UNIVERSITY OF CALIFORNIA, SAN DIEGO

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Effects of Biofield vs. Mock Healing for Fatigue, Cytokines, and Cortisol Variability in Breast Cancer Survivors: A Randomized, Controlled Trial

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

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The dissertation of Shamini Jain is approved, and it is acceptable in quality and form for publication on microfilm:

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Chair

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DEDICATION

To my parents, who have inspired and fostered my pursuits of scientific and spiritual truths, and who lead by their examples of unconditional love and selfless service to others.

To Vikas, my *jeevansathi,,* who teaches me daily about love, selflessness, and creativity.

To Suhani and Akaash, my heart, who bring joy to my life and meaning to all its pursuits.

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LIST OF ABBREVIATIONS

Area Under the Curve (AUC)

Analysis of Covariance (ANCOVA)

Cancer Related Fatigue (CRF)

Center for Epidemiological Studies for Depression Scale (CESD)

Complementary and Alternative Medicine (CAM)

General Clinical Research Center (GCRC)

Hierarchical Linear Modeling (HLM)

Interleukin-1 Receptor Antagonist (IL-1Ra)

Interleukin- 4 (IL-4)

Interleukin- 6 (IL-6)

Interleukin- 6 soluble receptor (sIL-6r)

Micro-liters (uL)

Milli-liters (mL)

Multidimensional Fatigue Symptom Inventory short form (MFSI-sf)

Pittsburgh Sleep Quality Inventory (PSQI)

Profile of Mood States –short form (POMS-sf)

Psycho-Neuro-Immunology (PNI)

Tumor Necrosis Factor-alpha (TNF-alpha)

University of California, San Diego (UCSD)

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ABSTRACT OF THE DISSERTATION

Effects of Biofield vs. Mock Healing for Fatigue, Cytokines, and Cortisol Variability in Breast Cancer Survivors: A Randomized, Controlled Trial

by

Shamini Jain
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University of California, San Diego, 2009
San Diego State University, 2009

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This randomized, placebo-controlled trial investigated the use of biofield healing (termed energy healing), compared to mock healing, for the alleviation of fatigue and inflammation after adjuvant or neoadjuvant therapy for breast cancer. Thirty-three women breast cancer survivors were studied at the UCSD General Clinical Research Center prior to and following 4 weeks of healing or mock healing, as well as immediately before and after healing or mock healing sessions. Participants received 8 one-hour sessions (twice per week) of either biofield or mock healing. Outcome measures included fatigue (via the MFSI-sf), depression (via the CESD), mood disturbance (via the POMS-sf), quality of life (via the FACT-B), and self-reported sleep quality (via the PSQI). In

addition, the study examined potential changes in pro- and anti-inflammatory cytokines and receptors (IL-6, sIL-6R, sIL-1Ra, IL-4, and TNF-RII), as well as circadian rhythms of the hormone cortisol. Participants also rated their guess of treatment (energy healing or touch alone). Intent-to-treat analyses were performed for all psychological outcome variables. Results indicated that both groups significantly decreased in overall fatigue over time. There was a trend toward significant differences between the healing group and mock group on overall MFSI-sf fatigue scores, with the healing group showing a notably steeper decline over time compared to the mock group. There was a significant group x time interaction for CESD scores, such that the healing group decreased in depression over time compared to the mock group. Both groups decreased significantly in overall POMS-sf Total Mood Disturbance over time. Expectation itself predicted changes in FACT-B scores. Repeated-measures ANCOVA analyses for cytokine data revealed a significant group x time interaction for IL-4, such that the healing group decreased in this marker over time compared to the mock group. There was also a significant group x time interaction for sIL-1Ra, such that the mock group increased in this marker over time compared to the healing group. This pattern was also reflected in a trend for a group x time interaction for IL-6. Both groups showed significant time effects for sIL-6r.

There were significant group x time interactions for cortisol slopes and mean cortisol, with women in the healing group had more negative slopes and decreased cortisol. Results suggest a differential outcome profile for breast cancer survivors who received healing sessions vs. those who received mock healing. Further research is warranted to better ascertain the specific vs. nonspecific effects of biofield healing for fatigue and immune function in breast cancer survivors.

Chapter 1

Introduction

Breast Cancer: Prevalence, Survivorship, and Side effects

Breast cancer is currently the most prevalent cancer among women. Each year, breast cancer affects roughly one million women worldwide, with costs to society estimated at $7 billion per year (Forbes, 1997). An estimated 178,480 new cases of breast cancer were expected to be diagnosed in the U.S. in 2007, with an estimated 40,460 patients in the U.S. dying from the disease (Society, 2007). Thankfully, due to improvements in primary and adjuvant treatment, there has been a slight decline (2.3%) in overall mortality from breast cancer. Indeed, there are an estimated 2.5 million women breast cancer survivors (women surviving with a breast cancer diagnosis) in North America (Society, 2007). Unfortunately, these survivors often experience lingering side effects well after treatment, most notably fatigue, depression, and decreased quality of life (Andrykowski, Curran, & Lightner, 1998; Bower et al., 2000).

Being diagnosed with and treated for breast cancer is perhaps one of the most challenging events that a woman can face in her life. The experience of being diagnosed with cancer often leads to distress surrounding treatment and possible progression of cancer, as well as fear of death, feelings of loss of control, and marked changes in quality of life (Aaronson et al., 1991; Redd et al., 1991; Spiegel, 1997). Fatigue and depressed mood are often experienced during and after treatment in breast cancer (Cordova et al., 1995; Greer et al., 1992), and are also associated with negative quality of life (Longman, Braden, & Mishel, 1999). In addition, these negative psychological states may impact disease progression in a deleterious manner (Musselman et al., 2001). Even after

treatment, breast cancer survivors experience considerable anxiety about the potential recurrence of the disease, with no specific recommendations given on how to cope with this anxiety (Johnson Vickberg, 2001).

Fatigue in breast cancer patients

In addition to the negative psychological effects that are often experienced by breast cancer patients in processing the reality of their disease, side effects from conventional treatment (e.g., biotherapy, chemotherapy, and radiation) pose additional hardships that cancer patients must face. Fatigue is perhaps the greatest reported and most troublesome side effect associated with cancer and cancer treatment. Recent reports estimate that 50-75% of cancer patients report feeling tired and weak, with these rates increasing up to 95% during chemotherapy/radiation therapy (Smets et al., 1998; Stasi, Abriani, Beccaglia, Terzoli, & Amadori, 2003; Winningham et al., 1994). Fatigue also continues to be a pervasive problem for breast cancer survivors even after treatment (Dow, Ferrell, Leigh, Ly, & Gulasekaram, 1996; Payne, 2002), with large-scale studies showing moderate to severe fatigue for approximately one-third of patients 10 years or more post-treatment (Bower et al., 2006; Bower et al., 2000; Lindley, Vasa, Sawyer, & Winer, 1998). Fatigue is also associated with decreased quality of life in these patients (de Jong, Courtens, Abu-Saad, & Schouten, 2002; Longman et al., 1999; Payne, 2002).

Cancer-related fatigue, as recently defined by the National Comprehensive Cancer Network, is "an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning"(Mock et al., 2000). Cancer-related fatigue has been reported by patients to differ from general fatigue in that it has a more rapid onset and is more energy-draining and severe than general fatigue, affecting

physical, social, cognitive, psychological, and spiritual aspects of functioning (Holley, 2000). Indeed, the experience of fatigue in breast cancer patients is multidimensional, spanning affective-sensory (e.g., feelings of depression and pain), physiological (e.g., increased anemia), and chronobiological (e.g., disturbances in sleep and other circadian rhythm processes) factors (de Jong et al., 2002; Hwang, Chang, Rue, & Kasimis, 2003; Roscoe et al., 2002). Interestingly, while fatigue has been noted to increase in response to several cancer treatments (including chemotherapy, radiation, and biotherapeutic agents), it is still unclear whether fatigue in breast cancer survivors is specifically associated with a particular type of treatment (Andrykowski et al., 1998; Berglund, Bolund, Fornander, Rutqvist, & Sjoden, 1991). Fatigue is also not correlated with stage of cancer (Jacobsen et al., 1999; Mast, 1998; Okuyama et al., 2000), though it has been found to be related to duration of illness and concurrent illness (Blesch et al., 1991; Bower et al., 2000). While fatigue is associated with psychological distress, it is not redundant with depression or total mood disturbance (Bower et al., 2000; Visser & Smets, 1998). Indeed, pharmacological treatments (i.e., SSRIs) for depression in cancer patients undergoing chemotherapy have had no effect on cancer-related fatigue (Capuron et al., 2002; Morrow et al., 2003; Roscoe, Morrow et al., 2005).

Fatigue Etiology: Theories and Evidence

The exact etiology of cancer-related fatigue is unknown, but is likely due to a number of factors surrounding breast cancer disease progression and treatment. It has been suggested that a common thread in understanding of cancer-related fatigue in various treatments relates to energy imbalance, which may be caused by a variety of biological processes (e.g., anemia, cachexia, infection, and metabolic dysfunction)

(Gutstein, 2001). With respect to biological underpinnings of cancer-related fatigue, there are two broad categories of fatigue that have been defined, with different suggested biological etiologies. One aspect of cancer-related fatigue has been classified as peripherally-related fatigue (e.g., fatigue associated with an inability for the musculature to transmit central nervous system signals; this type of fatigue is experienced more on a somatic level), and the other as centrally-related fatigue (e.g., fatigue that results in an inability to engage in or maintain voluntary activities; this would include cognitive, motor, emotional, and social aspects of fatigue) (Ryan et al., 2007).

Regarding peripheral fatigue, a widespread speculation is that physical fatigue during chemotherapy results from anemia or an accumulation of cell-destructive end-products during the treatment (Capuron et al., 2002). With respect to the anemia hypothesis, however, findings relating hemoglobin levels with fatigue have been mixed: while a few studies report associations with fatigue and hemoglobin levels in anemic cancer patients during various timepoints in chemotherapy (Cella, Kallich, McDermott, & Xu, 2004; Jacobsen et al., 2004), several have reported no significant association of fatigue with hemoglobin levels or oxyhemoglobin dissociation (Ahlberg, Ekman, & Gaston-Johansson, 2004; Brown, McMillan, & Milroy, 2005; Nieboer et al., 2005; P. C. Stone, Abdul-Wahab, Gibson, Wright, & Andrews, 2005; Wisloff, Gulbrandsen, Hjorth, Lenhoff, & Fayers, 2005). In addition, a recent task force report suggests that while erythropoietin treatment is effective for anemia, it does not show sufficient evidence for the reduction of cancer-related fatigue (Djulbegovic, 2005). It is possible that mixed findings in this field may be due to the use of different instruments to measure fatigue (e.g., somatic vs. cognitive, emotional, or other aspects). Previous theories on the

etiology of radiation-induced fatigue include fatigue induced by increased energy requirements for repairing damaged epithelial tissue during treatment (Haylock & Hart, 1979); this posited mechanism draws upon the evidence for lessened ATP synthesis and metabolic by-products sometimes found in peripheral fatigue.

There are several biological theories posited to help explain central nervous system fatigue. One theory suggests that fatigue may in part be caused by aberrant hypothalamic-pituitary-adrenal (HPA) axis activity, as indexed in altered diurnal variability of cortisol secretion as well as blunted cortisol responses to stressors for fatigued vs. non-fatigued survivors (Bower, 2007). Another theory suggests that cancer-related fatigue may be caused by circadian rhythm disruption in several biological systems, including sleep, endocrine secretion, and immune system function. This theory rests on evidence for altered circadian rhythms for cancer patients in rest-activity patterns, circulating neutrophil and leukocytes, cortisol, prolactin, and melatonin levels, and body temperature levels. Importantly, those with more advanced cancer tend to have greater aberrancies of circadian rhythm in these biological systems (Ryan et al., 2007). In addition, there is an increasing amount of evidence suggesting that altered immune processes, particularly those involved in the inflammatory immune response, are related to and potentially partially causal of cancer-related fatigue. In order to better understand the nature of the relationship between inflammation and cancer-related fatigue, it is worth examining how the prime mediators of inflammatory immune responses (i.e., inflammatory cytokines) play a role in cancer disease progression and treatment.

Inflammatory immune processes and cancer progression

Inflammatory immune processes comprise complex and dynamic interactions between several key constituents of immune as well as vascular systems, with a chief general aim being to protect an organism from acute infection and/or injury. The inflammatory response accomplishes this function largely through interactions between cytokines (immune transmitters that help orchestrate a wide variety of immune actions), chemokines (cytokine-like molecules which aid cell trafficking by creating chemical gradients that guide innate immune (and/or tumor) cells to move in a particular direction) cellular adhesion molecules (molecules expressed on the surface of endothelial cells and platelets that promote adherence and migration of immune (and/or tumor) cells to tissues), and pro-coagulant factors which are expressed on the surface of endothelial (as well as tumor) cells. Key constituents in the acute phase inflammatory response include the cytokines interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), although there are a number of other molecules (such as the chemokine interleukin-8, and soluble intercellular adhesion molecule-1) that play important roles in the acute inflammatory process.

While the transient effects of the inflammatory response serve to protect the organism from internal or external immune insults, increasing evidence suggests that chronic inflammation serves to perpetuate several forms of disease processes, including cancer (Aggarwal, Shishodia, Sandur, Pandey, & Sethi, 2006). The functions of many pro-inflammatory molecules (as well as some anti-inflammatory molecules (Olver, Apte, Baz, & Kienzle, 2007)) have been found to serve duplicitous roles in cancer disease

progression. Because the immune system is a rich and dynamic system where a cell's function is largely influenced by the surrounding immune environment (Millington, Zinselmeyer, Brewer, Garside, & Rush, 2007), the effects of particular inflammatory molecules in cancer are not always the same. Thus, pro-inflammatory (and some anti-inflammatory) molecules have been found to be both pro-tumorigenic and anti-tumorigenic (Knupfer & Preiss, 2007), likely depending of the relative regulation or dysregulation of the systems from which they emerge. This section will briefly highlight some of the varied roles that inflammatory processes play in breast cancer disease progression, while highlighting those molecules that are the most salient with respect to understanding the effects on chronic inflammation processes in cancer (and are used as biomarkers in some form in this study). Specific details on each study biomarker used, in terms of its relevance to cancer disease progression and psychosocial correlates such as fatigue and depression, are provided separately within the Method section.

Among the functions of pro-inflammatory cytokines are to promote the differentiation of naïve T-lymphocytes to Th1 or "cell-mediated immunity" T-lymphocyte subsets. This function, along with the other functions of the inflammatory response to promote the trafficking of these and other phagocytic cells to tumor sites for eventual apoptosis or necrosis of tumor cells (as well as eventual engulfment of their constituents) would seem to aid the cancer-fighting process. Certain molecules (such as tumor necrosis factor-alpha) were even named according to their abilities to help extinguish cancer progression. Indeed, TNF-α, when expressed locally by immune cells, was found two decades ago to be effective in stimulating apoptosis and necrosis in several different cancer cells lines (Haranaka, Satomi, Sakurai, & Haranaka, 1987). It

was also found to promote vascular disruption of tumor cells (van Horssen, Ten Hagen, & Eggermont, 2006), and was sometimes used as an anti-cancer agent. However, since then, it has become clear that TNF-α also promotes tumorigenesis by various mechanisms, including promoting cell transformation, angiogenesis of tumor cells, and trafficking of tumor cells (Mocellin & Nitti, 2008). These apparent inconsistencies in the function of TNF-α in cancer disease progression may in part be explained by the dosage and timing of expression or administration of the molecule: it is thought that high-dose, infrequent exogenous administration of TNF-α may help to destroy certain cancers, whereas low-grade, chronic endogenous TNF-α expression (as in the case of chronic inflammation) may promote cancer processes (Mocellin & Nitti, 2008). Similar to TNF-α, key pro-inflammatory molecules such as IL-1 and IL-6 have also been found to promote cancer disease progression by various mechanisms, including tumor growth, tumor migration, and chemotherapy resistance (Aggarwal et al., 2006; Arihiro, Oda, Kaneko, & Inai, 2000; Bachelot et al., 2003; Conze et al., 2001). The effects of chronic inflammation on cancer progression are often also facilitated by tumor cells themselves: tumor cells have been found not only to promote their continued growth by stimulating the release of pro-inflammatory cytokines from nearby T-lymphocytes and monocytes, but also appear to largely increase their growth through autocrine secretion of these same molecules, including IL-1, TNF-α, and IL-6 (Aggarwal et al., 2006; De Cicco, 2004; Pantschenko et al., 2003). Interestingly, the two-sided effects of cytokines in cancer do not appear to be limited to pro-inflammatory cytokines: recent evidence suggests that IL-4, a key anti-inflammatory cytokine (that is also associated with fatigue (Hanson, Gause, & Natelson, 2001)), may either aid in or hinder tumor clearance, depending on the type of

cells (innate vs. adaptive) that are mediating the response as well as depending on the stromal infrastructure of the tumor cells (Olver et al., 2007).

A common mechanism by which chronic inflammatory processes affect cancer disease progression appears to be through activation of the signaling of the family of transcription factors termed nuclear factor kappa-beta (NF-kβ). NF-kβ is comprised of five different genes and activation of its transcription factors appears to be mediated by a number of different signaling pathways, many of which are stimulated by pro-inflammatory cytokines such as IL-1 and TNF-α (Dolcet, Llobet, Pallares, & Matias-Guiu, 2005). Importantly, interleukins, chemokines, several growth factors, and TNF are all regulated by NF-kβ transcription, as well as affect NF-kβ activation. While NF-kβ is tightly regulated and generally present in inactive form on most cells, its presence in cancer tends to be in an chronically activated form, often through the stimulation by inflammatory constituents and carcinogens (Aggarwal et al., 2006). Importantly, NF-kβ activates the transcription of genes that are involved in apoptosis suppression, angiogenesis, tumor migration, metastasis, and resistance to chemotherapy and radiation treatment (Aggarwal et al., 2006; Dolcet et al., 2005). Recent evidence has demonstrated more directly that IL-1 and TNF-α -stimulated NF-kβ activation in cancer cells has mediated deleterious consequences in terms of cancer progression (Jung, Isaacs, Lee, Trepel, & Neckers, 2003; Qin et al., 2007). Thus, chronic inflammation may have its effects on cancer disease progression partially though the common signaling of NF-kβ pathways in cancer cells.

This description describes the complex physiology underlying the current understandings of the relations of chronic inflammation to cancer disease progression.

While the orchestration and all mediating markers of such processes as they relate to cancer are much more complex than depicted here, this example nevertheless provides an understanding of how the net effects of chronic inflammation appear to result in the promotion of tumor growth and metastasis.

Inflammatory immune processes and cancer-related fatigue

Given that inflammatory immune processes are directly relevant to cancer progression, and that increases in inflammation as well as fatigue are often found in cancer treatment, a logical step for researchers in psychoneuroimmunology has been to examine potential co-relations of inflammation with cancer-related fatigue. Initial evidence for relations of pro-inflammatory activity and fatigue was perhaps first noted during the administration of biological therapies for cancer, such as immunotherapy. Exogenous administration of pro-inflammatory cytokines results in sickness behavior, which include fatigue, cachexia, and cognitive disorientation (Gutstein, 2001). Since then, other direct evidence of inflammatory immune connections with cancer-related fatigue has surfaced. For example, it is well-known that most cancer patients (~80-90%) report large increases in fatigue during chemotherapy and radiation treatments (Hofman, Ryan, Figueroa-Moseley, Jean-Pierre, & Morrow, 2007). While the general immunosuppressive side effects of these therapies are well-known (i.e., chemotherapy generally causing leukopenia, erythropenia, neutropenia, and thrombocytopenia, often due to myelosuppression and sometimes myeloablation (Wijayahadi, Haron, Stanslas, & Yusuf, 2007)), it is only recently that studies have begun to examine the effects of these treatments on specific immune transmitters that play key roles in cancer progression. A few studies suggest that the process of chemotherapy for breast cancer patients alters

levels of inflammatory immune mediators such as interleukin-8, vascular endothelial growth factor (VEGF), and soluble intercellular adhesion molecule-1 (sICAM-1) throughout the course of chemotherapy, with the net effect of chemotherapy being to increase overall activity in these and other inflammatory markers related to chemotaxis and endothelial and platelet activation (Mills et al., 2008; Mills et al., 2004; Pusztai et al., 2004). Recent studies indicate a significant association between the fatigue felt during cancer treatment and alterations in cytokines. One study reported concomitant increases in IL-1β with fatigue for prostate cancer patients undergoing radiotherapy (Greenberg, Gray, Mannix, Eisenthal, & Carey, 1993). In addition, a few studies have reported significant correlations between the cytokine interleukin-6 and fatigue levels during radiotherapy (Ahlberg et al., 2004), although this result has not always been replicated (Geinitz et al., 2001). Others have reported significant associations of increased fatigue with inflammatory mediators such as VEGF and sICAM-1 during chemotherapy (Mills et al., 2005).

Even after chemotherapy and/or radiation treatments are over, fatigue lingers in about one-third of survivors (Bower et al., 2006). Interestingly, findings from several studies suggest that survivors who suffer from above-normative levels of fatigue have increased plasma levels of certain inflammatory cytokines, such as interleukin-6 (IL-6) and its soluble receptor (sIL6-R), interleukin-1 receptor antagonist (sIL-1Ra), soluble tumor necrosis factor receptor type II (TNF-RII), and neopterin (Bower, 2007; Schubert, Hong, Natarajan, Mills, & Dimsdale, 2007). These findings have been supported by ex vivo studies as well: comparative increases in IL-6 and TNF-alpha production by

stimulated monocytes have also been found for fatigued vs. non-fatigued breast cancer survivors (Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006).

Hypothalamic-Pituitary-Adrenal (HPA) axis dysfunction and its relations with fatigue and depression in breast cancer

Increases in inflammatory immune activity have often been found to occur during standard treatments such as chemotherapy and radiation, and may help to explain the increases in fatigue during such treatments. However, the question remains as to why cancer-related fatigue and inflammation may persist well after treatment. One possibility for the persistence of cancer-related fatigue may be that alterations in inflammatory immune activity during treatment dysregulate HPA axis activity, such that key HPA constituents, such as the hormone cortisol, are less effective in dampening the activity of pro-inflammatory cytokines.

The HPA axis plays an important modulatory role in regulating immune activity. Under normal circumstances, the presence of various positive and negative feedback loops of the HPA axis with pro and anti-inflammatory cytokine systems generally serve to provide balance not only between the HPA and immune systems, but also between pro- and anti-inflammatory processes. For example, pro-inflammatory cytokines stimulate HPA activation by increasing corticotrophin releasing hormone (CRH) from the hypothalamus, resulting in the release of adrenocorticotropin hormone (ACTH) from the anterior pituitary gland and eventual release of corticosterone from the adrenal cortex. Pro-inflammatory cytokines also affect the anterior pituitary and adrenal cortex directly, resulting in similar end-organ effects (i.e., glucocorticoid release). The ability of pro-inflammatory cytokines to affect HPA axis functioning at different downstream levels

ensures that some amount of glucocorticoid circulation is preserved in the organism even in the case of inhibition of pro-inflammatory processes (e.g., by anti-inflammatory cytokines). Conversely, in the normally-functioning system, glucocorticoids help to regulate their own release by inhibiting the production and release of pro-inflammatory cytokines, in part by activating anti-inflammatory cytokines (Jain & Mills, 2007).

However, in the case of HPA dysregulation, the negative feedback loops of the HPA in regulating pro-inflammatory activation of itself are compromised. This appears to be due at least in part by pro-inflammatory cytokine induced desensitization and/or downregulation of glucocorticoid receptors (Raison & Miller, 2001), with the net result being increased cortisol in the system as well as increased pro-inflammatory cytokine activity. Breast cancer disease progression as well as breast cancer treatment have been associated with dysregulations in HPA axis functioning, including hypercortisolemia and altered circadian rhythm of cortisol secretion (Lissoni et al., 2007; Sephton, Sapolsky, Kraemer, & Spiegel, 2000; G. van der Pompe, Antoni, & Heijnen, 1996).

