, education, and alcohol intake. The second model included fatigue interference as the dependent variable and the following covariates: fatigue severity, ethnicity, and employment status. For descriptive purposes, depressed mood was also examined as a psychological outcome variable via a 2x3 repeated measures ANCOVA with ethnicity and employment status as covariates.

Study 2, Aim 5. To assess whether CBSM intervention influences neuroimmune profiles in CFS/ME patients, a series of models were tested using a 2x3 repeated-measures ANCOVA for each neuroimmune variable as the dependent variable. These models included group assignment (CBSM vs. attention control condition) as the between-subjects factor, and three levels of the timepoint (BL, 5M, and 9M) as the within-subjects factor. The main neuroimmune variables examined were CARi, CARg, and IL-6 levels. CARi analyses included education as covariate, and IL-6 analyses included education, alcohol intake, and smoking status as covariates.

For descriptive purposes, additional cortisol-related variables were examined for potential group, time, and group-by-time effects. These included awakening cortisol, post-awakening cortisol, afternoon (4:00pm) cortisol, evening (9:00pm cortisol), and the diurnal change (9:00pm-awakening) in cortisol.

Study 2, Exploratory Aim A. Follow-up regression analyses of indirect effects were planned to test whether any significant group-related changes in neuroimmune

variables from Aim 5 were due in part to significant changes in fatigue interference over time from Aim 4. These analyses would have evaluated bias-corrected bootstrapped confidence intervals for an indirect effect, based on a resampling with replacement method described by Preacher and Hayes (2008). This modeling tool is ideal for testing indirect effects for multiple reasons. First, as elaborated by Hayes (2009), it uses bootstrapping, a method far more sensitive for measuring partial mediation than other techniques such as those offered by Sobel (1982) or Baron and Kenny (1986). Bootstrapping is a more powerful method and has greater Type 1 error control when compared to alternative techniques for estimating indirect effects (Hayes, 2009). It also does not require the indirect effect's sampling distribution to be normal, an assumption of Sobel's test that is frequently inadvertently violated (Bollen & Stine, 1990; Hayes, 2009; Stone & Sobel, 1990).

Therefore, using the Preacher and Hayes (2008) method, a series of regression models were to be constructed with group assignment as the independent variable (CBSM vs. attention control condition). Fatigue interference change scores from baseline to 5-months were to be calculated and entered as the mediating variable. Dependent variables were to be change scores in neuroimmune variables from baseline to 5-months and from 5-months to 9-months. After running the models for a 5000-iteration bootstrapping (Hayes, 2009), the 95% confidence intervals for each indirect effect are produced for interpretation. For each model, if the confidence interval for the indirect effect does not contain zero, the effect is significantly different from zero, implying partial mediation. The magnitudes of these effects were to be presented as unstandardized regression coefficients.

Study 2, Exploratory Aim B. This aim was to examine whether changes in fatigue interference from Aim 4 covaried with changes in specific perceived skills targeted by CBSM intervention. These analyses were intended to provide insight into the specific ingredient(s) of CBSM that is most influential in altering fatigue interference.

A series of change scores were to be calculated using the following MOCS Part A subscales: relaxation, stress awareness, assertiveness, and coping/cognitive restructuring. Change scores from BL to 5M and from 5M to 9M were to be derived. Next, four regression models would test whether changes in each skill from BL to 5M were significantly correlated with fatigue interference change scores from BL to 5M. This process would then be repeated using change scores from 5M to 9M. The magnitude and direction of significant regression coefficients were be examined to make comparisons across skills targeted by the CBSM intervention.

Study 2, Exploratory Aim C. In the absence of significant group-by-time interaction effects from Aims 4 and 5, correlates of time effects were examined. Timepoints were selected based on significant post-hoc analyses of omnibus time effects, thus identifying two timepoints capturing the change (i.e., BL to 5M, BL to 9M, or 5M to 9M). For reasons described below, potential correlates of change included: session attendance, illness duration, baseline psychosocial factors (depression, anxiety, and perceived stress), and symptom frequency and severity. In each analysis, a model was run regressing a potential correlate on the change score of a dependent variable (e.g., 9M CARi minus BL CARi). For all regressions, the following covariates were entered: group assignment, sociodemographic covariates with the dependent variable identified in preliminary analyses, and the BL value of the dependent variable.

Session attendance could yield insight into whether participants found equal benefit from both study conditions, assuming that higher attendance would more beneficial changes in fatigue-related and neuroimmune variables. Illness duration was selected because Hornig and colleagues (2015) recently found evidence for higher IL-6 levels among CFS/ME patients with shorter illness duration (3 years or less) than among longer-term patients. Whether changes in neuroimmune variables over time were different for patients based on session attendance and/or illness duration was therefore worth examination.

Furthermore, it has been suggested that abnormalities in the CAR of CFS/ME patients is explained by the presence of early childhood trauma (Heim et al., 2009). In the absence of data asking about participants' experiences with early trauma, measures of psychosocial distress (CES-D, POMS- anxiety-tension subscale, and PSS) obtained at baseline were examined as potential moderators of change in neuroimmune variables over time.

Finally, data were available on participants' self-reports of the frequency and severity of common CFS/ME symptoms. Correlations between changes in these ratings and changes in neuroimmune variables were also assessed.

Chapter 5

Study 2 Results

Preliminary Analyses.

Sample Description. A total of 93 adult women were randomized to receive either telephone-delivered CBSM (*n* = 53) or a telephone-delivered attention control condition (*n* = 40). Table 5 presents demographic data on participants obtained at the baseline assessment (BL).

Overall, there were no group differences between participants randomized to either condition on demographic factors. Participants in both conditions were approximately 50 years of age, primarily non-Hispanic white, and had earned a college degree. Participants were typically not employed full-time, married/partnered, or cigarette/cigar smokers. On average, participants reported having experienced CFS/ME symptoms for between six and eight years duration.

Retention and Completeness of Data. The Consort diagram is presented in Figure 1. Of the 95 women enrolled in the trial, 93 were randomized to either the CBSM or attention control condition. Two women withdrew prior to randomization due to reported lack of interest. Retention was indicated by completion of the survey, saliva, and/or blood draw for an assessment. At 5-months (5M), overall retention was 78% (79% for CBSM group and 78% for Control group). By 9-months (9M), overall retention was 100% of those from 5M and 85% of those randomized initially. Participants who completed all three assessments and those participants who did not did not differ by experimental condition or any demographic or medical variable (all *p*'s > .10).

Rates of missingness were also calculated for all variables at each timepoint. As analyses were based on intention to treat, missingness rates used $n = 93$ as the denominator and were thus sensitive to retention (e.g., minimum missingness for 5M was 22%). At BL, no variable had more than 27% missing data. At 5M and 9M, missingness ranges were 22% to 40% and 15% to 46% missing, respectively. Thus for all variables, the majority of data was available. Furthermore, all participants provided data for each variable at a minimum of one assessment timepoint.

<u>Primary Analyses.</u>

Study 2, Aim 4. To assess whether CBSM intervention influences fatigue interference in CFS/ME patients, a 2x3 repeated-measures analyses of covariance (ANCOVAs) was run. This model included fatigue interference as the dependent variable, two levels of the group assignment (CBSM vs. attention control condition), and three levels of the timepoint (BL, 5M, and 9M). Fatigue severity at each timepoint was entered as a covariate in addition to ethnicity and employment status.

Results of this ANCOVA are presented in Table 6. There were no effects of time (partial $\eta^2 = .01$, small effect), $p = .63$ or group-by-time (partial $\eta^2 < .01$, small effect), $p = .69$ on fatigue interference scores. A repeated-measures ANCOVA was also run with fatigue severity instead as the dependent variable. Similarly, there were neither effects of time (partial $\eta^2 = .02$, small effect), $p = .29$ nor group-by-time (partial $\eta^2 = .01$, small effect), $p = .33$ on fatigue severity.

Finally, depressed mood was examined as a supplementary indicator of participants' psychosocial functioning. As seen in Figure 2, there was a significant effect of time [$F(2,178) = 4.23$, $p = .02$, partial $\eta^2 = .05$ (small effect)] but not group-by-time,

partial $\eta^2 = .01$ (small effect), $p = .57$. Post-hoc analyses of these time effects revealed a significant decrease in depressed mood from baseline to 9-months, $F(1,89) = 7.39$, $p = .008$, partial $\eta^2 = .08$ (medium effect).

Study 2, Aim 5. To assess whether CBSM intervention influences neuroimmune profiles in CFS/ME patients, three primary models were tested using a 2x3 repeated-measures ANCOVA for each a neuroimmune variable as the dependent variable, two levels of the group assignment (CBSM vs. attention control condition), and three levels of the timepoint (BL, 5M, and 9M). The primary neuroimmune variables examined were CARg, CARi, and IL-6 levels. In addition, supplemental analyses were run examining effects on cortisol throughout the day. Results of Aim 5 are summarized in Table 6.

Cortisol-related variables were examined first. As seen in Figures 3 and 4, there were significant time effects on CARi [$F(2,180) = 3.38$, $p = .04$, partial $\eta^2 = .04$ (small effect)] and CARg [$F(1.86,169.52) = 14.08$, $p < .0001$, partial $\eta^2 = .13$ (medium effect)], but no group-by-time effects for either variable [CARi ($p = .06$), partial $\eta^2 = .03$ (small effect); CARg ($p = .69$), partial $\eta^2 < .01$ (small effect)]. Post-hoc tests of time effects revealed that CARi overall decreased from BL to 9M [$F(1,90) = 5.91$, $p = .02$, partial $\eta^2 = .06$ (medium effect)], and CARg overall decreased from 5M to 9M [$F(1,91) = 31.32$, $p < .0001$, partial $\eta^2 = .25$ (large effect)] and from BL to 9M [$F(1,91) = 17.25$, $p < .0001$, partial $\eta^2 = .16$ (large effect)].

Upon inspection, it was observed that CARg and CARi decreased from baseline to 9-months among 68% and 57% of participants, respectively. For descriptive purposes, participants were categorized dichotomously depending on whether their CARg or CARi decreased from baseline to 9-months. Pearson chi-square analyses indicated that study

condition (CBSM versus Attention Control) was not associated with being a "decreaser" or "increaser" on either CARg [$\chi^2(1) = 0.64, p = .42$] or CARi [$\chi^2(1) = 3.67, p = .06$].

