A PILOT STUDY EXPLORING THE ACUTE EFFECTS OF AEROBIC EXERCISE AND RELAXATION ON FATIGUE AND EXECUTIVE FUNCTION IN BREAST CANCER SURVIVORS

BY

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DISSERTATION

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Abstract

More than 250,000 new cases of invasive breast cancer, and roughly 63,000 new cases of in situ breast cancer were estimated to be diagnosed in 2017, within the United States (DeSantis, Ma, Goding Sauer, Newman, & Jemal, 2017). Chronic fatigue occurs at an extremely high rate in women diagnosed with breast cancer and can lead to increased sequelae and decreased quality of life. Aerobic exercise has been shown to improve certain aspects of cognitive functioning among breast cancer survivors (F. C. Dimeo, 2001). Additionally, common relaxation therapies such as guided mindfulness training (Deimling, Sterns, Bowman, & Kahana, 2005) have been shown to reduce fatigue, anxiety, and other negative affective states (DeSantis, Ma, Goding Sauer, et al., 2017). Though researchers have explored the separate impacts of aerobic exercise and relaxation methods (i.e., meditation and yoga) (Jacobs, Mehling, Goldberg, & Eppel, 2004; Sadja & Mills, 2013), the existing literature lacks a clear consensus regarding the effectiveness of acute aerobic exercise and relaxation techniques for reducing fatigue and related symptoms in breast cancer survivors. Driving this line of research are desires of survivors for an enjoyable, feasible intervention focused on the negative effects (e.g., fatigue) of chemotherapy treatment. Certain forms of chemotherapy (e.g., anthracycline-based) are more associated with decreased quality of life, including severe fatigue, as well as cognitive and physical functioning deficits. To date, no studies have tested the combined effects of acute aerobic exercise and adjuvant relaxation therapy delivered via technology for producing an enjoyable and feasible intervention to target fatigue and related outcomes within the breast cancer survivorship population.

The addition of guided mindfulness-based relaxation after aerobic exercise may increase perceived energy, reduce fatigue, enhance mental focus, and boost one’s overall interpretation of exercise experiences. This, in turn, may facilitate more favorable attitudes towards exercise and personal health and well-being.

To my family. in gratitude for all that they have taught me, and all that they have helped me to become.

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Chapter I: Introduction

Background and Problem

The World Health Organization estimates that the number of new cancer diagnoses will reach 22 million each year over the next two decades (Burstein et al., 2017) and roughly 1.7 million new diagnoses each year in the United States (Miller et al., 2016). Within the United States, cancer (as a whole) is the leading cause of death among women who are 40-79 years of age, and men who are 60-79 years of age. In total, cancer ranks second to heart disease as the leading cause of death among adults (18+) (Burstein et al., 2017; Irwin & Medicine, 2012). More than 250,000 new cases of invasive, as well as roughly 63,000 new cases of in situ breast cancer were diagnosed in 2017 within the United States (DeSantis, Ma, Goding Sauer, et al., 2017). Chemotherapy is one of the most common methods of treatment for breast cancer. One widely reported adverse impact of chemotherapy is chronic, cancer-related fatigue (Ebede, Jang, & Escalante, 2017). Cancer-related fatigue (Narayanan & Koshy, 2009) can be defined as:

> *A feeling of debilitating tiredness or total lack of energy that can last for days, weeks or months. This is more common than nausea, pain or depression; symptoms include feeling weak or worn out, having difficulties in climbing stairs, walking short distances and performing simple daily tasks.*

Due in large part to improved treatment methods, including stronger forms of chemotherapy, the estimated number of current breast cancer (BC) survivors in the United States exceeds 3.5 million and represents the largest group of cancer survivors (Miller et al., 2016). This population is swelling (and expected to grow to greater than 4.5 million individuals in 2026) yet, BC survivors (BCS) commonly report chronic problems that negatively impact their quality of life (Miller et al., 2016).

Specifically, more than 50% of BCS continue to suffer from fatigue after initial treatment has ceased (Broeckel, Jacobsen, Horton, Balducci, & Lyman, 1998; Roe et al., 2016). Fatigue is also associated with a lack of motivation for being active (Blaney et al., 2016), insufficient energy to complete activities of daily living (Zengarini et al., 2015), negative attitudes towards social activities and exercise (Blaney et al., 2016), and an imbalance in one's sleep-based homeostatic functioning (Bower et al., 2012), and well-being (Broeckel et al., 1998; Ho, Rohan, Parent, Tager, & McKinley, 2015). Following a cancer diagnosis and the ensuing primary treatment (i.e., surgery), one of the most prevalent forms of adjuvant treatment is chemotherapy (Vardy & Tannock, 2007). Unfortunately, this form of treatment is highly associated with innumerable adverse effects including further sickness (Myers, 2008), reduced physical function, affective and psychosocial difficulties, and severe fatigue (van Waart et al., 2015). More so, these individuals also experience cognitive impairments during and following treatment. Typically, patients who receive chemotherapy report experiencing a lack of concentration and short term memory loss for an extended period of time (up to years) following the completion of primary treatment (Hede, 2008). Often, these cognitive conditions are accompanied by increased anxiety and moderate to severe depressive symptoms (Schreier & Williams, 2004). To date, no behavioral intervention framework has been designed to appropriately address all of these factors.

Nevertheless, physical activity has been shown to improve some of the negative symptoms following treatment among BCS. For instance, objectively measured physical activity (at moderate to vigorous intensities) was found to be positively related to significant improvements amid health-related quality of life factors among 358 BCS (Phillips, Awick, et al., 2015). Further, the Better Exercise Adherence after Treatment for Cancer (BEAT Cancer) trial (n

= 222) found that physical activity program involvement significantly improved fitness, quality of life, fatigue, and treatment-related outcomes when compared to usual care (Rogers et al., 2015; Rogers et al., 2017). However, other exercise oncology research has resulted in inconsistent findings when examining changes in cancer-related fatigue (Berntsen et al., 2017). Oftentimes, these trials cite a lack of consistency among factors affected by physical activity, which may impact fatigue. Still, physical activity involvement among BCS has been associated with improved health, decreased symptoms such as pain, and decreased depression and anxiety (Bränström, Petersson, Saboonchi, Wennman-Larsen, & Alexanderson, 2015).

Exercise (in any form) has not always been supported as an intervention for improving health-related outcomes among individuals with chronic conditions like cancer (Callaghan, 2004; Schmitz et al., 2010). Yet, there is now evidence of cognitive, psychosocial, and physical functioning benefits (McNeely et al., 2006; Penedo & Dahn, 2005) as well as reduced fatigue (Rogers et al., 2015) following aerobic exercise among women with BC. These benefits appear to vary according to the nature of one's exercise involvement (e.g., time, type, and intensity). Though suggested aerobic exercise guidelines in certain clinical populations (e.g., breast cancer or stroke survivors) have been proposed (Billinger et al., 2014), BCS are recommended to adhere to the United States' Physical Activity Guidelines for healthy adults (Schmitz et al., 2010; Wolin, Schwartz, Matthews, Courneya, & Schmitz, 2012). However, these recommendations may not be suitable for this population, as demonstrated by the very low levels of physical activity among BCS (Phillips, Dodd, et al., 2015). Thus, more research is needed to determine physical activity intervention strategies that are most practical and effective for this population.

Despite the known benefits of physical activity, the effects of fatigue may pose a barrier that could hinder a BC survivors' exercise motivation. One meta-analytic review has shown that self-reported physical and mental fatigue are cited by survivors as primary barriers interfering with their physical activity levels (McNeely et al., 2006). Blaney and colleagues (2013) also found that more than 50% of surveyed BCS (n=456) from Northern Ireland reported fatigue to be the principal factor interfering with physical activity engagement. Fatigue may be a key component in explaining why merely 29.6% of cancer survivors meet the recommended 150 weekly minutes of moderate to vigorous intensity PA (Bellizzi, Rowland, Jeffery, & McNeel, 2005).

Further, the effects of fatigue may lower survivors' perceptions of their ability to successfully engage in exercise, if they wanted to. In fact, evidence suggests that low, exercise-specific self-efficacy is a factor that is highly associated with lower levels of physical activity in this population (Awick, Phillips, Lloyd, & McAuley, 2017; Burnham & Wilcox, 2002; Lynch et al., 2010). Specifically, on average, BCS spend about 36% of their day engaged in light physical activity, 2% in moderate activity and 62% in sedentary behavior time (Thraen-Borowski, Gennuso, & Cadmus-Bertram, 2017). In another study of 483 rural BCS, only 19.2% were found to be meeting physical activity recommendations (Olson et al., 2014). Roe and colleagues (2016) claimed that existing interventions aiming to increase physical activity (PA) levels among BCS have been insufficient and that research studies aiming to increase PA levels, improve efficacy, and reduce symptoms are needed. This is further supported by inconsistent findings of positive or null affective outcomes following aerobic and resistance exercise engagement (Bower, Ganz, et al., 2011; Courneya, Mackey, & McKenzie, 2002). Fatigue-related disturbances may also be affecting their interpretation of experiences beyond their PA engagement. This appears to be a perpetual cycle whereby survivors are already fatigued and then feel worse following attempts to engage in healthy behaviors intended to make them feel better. This in turn, could lead to feelings of helplessness (Seligman, 1972) and other negative emotions like sadness and cynicism (Nolen-Hoeksema, Girgus, & Seligman, 1986). Together, these data suggest that the overwhelming majority of BCS are not meeting public health guidelines, and that current recommendations (and programs) are insufficient for addressing this problem.

A complete understanding of the factors contributing to one's attitudes towards exercise engagement or interpretation of exercise experiences among BCS does not exist (Emslie et al., 2007). Ensuring a positive interpretation of and adherence to exercise can be particularly challenging due to a plethora of barriers, including but not limited to, fatigue. Fortunately, BCS have been shown to tolerate moderate changes (e.g., increased intensity levels resulting in small increases in cardiorespiratory fitness) to physical activity programs, which differ from standard guidelines. These modifications have resulted in reports of improved quality of life (Schmitz et al., 2005). The enhancements in quality of life (e.g., lowered anxiety) have been associated with increased exercise maintenance (Annemans, Lamotte, Clarys, & Abeele, 2007; Courneya & Friedenreich, 1997) and exercise self-efficacy (McAuley et al., 2006).

Given that some existing evidence suggests standalone exercise is insufficient for reducing fatigue and related disturbances in BCS (McNeely et al., 2006), development and testing of new methods is warranted. Approaches that aim to enhance affective or psychosocial experiences during and after exercise may yield more favorable results. One approach would be to include other evidence-based interventions (e.g., mindfulness-based relaxation training) with exercise. Previous trials, which aimed to determine the efficacy and impact of relaxation training following a physical stressor on perceived exercise experience for psychosocial improvements, have supported engaging in a short, post-exercise regimen of relaxation training (Nedstrand, Wyon, Hammar, & Wijma, 2006). Further, standalone relaxation training in the form of mindfulness training has resulted in reduced fatigue (Carlson & Garland, 2005; Lengacher et al., 2009). Findings from these preliminary studies suggest that relaxation training may improve fatigue among BCS. However, no studies have tested the combined effects of exercise followed by relaxation training on fatigue and related symptoms.

Recently, Yoga, a form of mind-body physical activity, which incorporates aspects of relaxation training, has become a popular form of behavioral treatment intended to deal with these symptoms. Cohen and colleagues (2004) conducted a randomized controlled trial (RCT) to test the efficacy of the Tibetan yoga practices of Tsa lung and Trul khor to improve fatigue and sleep in cancer survivors (n=900). At baseline, 30% of individuals reported experiencing insomnia, 20% reported using either sleeping pills or tranquilizers to get to sleep each night, and 60% reported needing to take at least one nap during the day. Further, the results showed that individuals randomly assigned to the Tibetan Yoga intervention reported experiencing less sleep disturbances, improved sleep quality, and a reduction in medication use when compared to the waitlist control group. These findings support the efficacy of combined mind-body approaches (e.g., physical activity and relaxation) in improving quality of life among cancer survivors (Deimling et al., 2005; Ferrell, Dow, Leigh, Ly, & Gulasekaram, 1995; Keating, Nørredam, Landrum, Huskamp, & Meara, 2005).

These forms of interventions are known for being ‘low impact’ and low intensity. Interestingly, it has been suggested that one possible reason why standalone aerobic exercise interventions are not always effective for reducing fatigue among BCS is high intensity levels, and the negative sensations and attitudes they produce (Berntsen et al., 2017). When considering the impact of aerobic exercise on affective responses, it is important to acknowledge that increasing physical activity beyond usual levels may lead to immediate, negative, post-exercise assessments. Following lower intensity aerobic exercise sessions, healthy adults (24 years and older) generally report positive affect and other perceptions regarding the exercise experience (Hardy & Rejeski, 1989; Reed & Ones, 2006). However, among obese women, a mere 10% increase above a self-selected speed was associated with increased self-reported exertion, objective oxygen uptake, and physical fatigue, as well as decreased negative affect (Ekkekakis & Lind, 2006). Varying treadmill walking intensities (derived from VO_{2max} assessments) has resulted in comparable affective changes irrespective of the duration of activity (Porcari et al., 1988). These results imply that time spent in activity may not be the key factor when examining affective improvement, and that individuals with chronic conditions may report less favorable interpretations of one's exercise experience following higher intensities. Additionally, there is no clear consensus regarding the differences in outcome effects among BCS engaging in brief (Blanchard, Courneya, & Laing, 2001) or prolonged aerobic exercise interventions (up to six months) (Mock et al., 2005). Due to this lack of clarity, it is important to delineate how acute engagement contributes to affective outcomes.

Aside from fatigue and its associated behavioral detriments, the majority of BCS (up to 75%) who receive chemotherapy, experience "chemo-brain" (Dong, Crone, & Wise, 2014). This phenomena has been defined as "mild affective and cognitive impairment following chemo-therapy" (Boykoff, Moieni, & Subramanian, 2009), which decreases overall quality of life (Staat & Segatore, 2005). When breast cancer patients begin to receive chemotherapy treatment, dysfunction of the hypothalamic-pituitary axis can occur (Constine et al., 1993), resulting in increased symptoms of fatigue, anxiety and depression (Crowne, Gleeson, Benghiat, Sanghera, & Toogood, 2015). Engaging in 30 minutes of moderately intense aerobic exercise per day for three days each week appears to be adequate for eliciting improvements among quality of life factors (Blanchard et al., 2003; Sharma, Madaan, & Petty, 2006). Underlying this improvement, it is theorized that aerobic exercise leads to increased cerebral blood flow and circulation (Guszkowska, 2003). These changes are thought to be at least partially responsible for improvements in anxiety, depression, fatigue, and other quality of life factors (Sharma et al., 2006). However, less is known about short-term changes in cognition following acute bouts of aerobic exercise among BCS.

Robust evidence of cognitive impairment in BCS who have received standard treatment methods (e.g., chemotherapy) exists. These complaints are mainly constituted of short-term memory abilities. Accordingly, distinct differences in cognitive functionality, (e.g., before and after beginning chemotherapy) have led researchers (Pusztai et al., 2004) to believe that chemotherapy may be directly and indirectly (e.g., through increases in cytokines and inflammation) responsible for a large portion of this negative cognitive change (Vardy et al., 2007). In addition to deficits in short-term memory, researchers have investigated other cognitive abilities such as spatial attention, working memory and processing speed. Penedo and Dahn (2005) compared 132 recently diagnosed breast cancer patients to a group of 45 healthy control participants. Patients diagnosed with invasive stage cancer (stage IV) performed significantly worse than those with non-invasive (stages I-III) breast cancer and healthy participants. Later stage diagnoses are often associated with aggressive forms of secondary treatment that result in neurophysiological effects on the brain. Silverman and colleagues (2007) conducted a study involving positron emission tomography among 16 chemotherapy-treated BCS with memory complaints, eight BCS who had never received chemotherapy and ten healthy control subjects. The results showed that women who had received chemotherapy treatment showed significantly lower resting brain metabolism compared to others, which was associated with a delayed-recall memory task activating a much larger portion of their frontal cortex. Lower resting brain metabolism in the frontal cortex was also associated with increased impairment and decreased performance on the delayed recall memory task. In short, chemotherapy further worsened the experienced side effects.