The theory that cancer-related fatigue and depression may be partially due to and prolonged by dysregulation of the HPA axis is supported by several pieces of evidence. First, several studies have pointed to dysregulations in diurnal variations of cortisol in cancer patients at various points during the cancer process, including during survivorship. The normal circadian rhythm of cortisol is characterized by highly increasing levels near awakening to peak levels in the morning, with a rather rapid decrease during the day and nadir levels being reached by night, peaking again the next morning (Spiegel, Giese-Davis, Taylor, & Kraemer, 2006). A normal rhythm such as this suggests a relatively steep and negative slope of change when assessing overall daytime cortisol rhythm.

However, such patterns have not been observed with breast cancer patients. One study indicated that two-thirds of the metastatic breast cancer patients studied showed dysregulated circadian rhythms of cortisol, all characterized by flatter slopes (i.e., decreased diurnal variability). Importantly, the decreased diurnal variability in this sample was predictive of mortality for up to 7 years later, independent of other prognostic indicators (Sephton et al., 2000).

Second, several studies of HPA dysregulation for breast cancer patients also link the dysregulation to fatigue or depressive states as well as pro-inflammatory activity. For example, a recent study indicated that decreased diurnal variation of cortisol is associated with fatigue in breast cancer survivors (Bower et al., 2005). Another recent study indicated that breast cancer patients with co-morbid depression showed increased basal cortisol levels (as indicated by non-suppression of cortisol release by dexamethasone administration) compared to breast cancer patients without depression, depressed patients who are otherwise healthy, and healthy patients with no depression. Further, the patients with depression and breast cancer also showed elevated IL-6 levels compared to the other groups (Soygur et al., 2007). This study was a partial replication of a prior study conducted with a heterogeneous cancer sample, in which cancer patients with co-morbid depression also showed increased non-suppression of cortisol in response to dexamethasone and showed increased IL-6 levels compared to cancer patients without depression (Musselman et al., 2001).

Finally, recent studies indicate that HPA dysregulation in breast cancer patients is also reflected in responses to acute and socially-relevant laboratory stressors. A recent study demonstrated blunted cortisol reactivity for metastatic breast cancer patients

undergoing a modified Trier Social Stress Test (Giese-Davis et al., 2006). These results were replicated in a study examining the same stressor for fatigued vs. non-fatigued breast cancer survivors. Furthermore, blunted cortisol responses in fatigued (vs. non-fatigued) breast cancer survivors were significantly associated with an increase in pro-inflammatory immune activity (Bower et al., 2007), suggesting a link between HPA axis dysregulation and pro-inflammatory cytokine activity even during response to acute stressors. Taken together, these data suggest that HPA dysregulation in breast cancer is not only associated with breast cancer disease processes but also with depression and fatigue, and that the continuation of HPA dysregulation may in part be due to increased pro-inflammatory activity that has also been found to be associated with fatigue at numerous points within the cancer process. Importantly, the increased inflammatory activity and HPA axis dysregulation in breast cancer may place fatigued patients and survivors at more risk for more deleterious outcomes, including tumor growth, metastasis, treatment resistance, and risk of cancer recurrence. In addition to the potential physiological ramifications, fatigue is associated with depression and decreased quality of life in cancer patients. This information, combined with the fact that cancer patients report fatigue as one of the most troubling side effects that are yet not adequately addressed (Dillon & Kelly, 2003; P. Stone et al., 2003), points to the great need for interventions to reduce fatigue in breast cancer patients and survivors.

Adjunct treatment for cancer-related fatigue

The literature has not supported pharmacological treatment of cancer-related fatigue. Although erythropoietin for anemic patients has proven useful for improving hemoglobin levels in cancer patients undergoing chemotherapy, there is not sufficient

evidence that it significantly improves cancer-related fatigue (Djulbegovic, 2005). Approaches for treating fatigue have included exercise, supportive and/or psychoeducation interventions, sleep hygiene approaches, and energy conservation strategies, with mixed findings reported for all types of interventions.

To date, most behavioral approaches for the treatment of fatigue in cancer patients have focused on exercise interventions, both during and after treatment. While exercise interventions are commonly regarded by the medical community as effective treatment for cancer-related fatigue (Kirshbaum, 2005; Sood & Moynihan, 2005), the majority of these studies have yielded mixed findings.(Burnham & Wilcox, 2002; Christopher & Morrow, 2004; Courneya, 2003; Oldervoll, Kaasa, Hjermstad, Lund, & Loge, 2004; Turner, Hayes, & Reul-Hirche, 2004) A recent meta-analysis of exercise for cancer patients concluded that there was no evidence for an overall effect for exercise for improving symptoms of fatigue in patients overall; however, there was modest evidence for an effect for those studies that only examined breast cancer. The authors also note that the overall methodological quality of trials thus far was poor.(Stevinson, Lawlor, & Fox, 2004) Another recent meta-analysis on physical activity trials specifically for cancer survivors concluded that these interventions had relatively strong evidence for improving quality of life at post-treatment, but weak evidence for improving fatigue either during or after treatment.(Schmitz et al., 2005) In general, the methodological quality of exercise studies conducted with breast cancer survivors has been less rigorous compared to other exercise intervention studies with this population, and thus definitive conclusions regarding the utility of exercise in reducing fatigue for cancer patients and survivors remain unclear (Courneya, 2003).

Psychoeducation interventions for fatigue have also been recently reported in the literature, with mixed findings. A recent multi-site study found that an educational videotape was effective in reducing fatigue in breast cancer survivors, compared to no treatment or videotape plus therapy (Stanton, Ganz, Meyerowitz, Rowland, & Krupnick, 2004); however, a recent study using psychoeducation for symptom management in breast cancer patients via audiotape reported no significant reduction in fatigue compared to controls (Williams & Schreier, 2005). Another study examining the effects of a psychoeducation/supportive intervention for breast cancer patients (including information on energy conservation and sleep hygiene) reported no significant differences in fatigue between groups during chemotherapy (Yates et al., 2005). One study reported on the efficacy of an energy conservation intervention (which included psychoeducation, skill building, and skill assessment) for decreasing fatigue in a heterogeneous group of cancer patients, compared to a control group (Barsevick et al., 2004). With respect to other cancer populations, one study reported decreases in fatigue for malignant melanoma patients as a result of psychoeducation intervention (Boesen et al., 2005). One study examining the effects of an 18-week nursing intervention based on problem-solving and symptom management) for cancer patients undergoing chemotherapy (compared to a control group reported no significant differences between groups on fatigue; however, more people in the intervention group reported low fatigue compared to those in the control group (B. Given et al., 2002).

There have been a number of studies reporting on effects of cognitive-behavioral therapy (CBT) and supportive approaches for cancer patients. While these interventions have generally been tailored to ameliorate depression, insomnia, or global side effects of

cancer treatment, they have often examined fatigue as a secondary outcome, and results have been mixed. A group cognitive therapy intervention for depression in metastatic cancer patients reported significant intervention effects on depression and total mood disturbance, but not fatigue (Sarah Edelman, 1999). One study reported that a CBT approach for reducing fatigue in chemotherapy were only found for patients who were not experiencing neutropenia (B. A. Given, Given, Jeon, & Sikorskii, 2005). Another recent study examining a behaviorally-oriented intervention vs. a control group for a heterogeneous group of cancer patients reported no improvements in overall fatigue (Armes, Chalder, Addington-Hall, Richardson, & Hotopf, 2007). Finally, a recent study integrating several aspects of CBT (on an individual-therapy basis reported positive effects on relieving fatigue for chronically fatigued cancer survivors, as compared to a wait-list control group (Gielissen, Verhagen, Witjes, & Bleijenberg, 2006).

Interestingly, there is an increase in CBT approaches that address sleep-related symptomatology that is associated with fatigue. While these approaches have been successful in improving sleep and mood, evidence for these studies relieving fatigue has been mixed and at present, studies with control groups do not support the efficacy of these interventions for relieving fatigue. Three studies utilizing CBT approaches for sleep reported some indication of reduced fatigue for the patients studied (Berger et al., 2003; Quesnel, Savard, Simard, Ivers, & Morin, 2003); however, all these studies lacked control groups. One RCT with a wait-list control group examined the effects of a CBT intervention designed to treat insomnia secondary to breast cancer reported improvements in sleep and other measures, but not fatigue (Savard, Simard, Ivers, & Morin, 2005). Finally, a recent cross-over study examining CBT-I for breast cancer survivors reported

improvements in sleep, but not fatigue, compared to treatment-as-usual (Fiorentino, 2007).

Complementary and Alternative Medicine use in Breast Cancer Patients

Complementary and alternative medicine (CAM) approaches are often sought out by breast cancer patients, with recent estimates of use across U.S. states ranging from 28-73% (Ashikaga, Bosompra, O'Brien, & Nelson, 2002; Burstein, Gelber, Guadagnoli, & Weeks, 1999; Gotay, Hara, Issell, & Maskarinec, 1999; R. E. Gray, Fitch, Goel, Franssen, & Labrecque, 2003; Henderson & Donatelle, 2004; Lee, Lin, Wrensch, Adler, & Eisenberg, 2000; Lengacher et al., 2002; Navo et al., 2004; Richardson, Post-White, Singletary, & Justice, 1998; Shen et al., 2002; VandeCreek, Rogers, & Lester, 1999). The most common forms of CAM used in the U.S. by breast cancer patients include nutrition supplements, mind-body approaches, and energy medicine approaches, including spiritual healing (Henderson & Donatelle, 2004; Lengacher et al., 2002; Nahleh & Tabbara, 2003). In terms of predictors of CAM use, a number of studies in the U.S. have indicated that breast cancer patients who use CAM tend to be younger in age as and generally have higher levels of education than those who do not use CAM (Alferi, Antoni, Ironson, Kilbourn, & Carver, 2001; Ashikaga et al., 2002; Gotay, 1999; Henderson & Donatelle, 2003, 2004; Navo et al., 2004; Shumay, Maskarinec, Gotay, Heiby, & Kakai, 2002). A few studies have also indicated that breast cancer patients who have higher perceptions of control and curability of cancer are more likely to use CAM treatments (Beadle et al., 2004; Henderson & Donatelle, 2003).

Importantly, studies indicate that CAM use in breast cancer patients tends to be complementary as opposed to alternative and is thus sought in addition to standard

treatment (Burstein et al., 1999; Shen et al., 2002). Breast cancer patients often report that they use CAM to enhance physical, emotional, and spiritual quality of life as well as reduce stress and enhance the immune system (Henderson & Donatelle, 2004; Shumay et al., 2002; Tatsumura, Maskarinec, Shumay, & Kakai, 2003). One study reported that early-stage breast cancer patients who sought out a variety of CAM treatments for the first time reported poorer quality of life and mental health than those who had never used CAM (Burstein et al., 1999). However, other studies have failed to replicate this result (Alferi et al., 2001; Astin, 1998; Shumay et al., 2002). A few studies suggest that persons who use CAM are more likely to espouse holistic worldviews, both in relation to views of health as well as in other sociopolitical arenas (Astin, 1998; O'Callaghan & Jordan, 2003). For example, Astin found that those persons who were classified as "cultural creatives" (people with marked interest in spirituality and person growth psychology, among other holistic social principles such as environmentalism) were significantly more likely to use CAM (Astin, 1998).

CAM-Based Mind-Body Techniques for Fatigue in Breast Cancer

Mind-body approaches such as yoga and meditation have also been examined for possible effects on relieving fatigue in cancer patients and survivors. While yoga appears to provide benefits for quality of life and related factors, studies so far do not show evidence for relieving fatigue. An RCT of a Tibetan yoga program for lymphoma patients reported significant improvements in sleep quality and decreased sleep latency, but no changes in fatigue (Cohen, Warneke, Fouladi, Rodriguez, & Chaoul-Reich, 2004). Similar non-significant results for fatigue were found for an RCT examining yoga for breast cancer survivors, although whether these survivors were all fatigued is unclear

(Culos-Reed, Carlson, Daroux, & Hately-Aldous, 2006). Finally, a recent RCT of yoga for a multiethnic sample of patients found significant improvements in quality of life and distressed mood, but not fatigue (Moadel et al., 2007). Similar to exercise interventions, a key factor may be adherence to the intervention; a recent uncontrolled study found that actual daily practice of yoga was directly related to decreased ratings of pain and fatigue over time (Carson et al., 2007).

With respect to meditation for cancer outpatients, one uncontrolled study reported significant improvements in fatigue ratings after an 8-week Mindfulness Based Stress Reduction (MBSR) program (Carlson & Garland, 2005), and one RCT reported increased vigor as a result of an MBSR intervention (Speca, Carlson, Goodey, & Angen, 2000). However, these studies did not examine fatigue as a primary outcome.

Taken together, current research suggests the efficacy of behavioral interventions (such as exercise, psychotherapeutic approaches, sleep management interventions, and mind-body interventions) are mixed. While to date no specific approach has been consistently found to ameliorate cancer-related fatigue, exercise, energy conservation, sleep management, and meditation interventions show potential promise. Future larger-scale studies with adequate control groups are needed to determine the efficacy of these and other behavioral approaches to mitigating cancer-related fatigue.

Biofield Healing: Use by cancer patients and other populations

Interestingly, energetic and spiritual healing are among the highest-ranked CAM modalities utilized by breast cancer patients (Gotay et al., 1999; Henderson & Donatelle, 2004; Lengacher et al., 2002). These modalities have recently been termed biofield

therapies[1] by NIH's National Center for Complementary and Alternative Medicine. This term has been applied to these techniques chiefly because the theoretical premise of such techniques rests on the utilization of purported "subtle energy" fields for the purposes of eliciting a healing response. The mechanisms by which these therapies are advocated to work are currently not explainable by western scientific medical theory and knowledge, and more generally, have not been elucidated.

The concept of subtle energy and methods of its use for healing has been described by numerous cultures for thousands of years. Indeed, many Eastern "traditional medicines" such as Ayurveda and Traditional Chinese Medicine are founded on a conceptual understanding of subtle energy effects on the body-mind (Lei, Lee, & Askeroth, 2004; Sah, Joshi, & Joshi, 2002). Theories of health that include vital energy concepts (which include the Indian term prana, the Chinese term ch'i, and the Japanese term qi) all refer to so-called "subtle", non-physical energies that permeate existence and have specific effects on the body-mind of all conscious beings. Writings on the interaction of subtle energy with health may be dated back to at least 3000-6000 years prior, and have been documented in the writings of texts such as the Yi Jing or I Ching (Book of Changes, c.1122B.C.), Zhuang Zi's Nan Hua Jing (c. 300 B.C.),and Patanjali's Yoga Sutras (c.300 B.C.). Similar concepts in the West are reflected in the concepts of Holy spirit, or spirit, and can be dated back to writings in the Old Testament as well as the practice of laying-on of hands (MacNutt, 1974).

[1] NCCAM describes biofields as "putative energy fields [that] have defied measurement to date by reproducible methods. Therapies involving putative energy fields are based on the concept that human beings are infused with a subtle form of energy." (NIH, 2004)

Although theoretical etiologies of the origins of such "subtle energy" vary among cultures, the theories are similar in that they all refer to non-physical, yet physically influential vital forces that influence health and disease processes. Another common thread is the development of specific systems that purport to use subtle energy to stimulate one's own healing process. These are clearly reflected in internal (intrapersonal), movement-oriented practices such as yoga, tai-chi, and internal qi-gong, for example. They are generally less explicitly discussed, yet often recognized as part of, the experience of meditation and prayer. In addition, different cultures have developed external (interpersonal) practices that purport to specifically use subtle energies for the process of healing another. These include practices where a "healer" transmits energy to a recipient. Although many of these practices have been used over millennia in various cultures, they have only recently been examined by current Western empirical methods. The impetus for the research in the West is likely due to a resurgence of public popularity in some of these biofield therapies, such as Therapeutic Touch, Healing Touch, and Reiki, which are often taught and used in hospital and clinical settings. These as well as other biofield therapies are similar to each other in that they are often used to alleviate distress and facilitate healing responses in patients. However, they sometimes differ from each other in terms of theoretical etiology of the energy being utilized for healing purposes (e.g., universal life energy vs. chi), specific practitioner techniques (e.g., placement of hand positions, hands-on vs. hands-off healing, and direct versus non-direct methods of energy re-patterning), and incorporation or non-incorporation of certain symbols or spiritual elements in the healing process.

In addition to their widespread use among breast cancer patients, biofield modalities are also often used and/or requested by other cancer patients (Dy et al., 2004; Molassiotis et al., 2005; Pud, Kaner, Morag, Ben-Ami, & Yaffe, 2005) as well as palliative patients (Abbot et al., 2001) and pain patients (Barnes, Powell-Griner, McFann, & Nahin, 2004). These techniques are also used fairly frequently by the general U.S. population. In a survey conducted from 1990-1998, Eisenberg and colleagues reported that energetic healing was among the top CAM modalities used, with national estimates at 3.8 % (Eisenberg et al., 1998). A more recent survey from the National Center of Health Statistics estimated that over 5% of respondents had used Reiki, Qigong, or healing rituals (Barnes et al., 2004). Finally, a recent large-scale healthcare survey found that the perceived efficacy of energetic healing modalities used was the highest of all CAM-related modalities used, with efficacy ratings of 98% (C. M. Gray, Tan, Pronk, & O'Connor, 2002).

Unfortunately, the scarcity of published research investigating the potential utility and mechanisms of action of biofield healing approaches does not at all parallel patient demand and use of these modalities (J. S. Jacobson, Workman, & Kronenberg, 2000). A recent systematic review of 65 studies (S. Jain & Mills, 2005) of biofield therapies for various populations indicates that these therapies have demonstrated consistent effects in improving quality of life and decreasing pain perception, as well as eliciting an acute relaxation response in terms of reduced blood pressure, heart rate, respiration, and increased immunoglobulins. While initial studies with biofield therapies show promise for these interventions to enhance global immunity and reduce fatigue, more large-scale, methodologically sound studies with multidimensional measures of fatigue and

clinically-specific immune markers are needed. Effects of biofield therapies on anxiety, depression, functional ratings, and long-term clinical outcomes are mixed, and potential mechanisms for the effects of biofield therapies on clinical outcomes are still unclear.

Biofield therapies for the treatment of cancer-related fatigue

In terms of studies examining biofield therapies as complementary treatments for cancer, a few recent studies have specifically examined fatigue and related psychosocial functioning in the treatment of cancer patients, but not survivors. A recent, small crossover study examining five 45-minute daily sessions of Reiki for fatigue in cancer patients reported significant reductions in fatigue and improvements in quality of life following the Reiki condition (Tsang, Carlson, & Olson, 2007). A large-scale crossover study compared Healing Touch (HT) with massage and presence of a healthcare professional for 230 cancer patients undergoing chemotherapy. This study reported significant decreases in fatigue for persons receiving four 45-minute weekly sessions HT, but not for identical doses of massage therapy or presence alone. In addition, this study reported changes in autonomic nervous system functioning immediately following treatment (heart rate and blood pressure decreased in both the HT and massage conditions compared to the control condition and presence alone) (Post-White et al., 2003). Another study comparing the immediate effects of six 30-minute sessions of HT vs. mock treatment on 78 breast and cervical cancer patients undergoing radiation therapy reported a non-significant decrease in fatigue immediately following a HT vs. mock session (Cook, Guerrerio, & Slater, 2004). This study also reported significant reductions in mood disturbance and pain ratings as well as an increase in physical functioning and vitality for the HT vs. mock HT group; however, their statistical analyses were

suboptimal (they examined only within-subject effects with no between-group comparisons, and did not utilize alpha control for multiple subscales). Another study with a very small sample size (n = 15) reported short-term decreases in fatigue for patients receiving two 60-minute weekly sessions of Polarity Therapy compared to controls (Roscoe, Matteson, Mustian, Padmanaban, & Morrow, 2005).

With respect to other symptoms in cancer, one study with terminal cancer patients reported decreases in state anxiety for patients receiving three 20-minute consecutive daily sessions of Therapeutic Touch, compared to controls (Giasson & Bouchard, 1998). Another study examining the effects of two 90-minute Reiki sessions within one week for advanced cancer patients reported decreases in pain perception relative to a control condition (Olson, Hanson, & Michaud, 2003). None of these studies examined immune function, although a few studies examining healthy populations have reported increases in global immune measures such as immunoglobulin levels as well as lymphocyte subsets and cytotoxicity (Naito et al., 2003; Wardell & Engebretson, 2001; Wilkinson et al., 2002).

In summary, a small handful of studies with biofield therapies have reported positive findings for decreasing fatigue, pain and negative mood as well as improving quality of life in cancer patients. Given the evidence thus far, an independent research report issued by the Oncology Nursing Society rates biofield therapies as "likely to be effective" in treating cancer-related fatigue (Mitchell, Beck, Hood, Moore, & Tanner, 2007). However, the majority of studies with biofield therapies are underpowered and/or uncontrolled, with relatively low dosages of intervention, making definite conclusions on the efficacy of such therapies for fatigue and other symptomatology in cancer patients

unclear. In addition, no studies to date have examined clinically-relevant immunological or neurohormonal markers in response to a biofield vs. placebo-controlled therapy.

Energy Healing: The proposed form of biofield-based intervention

Energy healing is a biofield-based therapy that falls under the general rubric of "energy medicine", a term often used to describe therapies that purport to involve the use of energy fields for the purposes of healing. As with other forms of biofield therapy, the practitioner conducting energy healing is said to work with specific energy fields that surround the physical body. It is believed that these energy fields are not epiphenomena of the physical body; rather, the physical body is enveloped by energy fields that have a direct influence on health and disease (Brennan, 1993). These purported fields correspond to several levels of functioning, including sensate, emotional, mental, inter-relational, sense of purpose, and spiritual aspects of being (Brennan, 1993). Energy healers attempt to directly work with these fields in order to facilitate healing and wellness on multidimensional levels (i.e., physical, emotional, mental, social, and existential/spiritual levels). Thus, EH is presented as an integrative method of facilitating healing. Similar to other biofield therapies such as Reiki, the practitioner of EH does not purport to utilize his or her own energy for the healing, but rather acts as a conduit to connect with a universal healing energy (conceptually similar to the Chinese term chi and the Indian term prana). The connection with universal energy enables the practitioner to clear and ground his or her own biofield and utilize the universal healing energy to help restore any imbalances in the patient's energy fields as well as elicit the patient's own healing response. Unlike Reiki, EH does not employ the use of specific symbols nor does it require formal initiations to advance to a higher level of healing capacity. Similar

to Healing Touch, certain techniques in EH are based on sensing imbalances in the biofield and attempting to restore balance to the field in order to promote further healing of the individual.

Aims of Study

This Ph.D. dissertation study investigated the use of a biofield-based healing compared to mock healing for the alleviation of fatigue and other common side effects experienced after adjuvant or neoadjuvant therapy for breast cancer. Several dimensions and correlates of fatigue were examined, as well as immune markers and hormone measures that are known to be associated with fatigue and that bear clinical significance for breast cancer survivors. Survivors were defined as those breast cancer patients who have successfully completed their cancer therapy without recurrence of the disease. Eight sessions of either biofield healing or mock healing were given to each patient within a one-month duration (i.e., sessions were twice a week for four weeks). Each session was 60 minutes in length. Treatment effects were examined throughout the intervention. The study's specific aims and hypotheses were as follows:

Specific Aim 1: Examine and compare the effects of biofield vs. mock healing on alleviating fatigue and related psychological symptomatology in breast cancer survivors after a 4-week intervention (endpoint).