Cortisol levels throughout the day were examined as well. There were significant time effects for post-awakening levels [$F(2,182) = 7.11, p = .001$, partial $\eta^2 = .07$ (medium effect)], but not for awakening ($p = .08$, partial $\eta^2 = .03$, small effect), afternoon ($p = .63$, partial $\eta^2 = .01$, small effect), evening ($p = .41$, partial $\eta^2 = .01$, small effect), or diurnal change ($p = .11$, partial $\eta^2 = .02$, small effect). No group-by-time effects were demonstrated for these cortisol variables, $ps > .23$ (awakening partial $\eta^2 < .01$, small effect; post-awakening partial $\eta^2 = .02$, small effect; afternoon partial $\eta^2 = .02$, small effect; evening partial $\eta^2 = .01$, small effect; change partial $\eta^2 = .01$, small effect). Figure 5 represents post-awakening cortisol levels across study timepoints. Post-hoc tests indicated that post-awakening levels decreased from 5M to 9M [$F(1,91) = 7.93, p = .006$, $\eta^2 = .08$ (medium effect)] and BL to 9M [$F(1,91) = 13.75, p < .0001$, $\eta^2 = .13$ (medium effect)].

Finally, a model was run examining the effects of group assignment and time on participants' IL-6 concentrations. These values are represented in Figure 6. Results revealed a time effect [$F(2,176) = 4.77, p = .01$, $\eta^2 = .05$ (small effect)] but no group-by-time effect ($p = .42$, partial $\eta^2 = .01$, small effect). Post-hoc tests indicated that IL-6 levels overall decreased significantly from BL to 9M, $F(1,88) = 8.65, p = .004$, $\eta^2 = .09$ (medium effect).

It was observed that 66% of participants evidenced a decrease in IL-6 from BL to 9M. As with CARg and CARi, a dichotomous variable was created for descriptive purposes indicating whether a participant was a "decreaser" or "increaser" for IL-6 over

the 9-month window. Pearson chi-square analyses indicated that study condition (CBSM versus Attention Control) was not associated with being a "decreaser" or "increaser" on IL-6 [$\chi^2(1) = 3.11$, $p = .08$].

Study 2, Exploratory Aim A. In the absence of significant group-by-time effects found in Aims 4 and 5, analyses of indirect effects were not conducted to assess whether CBSM participation reduces indices of neuroimmune dysfunction via reductions in fatigue interference over time.

Study 2, Exploratory Aim B. This exploratory aim was to examine whether changes in perceived stress management skills over time related to significant changes in fatigue interference over time. As no significant changes in fatigue interference were demonstrated from analyses conducted under Aim 4, analyses for this exploratory aim were not conducted.

Study 2, Exploratory Aim C. Significant time effects were demonstrated for several study variables. Overall reductions from baseline to 9-months were found in levels of depressed mood, CARi, CARg, post-awakening cortisol, and IL-6. To better understand these longitudinal patterns, exploratory regression analyses were conducted to ascertain correlates of observed time effects.

Session Attendance. First, session attendance was examined. Both study conditions consisted of 10 sessions. As illustrated in Table 7, three-fourths of participants attended between eight and 10 study sessions, independent of group assignment. A dichotomous variable was created to indicate whether each participant's attendance was High (at least eight sessions attended) or Low (seven or fewer sessions attended). Overall session attendance was examined as both a continuous (number

attended) and categorical (High or Low) variable. Neither attendance variable was associated with longitudinal change scores in depressed mood (standardized Betas = -.07 and -.10, *ps* ≥ .22), CARi (standardized Betas = -.07 and -.04, *ps* ≥ .38), CARg (standardized Betas = .01 and .03, *ps* ≥ .63), post-awakening cortisol (standardized Betas = -.06 and -.05, *ps* ≥ .60), or IL-6 (standardized Betas = .03 and .11, *ps* ≥ .16).

Pearson chi-square analyses then were conducted to test whether being a "decreaser" or "increaser" for CARi, CARg, or IL-6 from baseline to 9-months was predicted by High or Low session attendance. Being a CARg "decreaser" was not associated with having High or Low session attendance, $\chi^2(1) = 0.35$, $p = .63$. However, having High session attendance was significantly related to being a CARi "decreaser" [$\chi^2(1) = 4.82$, $p = .03$] as well as an IL-6 "increaser" [$\chi^2(1) = 4.54$, $p = .03$] during the 9-month window.

Illness Duration. Next, illness duration was examined. A recent study documented higher plasma IL-6 levels among patients who have had CFS/ME symptoms for three years or less as compared with longer-term patients (Hornig et al., 2015). Illness duration has been underexplored as a correlate to cortisol in CFS/ME. In the present study, patients self-reported the frequency, severity, duration, and onset of their CFS/ME symptoms as part of the questionnaire administered at each assessment. Illness duration was calculated by subtracting the most temporally distal onset from the date of baseline assessment. This variable was dichotomized as either Short (three years or less) or Long (more than three years) in duration.

Overall, 69% of participants had Long duration of symptoms. Both the continuous and categorical levels of the variable were examined. Neither illness duration

variable was associated with baseline levels or longitudinal changes in depressed mood (standardized Betas = -.04 and <-.01, *ps* ≥ .43), CARi (standardized Betas = .04 and .06, *ps* ≥ .38), CARg (standardized Betas = .02 and .06, *ps* ≥ .30), post-awakening cortisol (standardized Betas = .07 and .08, *ps* ≥ .44), or IL-6 (standardized Betas = .06 and -.06, *ps* ≥ .41).

Premorbid Distress. Baseline measures of psychosocial distress (CES-D, POMS anxiety-tension subscale, and PSS) were examined in lieu of unobtained data on the presence of early childhood trauma, a factor that may influence hormone levels in CFS/ME including cortisol (Heim et al., 2009). It was reasoned that early childhood trauma could inflate scores on these measures of present functioning. Similarly, baseline alcohol intake and smoking status were examined, as these behaviors more prevalent among trauma survivors (Breslau et al., 2003). Data from the CES-D were operationalized as continuous total scores, categorical scores (Above or Below clinical cutoff score of 16), and depressed mood only. Continuous scores from POMS anxiety-tension subscale and PSS were used.

None of these variables were associated with longitudinal changes in the neuroimmune variables examined (standardized Betas ≤ |.05|, *ps* ≥ .24). No relationships with depressed mood changes were found when examining the PSS (standardized Beta = .21, *p* = .08), the POMS anxiety-tension subscale (standardized Beta = .07, *p* = .61), alcohol intake (standardized Beta = -.02, *p* = .82), or smoking status (standardized Beta = .09, *p* = .31).

CFS/ME Symptoms. Finally, participants' self-reports of the frequency and severity of common CFS/ME symptoms were examined. These symptoms included: sore

throat, tender lymph nodes, diarrhea, post-exertional malaise, muscle aches/pain, joint

pain, fever, chills, unrefreshing sleep, problems falling asleep or waking, severe

headaches, memory problems, nausea, stomach pains, sinus/nasal symptoms,

numbness/tingling, general weakness, shortness of breath, light sensitivity, and

depression. Both baseline levels of the frequency and severity of individual symptoms as

well as their change scores (BL to 9M) were explored as correlates to observed time

effects on depressed mood, CARi, CARg, post-awakening cortisol, and IL-6. Overall, all

regression analyses yielded non-significant associations (standardized Betas $\leq |.18|$, *ps* $\geq$

.12).

Chapter 6
Discussion

The present investigation consisted of two studies that, broadly speaking, examined the perceived impact of chronic fatigue on daily living among adult women with CFS/ME, its relationships with parameters of neuroimmune function, and how these factors may be influenced by a telephone-delivered cognitive behavioral stress management (CBSM) intervention. The first of these studies consisted of several aims that were analyzed using cross-sectional data.

Previously, no study had assessed and quantified fatigue interference scores among CFS/ME patients and compared them to these scores among cancer survivors with chronic cancer-related fatigue. Both populations tend to nominate difficulties with chronic fatigue among their most pressing concerns, as previous comparisons of their fatigue-related experiences have shown (Bennett et al., 2007; Servaes et al., 2002; Servaes, van der Werf, Prins, Verhagen, & Bleijenberg, 2001). In Aim 1, fatigue interference scores from women with CFS/ME and five-year breast cancer survivors were compared after controlling for fatigue severity. All participants endorsed clinically elevated levels of fatigue using criteria established by Donovan et al. (2008). As hypothesized, the CFS/ME sample endorsed higher levels of fatigue interference after accounting for the severity of fatigue symptoms. In fact, women with CFS/ME endorsed almost three times greater interference than did their counterparts, on average scoring seven on a scale from zero (No Interference) to 10 (Extreme Interference). This discrepancy between the two samples may have multiple explanations. While both groups of women endorsed experiencing persistent fatigue, perhaps there are distinctions in the qualities of fatigue that lead to differential appraisals of interference. For instance,

Servaes and colleagues (2001) found that while reports of motivation and physical activity were similar among groups of CFS/ME patients and severely fatigued disease-free cancer patients, the CFS/ME sample reported greater difficulties with concentration. In contrast, Bennet and colleagues' (2007) qualitative study with these populations concluded that both groups experience similar cognitive difficulties. Whether these patient groups experience disparate cognitive impairment or subjective "mental fatigue" is unclear, and potential links with fatigue interference remain unknown.

Alternatively, perhaps CFS/ME patients in the present study reported greater fatigue interference because of a relative paucity in social resources for them. Compared with CFS/ME, breast cancer has a higher prevalence in the general population and, arguably, greater research funding, availability of knowledgeable physicians, online resources, and presence in public media. A recent review of CFS/ME published in *American Journal of Psychiatry* emphasized providers' uncertainty as a major barrier to symptom management (Afari & Buchwald, 2014). Indeed, CFS/ME patients report having less self-efficacy regarding self-management of fatigue than do fatigued cancer survivors (Servaes et al., 2002). Resultantly, CFS/ME patients may perceive having relatively fewer resources available for managing their symptoms and therefore greater interference in their daily life stemming from fatigue.