Individuals who have not received chemotherapy frequently show higher metabolic activity in their inferior frontal cortices during cognitively demanding tasks (de Ruiter et al., 2011). BCS who have received chemotherapy have also displayed a disrupted pattern of brain activation in their bilateral prefrontal regions (McDonald, Conroy, Ahles, West, & Saykin, 2012). However, while cancer patients who have undergone chemotherapy experience longer lasting and worse deficits (Ahles et al., 2008), cancer patients who have not received chemotherapy report similar, but lesser complaints as well. Indeed, Von Ah, Russell, Storniolo, and Carpenter (2009) found that 44% of BCS indicated that they were still suffering from cognitive impairment nearly five years following completion of treatment. Many of the problems reported by BCS appear to reflect deficiencies in executive function. Executive functions are processes that control and regulate thoughts and actions (Friedman et al., 2006). Martin and Failows (2010) further define these as a series of higher order cognitive processes responsible for self-control, planning, cognitive flexibility, and strategic development with specific purpose. Additionally, stronger executive function capacities are related to positive affective responses and experiences, whereas poor executive function is associated with anxiety-based apprehension and avoidance (Sharp, Miller, & Heller, 2015).

One oft-used method for reducing avoidance from exercise and improving the negative, affective experience of BCS following chemotherapy treatment is through the addition of a technology-based component to an intervention (Morris, Lambe, Ciccone, & Swinnerton, 2016).

The supplementation of technology has long been thought to improve enjoyment in exercise-based interventions (Dickinger, Arami, & Meyer, 2008; Igbaria, Iivari, & Maragahh, 1995; Nakamura, Minakuchi, & Tanaka, 2005; Rimmer, Lai, & Young, 2016), because novelty stimulates the user experience and engagement. Focusing on technology and its relationship to physical activity, Lloyd and colleagues (2016) surveyed BCS and found that 87% of individuals acknowledged that prolonged sedentary periods were detrimental to their health and well-being, and that 88.40% agreed that a reduction in sedentary time could improve their health. The majority (79.90%) of individuals also reported interest in taking part in technology-based exercise interventions, showing a large willingness to engage in this type of program. Technology-based relaxation interventions may facilitate a reduction in fatigue and improve affect by calming exercise-induced mind and body stimulation. This could, in turn, facilitate more positive interpretations of the exercise experience. According to Martin and Sinden (2001) BC survivors' adherence to short-term exercise interventions is lower in comparison to healthy adults, and standalone aerobic exercise has unclear effects on quality of life factors (Courneya et al., 2007). Therefore, technology may enhance enjoyment and engagement for BCS, and it may be particularly important to implement this component early on when introducing a physical activity intervention.

Technology-delivered mindfulness training has been compared to traditional practices and has shown promising results when targeting engagement, attention, and affective-related outcomes (Wisner, 2017). The addition of technology to relaxation-based interventions in healthy adults has been shown to improve attention (as indicated by scores on the Stroop task) and subjective wellbeing (the Brief Symptom Inventory) relative to an online cognitive training program (Bhayee et al., 2016). Additionally, a meta-analysis focused on behavioral interventions delivered through technology in cancer survivors showed that enjoyment and satisfaction were high among participants assigned to the technology intervention conditions (Kopp et al., 2017). Supplementary research on combined physical activity (yoga) and technology-based relaxation interventions has previously demonstrated high feasibility for reducing negative symptomology, increased intervention adherence, and a positive program evaluation in the endometrial cancer survivorship population (Lucas, Focht, Cohn, Buckworth, & Klatt, 2017), however, the combination of aerobic exercise and relaxation training has yet to be studied among BCS. Lucas and colleagues (2017) reported that feasibility (determined by intervention completion surveys, attendance and adherence data), efficacy (determined by high rates of enjoyment), reported changes in physical activity, and health-related quality of life showed improvements following baseline, at eight weeks, and 14 weeks. The researchers concluded that combining mindfulness training with a behavioral intervention is feasible among female cancer survivors, and engagement in this type of program may promote quality of life improvement. Further, Lucas and colleagues (2017) suggested that high enjoyment and satisfaction with this technology could be explained by the detailed feedback provided, the user-friendly interface, or the novelty of the combined program. Inherently, the use of device-delivered relaxation training increases consistency and reduces the chance of bias and other confounding factors.

Objective of the Study

Indeed, no studies have examined the combined effects of aerobic exercise and mindfulness training compared to standalone aerobic exercise or standalone mindfulness training, which presents a gap in the field of exercise oncology and the outcomes in focus. Given the ability of technology to improve one’s experience, and enjoyment through improved affective components, and stronger engagement with the prescribed intervention (Riva, Banos, Botella, Wiederhold, & Gaggioli, 2012), this approach has the potential to improve fatigue in BCS, beyond findings from prior studies involving in-person or group-based relaxation methods (Demiralp, Oflaz, & Komurcu, 2010). Indeed, it seems reasonable to expect that aerobic exercise combined with mindfulness-based relaxation training may improve perceptions of quality of life (e.g., fatigue), energy levels, and other related outcomes (e.g., cognitive function), more so than aerobic exercise alone.

Significance of the Study

Although the use of technology as a delivery method in previous mind-body interventions has resulted in improved adherence, PA levels, and quality of life factors, there has not yet been a trial, which examines the impact on fatigue among BCS. Participants in one RCT were prescribed 150 minutes of moderate-to-vigorous physical activity (MVPA). Of the participants randomized to a technology-delivered mind & body gaming condition, 31.40% (n=16) of the survivors who completed the prescribed weekly MVPA. Only 4.40% (n=2) of those in a standalone aerobic exercise condition completed the same amount of MVPA. Albeit not the recommended weekly amount, 84.30% (n=43) of cancer survivors in the active mind & body gaming condition completed 60-minutes of MVPA, yet only 22.20% (n=10) of survivors in the standalone exercise condition successfully completed the same amount. These findings lend support to the thesis that a technology-based component may improve participant's willingness to become involved with exercise and increase adherence. However, no improvements in quality of life or affective factors (e.g., anxiety and depressive symptoms) were found, even for those who increased weekly minutes of MVPA (Courneya, Friedenreich, Sela, Quinney, & Rhodes, 2002). Interestingly, BCS have shown excellent acceptance, compliance to, and enjoyment of mindfulness-based training programs. However, to date, no studies have investigated fatigue-related outcomes of combined aerobic exercise and technology-based mindfulness training among BCS. If this form of intervention is associated with reduced fatigue following acute engagement, future research targeting fatigue and related symptoms among BCS will be able explore the long-term effects to better understand the application of this form of treatment, opposed to current methods.

Summary

Together, these findings suggest that aerobic exercise can improve fatigue and related outcomes but may not fully attenuate the symptoms experienced by BCS. Adherence to regular exercise is a large problem for the general population (Daley, Crank, Mutrie, Saxton, & Coleman, 2007), but the addition of a cancer diagnosis, medical appointments, treatment sessions, increased fatigue and depressive affect all lead to additional side effects and sequelae in BCS. These factors make exercise engagement increasingly more difficult for this population as BCS are being asked to attain the recommended levels set forth for their healthy peers. To date, no research has focused on the combined effects of aerobic exercise and relaxation training on fatigue and its related symptoms in BCS. This trial will aim to explore whether or not aerobic exercise combined with mindfulness training is more efficacious in reducing fatigue when compared to aerobic exercise, or mindfulness training among BCS within the context of an acute randomized pilot trial. A more detailed theoretical account of the mechanisms responsible for physiological, cognitive, and psychological changes can be found in the following chapter.

Purpose & Hypotheses

The purpose of the present project, the Responsiveness to Acute Changes in Exercise & Relaxation (RACER) trial is to better understand a novel method for improving fatigue and cognition among BCS. The aims and hypotheses are as follows:

1. This trial aims to understand the overall enjoyment and satisfaction of an innovative intervention for reducing fatigue among BCS. To this end, a brief study evaluation survey will be administered, and it is hypothesized that participants randomized to the COMBINED group will report higher levels of enjoyment when compared to those participants randomized to the AERO or RELAX conditions.
2. As the RACER trial aims to test the effects of brief engagement (three sessions) in a randomly assigned intervention activity (aerobic exercise, mindfulness, or both) on fatigue. It is hypothesized that following three days of engagement with the COMBINED condition (20-minutes of aerobic exercise and 20-minutes of a technology-delivered mindfulness training) activity, will result in significant improvements in fatigue when compared to time-matched engagement with aerobic exercise and quiet rest (AERO) or mindfulness training and quiet rest (RELAX), which are consistent with standalone interventions in the existing BCS literature. Both the AERO and RELAX groups are hypothesized to improve in their perceived fatigue scores.
3. Additionally, this trial aims to explore the effects that the randomized interventions have on higher order cognitive function among BCS. Following completion of the three sessions, the COMBINED intervention group is hypothesized to show change scores that are more favorable as indicated by significant group differences in higher order cognitive functioning relative to the AERO and RELAX conditions.

Chapter II: Literature Review

In the previous chapter, I discussed the negative impact of fatigue and related consequences for BCS. Additionally, I reviewed the current state of exercise oncology and common approaches to the problem, as well as a novel method for improving fatigue. This chapter will provide an in-depth review of the existing scientific literature, discuss the practical implications of the proposed intervention, and offer a comprehensive, theoretically informed framework that will guide this empirical study designed to test the efficacy of combining two established interventions (namely aerobic exercise and relaxation) on fatigue and related health outcomes.

Fatigue

Following chemotherapy treatment(s) fatigue is one of the first, most enduring, and resistant symptoms experienced by patients (Byar, Berger, Bakken, & Cetak, 2006). Among healthy individuals, it is a normal process and commonly occurs after exhaustive activity in order to prevent the brain and body from overexertion (F. C. Dimeo, 2001). Among BC patients, fatigue can begin to appear prior to treatment and during activities of daily living (De Jong, Candel, Schouten, Abu-Saad, & Courtens, 2004). Cancer-related fatigue (CRF) is exacerbated by aggressive and cytotoxic (as well as cardiotoxic) treatments such as chemotherapy. Over 75% of patients who receive chemotherapy treatment report experiencing increased mental and physical manifestations of fatigue (Gerber, 2017; Smets, Garssen, Cull, & De Haes, 1996). It is believed that these experiences eventually lead to high rates of alternative treatment-seeking and dropout from traditional intervention programs (Henderson & Donatelle, 2004). The high rates of CRF and the desire for alternative treatments displayed by women with BC demonstrate the need to further research the CRF experience and methods for improving it.

Female cancer patients and survivors have reported experiencing higher levels of CRF, anxiety, memory impairment and depression scores (compared to male cancer patients and survivors) (Bower et al., 2000; Tel, 2008). Servaes and colleagues (2002) found CRF to be prevalent in 25-99% of cancer patients during adjuvant treatment cycles; specifically, in the six studies (out of 22 reviewed) focusing on BC patients, a majority of women reported experiencing CRF. An additional review examining fatigue levels across cancer survivors who had successfully completed chemotherapy treatment and entered remission, showed that symptoms were still found to be prevalent in 19-38% of cancer-free survivors (Prue, Rankin, Allen, Gracey, & Cramp, 2006; Servaes et al., 2002). However, the literature on effective interventions remains unclear when it comes to understanding the relationships among physiological, cognitive, and psychosocial factors associated with fatigue in BCS (Phillips, Lloyd, Awick, & McAuley, 2017). For instance, one poorly understood, and very specific and ubiquitous fatigue–related symptom, which occurs both during and following chemotherapy treatment is cognitive impairment (Collins, MacKenzie, Tasca, Scherling, & Smith, 2013).

Cognitive Impairment

While cognitive impairments occur for BCS experiencing multimodal therapy (e.g., chemo, radiation, hormonal therapy) (J. Dietrich, Monje, Wefel, & Meyers, 2008) focusing on the effects of chemotherapy is important due to the prevalence of its many varieties and uses in this population.(Du & Goodwin, 2001). The typical cognitive repercussions associated with BC and chemotherapy are a lack of concentration and short term memory loss for an extended period of time (up to years) following completion of treatment (Hede, 2008). As many as 70% of patients who have undergone chemotherapy report experiencing lasting, negative cognitive symptoms (Bray et al., 2016). Perceived cognitive impairment has also been associated with higher levels of anxiety, depression, fatigue and lower quality of life (Castellon et al., 2004; Von Ah, Allen, & Wulff, 2011). Among BCS, certain cognitive functions appear to be more susceptible to decreased performance, namely, executive function, relative to others. Executive functions are a series of higher order cognitive processes responsible for self-control, planning, cognitive flexibility, and strategic development with specific purpose or outcome (Martin & Failows, 2010). As reported in a review by Ahles and colleagues (2012), an abundance of evidence has shown that treatment is affecting neural structure and function. This is hypothesized to occur directly through the inflammatory responses triggered by the cancer itself and the ensuing increase in neurotoxic cytokines, or through limited DNA repair mechanisms. These biological experiences regularly result in limited cognitive abilities and have been shown to impact daily living processes. Weakened abilities of these functions can cause serious detriment to one’s life.

Executive Function

Support for this hierarchical view of executive function comes from large datasets and evidence of confirmatory factor structures showing shared variance across performance on related tasks (Miyake et al., 2000; Salthouse, 2005; Zelazo et al., 2013). In these models, executive function is comprised of shifting, updating and inhibitory abilities. These abilities are shown to be (at least in part) controlled by the frontal and prefrontal cortical areas of the brain (Collette et al., 2005; Royall et al., 2002). The component of cognitive shifting includes set switching, set shifting, verbal working memory, spatial working memory, self-monitoring and regulation, and self-awareness. This constituent has been found to be controlled by the frontolateral (Derrfuss, Brass, Neumann, & von Cramon, 2005) and ventromedial (Wager, Jonides, Smith, & Nichols, 2005) portions of the cortex. Interestingly, it has been theorized that these areas of the brain contribute to the sensation, perception, and experience of fatigue (Gibson et al., 2003). In fact, the emotional aspects of fatigue (i.e., anger and fear) are thought to be regulated by the ventromedial prefrontal cortex. This area is also responsible for the cognitive decision making process reflected across executive function capabilities (Hiser & Koenigs, 2017). Further, the prefrontal cortex, an area associated with working memory, is believed to be the primary brain area responsible for recognizing irregular axonal firings, and producing an ambiguous response which is experienced by an individual as the sensation and perception of fatigue (Gibson et al., 2003). The prefrontal cortex embodies the shared, physical connection between fatigue and certain aspects of cognition. This relationship exemplifies the necessity for researching methods to reduce fatigue and negative affect, while improving cognition within the BCS population.