Hypothesis 1a. At endpoint, survivors in the biofield healing group will report decreased total fatigue compared to those in the mock healing group.

Hypothesis 1b. At endpoint, survivors in the biofield healing group will report decreased depression, decreased mood disturbance, and increased quality of life compared to those in the mock healing group.

Specific Aim 2: Examine and compare the effects of biofield healing vs. mock healing on cytokines, cytokine receptors, and hormonal (cortisol variability) markers. Relate biomarkers to changes in psychosocial functioning.

Hypothesis 2a. At endpoint, compared to the mock group, survivors in the biofield healing group will show decreases in plasma levels of the cytokines interleukin-6 (IL-6), interleukin-4 (IL-4), the soluble receptor for interleukin 6 (IL-6sR), interleukin 1 receptor antagonist (sIL-1Ra), and tumor necrosis factor receptor II (TNF-RII). Post-intervention decreases in sIL-6r and sIL-1Ra will be associated with decreases in fatigue.

Hypothesis 2b. At endpoint, survivors in the biofield healing group will show increased cortisol variability compared to the mock treatment control group. Increased cortisol variability will be associated with decreases in depressed mood.

Chapter 2

Method

This Ph.D. dissertation study examined the effects of a specific biofield healing technique versus mock healing in the treatment of fatigue, psychosocial distress and quality of life, and relevant biomarkers in breast cancer survivors after cancer therapy (chemotherapy, surgery, or radiation). The protocol took place on the UCSD General Clinical Research Center (GCRC), located at the UCSD Medical Center, as well as at the GCRC Satellite Clinic on the UCSD Campus. Quiet rooms were especially selected and reserved for the study in both GCRC locations.

Participants

Recruitment

Sixty-seven women inquired about or were referred for the study, from various sources. A number of participants received information about the study through brochures mailed to them by the UCSD Moores Cancer Center. In addition, brochures and flyers were distributed widely throughout the San Diego community, including at kiosks at various cancer centers, breast cancer groups and breast cancer community gatherings, and wig shops. Advertisements were also sent through the UCSD staff and faculty listserv and other San Diego-based integrative medicine listserves. A website for the study was linked with various breast cancer national and local websites (including the NIH Clinical Trials, Living Beyond Breast Cancer, and San Diego Cancer Navigator websites). Presentations were also made to UCSD Moores Breast Cancer Center Support groups. Finally, two local television appearances and word-of mouth garnered a number of calls from eligible participants. Unfortunately, despite efforts to encourage

oncologists to refer patients to the study, none were referred to the study through oncologists. A list of recruitment strategies and relative number of referrals generated by each strategy may be found in Table 1.

Of the sixty-seven inquires, 7 women were ineligible, and 24 women declined participation. Those who declined participation gave reasons such as commuting distance (several inquires were from people in other cities and sometimes other states), scheduling difficulties, and non-willingness to do blood draws. Three women planned to enroll but postponed their entry date due to situational factors (in two cases, the San Diego fires of 2007, and in one, a car accident). Thus, 33 fatigued women breast cancer survivors planned to be enrolled in the study. Of these participants, 2 changed their minds after the initial screening visit and thus received no sessions. Both women cited scheduling difficulties as the reason for not participating. Two participants dropped from the study after enrolling and receiving treatment sessions (one after receiving 2 sessions of healing, and one after receiving 4 sessions of mock healing). The participant who dropped from the mock healing arm cited feeling too overwhelmed with situational factors (car accident, scheduling difficulties) to continue participation. The participant who received two sessions of energy healing cited feeling strong emotional difficulties (i.e., depression) as the reason for ceasing participation; she felt that she needed to seek traditional psychotherapy. This participant was directed to resources for traditional psychotherapy for depression. Thus, 29 women completed all sessions in the study (16 in the healing arm, and 13 in the mock healing arm). A flow chart of recruitment and enrollment may be found in Figure 1.

All enrolled participants signed informed consent. Participants were included if they met the following criteria: female breast cancer survivors between 18-70 years of age, ability to give informed consent, completion of adjuvant or neo-adjuvant therapy for breast cancer (including surgery, radiation, and/or chemotherapy) between 1 month to 5 years prior, diagnosed stage between I – IIIa, and reports of above-normative fatigue levels as measured by the RAND vigor-fatigue subscale.

Patients were excluded if they met any of the following criteria: currently receiving or scheduled to receive radiation or chemotherapy during or after the course of the intervention study, presence of current psychotic disorder or otherwise unable to sign informed consent, current diagnosis of uncontrolled disease known to affect fatigue and inflammation levels (e.g., untreated sleep apnea or thyroid disorder), history of other cancers or stage IV cancer, current substance abuse or dependence, male patients with breast cancer, or current/continued use of another biofield-based intervention (e.g., Reiki, Therapeutic Touch, Qigong).

Screening Procedure

Breast cancer survivors were phone screened to ensure eligibility according to the inclusion and exclusion criteria listed above. Survivors were screened for above-normative levels of fatigue based on their scores of the energy/fatigue subscale of the well-validated RAND SF-36 (Hays, Sherbourne, & Mazel, 1993). This 4-item subscale has been used in assessing fatigue in breast cancer survivors and has demonstrated good reliability as well as validity with other fatigue scales used with breast cancer patients. In addition, this subscale has successfully distinguished high and low fatigued survivors in terms of inflammatory immune variables and cortisol variability (Bower, Ganz, Aziz,

Fahey, & Cole, 2003). Consistent with other studies distinguishing fatigued survivors with this scale, participants scoring 50 or below were included in this study (barring other criteria that might exclude them from the study).

Overview of Research Design and Flowchart

This was a two-armed randomized placebo-controlled study of breast cancer survivors, with one arm receiving 8 sessions of Energy Healing (EH) and one arm receiving 8 sessions of mock healing (mock EH, termed "touch alone" to participants). During recruitment, survivors were told that they would have an equal chance of being randomly assigned either to energy healing or touch alone, and that they would not be told which group they were assigned to until the end of the intervention. Thus, participants were blinded to group status until the end of the study period. If assigned to mock healing, participants were offered 5 free sessions of EH to be scheduled at their convenience after their participation in the study was completed and their group status was disclosed. Participants were block randomized to energy healing (EH) or mock EH using a computer-generated randomization table. Treatment allocation was concealed via the following procedure: a statistician not affiliated with the study generated the randomization table, and a research assistant created sealed envelopes for each participant with the allocated group assignment. Envelopes remained unopened until group assignment for a particular subject became necessary.

The intervention period comprised 4 weeks, with 8 sessions (two sessions per week) given for both EH and mock EH participants. Each session was of one hour's duration. Figure 2 depicts a flowchart of the protocol.

A comprehensive battery of psychosocial functioning, as well as blood and saliva measures, was assessed throughout the intervention. Blood samples were drawn at Visit 1 (Pre-intervention screening) and visit 9 (Post-intervention). A GCRC nurse and trained phlebotomist discreetly drew the blood samples via catheter. Salivary samples were collected by patients two days before visits 1 and 6, and two days after visit 9, at four timepoints (on rising, at noon, at 5pm, and at 9pm).

In order to control for diurnal variability of immune and hormonal measures, on visits where blood was drawn (i.e., visits 1 and 9) all patients were studied from 12 - 4pm, with the time of each visit remaining constant for each patient.

Intervention Methods

Energy Healing (EH)

Although there are several techniques taught within energy healing, there are specific approaches that long-practicing energy healers believe are most beneficial for treating cancer survivors. The specific technique used in this study is termed *energy chelation*, and is utilized in various forms of biofield-based energy therapies (Brennan, 1993; Bruyere, 1989; Post-White et al., 2003). Energy chelation, as defined here, refers to a process by which the human energy field or aura is filled and balanced with universal energy from the universal energy field (Bruyere, 1989). During energy chelation, the practitioner practices hands-on-healing with standard hand positions. The first position starts with hands on the feet, then moves up the body to the knees, hips, bladder area, stomach, hands, elbows, shoulders, heart, throat, head, and back to the heart. The practice of energy chelation is 45 minutes to an hour in duration, with a practitioner generally focusing 5-7 minutes on each hand position before moving to the next one, directed by a

perceived change in the energy flow that guides the practitioner to move to the next position. Energy chelation is regarded by practitioners as an essential technique to use for cancer survivors, because of the belief that this technique helps to restore energy level and help rid the patient of unnecessary wastes and toxins that may linger well beyond treatment and cause undesirable side effects (Brennan, 1993; Bruyere, 1989). It is thus thought to be a technique specifically useful in reducing fatigue and improving vigor in these survivors. This technique is also standardized in that it is based on a specific hands-on approach with particular hand positions that are used for every patient, thus making it simple to train mock EH practitioners to mimic the actions of actual EH practitioners.

Energy healing practitioners

Four female energy healing practitioners were used for the study. All practitioners were graduates of a well-regarded four-year training program in Energy Healing. Each practitioner had sufficient training in the intervention techniques, as well as several years of interaction and energy healing experience with various patient populations, including breast cancer survivors.

Mock EH practitioners

Four female basic science and social science (e.g., biology, medicine, and anthropology) researchers served as the mock EH practitioners in this study. These persons were naïve or skeptical towards biofield-based therapy and had no experience in having trained in or having received biofield therapies (including biofield-related disciplines such as tai chi, chi gong, or martial arts). Mock practitioners were briefed on the nature of the study as well as their specific role on the project.

Quality control of practitioners

Given that EH practitioners would have more experience interacting with touching clients than mock EH practitioners, it was necessary to train and confirm that mock EH practitioners would present well as practitioners and be able to perform the hand placements accurately and without hesitation. Potential mock EH practitioners were first interviewed by the PI and their comfort level with working with strangers in the context of the study was assessed. If the potential practitioners demonstrated good communication skills and comfort with their role in the study, they were then taught the specific hand placements in energy chelation. Mock practitioners subsequently practiced the hand positions on the PI and trained research assistant until the PI was satisfied that the mock practitioner demonstrated mastery of the hand placements as well as confidence to interact and field potential questions that a patient might present to the mock practitioner.

In addition, both EH and mock EH practitioners were informed of the necessity of preserving blindness in the clients and agreed to not disclose their status as practitioners to clients, clients' friends or relatives, or other personnel within the study. In order to minimize variance associated with potential psychotherapeutic effects, both EH and mock EH practitioners conducted their sessions in silence. All practitioners were instructed on how to answer potential questions that participants might have during the intervention process, and were instructed to refer patients to the PI if the patients had any questions that they felt they were not able to answer.

Immune and Hormonal Data

A limitation of previous studies on effects of mind-body interventions for cancer patients is the exclusion of examining relevant biomarkers of side effects and disease progression. To help bridge this gap, this study examined specific biomarkers for the purposes of investigating whether energy healing versus mock healing impacts physiological correlates of fatigue. While there were potentially many biomarkers that could have been included, biomarkers for this study were chiefly chosen based on 1) their relevance to the population studied in terms of being associated with fatigue and 2) their ability to be reliably assessed in peripheral circulation for this population. A synopsis of each biomarker and its relevance to the study design is presented below:

Interleukin-1 Soluble Receptor Antagonist (sIL-1Ra): Soluble, or secretory, sIL-1Ra (sIL-1Ra) is one of several isoforms of receptor antagonists for interleukin-1 (the other isoforms being cell-bound) (Arend, 2002). sIL-1Ra binds to the active IL-1 receptor (IL-1RI) and functions as a competitive antagonist to the pro-inflammatory cytokine IL-1, binding with similar affinity to the receptor as to the isoforms of IL-1 to the receptors, but producing no intracellular response (Arend, Malyak, Guthridge, & Gabay, 1998). Similar to IL-1, sIL-1Ra is produced by a number of different cell types, including monocytes, macrophages, neutrophils, and hepatocytes (Perrier, Darakhshan, & Hajduch, 2006). Release of sIL-1Ra often occurs in response to the same stimuli (e.g., inflammation) as IL-1 itself (Arend et al., 1998). In addition, studies of *in-vivo* acute-phase responses using lipopolysaccharide (LPS) stimulation suggest that sIL-1Ra's production and secretion by hepatocytes appears to be independent of IL-6 and that it functions in this regard as an acute phase protein (Gabay, Gigley, Sipe, Arend, & Fantuzzi, 2001). Thus SsIL-1Ra is produced by a variety of cells, with its main function

being to serve as a competitive inhibitor of IL-1. Since IL-1 levels are difficult to measure because of the low concentration in serum or plasma, sIL-1Ra is often used as a proxy measure of IL-1 (Bower, Ganz, Aziz, & Fahey, 2002).

With regards to clinical relevance for cancer, IL-1 and sIL-1Ra expression both occur in breast tissue and have been found in numerous studies to be expressed in breast cancer cell lines and within the tumor microenvironment (Miller et al., 2000; Pantschenko et al., 2003; Singer et al., 2003) . Activation of the IL-1/sIL-1Ra system induces secondary expression of protumorigenic cytokines, promoting angiogenesis and tumor proliferation (Miller et al., 2000; Pantschenko et al., 2003). Elevated levels of sIL-1Ra have been shown to be associated with certain cancer malignancies as well as complications from cancer surgery (Niedzwiecki et al., 2007; Szczesny et al., 2007). Interestingly, sIL-1Ra has also been found to be elevated for fatigued vs. non-fatigued breast cancer survivors; this increase appears to be T-cell mediated (Bower et al., 2003; Collado-Hidalgo et al., 2006).

There is a large amount of evidence that also links IL-1 with psychological maladies, most notably, depression. Elevated IL-1 levels effects on the brain are associated with sickness behavior, a cluster of symptoms (including fatigue, cachexia, and depression) often associated with cancer treatment by interferons (Mills & Dimsdale, 2004). In addition, IL-1 and IL-Ra are strongly associated with depression; serum sIL-1Ra levels are reported to be increased in depressed patients versus controls (Maes et al., 1997; Maes et al., 1995), and a recent study reports genetic polymorphisms for IL-1α, IL-β, and sIL-1Ra genes in dysthymic patients versus normal controls (Fertuzinhos et al., 2004).

There are several biological mechanisms by which the IL-1 family may be involved in depression. First, evidence suggests that IL-1 receptors exist within the brain and that IL-1 and IL1ra are biologically active within the brain (Boutin, Kimber, Rothwell, & Pinteaux, 2003). Some have posited that the abilities of IL-1 to stimulate catabolite synthesis for (and eventual increased release of) numerous neurotransmitters (including serotonin, norepinephrine, and acetylcholine) within limbic system structures such as the hypothalamus and amydgala may account for some of the influence of IL-1 on depression (Dunn, 2006; Hayley, Poulter, Merali, & Anisman, 2005). Others have hypothesized that IL-1 may be linked to the biology of depression by promoting neurotrophic effects on certain (prefrontal) brain regions, through stimulating microglial cells to release reactive oxidative species (Hayley et al., 2005). Finally, some evidence suggests that the effects of the IL-1 family (as well as other acute-phase inflammatory cytokines such as IL-6 and TNF-alpha) on HPA axis functioning may play a role in depression. Studies indicate that the hypercortisolemia found in certain subtypes of depression (i.e., melancholic depression) may at least in part be caused by IL-1 stimulated release of corticotrophin-releasing factor (CRF) by hypothalamic neurons (Maes, Bosmans, Meltzer, Scharpe, & Suy, 1993). In addition, there is evidence suggesting that continuous stimulation of pro-inflammatory cytokines including IL-1, IL-6 and TNF-alpha may alter the HPA negative feedback control system, ultimately resulting in down-regulation of corticosteroid receptors and further dysregulation of HPA axis functioning (Maes et al., 1993).

Given the strong associations with sIL-1Ra with cancer disease progression, depression, and fatigue in breast cancer survivors, as well as the relative ease in detecting

this marker using standard ELISA techniques, this study opted to examine sIL1-Ra as a potential biomarker of change for the intervention. Specifically, this study examined whether sIL-1Ra levels would reduce for those receiving energy vs. mock healing, and whether potential reductions in depression and fatigue would be associated with changes in sIL-1Ra levels.

Interleukin-6: Interleukin-6 is a pro-inflammatory cytokine that plays a significant role in the regulation of breast cancer (Arihiro et al., 2000; Kozlowski, Zakrzewska, Tokajuk, & Wojtukiewicz, 2003). With respect to non-malignant cells, IL-6 is largely produced by monocytes and macrophages as well as B- and T-lymphocytes, endothelial cells, and epithelial cells, including breast tissue (Knupfer & Preiss, 2007; Lukaszewicz, Mroczko, & Szmitkowski, 2007). In addition, mounting evidence suggests that IL-6 is present in malignant breast cancer tissue (Knupfer & Preiss, 2007).

Given the pleitropy of IL-6, it is not surprising that the literature has noted that its effects may be either pro- and anti-tumorigenic (Knupfer & Preiss, 2007). However, numerous studies provide evidence for functions which link IL-6 to negative prognosis in breast cancer. For example, autocrine production of IL-6 has been shown to promote resistance to chemotherapy (Conze et al., 2001). IL-6 has also been shown to enhance migration of cancer cells (Arihiro et al., 2000), and distinguish metastatic from non-metastatic breast cancer (Benoy et al., 2002). Elevated levels of IL-6 have been found for breast cancer patients compared to healthy controls (Asgeirsson, Olafsdottir, Jonasson, & Ogmundsdottir, 1998; Kozlowski et al., 2003) and IL-6 is positively associated with cancer stage, grade, and presence of metastasis (Garcia-Tunon et al., 2005; Zhang & Adachi, 1999). The elevation in IL-6 found for breast cancer patients appear to be due to

increased IL-6 production by breast tumor cells as well as increased response to IL-6 by breast tumor cells (Garcia-Tunon et al., 2005). Finally, IL-6 has an important role in regulating estrogen synthesis in peripheral tissues, including breast tissue (Purohit, Newman, & Reed, 2002), and recent studies point to the function of IL-6 as a growth factor for estrogen-receptor positive metastatic breast cancer (Sasser et al., 2007).

In addition to its implications for breast cancer prognosis, IL-6, similar to IL-1, has been linked to depression in the general population (Craddock & Thomas, 2006; O'Brien, Scott, & Dinan, 2004). Interestingly, there are a number of studies linking increased IL-6 to depression in cancer patients (C. M. Jacobson, Rosenfeld, Pessin, & Breitbart, 2008; Kudoh, Katagai, & Takazawa, 2001; Musselman et al., 2001). IL-6 has also been found to be significantly associated with poorer quality of life in ovarian cancer patients (Costanzo et al., 2005), and a recent study has linked higher levels of IL-6 to be associated with fatigue in terminally ill cancer patients (Inagaki et al., 2008). Potential biological mechanisms linking IL-6 to depression and related constructs are similar to those posited for IL-1, but the most notable evidence linking IL-6 with depression in cancer supports the hypothesis of pro-inflammatory induction of HPA axis dysregulation as a contributor to depressive symptoms (Jehn et al., 2006; Soygur et al., 2007).

Thus, IL-6 is a highly relevant biomarker in cancer; it is associated with disease mechanisms, resistance to cancer therapy, and depression in cancer patients. This study aimed to examine potential intervention effects on IL-6 as a clinically relevant biomarker for depression and fatigue in survivors.

Interleukin-6 soluble receptor (sIL-6R): The soluble receptor for IL-6 (termed sIL-6R) acts as an agonist for IL-6, and is found in various body fluids. It is generated by

two mechanisms: shedding of the membrane-bound IL-6 receptor (IL-6R), and via the product of differential mRNA splicing (Jones, Horiuchi, Novick, Yamamoto, & Fuller, 1998). The membrane-bound receptor for IL-6 is expressed on a limited number of cells, including monocytes, macrophages, some lymphocytes, and hepatocytes (Rose-John, Scheller, Elson, & Jones, 2006). However, the pleitropy of IL-6 can be understood through its pairing with sIL-6R. The formation of the IL-6/sIL-6R complex enables IL-6 to exert its effects on a wide variety of cells through the association of the transmembrane signaling protein gp130, which is found on nearly all cells (Scheller, Ohnesorge, & Rose-John, 2006). This process of trans-signaling, enabled by the sIL-6R/IL-6 complex, is thought to be a crucial component of feed-forward mechanisms that help perpetuate inflammatory mechanisms in breast cancer and potentially fatigue (Kallen, 2002; Scheller et al., 2006). A recent in-depth immunological study examining biomarkers of cancer-related fatigue in breast cancer survivors found not only that fatigued survivors showed significantly elevated plasma levels of sIL-6r compared to their non-fatigued counterparts, but they also showed significant decreases in monocyte cell-surface IL-6r expression (which correlated with the increase of plasma sIL-6r). Further, they found that the fatigued vs. non-fatigued survivors had significantly decreased *in vitro* shedding of IL-6r from peripheral mononuclear blood cells (PBMCs) stimulated with IL-6, TNF-α, and IL-1β. Taken together, these findings provide a strong case for increases in inflammation-mediated shedding of the IL-6 receptor for fatigued breast cancer survivors. Finally, multivariate linear discriminant function analysis indicated that the ratio of sIL-6R to monocyte-produced IL-6 was very strongly predictive of fatigue diagnosis (Collado-Hidalgo et al., 2006). Given the strong association of sIL-6R with

fatigue in breast cancer survivors, and the relative ease of detecting this marker via enzyme-linked immunosorbant assay (ELISA), this study examined sIL-6R as a relevant biomarker of potential changes in fatigue and depressed mood for cancer patients during the course of the intervention.

Soluble Tumor Necrosis Factor Receptor II (sTNF-RII): Soluble TNF-RII is the larger of the two soluble receptors for the multifunctional cytokine TNF-α (the other being TNF-RI). TNF-α is a proinflammatory cytokine that plays a major mediating role in infection and inflammation. It is expressed by a number of cells, including monocytes, macrophages, lymphocytes, mast cells, cardiac monocytes, adipose tissue, and neuronal tissue (Mocellin & Nitti, 2008). Importantly, TNF-alpha has also been found to be expressed by numerous types of tumor cells, including breast tumor cells (Aggarwal et al., 2006).

TNF-alpha and its receptors are highly relevant to cancer processes and progression. The duplicitous effects of TNF-α in cancer are demonstrated by its named ability to selectively stimulate necrosis in certain tumor cells (Mocellin & Nitti, 2008) as well as its ability to act as a tumorigenic cytokine (Fujiki et al., 1994) that promotes angiogenesis, in part via stimulation of angiogenic factors such as vascular endothelial growth factor or VEGF (Mocellin & Nitti, 2008). TNF-α also induces expression of cellular adhesion molecules which promote invasion and metastatic behavior of tumor cells (Ioculano et al., 1995). Further, similar to IL-6 production in tumor cells, autocrine production of TNF-α serves to promote tumor cell proliferation (Aggarwal et al., 2006). TNF-α and its soluble receptors are elevated in breast cancer patients (D. Aderka et al., 1991; Tesarova et al., 2000) and are considered to be important prognostic indicators for

cancer progression as well as survival (Brenne et al., 2004; Diez-Ruiz et al., 1995; Jablonska et al., 2001). TNF receptors have also been found to transiently increase during chemotherapy (Perik, De Vries et al., 2006).

TNF receptors I and II are found on nearly all cells, save unstimulated T-lymphocytes and erythrocytes (Mocellin & Nitti, 2008). TNF-RI is perhaps best known for its binding with TNF-alpha to stimulate the signaling pathway for apoptosis (Mocellin & Nitti, 2008). While the specific effects of TNF-RII are less well-known, a recent study suggests that levels of sTNF-RII, and not sTNF-RI, may distinguish benign breast diseases from *in sit*u breast carcinoma and from infiltrating breast carcinoma (with levels of sTNF-RII respectively increasing in each case) (Garcia-Tunon et al., 2006). In addition, sTNF-RII levels appeared to be increased in disease-free breast cancer survivors versus controls, in contrast to sTNF-RI, which showed no such relationship (Perik, Van der Graaf et al., 2006). Increased levels of sTNF-RII have also been shown to be elevated in fatigued vs. nonfatigued breast cancer survivors (Bower et al., 2002).