Neuroimmune Correlates of Fatigue Interference. In the second aim of Study 1, parameters of endocrine function and inflammatory states were examined as potential correlates with fatigue interference. As detailed in the Introduction, CFS/ME patients tend to exhibit hypocortisolism and high levels of inflammation. Specific biomarkers of these regulatory systems were identified based on prior literature examining baseline

differences between patients with CFS/ME and healthy controls. For markers of

endocrine dysregulation, two indices of the cortisol awakening response were selected:

CARi and CARg. The CARi is a measure of change in cortisol levels from awakening to

post-awakening. Similar to the CARi, the CARg also reflects morning cortisol levels yet

is a measure of total cortisol output from morning through awakening. As an indicator of

immune activation, pro-inflammatory cytokine IL-6 was selected.

In Study 1, levels of the CARi and CARg, as well as cortisol levels measured in

the afternoon and evening, were comparable to those previously observed among women

with CFS/ME (Jerjes et al., 2005; Roberts et al., 2004; Roberts et al., 2008; Nater et al.,

2008). The present study used rigorous methods to maximize the integrity of cortisol-

related data. These considerations included providing clear instructions to participants

and a two-fold inspection of obtained data. Specifically, self-reported timing of samples

and CARi slopes were examined, practices which are historically uncommon or

underreported but are becoming increasingly popular in the psychoneuroendocrinology

literature (Breslau, Davis, & Schultz, 2003; Hall et al., 2011; Kupper et al., 2013; Fischer

et al., 2014). In addition to cortisol, IL-6 levels were also comparable to those previously

reported among women with CFS/ME (Fletcher et al., 2009; Hornig et al, 2015).

It was hypothesized that greater fatigue interference would relate with lower

CARi and CARg levels, greater IL-6 levels, and that greater depressed mood would

amplify these relationships. Overall, results yielded mixed support for these hypotheses.

As hypothesized, fatigue interference was negatively associated with the CARi. Each

standard deviation increase in fatigue interference was associated with a .28 standard

deviation decrease in the CARi. Contrary to hypotheses, fatigue interference was not

related with CARg or IL-6 levels. Analyses of these models controlled for fatigue

severity, which was not significantly related to any neuroimmune variable examined.

Finally, levels of depressed mood did not moderate these relationships.

Taken together, these findings contribute to literature linking patients' subjective

illness experiences to objective physiological phenomena in CFS/ME. In particular,

Study 1 data indicate that patients who perceive their fatigue to be negatively impacting

their life tend to have a smaller rise in cortisol levels after waking up in the morning.

What mechanism might explain this relationship?

Data from Study 1 are cross-sectional, so unfortunately directionality and causal

interpretations cannot be inferred. One potential explanation incorporates the concept of

"allostatic load", whereby chronic exposure to acute stressors over time creates a burden

on one's biological regulatory systems and lowers their basal functioning (McEwen,

1998). The HPA axis is considered to be sensitive to this phenomenon, with persistent

acute activations leading to a dampening of basal diurnal patterns over time (McEwen,

1998). In a hallmark meta-analysis of stress and cortisol, Miller, Chen, & Zhou (2007)

found that chronic stressors of longer duration were associated with lower morning

cortisol levels across many psychiatric and medical populations. The present CFS/ME

sample had chronic fatigue symptoms for on average seven years, so it is plausible that

they had fatigue interference for a similar duration. Daily feelings of being limited by

fatigue may have been a psychosocial stressor that, over time, lowered patients' HPA

axis activity soon after waking (i.e., CARi). This explanation builds on findings that

hypocortisolism in CFS/ME is positively related to chronic stress (Heim et al., 2000; Papadopoulos & Cleare, 2012; Tak et al., 2011) and inversely related to perceived stress management skills (Hall et al., 2014).

Conversely, fatigue interference was not associated with the CARg. Currently, our understanding of the differences between the CARi and CARg in CFS/ME is emergent. Studies cited in this manuscript vary in their reporting of significant effects with either or both the CARi and CARg, and none had hypotheses about differential results for each. A recent meta-analysis of unstimulated cortisol in CFS/ME purported that future studies assess and describe both parameters, in hopes of clarifying their differences as this literature develops (Powell et al., 2013). Here, findings indicate that greater fatigue interference was related to a dampened *change* in HPA axis activity in the period of time between awakening and around 30 minutes after, relative to awakening levels (i.e., CARi). It would be interesting to see in future studies whether CFS/ME patients perceive that their fatigue impacts them the most immediately after awakening, when cortisol levels may be most dysregulated. Alternatively, perhaps the temporal relationship is staggered; morning cortisol levels may be affected by the previous day's experiences of feeling threat and lack of control (Adam, Hawkley, Kudielka, & Cacioppo, 2006), factors conceptually related to the perception of fatigue-related interference.

Regarding IL-6, the null findings reported here are not consistent with previous reports linking this pro-inflammatory cytokine with the presence of fatigue-related concerns (Arnold et al., 2002; Bansal et al., 2012; Fletcher et al., 2009; Gaab et al., 2005; Lattie et al., 2012; Nas et al., 2010; Patarca-Montero et al., 2001). It may be that for the

present sample, behavioral factors could better account for levels of IL-6, such as physical activity (White et al., 2011; Wiborg, Knoop, et al., 2010). Indeed, IL-6 levels were positively related to smoking and negatively related to alcohol intake, consistent with literature on health behaviors related to inflammation (O'Connor et al., 2009).

Additionally, perhaps the pathway linking fatigue interference and IL-6 exists but is distal; more complex modeling that includes intermediary variables may elucidate indirect effects. One such intermediary could be differential gene expression of glucocorticoid receptors on peripheral blood mononuclear cells (PBMCs) that respond to inflammation in the body. Support for this idea comes from work by Sheldon Cohen, Gregory Miller, and colleagues (2012), who compared susceptibility to developing the common cold among individuals with and without major chronic life stress. One of their findings was that stressed participants had greater pro-inflammatory cytokine production, effectively due to a quieting of their PBMCs' ability to bind with (the anti-inflammatory hormone) cortisol. Future models linking fatigue interference with IL-6 in CFS/ME could thus include cortisol and glucocorticoid receptor gene expression in PBMCs as potential mediators.

Interaction of Fatigue Interference and Depressed Mood. In the third aim of this study, the potential moderating role of depressed mood in amplifying associations among fatigue interference and neuroimmune variables was tested. On the one hand, previous literature on the experiences of fatigue and depression in CFS/ME suggests that the psychosocial impact of fatigue is worsened by comorbid depressive symptoms (Anderson et al., 2014; Dansie et al., 2012; Friedberg & Krupp, 1994). For instance, the perceived burden of fatigue on one's ability to socialize with friends may be heightened if the

patient's mood is highly negative. On the other hand, depressive symptoms have been associated with elevated IL-6 levels and examined as correlates to hypocortisolism in CFS/ME. Therefore perhaps high negative mood could interact with high fatigue interference to predict the lowest CAR and highest IL-6 levels.

Here, the data did not implicate depressed mood a correlate of the CARi, CARg, or IL-6, or as a moderator of the relationships tested in Aim 2. That is, the negative relationship between fatigue interference and the CARi did not differ among patients with higher or lower depressed mood.

This finding is congruent with null or inconclusive results from previous studies that examined depressed mood as a correlate of the CAR in CFS/ME (Nater et al., 2008; Roberts et al., 2009; Roberts et al., 2004; Tak et al., 2011). In contrast, prior studies have linked depressed mood with elevated IL-6 levels in the general population (Dowlati et al., 2010; Howren, Lamkin, & Suls, 2009; Voorhees et al., 2013; Zorrilla et al., 2001). Perhaps this pattern was not observed among the present CFS/ME sample due to a ceiling effect, as women with CFS/ME tend to have elevated IL-6 levels relative to healthy controls (i.e., Fletcher et al., 2009). A recent review of biomarkers of immune dysregulation in CFS/ME discussed the paucity of consistently identifiable psychological factors that might relate to pro-inflammatory cytokines (Fischer et al., 2014), which was echoed by a recent multi-site cohort study published in *Science Advances* (Hornig et al., 2015). Thus future work is warranted to identify psychological factors related to levels of IL-6 in this population.

Telephone-Delivered Cognitive Behavioral Stress Management. Prior trials of cognitive behavioral stress management (CBSM) intervention in a variety of patient

populations have demonstrated positive effects on psychosocial and neuroimmune function (Antoni et al., 1991; Antoni et al., 2000; Antoni et al., 2001; Antoni et al., 2012; Lutgendorf et al., 1998; Penedo et al., 2004; Penedo et al., 2006; Stagl et al., 2015). Among breast cancer patients, CBSM has been found to decrease fatigue interference (Vargas et al., 2014). Specifically among patients with CFS/ME, CBSM has been shown to improve quality of life, perceived stress, mood, and symptom severity (Lopez et al., 2011). To date, it is unknown whether CBSM also improves fatigue interference and neuroimmune function among patients with CFS/ME. In Study 2, it was hypothesized that, compared to an attention control condition, CBSM would lead to greater decreases in fatigue interference and IL-6, as well as greater increases in the CARi and CARg among female patients over a five and nine month longitudinal follow-up period. A series of specific aims (4 and 5) and exploratory aims (A and B) were to examine hypotheses about potential group-by-time effects, their potential correlates, and their potential mediators. However, no statistically significant differences on levels of main study variables over time were found between participants randomized to either group condition.

Several factors may have accounted for the paucity of differential time effects between the CBSM and attention control conditions. One such factor was the modality of CBSM delivery. Telephone delivery has been lauded for its potential to address several common barriers to patient care, including logistical concerns (e.g., transportation problems, access to local resources and services, child care, lack of financial resources, busy daily schedule), psychological concerns (e.g., lack of motivation, stigma, body image difficulties), and physical health concerns (e.g., ambulatory difficulties, pain, low

energy) (Alvidrez & Azocar, 1999; Hollon et al., 2002; Zinzow et al., 2012). In Study 2, the high rates of session attendance – three-fourths of participants attended at least 80% of sessions – suggest that these potential barriers may have been circumvented by telephone delivery.