Five meta-analyses have provided convergent and robust evidence of cancer survivors experiencing the greatest degree of cognitive impairment disproportionately overrepresented by executive functioning (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005; Jim et al., 2012; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006). Kesler and colleagues have theorized that through BCS' involvement in activities such as cognitive training (2013), the negative effects of chemotherapy may be counteracted. Additionally, involvement in physical exercise (Crowgey et al., 2013), healthy eating (Riggs, Spruijt-Metz, Sakuma, Chou, & Pentz, 2010), and relaxation strategies (Tang, Yang, Leve, & Harold, 2012) may counteract the harmful effects of treatment and enhance cognitive abilities including executive function skills.

Chang and Etnier (2009) have shown exercise to be related to improvements across multiple aspects of executive function, however it is unknown if these effects are sustained following the onset of chemotherapy. A large portion of self-reported cognitive problems among women who have completed chemotherapy may actually represent brief memory lapses. Further, high rates of reporting these issues and issues with higher order cognitive processes may result from emotional or mood-related changes stemming from a disease diagnosis and stigmatization (Shilling & Jenkins, 2007). While some BCS show a decline in executive function abilities as indicated by objective neuropsychological assessments, the majority of evidence for such cognitive issues stem from self-reported measures (Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012).

According to Li and colleagues (2016), women diagnosed with BC are more likely to show both subjectively and objectively measured cognitive impairment when compared to other subpopulations of cancer. BCS express cognitive impairment as their most impactful and problematic side-effect from treatment (e.g., chemotherapy), such that the impairment had significantly reduced their independence (Boykoff et al., 2009). A large portion of BCS' cognitive complaints involve being unable to inhibit their impulses and engagement in undesired behaviors (McDonald, Conroy, Smith, West, & Saykin, 2013). Moreover, great variation exists in the neuropsychological tests used to examine the relationship between self-reported cognitive complaints and clinically diagnosed functional and structural abnormalities (Falleti et al., 2005), complicating the interpretation of these findings. Therefore, a standardized set of cognitive tasks, such as those used in the NIH Toolbox should be used to allow for clear comparisons across the BC population and other clinical and healthy populations (Weintraub et al., 2013).

Inhibitory Control

Inhibitory control is an additional component of executive function, which is negatively affected by BC and its treatment and shown to be decreased among BCS (Ono et al., 2015). The

Stroop task (requiring participants to indicate the color of the stimuli font, not the spelling of the stimuli) has been shown to display these specific cognitive deficits in women with BC, following the onset of treatment (Jenkins et al., 2006). Intact inhibitory control enables an individual to terminate a desire or involuntary reaction that is inappropriate within a specific situation. The problems that BC patients and survivors report with inhibitory control are commonly conveyed as an inability to cease behaviors that they do not want to do (Graves, 2003), as well as decreased control over response inhibition (Hutchinson et al., 2012). Chemotherapy treatments often result in deleterious effects on the prefrontal cortex, with consequences being further proportioned according to anatomically distinct areas associated with the dorsolateral prefrontal cortex (DLPFC), and interior frontal cortex (Aron, Robbins, & Poldrack, 2004). Researchers may be able to better understand mechanisms for delaying or reducing cancer-induced neuronal degradation in the DLPFC and its associated cognitive dysfunction by developing interventions that work to combat the negative effects of BC and chemotherapy in these brain areas. Certain activities such as aerobic exercise (Yanagisawa et al., 2010), and mindfulness training (Creswell et al., 2016) have been shown to improve functions controlled by the DLPFC, however no imaging studies have confirmed structural improvement. Reducing and delaying these effects through aerobic exercise may also benefit working memory, another closely-related component of executive function (McMorris, Sproule, Turner, & Hale, 2011).

Working Memory

Working memory impairment is the most commonly reported and objectively measured cognitive dysfunction in cancer patients who have been treated with chemotherapy (Hutchinson et al., 2012). Relatedly, two distinct forms of memory storage exist, short-term and long-term memory (Kellogg, 2002), and show measurable differences between the amount of information they can store, and the permanency of the information held within them. The main neurophysiological difference between short-term memory storage and long-term memory storage occurs when experiences go through the modification processes of neuronal re-organization during long-term potentiation (LTP) and enter long-term memory (Cahill & McGaugh, 1998). LTP's efficiency has been shown to be diminished following chemotherapy treatment (Pechnick, Alkam, Baudry, & Lin, 2016), and is correlated with one's working memory capabilities (Hasselmo & Stern, 2006). A commonly used neuropsychological paradigm for assessing working memory performance, is the dual task model. This procedure assesses performance on simultaneously delivered primary and secondary tasks. Participants are instructed to apply response priority to the primary task, while remaining cognizant of the requirements for the second task (Sala, Baddeley, Papagno, & Spinnler, 1995).

These types of tasks require greater demand of executive resources (compared to other working memory assessments), which is negatively affected by the disease (Kesler, Kent, & O'Hara, 2011), and the treatments that follow (Anderson-Hanley et al., 2003). Li and colleagues (2017) have used dual task paradigms to confirm subjective working memory complaints among BCS. The general brain region believed to be most associated with working memory abilities is the pre-frontal cortex (Fuster, 2001). Specifically, the dorsolateral pre-frontal cortex (Jaeggi et al., 2003) and frontal gyrus are the areas believed to be responsible for working memory capabilities (Wong et al., 2015). Behavioral interventions (e.g., physical activity programs) that target and train working memory capacities can function as remediating methods for decreased cognitive performance involved in daily living activities among aging adults (de Paula et al., 2015). Indeed, certain types of cancer (e.g., BC) and their treatments, (Kesler et al., 2011) have been shown to impact brain structures related to working memory, and these deficits have been confirmed in brain activation patterns following chemotherapy or radiation (McDonald et al., 2012). Activation changes in these brain structures correlate with increased amounts of performance errors and increased time for completion on working memory tasks, when compared to healthy controls and BCS who did not receive chemotherapy. This is further demonstrated by survivors who had received chemotherapy reporting higher levels of executive function deficits compared to BCS who did not receive chemotherapy (Kesler et al., 2011). These reported deficits were highly correlated with lower activation in the left caudal lateral middle frontal gyrus and the left medial frontal gyrus (Kesler et al., 2011). Several memory-based studies have observed positive associations between physical activity engagement and performance, however, few have investigated this association in the context of a brief intervention designed to improve working memory and fatigue among BCS (Ehlers, Rogers, Courneya, Robbs, & McAuley, 2018). Similar performance deficits have also been shown in processing speed abilities (Krull et al., 2016). While it is not an executive function, processing speed is a highly related cognitive construct

Processing Speed

Although processing speed (PS) is not considered to be one of the three main constituents of executive function (e.g., inhibition, working memory, and cognitive flexibility), it is associated with the frontal gyrus (Hirano et al., 2013), and declines with natural aging (Tam, Lam, Huang, Wang, & Lee, 2015). Researchers have posited and also provided some evidence that PS underlies executive function (Rose, Feldman, & Jankowski, 2011; Salthouse, 2005). Further, we are beginning to understand the relation between this specific waning in PS abilities and a neurological chain of events in the brain. This is believed to result directly from a decrease in regular physical activity involvement, such as a lack of increase in cerebral blood flow, which usually occurs post-exercise (Cotman, Berchtold, & Christie, 2007). The literature suggests that improved working memory capabilities are reflected in increased PS, such that faster rehearsal and encoding may be a result of a larger cache of information being presently stored within ones working memory (Baddeley, 1986, Heinzel et al., 2016).

Psychosocial Factors

Strong relationships also exist between perceptions of cognitive difficulties and psychosocial components such as depression and anxiety (Mehnert et al., 2007). Indeed, perceived cognitive impairments in areas such as PS abilities are associated with decreased quality of life for up to a year following completion of chemotherapy treatment (Booth-Jones, Jacobsen, Ransom, & Soety, 2005; Reid-Arndt, Hsieh, & Perry, 2010; Shilling & Jenkins, 2007). Finally, behavioral interventions resulting in perceived improvement in cognitive function have been associated with improved symptoms of fatigue, anxiety and depression (Jenkins et al., 2006; Shilling & Jenkins, 2007; van Dam et al., 1998). To date, very little is known about the extent to which perceptions of cognitive performance are sensitive to immediate change following a brief intervention.

Unlike perceptions of cognitive function, certain modifiable psychosocial factors, such as self-efficacy have been shown to be positively associated with exercise engagement (McAuley, Jerome, Elavsky, Marquez, & Ramsey, 2003). Interestingly, self-efficacy is also theorized to have an association with cognitive functioning, such that improved self-efficacy for cognitive function is a factor believed to be responsible for objective improvements in cognitive tasks (Bandura, 1989). Evidence from Social Cognitive Theory-guided interventions, which target health behaviors suggests that the use of planning and associated cognitive strategies relate to higher self-efficacy for, and sustained engagement in, the targeted health behavior (Bandura, 1993). Accordingly, Liu-Ambrose and colleagues (2010) have shown that improved self-efficacy for a health behavior is correlated with unique effects on changes in executive function, with those changes predicting older adults' adherence to a single week of exercise participation. This reciprocal effect between adherence and cognitive control has been highlighted extensively and has been shown to selectively act upon constructs of SCT including self-efficacy (Buckley, Cohen, Kramer, McAuley, & Mullen, 2014).

Consistent with Bandura's original SCT framework and other perspectives on perceived exertion (Tenenbaum & Hutchinson, 2007), it is theorized that BCS' interpretations of exercise experiences, and self-efficacy for completing exercise is most likely modified by personal factors unique to their disease condition (Lerman et al., 1995). For example, demographics (e.g., age, gender, education), disease & treatment factors (e.g., cancer type, location, stage/severity, treatment type and length), individual differences in self-perceptions (e.g., self-efficacy, perceived stigma), outcome expectations and interpretations of the exercise experience (e.g., reduced anxiety, cognitive enhancement), and socio-environmental factors (e.g., support groups, access to resources) may be responsible components. However, high-levels of existing fatigue have been shown to be associated with a reduction in one's self-efficacy for, and engagement in exercise (Zimmerman, 2000). Thus, it is necessary to find a method (involving physical activity) for reducing fatigue that is capable of producing an attractive experience that may increase one's self-efficacy for exercise engagement. Indeed, a knowledge gap exists regarding the mediating effects of changes in one's perceptions of self-efficacy on fatigue and related outcomes following an intervention (Akin & Guner, 2017).

Physiological Factors

Other factors such as perceptions of physiological changes (i.e., one's view of their experienced bodily changes and satisfaction with such changes) and cognitive performance are theorized to influence exercise experiences (Mullen et al., 2011; Rothman, 2000; Vitale et al., 2016). However, the existing knowledge regarding the relationship among self-perceptions of physiological changes, cognitive function and fatigue are unclear (Sarkisian, Prohaska, Wong, Hirsch, & Mangione, 2005). Self-efficacy for these factors are theorized to be highly sensitive to improvement through positively perceived engagement in aerobic exercise and other activities such as relaxation training (Demiralp et al., 2010). Yet, minimal research has examined the relationships between modified psychosocial constructs and aerobic exercise in the breast cancer population (Jacobsen, Donovan, Vadaparampil, & Small, 2007), and the existing evidence may only be applicable to breast cancer patients, as it has not been thoroughly studied among BCS who have completed treatment (Demiralp et al., 2010).

Exercise and BCS

A multitude of studies have presented beneficial findings of exercise involvement during adjuvant chemotherapy treatment (Adams et al., 2016; Courneya et al., 2007; Courneya et al., 2016; Schmidt et al., 2015), with findings suggesting that only a small portion of BCS engage in enough physical activity to experience these benefits. The overbearing symptom of CRF is likely a driving force for elucidating a desire to minimize physical exertion and remain inactive both during and following treatment. It is natural for an individual diagnosed with breast cancer to physically, mentally, and emotionally desire to remain at rest and take part in minimal amounts of physical activity (Coon & Coleman, 2004). In fact, any level of CRF (which is stronger than fatigue experienced by a healthy individual) can be found in 70% to 100% of patients who have completed or are currently undergoing some form of cancer-specific treatment, with symptoms lasting from months to years following the conclusion of treatment (Bourmaud et al., 2017; Curt et al., 2000). Evidence suggests beneficial effects of acute aerobic exercise involvement on fatigue during adjuvant chemotherapy treatment exist (Courneya et al., 2007), but little research has been conducted on this relationship following the end of treatment (Meneses-Echávez, González-Jiménez, & Ramírez-Vélez, 2015). Furthermore, some of the limited research that has involved aerobic exercise among BCS has shown improvements in fatigue (Mustian et al., 2017), whereas other research has resulted in conflicting evidence (Pfaff, 2017). Due to CRF and physical deconditioning, BCS have often indicated that involvement in even moderate exercise is extremely difficult (Blaney et al., 2016). However, BCS remain highly motivated to return to exercise and introducing these individuals to short bouts (i.e., around 15-20 minutes) of moderately intense aerobic exercise appears to be an acceptable starting point (Blaney et al., 2016). Furthermore, the barrier posed by CRF exemplifies the need to find efficacious methods for fostering a positive exercise experience that could assist in reducing CRF and thereby increase the appeal of exercise.

Another element believed to contribute to low rates of exercise involvement within this population is that patients and survivors may not be fully aware of the benefits of exercise involvement during the diseased and treatment stages (Falzon, Radel, Cantor, & d’Arripe-Longueville, 2015). Therefore, designing interventions informed by the specific, exercise-focused preferences of this population seems logical. BC patients undergoing chemotherapy treatment have expressed a strong preference and interest in beginning a home-based, walking program of low to moderate intensity (Rogers, Markwell, Verhulst, McAuley, & Courneya, 2009; Windsor, Potter, McAdam, & McCowan, 2009). Among BC patients, this form of exercise has been shown to positively affect physiological, psychological, and psychosocial concerns (Windsor, Potter, McAdam, & McCowan, 2009).

In addition to walking interventions among BC patients, one RCT focused on a different form of aerobic exercise (bicycle ergometer while in the supine position) for 30-minutes during hospital treatments (F. Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997) examined participants (n=80) presenting with solid tumors. All participants chose to take part in high-dose chemotherapy (HDC) treatment (ranging from 1-4 rounds). Those in the exercise training condition (compared to HDC and no exercise) performed 1-minute bouts of supine biking, working up to 50% of their individual cardiac reserve, followed by 1-minute bouts of rest; resulting in a 15-interval, 30-minute training session. For those in the exercise condition, significant improvements occurred for maximal speed performance, hemoglobin concentration, lower levels of physical performance loss, as well as duration of neutropenia, days spent in the hospital, severity of diarrhea, and severity of pain. These findings lend support to the use of stationary cycling in order to bring about desirable outcomes and changes during adjuvant HDC treatment, which may have further effects on lasting post-treatment symptoms (e.g., fatigue). Yet, this hasn’t been researched in the context of a RCT in patients or survivors. Although individuals may differ in their response to aerobic exercise involvement (indirectly dependent on age, cancer type or stage) it can be expected that aerobic exercise involvement will positively affect physical and cognitive performance, as well as anxiety and fatigue.

Despite the physiological, cognitive, and psychosocial benefits of exercise engagement, individuals face many barriers, which disrupt their involvement. This can contribute to chronically elevated levels of CRF. Common reasons given by cancer patients for missed exercise sessions include fatigue and pain, attributable to chemotherapy treatments (Milne, Wallman, Gordon, & Courneya, 2008), followed by mental lapses, and poor quality of life factors (Waart et al., 2016). When designing an intervention involving exercise for cancer survivors, researchers, practitioners and medical professionals should be sure to focus on more holistic factors (e.g., physiological, cognitive, and psychosocial) of individuals' lives. These factors may better inform the questions asked by the research design.