Soluble TNF-RII is inhibitory in high concentrations, binding circulating TNF-α, preventing this cytokine from binding to an active cell-bound receptor (D Aderka, Engelmann, Maor, Brakebusch, & Wallach, 1992; Mohler et al., 1993; Opal & DePalo, 2000). At lower concentrations, sTNF-RII appears to preserve TNF-α alpha functioning by stabilizing the TNF structure, thus preventing TNF decay ((Opal & DePalo, 2000). Soluble TNF receptors have been suggested to be long-term markers of TNF-α; some regard the soluble receptors (particularly TNF-RII) to be a more stable marker of TNF activity than examining circulating levels of TNFα directly (Diez-Ruiz et al., 1995). Given the data indicating that sTNF-RII (and not TNF-RI) distinguishes breast cancer

survivors from healthy controls as well as distinguishes fatigued from non-fatigued survivors than TNF-RI (Bower et al., 2002; Perik, Van der Graaf et al., 2006), and given the indications that TNF-RII may be a more sensitive measure than TNF-RI for a general indication of TNF-α levels (Diez-Ruiz et al., 1995), this study included sTNF-RII as a potential biomarker of changes in fatigue as a result of intervention participation.

Interleukin-4 (IL-4): Interleukin-4, while considered an anti-inflammatory cytokine, appears to be implicated in fatigue as well as has contradictory roles with respect to tumor growth. IL-4, secreted by $CD4^+$ Th2 cell subsets, is a potent initiator of B-cell proliferation and differentiation, as well as an initiator of CD8+ proliferation (Nagai & Toi, 2000). IL-4 is also known to be a suppressor of angiogenesis (Volpert et al., 1998). Because of these and other functions, use of recombinant IL-4 infusions were initially therapeutically for the treatment of certain types of cancer, such as melanoma, renal cell carcinoma, non-Hodgkin's lymphoma. However, infusion with this cytokine was not found to be effective treatment for the above conditions, and administration was often was associated with profound "sickness behavior", with the hallmark symptom of fatigue (Stadler, Rybak, & Vogelzang, 1995; Taylor et al., 2000; Whitehead et al., 1998).

While chiefly secreted by Th2 helper subsets and mast cells, IL-4 and its respective and essential receptor IL4r, are also directly secreted by some cancer cells, including breast cancer cells (Mat, Larche, Melcher, & Ritter, 1990). Early studies examining the effects of IL-4 secretion by breast cancer cells indicated that the autocrine secretion served to prevent tumor growth only for proliferating cancer cells, but not for unstimulated tumor growth (Gooch, Lee, & Yee, 1998). More recent studies with breast cancer cell lines forms indicate that the secretion of IL-4 by tumor cells increases

resistance to chemotherapy and apoptosis (Nagai & Toi, 2000; Todaro et al., 2008). A recent review suggests that these "duplicitous" effects of IL-4 may be explained in part by the cellular microenvironment, such that the particular tumor modality as well as the cytokine-secreting profile of the CD4+ and CD8+ cells help determine whether the net effect of IL-4 will serve to suppress tumor growth, or prevent tumor clearance (Olver et al., 2007). With respect to fatigue, besides the repeated demonstrations of extreme fatigue associated with IL-4 infusion, IL-4 has been found to be increased in patients with chronic fatigue syndrome compared to normal controls (Hanson et al., 2001; Skowera et al., 2004). This study examined IL-4 as a potential biomarker of fatigue and explored whether the intervention impacted anti-inflammatory markers associated with fatigue, as indexed by potential changes in IL-4.

Diurnal Cortisol Variability: Cortisol, an indicator of the hypothalamic-pituitary-adrenal (HPA) axis, is a stress hormone that has particular relevance for breast cancer. Among the abnormalities in physiology that are observed in breast cancer patients are several disturbances in circadian rhythms, including cortisol rhythms. Breast cancer patients appear to have an abnormal circadian rhythm of cortisol that is marked by slightly elevated basal levels, irregular peaks and troughs, and flattened diurnal slopes (Sephton et al., 2000; Touitou et al., 1995; Gieta van der Pompe, Duivenvoorden, Antoni, Visser, & Heijnen, 1997). A study examining circadian rhythm alteration in metastatic breast cancer patients found that the alterations in slopes were similar to those of depressed patients, and importantly, predicted mortality (Sephton et al., 2000). Cortisol has been shown to increase during times of stress and in depression, leading to negative immune consequences (Leonard, 2000). Recently, it has been reported that diurnal

variability of cortisol is even more decreased in fatigued versus non-fatigued cancer survivors, with fatigued survivors showing flatter slopes due to less decline in afternoon to evening cortisol levels. Levels of fatigue in these patients correlated with less diurnal variability (Bower et al., 2005).

A few studies examining cognitive-existential and mindfulness meditation techniques for stress reduction in breast cancer patients have found an association of decreased cortisol and increased cortisol variability with increased quality of life (Carlson, Speca, Patel, & Goodey, 2004) as well as increased benefit finding (Cruess et al., 2000). Thus, there is evidence suggesting that mind-body interventions may help to normalize cortisol rhythms in breast cancer patients, potentially by enhancing quality of life and sense of meaning, which could protect against further negative immune consequences and potential increased disease progression due to stress and depression. Further, there is ample evidence that cortisol is sensitive to short-term change, both in response to psychological stress (Dickerson & Kemeny, 2004) and brief stress-reduction interventions (Antoni, 2003; Burns, Harbuz, Hucklebridge, & Bunt, 2001; Khalfa, Bella, Roy, Peretz, & Lupien, 2003; Pawlow & Jones, 2002; Pawlow, O'Neil, & Malcolm, 2003; Wardell & Engebretson, 2001). This study examined salivary cortisol diurnal variations as potential biomarkers of decreased fatigue and depression as a result of participation in the study intervention.

Salivary cortisol has been shown to be a reliable method of obtaining estimates of circulating blood levels and has become a standard method of choice in most behavioral medicine studies that examine biological correlates of psychological processes in a variety of populations (indeed, all the studies mentioned above utilized salivary cortisol

indices to measure cortisol function). It is believed that only unbound cortisol reaches tissue to exert glucocorticoid effects, leaving enough cortisol in the circulation to assess overall HPA activity. Because cortisol enters the saliva through non-active transport mechanisms (including passive diffusion), levels of cortisol in saliva are unaffected by saliva flow rate. In addition, acinar cells lining the salivary glands help protect saliva (and thus the measurement of salivary cortisol) from being contaminated by proteins and protein-bound molecules (Kirschbaum & Hellhammer, 1989). The assessment of saliva vs. blood for cortisol levels offers a large degree of convenience to the researcher, as the assessment and processing of samples is less costly. Perhaps more importantly, however, the assessment of cortisol using salivary samples is much more comfortable and convenient for patients providing the samples. In the case of assessing diurnal cortisol variability, where assessment at multiple timepoints is required, assessment of cortisol by blood may prove to be difficult if not impossible; in addition, acute stress effects of multiple blood draws could skew results. Nevertheless, studies examining the correlations between serum and plasma vs. saliva cortisol measurements generally find high agreement between the two approaches (Kirschbaum & Hellhammer, 1994). For accurate estimation of area-under-the curve and slopes using salivary cortisol, it is recommended to assess salivary cortisol at multiple timepoints throughout the day, including during awakening, afternoon/evening levels, and evening levels, over two or more days if possible (Kirschbaum & Hellhammer, 1994). This study utilized these guidelines in salivary data collection.

Physiological Data Collection and Processing

Venous blood samples were drawn in EDTA tubes by a nurse and trained phlebotomist and assessed for inflammatory molecules. Plasma samples were separated by centrifugation of blood and were stored at –80° C until the assays were performed. Assays were chiefly conducted by GCRC Core Laboratory technicians who were blind to all subjects' group assignment.

Assays for sIL-1Ra, sIL-6r, IL-6, IL-4, and TNF-RII were performed using standard, or high sensitivity where appropriate, enzyme-linked immunoabsorbent assay (ELISA) kits (R & D systems, Minneapolis, MN or Meso Scale Discovery (MSD), Gaithersburg, Maryland). Immune assay performance characteristics were as follows: Inter-assay coefficients of variation (CV) for sIL-1Ra ranged between 3.1 and 8.4%, with an intra-assay CV of 5.8%. Sensitivity was < 14 pg/mL. Inter-assay CVs for sIL-6r ranged between 2.9 and 3.6%, with an intra-assay CV of 3.2%. Sensitivity was < 1.5 pg/mL. Inter-assay CVs for TNF-RII ranged between 1.9 and 3.6%, with an intra-assay CV of 2.6% and a sensitivity of .2 pg/mL. Inter-assay CVs for IL-6 ranged between 3.7 and 7.5%, with an intra-assay CV of 5.4%. Sensitivity was < .32 pg/mL. Inter-assay CVs for IL-4 ranged between 6.3 and 11.2%, with an intra-assay CV of 8.5%. Sensitivity was < 1.32 pg/mL.

For salivary cortisol collection, participants were instructed on the proper use and storage of the salivettes, including refraining from eating, smoking and caffeine 2 hours before use. Samples were collected from the participant and centrifuged. The supernatants were then frozen until assayed in the GCRC Core Laboratory and subsequently measured via ELISA. The cortisol assay performance characteristics were as follows: Inter-assay coefficients of variation for cortisol ranged between 1.1 and 11%,

with an intra-assay CV of 6.1%. Sensitivity was .003 ug/dL. All blood and saliva samples from a single subject were assayed together to avoid effects of inter-assay variation.

Psychological Questionnaires

Demographic questionnaire: A demographic questionnaire was administered at pre-intervention to obtain information on the subject's identified ethnicity, age, education, marital status, family income, stage of cancer, duration of illness and medications used. This information was provided by the patient and was not accessed by medical records by the investigator. This information was used to track characteristics of participants in each group as well as utilize for potential covariate analyses if needed. *Completion time: 4 min*.

Multidimensional Fatigue Symptom Inventory-short form (MFSI-sf): The MFSI-sf is a 30-item questionnaire designed to assess cancer-related fatigue from a multifaceted approach. In addition to providing a total score on all aspects of fatigue, the MFSI-sf incorporates subscales assessing vigor and general, emotional, mental, and physical aspects of fatigue. To generate a total fatigue score for the MFSI, a sumscore for the General, Physical, Emotional, and Mental subscales is created, and the Vigor score is subtracted from this subscore. The range of possible scores for each subscale is 0 to 24. Higher scores indicate more severe fatigue, except for the Vigor subscale (where a higher score indicates less fatigue).The range for the MFSI-sf total score is -24 to 96. A score of 16 or higher signifies clinically significant fatigue. The MFSI-sf has been shown to have good reliability and validity, and has been designed to be sensitive to change, making it particularly useful for clinical intervention studies (K. D. Stein, Jacobsen, Blanchard, &

Thors, 2004) This questionnaire was administered more often than other questionnaires due to it being the primary outcome questionnaire. In order to more accurately determine dose-response in terms of the effects of the intervention on alleviating fatigue, as well as to increase power in detecting significant effects, the MFSI-sf was administered at five timepoints throughout the intervention.

Center for Epidemiological Studies Depression Scale-revised (CESD-R): The CESD-R is a 20-item updated version of a gold-standard depression scale originally developed in the 1970s. It is often used in outcomes research with clinical populations and has been shown to have excellent reliability and validity in several populations, including cancer patients.(Eaton, Muntaner, Smith, Tien, & Ybarra, 2003; Hann, Winter, & Jacobsen, 1999) The CESD-R is not heavily weighted on somatic symptoms (such as fatigue) and is thus thought to provide better assessment of depression in cancer patients who may be experiencing somatic symptoms regardless of depression levels. Scores of 16 or greater are considered to be indicative of major depression. This questionnaire was administered at the beginning, middle, and end of the intervention to assess potential changes in depression as a result of receiving EH or mock EH.

Profile of Mood States-Short form (POMS-sf): The POMS-sf is a 37-item short form questionnaire of the Profile Of Mood States.(McNair, Lorr, & Droppleman, 1971) It was originally designed for use with cancer patients in order to alleviate subject burden and has been found to have good reliability and validity in this population. (Baker, Denniston, Zabora, Polland, & Dudley, 2002; Shacham, 1983) The POMS-sf assesses the original POMS dimensions of tension-anxiety, depression, anger, vigor, fatigue, and confusion, and is often used in outcomes assessment research. In order to determine

short as well as long-term effects of biofield vs. mock healing on acute mood, the POMS-sf was administered pre and post each session.

Functional assessment of cancer therapy -breast (FACT-B): The FACT-B is a 44-item scale specifically designed to measure quality of life and functional outcome in breast cancer patients. It is comprised of four subscales (physical well-being, social/family well-being, emotional well-being, and functional well-being) which combine for a total score to measure overall quality of life. Higher scores are indicative of higher quality of life ratings. The FACT-B has been found to be reliable and valid in breast cancer populations (Brady et al., 1997). This questionnaire was administered at the beginning, middle, and end of the intervention to examine potential changes in quality of life as a result of EH vs. mock EH treatment.

Pittsburgh Sleep Quality Index (PSQI): The PSQI is a 19-item questionnaire that measures several different components of sleep, including sleep quality, sleep latency, sleep efficiency and daytime dysfunction. A global sleep quality score derived from the PSQI can be used to index overall quality of sleep. The PSQI has been shown to have high reliability (0.85) and validity (Backhaus, Junghanns, Broocks, Riemann, & Hohagen, 2002; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The range of global sleep quality scores range from 0-21, with high scores reflecting poor sleep quality. Scores below 5 are considered to be indicative of good sleep. The PSQI was administered at the beginning, middle, and end of the intervention to determine whether overall sleep quality may have changed for the participants in the healing vs. mock group.

Treatment and practitioner rating questionnaire: This questionnaire was developed for study purposes and was administered at the end of each session.

Participants were asked to guess which treatment (hands-on-healing or touch alone) they just received. Next, using a 5-point Likert scale, participants were asked to rate their feelings of (a) practitioner warmth and friendliness, (b) connection with practitioner, (c) feelings that the treatment is helping them with side effects such as fatigue, (d) feelings that the treatment is helping improve their immune functioning, and (e) feelings that the treatment is helping them with their well-being. This questionnaire was used in preliminary and exploratory analyses to examine and potentially control for therapist effects as needed, as well as examine potential moderating effects of beliefs of treatment assignment on outcome.

Data Quality Control and Participant Confidentiality

The study protocol was reviewed and accepted by the Institutional Review Boards for both University of California San Diego (UCSD) and San Diego State University (SDSU). All questionnaire data was administered by the PI or a trained research assistant who was available to answer any questions the survivors might have had about the procedure. Completed questionnaires were locked in a secure file cabinet in the UCSD Medical Center. Medical information, as well as questionnaire, blood and saliva data, was entered into a secure spreadsheet system without the participant's personal information. Data was independently checked to ensure accurate entry.

Data Analytic Procedures

Power Analysis

A power analysis was conducted for Specific Aim 1 (examining changes in fatigue levels from beginning to end of intervention for the two groups) using the multivariate approach in the G-Power program. A small effect size was estimated (f^2 =

.01). The inter-correlation between MFSI scores over time was calculated using previous repeated measures data for the MFSI total scores collected by our group in women breast cancer patients. The inter-correlation between MFSI measurements was $\rho = .76$. The number of levels of repeated factors was $m = 5$ resulting in an adjusted $f^2 = (m * f^2 / (1 - \rho)) = .21$. For a power of .8 and alpha = .05, numerator degrees of freedom = 1 (number of groups -1), and denominator degrees of freedom = n – p – 1 (where p = levels of repeated factor – 1), 40 participants were needed.

Demographic and Baseline Group Analyses

Chi-square and t-tests were run to assess potential group equivalences across demographic and disease variables (i.e., age, BMI, menopausal status, menopausal status due to chemotherapy, cancer stage, cancer grade, prior chemotherapy treatment, prior surgery, prior radiation treatment, HER-2 status, and ER status). In addition, t-tests were run on baseline data for each outcome variable with group as the predictor variable, to assess for any potential baseline differences between groups on outcome variables.

Analyses for Self-Report Questionnaires and Inflammatory Markers

In order to test for significant group differences on fatigue, depression, mood, and quality of life as a result of the intervention, analyses were conducted via repeated-measures ANOVA/ANCOVA, with the two groups constituting the between subject factor, and the repeated measures for each respective questionnaire (i.e., MFSI-sf, CESD, POMS-sf, FACT-B and PSQI, respectively) representing the within subject factors. Intent-to-treat analyses were conducted with all questionnaire data, with the "last score carried forward" approach. The repeated measures option with the mixed-model approach in the GLM interface (SPSS 15.0) was used for this analysis. Possible rejection

of the null hypothesis was examined using omnibus tests for the time and the group x time interaction terms. To account for minor compound symmetry violations, Greenhouse-Geisser corrections were used for omnibus tests. If compound symmetry/sphericity was grossly violated (i.e., epsilon < .75), the multivariate test was used instead. For any analysis when three or more repeated measures were used and trends or significant findings resulted for group x time interactions, tests for interaction contrasts were examined via trend analysis. Partial eta-squared values were obtained to estimate effect sizes. An alpha level of p = .05 was set for each outcome measure. If the total score of an outcome measure was significant (e.g., MFSI-sf total), subscales comprising the total measure (e.g., MFSI-sf subscales) were examined for significance at an alpha of p = .05 (Bonferroni corrections were not applied to avoid Type II errors). Demographic and treatment variables were assessed as potential covariates and were entered into the model as covariates if found to be robustly and significantly associated ($|r| > .33$ and $p < .1$) with outcome variables. Analyses for inflammatory markers (i.e., TNFRII, sIL-6R, IL-6, IL-4, and IL1Ra) were conducted in the same manner as those for questionnaire data, using pre-intervention and post-intervention inflammatory data. However, intent-to-treat analyses were not performed for inflammatory data as the "last score carried forward" approach would not be considered valid for biological markers in this context and are generally not performed.

Analyses for Salivary Cortisol

Hierarchical linear modeling (HLM) was used (Byrk & Raudenbush, 1992) to determine potential intervention effects on diurnal variability of cortisol. HLM is a very flexible tool in the analysis of longitudinal data where the repeated measures are

designated as Level-1, and other higher-order levels (e.g., predictors, static covariates, or fixed factors such as group membership) are incorporated if deemed warranted (Hox, 2000). HLM holds several advantages over traditional mixed-model ANOVA designs for this type of analysis: Firstly, in HLM, time is not considered a fixed factor and therefore can be modeled appropriately while handling temporality that varies across occasions and subjects (Hox, 2000; Maxwell & Delaney, 2004). This helps to more appropriately model time in the statistical design as well as to incorporate data that may have missing timepoints for certain participants. In addition, should covariates need to be added into the model, an HLM approach is advantageous over a repeated-measures ANCOVA design as it does not assume homogeneity of slopes between groups.

In keeping with recent leading research in the field of cortisol measurement with fatigued breast cancer survivors (Bower et al., 2005), three basic measurements were utilized to assess cortisol variability and cortisol levels. As the primary outcome of interest was diurnal cortisol variability, slopes were first estimated and analyzed. In order to better understand the nature of any potential changes in slope as a result of the intervention, and to better assess overall cortisol levels, the standard measures of area-under-the curve (with respect to ground) or AUCg as well as mean cortisol levels were also calculated and examined for potential changes as a result of the intervention.

To assess potential changes in diurnal variability over time for the two groups, slopes of change over time were estimated for each day of data collection; these data were then entered as a level-1 outcome measure for HLM. Slopes were calculated by regressing cortisol values on the four times of day (rising, 12pm, 5pm, and 9pm) for each day of collection (i.e., slopes were calculated for Visit1Day1, Visit1Day2, Visit6Day1,

Visit6Day2, Visit9Day1, and Visit9Day2). In addition, in keeping with the standards of current research in this field (e.g., Abercrombie et al., 2004; Bower et al., 2005), measures of total cortisol amount during the day (area-under-the curve with respect to ground (AUCg), and mean cortisol levels) were also calculated for log-transformed cortisol values for each day among the four timepoints (rising, 12pm, 5pm, and 9pm). Area-under-the curve data were calculated for each day of data collection using the standard formula (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003):

$$AUCg = \sum_{i=1}^{n-1} \frac{(m_{(i+1)} + m_i)}{2}$$

Similar to the procedure previously utilized in other studies (Bower et al., 2005), two-level HLM analyses were performed. Cortisol slopes were entered as the primary within-subjects (level-1) outcome measure, with time in days during the intervention entered as a level-1-predictor. Any demographic or disease variables significantly associated with baseline levels of the outcome measure were entered as time-unvarying (level-2) covariates. Treatment group (mock vs. healing) was entered as a between-subjects (level-2) predictor. The HLM equations representing the general model tested follow:

Level-1 Model

$$Y = B_0 + B_1*(TIME) + R$$

Level-2 Model

$B0 = G_{00} + U_0$

$B1 = G_{10} + G_{11}$*(TXGROUP)

In this model, the primary regression coefficient of interest for statistical testing is G_{11}, as it reflects the difference between the groups on changes in slope values over time. Similar analyses were performed using AUCg and mean cortisol level as separate level-1 outcome variables. All analyses were followed up with inclusion of treatment guesses as a time-varying (Level-1) covariate to account for expectation effects.

Examining associations between variables

In order to determine whether potential changes in psychological outcome variables were associated with changes in immune or cortisol data, change scores were first calculated for each psychological and physiological variable (V9-V1). Correlation analyses were then run to determine the existence of potential significant ($p < .05$) associations between the change scores for psychological and cytokine variables, psychological and cortisol variables, and cortisol and cytokine variables.

Chapter 3

Results

Demographic and Disease Characteristics

Women in the two study arms were examined for equivalence on various disease and demographic characteristics, using chi-square or t-tests where appropriate. A summary of these results may be found in Table 2. The mean age of women in the study was 52.5 years. Nearly all women (n = 32) were Caucasian; one woman was African-American. Twenty-eight women were postmenopausal and 4 were pre-menopausal, and 1 did not answer. Of the 28 postmenopausal women, 15 reported being menopausal due to chemotherapy. With respect to previous cancer stage diagnosis, 3 patients reported having DCIS/Stage 0 breast cancer; 13 reported having Stage Ia or Ib, 9 reported having Stage IIa or b, and 6 reported having Stage IIIa. Two patients did not know and could not access their medical records. Twenty-three participants had had prior chemotherapy. Twenty reported having prior radiation treatment. All patients reported having prior surgery.

Assessing for Baseline Differences between Groups

There were no significant baseline differences between groups for any outcome measure examined. While there were no significant differences between groups on demographic and disease characteristics, there were trends for significance on some measures: patients in the mock group tended to have shorter times since diagnosis ($p = .07$) and time since chemotherapy ($p = .08$). Also, although not significant, participants in the mock healing group tended to have shorter times since radiation ($p = .20$) and times since surgery ($p = .12$). Thus, overall, patients randomized to the mock group tended to

be out of cancer diagnosis and treatment sooner than those randomized to the healing group.

Expectation Effects

In order to test whether participant blinding was successful and whether groups differed by treatment expectation, participants rated their guess of treatment (energy healing or touch alone) after each session. These data were tabulated to determine an overall treatment guess variable per participant. This binary variable was used in subsequent ANOVA analyses to co-vary for expectation (for HLM analyses, ratings of each session were used as a time-varying covariate). All participants except for two were highly consistent in their responses throughout sessions.

Overall, 75% of women thought they were getting healing regardless of group assignment. Of the healing group, 87% thought they were getting healing, and of the mock healing group, 72% thought they were getting healing. Chi-square analyses indicated no significant difference between groups based on treatment expectation ($p = .35$).