Still, it is possible that CBSM effects would have been observed had it been delivered in person via live groups. Prior research comparing these modalities has yielded mixed findings. Preliminary findings comparing telephone and in-person delivery of CBSM to CFS/ME patients have shown larger decreases in total symptom severity with in-person delivery (Antoni et al., 2013). In contrast, other findings show similar efficacy between these modes of delivery for manualized, CBT-based interventions among patients with CFS/ME (Burgess, Andiappan, & Chalder, 2012) as well as other illnesses (Mohr et al., 2005; Mohr et al., 2012; Hammond et al., 2012; Himelhoch et al., 2013). However, these studies delivered CBT to individual patients rather than groups of patients. Using an individual format may have maximized participants' communication with their therapist and uptake of CBT-related skills. In the present study, participants may have been less engaged during sessions than in previous in-person CBSM trials. If, for instance, a patient was not engaged in relaxation exercise demonstrations, she may not have learned those skills or benefited from practicing relaxation. Unfortunately, therapists in Study 2 were not able to see participants and acquire real-time feedback about their nonverbal engagement in sessions.

Relatedly, it is unclear whether the benefits found among participants in telephone-delivered cognitive behavioral interventions are effective due to the content versus the general support obtained. Perhaps the greatest benefit is derived from having a

weekly discussion with an invested therapist or healthcare provider. Thus another explanation for the lack of differences observed between CBSM and control groups in Study 2 is that both groups benefited similarly from having weekly contact. A recent trial by Heckman and colleagues (2013) compared three arms of treatment for depression among adults with HIV: telephone-delivered supportive-expressive therapy (SET), telephone-delivered coping effectiveness training (CET), and treatment-as-usual. Post-treatment, patients in the SET group had fewer depressive symptoms compared to the other groups, indicating that increased social support accounted for the greatest therapeutic gains. In Study 2, high session attendance was observed in both conditions, so participants had frequent opportunities to benefit from weekly contact with their counselors.

A third explanation is that participants in both groups developed enhanced self-efficacy due to learning new material. The attention control condition provided psychoeducation about health promotion topics, and participants in this condition were encouraged to set healthy goals about nutrition, sleep hygiene, and communication with physicians. Similarly, participants randomized to receive CBSM were taught and asked to practice new skills related to relaxation, stress awareness, cognitive restructuring, problem solving, interpersonal communication, social support, and quality of life. Therefore all women had opportunities to develop a sense of achievement, mastery, and confidence. Previously, a health-related education intervention was observed to be as effective as CBT on improving mental and physical health concerns (Carmody et al., 2013), perhaps due to increased competence and satisfaction from practicing self-regulation (Knoop & Wiborg, 2015; Ryan & Deci, 2000). However, one could also argue

that a sense of mastery of cognitive-behavioral skills would translate to more mood improvements than a mastery of general health promotion skills due to more skillful emotion regulation. Patients' mastery of cognitive restructuring skills targeting catastrophic thinking and symptom magnification has been posited to mediate CBT-related gains among depressed adults with and without CFS/ME (Friedberg & Krupp, 1994). However, that study did not compare CBT to a health-promotion attention control but rather treatment-as-usual.

Finally, it is possible that the followup window in the present study was too short to detect significant differences between the CBSM and attention control groups. Deale and colleagues (1997) conducted an RCT comparing the longitudinal effects of a 13-session CBT intervention with graded activity versus a relaxation skills intervention among patients with CFS/ME. On self-reported measures of mental and physical health, CBT outperformed the relaxation intervention, with greatest effects demonstrated at the final, 6-month post-intervention assessment. At a five-year followup, gains in the CBT-randomized group were even more pronounced (Deale, Husain, Chalder, & Wessely, 2001). Thus perhaps in Study 2 there were meaningful group condition differences over time, but the assessment schedule terminated too soon to capture these effects.

Time-Related Effects on Fatigue Interference. No changes were observed in either fatigue interference or fatigue severity across all three study timepoints. The data suggest that among women with CFS/ME, perceptions of the impact of fatigue on daily living were consistently negative, as were their ratings of fatigue severity. At each timepoint, average fatigue interference ratings were approximately a seven on a scale

from zero (No Interference) to 10 (Extreme Interference), indicating that study participants were experiencing a persistently high degree of psychosocial burden attributed to their fatigue.

These findings underscore the psychosocial impact of fatigue on women with CFS/ME and the importance for better understanding modifiable targets for intervention on this concern. Factors not examined in Study 2 that could directly or indirectly influence fatigue interference might include: behavioral factors (i.e., sleep behaviors, diet, physical activity level, hoarding), psychological factors (i.e., early adverse experience, trait-level neuroticism, illness-related anxiety), or environmental factors (i.e., geographically-related weather and climate, proximity to goods and services). Some of these factors have previously been linked to CFS/ME (Ayers, Iqbal, & Strickland, 2014; Heim et al., 2006; Sáez-Francàs et al., 2014), but their relationships with fatigue interference remain unexamined.

Time-Related Effects on Depressed Mood. In Study 2, participants' levels of depressed mood decreased significantly from BL to 9M. This improvement in patients' subjective mental health could be due to several factors. As discussed previously, patients may have found supportive benefit from participation in a study that provided weekly phone contact with a dedicated counselor, resulting in a less negative mood state. However, if this were true one might expect to observe the greatest mood improvement at the 5M assessment, when sessions had recently completed. From 5M to 9M, participants did not receive weekly contacts from study staff, yet mood ratings continued to improve to levels significantly less negative than those at BL.

Alternatively, perhaps the longitudinal assessments were capturing the natural phenomenon of recovery, whereby an individual has a gradual return to their level of functioning prior to an acute psychosocial event (for discussion of recovery versus resilience, see Bonnano, 2004). Most of the women who enrolled in the Study 2 parent trial were recently experiencing negative mood, which could have motivated their interest in joining the study. At the BL assessment, over 70% of women endorsed clinically elevated symptoms of depression (CES-D total score $\geq$ 16), far higher than rates observed in other studies of women with CFS/ME (Cella et al., 2013, Prins et al., 2005), although this estimate may be inflated due to the somatic overlap of depression and CFS/ME symptoms (Jason et al., 2015). Examination of CES-D items assessing mood alone still indicates that women tended to have mild mood disturbance. Over time, the levels of mood distruption may have organically rebounded to levels more commonly observed in this population (i.e., regression to the population mean), a pattern commonly observed in longitundal studies (Yudkin & Stratton, 1996).

It is also plausible that negative mood improved due to a placebo effect. CFS/ME patients who enrolled in the Study 2 parent trial were aware they were participating in a NIH-funded RCT. Although no direct benefits were promised from participation, patients may have anticipated that they would experience psychological benefits by the end of the 9-month assessment timeframe.

Time-Related Effects on Biomarkers of Neuroimmune Function. Statistically significant changes were observed in levels of cortisol (CARi, CARg, and post-awakening values) and IL-6 across the study timepoints. Little is known about longitudinal changes in biomarkers of neuroimmune function among CFS/ME patients.

While hypocortisolism has been previously associated with CFS/ME (i.e., Jerjes et al., 2005; Nater et al., 2008; Papadopoulos & Cleare, 2012), there is a paucity of literature decribing both: (a) the cross-sectional correlation of illness duration on morning cortisol levels in CFS/ME, and (b) how levels change over time. In non-elderly adults without CFS/ME, unbound cortisol levels tend to stay constant or to decrease over time (discussed in Roberts et al., 2009). Data from Study 2 suggest that among women with CFS/ME, hypocortisolism may magnify over time.

Over the 9-month followup period, women with CFS/ME experienced a decrease in the total morning cortisol output (i.e., CARg), a dampening of the change from waking to 30 minutes post-awakening cortisol levels (i.e, CARi), and overall lower post-awakening levels. For the CARg, these effects were evidenced from BL to 9M and 5M to 9M, though they were most pronounced during the latter timeframe. Decreases in the CARi and post-awakening cortisol were also evidenced from BL to 9M.

Of note, cortisol levels did not significantly change during the BL to 5M. During this timeframe, participants were completing the CBSM or attention control 10-week program. Subsequently, CARi, CARg, and post-awakening levels dropped from 5M to 9M, resulting in the statistically significant overall decreases observed from BL to 9M.

It is possible that the constant cortisol levels from BL to 5M reflect a buffering against the decline in levels from 5M to 9M, when participants were no longer completing active sessions. From BL to 5M, participants may have derived benefits from processes discussed in the previous section, resulting in a stabilization of neuroendocrine

and immune function. However, as the natural course of cortisol changes in CFS/ME over time are not established and no waitlist-control group was assessed, this interpretation remains speculative.

In addition, decreases in IL-6 were observed over time from BL to 9M. As with cortisol, IL-6 levels did not decrease from BL to 5M, but by 9M they had decreased significantly. Potential benefits from participation in either 10-week program may have been lagged, with effects in immune activity only becoming detectable by the 9M assessment. Effects of cognitive behavioral interventions have previously been observed to be delayed several months or longer in CFS/ME (Deale et al. 1997; Deale et al., 2001). Among breast cancer survivors, effects of CBSM on symptoms related to IL-6 levels (i.e., sickness behavior) were most pronounced 15 months post-intervention (Birnbaum-Weitzman, 2009). Thus potentially the decrease in IL-6 levels from BL to 9M observed in Study 2 reflects a lagged effect of participation in a 10-session protocol, either CBSM or the attention control condition.

Alternatively, the observed decline in IL-6 levels over time may be a natural phenomenon in the course of CFS/ME. A recent report by Horning et al. (2015) pooled plasma cytokine data from 298 adults with CFS/ME and 348 healthy controls matched on age, sex, geographic site, and season of the year. Controlling for age, patients with a long illness duration, defined as greater than three years, had significantly lower levels of IL-6 than did those with a short duration of symptoms. The authors posited this may have been due to an exhaustion of cytokine-producing cells during the early phase of CFS/ME. This explanation is similar to hypotheses about CFS/ME-related hypocortisolism. In

contrast with their findings, in the present study, illness duration (continuous or categorical High vs. Low) was not significantly associated with changes in IL-6 levels over time.