Conceptual Framework and Model

Several models have been proposed to address the associations of pre-existing factors with fatigue. The conceptual framework of the neuroendocrine-based regulatory fatigue (NRF) model (Figure 1) (Payne, 2004) is founded on a review of the existing empirical data targeting the underlying mechanisms responsible for intervention effects on fatigue. The NRF model recognizes that pre-existing factors (physiological & psychological) can moderate the effects of an intervention targeting fatigue. Further, this model operates under the assumption that changes in fatigue are the result of biochemical energy reactions, and is more so focused on biochemical markers that may underlie self-reported fatigue rather than behavioral mechanisms (although researchers acknowledge that behavioral mechanisms of the physiological and psychological constructs can affect fatigue). Due to its empirical foundation, this is a sound framework for examining change in fatigue. Nevertheless, the existing model is missing key components of fatigue experienced by BCS, including antecedent levels of physiological, cognitive, and psychosocial functioning.

By introducing a more comprehensive biopsychosocial perspective, factors of the neuroendocrine system (from the original model) may be used interchangeably with psychosocial measures like anxiety and other stress-related variables (Santa Mina et al., 2014). These antecedent factors are proposed to moderate the impact of the intervention on an individual. In turn, the intervention has a direct effect on the physiological, cognitive, and psychosocial factors. As shown in Figure 1., these antecedent factors have direct and indirect effect on one's fatigue. This revised, working model (Figure 1., indicated by dashed lines) specifies modifications, based on theory and research. This study is designed to test the inherent predictions in the modified model. Together, these findings should inform theory and practice.

Theoretical Contribution

To assess the theorized perceptions of change among the three antecedent constructs in the working model, this trial will utilize concepts from Albert Bandura's SCT (1991), and related principles of social neuroscience (Lieberman, 2007), and biobehavioral systems (Payne, 2004). SCT posits that a triadic reciprocal determinism exists among personal, behavioral, and environmental factors. This means that bi-directional relationships occur among the factors, which may result in each factor influencing another. Here, exercise behavior (acting as the behavioral factor) is the component in focus and it is theorized to be influenced by outcome expectations, sociostructural factors, goals, and self-efficacy. This trial will target self-efficacy because it is highly malleable and has been shown to have an effect on affective (Feltz, 1982) and psychosocial outcomes (Paluska & Schwenk, 2000). Self-efficacy is the belief in one's own ability to successfully complete a specific behavior or action (Bandura, 1982). There are four distinct sources that can improve one's self-efficacy. According to theory, the most prominent source of self-efficacy is *mastery experience*. The experience(s) of successful, mastery performances of an action lead to higher levels of self-efficacy, while unsuccessful performances can be detrimental to one's self-efficacy (Bandura, 1997). Additionally, *vicarious learning and modeling* (experiencing others correctly complete a behavior), *verbal persuasion* (from a trusted and competent source) and *physiological state interpretations* (favorable elucidations of their experiences and sensations) are the three other sources that can modify self-efficacy (Bandura, 1977). Moreover, within the context of aerobic exercise, efficacy beliefs and outcome expectations are important determinants of exercise behavior (McAuley & Blissmer, 2000).

Behavioral Intervention in the Framework

Following the structure of the working model, aerobic exercise will be used as one component of the intervention in order to investigate changes in CRF. Indeed, general health-related benefits attained through adherence to the recommended amount of aerobic activity participation (150 min/week) include, but are not limited to: improvements in sleep, stamina, sex drive, stress relief, mood/valence (Callaghan, 2004), and energy (Fogarty, Happell, & Pinikahana, 2004). Further, reductions in depressive & anxiolytic symptoms (Guszkowska, 2003) are seen in the general population, even following one bout (Petruzzello, Landers, Hatfield, Kubitz, & Salazar, 1991; Ströhle, 2009). Furthermore, regularly active adults report a reduced sense of tiredness and fatigue, increased alertness, less adipose tissue, lower cholesterol, and greater cardiovascular fitness (Sharma et al., 2006). These effects have also been demonstrated within the BCS population and greatly benefit their disease-related symptoms (McNeely et al., 2006; Nelson et al., 2007; Penedo & Dahn, 2005).

Findings from a systematic review suggest that participation in aerobic exercise can result in significant improvements in psychological and quality of life factors (Gillison, Skevington, Sato, Standage, & Evangelidou, 2009). Additionally, exercise engagement is associated with a reduction in negative affective characteristics such as depression rates and symptoms (Blake, Mo, Malik, & Thomas, 2009; Bridle, Spanjers, Patel, Atherton, & Lamb, 2012; Sjösten & Kivelä, 2006). Finally, anxiolytic symptoms and other stress-based responses tend to be reduced after completing a bout of aerobic exercise (Conn, 2010). Often, affective and psychosocial improvements occur roughly 10-minutes after the completion of an exercise session (in which homeostatic stress levels are elevated) (Mann, Webster, Lamberts, & Lambert, 2014). Evidence suggests that this time period represents an opportunity for alternative treatment methods such as relaxation training to positively affect the systems associated with the experience of CRF in BCS (Hilfiker et al., 2017b). To better understand such acute effects and their mechanisms, as well as long-term effects, more research on brief and cumulated bouts of exercise is needed (Dethlefsen, Pedersen, & Hojman, 2017). The use of exercise in this trial is intended to improve the theorized mediators (e.g., physiological, cognitive and psychosocial factors) of changes in perceived fatigue. BCS still show extremely high levels of fatigue irrespective of their activity levels. It is possible that exercise alone may not be satisfactory for reducing these symptoms. Previous studies have examined CRF and associated outcomes following aerobic exercise and relaxation training among BC patients (F. Dimeo, Thomas, Raabe-Menssen, Pröpper, & Mathias, 2004). However, no research has examined the additive effects in either BC patients or survivors, providing the opportunity to explore this relationship.

Physiological Construct in the Framework

The first antecedent component of the working model is the physiological construct. A natural aspect of aging (after 25 years) is its progressive degeneration of muscle mass, strength, and functional capacity (Lexell, Taylor, & Sjöström, 1988) with each decade that passes accounting for a ~ 9% decrease for inactive adults (Heath, Hagberg, Ehsani, & Holloszy, 1981). Over time, this often leads to decreased physical function and quality of life. In addition to these physical symptoms, inactive individuals report suffering from extended fatigue, similar to that experienced by cancer patients (Hortobágyi, Mizelle, Beam, & DeVita, 2003). In non-BC populations, exercise involvement has specific physical and physiological improvements for individuals with chronic symptomology (Douglas, Pearson, Ross, & McGuigan, 2017). However, the addition of breast cancer and its treatment only intensifies these negative consequences as well as the impact experienced among related factors such as quality of life (Rejeski & Mihalko, 2001) and cognitive and psychosocial well-being (Crane, MacNeil, & Tarnopolsky, 2013). Indeed, regular engagement in aerobic exercise may preserve and enhance cardiovascular fitness levels and function while conserving the integrity of lean muscle mass, strength, and capacities. Expectedly, these enhancements have associations with psychosocial and cognitive factors (Tsatsoulis & Fountoulakis, 2006), while the opposite effects have been observed following periods of prolonged physical inactivity (Wei, Gibbons, Kampert, Nichaman, & Blair, 2000). These effects are demonstratively exacerbated among the BC population, and the risk for developing cardiovascular disease is further increased (Zagar, Cardinale, & Marks, 2016). Finding an efficacious method for allowing BCS to have a positive experience while completing aerobic exercise may increase the likelihood that they continue to engage in it. Further, taking part in aerobic exercise may assist in combatting the physiological consequences that this population experiences. This in turn, as illustrated in the working model, may facilitate a reduction in CRF.

Declining levels of cardiovascular fitness is another natural aspect of aging is (Colcombe, Kramer, McAuley, Erickson, & Scalf, 2004). These fitness levels are further negatively impacted following a breast cancer diagnosis and the ensuing treatment (Pinto, Clark, Maruyama, & Feder, 2003). Swain and Franklin (2006) examined whether the effects of higher intensity (6+ METS) aerobic exercise resulted in more advantageous cardio-protective benefits when compared to moderate and lower intensity-based aerobic exercise. The researchers found that non-clinical populations experienced the largest decrease in cardiovascular and coronary heart disease risk, as well as improved perceptions of physical function when engaging in high intensity exercise, but found mixed evidence regarding lower intensity exercise in healthy individuals. However, 12 RCT's specifically testing the effects of aerobic fitness levels and training exercises among BCS have demonstrated efficacy (Schmitz et al., 2010). Whereas sustained, high intensity aerobic exercise engagement is related to clear cardio-protective benefits among non-clinical populations (Services, 1996), moderate intensity aerobic exercise is sufficient to achieve similar benefits, although not to the same extent among clinical populations (Devin et al., 2016; Schmitz et al., 2010; Tsukamoto et al., 2016). However, opportunity exists to maximize the aerobic exercise-based benefits for BCS. One prevailing thought, which has been demonstrated within the schizophrenic population (Oertel-Knöchel et al., 2014), is that the addition of relaxation training following a bout of moderately intense aerobic exercise may help optimize experienced physiological improvements by modifying perceptions of pain and muscular fatigue (Larun, Brurberg, Odgaard-Jensen, & Price, 2017). The value of producing cardiovascular benefits among BCS (a population with an average diagnosis age of 62 (DeSantis, Ma, Goding Sauer, et al., 2017)), is that these women would benefit from aerobic exercise by receiving known effects on cognitive function, which have been established among aging adults (McAuley, Kramer, & Colcombe, 2004).

Cognitive Construct in the Framework

Cognitive factors comprise the second antecedent construct of the working model. Cognitive aging coincides with the physiological effects of natural aging and this is exacerbated by the addition of chemotherapy for women with BC (Koppelmans et al., 2014; Szychot et al., 2017). The deterioration in brain structure and function is more prevalent in the areas responsible for executive functions (frontal, parietal and temporal lobes) (Raz, 2000), and cognitive processes such as planning, inhibitory control and memory updating are compromised (Park, Polk, Mikels, Taylor, & Marshuetz, 2001). Nevertheless, engagement in aerobic exercise has been associated with improvements in higher order cognitive functioning (Kramer et al., 1999). Taking part in aerobic exercise may help to combat the negative consequences experienced by BCS who have received chemotherapy and may still be experiencing difficulty with planning, inhibitory control, and memory updating (Colcombe & Kramer, 2003).

Favorable changes in cognitive performance resulting from exercise depend upon modifiable training factors (i.e., duration, intensity, frequency, exercise type), prior exercise history, and the cognitive domain being examined (i.e., working memory vs. processing speed). The consensus within the literature is that exercise has specific detrimental effects on cognitive processes during the exercise bout, but is associated with improved cognitive effects after a particular amount of time following the completion of the aerobic exercise task (Lambourne & Tomporowski, 2010). As aerobic exercise intensity increases, so does heart rate, rate of blood flow, brain derived neurotrophic factor (BDNF) levels, and catecholamine levels (Curtelin et al., 2017; Hedlund, Nylin, & Regnström, 1962). Other mechanisms may play a role in the change in cognition following exercise and causal pathways are uncertain.

Chang and colleagues (2012) opine that if a higher intensity aerobic exercise bout results in higher levels of circulating BDNF, and specific post-exercise cognitive testing reveals improvements, then BDNF can logically be theorized to be a mechanism of aerobic exercise’s effects on specific aspects of cognitive functioning. The areas of cognitive functioning which display the largest improvements following (but not during) an acute bout of aerobic exercise are those based in motor skills, academic achievement, executive function tasks, and other frontal lobe-based faculties. These findings lend support to the transient hypofrontality thesis (A.

Dietrich, 2003). This theory states that engagement in exercise causes a decrease of blood flow in certain areas during exercise (causing hypo-functionality) and an increase of blood flow to the motor cortices following exercise (causing hyper-functionality), which comes at the expense of other areas of the brain and the according functions they help to control (A. Dietrich, 2004). This proposed fluctuation in blood flow is the theorized mechanism for acute change in executive function within this theory. Admittedly, the relationship between intensity of exercise and certain cognitive outcomes is unclear and debated. In one study by Labelle and colleagues (2013), light and moderate intensity exercise was associated with immediate positive cognitive effects, whereas hard, very hard and maximal intensities did not show the same effect. However, when a longer delay (10+ minutes) followed the exercise bout prior to administering the cognitive testing, all intensity conditions were associated with positive cognitive changes, except for very light intensity. Therefore, exercise dose and measurement timing are important considerations to maximize power to find hypothesized acute effects.

Memory functioning is typically worse among cancer survivors relative to healthy populations (L. Wang et al., 2016). Whereas long-term exercise engagement has resulted in positive cognitive effects (e.g., reduced working memory impairment and increased clarity of thinking) (Courneya, Mackey, et al., 2002) among BCS, the acute effects of aerobic exercise on working memory are unknown. However, acute working memory improvements following bouts of aerobic exercise among healthy adults are well established (Pontifex, Hillman, Fernhall, Thompson, & Valentini, 2009) suggesting that there may be a more immediate working memory benefit realized by BCS following acute bouts of aerobic exercise. Such cognitive abilities (e.g., short-term memory and working memory) have been researched by measuring performance on active storage, maintenance and management of information in a brief time period, following exercise (Kane & Engle, 2002). To test the short-term memory effects of aerobic exercise, Pontifex and his colleagues (2009) used the Sternberg task. The Sternberg task is a well-established test of working memory that requires participants to determine if the corresponding probe stimuli was or was not shown to them in the previous series of stimuli. Participants completed maximal graded aerobic and resistance fitness testing at baseline. Prior to engaging in fitness testing, participants completed the Sternberg task and did so again after 30-minutes of a randomly assigned post-fitness testing activity (lower body resistance or aerobic exercise). On the following three days, participants either ran or walked on a treadmill (60-70% $VO_{2\ max}$), completed 30-minutes of resistance exercise performed in three sets of eight to 12 repetitions at 80% of their one-rep max, or took part in quiet, seated rest (within subjects and counterbalanced to remove possible learning effects). Analysis of absolute (total pre-test, post-test and 30-minutes post-test) reaction time (RT) revealed a positive main effect for the aerobic exercise condition compared to the resistance exercise and quiet sitting conditions. The condition effect showed decreased post-activity testing RT as well as decreased RT 30-minutes after completion of post-activity testing. Analysis of relative (difference between measurement time points) RT revealed a significantly larger reduction in RT when compared to the resistance exercise and quiet seated condition. Overall, these findings suggest that acute aerobic training has favorable effects on short-term working memory RT latency, compared to resistance training and normal activity (quiet, seated rest).

In non-cancer populations, aerobic exercise has been associated with significant improvements in tasks reflecting cognitive flexibility (Coles & Tomporowski, 2008) as well as for information-processing (Audiffren, Tomporowski, & Zagrodnik, 2008), and visual search tasks (Lambourne & Tomporowski, 2010). Further, other tasks including inhibition (measured with the Stroop task) (Guiney & Machado, 2013), verbal fluency (Fabre, Chamari, Mucci, Masse-Biron, & Prefaut, 2002), incongruent RT, and decision-making have shown significantly improved scores following aerobic exercise engagement (Quaney et al., 2009). Chang and colleagues (2012) have demonstrated that memory tasks such as visual short-term and free recall are sensitive to positive change following similar doses of exercise. Acute bouts of aerobic exercise have also been shown to improve specific aspects of cognitive function that operate on lower-level processing abilities both during (Adam, Teeken, Ypelaar, Verstappen, & Paas, 1997; Allard, Brawley, Deakin, & Elliot, 1989; Davranche & Audiffren, 2004; McGlynn, Laughlin, & Bender, 1977; McGlynn, Laughlin, & Rowe, 1979; McMorris & Graydon, 1997), and after (Fleury & Bard, 1987; Fleury, Bard, Jobin, & Carrière, 1981; Hogervorst, Riedel, Jeukendrup, & Jolles, 1996) exercise engagement. Similar effects have been found by Chang and colleagues (2009) when examining outcomes following resistance training.