Results for Psychological Measures

MFSI-sf Total Score

Correlation analyses indicated that time since radiation was significantly correlated with MFSI-sf scores ($r = -.38$, $p = .06$), such that increased time since radiation was associated with lower MFSI-sf total scores. In addition, this variable appeared to be disparate (though not significantly so) between groups, such that women in the healing group had radiation almost twice as long ago as those in the mock group (mean scores for time since radiation for mock and healing groups were 12.2 and 23 months, respectively).

Thus, this variable seemed appropriate to enter as a covariate for the MFSI-sf total score analyses.

There was a significant time effect for both groups for total MFSI-sf scores over the 5 timepoints, such that both groups decreased over time ($F_{(4, 12)} = 6.85$, $p = .004$, partial etasquared = .67). However, there was also a trend ($p = .085$) for a group x time interaction, such that the mock healing group showed a steeper decline of total fatigue over time compared to the mock group (partial etasquared = .47). This effect is depicted in Figure 3a. Interaction contrasts revealed a trend for linear differences between groups ($p = .12$, partial etasquared = .17). Expectation was not related to MFSI-sf scores over time. However, inclusion of the expectation variable as an additional covariate rendered the group x time interaction insignificant. Post-hoc power to test the interaction was considerably reduced with the inclusion of expectation as an additional covariate (observed power for interaction with time since radiation covariate = .56, with time since radiation and expectation covariate = .38).

It was noted that the inclusion of the time since radiation covariate truncated the sample size used (from n = 28 to n = 18). It was also slightly less representative of the entire sample, since the nature of the covariate excluded any women in the study who did not have radiation. Therefore, the analysis was re-run with the larger sample and excluding the covariate. For this analysis, there was a significant time effect ($F_{(3.04, 79.4)} = 11.3$, $p < .0005$, partial etasquared = .30), but no significant group x time interaction. Again, expectation was not related to MFSI-sf scores in the larger sample, and there was no change in results when co-varying for expectation. A pictorial graph with MFSI-sf

results excluding the time since radiation covariate may be found in Figure 3b. Means and standard deviations for both analyses may be found in Tables 3a and 3b.

MFSI-sf subscales

Next, MFSI-sf subscales were examined for potential intervention effects. Examination of correlations with demographic and disease variables for these subscales revealed that the Vigor subscale was also highly correlated with time since radiation ($r = .46$, $p = .02$), as well as with cancer grade ($r = -.38$, $p = .037$). Emotional fatigue was also correlated with cancer grade ($r = .39$, $p = .032$). The General and Physical subscales were not significantly correlated with any variable. The Mental fatigue subscale was significantly correlated with a number of variables, including menopausal status due to chemotherapy ($r = .37$, $p = .035$), chemotherapy status ($r = -.39$, $p = .012$), time since chemotherapy ($r = -.375$, $p = .045$), and time since surgery ($r = -.36$, $p = .022$). It was noted that menopausal status due to chemotherapy was highly and significantly correlated with the other 3 covariates ($.38 > |r| > .42$; $p < .035$ in all cases). Thus, to reduce multicolinearity, only menopausal status due to chemotherapy was included as the covariate for the Mental fatigue subscale analysis.

Results for the General fatigue subscale revealed a borderline ($p = .052$) group x time interaction, with the healing group showing steeper decreases in General fatigue over time (partial etasquared = .093). Interaction contrasts revealed a significant linear difference ($p = .025$, partial etasquared = .16) between groups over time.

For the MFSI Vigor subscale, there was a trend for a group x time interaction with a large effect size of increased vigor over time for the healing group compared to the mock group ($p = .10$, partial etasquared = .68). Interaction contrasts suggested that the

increase in vigor for the healing compared to the mock group were due to both linear (p = .08, partial etasquared = .30) and quadratic (p = .07, partial etasquared = .32) differences between groups over time.

There were significant time effects for Physical fatigue (p = .0003, partial etasquared = .21) and Emotional fatigue (p = .017, partial etasquared = .053, respectively), with both groups decreasing over time. There was no effect for Mental fatigue for either group. Graphical results for MFSI-sf subscales may be found in Figure 4. Means and standard deviations for MFSI-sf subscales may be found in Table 4.

CESD

Next, a repeated-measures ANOVA was run for CESD scores over the three timepoints (beginning, middle, and end of intervention), to determine whether either intervention affected depressive levels. The CESD was not significantly correlated with any demographic or disease variable. There was a significant group x time interaction ($F_{(2, 27)} = 4.4$, p = .02, partial etasquared = .24) for the CESD, with the healing group decreasing in depression over time compared to the mock group, who actually increased in depression over time. Interaction contrasts were suggestive of a quadratic difference between groups (p = .08, partial etasquared =.10), such that the healing group decreased in depressive scores from the middle to the end of the intervention, and the mock group increased in depressive scores from the middle to the end of the intervention. Expectation was not significantly related with CESD scores over time, and co-varying for expectation did not change results. These results are displayed graphically in Figure 5. Means and standard deviations may be found in Table 5a.

POMS-sf

Next, analyses were run to determine whether the intervention had any effects on total mood disturbance and specific mood subscales. Correlation analyses revealed that POMS-sf Total Mood Disturbance scores were significantly and robustly correlated with chemotherapy status ($r = .39$, $p = .013$), such that women who had previously had chemotherapy had higher mood disturbance. Thus, this variable was used as a covariate in the subsequent analyses.

There was a significant time effect for POMS-sf total mood disturbance, such that both groups showed a large decline in mood disturbance over time ($F_{(1.8, 45)} = 8.3$, $p = .001$, partial etasquared = .25). Expectation did not predict POMS-sf total scores over time, and co-varying for expectation did not alter results.

POMS-sf Subscales

Of the POMS-sf subscales, only the Confusion and Depression subscales were associated with chemotherapy status ($.35 > r > .43$; $p < .03$ in both cases). In addition, POMS Confusion was associated with cancer stage ($r = .34$, $p = .04$), and POMS depression was associated with cancer grade ($r = .44$, $p = .02$). These covariates were included in analyses of their respective subscales. No other subscales were associated with demographic or disease characteristics.

Results for POMS-sf subscales revealed significant time effects for the Anger, Tension, Depression, and Fatigue subscales ($p < .05$ in all cases). There was a trend for a time effect for the Confusion subscale ($p = .09$). Similar to the significant results with the CESD, there was a trend for a group x time interaction for Depression ($p = .11$, partial etasquared = .13), with the healing group decreasing in depression from mid-intervention to endpoint, and the mock group returning to their baseline scores of depression from

mid-intervention to endpoint. There was no effect for Vigor. Results for the time effect for the POMS-sf total score and the group x time trend for POMS-sf Depression subscale are depicted pictorially in Figures 6a and 6b. Means and standard deviations for the POMS-sf total scores are shown in Table 5b.

FACT-B

To determine whether the intervention had any impact on survivors' quality of life, a repeated-measures ANCOVA was run on FACT-B scores collected over three timepoints (beginning, middle, and end of intervention). FACT-B scores were significantly correlated with chemotherapy status ($r = -.36$, $p = .024$), such that women who had undergone chemotherapy reported lower quality of life. This variable was used as a covariate in subsequent FACT-B total score analyses.

There was a significant time effect for FACT-B total scores ($F_{(1.5, 45)} = 3.8$, $p = .04$, partial etasquared = .12), such that both groups increased in total ratings of quality of life over time. However, expectation itself was a significant predictor of FACT-B scores ($F_{(1.6, 41)} = 3.3$, $p = .04$, partial etasquared = .12), and inclusion of this variable as a covariate rendered the time effect non-significant ($p = .16$, partial etasquared = .07). There was unfortunately limited power to test a treatment guess x group interaction for this variable. Depiction of the expectation effects on FACT-B total scores may be found in Figure 7. Means and standard deviations for the FACT-B across mock and healing as well as across groups based on expectation may be found in Tables 5c and 5d.

FACT-B Subscales

None of the FACT-B subscales were significantly correlated with demographic or disease variables. However, given that total FACTB scores were largely influenced by

treatment expectation, analyses with FACT-B subscales were examined with expectation as a covariate. There were significant time effects for increased Physical and Functional well-being ($p < .001$ in both cases); these effects held when co-varying for expectation. There was a trend for time effects for Emotional well being ($p = .09$) which remained when co-varying for expectation. There was no effect on Social or Family Well-being.

PSQI

To determine whether the intervention had any effect on sleep quality, PSQI scores were examined before and after the intervention. PSQI scores were highly correlated with age ($r = .42$, $p = .007$), such that older women reported poorer sleep quality. Repeated-measures ANCOVA with age as a covariate revealed no significant effects of the intervention on PSQI scores over time. Means and standard deviations for this measure may be found in Table 5e.

Results for Cytokine Measures

As physiological data is often significantly skewed, distributions for cytokines were checked and log-transformed to correct for skew and better approximate a normal distribution as needed. Data were also examined for outliers; values that were above 3 SD and otherwise implausible given known ranges of values for a given marker were excluded from analyses. Baseline data was also examined across groups; there were no significant baseline differences between groups on any cytokine measure. Similar to the psychological outcome analyses, demographic or disease variables associated with any outcome variable at $|r| > .33$ and $p < .1$ were used as covariates, and analyses were re-examined using expectation as a covariate. Means and standard deviations for each

cytokine measured at pre-intervention (V1) and post-intervention (V9) can be found in Tables 6a-e.

sIL-1Ra

Data for sIL-1Ra were log-transformed to correct for significant positive skew and analyses were run with log-transformed sIL-1Ra data. BMI was significantly associated with baseline sIL-1Ra data ($r = .55$, $p < .0005$) and was included in the analysis. Repeated-measures ANCOVA with pretest and posttest sIL-1Ra values revealed a significant group x time interaction with a notable effect size ($F_{(1,17)} = $, $p = .048$, partial etasquared = .21). The interaction was characterized by an increase in sIL-1Ra for the mock group, and a slight decrease in IL1-Ra for the healing group. These results are depicted pictorially in Figure 8a. Inclusion of expectation as a covariate slightly increased the significance and magnitude of the group x time interaction ($p = .042$, partial etasquared = .23).

IL-6

There were two outliers for IL-6 data ($SD > 4$) with implausible values that appeared to be an artifact of sample contamination or assay error. These two outliers were excluded from analysis. Following exclusion of these outliers, data for IL-6 followed a normal distribution with no significant skew and therefore did not need to be log-transformed. Baseline IL-6 data was significantly correlated with age ($r = .48$, $p = .003$) and menopausal status ($r = -.37$, $p = .047$); these were entered as covariates in the analysis. Repeated-measures ANCOVA revealed a trend for a group x time interaction, again with a notable effect size ($F_{(1,17)} = 4.0$, $p = .06$, partial etasquared = .19). This interaction was characterized by a similar pattern as the one for IL1Ra; the mock group

increased over time, while the healing group decreased slightly. These results are depicted pictorially in Figure 8b. Inclusion of expectation as a covariate did not change results (p-value for interaction = .056, partial etasquared = .20).

sIL-6r

Data for sIL-6r followed a normal distribution with no significant skew and therefore did not need to be log-transformed. Baseline sIL-6r scores were significantly correlated with radiation status (r = -.38, p = .047) and menopausal status (r = .45, p = .01); these were entered as covariates in the model. Repeated-measures ANCOVA revealed a significant time effect of sIL-6r ($F_{(1,18)} = 10.6$, p = .02, partial etasquared = .32), with both groups decreasing over time. The healing group showed a greater decrease in sIL-6r compared to the mock group (partial etasquared = .07), although these results were not significant (p = .3). Including expectation as a covariate did not significantly alter results (p = .04, partial etasquared = .27). These results are depicted in Figure 8c.

IL-4

Data for IL-4 were log-transformed to correct for significant positive skew and analyses were run with log-transformed IL-4 data. Baseline IL-4 data were significantly associated with chemotherapy status (r = -.52, p = .003) and years of education (r = .51, p = .002); these were included as covariates. Repeated-measures ANCOVA revealed a borderline significant group x time interaction with a notable effect size ($F_{(1,15)} = 4.5$, p = .051, partial etasquared = .21). This interaction was characterized by a notable decrease in IL-4 for the healing group and a small increase in IL-4 for the mock group. These results are depicted pictorially in Figure 8d. Co-varying for expectation effects increased the significance and effect size of the interaction (p = .041, partial etasquared = .27).

TNF-RII

There was one outlier for TNF-RII data (SD >4) that was excluded. Following exclusion of this outlier, data for TNF-RII approximated a normal distribution. BMI was significantly associated with baseline TNF-RII data ($r = .38$, $p = .027$) and was included in the analysis. Repeated-measures ANCOVA revealed no significant time or group by time effect ($p > .5$) for this measure. Including expectation as a covariate did not change results. These non-significant results are depicted in Figure 8e.

Results for Salivary Cortisol

Initial analyses of the salivary data revealed four outliers (SD > 3) that had implausible cortisol levels and were likely due to an artifact of data collection or assay analyses. These outliers were excluded from further analyses. As is often the case with cortisol data, raw salivary cortisol data were positively skewed; in keeping with previous study procedures (Bower et al., 2005; Sephton et al., 2000), data were thus log-transformed to approximate a normal distribution before performing calculations for slope, overall means, and AUCg indices.

In order to determine whether the intervention had any impact on diurnal variability of cortisol for the survivors in the study, analyses were first run with cortisol slope as the primary (Level-1) HLM outcome measure. These analyses were then followed up with HLM analyses examining AUCg and mean cortisol values separately as (Level-1) outcome measures, to see whether the intervention significantly affected overall cortisol levels during the day as well as slopes of change. Post-hoc analyses were conducted to explore what timepoints, if any, changes in cortisol levels may have occurred. Similar to previous analyses, demographic and disease variables that were

significantly correlated with the cortisol outcome measure were included as Level-2 covariates. In addition, expectation was entered as a Level-1, time-varying covariate, with treatment ratings associated with each timepoint (i.e., Visits 1, 5, and 9) entered into the model. For ease of visual presentation, repeated-measures ANOVA with cortisol slope, means, and AUCg levels over visits (averaged over days 1 and 2 for each visit) are presented in Figures 9a-c.

Cortisol Slope

Cortisol slope was significantly associated with HER-2 status ($r = -.56$, $p = .005$), such that women with positive HER-2 status had less negative (i.e., flatter) slopes. HER-2 status was entered as a covariate into the subsequent analyses. Results revealed a significant group x time interaction for cortisol slope, such that the healing group slope was more negative over time than the mock healing group ($G_{11} = -.03$, $p = .016$); this overall effect is depicted in Figure 9a. Further, the chi-square value for the variance component of this model suggested a good model fit (chi-square = 17.88, $p = .33$) such that adding more predictors was unnecessary to sufficiently explain the variance of the data. Nevertheless, expectation effects were added to the model as a Level-1 time-varying covariate. Adding this variable did not change results.

Cortisol Means

Time since diagnosis was significantly associated with mean cortisol levels ($r = .34$, $p = .09$) such that women further out from diagnosis had higher mean cortisol levels over the day. This variable was entered as a covariate into the subsequent analyses. Results revealed a significant group x time interaction for mean cortisol, such that the healing group showed decreased mean cortisol over time compared to the mock group

(G_{11} = -.009, p = .027); this overall effect is depicted in Figure 9b. However, the chi-square value for the variance component of this model suggested that more predictors could be added to better explain the variance of the model (chi-square = 71.71, p < .0005). When expectation effects were added to the model as a Level-1 time-varying covariate, the group x time interaction remained significant, and expectation did not predict outcomes.

Cortisol AUCg

Similar to the cortisol mean data, AUCg levels were significantly associated with time since diagnosis (r = .43, p = .037), such that women further out from diagnosis had higher AUCgs. This variable was entered as a covariate into the subsequent analyses. There was a trend for significant group x time effects for AUCg outcomes (G_{11} = -.005, p = .10); this overall effect is depicted in Figure 9c. Similarly to the findings for mean cortisol, participants in the healing group had decreased AUCg over time compared to the mock group. Entering expectation as a time-varying covariate did not alter results, and expectation was not a significant predictor. The chi-square value for the variance component of this model suggested a poor model fit (chi-square = 56.88, p < .0005) suggesting that other predictors could be used to further explain the variance associated with this model.

Thus, results for the cortisol data indicated that women in the healing group showed increased variability of cortisol over time, while also showing apparent decreases in overall cortisol levels over time. In order to better determine whether there were certain timepoints in which the women in the healing group showed decreases in cortisol that would increase the variability, post-hoc, exploratory repeated-measures ANOVA

with raw cortisol values over the intervention were run for each timepoint (i.e., ANOVAs were conducted separately for rising, 12pm, 5pm, and 9pm timepoints, with time of intervention (pre and post) as the within-subjects factor, and group as the between-subjects factor). While not statistically significant, these exploratory analyses suggested that the differences between groups were chiefly in rising cortisol levels ($p = .17$, partial etasquared = .09) and potentially in 5pm cortisol levels ($p = .29$, partial etasquared = .05), with the healing group showing decreases in cortisol levels at these timepoints compared to the mock group at post-intervention.

Examining Associations between Psychological and Physiological Changes

Change scores for MFSI-sf, CESD, FACT-B, PSQI, and POMS questionnaires were examined for possible associations with change scores for immune markers sIL-1Ra, IL-6, sIL-6r, IL-4, and TNF-RII. There were no significant correlations between psychological variables and cytokine data. Correlation analyses for cortisol indices (slope, AUCg, and means) with psychological measures indicated that intervention changes in cortisol AUCg were significantly associated with change scores for the CESD ($r = .49$, $p = .028$) and notably associated with MFSI-sf change scores ($r = .44$, $p = .058$). There were no other significant or notable associations with cortisol indices and psychological variables. When examining correlations between cortisol and cytokine variables, analyses revealed a significant positive association between change scores for mean cortisol and changes in IL-4 ($r = .49$, $p = .03$).

Given the significant correlations for change scores found between the cortisol, cytokine, and psychological variables, despite the modest sample size in the two treatment groups, it was of interest to determine whether any of these correlations were

specific to changes in the healing vs. the mock healing group. None of the significant associations between change scores found for the entire sample held for the subgroups.

Chapter 4

Discussion

This randomized controlled trial aimed to examine whether biofield healing, compared to mock healing, was an effective intervention for the treatment of fatigue, depression, and quality of life in breast cancer survivors. The study also aimed to examine whether biofield healing demonstrated any unique effects on hormonal, inflammatory and anti-inflammatory biomarkers associated with fatigue. The mock healing group was chosen as an active comparison group to control for expectation as well as other non-specific effects. For example, it could be argued that any positive effects thus far found in the literature for biofield healing for fatigue and other ailments in cancer patients (Olson et al., 2003; Roscoe, Matteson et al., 2005; Tsang et al., 2007) could be more due to non-specific effects such as expectation (i.e., thoughts that one is receiving healing) relaxation (i.e., from taking scheduled time to lie down and rest quietly), or social support (e.g., pleasant verbal exchanges and feelings of connection with practitioner and other staff members). Certainly all of these factors have been shown to be effective within or compared to different psychotherapy approaches (Buckley, Pettit, & Adams, 2007; Wampold, Minami, Tierney, Baskin, & Bhati, 2005), and may be powerful aspects of a therapeutic intervention in their own right. The mock group was selected as an "active control" group to help test whether any positive effects due to biofield healing may be more due to these non-specific factors as opposed to something unique about the process of biofield healing.

Psychological Data

Results for psychological data indicate that biofield healing may show promise over and above non-specific effects for fatigue and depression, but there was no evidence for unique effects of biofield healing with respect to total mood disturbance or quality of life. In this study, both the mock healing and the healing group showed notable reductions in total mood disturbance throughout the intervention. These reductions were characterized by reductions in tension, anxiety, and fatigue subscales. Both groups also showed increases in overall quality of life during the intervention; however, these changes were better explained by expectation of receiving healing, rather than by the interventions themselves. Sleep quality did not appear to be impacted by either intervention.

Analyses indicate that the mock group as well as the healing group showed decreases in overall fatigue as measured by total scores of the MFSI-sf. However, the magnitude of the differences between the two groups was notable and clinically significant: by the end of the intervention, the healing group decreased in overall fatigue well-below the standard clinical cutoff score of 16, while the mock group stayed just at the clinical cutoff score for fatigue. The largest decrease for fatigue was found at V7 for the healing group, where the mean score was 4.1. By the end of the intervention, the mean MFSI-sf score for the healing group was 9.5. In contrast, the lowest mean score for the mock group (also found at V7) was 15.75, where it remained for the end of the intervention. Thus, while the difference between the groups on total MFSI-sf scores did not reach the $p = .05$ level of significance ($p = .085$ for the group x time interaction), the relative effect size of the healing group decrease compared to that of the mock group, as well as the clinical significance of the decrease in the healing group, suggests that

biofield healing may be more effective than mock treatment for overall fatigue. This clinically significant reduction in fatigue for the healing vs. mock group holds regardless of the inclusion or exclusion of time since radiation as a covariate for MFSI-sf analyses, although the group x time interaction for the MFSI-sf with the larger sample (without the covariate) is not significant.

In examining the MFSI-sf subscales, the differences between the groups seemed to lie chiefly in the General Fatigue subscale, as well as the Vigor subscale, with the healing group showing decreased general fatigue as well as a trend for increased vigor. Both groups were similar on the other subscales. General fatigue subscale items include statements such as "I feel pooped", "I feel fatigued", and "I feel run down"; Vigor subscale items include statements such as "I feel lively", "I feel refreshed", and "I feel energetic". Interestingly, the General Fatigue subscale for the MFSI-sf has been shown in validation studies to have the highest internal consistency of all subscales (alpha = .096). In addition, the General fatigue subscale has the highest concurrent validity (as indexed by its correlation with other established fatigue measures such as the Fatigue Symptom Inventory), as compared to all subscales *and* the MFSI-sf total score (the correlation for the MFSI-sf General fatigue with the FSI was .82, compared with .74 for MFSI-sf total, which had the next highest correlation) (Stein et al., 2004).

With respect to depression and depressed mood, there was a significant group x time interaction for depression for the CESD and a trend for a group x time interaction for POMS-sf Depression scores, both indicating that the healing group decreased in depressive symptoms over time compared to the mock group. Interestingly, both outcomes for depression indicated that decreases in depression occurred after mid-

intervention for the healing group, but not for the mock group. These findings suggest that biofield healing may uniquely reduce depression in fatigued breast cancer survivors (compared to mock treatment), and that temporally, the reductions in depression follow initial reductions in fatigue. It is worth noting that the decreases in CESD scores of depression for the healing group approached clinical significance (CESD scores at endpoint for the healing group were 16.8, close to the clinical cutoff score of 16 for depression). However, the reason for the apparent slight increase in CESD for the mock group is unclear.

Cytokine Data

Results for the cytokine and cytokine receptor data were intriguing and warrant further study. While several significant or borderline group x time interactions appeared, independent of expectation effects, the directionality of some effects suggests the need for further research. For example, the group x time interactions for IL1Ra and IL-6 are similar in nature, with the mock group increasing in these biomarkers over time, and the healing group showing relatively little change. While the maintenance or slight decrease in these markers for the healing group could be seen as a beneficial effect of the intervention (i.e., as a maintenance or slight decrease in inflammatory markers shown specifically to be related to fatigue in breast cancer survivors), it is unclear why the mock group showed such increases in these markers over the one-month intervention period. Given these curious results, cytokine data was double-checked very carefully for potential outliers that could be unduly influencing the data; however, no such outliers were found. In addition, the parallel findings for these markers, which are relatively closely related in terms of the temporality of the cytokine cascade (e.g., secretion of IL-6

instigates IL-1Ra production (Arend et al., 1998)), suggest that these findings are not spurious.