In Exploratory Aim 3, potential correlates of the decreases in morning cortisol and IL-6 over time were examined. These included psychological and behavioral factors (alcohol intake, smoking status, baseline levels of anxiety, stress, and depression) and illness-related factors (illness duration and CFS/ME symptom severity and frequency). Overall, none of these factors related to changes in morning cortisol or IL-6 levels from BL to 5M, 5M to 9M, or BL to 9M.

In addition to these variables, session attendance was examined. It was observed that when session attendance was High (80% or higher), women were more likely to have had lower CARi and higher IL-6 levels at 9M than at BL. It may be that women with the poorest trajectory of neuroimmune function over the 9-month study were more motivated to attend sessions, perhaps to learn more about their health and strategies to help them cope with symptoms. However, caution is warranted when interpreting this finding, as time effects were not related to attendance when it was examined as a continuous variable. Qualitative data about motivation for participation may have helped to provide insight into this trend.

Strengths, Limitations, and Future Directions. An important consideration for this trial was how to appropriately address missing data. In Study 2, rates of missing data ranged from 0% (at BL) to 46% (at 5M). Missing data were most frequently characterized by the following instances: A patient had insufficient saliva for a salivette to be processed or had missed a single sampling at a timepoint; other occasions, a patient

skipped the last item on a questionnaire measure. Missingness was not related to study

condition or auxiliary variables (age, symptom duration, or fatigue severity) and

exhibited patterns of scatter, suggesting data were missing at random. A total of 21

imputations were derived and pooled for each missing cell of data using all available data

across BL, 5M, and 9M timepoints. For the missing data examples described above,

multiple imputation allowed for the use of the patient's entire timepoint of saliva or total

score for the measure.

   The adoption of this approach was therefore a methodological strength, and it is

consistent with guidelines published in *Statistical Methods for Medical Research* and *The*

New England Journal of Medicine for addressing missing data in longitudinal

randomized controlled trials (RCTs) (Bell & Fairclough, 2014; Little et al., 2012).

Missing data due to attrition and/or other factors have been observed within more than 90

percent of RCTs (Powney, Williamson, Kirkham, & Kolamunnage-Dona, 2014).

Traditional methods using complete-case analyses have been criticized for increasing the

chance of producing biased results (Powney et al., 2014) or Type 2 error rates due to

reduced sample sizes (Little et al., 2012). In trials testing psychosocial interventions with

medical patients, samples are often small and vulnerable, creating an ethical impetus to

use all data obtained from participants.

   A potential limitation was the inability to control for factors that may influence

cortisol and/or IL-6 levels, including: menopausal status, stage of menstrual cycle, use of

oral contraceptives, use of hormone replacement therapy, body mass index, and early life

trauma (Heim et al., 2006; Heim et al., 2009; O'Connor et al., 2009). These variables

were not measured and thus could not be examined as potential covariates. Future studies examining biomarkers of neuroimmune function in CFS/ME would benefit from collecting these data.

Modest sample sizes were another limitation, as they limited both the statistical power to test hypotheses as well as the use of advanced statistical methods that model change over time. In Study 2, 64 participants were needed in each study condition in order to detect a modest effect of 0.25 with 80% power and $\alpha = .05$, two-tailed (Faul et al., 2009). The data in this study included only female participants, which may have contributed to the smaller sample sizes observed for CBSM ($n = 53$) and attention control ($n = 40$) groups. While this restriction was important due to neuroimmune differences between sexes (Nater et al., 2008; Goetzl et al., 2010; Fletcher et al., 2009), it nonetheless may have hurt statistical power to detect group effects.

Furthermore, structural equation modeling techniques such latent growth curve modeling could have allowed for a nuanced investigation of Study 2 hypotheses, including tests of group-related differences in trajectories of fatigue interference, cortisol, and IL-6 levels across the study timepoints. This type of modeling can also be used to examine time-lagged associations among variables. Given what is known about the role of cortisol in immune regulation, tests of lagged effects of the CAR on IL-6 would be particularly relevant. For instance, as the CARg has been linked previously to post-exertional malaise in CFS/ME (Hall et al., 2014), it would be worth investigating whether CARg levels at BL or 5M predict changes in IL-6 and/or symptoms from 5M to 9M. Future studies examining psychosocial intervention effects on fatigue interference and

neuroimmune functioning in patients with CFS/ME may thus benefit from recruiting larger samples and modeling nuanced patterns of change among variables over time.

A strength of the present study was its use of telephone delivery. Given the nature of CFS/ME, physical mobility can be a barrier to receiving regular psychosocial support, and the most impaired patients tend to be homebound (Wiborg, van der Werf, et al., 2010). Telephone-delivered services, including CBT, therefore have the potential to reach CFS/ME patients experiencing the greatest need. Telehealthcare has been lauded for having less attrition than face-to-face CBT, indicating that it is acceptable to patients (Mohr et al., 2012). Given the high attendance rates observed in Study 2, it was surprising that intervention effects were not observed. Potentially, other delivery media such as videophone or computer tablets would have enhanced participants' engagement in CBSM, while allowing participants and counselors to see each others' faces in real-time. In this way, videophone technology could have the benefits of both telephone-delivery (circumventing distance) and face-to-face delivery (enhancing engagement). Future studies could investigate the comparative effects of live CBSM (Lopez et al., 2011), telephone-delivered CBSM, and videophone-delivered CBSM. Relatedly, it will be important for future research to study the acceptability of telehealthcare among medical specialists treating patients with CFS/ME. Previously, CBT for CFS/ME has been shown to be feasible and effective among clinicians in primary care settings (Akagi, Klimes, and Bass, 2001). However, it is unknown whether CFS/ME care providers in hospitals and private clinics can feasibly use telehealthcare and videohealthcare technologies to deliver CBT-based psychosocial interventions to patients.

Finally, the etiology of CFS/ME and diagnostic biomarkers of the illness remain unclear. This investigation analyzed only a subset of biological factors that have been implicated in this population. Future studies of the effects of CBSM on fatigue interference and biomarkers of neuroimmune function could assess additional biomarkers previously found to differentiate patients with CFS/ME from healthy controls. These include: cytokines that influence B cell maturation such as CD40L; pro-inflammatory cytokines such as INFγ, IL-1α, and TNFα; anti-inflammatory cytokines such as IL-1RA and IL-4; transcription-related protein NF-κB; mitochondrial dysfunction; and Toll-like receptor expression on intestinal cells (Gambuzza et al., 2015; Hornig et al., 2015; Klimas et al., 2015; Morris & Mayes, 2013; Twisk, 2014).

Conclusions. This study examined fatigue interference among adult women with CFS/ME and its relationships with neuroendocrine (i.e., salivary cortisol awakening response) and immune (i.e., plasma interleukin-6 levels) function. Furthermore, the effects of a 10-session, telephone-delivered cognitive behavioral stress management (CBSM) intervention on these variables over time were assessed. Results of this study indicate that women with CFS/ME experience more fatigue interference as compared with fatigued breast cancer survivors, a population that similarly has medically undertreated chronic fatigue symptoms. Moreover, among women with CFS/ME, higher levels of fatigue interference were associated with a decreased cortisol awakening response with respect to increase (CARi).

Several neuroimmune variables, including the CARi, CARg, post-awakening cortisol, and IL-6, were observed to decrease in magnitude over time. Changes from 5-months to 9-months appear to account for these patterns, which may reflect benefits

received during the 10-week program delivered between baseline and 5-months. Intervention effects were not observed, perhaps due to the engaging attention control condition used to assess the relative efficacy of CBSM on the variables examined. Alternatively, the telephone-delivery of the intervention may have been less engaging that other forms of delivery, such as face-to-face or videophone. Future studies are warranted to compare these modalities directly, and may benefit from assessing additional biomarkers of neuroendocrine and immune dysfunction in this population.

Table 1.

Demographic characteristics of study 1 participants

Participant Characteristics	CFS/ME (*n*=95)	Breast Cancer (*n*=67)	*p*
Age in years, M (SD)	51.31 (11.03)	55.39 (8.48)	<.01
Completed college, *n* (%)	42 (44%)	54 (81%)	<.01
White non-Hispanic, *n* (%)	73 (77%)	48 (72%)	.45
Married/Partnered, *n* (%)	41 (43%)	41 (61%)	.02
Employed full-time, *n* (%)	17 (18%)	46 (69%)	<.001
Number of children, M (SD)	1.07 (1.24)	1.48 (1.13)	.04
Years since diagnosis, M (SD)	7.23 (6.59)	5.22 (0.12)	.01

Note: M=Mean. SD=Standard Deviation. Group differences on continuous variables determined by independent-samples t-test. Group differences on dichotomous variables determined by Pearson Chi-Square test.

Table 2.

Descriptive statistics of study 1 main variables

Variable	Mean/N (SD/%)	Range
Breast Cancer Survivor Sample (*n*=67)		
FSI Interference	2.62 (2.11)	0.00 – 9.46
FSI Severity	4.65 (1.53)	3.13 – 10.00
CES-D Mood	3.42 (3.55)	0.00 – 21.00
CES-D Total	12.59 (9.27)	0.00 – 50.00
CES-D Frequency above 16	17 (25%)	
CFS/ME Female Sample (*n*=95)		
FSI Interference	7.03* (1.86)	1.45 – 10.00
FSI Severity	6.83* (1.33)	3.75 – 9.50
CES-D Mood	7.62* (6.27)	0.00 – 21.00
CES-D Total	25.69* (12.55)	2.00 – 57.00
CES-D Frequency above 16	69* (72.6%)	
Cortisol		
Day 1 Awakening (µg/dl)	0.33 (0.25)	0.01 – 0.96
Day 2 Awakening (µg/dl)	0.31 (0.25)	0.01 – 0.90
Day 1 Post Awakening (µg/dl)	0.55 (0.34)	0.05 – 1.24
Day 2 Post Awakening (µg/dl)	0.52 (0.36)	0.01 – 1.55
Avg CARi (µg/dl)	3.33 (2.65)	0.02 – 12.20
Avg CARg (µg/dl)	12.36 (6.00)	0.14 – 32.11
Day 1 4:00pm (µg/dl)	0.33 (0.25)	0.01 – 0.96
Day 2 4:00pm (µg/dl)	0.33 (0.25)	0.01 – 0.96
Day 1 9:00pm (µg/dl)	0.33 (0.25)	0.01 – 0.96
Day 2 9:00pm (µg/dl)	0.33 (0.25)	0.01 – 0.96
Avg 9:00pm-Awakening (µg/dl)		
Interleukin-6 (pg/ml)	6.42 (4.02)	0.80 – 14.84

Note: M = Mean. SD = Standard Deviation. FSI = Fatigue Symptom Inventory. CES-D = Center for Epidemiological Studies – Depression measure. * $p<.001$. Group differences on continuous variables determined by independent-samples t-test. Group differences on dichotomous variables determined by Pearson Chi-Square test. CARi = cortisol awakening response with respect to increase. CARg = cortisol awakening response with respect to ground.