Further, imaging studies in non-cancer populations have shown that exercise involvement results in post exercise increases in cerebral blood flow across brain areas, particularly those involved in memory and attention (Curtelin et al., 2018; Guiney, Lucas, Cotter, & Machado, 2015). Aerobic and resistance exercise call upon different systems within the body, as well as differing requirements for oxygen consumption, systemic blood flow, and cerebral blood flow. These components respond and interact differently, which could contribute to variation in cognitive performance (Rowland & Fernhall, 2007). Whereas aerobic exercise has consistently proven to be a viable non-pharmacological treatment for improving cognitive functioning in non-clinical populations (Hillman, Erickson, & Kramer, 2008), the strength of that association is unclear among BCS who have undergone chemotherapy treatment. A recent systematic review conducted by Zimmer and colleagues (2016) showed a favorable relationship between engagement in exercise interventions and a reduction in cancer-related cognitive impairment. Authors also underscored the need for RCTs using standardized neuropsychological assessments as well as statistical controls for possible confounding variables. Nevertheless, Zimmer and colleagues (2016) claimed that exercise that involves some form of relaxation-based component may be ideal for cognitive and related benefits. Still, a knowledge gap exists with respect to the specific acute effects of aerobic exercise on cognitive functioning in BCS. The use of aerobic exercise and a relaxation-based therapy in this study may help to fill in that gap as well as inform our understanding of the intervention's impact on fatigue, as shown by the structure of the working model.

Psychosocial Construct in the Framework

The final construct in the working model, which is proposed to mediate the interventions' effect on fatigue, is the psychosocial factor. This construct contains quality of life components such as stress and anxiety that share an association with mobility and physical capabilities (Lox, Ginis, & Petruzzello, 2017), which have both been shown to be improved through aerobic exercise. The pathway in the working model allows for testing the supposition that one's physical activity involvement has a clear relationship to other aspects of one's life, including psychosocial well-being (Crane et al., 2013), and its effect on the outcome factor of fatigue. Aerobic exercise has been associated with reduced depression and anxiety (Callaghan, 2004; Knapen, Vancampfort, Moriën, & Marchal, 2015) as well as the ability to elevate mood and various aspects of one's psychosocial beliefs (i.e., exercise specific self-efficacy) (C. Wood, Angus, Pretty, Sandercock, & Barton, 2013). These changes in turn, may improve factors such as self-efficacy for cognitive function (Dreisbach & Goschke, 2004) and perceptions of reduced fatigue among breast cancer patients (Van Vulpen, Peeters, Velthuis, Van Der Wall, & May, 2016).

To test these interrelationships, Rogers and colleagues (2017) conducted a three-month multicomponent exercise intervention (physical activity combined with behavior coaching, vs. printed health materials). This trial aimed to improve anxiolytic and depressive symptoms among BCS. Results showed clinically significant findings regarding reductions in fatigue and depressive & anxiolytic outcomes following exercise program engagement. Further, components targeting improvements among psychosocial constructs, including self-efficacy, also showed promising outcomes. Altogether, this multicomponent intervention provided strong support for combining aerobic exercise with an additional intervention to meet the psychological needs specific to BCS. However, behavior coaching can be costly and time consuming. Additionally, scalability and implementation of this type of intervention is questionable.

Existing Methods to Improve CRF and Related Symptoms

Testing complementary therapies that require greater exertion and strain on the mind and body may sound counterintuitive as a means to reduce fatigue, but being active and exerting both mental and physical effort appears to be beneficial for combatting CRF (Hilfiker et al., 2017a; LaVoy, Fagundes, & Dantzer, 2016). Aerobic exercise has been the intervention de jour for researchers aiming to reduce CRF (Cramp & Daniel, 2008; Galvão & Newton, 2005). However, findings from these trials are unclear regarding the underlying mechanisms responsible for changes in CRF.

Other therapies have been tested for their effects on physical, cognitive, and psychosocial outcomes among cancer survivors. For example, hormonal therapies have targeted physiological neuropathies and depressive symptoms (Schmitz et al., 2010), whereas physical therapy has been used to ease general pain, discomfort, and anxiolytic symptoms (Siegel et al., 2012). Additionally, resistance exercise and flexibility training have been explored for their capacities to improve cognitive and psychosocial functioning (Campbell, Mutrie, White, McGuire, & Kearney, 2005; Markes, Brockow, & Resch, 2006). Overall, these therapies have been effective in their efforts to improve outcomes among cancer survivors. It has been suggested that other treatment methods (e.g., relaxation training) paired with aerobic exercise may improve working memory and processing speed (Chiesa, Calati, & Serretti, 2011). Thus, the proposed intervention combining aerobic exercise and mindfulness-based relaxation training may improve fatigue and related components in this population.

Mindfulness-Based Relaxation Training

Mindfulness-based relaxation training is an appealing complementary therapy option and originates from Eastern meditative practices. It can be defined as brining one's complete and full attention into present awareness (Marlatt & Kristeller, 1999). There are many methods of mindfulness training and most forms encourage practitioners to be non-judgmental. Practitioners understand that any thoughts entering their mind during the training should not be evaluated as either good or bad, true or false, appropriate or inappropriate, or important or unimportant (Kabat-Zinn, 2000). Rather, the thoughts should be acknowledged and then the practitioner should allow their mind to return to a state of openness. Although this training is often tied in with religious or spiritual practices (Buddhism), one does not need to engage in such practices to reap the relaxing benefits of mindful meditation (Salmon, Santorelli, & Kabat-Zinn, 1998). BCS are highly open towards engaging in mindfulness training (Cramer, Lauche, Paul, & Dobos, 2012) which has been shown to be more effective for reducing psychosocial distress (Carlson et al., 2013) and physiological ailments (Shapiro, Carlson, Astin, & Freedman, 2006) when compared to other forms of non-exercise therapies among cancer patients and survivors. However, RCTs are needed to test effects on fatigue and related physiological, cognitive, and psychosocial components outcomes (Keng, Smoski, & Robins, 2011).

Shapiro and colleagues (2006) proposed a model to serve as a framework for testing hypothesized relations between psychological states of mindfulness and positive changes among psychological and physical symptoms. They posited that mindfulness was experienced when the axioms of intention (i.e., why you are practicing), attention (i.e., returning focus to moment-to-moment) and attitude (i.e., valence of one's views of the practice) were cultivated simultaneously. Following the occurrence of mindfulness, an individual can experience a shift in perspective, which is termed re-perceiving. This shift can then result in improved experiences of self-regulation, values clarification, cognitive-behavioral flexibility, and exposure. However, the authors noted that future research should examine pathways that will help to inform the understanding of how experiences following the shift in perspective can relate to well-being outcomes. Studying outcomes beyond just the reported experience of mindfulness will allow for a greater understanding of how mindfulness practice contributes to well-being.

BCS appear to be well-suited and willing to partake in mindfulness practice (Shapiro, Bootzin, Figueredo, Lopez, & Schwartz, 2003). The use of breathing-focused mindfulness training as an effective behavioral method for targeting fatigue-based reductions has been validated in non-clinical (Levinson, Stoll, Kindy, Merry, & Davidson, 2014) and certain cancer populations (Ledesma & Kumano, 2009). A recent systematic review has shown that there is some evidence for cognitive improvement among BCS following engagement in mindfulness-based training interventions (Cifu, Power, Shomstein, & Arem, 2018), resulting in improvements in executive function (Amso & Scerif, 2015), and fatigue. These findings give credence to the theory that mindfulness training may have similar effects among BCS.

A diagnosis of BC and the ensuing treatment(s) are commonly associated with experiences of psychological distress, for which many individuals lack the necessary coping skills (Sellick & Edwardson, 2007). Further, the bio-physiological components of the disease itself act on the brain areas (i.e. prefrontal cortex and the amygdala) that are related to the central circuitry responsible for the perceptions of anxiety and negative affect (Davidson, 2002). Medical costs, financial burden, and uncertainty of life expectancy combined with complex treatment programs likely add to the fatigue, anxiety, uncertainties, and stress already associated with cancer (Garland, Tamagawa, Todd, Speca, & Carlson, 2013; Stanton, Revenson, & Tennen, 2007; Zainal, Booth, & Huppert, 2013). Chang and colleagues (2004) have demonstrated that engaging in mindfulness-based relaxation training aimed at reducing stress and anxiety improves self-efficacy for being able to relax, as well as self-efficacy for improving mood and fatigue (Caldwell, Harrison, Adams, Quin, & Greeson, 2010), and self-efficacy for being able to take part in aerobic exercise (Buckelew et al., 1998). These improvements in self-efficacy are also found following exercise engagement (Anderson & Shivakumar, 2013). Therefore, it is reasonable to theorize that the combined effects of aerobic exercise and mindfulness-based relaxation training will strengthen multiple skills and self-efficacy as implied by the working model, when compared to standalone exercise or relaxation training. In turn, self-efficacy for relaxation should improve one's perceptions of fatigue following completion of the acute aerobic exercise and relaxation training intervention.

Combined Exercise and Relaxation Methods

Although no RCTs have explored the effects of combined aerobic exercise and mindfulness training interventions among BCS, one proof of concept study has been proposed. This study intends to examine outcome effects on cognitive function in older adults in order to determine the efficacy of such an intervention (Salmoirago-Blotcher et al., 2018). Existing support for the cognitive implications of a combined exercise and relaxation intervention comes from Edwards and Loprinzi's (2018) work with healthy individuals. Participants were randomly assigned to complete an acute (ten-minute) bout of walking either preceded or followed by ten minutes of meditation, or to a control condition (i.e., quiet sitting). Executive function was assessed before and after activity completion. They found significant group effects on inhibition/attention (as measured by Stroop congruent RT) for the walking and meditation interventions, but not in the control group. Although working memory and cognitive flexibility did not show significant improvements (e.g., in accuracy or RT), the authors state that future research should evaluate these effects among different populations and different forms of aerobic exercise.

One alternative form of treatment that combines aspects of aerobic exercise and relaxation training and lends support for mind-body applications is the practice of Hatha yoga. This style of yoga is based around synchronized movements and breathing patterns. Recently, researchers have studied Hatha yoga and its theorized effects on the brain and found evidence to suggest that yoga training has positive effects on executive function (Luu & Hall, 2016; Miyake & Friedman, 2012). Specifically, acute bouts of Hatha yoga have been associated with significant improvements in inhibitory control (Gothe, Pontifex, Hillman, & McAuley, 2013), working memory (Gothe et al., 2013; Telles, Bhardwaj, Kumar, Kumar, & Balkrishna, 2012) and attentional processes (Telles et al., 2012). Additionally, the physiological (i.e., cortisol reduction) and psychosocial (i.e., perceived reductions in stress) mechanisms underlying deliberate and effortful breathing during Hatha yoga are theorized to be responsible for decreases in cortisol levels (Starkman et al., 1999), anxiety (Nemeroff, 2003), and perceived stress responses (Granath, Ingvarsson, von Thiele, & Lundberg, 2006; Rocha et al., 2012; West, Otte, Geher, Johnson, & Mohr, 2004). These findings imply that Hatha yoga and its inherent relaxation practice present significant psychosocial and cognitive benefits, which are constructs that are negatively impacted by cancer. Specialized, long-term yoga interventions have shown promising results for reducing CRF among BCS. However, Bower and colleagues (2012) expressed that mechanisms, duration of intervention engagement necessary to realize benefits, and duration of benefit experience are areas that require focus in future research. Accordingly, researchers also express the need to examine methods combining exercise and relaxation in the context of RCT's to better understand the questions at hand (Bower, Garet, & Sternlieb, 2011).

The combination of aerobic exercise and mindfulness-based relaxation training's influence on self-efficacy for cognitive function, relaxation, and exercise has received little attention. In light of that, this study will incorporate a form of mindfulness-based relaxation training that aims to affect these components and reduce CRF. A meta-analysis reviewing the effects of traditional mindfulness training on health-related outcome variables among healthy and clinical populations reported strong effect sizes for improved levels of anxiety, depression, distress, and disease-state recovery; however, cancer was not included (Grossman, Niemann, Schmidt, & Walach, 2004). Evidence also supports the use of brief mindfulness training interventions for improving selective aspects of memory and executive function abilities when compared to no intervention (Chambers, Lo, & Allen, 2008) and other forms of relaxation training (e.g., silent meditation) (Tang et al., 2007). Furthermore, one systematic review examined the impact of mindfulness training on cognitive abilities, including attention, memory, and executive attention across healthy and clinical populations (Chiesa et al., 2011). Results showed that although evidence exists to suggest that this form of training can enhance cognitive functions, the evidence should be considered with caution, as further studies of high quality are needed. There is evidence from a quasi-experimental study, which suggests that brief engagement with mindfulness training can improve physiological outcomes among BCS (Matchim, Armer, & Stewart, 2011), warranting a more rigorous RCT testing effects on a broader scope of biopsychosocial outcomes.

Although mindfulness training has been associated with benefits in areas related to psychosocial problems affecting BCS (Rahl, Lindsay, Pacilio, Brown, & Creswell, 2017), a lack of evaluation regarding construal of instructions for use exists, specifically for the abundance of available technology-delivered forms (Mani, Kavanagh, Hides, & Stoyanov, 2015). By using technology to deliver the mindfulness-based relaxation training in this trial, we can improve consistency in how participants interpret instructions. This should enhance fidelity of the trial, an inherent weakness of many mindfulness training programs. Presently, there is no consensus on best practices for delivering instructions and guidance for this form of treatment (Davidson & Kaszniak, 2015). Finally, no studies have compared technology-delivered mindfulness to traditional intervention forms such as aerobic exercise, which are associated with improvements among BCS, notably fatigue, and cognitive function.

Technology Delivered Mindfulness Training

In an effort to clarify issues regarding the delivery and practice of mindfulness-based relaxation training, this study will utilize the commercially available Muse app and device, created by InteraXon, which delivers guided mindfulness-based relaxation training. Although this device was not designed to focus on specific clinical populations, its intended usage does qualify it as a potentially advantageous component for individuals experiencing symptoms of chemo-brain. This technology is intended to gather brainwave data, which in turn can be used to provide neurobiofeedback and tailored relaxation training. A unique quality of the Muse is that it contains features, which offers all four sources of self-efficacy information. *Mastery experiences* occur through the auditory and visual feedback provided by the app after each session. *Vicarious experiences* occur through the app's ability to create a visual and auditory experience that enables the user to feel like they are in a natural, outdoor setting (i.e., sitting on a beach or in a rainforest). Also, ideal performances are modeled for them by the app. *Verbal persuasion* occurs through the app's performance-based auditory guidance and feedback during the relaxation session. This directs the user to allow their thoughts to pass and return to a breathing-centered focus. Finally, *physiological interpretation* occurs at the conclusion of the relaxation session, when then app provides a visual evaluation and output of the user's performance during the session.