There are several ways in which future studies could help clarify these findings. One obvious solution to help clarify potential mock versus healing group effects would be to include a no-treatment control group to determine whether increases in these markers would generally be found over time in this population (as there is little to no literature describing the patterns of cytokine secretion for this population over short durations of time). Also, examining related markers (such as the pro-inflammatory cytokines IL-1 and interferon-gamma (IFN-γ)) would help to clarify whether the increases found for the mock group in IL1-Ra and IL-6 are in fact responses to increases in pro-inflammatory cytokine activity, or perhaps more due to a relative decrease in anti-inflammatory activity. Unfortunately, human IL-1 and IFN-γ have notoriously poor detection limits in peripheral circulation.

Findings for this study indicated that both groups showed significant decreases in sIL-6r over the course of the intervention. This finding appears important and may show clinical relevance for a few reasons. First, sIL-6r has been found in the literature to be one of the most robust markers of fatigue in breast cancer survivors (Collado-Hidalgo et al., 2006). Although changes in sIL-6r were not significantly correlated with MFSI-sf change scores in our small sample, they were related ($r = .20$). Second, the majority of IL-6's effects depend on its binding with sIL-6r, particularly its effects with relevance to cancer (Kallen, 2002; Scheller et al., 2006). Thus, a decrease in sIL-6r could hinder any potential global pro-inflammatory effects of IL-6.

In terms of better understanding the pattern of findings for IL-6 and sIL-6r for both groups, the use of flow cytometric and *in vitro* methods would be advantageous for clarifying the nature and pattern of secretion for these markers. For example, one could determine whether the relative decrease in sIL-6r is due to increased expression or downregulation of the IL-6 receptor on certain immune cell subtypes (such as on T-lymphocytes or macrophages). *In vitro* experiments with cell stimulation could be conducted to help determine whether decreased circulating sIL-6r is due to decreased shedding of the receptor by a cell type in response to a specific antigen (such as by pro-inflammatory cytokines) or nonspecific stimulation (such as by lipopolysaccharide). Finally, examination of levels of the IL6/sIL-6 complex itself could be derived from ELISA analysis and would give a better indication of the effects of the intervention on IL-6 with respect to its global functionality (Rose-John et al., 2006).

Another interesting finding was the group x time interaction for IL-4, characterized by a decrease in IL-4 for the healing group and a slight increase for the mock group. Interestingly, decreases in intracellular production of IL-4 were recently reported in a 1-year follow-up study of mindfulness meditation for breast and prostrate cancer patients (Carlson, Speca, Faris, & Patel, 2007), although no speculation was given regarding the potential clinical meaning of these results. There is little in the literature discussing IL-4 in the context of cancer survivorship and psychological functioning, as most investigators have chosen to focus on pro-inflammatory cytokines as they relate to fatigue and depression in breast cancer survivors. However, given the repeated findings of increased IL-4 in chronic fatigue patients vs. non-fatigued controls, this result may indicate that biofield healing is uniquely associated with reductions in an anti-

inflammatory cytokine found to be associated with fatigue. Moreover, the significant correlation of IL-4 change scores with change scores in mean cortisol levels found in this study suggests that the reduction in IL-4 found for the healing group may be explained in part by the reduction in the mean cortisol levels over time for the healing group (i.e., it is possible that the reductions in cortisol served to reduce anti-inflammatory activity by decreasing inhibition of pro-inflammatory activity). However, given the limited ability to examine the association of IL-4 and cortisol change scores in the healing group, this preliminary conclusion would need to be fortified with additional data that would replicate the results found here more robustly, as well as provide more information on circulating cell subsets and temporality of changes for cortisol and IL-4.

Finally, no changes were found for TNF-RII for either group during the intervention. While TNF-RII was initially found to be associated with fatigue in a sample of breast cancer survivors (Bower, 2002), subsequent studies examining this marker did not confirm its correlations with fatigue in breast cancer patients (Bower, 2007). Although TNF-RII appears to be a highly relevant marker in terms of cancer disease progression (Garcia-Tunon et al., 2006; Perik, Van der Graaf et al., 2006)); to date, no other studies have linked TNF-RII to depression or fatigue in cancer patients. Therefore, it is possible that TNF-RII may not have been as sensitive a marker for intervention changes in this context.

In summary, the cytokine and cytokine receptor data generally suggest a differential effect for the healing vs. mock healing group on fatigue-related biomarkers through the intervention, with the healing group showing more of an overall decrease in cytokine activity associated with fatigue, and the mock group (excepting for the findings

of sIL-6r) showing a relative increase in pro-inflammatory cytokine activity and relatively no change in anti-inflammatory cytokine activity. However, these results must be replicated with larger sample sizes and additional immune data before any firm conclusions could be made as to their clinical relevance.

Cortisol Data

The increase in cortisol variability for the healing vs. mock group (as reflected by the group x time interaction for cortisol slope, with the slope being more negative for the healing group) suggests that, compared to the mock group, biofield healing uniquely increased circadian rhythm variability of cortisol. These results are supported by the significant finding of reduced overall mean cortisol for the healing vs. mock group over time as well as the trend for reduced AUCg for the healing vs. mock group over time. However, the lack of finding significant differences for cortisol levels at specific timepoints between the groups via post-hoc testing suggests the need for replication of these data with larger sample sizes. The notable correlations of AUCg change scores with depression and fatigue change scores suggests that, within the context of this study, changes in cortisol levels may be more sensitive biological reflectors of changes in fatigue and depression than changes in the cytokines examined. Given previous research demonstrating the relative lack of variability for fatigued breast cancer survivors and the relations of this decreased variability to increased depression and poorer prognosis (Bower et al., 2005; Sephton et al., 2000), the finding of increased cortisol variability as a result of receiving the healing intervention is an important clinical finding and should be examined more closely in replication studies.

The search for "mechanism"

The study's significant findings with respect to both psychological and physiological outcomes may bring forth the question of what the underlying mechanism(s) may be that enable biofield healing to bring forth such effects in the different systems within the mind-body. Skeptics of biofield therapies generally speculate that any positive findings reported within the literature are due to poor methodology, or at best, a placebo effect (Ernst, 2007). However, results here suggest that findings are not solely due to non-specific factors such as expectation, relaxation, or social support. The question remains: if biofield therapies are indeed more effective than their non-specific counterparts, why?

The answer to this question would be provided differently depending on the perspectives of the inquirer. For example, a perspective more influenced by a reductionist viewpoint (as is generally adopted in western-based third-person scientific inquiry) would likely search for the most parsimonious, mechanistic explanation for the phenomenon, and therefore would shun the idea that "subtle biofield energy" plays a role in the outcomes reported in this and other clinical studies. Given that the actual purported "energy" component of biofield therapies is supposedly non-physical by nature, its existence cannot be directly verified, only inferred. Unfortunately, methods for measuring these putative energy fields are still in their relative infancy. While reliability for some of these methods (e.g., the Gaseous Discharge Voltometer (GDV) and Super-conducting Quantum Interference Device (SQUID)) have been established, they are difficult to obtain, require very strict experimental conditions for accurate measurement, and have not been established in terms of clinical validity. Thus, at this point, reliance on instruments designed to measure physical aspects of putative subtle

energy processes, while certainly valuable, is not sufficient to explain the potential clinical benefits of receiving biofield healing.

An inquirer with a more reductionist-based approach would therefore search for other non-subtle energy focused explanations to explain the effects found in this study. Such an explanation could be, for example, that the combination of some unknown physical or psychological factor that was unique to the biofield healing group, combined with the non-specific effects of relaxation, expectation and social support, provided the patient with a sense of subjective relief from fatigue and depression symptoms. Any physiological changes could be posited to have resulted in part from "top-down" (i.e., cortical-hormonal-immune) processes related to the cognitive components of reductions in fatigue and depression, as well as from the physical rest/relaxation incorporated in both treatment arms (i.e., from 1 hour of lying down quietly twice a week).

However, a biofield-based practitioner's view and explanation of the phenomena and outcomes reported in this study would be quite different from a reductionist approach. Biofield theories often discuss the healing experience in "psycho-energetic" terms. In such theories, detailed explanations are given about putative layers of energy fields, and the resulting problems that may occur if different layers are impacted by psychological and/or physical events. More specifically, for example, fatigue and related symptomatology is viewed by consultants and practitioners in our study as partially being a result both of toxicity buildup from treatment as well as stagnation and depletion of vital energy, often found in the first layer of the energetic field (Bruyere, 1989). This is similar to explanations found in other CAM modalities, such as Traditional Chinese Medicine. However, biofield practitioners also assert that specific cancer treatments

impact certain layers of the field differently (e.g., radiation treatment is thought to disrupt the structure of a certain layer of the energy field, which would enable further energy depletion as this is considered a "protective" layer of the field that shields from environmental toxicities and holds the integrity of the biofield itself (Brennan, 1988)). Moreover, some psychological experiences (such as anger and depression) are thought to be related to the physical experience of breast cancer, and are also related to dysfunction in certain layers of the energy field. During initial assessment, the biofield practitioner may become aware of aspects of physical and psychological maladies that accompany the main complaint (in this case, fatigue) of the patient. Thus, treatment (in a real-world context) would be focused not only on allowing universal energy flow to transmit through the practitioner to the client, but may also include directive efforts to "correct" or "repair" certain layers of the energy field that were damaged, and/or bring to awareness certain psychological issues that appear to be associated with the chief complaint (with the intention of helping the patient let go of energetic concomitants of maladaptive psychological patterns that enable the disease process to continue).

In this study, biofield practitioners focused solely on the technique of energy chelation for treatment (with the purpose being to stimulate vital energy and help remove putative toxicities from prior cancer treatment). Practitioners did not engage in any verbal exchanges with patients, or other non-verbal practices that deviated from this basic technique. However, the basic biofield theoretical model put forth above would still be the one used to explain the effects of the intervention.

In better understanding the assessment process that occurs in biofield-based modalities such as the one studied here, one is still left with the question of "mechanism".

In this case, the concept of "mechanism" would not apply, as the nature of the term suggests that the overall phenomena could be reduced to a set of, at best, bi-directional associations that do not evolve over time. Theories such as those put forth by biofield and other integrative medicine practitioners imply that the mind and body do not simply *interact*, they *transact*– meaning that they continually influence each other to create an evolving system that fluctuates over time. Thus, one cannot simply infer that during an intervention, one aspect of the organism (i.e, mind or body) is affected and then linearly affects another – but rather that the entire organismic whole (including aspects of mental, physical, psychological, social, and spiritual functioning) changes and evolves as a result of perturbation of the system (whether or not the intended purpose was to influence the entire system or simply one aspect of the system). Whilst such theories may be thought of as lofty or circumvented explanations that avoid the possibility of practical study of integrative medicine techniques, recent research suggests that in fact human physiology is better understood as a dynamic, nonlinear complex system, and that the understanding of diseases (such as cancer) may be better explained by adopting such complexity models in theories of etiology and treatment (Coffey, 1998).

However, theories such as these may present problems in terms of testing specific hypotheses related to clinical outcomes. For example, typical methods of data analysis rely on linear, parametric statistics to examine standard outcome variables such as self-report data and immune parameters. Holistically-oriented models such as the ones proposed by leading experts in integrative medicine research (Bell & Koithan, 2006) require complexity and non-linear approaches to data analysis that are often precluded by practicalities such as allowed sample sizes or outcome timepoints. Non-linear and

complexity-based approaches are possible to use (and have shown to be extremely useful for clinical prognosis) with ECG and EEG measures (Janjarasjitt, Scher, & Loparo, 2008; P. K. Stein, Domitrovich, Huikuri, & Kleiger, 2005); however, these types of measures allow for a multitude of sampling points. The potential application of nonlinear analysis and modeling approaches to the field of psychoneuroimmunology are just beginning to be explored (Hanson et al., 2001), and thus, it would be difficult at this point to test theories related to mechanism from a biofield theorist's point of view.

In summary, it is suggested that attempts to elucidate actual specific "mechanisms" for biofield therapies could be viewed as premature at best. Given the current dearth of research within biofield healing combined with the great need for patients such as fatigued survivors for interventions that alleviate their suffering and promote well-being, perhaps for now, the most important questions to be answered are less centered around theories of "mechanism" and more centered around the practicalities of patient care. If results from this study are replicated, it would indicate that biofield therapies are effective in reducing fatigue as well as depression in breast cancer survivors. Given the tolerability of the intervention and the low attrition rate, these results, if replicated, suggest that biofield interventions would be useful as complementary care for survivors who are experiencing fatigue after breast cancer treatment, and therefore should be better integrated into cancer care clinics. There is an increasing trend to include such therapies in comprehensive care models for cancer, including in San Diego (Sharp Hospital, 2007). However, further clinical studies need to be conducted with biofield therapies in this population to better determine effects and impacts on hormonal and immune functioning, as well as help determine adequate

tolerability and dosage for women at different stages of the breast cancer treatment process.

Study Limitations

There are several limitations to this study. Perhaps the most salient limitation is the relative lack of power in determining interaction effects, particularly for the MFSI-sf. While the lack of power may be attributed to reduced sample size (*a priori* power analyses with a small computed effect size estimated a needed sample size of 40 participants), it also appears to be due to large variability of responses within the sample for the MFSI-sf (standard deviations for MFSI-sf means at all timepoints ranged from 12 to 23, regardless of the value of the means). This variability of responses is likely due to the heterogeneity of the sample in terms of treatment modalities as well as time since treatment(s). Given that the effect size for the MFSI-sf is larger than anticipated but the standard deviations are also higher than anticipated, the reduced power for these analyses appear to be more a function of high variability of responses for the measure and less a function of small effect size/smaller sample size. Future studies that choose to utilize the MFSI-sf as an outcome measure may choose to either screen more stringently for baseline fatigue (e.g., perhaps by utilizing clinical cutoff scores of 16 on the MFSI-sf itself), or create a more homogenous sample (e.g., by only studying women who have had radiation treatment within one year).

The modest sample size for this study is reflective of the difficulties in recruiting breast cancer survivors for clinical trials at UC San Diego, and is still certainly a limitation of the study. Survivors were recruited and enrolled for the study over an 18-month period; thus, the current sample size reflects an average enrollment rate of about 2

patients per month. While several different approaches were attempted to recruit survivors, the most effective methods appeared to be disseminating information about the study via media and direct mailings. The difficulties in recruiting survivors for this study could be due to a wariness of survivors to engage in clinical trials research, but is also likely due to a lack of dissemination of information about the clinical trials available for the treatment of fatigue symptomatology after breast cancer treatment. With respect to wariness of engaging in this particular trial, no survivors who inquired about the study chose not to participate due to the nature of the biofield intervention. However, several survivors refused to participate when finding out that routine blood draws would be a part of the intervention process. While the majority of inquirers expressed no discomfort about providing blood samples, it is important to note that the sample was self-selected not only in terms of being relatively enthusiastic about complementary medicine, but also in terms of comfort level with being in clinical hospital settings and receiving blood draws.

As suggested earlier, the inclusion of a heterogeneous sample of fatigued breast cancer survivors in terms of previous duration of survivorship and type of treatment (i.e., surgery, chemotherapy, and/or radiation) could be viewed as a possible limitation. However, given the preliminary nature of the study, it seemed important to include fatigued survivors regardless of treatment history, in order to determine whether biofield healing demonstrated significant effects for reducing fatigue and other related variables in a more representative sample of fatigued survivors. Still, the heterogeneity of the sample combined with the relatively small sample size limited the power for analyses and

completely disallowed the ability to test for potentially interesting three-way interaction effects (such as treatment guess x group x time effects).

In terms of physiological data collection, one limitation of the study was the inclusion of only pre-intervention and post-intervention indices of cytokine and cytokine receptor data, and the relatively small sample size even when only including these two timepoints. Because intent-to-treat analyses would not be valid for cytokine data analyses, sample size was slightly truncated compared to that for psychological data. In addition, although most women agreed to continue with blood draws while enrolled in the study, several participants had trouble actually giving the blood (i.e., the nurses were unable to obtain blood samples due to lack of blood flow to the catheter), and several planned timepoints for blood collection were either missing or invalid as a result. It could be argued that this lack of blood flow might have been attributed to anxiety about the draws that was not explicitly expressed by the participant. If this were the case, it could certainly affect plasma cytokine levels, although it is unclear whether such acute stress would have differentially affected women in the two groups. Regardless, the lack of additional timepoints for the analysis of cytokine data could be viewed as a limitation.

Finally, some may view the rather narrow focus of the design (i.e., placebo-controlled RCT) as a limitation, as the study of biofield healing in this context does not truly approximate the practice of biofield healing in actual real-world settings. Not approximating the real-life context of the intervention delivery as well as the phenomenological experiences of the client and the practitioner may prevent the researcher from obtaining useful data that could help to explain any positive outcomes reported as a result of receiving biofield-based interventions. However, given the large

variability of modalities and techniques practiced within the field of biofield therapies, at this point, effectiveness-oriented studies would prove difficult in helping determine whether specific practices within biofield-based healing approaches (i.e., energy chelation) are in fact useful for relieving a particular symptom for a population (i.e., fatigue in breast cancer survivors). Thus, due to the reductionist nature of the hypotheses that were to be tested, an efficacy study was more appropriate than an effectiveness study in this case. However, it should be noted that the lack of inclusion of qualitative data in this study is a definite limitation, as it reduces the opportunity to better understand first-person experiences of receiving biofield healing sessions vs. mock healing sessions.

Study Strengths

Despite the limitations noted above, there are several strengths to this study. First, to the author's knowledge, it was the first study of its kind to examine the effects of biofield healing vs. an active placebo-control on fatigue-related cytokine activity and cortisol rhythms as well as on self-report data. While the physiological data is certainly preliminary and would need to be confirmed by additional studies, the significant findings for the cytokine and cortisol data suggest that the effects of biofield interventions are not necessarily limited to psychological outcome domains, and may in fact have important and clinically significant impact on biological systems associated with psychological functioning.

The assessment of and inclusion of expectation effects as a covariate in the study was a definite strength and provided information that, except for the FACT-B data, significant findings could not be explained simply by the expectation of receiving healing. Moreover, the randomized, placebo-controlled nature of the study also helped to

provide stronger evidence that any significant findings for the biofield vs. mock healing group could not be attributed solely to non-specific effects such as relaxation or expectation. Finally, an aspect of the study that could be distinguished as a strength was the relatively low attrition rate (12% total, with 6% of those having dropped after receiving sessions). This is especially notable given the cited 1/3 attrition rate for behavioral medicine interventions in general (Davis & Addis, 1999; Lengacher et al., 2002) and the 15+% attrition rate often reported for lifestyle interventions for breast cancer survivors (Stull, Snyder, & Demark-Wahnefried, 2007). Feedback from the participants in this trial, regardless of group assignment, was overwhelmingly positive.

In summary, findings from this study suggest that biofield healing is associated with unique and beneficial effects for reducing depression, reducing cytokine activity, and increasing cortisol variability and decreasing overall cortisol levels, over and above non-specific effects associated with a placebo-based control (mock healing). In contrast, non-specific effects of biofield healing may contribute to reductions in total mood disturbance, and expectation of receiving healing may better explain increases in quality of life than other specific or non-specific aspects of biofield healing. Importantly, findings also suggest that while non-specific effects may contribute to the reduction of overall fatigue as a result of participation in biofield healing, there may be a unique process to biofield healing that affords greater and clinically significant reductions in fatigue. Finally, neither specific nor non-specific effects associated with biofield healing appear to have any influence on sleep quality, a complaint often associated with fatigue in breast cancer survivors. Further research investigating the psychological and

physiological impact of biofield therapies for fatigued breast cancers is warranted to confirm and extend these preliminary findings

Table 1.

List of Recruitment Strategies and Relative Successes.

RECRUITMENT STRATEGY	Number of Inquiries
Television appearance and link to website	12
Brochures mailed by UCSD Moores Cancer Center	11
Word-of Mouth through study participant	10
Brochure found in patient's cancer center	10
Website links (excluding television links)	6
Listserv advertisement	3
Presentation at Breast Cancer Support Group	3
Non-UCSD Breast Cancer Support Group	3
Referral from UCSD Staff Member	2
Referral from Social Worker	2
Oncologist or Oncology Nursing Referral	0
Unknown	5

Table 2.
Assessment of baseline equivalence between groups.

Demographic/Disease Variable	MOCK	HEALING	P-value
Mean Years Age	53.8	52.2	0.69
Mean Years Edu	15.9	16.3	0.59
BMI	29.4	26.9	0.21
# Premenopausal	2	2	0.79 (chi-square)
# Postmenopausal	12	16	See above
# Menopausal due to Chemotherapy	6	9	0.74
# Stage 0 / DCIS	2	1	0.92 (chi-square)
# Stage I	6	7	See above
# Stage II	4	5	See above
# Stage IIIa	3	3	See above
Time Since Diagnosis (months)	20	33	0.07
Time since Surgery (months)	16	28	0.12
# Received Radiation	9	11	0.80
Time since Radiation (months)	12.2	23	0.20
# Received Chemotherapy	9	14	0.27
Time since Chemotherapy (months)	13.2	29	0.08
Estrogen Receptor (ER) positive	8	12	.78
Human epidermal growth factor receptor 2 (HER-2) positive	2	4	.58

Table 3a.
Multidimensional Fatigue Symptom Inventory Total Score Means and Standard Deviations with covariate.

Timepoint*	Group	Mean	Std. Deviation	N
MFSIsf_Total_V1 (Pretest)	Mock Group	27.13	19.119	8
	Healing Group	25.30	21.056	10
MFSIsf_Total_V3	Mock Group	14.00	19.719	8
	Healing Group	12.50	12.972	10
MFSIsf_Total_V5	Mock Group	11.88	21.384	8
	Healing Group	6.00	18.809	10
MFSIsf_Total_V7	Mock Group	15.75	20.872	8
	Healing Group	4.10	19.232	10
MFSIsf_Total_V9 (Posttest)	Mock Group	15.75	23.729	8
	Healing Group	9.50	23.590	10

Table 3b.
Multidimensional Fatigue Symptom Inventory Total Score Means and Standard Deviations without covariate.

Timepoint*	Group	Mean	Std. Deviation	N
MFSIsf_Total_V1 (Pretest)	Mock Group	32.54	17.652	13
	Healing Group	25.27	17.746	15
MFSIsf_Total_V3	Mock Group	22.15	19.697	13
	Healing Group	13.07	12.770	15
MFSIsf_Total_V5	Mock Group	22.23	21.883	13
	Healing Group	7.67	17.871	15
MFSIsf_Total_V7	Mock Group	17.77	16.574	13
	Healing Group	5.27	17.148	15
MFSIsf_Total_V9 (Posttest)	Mock Group	21.69	23.318	13
	Healing Group	8.20	21.217	15

*Timepoints are as follows: V1 = Pretest (before intervention), V3 = Visit 3 (after 2 sessions), V5 = Visit 5 (after 4 sessions), V7 = Visit 7 (after 6 sessions), V9 = Posttest (end of intervention, after 8 sessions).

Table 4a.
Multidimensional Fatigue Symptom Inventory General Fatigue Means and Standard Deviations.

Timepoint	Group	Mean	Std. Deviation	N
MFSIsf_General_V1 (Pretest)	Mock Group	16.43	6.756	14
	Healing Group	15.60	4.339	15
MFSIsf_General_V3	Mock Group	13.07	7.529	14
	Healing Group	10.20	5.931	15
MFSIsf_General_V5	Mock Group	13.86	7.705	14
	Healing Group	7.60	6.401	15
MFSIsf_General_V7	Mock Group	12.86	6.735	14
	Healing Group	6.47	5.630	15
MFSIsf_General_V9 (Posttest)	Mock Group	14.00	7.923	14
	Healing Group	7.40	6.288	15

Table 4b.
Multidimensional Fatigue Symptom Inventory Vigor Means and Standard Deviations.