Table 3.

Study 1, Aim 2: Models predicting neuroimmune parameters from fatigue interference

Variable	B	SE	Beta	t	*p*
Model 1: Predicting CARi					
Step 1					
Number of Children	.83	.35	.24	2.35	.02
Step 2					
Fatigue Severity	.19	.33	.06	.58	.56
Step 3					
Fatigue Interference	-.65	.28	-.28	-2.31	.02
Model 2: Predicting CARg					
Step 1					
Race/Ethnicity (White)	.25	.17	.16	1.50	.13
Number of Children	-.09	.06	-.17	-1.63	.10
Step 2					
Fatigue Severity	-.06	.05	-.13	-1.19	.23
Step 3					
Fatigue Interference	.02	.05	.05	.43	.67
Model 3: Predicting IL-6					
Step 1					
College (yes)	-.27	.14	-.18	-1.88	.06
Alcoholic Drinks/Wk	-.06	.03	-.21	-1.98	.05
Smoker (yes)	.55	.22	.25	2.53	.01
Step 2					
Fatigue Severity	-.01	.05	-.02	-.24	.81
Step 3					
Fatigue Interference	.02	.05	.04	.33	.75

Table 4.

Study 1, Aim 3: Models examining depressed mood as moderator of fatigue interference relationships with neuroimmune parameters

Variable	B	SE	Beta	t	p
Model 1: Predicting CARi					
Step 1					
Number of Children	.83	.35	.24	2.35	.02
Step 2					
Fatigue Severity	.19	.33	.06	.58	.56
Step 3					
Centered Fatigue Interference	-.68	.30	-.29	-2.28	.02
Centered Depressed Mood	.03	.08	.04	.34	.74
Step 4					
Interaction Term	<.01	.04	.01	.07	.94
Model 2: Predicting CARg					
Step 1					
Race/Ethnicity (White)	.25	.17	.16	1.50	.13
Number of Children	-.09	.06	-.17	-1.63	.10
Step 2					
Fatigue Severity	-.06	.05	-.13	-1.19	.23
Step 3					
Centered Fatigue Interference	.01	.05	.03	.25	.80
Centered Depressed Mood	.01	.01	.06	.58	.56
Step 4					
Interaction Term	<-.01	.01	-.02	-.19	.85
Model 3: Predicting IL-6					
Step 1					
College (yes)	-.27	.14	-.18	-1.88	.06
Alcoholic Drinks/Wk	-.06	.03	-.21	-1.98	.05
Smoker (yes)	.55	.22	.25	2.53	.01
Step 2					
Fatigue Severity	-.01	.05	-.02	-.24	.81
Step 3					
Centered Fatigue Interference	<.01	.05	.01	.05	.96
Centered Depressed Mood	.01	.01	.11	1.00	.32
Step 4					
Interaction Term	.01	.01	.17	1.57	.12

Table 5.

Demographic characteristics of study 2 participants at baseline

Participant Characteristics	CBSM (*n*=53)	Control (*n*=40)	Test Statistic
Age in years, M (SD)	51.43 (10.28)	50.45 (11.87)	$t(91)=-0.43$, *p*=.67
Completed college, *n* (%)	30 (57%)	24 (60%)	$\chi^2(1)=0.11$, *p*=.74
White non-Hispanic, *n* (%)	40 (75%)	31 (78%)	$\chi^2(1)=0.05$, *p*=.82
Married/Partnered, *n* (%)	24 (45%)	15 (38%)	$\chi^2(1)=0.57$, *p*=.45
Employed full-time, *n* (%)	9 (17%)	8 (20%)	$\chi^2(1)=0.14$, *p*=.71
Number of children, M (SD)	0.88 (1.17)	1.23 (1.35)	$t(91)=-1.35$, *p*=.18
Duration of CFS/ME symptoms, M (SD)	6.08 (6.54)	7.87 (6.35)	$t(91)=-1.33$, *p*=.19
Alcoholic drinks/week, M (SD)	1.73 (2.70)	1.52 (1.90)	$t(91)=-0.37$, *p*=.71
Smoker, *n* (%)	8 (15%)	3 (8%)	$\chi^2(1)=1.26$, *p*=.26

Note: M=Mean. SD=Standard Deviation. Group differences on continuous variables determined by independent-samples t-test. Group differences on dichotomous variables determined by Pearson Chi-Square test.

Table 6.

Study 2 fatigue-related and neuroimmune variables at baseline (BL), 5-months (5M), and 9-months (9M) as well as time and group-by-time effects among participants assigned to Cognitive Behavioral Stress Management (CBSM) and control conditions

	CBSM Condition (n=53)			Attention Control Condition (n=40)			Time (BL, 5M, 9M)		Group-by-Time
	BL	5M	9M	BL	5M	9M	Omnibus Effect	Post-Hoc Comparisons	Omnibus Effect
Fatigue & Mood									
Fatigue Interference	7.12(1.82) 1.71-10.00	6.90(2.00) 1.14-10.00	7.11(1.89) 1.17-10.00	6.90(1.96) 1.45-10.00	6.13(1.92) 0.00-10.00	6.45(1.79) 1.17-9.86	ns	Not tested	ns
Fatigue Severity	6.95(1.28) 3.75-9.50	6.94(1.33) 4.00-9.25	7.04(1.50) 2.50-9.75	6.70(1.43) 4.00-9.50	6.24(1.41) 1.86-8.50	6.38(1.71) 1.50-9.00	ns	Not tested	ns
Depressed Mood	7.42(6.36) 0.00-21.00	6.75(5.37) 0.00-20.00	6.24(5.18) 0.00-20.00	8.13(6.25) 0.00-21.00	6.63(4.81) 0.00-19.00	6.12(5.02) 0.00-21.00	*	↓ BL–9M**	ns
Cortisol									
CARi	3.80(2.76) 0.02-11.38	3.59(1.83) 0.00-9.08	2.34(1.50) 0.03-7.30	2.77(2.36) 0.21-10.51	3.13(1.84) 0.23-7.12	2.66(1.89) 0.04-7.58	*	↓ BL–9M*	ns
CARg	12.75(5.66) 0.14-30.44	12.58(4.80) 1.20-27.37	9.03(3.88) 1.50-20.03	11.81(6.32) 0.87-30.44	12.38(5.11) 1.56-27.37	9.23(2.81) 3.88-18.07	***	↓ 5M–9M*** ↓ BL–9M***	ns
Awakening	0.32(0.19) 0.02-0.86	0.30(0.18) 0.01-0.81	0.27(0.21) 0.01-0.89	0.31(0.19) 0.01-0.79	0.32(0.20) 0.01-0.85	0.26(0.19) 0.01-0.74	ns	Not tested	ns
Post-Awakening	0.56(0.24) 0.09-1.14	0.52(0.27) 0.01-1.20	0.39(0.24) 0.01-1.01	0.51(0.26) 0.04-1.14	0.49(0.26) 0.03-1.20	0.43(0.25) 0.01-1.01	***	↓ 5M–9M** ↓ BL–9M***	ns
Afternoon	0.12(0.05) 0.01-0.22	0.09(0.05) 0.01-0.22	0.10(0.06) 0.01-0.22	0.11(0.05) 0.01-0.22	0.10(0.06) 0.01-0.22	0.09(0.05) 0.01-0.22	ns	Not tested	ns
Evening	0.06(0.04) 0.01-0.14	0.06(0.04) 0.01-0.14	0.06(0.05) 0.01-0.14	0.07(0.04) 0.02-0.14	0.06(0.03) 0.01-0.14	0.06(0.04) 0.01-0.14	ns	Not tested	ns
Diurnal Change	-0.25(0.17) -0.74-0.06	-0.24(0.18) -0.76-0.06	-0.21(0.20) -0.78-0.09	-0.24(0.19) -0.71-0.06	-0.26(0.20) -0.76-0.07	-0.20(0.19) -0.70-0.09	ns	Not tested	ns
Inflammatory									
IL-6	6.99(4.22) 0.80-14.84	6.28(3.93) 1.30-14.40	4.73(3.35) 1.13-14.40	5.65(3.75) 1.23-14.40	4.94(3.05) 1.67-16.20	4.34(2.57) 0.60-14.40	**	↓ BL–9M**	ns

Note: * p≤.05, ** p≤.01, *** p≤.001, *ns*=not statistically significant (α=.05); Analyses of Fatigue Interference controlled for Fatigue Severity; CARi = cortisol awakening response with respect to increase (µg/dl); CARg = cortisol awakening response with respect to ground (µg/dl); IL-6 = interleukin-6 (pg/ml). Post-hoc comparisons only conducted if omnibus effect was statistically significant.

Table 7.