Based on the user's activity during training, each session's results are determined by information regarding the amount of time spent shifting between active, neutral, and calm states. Information concerning each user's ability to recover from mind-wandering fluctuations in order to return to a relaxed state is also made available at the end of the session. Together, these outcome factors can reasonably be assumed to improve an individual's self-efficacy for engaging in relaxation training, which has been shown to be related to improvements in other forms of self-efficacy (Buckelew et al., 1998; Caldwell et al., 2010; V. Chang et al., 2004). Research using the Muse app and device has shown that negative somatic symptoms were reduced and well-being-related variables (e.g., depression, anxiety, and distress) were improved following six weeks of daily use (Bhayee et al., 2016). However, no published, scientific research has evaluated the acute effects of training on the Muse app and device on fatigue, relaxation, or other related outcomes. Further, the feasibility for use of technology-delivered relaxation training has not yet been shown within BCS. To this accord, research focusing on cognitive outcomes among BCS has produced results that leave much to be answered in terms of optimal methods and interventions.

In a RCT, Peterson and colleagues (2018) aimed to improve cancer-related cognitive impairment through the use of aerobic exercise combined with cognitive training. Participants (n=28) varied in their form of cancer diagnoses and were randomized to complete a computer-based cognitive training, aerobic exercise, combined computer-based cognitive training and aerobic exercise or flexibility training. Although the aerobic exercise condition showed improvements in cognitive function, the combined computer-based cognitive training and aerobic exercise condition did not. Peterson et al., suggest the possibility for outcome variables to be improved if exercise and technology-delivered adjuvant therapies are delivered separately, as opposed to simultaneously, as this may be too physically or cognitively demanding for some individuals (2018). Although evidence within the cancer survivorship population has shown support for aerobic exercise (Hsieh et al., 2008; C. Schneider, Hsieh, Sprod, Carter, & Hayward, 2007a, 2007b), and technology-delivered treatments (e.g., computerized biofeedback, computerized education modules, and mobile cognitive training) (Alvarez, Meyer, Granoff, & Lundy, 2013; Dow Meneses et al., 2007; Kesler et al., 2013) for quality of life improvements, it remains unclear whether the combination of these two intervention modalities may provide additive benefits among BCS. To assess the value of the technology-delivered mindfulness training, certain constructs from the revised Technology Acceptance Model will be measured

(Wu & Wang, 2005). These constructs include risk, cost, compatibility, perceived usefulness, perceived ease of use, behavioral intention to use, and actual use. However, it should again be noted that no studies have investigated the impact of combined of aerobic exercise and mindfulness training for fatigue improvement in BCS who have received chemotherapy. This intervention will serve to lay the base understanding for acceptance and efficacy.

Summary

BCS experience a variety of negative effects following diagnosis and the accompanying treatment. Fatigue is commonly reported to be one of the most prevalent and consequential symptoms experienced. Prior research has investigated many forms of interventions for improving fatigue, but their effects are unclear among BCS. However, it is clear that aerobic exercise is associated with improvements in areas that are also affected in BCS, such as physiological factors, cognitive function, and anxiolytic symptoms. Further, relaxation training has been shown to be associated with improvements in fatigue and related symptoms. To date, no studies have explored the combined impact of these treatments on CRF in the BCS population. Further, the lack of consistency found among study design methods and guidelines for practicing certain forms of mindfulness training has resulted in unclear conclusions regarding the most efficacious forms of training for BCS. Therefore, this trial will adhere to a rigorous design, incorporating technology (a medium that the BCS population is open to using) as an innovative delivery method for mindfulness training. Additionally, mechanisms underlying changes in CRF and related concepts are unclear. Together, the methodology used in this trial intends to optimize fatigue and related cognitive issues experienced among BCS while informing the knowledge gaps regarding responsible mechanisms.

In order to address the lack of clarity surrounding the relationships among aerobic exercise, mindfulness training and fatigue, this pilot trial will incorporate an acute design to offer insight into the brief effects of combining aerobic exercise and mindfulness training, when compared to standalone aerobic exercise or mindfulness training. The inclusion of multiple measures within the working latent variable model should reduce measurement error, and allow for testing simultaneous theorized relationships between CRF and biopsychological mediators that are not well understood within this population. However, limitations still exist for this study design. These include the use of stationary cycling as opposed to other forms of aerobic exercise such as walking or treadmill use. Inherently, the smaller sample sizes used in pilot trials may not be entirely representative of the true population. Further, the sample may not enjoy using a technology-delivered form of mindfulness training. Nonetheless, this pilot trial is designed to inform a new research paradigm for assessing complementary therapies in the BCS population, and must not address all issues described in the existing literature.

Chapter III: Research Design and Methods

Sample and Procedure

Adult (18+), female, breast cancer survivors (ductal carcinoma in situ or stages I-IV) from the Central Illinois area (*N*=40), who had completed treatment within the past five years were recruited for the Responsiveness to Acute Changes in Exercise & Relaxation (RACER) trial. Champaign County, located in Central Illinois, mirrors national rates of diagnosed breast cancer cases, making this community reflective of the national population (Health Data, 2014). Primary and secondary outcomes were assessed across three separate appointments (the first and third appointments lasted two hours, and the second appointment was a single hour). All participants provided medical clearance prior to randomization and participation. Participants received $50 in cash ($10 per hour) upon completion of all study requirements.

All recruitment, screening, and randomization took place on a rolling basis occurring between October 15th, 2018 and March 1st, 2019. The primary method of recruitment was through a University maintained email listserv. Additionally, recruitment involved speaking with local breast cancer groups, posting on social media platforms (e.g., Facebook), advertising on a laboratory website, and utilizing local breast cancer listservs. Recruitment also involved speaking with recreational activity groups, religious groups, and neighborhood associations in the area. Local centers, health-based group meetings, yoga studios, religious sites and offices of healthcare practitioners were targeted in order to assist with the recruitment process. These locations possessed strong outreach into the local BCS population. Prospective participants were directed to a website that offered details and information regarding inclusionary criteria as well as details on how to contact the trial's research in assistants in order to join. Each source of recruitment material contained contact information (e.g., study e-mail address, and phone number), as well as basic information regarding the study premise and targeted population and the address for the study’s website. Those who were interested were screened via telephone in order to ensure that eligibility requirements were met. Through the recruitment media, potential participants were instructed to contact the study coordinator and conduct a brief screening phone call to ensure eligibility criteria was met. Following successful screening, participants were mailed two copies of the university’s Institutional Review Board approved informed consent document, as well as a form providing permission to contact each participant’s physician, and the physician’s clearance form. Upon receipt of these signed documents, the participant’s physician was faxed, and following receipt of a signed physician’s clearance, a baseline survey link was sent to the participant. Once the survey was completed, participants were considered to be enrolled, and three testing appointments (separated by a minimum of 24 hours) were scheduled. All appointments were required to occur within a 7-day period. All participant data was stored in a secure database within the research lab. Also, research assistants (trained in CPR, AED & First Aid, as well as CITI requirements) conducting recruiting, screening and testing had no prior relation to the participants and were not involved in data entry or analysis.

Inclusion/Exclusion Criteria

Participants (18 years and older) who qualified for study inclusion were previously diagnosed with breast cancer (ductal carcinoma in situ or stages I-IV), and had completed at least one cycle of chemotherapy treatment, with all treatment having been completed within the last five years. Further, participants had reliable access to the Internet. All participants reported at least one complaint of an issue with physical function, fatigue, memory, planning, thinking abilities, negative mood, depressive symptoms, or anxiety. Participants’ basic memory abilities were assessed using the Telephone Interview for Cognitive Status inventory (Brandt, Spencer, &

Folstein, 1988). All participants reported being capable of engaging in sustained stationary cycling at a moderate intensity. Additionally, participants were excluded if they were deaf in both ears, and unable to comfortably wear a pair of ear-bud headphones. Further exclusionary criteria included being color-blind and failing to have vision of at least 20/40 with the aid of contacts or glasses. Finally, a history or diagnosis of epilepsy was exclusionary.

Blinding Procedures

The primary investigator was blinded to group assignment, and only took part in data analysis as well as ensuring all documents were handled correctly. Separate research assistants, who were blinded to the study's purpose, were responsible for randomization, testing, intervention administration and data collection. A different research assistant served as the telephone screener and handled all phone, e-mail and website contacts.

Environment

This trial took place entirely at the Chez Center for Wounded Veterans in Higher Education at the University of Illinois at Urbana-Champaign. Aerobic exercise sessions occurred in the Center's exercise room and all post-exercise activity sessions took place in a quiet, unoccupied, adjacent room. Baseline questionnaire completion was finished at home prior to the intervention appointment, and baseline cognitive testing, post-intervention questionnaire and exercise & activity engagement occurred in the Center's research computer lab.

Study Design (see Figure 2 for Study Flow Chart)

Upon successful screening, participants were asked to fill out an informed consent, which was also mailed to them along with a calendar detailing study procedures. A document requesting permission to contact the individual's physician and a form detailing the study for the physician to sign was also included in the mailing. It was requested that the form be brought directly to the physician (it was also offered to be faxed) for approval, signatures, and returned for proper documentation. Participants had the option to meet a research assistant (RA) at the laboratory to sign the paperwork. The University Review Board approved all documents for use. Following receipt of the required documentation, an e-mail was sent and a phone call was made in order to schedule the three appointments. At the first testing appointment the RA ensured that all baseline questionnaires have been completed before proceeding with cognitive testing.

Following submission of the required study enrollment paperwork, all additional surveys, questionnaires and testing were assessed electronically. The baseline and post-trial questionnaire battery were comprised of psychosocial questionnaires evaluating fatigue, memory, affect, and perceived cognitive, physical and psychosocial functionality. The average time to complete this inventory was approximately 20 minutes. At the initial appointment, participants completed a brief survey prior to cognitive testing in order to assess their current affective states, which was checked for completion by the accompanying RA once the responses had registered. Questions regarding one's self-efficacy for cognitive abilities, stationary cycling duration and relaxation training were assessed prior to cognitive testing during the first appointment and again at the conclusion of the third appointment. Following completion of cognitive testing at the first appointment, participants took part in their randomized intervention before proceeding to complete a short follow-up questionnaire. During each participant's second appointment, they only completed a brief questionnaire before moving on to their randomized intervention and follow up questionnaire. Post-intervention activity follow-up questions during each of the three appointments took 5-minutes to complete.

Cognitive testing batteries at the first and third appointments were comprised of three brief cognitive assessments focusing on each construct of executive function (all three tasks require a combined 14 minutes to complete). These tests were administered prior to the exercise and activity intervention portion of the session at the first appointment and again following the post-intervention testing session at the third appointment. All participants responded to a survey focused on their likes and dislikes, satisfaction, recommendations, and enjoyment of the assigned training session at the third appointment.

The RACER trial was a three-armed, randomized pilot trial designed to examine the acute effects of three different interventions focused on moderate intensity aerobic exercise, relaxation training, or a combination of the two, on fatigue and related deficits in executive function (measured at baseline, and immediately following the conclusion of randomized activities at the third session). Each activity session was randomly counter-balanced (i.e., the order of exercise or mindfulness training and quiet rest). The experimental intervention condition (comprised of 20-minutes of aerobic exercise followed by 20-minutes of relaxation training) was compared to two, single component conditions (i.e., either aerobic exercise or relaxation training followed by 20-minutes of quiet sitting), which served to reflect currently used interventions among BCS and create a time-matched period for each condition. The length of time chosen for exercise is a validated and reasonable length which took into account concerns regarding baseline levels of activity and chronic fatigue, and incorporated a five minute warm-up with no resistance (Blaney et al., 2016).

Aerobic Exercise Only Group (AERO)

Participants randomized to the AERO group engaged in three separate 20-minute sessions comprised of a 5-minute, resistance-free warm-up, and 15 minutes of moderate intensity stationary cycling (50-70% age predicted heart rate max) aerobic exercise. Each of these sessions also included 20 minutes of uninterrupted quiet rest, which reflects existing interventions used among this population. The order of activities were randomly determined for each session. All participants randomized to a condition involving stationary cycling utilized the Cybex stationary bike, model #525C for the aerobic exercise portion of this study. This stationary bike provided the necessary data feedback to ensure that exercise remained aerobic, including speed, rotations per minute, resistance, time, and power output. In order to ensure engagement and internal validity for the exercise portions of the trial, RAs collected information regarding levels of effort during exercise using the Borg Ratings of Perceived Exertion scale, as well as heart rate (measured by a fingertip oximeter), and speed information every five minutes. Heart rate was also measured during the quiet rest period.

Relaxation Only Group (RELAX)

Participants in the RELAX group completed three separate sessions of 20-minutes of relaxation training using a commercial biofeedback device (Muse headset & smartphone app), which has been used for intervention and measurement applications (Ijjada, Thapliyal, Caban-Holt, & Arabnia, 2015; Stirenko et al., 2017). The Muse device collected data from seven sensors to record brain activity. Two sensors are placed on the scalp over the frontal lobes, two over the temporal lobes, and three reference sensors are placed around the forehead and ears. The recorded activity is processed within the app and interpreted as affective stress states including relaxation, calmness and alertness. The Muse's software was designed to help users achieve relaxation by training breathing strategies shown to be effective for reducing beta brainwaves and increasing alpha brain waves. During this process, participants were informed about how to calibrate the headset by a tutorial so that the sensors were able to get a baseline measure of brain activity. Instructions were then given to focus on one's breathing cycle by counting their breaths up to 10 and then returning back to one. Participants were informed that real time auditory feedback was provided through the sounds of wind, when one's mind was calm, so was the wind; when one's mind was active, the winds picked up and blew. The app ran on an iPad Air 2, and connected to the wearable headband portion via Bluetooth. Following completion of each session, a visual report was generated, which contained information regarding the affective states being monitored and the user's brain activity in general. Participants were also asked to take part in 20 minutes of uninterrupted quiet rest in order to match the time of the AERO condition and reflect additional interventions used among this population. The order of activities was randomly determined for each session. Heart rate was measured throughout the mindfulness activity by observation of the fingertip oximeter without having to have interrupted the participant; heart rate was also measured during quiet rest.

Aerobic Exercise and Relaxation Training - Intervention Group (COMBINED)

Participants randomized to the COMBINED group completed three separate sessions comprised of 20 minutes of aerobic exercise following baseline testing. This condition completed the same questionnaires as the AERO condition, including a questionnaire focused on their anxiolytic state following exercise. Data regarding effort levels, as measured by RPE were also collected every five minutes during the exercise portion of the session. This condition was also asked to wear the same commercial biofeedback device as the RELAX condition and complete 20-minutes of relaxation training. The order of activities was randomly determined for each session. As no previous interventions have researched the combined effects of aerobic exercise and relaxation training among BCS, this intervention was intended to explore a novel method for further reducing fatigue and its associated factors. In order to ensure optimal engagement with the device, participants were notified that their performance was recorded and monitored by the app during their session. Upon completion of the intervention at the third appointment, participants completed cognitive testing and a post-activity survey regarding engagement and enjoyment of the training sessions.

Measures

Demographics

Standard demographic questions inquired about gender, race, marital status, activity levels as measured by the Godin Leisure-Time Exercise Questionnaire (GLTEQ), employment and education status, and questions inquiring about type, length and end of primary breast cancer treatment.

Feasibility, Enjoyment, and Acceptance

At the conclusion of the third appointment all participants completed an adapted (to reflect the nature of the intervention's exercise and relaxation components) version of Davis (1989) and Davis et al., (1989) perceived usefulness and perceived ease of use questionnaire (e.g., "Using the technology-delivered relaxation training program improved my thinking", "I found the technology-delivered relaxation training program to be easy to use"). These items will be measured using a 7-point Likert scale (1 = Strongly disagree, 4 = Neutral, 7 = Strongly agree) and will assess attitudes towards the technology-delivered relaxation-training program, standalone relaxation training, and standalone aerobic exercise. Cronbach's alpha reliability was found to be $\alpha = .97$ for usefulness and $\alpha = .91$ for ease of use questions within the original questionnaire. Additionally, a systematic evaluation of the trial was included. Questions (e.g., I enjoyed using the mindfulness training device) using a 7-point Likert scale (1 = Not at all, 4 = Neutral, 7 = Completely) inquiring about overall enjoyment, satisfaction, and likes and dislikes were administered. Questions focused on feasibility using a 3-point Likert scale (1 = Agree, 2 = Disagree, 3 = Unsure). The adapted questionnaire used in this trial had a reliability of $\alpha = .93$.