Timepoint	Group	Mean	Std. Deviation	N
MFSIsf_Vigor_V1 (Pretest)	Mock Group	10.50	3.937	6
	Healing Group	8.29	4.348	7
MFSIsf_Vigor_V3	Mock Group	11.67	3.266	6
	Healing Group	9.86	3.338	7
MFSIsf_Vigor_V5	Mock Group	11.50	4.087	6
	Healing Group	13.29	6.102	7
MFSIsf_Vigor_V7	Mock Group	11.17	4.355	6
	Healing Group	13.29	5.024	7
MFSIsf_Vigor_V9 (Posttest)	Mock Group	10.83	5.345	6
	Healing Group	13.00	6.608	7

Table 4c.
Multidimensional Fatigue Symptom Inventory Physical Fatigue Means and Standard Deviations.

Timepoint	Group	Mean	Std. Deviation	N
MFSIsf_Physical_V1 (Pretest)	Mock Group	8.86	5.545	14
	Healing Group	6.20	3.821	15
MFSIsf_Physical_V3	Mock Group	6.64	5.017	14
	Healing Group	4.00	3.207	15
MFSIsf_Physical_V5	Mock Group	6.86	5.842	14
	Healing Group	3.80	3.075	15
MFSIsf_Physical_V7	Mock Group	5.64	5.063	14
	Healing Group	3.00	3.207	15
MFSIsf_Physical_V9 (Posttest)	Mock Group	6.14	6.550	14
	Healing Group	3.60	3.661	15

Table 4d.
Multidimensional Fatigue Symptom Inventory Emotional Fatigue Means and Standard Deviations.

Timepoint	Group	Mean	Std. Deviation	N
MFSIsf_Emotional_V1 (Pretest)	Mock Group	5.44	3.321	9
	Healing Group	6.00	5.292	12
MFSIsf_Emotional_V3	Mock Group	3.78	4.024	9
	Healing Group	3.50	2.611	12
MFSIsf_Emotional_V5	Mock Group	3.56	3.395	9
	Healing Group	3.00	3.766	12
MFSIsf_Emotional_V7	Mock Group	3.33	3.969	9
	Healing Group	3.08	3.232	12
MFSIsf_Emotional_V9 (Posttest)	Mock Group	4.67	3.905	9
	Healing Group	3.17	3.639	12

Table 4e.
Multidimensional Fatigue Symptom Inventory Mental Fatigue Means and Standard Deviations.

Timepoint	Group	Mean	Std. Deviation	N
MFSIsf_Mental_V1 (Pretest)	Mock Group	9.30	5.926	10
	Healing Group	7.92	5.408	13
MFSIsf_Mental_V3	Mock Group	8.20	5.432	10
	Healing Group	5.69	4.479	13
MFSIsf_Mental_V5	Mock Group	7.90	5.877	10
	Healing Group	4.77	5.776	13
MFSIsf_Mental_V7	Mock Group	5.70	4.244	10
	Healing Group	4.31	5.360	13
MFSIsf_Mental_V9 (Posttest)	Mock Group	6.70	5.334	10
	Healing Group	5.00	6.028	13

Table 5a. ***Center for Epidemiological Studies Depression Scale Means and Standard Deviations.***

Timepoint	Group	Mean	Std. Deviation	N
CESD_TotalScore_V1 (Pretest)	Mock Group	18.85	7.658	13
	Healing Group	18.76	11.519	17
CESD_TotalScore_V6	Mock Group	17.77	10.513	13
	Healing Group	18.37	10.287	30
CESD_TotalScore_V9 (Posttest)	Mock Group	19.54	10.990	13
	Healing Group	16.82	11.221	17

Table 5b. ***Profile of Mood States Total Means and Standard Deviations.***

Timepoint	Group	Mean	Std. Deviation	N
POMS_sfTotal_V1	Mock Group	24.21	19.893	14
(Pretest)	Healing Group	26.36	20.802	14
POMS_sfTotal_V6	Mock Group	9.00	15.059	14
	Healing Group	6.64	16.832	14
POMS_sfTotal_V9	Mock Group	6.36	18.215	14
(Posttest)	Healing Group	-1.64	12.087	14

Table 5c. ***Functional Assessment of Cancer Therapy-Breast Total Means and Standard Deviations.***

Timepoint	Group	Mean	Std. Deviation	N
V1 FACTb total	Mock Group	101.1275	17.86744	14
(Pretest)	Healing Group	102.8512	17.20213	18
V6 FACTb total	Mock Group	106.5955	17.49429	14
	Healing Group	111.6667	18.10102	18
V9 FACTb total	Mock Group	107.3524	22.81344	14
(Posttest)	Healing Group	113.9650	17.24211	18

Table 5d. F*unctional Assessment of Cancer Therapy-Breast Total Means and Standard Deviations based on expectation.*

Timepoint	Expectation	Mean	Std. Deviation	N
V1 FACTb total	Guessed Healing	101.1994	16.98314	23
(Pretest)	Guessed Touch	104.7886	21.54779	7
V6 FACTb all sub	Guessed Healing	110.6233	17.59647	23
	Guessed Touch	107.4286	21.57821	7
V9 FACTb all sub	Guessed Healing	113.7958	18.30369	23
(Posttest)	Guessed Touch	104.4286	26.39986	7

Table 5e.
Pittsburgh Sleep Quality Inventory Total Means and Standard Deviations.

Timepoint	Group	Mean	Std. Deviation	N
V1PSQI	Mock Group	87.9415	15.48573	13
(Pretest)	Healing Group	90.2647	24.55813	15
V9PSQI	Mock Group	80.4662	22.38709	13
(Posttest)	Healing Group	84.7633	26.61119	15

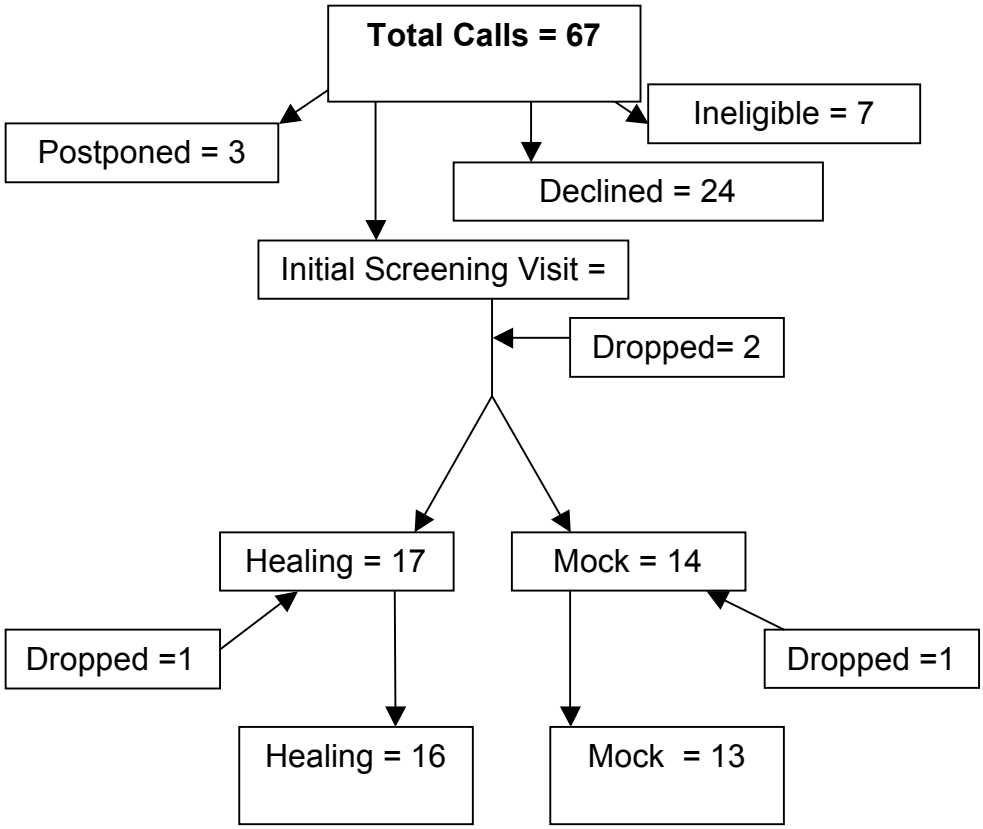

Figure 1. Flow Chart of Recruitment and Enrollment.

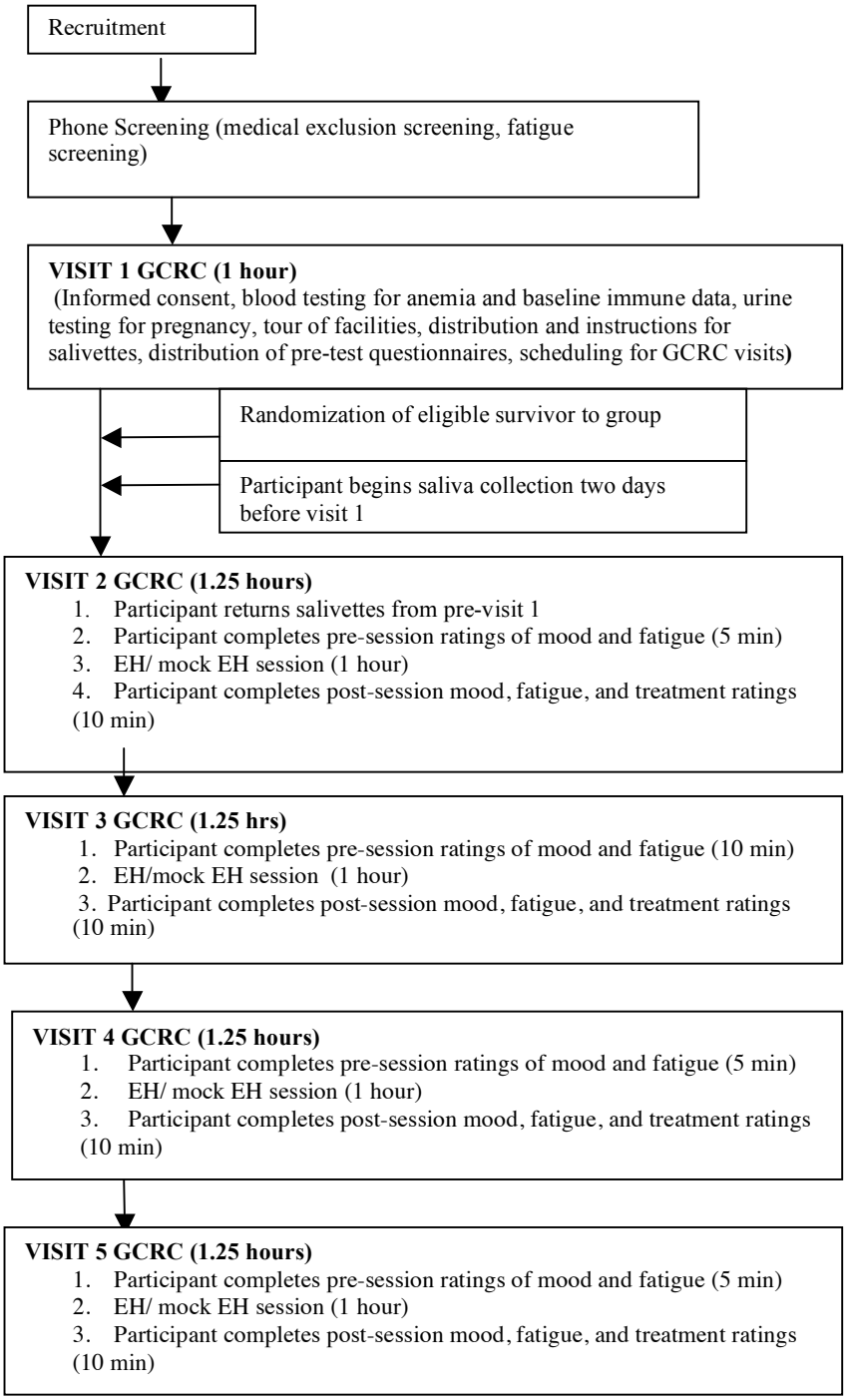

Figure 2. Protocol Flow Chart.

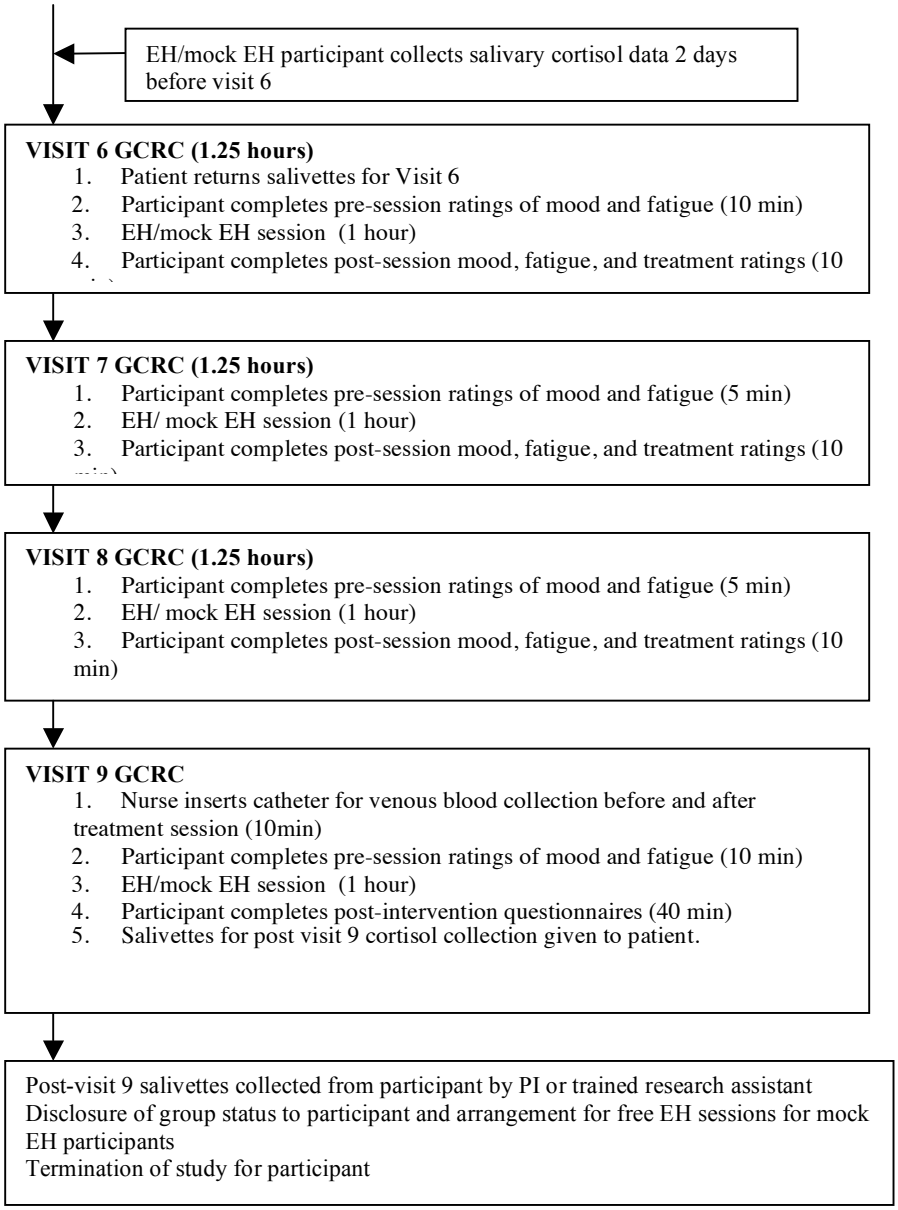

Figure 2. Protocol Flow Chart, Continued.

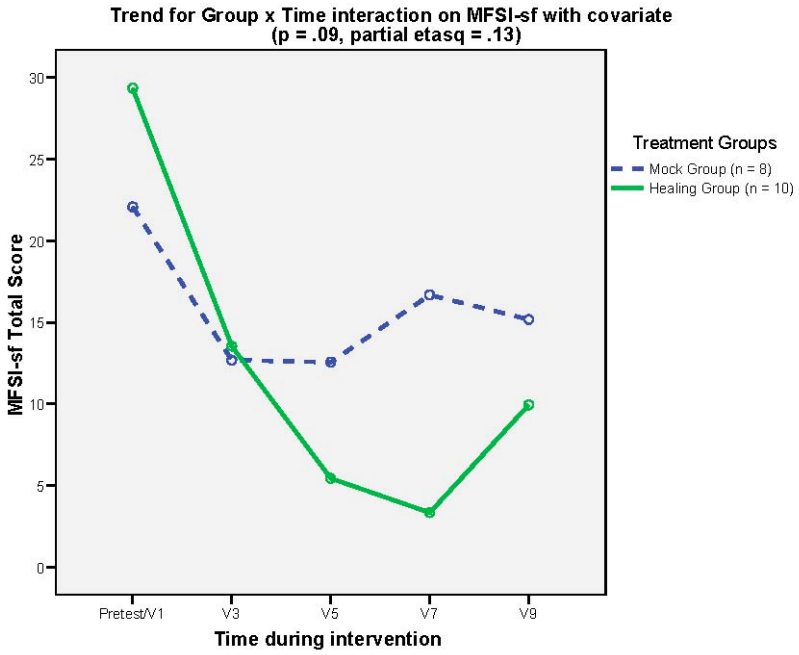

Figure 3a. Depiction of MFSI-sf total scores over time, with since radiation covariate

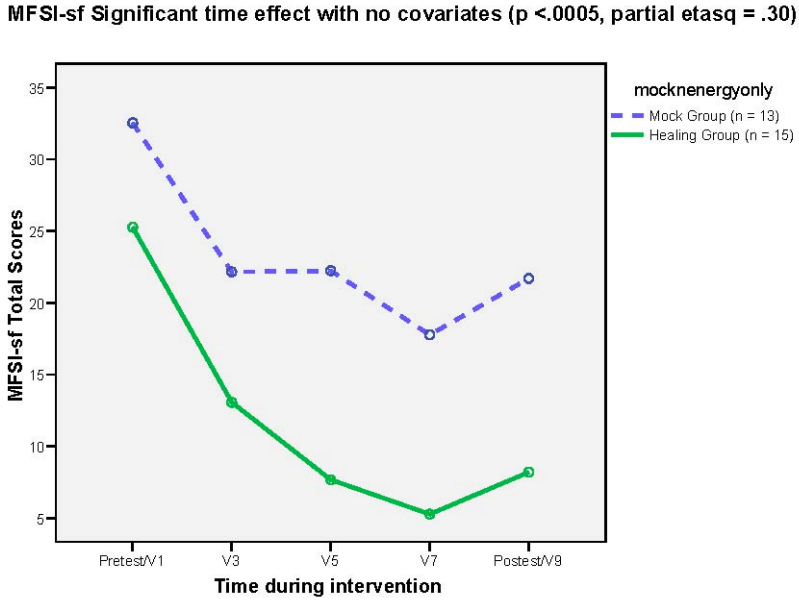

Figure 3b. Depiction of MFSI-sf total scores over time, without time since radiation covariate

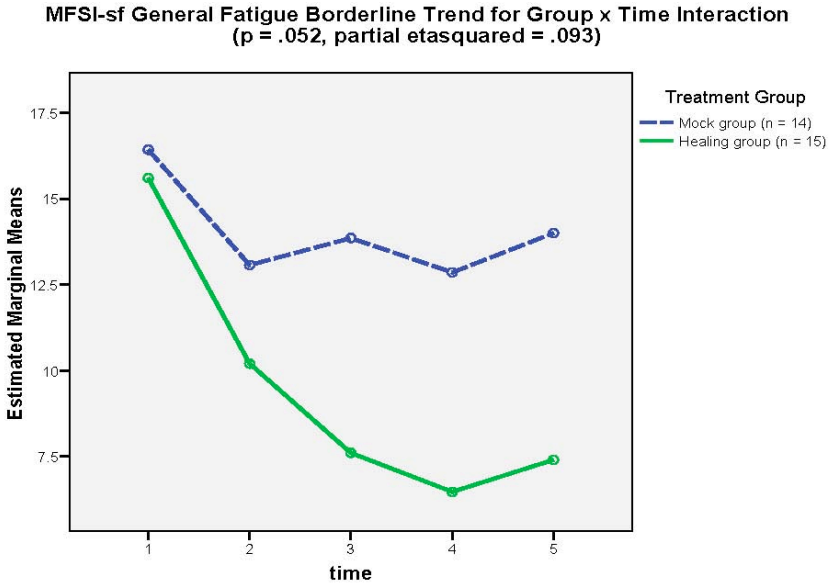

Figure 4a. Depiction of scores for MFSI-sf General subscale for both groups over time.

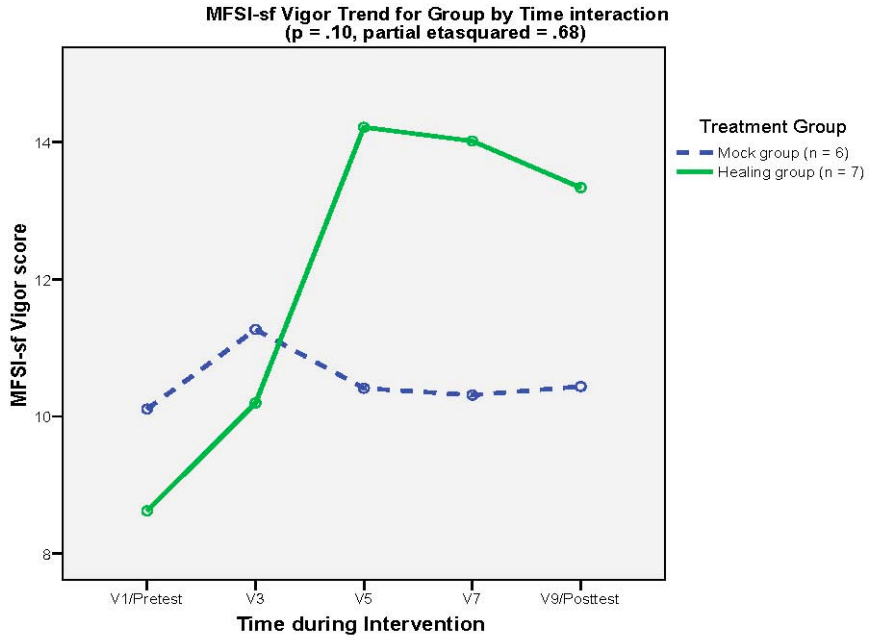

Figure 4b. Depiction of scores for MFSI-sf Vigor subscale for both groups over time.

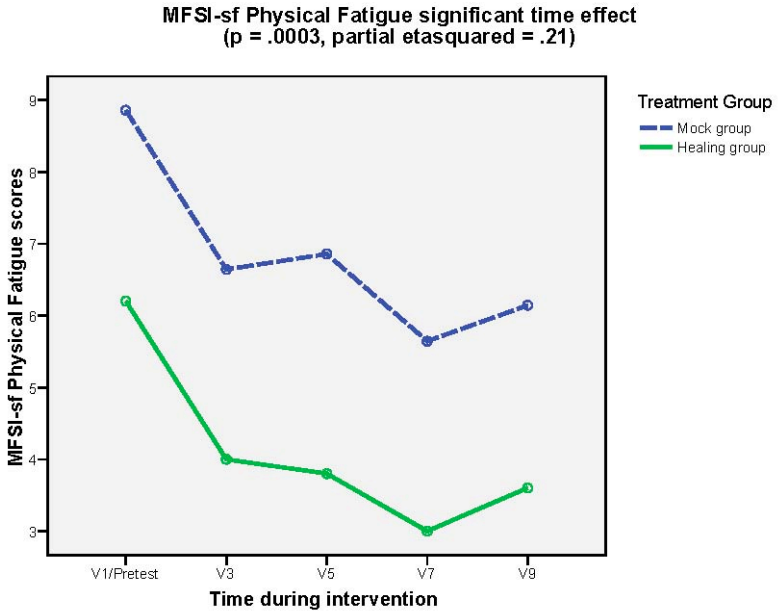

Figure 4c. Depiction of scores for MFSI-sf Physical subscale for both groups over time.