<u>Session attendance for CBSM and Control conditions</u>

<u>Participation</u>	<u>10 sessions</u>	<u>8-10 sessions</u>	<u>0 sessions</u>
CBSM (*n*=53)	12 (23%)	41 (77%)	2 (4%)
Control (*n*=40)	30 (75%)	30 (75%)	7 (18%)
Total (*n*=93)	42 (45%)	71 (76%)	9 (10%)

Figure 1

Study 2 flow diagram of participants throughout study duration.


```
                    ┌──────────────────┐
                    │   95 female      │
                    │   patients with  │      ┌─────────────────────┐
                    │   CFS/ME enrolled│      │ Withdrew prior to   │
                    └──────────────────┘      │ randomization       │
                     /              \         │ (n = 2)             │
                    /                \        └─────────────────────┘
                   ↙                  ↘
   ┌──────────────────┐          ┌──────────────────┐
   │ CBSM Baseline    │          │ Control Baseline │
   │ (n = 53)         │          │ (n = 40)         │
   └──────────────────┘          └──────────────────┘
            │                              │
            ↓                              ↓
   ┌──────────────────┐          ┌──────────────────┐
   │ CBSM 5M          │          │ Control 5M       │
   │ (n = 42)         │          │ (n = 31)         │
   └──────────────────┘          └──────────────────┘
            │                              │
            ↓                              ↓
   ┌──────────────────┐          ┌──────────────────┐
   │ CBSM 9M          │          │ Control 9M       │
   │ (n = 47)         │          │ (n = 32)         │
   └──────────────────┘          └──────────────────┘
```
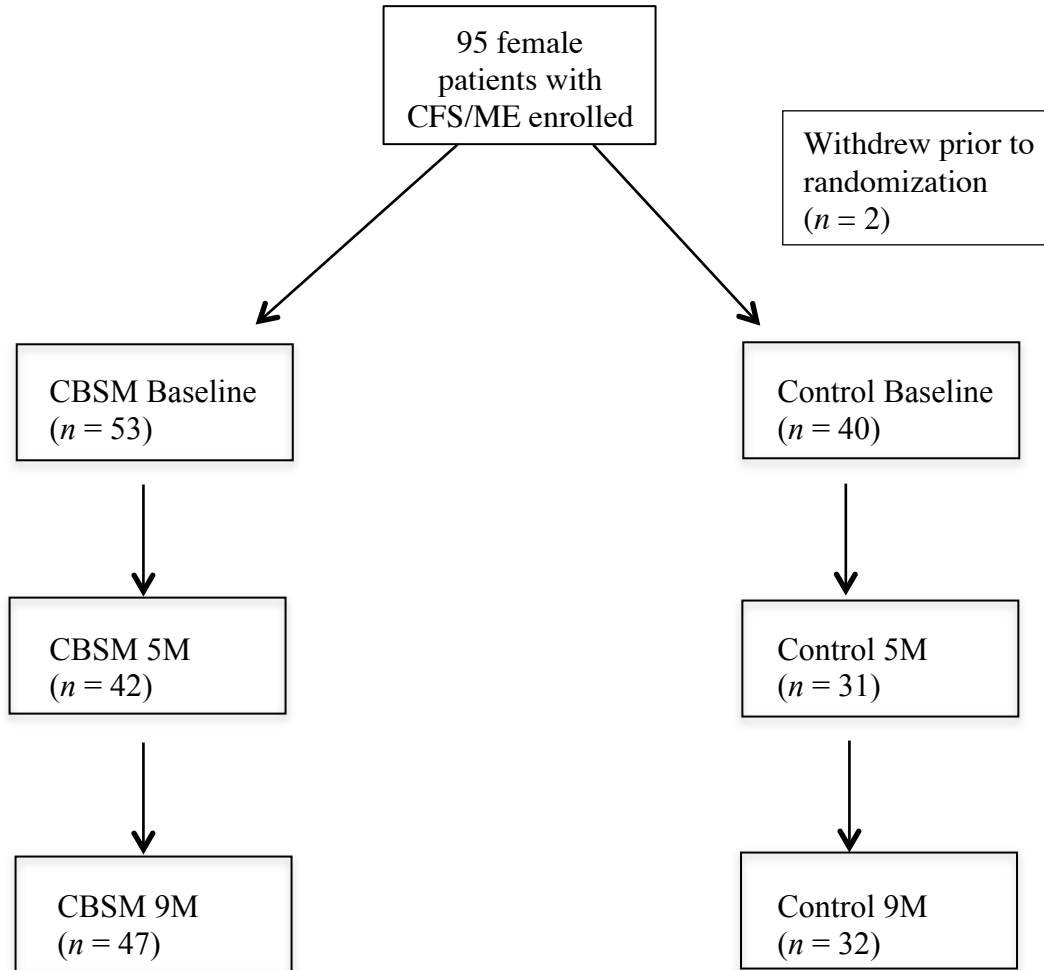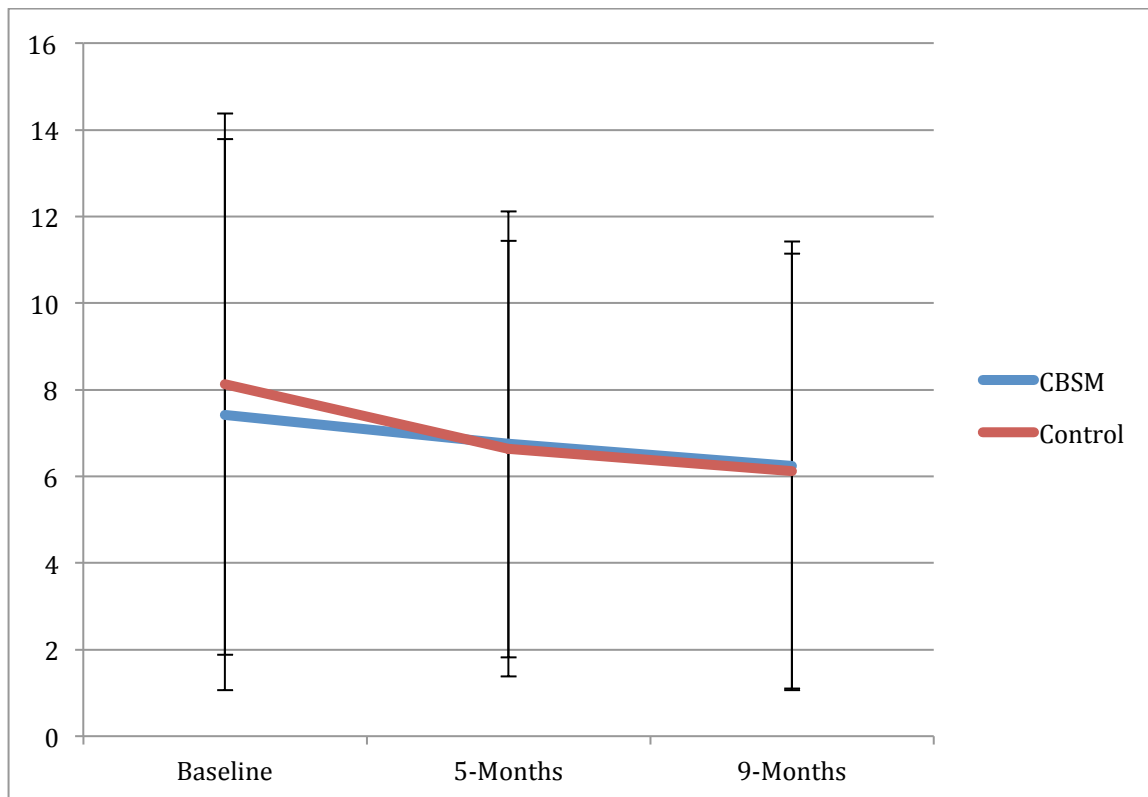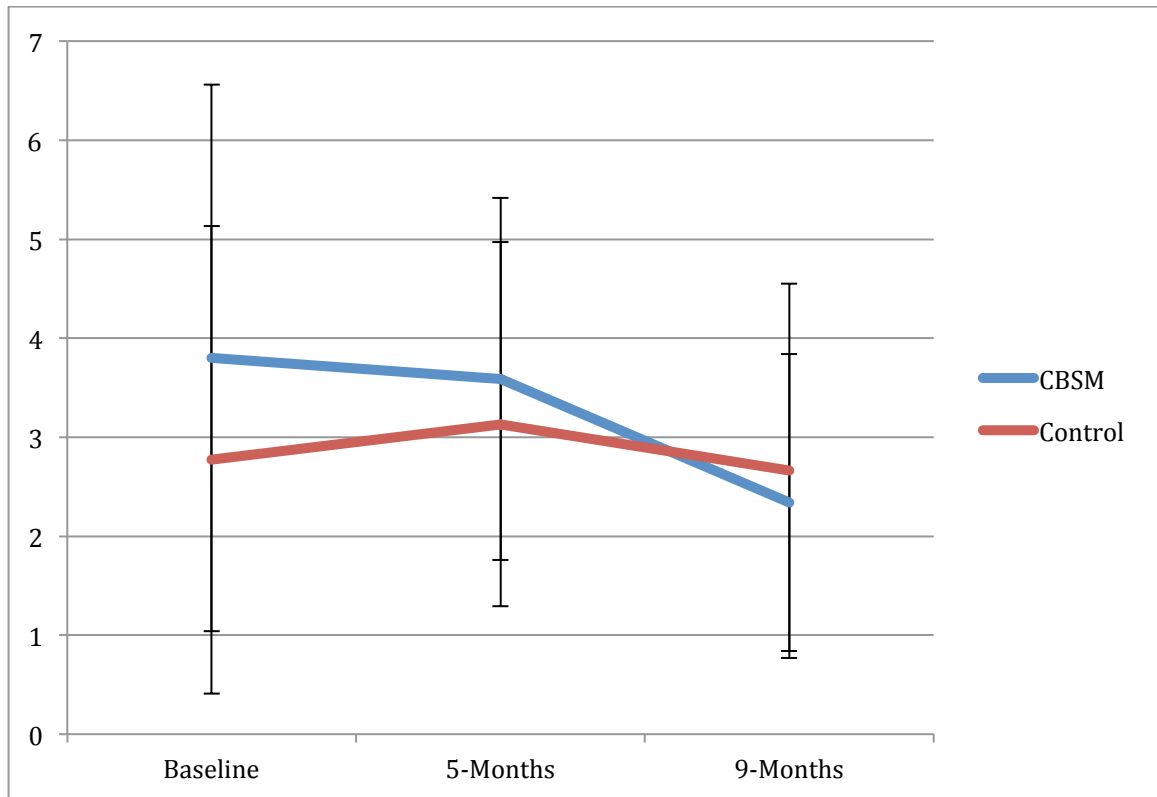
Figure 2