Further, an open-ended qualitative question asking about overall recommendation, and modifications was included.

Fatigue

Prior to, and following activity engagement at each appointment (as well as quiet rest, totaling three occurrences at each appointment), participants completed the revised, 12-item *Piper Fatigue Scale* (PFS) (Piper et al., 1998). This scale measured current, in the moment fatigue levels, and is more sensitive in assessing acute, short-term effects following physical activity among cancer survivors than other established measures (Fong et al., 2012). This scale required respondents to select their answers according to a "0" (most positive or desirable response) to "10" (most negative, fatigue is having a strong impact) scale. A total fatigue score is calculated by summing each of the 12 responses and dividing by 12; accordingly, a total fatigue score of 0 corresponds to no fatigue, a score of 1-3 is labeled as mild, 4-6 is labeled as moderate, and 7-10 is labeled as severe. Fatigue scores used for statistical analyses were the total score reported at the end of each session, allowing the scale to capture in the moment levels of perceived fatigue. This scale has been validated among breast cancer survivors (Reeve et al., 2012) and showed a reliability score of $\alpha = 0.92$. When assessed in this sample, the scale contained a reliability score of $\alpha = 0.92$.

Participants also completed two subscales of the *Activation Deactivation Adjective Checklist* (AD ACL) (Thayer, 1986), in order to measure changes in tiredness (Tiredness subscale) prior to activity engagement at each appointment and energy (Energy subscale) levels reported at post-session assessment, to allow for the accumulated experiences of the activities to have their effects on reported energy. The Tiredness subscale contained two items that were reverse scored and contains four possible response options including 1 "Very Much So," 2

"Moderately So," 3" "Somewhat," and 4 "Not at All." Whereas the Energy subscale is also comprised of 5 items with responses ranging from 1 "Not at All," 2 "Somewhat," 3 "Moderately So," and 4 "Very Much So." Responses for each of the five questions (respective of their subscale) were summed together to create an overall score. Overall scores ranged from five to 20. These measures have been validated in studies involving aerobic exercise. In this trial, the Energy subscale had a reliability score of $\alpha = 0.81$, and the Tiredness subscale had a reliability of $\alpha = 0.86$. This inventory has previously been used in acute exercise trials in order to asses short-term changes in quality of life components (Barr, Ginis, & Arent, 2010). Finally, participants also completed the Perceived Mental Fatigue Questionnaire (PMFQ), a novel inventory which is informed by established batteries (Beurskens et al., 2000; Johansson, Starmark, Berglund, Rödholm, & Rönnbäck, 2010; G. Wood, Bentall, Göpfert, & Edwards, 1991).

Cognitive Measures

All cognitive testing was delivered via an iPad Air-2 during the first and third sessions, using the NIH toolbox. All cognitive tasks reported automatically generated scores following task completion. All scores were corrected for age, gender, education and handedness.

Working Memory

Working memory abilities were measured with the *NIH Picture Sequence Memory Task*. This 7-minute task involved recalling the order of images, which were presented one at a time in a particular order on the iPad screen. Participants were then asked to recall the correct sequence of pictures over two learning trials; sequence length varied from 6-18 pictures. The variation in amount of stimuli is incorporated as a method for increasing difficulty as the task continues in sequence. Participants were then given credit for each adjacent pair of pictures (i.e., if pictures in locations 7 and 8 and placed in that order and adjacent to each other anywhere – such as slots 1 and 2 – one point will be awarded) they correctly place, up to the maximum value for the sequence, which is one less than the sequence length (if there are 18 pictures in the sequence, the maximum score is 17, because that is the number of adjacent pairs of pictures that exist). The outcome measure of the participant's score was the cumulative number of adjacent pairs of pictures remembered correctly during the testing sessions two trials regardless of the number of pictures in the sequence. The test took approximately 7 minutes to administer. This task had a test-retest reliability of $\alpha = 0.84$, and a discriminant validity of $\alpha = 0.04$, when compared with relevant gold-standard measures such as the N-back task (Dikmen et al., 2014).

Inhibitory Control and Attention

The Flanker Inhibitory Control and Attention Task measured inhibition and required the participant to focus on a given stimulus while inhibiting attention to the stimuli flanking it. Sometimes the middle stimulus was pointing in the same, congruent direction (→ → → → →) as the flanker arrows and sometimes in the opposite, incongruent direction (→ → ← → →). The NIH toolbox automatically calculated an overall correct score, which took into account the correct number of responses accuracy and ranged from "0" (worst performance) to "20" (best possible performance). A change (post minus baseline) score was used to address the inhibitory aspect of cognitive function. This task took approximately 3 minutes to administer. This task has been validated among individuals with neurological disorders (Zelazo et al., 2013).

Cognitive Flexibility

The *Dimensional Change Card Sort* task (DCCS) measures cognitive flexibility and task-switch capabilities. Two target pictures were presented that vary along two dimensions (e.g., shape and color). Participants were asked to match a series of bivalent test pictures (e.g., yellow balls and blue trucks) to the target pictures, first according to one dimension (e.g., color) and then, after a number of trials, according to the other dimension (e.g., shape). The ensuing "switch" trials were also employed, in which the participant was required to change the dimension being matched. For example, after four straight trials matching on shape, the participant may have been asked to match on color on the next trial and then go back to shape, thus requiring the cognitive flexibility to quickly choose the correct stimulus. The NIH toolbox automatically calculated an overall correct score, which took into account the number of correct responses and ranged from "0" (worst performance) to "40" (best possible performance). This task has been validated among individuals with neurological disorders (Zelazo et al., 2013).

Ancillary Measures and Outcomes

Anxiety and Depression

Anxiety and depression was assessed during the initial phone screening using the *Hospital Anxiety and Depression Scale* (Zigmond & Snaith, 1983), which has been validated in clinical populations. This survey required participants to respond to 14 questions on a scale from 0-3 (some questions are reverse scored due to valence of response options). This scale produced separate overall anxiety and depression scores. The test re-test reliability for this scale is $r = 0.84$ (Poole & Morgan, 2006). In this sample, a reliability score of $\alpha = 0.64$ was found.

To further investigate anxiolytic factors before and after intervention engagement, the *Beck Anxiety Inventory* (BAI) (Beck, Epstein, Brown, Steer, & psychology, 1988) was administered (with instructions to explicitly inquire about change over the past 7-days). Participants answered 21 questions on a 1-4 scale (1 = Not at all, 2 = Mildly but it didn't bother me much, 3 = Moderately- it wasn't pleasant at time, 4 = Severely- it bothered me a lot). A total state anxiety score was calculated by adding together the scores of individual responses. A higher score is positively correlated with higher levels of state anxiety. This inventory had a test re-test reliability value of $\alpha = .75$ (Beck, Epstein, Brown, & Steer, 1988). The reliability for this scale in this population was $\alpha = 0.55$.

Intervention Expectancies

Expectations of change following exercise and/or relaxation training involvement were assessed using a novel 15-item questionnaire for the purpose of inclusion in future analyses. These questions are modeled after Sears and Stanton's (2001) work with expectancies following exercise engagement. Questions focused on the perceived capabilities of relaxation training and aerobic exercise for improving outcomes such as fatigue, memory, negative affect and health-related quality of life. Each question contains a seven-option response ratings scale (1 = Completely unsuccessful, 2 = Fairly unsuccessful, 3 = Somewhat unsuccessful, 4 = I have absolutely no expectation, 5 = Somewhat successful, 6 = Fairly successful, 7 = Completely successful). An overall confidence score was calculated by averaging responses across the applicable items (a score closer to 1 represents higher confidence). In this sample the reliability for this scale was $\alpha = 0.92$.

Self-Efficacy for Stationary Cycling

To account for eventual analysis of exercise-specific self-efficacy, each participant completed the *Self-Efficacy for Cycling Duration* (SEDU) questionnaire. This survey was comprised of six questions, which asked participants to rate their confidence in their ability to "cycle at a moderately hard pace" for a certain period of time (e.g., 10 minutes, 20 minutes, etc...) without stopping. Ratings range from "0" (not at all confident) to "100" (highly confident). Similar measures have been validated for acute exercise bouts (Treasure & Newbery, 1998). In this sample the reliability for this scale was $\alpha = 0.97$.

Self-Efficacy for Relaxation

Self-efficacy for relaxation training was measured using novel self-efficacy items inquiring about one's confidence in their ability to complete the specific form of training incorporated in the trial and achieve a relaxed state. These items focused on one's ability to complete a specific form of relaxation training for periods of 5, 10, 15, and 20 minutes and inquired about their confidence to feel relaxed after that specific amount of time. Each item used ratings ranging from "0" (not at all confident) to "100" (highly confident). These items will also be incorporated into future analyses. In this sample the reliability for this scale was $\alpha = 0.94$.

Self-Efficacy for Memory

Memory self-efficacy was evaluated using the *Memory Self-Efficacy Questionnaire* (MSEQ). The MSEQ was comprised of 50 questions, covering ten memory tasks (e.g., errands, maze travel and digit recall). Relevant subscales focusing on ability to remember items on a grocery list and driving directions were used in analyses. Confidence in one's memory ability was recorded by selecting perceived abilities for multiple memory-based situations, ranging from 0 to 100% confident, separated by increments of 10. The reliability estimate for this questionnaire is $\alpha = 0.90$ (Berry, West, & Dennehey, 1989). Each question among the self-efficacy surveys ended with "if I wanted to." This addendum has been theorized to remove any measurement ambiguity between motivation and ones belief in their ability to control the completion of the behavior in question (Rhodes & Courneya, 2004).

Perceptions of Physiological Changes

A 5-item scale, modeled on the *Experienced Bodily Changes Scale* (EBCS) (O'Connor, Rousseau, & Maki, 2004), was used to assess energy levels, breathing, mental stress, mindfulness and awareness, mood, and heart rate controllability "over the previous seven-day period.” Each item was scored on an 11-point scale from -5 to 0 to +5 (signifying a continuum of decline to stability/no change to improvement; exact anchor varied according to the item). Given the many changes to the scale, psychometrics reported by Mullen (2011) and O’Connor, Rousseau, and Maki (2004), are irrelevant. However, the items were assessed for internal reliability and construct validity within the context of latent variable modeling. This scale was administered at the completion of the third appointment to obtain evaluations of each participant’s physiological interpretations. In this sample the reliability for this scale was α = 0.77.

Quality of Life

The *Brief Fatigue Inventory* (BFI) was used to assess short-term changes in fatigue and their effects on common disturbances among quality of life related components for BCS over the course of one week and will be incorporate into future analyses. For this inventory, respondents rated nine items according to a “0” (no fatigue) to “10” (fatigue as bad as one can imagine) scale. The scores were defined as: Mild (1-3), Moderate (4-6), and Severe (7-10). A global fatigue score was calculated by averaging the responses from the nine items (Mendoza et al., 1999). This inventory has been validated among individuals with cancer showing strong concurrent validity with the 41-item *Functional Assessment of Cancer Therapy: Fatigue* (FACT-F) questionnaire (r = 0.88) as well as the *Profile of Mood States* (r = 0.84). Internal consistency for this inventory is α = 0.96 (Shahid, Wilkinson, Marcu, & Shapiro, 2011). In this sample the reliability for this scale was α = 0.96.

Attitudes Towards Exercise

Wang’s (2011) 5-item *Anticipated Negative Affect Questionnaire* (ANAQ) was assessed prior to activity at the first appointment and following the completion of activity at the third session in order to evaluate changes in one's attitudes towards exercise engagement. The ANAQ assessed about one's feelings towards "not regularly participating in physical activity "over the next four weeks" and how it would make them feel. Each of the five questions in the ANAQ ranged from "1" (e.g., relaxed, not guilty, no regret, not angry, and displeased) to "7" (e.g., tense, guilty, regret, angry, and pleased). In order to calculate a global negative affect score, items one through four were summated, along with the score from item five, after it was reverse coded. Higher global scores were indicative of higher negative affect related to not taking part in physical activity. In this sample the reliability for this scale was $\alpha = 0.71$.

Mental Engagement in Training

A modified version of Brockmyer and colleagues' (2009) 19-item Game Engagement Questionnaire (GEQ-M) was used to measure participants' engagement and adherence to instructions for their randomized intervention activity. This questionnaire is vital for eventually investigating and understanding how participants interacted with their randomized activities and the impact that may have had on outcomes in focus. Responses included 0 = no, 1 = sort of, and 2 = yes. Additional components inquiring about intervention feasibility and acceptability were used. In this sample the reliability for this scale was $\alpha = 0.80$.

Biometric Measures

Prior to cognitive testing (and all ensuing activities), heart rate was measured in a quiet room with a fingertip oximeter five minutes after the participant's arrival, in order to allow levels to return to normal prior to recording a baseline value. Participant's baseline resting blood pressure was measured using an automated Omron BP785n (supine, sitting & standing). Height and weight were recorded using an electronic scale and height device. Body-fat percentage and body mass index were assessed using an Omron HBF-306C device. This device was very susceptible to metal jewelry, digested liquids, and electrolytes. Therefore, participants were instructed to be conscious of this before coming in to each of their sessions. Throughout the exercise portion of the aerobic session, and silently (by observing the oximeter screen, as to not interrupt the participant) during mindfulness and quiet rest sessions, RAs collected heart rate at five-minute intervals using a fingertip oximeter. Additionally, ratings of perceived exertion and affective valence were also evaluated every five minutes through the use of the Borg and Feelings scales, respectively. Future analyses are planned to explore changes among biometric variables over the course of the intervention.

Data Analytic Plan

Power Analysis

An a-priori G*power analysis with and without covariates, using the fixed effects for a repeated measures ANCOVA suggested a range of 51-62 individuals in order to be powered at a 80% to detect a large effect (*f*). However, the analysis revealed the need for 41 individuals using an α value of .05 and a β value of .25 (to target 75% power) in order to reveal a large (.40) effect size (partial $\eta^{2)}$ among change scores for a statistical analysis using 3 groups. While a minimum of 41 participants were needed for these analyses, targeting a study sample of $n = 45$ accounted for potential attrition of 10%.

Although this trial served as the first randomized pilot trial of its kind among BCS, the desired sample size was similar to previously conducted trials (F. Dimeo, Schwartz, Wesel, Voigt, & Thiel, 2008; Peterson et al., 2018; Themanson & Hillman, 2006). Among BC patients, Dimeo and colleagues assigned 32 participants with mild to severe fatigue to take part in an exercise program. This sample size was used to detect an outcome score difference of 30% or more (which is considered to be clinically relevant) in fatigue, depression and anxiety, and cognitive performance measures. Further, in a non-cancer, acute aerobic exercise trial, Themanson and Hillman (2006) compared behavioral and cognitive changes among 28 individuals (14 per group) through repeated measures analysis of variance in order to determine group differences. These data were sufficient for demonstrating relationships and changes among exercise and cognitive and behavioral outcomes in preliminary trials. Specifically, significant effects were seen for accuracy on congruent trials $F(1,26) = 56.64$, $P < 0.01$, $\eta^2 = .68$. Additionally, Gothe, Pontifex, Hillman, and McAuley (2013) employed a repeated measures design using 30 individuals (no cancer diagnoses) to complete 3 sessions of yoga, aerobic exercise, and baseline rest in order to explore effects on executive function. The yoga condition (reflecting the nature of the combined aerobic and relaxation training condition employed in this trial) was superior to the standalone aerobic exercise and baseline rest conditions for executive function performance.