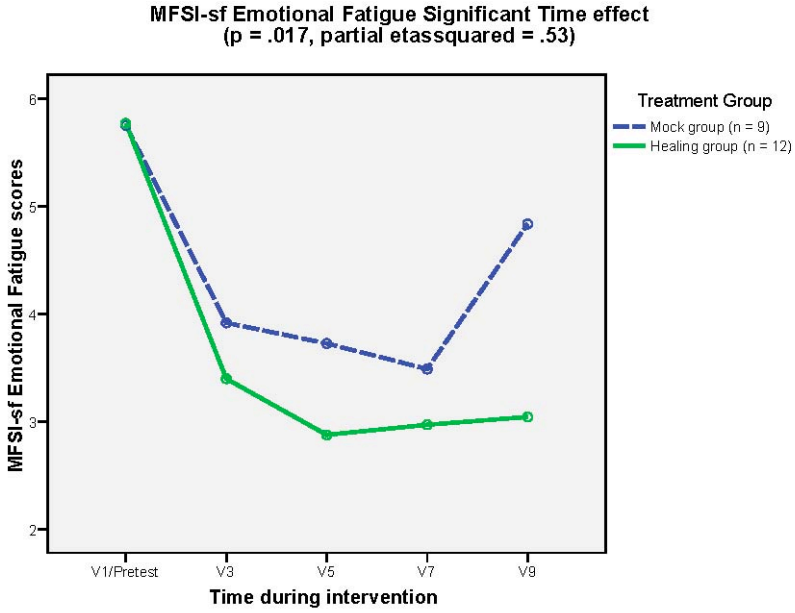

Figure 4d. Depiction of scores for MFSI-sf Emotional subscale for both groups over time.

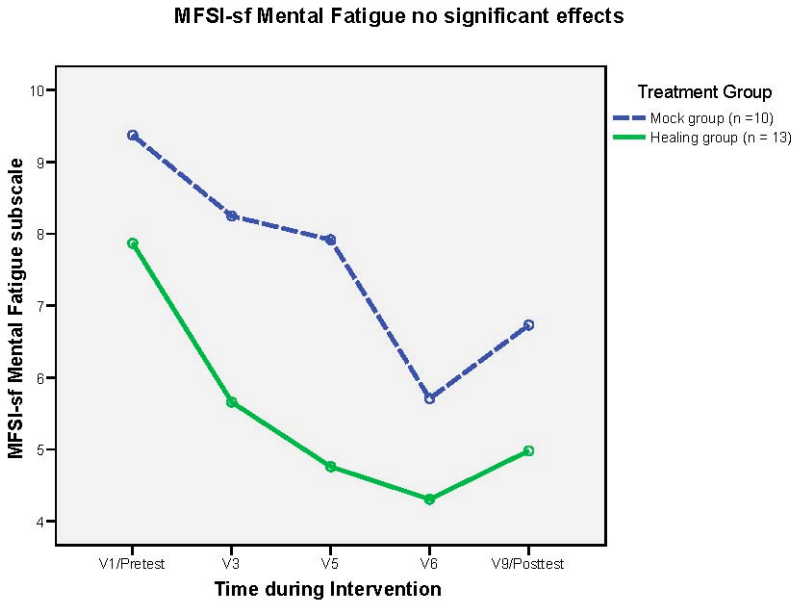

Figure 4e. Depiction of scores for MFSI-sf Mental subscale for both groups over time.

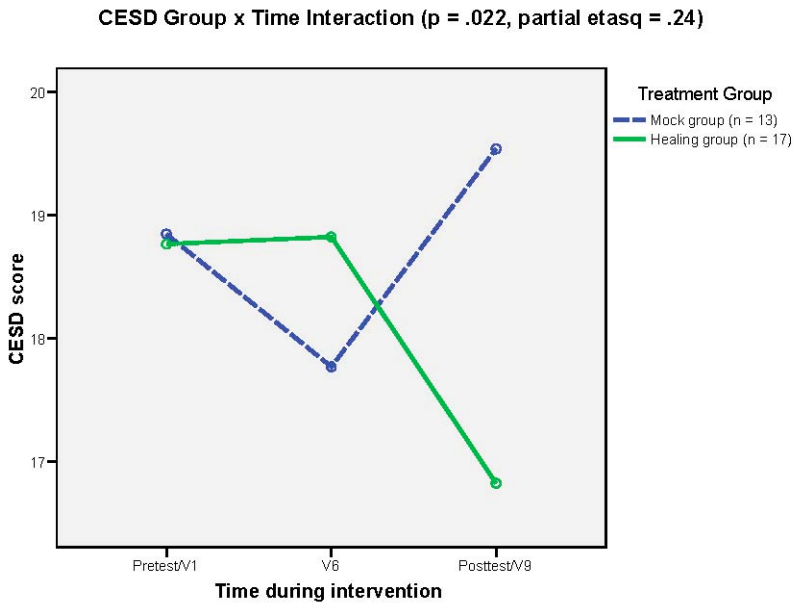

Figure 5. Depiction of scores for CESD scores for both groups over time.

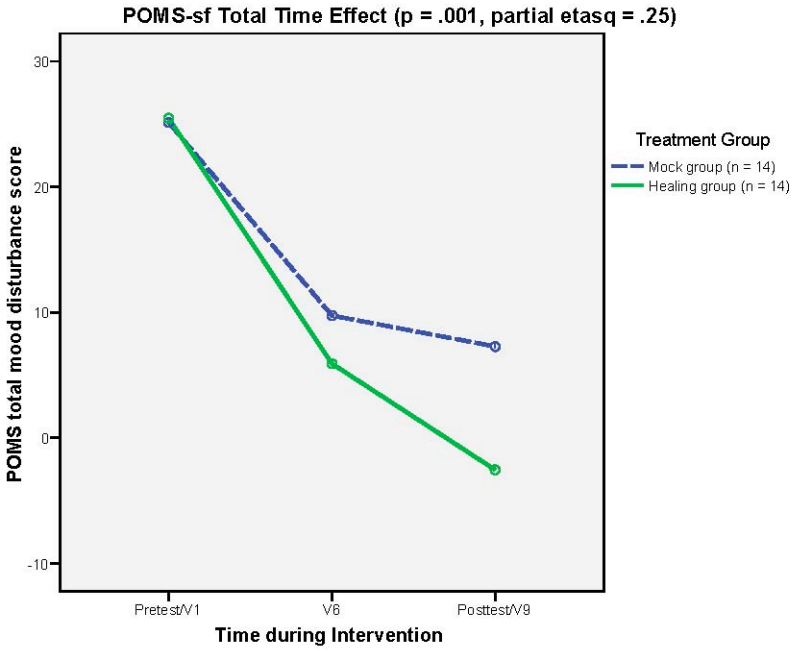

Figure 6a. Depiction of POMS-sf Total Mood Disturbance scores for both groups over time.

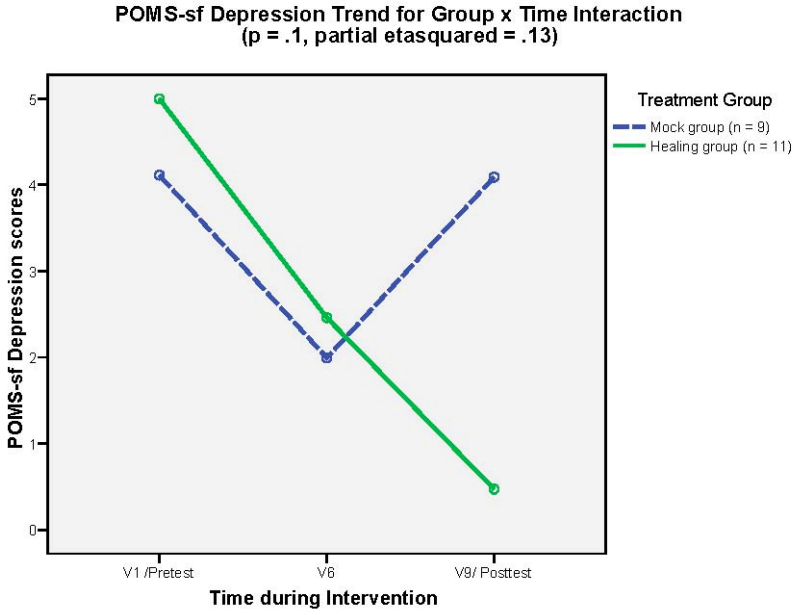

Figure 6b. Depiction of POMS-sf Depression scores for both groups over time.

Figure 7. Depiction of FACT-B treatment expectation by time interaction effects.

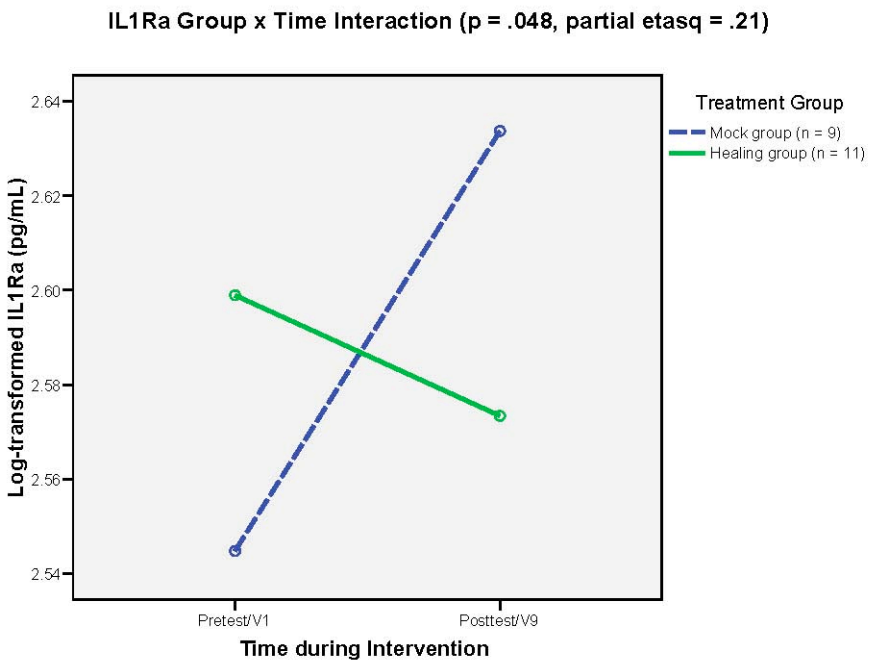

Figure 8a. Depiction of IL-1ra pre-post changes for both groups.

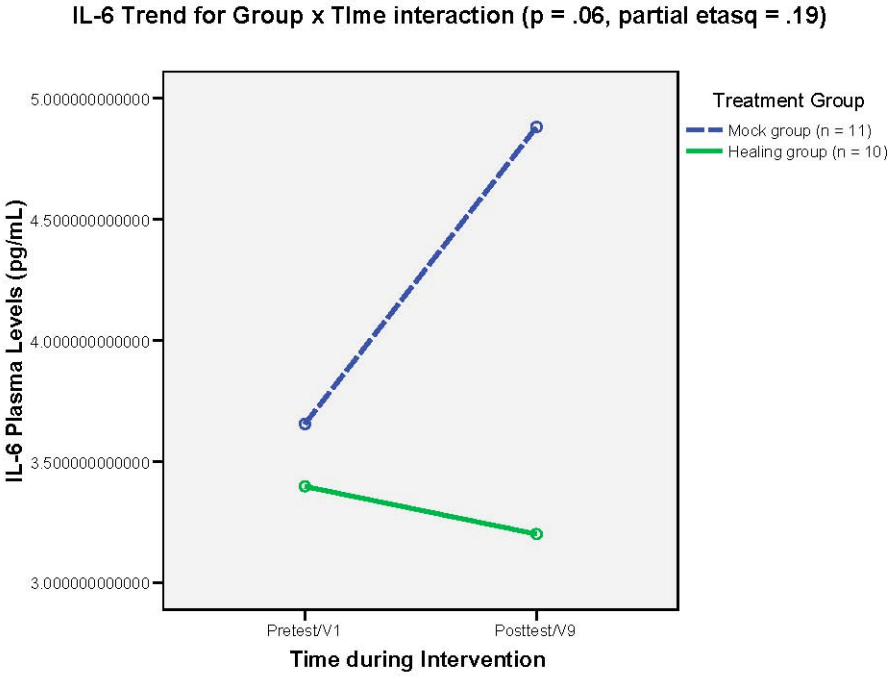

Figure 8b. Depiction of IL-6 pre-post changes for both groups.

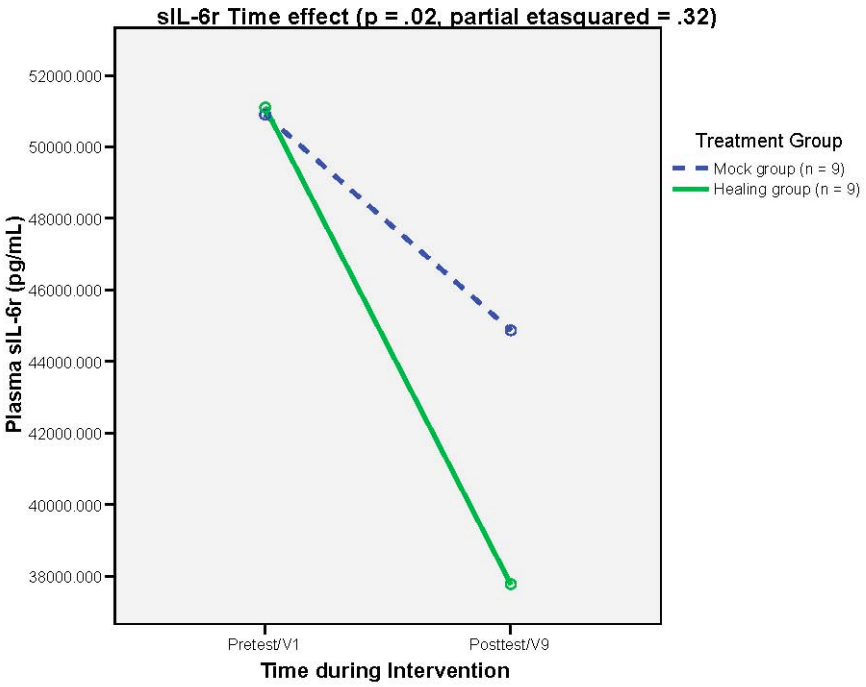

Figure 8c. Depiction of sIL-6r pre-post changes for both groups.

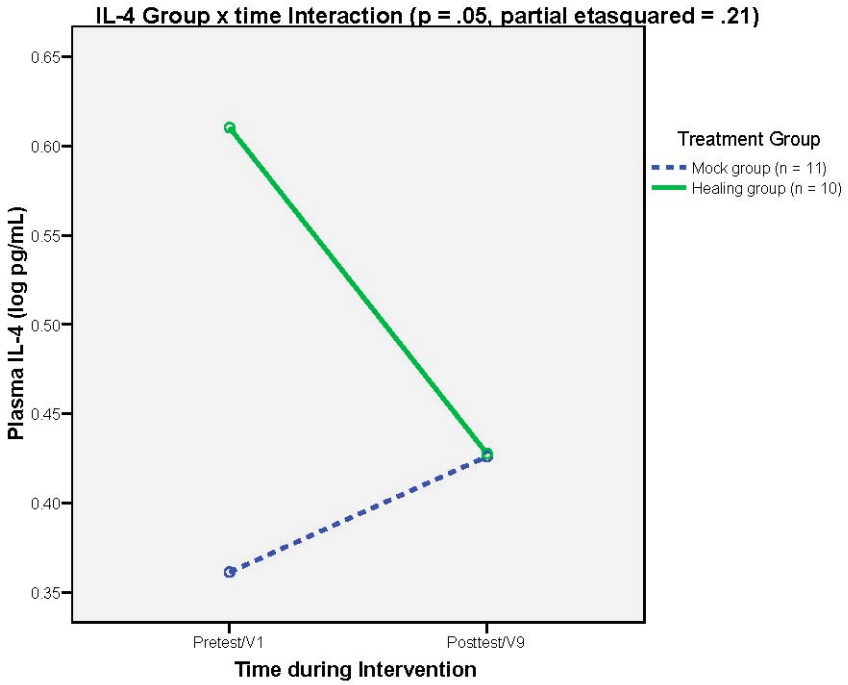

Figure 8d. Depiction of IL-4 pre-post changes for both groups.

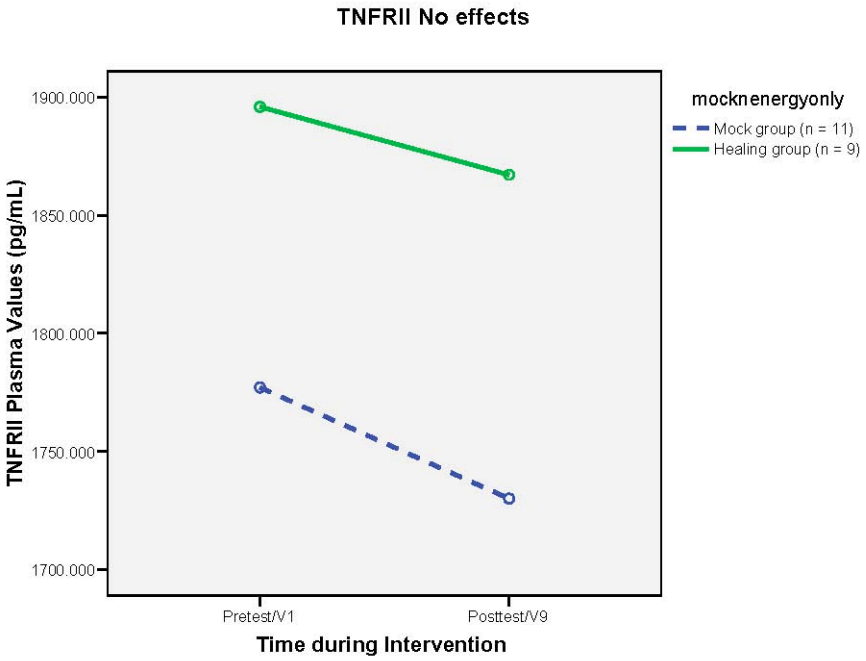

Figure 8e. Depiction of TNF-RII pre-post changes for both groups.

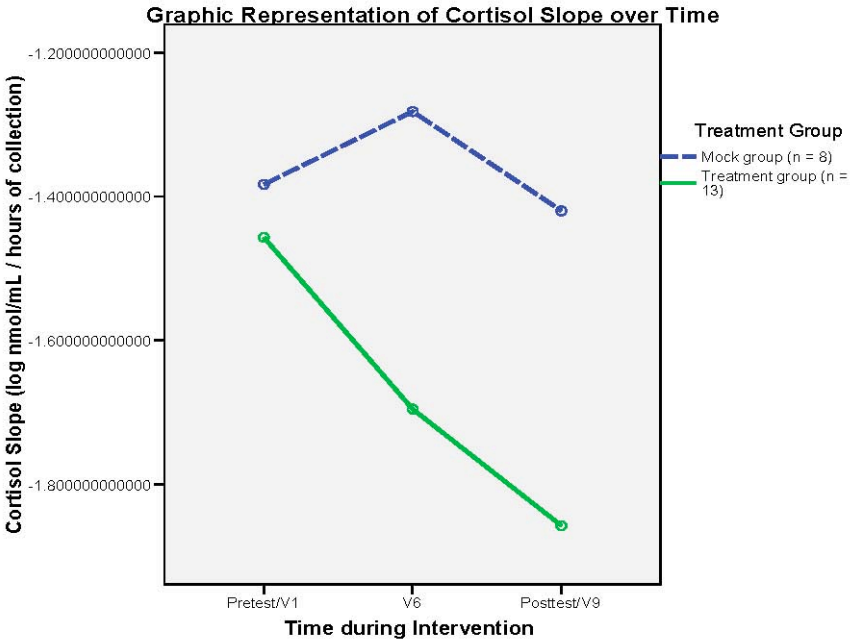

Figure 9a. Depiction of changes in average cortisol slope values per visit for both groups.

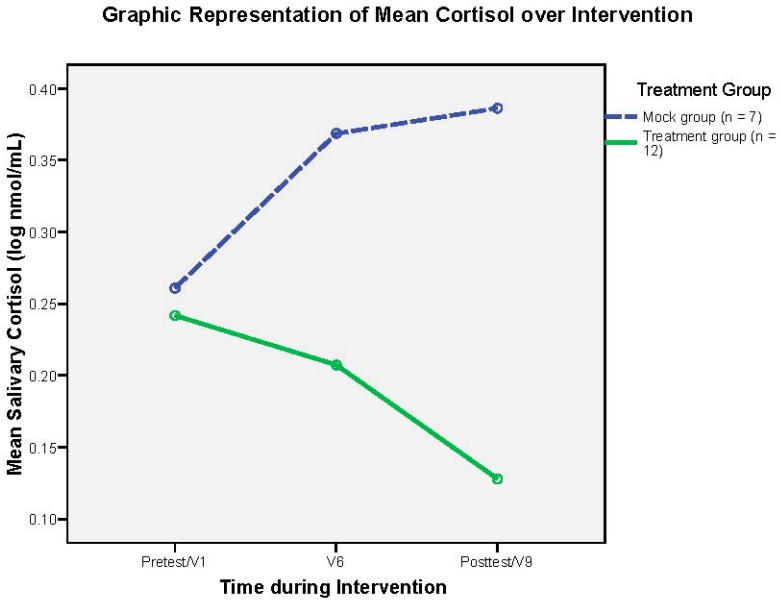

Figure 9b. Depiction of changes in average cortisol mean values per visit for both groups.

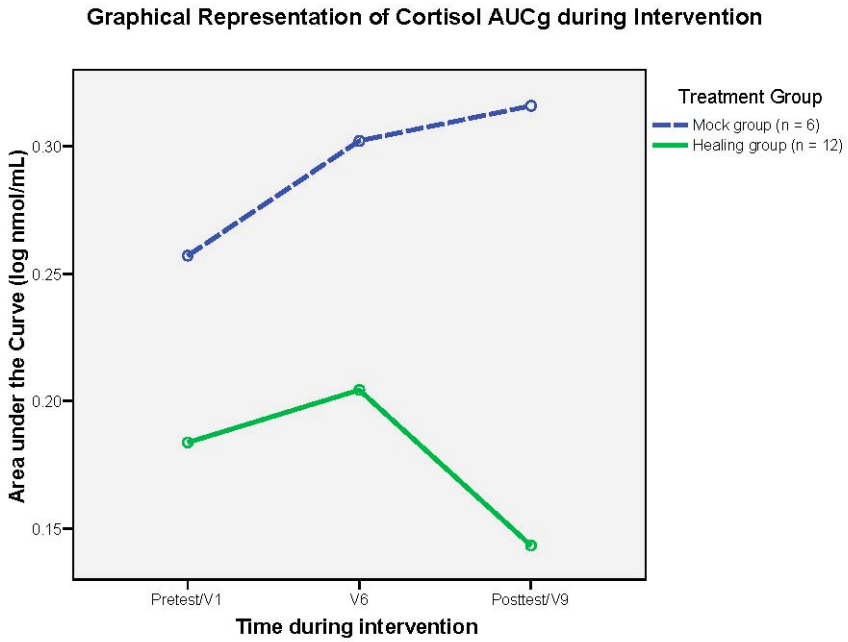

Figure 9c. Depiction of changes in average cortisol AUCg values per visit for both groups.

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