Study 2 means and standard deviations of depressed mood across three timepoints by study condition

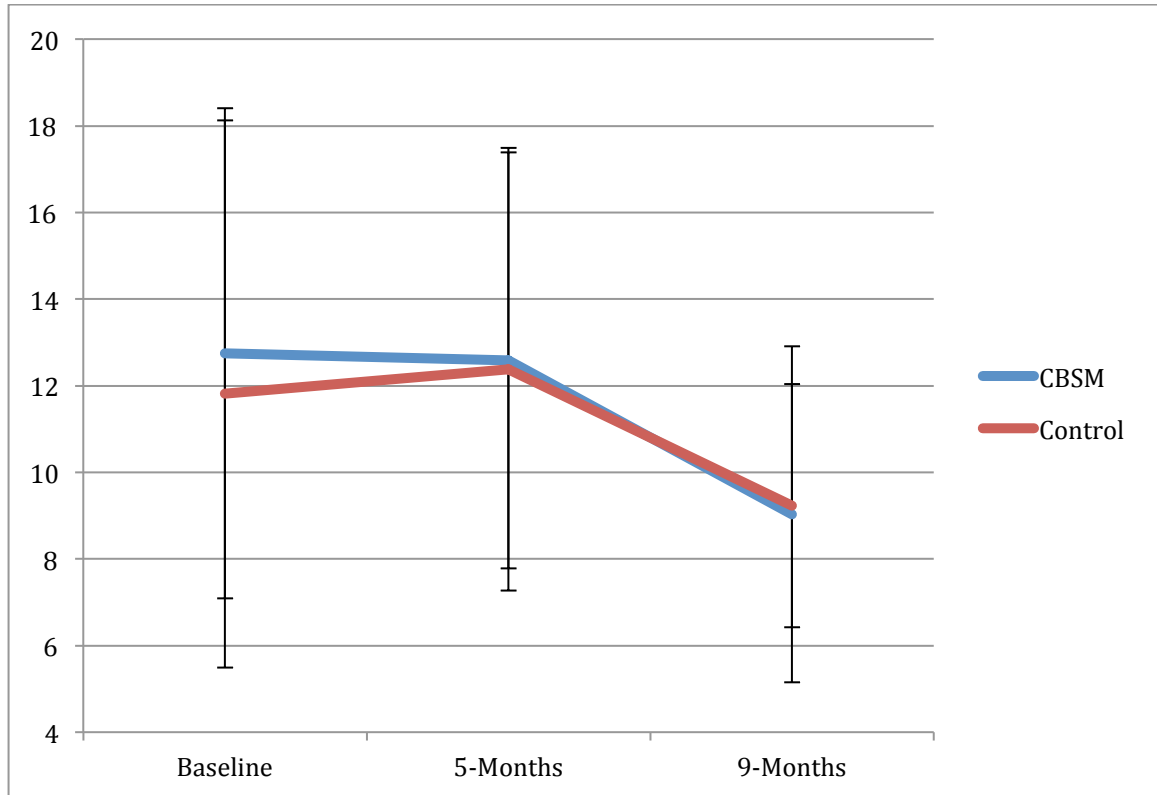Note: Significant time effects evidenced from baseline to 9-months ($p<.05$).

Figure 3

Study 2 means and standard deviations of CARi across three timepoints by study condition

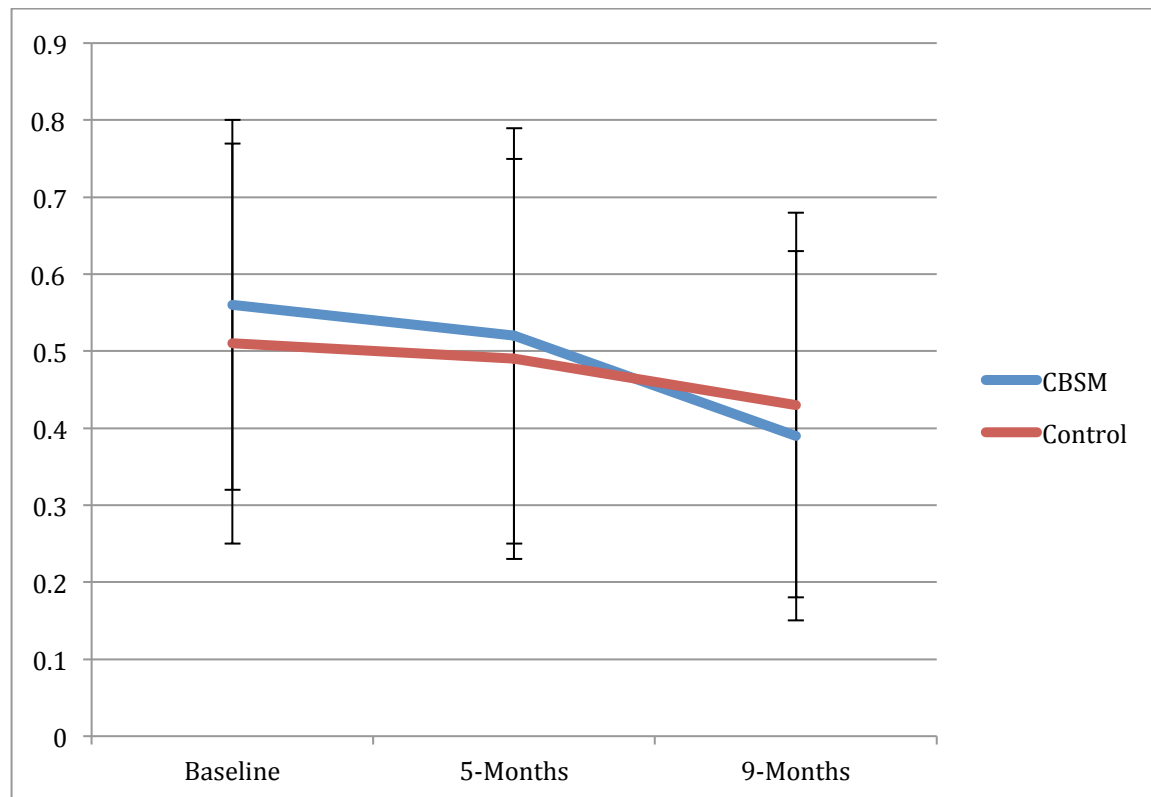Note: Y-axis units are µg/dl. Significant time effects evidenced from baseline to 9-months (p<.05).

Figure 4

Study 2 means and standard deviations of CARg across three timepoints by study
condition

Note: Y-axis units are µg/dl. Significant time effects evidenced from 5-months to 9-
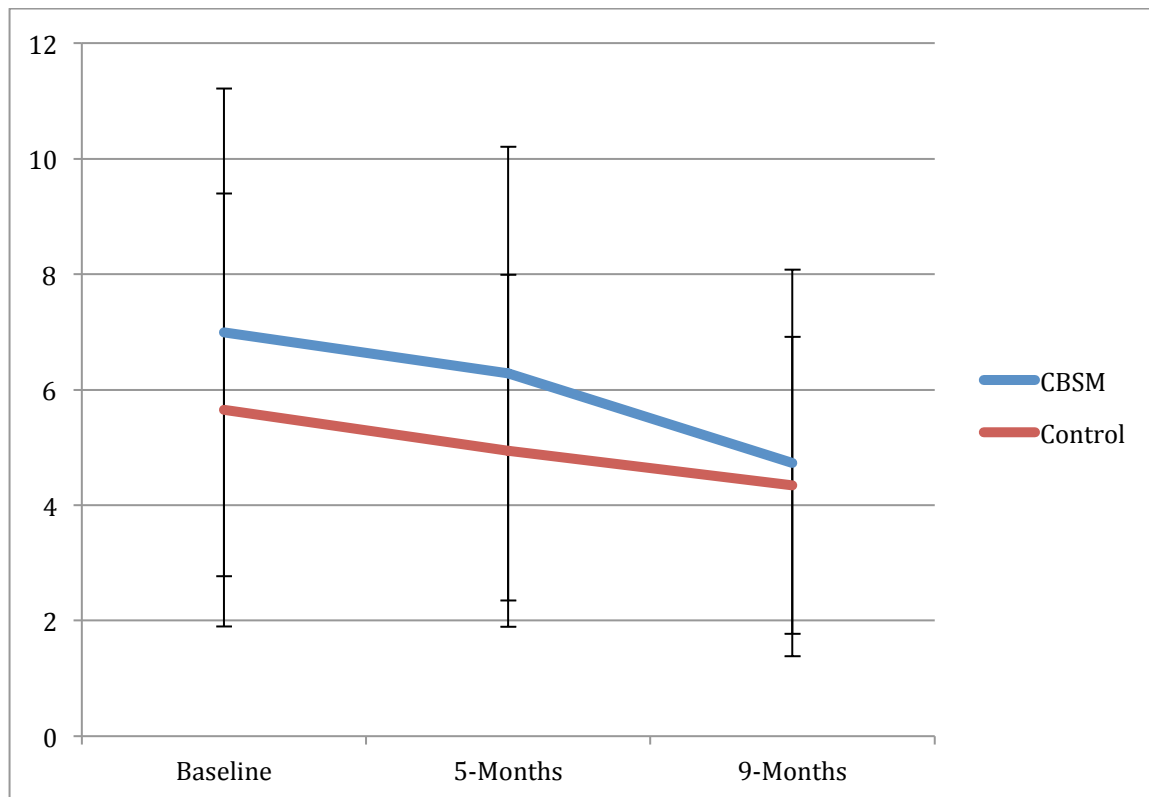months ($p<.001$) and baseline to 9-months ($p<.001$).

Figure 5

Study 2 means and standard deviations of post-awakening cortisol across three timepoints by study condition

Note: Y-axis units are µg/dl. Significant time effects evidenced from 5-months to 9-months ($p<.01$) and baseline to 9-months ($p<.05$).

Figure 6

Study 2 means and standard deviations of Interleukin-6 (IL-6) across three timepoints by study condition

Note: Y-axis units are pg/ml. Significant time effects evidenced from baseline to 9-months ($p<.01$).

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