Further, a combined aerobic exercise and technology-delivered cognitive training feasibility trial focusing on cognition reported a sample size of 28 (Peterson et al., 2018). The sample size (n = 28) allowed for analysis of pre-to post means, SD, mean differences, and 95% confidence intervals for each cognitive measure tested. Along with the G*power analysis and in accordance with previously conducted pilot trials and trials using measures that are assessed within this trial, I aimed to recruit 45 participants (15 into each condition). This sample size was shown to be able to provide adequate statistical power for detecting change among the primary outcome as well as changes across the secondary outcomes, which will help to inform future research resulting from the outcomes of this pilot trial.

Quality Control and Data Checking

Data were reviewed, cleaned and recoded following completion of all data collection. Using SPSS v.22 (IBM Corp, Armonk, NY). Missing and erroneous data were explored using descriptive and frequency statistics for all measures. Due to the forced entry requirement of all survey and cognitive data, and extreme vigilance of all RAs, no multiple imputation analyses were required. Data were manually inspected within SPSS v.22 in order to check for any errors, missingness, or outliers.

Statistical Analyses

All demographic data were compared using an ANOVA to allow for detection of differences across groups at baseline. Differences in feasibility, enjoyment, evaluation, and acceptance were analyzed through the use of multiple univariate ANOVAs. For the fatigue data analyses, a repeated-measures univariate analysis of variance (RMANOVA) was used to examine “in-the-moment” differences in post-session fatigue-specific scores as measured by the PFS and through post-session values, and pre-session values of two AD-ACL subscales (e.g., Energy and Tired respectively) across the three sessions. Theoretically relevant and established covariates (following initial analysis of shared variance) for the RMANOVA included body mass index, the global score from the *Godin Leisure Time Questionnaire* (GLTEQ), treatment composite (incorporating time since end of treatment and treatment type[s]), age, and memory self-efficacy.

Covariates were chosen based on the existing literature (Hong et al., 2007), and included levels of leisure time physical activity, anxiety and depression levels, age, and body mass index. Change scores for each cognitive task were evaluated using a univariate ANOVA in SPSS v.22. Differences in cognitive function were analyzed through univariate ANOVAs. Cognitive change score analyses were conducted using the same covariates as the RMANOVA used for the primary data analysis. Finally, a univariate ANOVA being used to assess change in the PMFQ. Change scores producing a *p*-value of 0.05 or less were considered statistically significant. Post-hoc analyses followed specific instructions set forth in accordance with assumptions and violations (Frison & Pocock, 1992).

Chapter IV: Results

Study Participant Recruitment

The most common form of advertising according to screened individuals was through in-person announcements at local breast cancer support group meetings (*n* = 16). Seventeen individuals did not qualify for the study during screening (see Figure 3). The majority of initial contacts were enrolled into the trial at a 70% acceptance rate. Following screening, participants were randomized to one of three intervention conditions in a pre-determined random, rolling block order of one individual per condition. In the end, 40 eligible participants (89% of the target recruitment goal) were enrolled and 100% completed all study requirements (pre and post testing appointments and training sessions).

Sample Characteristics

Detailed characteristics of the 40 enrolled participants can be found in Table 1. In short, no significant differences were found across groups, all participants were female, (M_{age} = 57.33 ± 8.75), while a majority were Caucasian (95%), and earned at least a college degree (82.50%). The sample had an average baseline resting heart rate of 80 beats per minute. Additionally, 75% of participants were married, and 67.50% were employed full time. Within the sample, 15 women reported undergoing alkylating agent based primary chemotherapy, while 6 reported being given plant alkaloids, and 19 noted that they received anti-tumor antibodies. Additionally, 31 out of 40 women reported receiving chemotherapy treatments from multiple classification categories over the course of their treatment. The sample average depression score as measured by HADS (where 8 is seen as a quantified cutoff) was 7.87. The sample average BMI was 27.38. Nationwide, the most common age (representing 25.80% of all new diagnoses) for a breast cancer diagnosis are between 55 and 64, with 81% of diagnoses occurring after the age of 50 (DeSantis, Ma, Sauer, Newman, & Jemal, 2017). Further, as reflected in the racial composition of our survivorship sample, BC diagnoses (e.g., luminal A, luminal B, HER2+, and triple negative) are most common among non-Hispanic white women (DeSantis, Ma, Sauer, et al., 2017). In other words, the sample was representative of survivorship demographics nationwide.

At baseline, BMI was negatively correlated with activity levels (i.e., GLTEQ), $r = -0.38$, $n = 40$, $p = 0.05$. No significant correlations were found between baseline demographic variables and baseline measures of fatigue. Baseline correlations between primary and secondary outcome measures can be found in Table 2.

Intervention Enjoyment

A single item was assessed at the conclusion of the study to analyze possible group differences in overall enjoyment of randomized intervention. A significant difference between groups was revealed following a one-way ANOVA [$F(2, 37) = 4.00$, $p < .05$]. As the data did not meet the homogeneity of variances assumption, the Games Howell post hoc test was conducted. No significant difference was found between mean enjoyment scores for the AERO ($M = 6.79$), and RELAX ($M = 6.31$), however findings were compatible with hypotheses, as the COMBINED group ($M = 7.00$) which had the highest score overall, presented a trend towards greater enjoyment ($p = .08$) relative to the AERO group. Mean scores of enjoyment for each group can be found in Table 5.

Intervention Effects on Fatigue

To assess the hypothesis that the COMBINED group would show the greatest reduction in fatigue, the three post-session scores for the *Piper Fatigue Scale* (PFS) were entered into a three (day) by three (group) by two (time) RMANOVA (Sphericity assumed, and non-heterogeneous variance ratios). Results revealed a significant effect of group on PFS [$F(2, 32) = 3.29$, $p = .05$] while adjusting for age, BMI, age, GLTEQ, anxiety, and depression. The partial η^2

value indicated a large effect size ($\eta^2 = 0.17$). Post hoc comparisons using a Bonferroni correction revealed a statistically significant difference between the AERO and COMBINED groups ($p < 0.05$). Comparison of the estimated marginal means controlling for the covariates showed that the COMBINED group ($M = 2.63$ points) had the lowest scores on the PFS, followed by the RELAX group ($M = 3.68$ points), whereas the AERO group ($M = 3.94$ points) had the highest scores at the final assessment point. A graphical representation of mean scores can be found in Figure 4. No other main effects or interactions were found to be statistically significant. Additionally, the *AD ACL subscales for Energy* (pre to post-session change scores) and *Tiredness* (pre-session scores) were used to assess to further quantify the extent of the potential effects of each intervention. Therefore, the same three (day) by three (group) by two (time) RMANOVA with Sphericity assumed (e.g., Mauchly's Test of Sphericity was not violated), and non-heterogeneous variance ratios were conducted for both scales. For Energy, no statistically significant group effect was found [$F(2, 32) = .767$, $p = .47$] partial $\eta^2 = 0.05$, while adjusting for age, BMI, MSEQ, Cancer treatment and disease components, and GLTEQ. A graphical representation of mean scores can be found in Figure 5. As for the *Tired* subscale, a RMANOVA (with statistical assumptions met and identical adjustments), revealed a non-significant group effect [$F(2, 32) = 3.18$, $p = 0.24$] partial $\eta^2 = .09$. A graphical representation of mean scores can be found in Figure 6. Significant positive correlations were found between PFS and AD ACL Tired Subscale on day 1 ($r = .39$, $p < .05$), day 2 ($r = .31$, $p < .05$), and day 3 ($r = .52$, $p < .05$), AD ACL Tired Subscale and Energy Subscale on day 1 ($r = 0.33$, $p < .05$), day 2 ($r = .53$, $p < .05$), and day 3 ($r = .46$, $p < .05$). Finally, a full display of means and standard deviations of all primary aim fatigue measures can be found in Table 3.

PMFQ

The PMFQ, which has not been validated among cancer populations, was used to assess group differences in mental fatigue as measured by values at the end of each session. An ANOVA revealed a significant effect of group [F(2, 37) = 4.12 $p < .05$ partial $\eta^2 = 0.20$], however a follow up ANCOVA revealed no significant group effect [F(2, 32) = 2.12, $p = .14$ partial $\eta^2 = 0.12$] after adjusting for age, BMI, MSEQ, weighted chemotherapy variable, and GLTEQ.

Further, in order to assess intra-session changes (post-testing minus baseline values). An ANOVA revealed a significant effect of group [F(2, 37) = 4.85, $p < .05$ partial $\eta^2 = 0.18$]. A follow up ANCOVA revealed no significant effect of group [F(2, 32) = 0.85, $p = .44$] after adjusting for age, BMI, MSEQ, weighted chemotherapy variable, and GLTEQ. Finally, no significant differences between groups were found between groups for changes in values from pre-to-post session on day 1 as revealed by a univariate ANOVA F(2, 37) = 1.97, $p = .15$.

Intervention Effects on Cognitive Function

Baseline means and standard deviations for cognitive scores, as corrected by the NIH Toolbox can be found in Table 4.

Working Memory

The correct response change score of the *NIH Picture Sequence Memory Task* was used to assess possible difference in working memory capabilities across the three groups. A univariate ANOVA controlling for BMI, levels of physical activity (GLTEQ), age, anxiety, depression revealed no statistically significant difference between groups [F(2, 33) = 0.72, $p = .93$]. Mean scores of *NIH Picture Sequence Memory Task* changes scores can be found in Figure 7.

Inhibitory Control and Attention

Correct response change scores of the *NIH Flanker Task* were assessed in order to explore possible group differences. A statistically significant difference was found between groups [F(2, 32) = 6.00, $p = .01$] partial $\eta^2 = 0.13$ by a univariate ANOVA controlling for BMI, GLTEQ, age, anxiety, and depression. Post hoc comparisons using a Tukey's honestly significant difference correction revealed a trend for statistically significant difference between the RELAX and AERO groups (p = .06). Comparison of the estimated accuracy means showed that AERO group had a mean difference of 2.49 less correct responses when compared to the change score of the RELAX group.

Cognitive Flexibility and Task-Switch

Accuracy scores of the NIH Dimensional Change Card Sort Task were assessed in order to reveal possible group differences. A univariate ANOVA controlling for BMI, GLTEQ, age, anxiety, and depression revealed no between-group differences [F(2, 32) = 1.50, $p = 0.23$]. Mean scores of *NIH Dimensional Change Card Sort Task* change scores can be found in Figure 8.

Ancillary Outcomes

A RMANOVA (adjusting for same covariates as primary analyses) showed no significant effect of group on heart rate changes across the sessions [F(2, 32) = 0.69, $p = 0.50$]. However, a significant effect of the weighted cancer diagnosis and treatment variable was found [F(2, 32) = 10.95, $p < .05$]. This revealed a small effect size (partial $\eta^2 = .26$). Further, averages for all baseline measures assessed can be found in Table 5, whereas end of study and change scores can be found in Table 6. Further, there were no differences found between changes in levels of self-efficacy for relaxation and stationary cycling when analyzed by the same methods.

Chapter V: Discussion

General Overview

This trial aimed to test the effects of three, brief, randomly assigned interventions among breast cancer survivors who had completed their chemotherapy treatment within the last five years. The RACER trial was primarily designed to test the efficacy of an experimental COMBINED (aerobic exercise and relaxation) intervention that was hypothesized to create a enjoyable and feasible intervention producing greater fatigue reduction when compared to interventions found in the existing literature (e.g., standalone aerobic exercise and relaxation). All remarks herein should be paired with consideration regarding the effects the clinical factors and related influences (e.g., doctor appointments, regaining a normal social life, and family issues) may have on these outcomes. Though initial analyses only partially supported this hypothesis, the findings are encouraging, as evidenced by a more favorable profile of perceptions of fatigue following the brief training prescription. The hypothesized effect of group on fatigue showed a robust pattern of improvement for those individuals randomized to the COMBINED as measured by the Piper Fatigue scale, while showing improvement as a group across the AD ACL Energy and Tiredness subscale measures. It is possible that a larger dose of intervention activities, specifically the mindfulness-based training would have allowed for participants to become better acquainted with the skills necessary to achieve a state of relaxation. This may have allowed for more robust intervention effects and a more reliable interpretation of the effects found in this trial. These outcomes emulate fatigue reduction observed in a prior study of post-operation cancer patients who were concurrently involved in treatment, while engaging in an intervention consisting of recumbent-bike pedaling and meditation (F. Dimeo et al., 2004). However, the innovative component of the RACER trial was that improvements in fatigue were found after acute intervention bouts in survivors experiencing long-lasting CRF, as opposed to more recent, treatment-induced fatigue. Together, these findings suggest that these types of interventions are effective for reducing immediate onset and persistent CRF.

Enjoyment, Feasibility, and Acceptability

This pilot trial was designed to assess the extent to which breast cancer survivors were capable of actually doing the intervention (carrying it out as intended), and whether they liked it and perceived benefits or burden as a result of their participation. This was informed by utilizing an adapted questionnaire based the work of Wu and Wang (2005), and (1989), that specifically highlights the incorporation and optimization of technology within an intervention. Supporting the secondary hypothesis, all 13 participants in the COMBINED group reported the highest level of enjoyment when asked about their participation. Although the RELAX and AERO groups reported high enjoyment, the COMBINED group uniformly reported optimal enjoyment.

Further, the COMBINED group also reported the highest levels of willingness to recommend their post-exercise guided-relaxation training to those who may be experiencing similar symptoms (albeit, not statistically significant relative to the RELAX and AERO groups). The COMBINED group also appeared to be the most satisfied (again, not statistically significant relative to the RELAX and AERO groups) with their activities for reducing fatigue (Table 4). A single item focusing on feasibility (i.e., “I found this to be convenient, easy and worthwhile”) was also assessed at the conclusion of the study. Although there were no statistically significant differences between group means, overall mean value across groups was 6.70, out of 7 (the highest level agreement; *SD*=0.69). Apparently all three interventions were well-received by this sub-population.

Responses to the open-ended question about “one’s thoughts regarding their involvement in the RACER trial” highlighted both positive and negative components of the study. Participants noted several positive aspects of relaxation training, such as “I think the activities of clearing your mind to concentrate on your breathing is helpful to combat stress and anxiety and is useful at any age and capacity of physical or mental state.” With regard to the relaxation technology used by those in the COMBINED and RELAX groups, participants indicated, “I cannot think of anything that I dislike about the [device]…,” “I really loved the [device], I wish I could have used it for a longer period,” and “I found this to be a very unique method of relaxing.” There was even evidence to suggest that the device facilitated training transfer to assist in the development of self-regulated mindfulness and self-reflection outside the laboratory. Specifically, one participant said, “While I was home during the week, I tried practicing the mindfulness activities without the device,” and “I noticed a change in how I felt, and reflected upon this and the ideas of the training during the week.”

Constructive feedback was also provided by participants, which may offer insight into methods for maximizing technology-driven relaxation training. For example, one participant noted that “I feel more guided instruction in conscious relaxation techniques would have been helpful, it takes more training [than] the average person realizes or even knows how to begin.” Coinciding with this idea, another participant stated, “I feel a little more education with the [device] system might be helpful. Meditation is not something I practice, but I do feel it could be helpful to overall health.” Accordingly, any future research conducted with this device should include a more elaborate orientation/instructional session prior to engagement. A brief introduction was included on the first day if participants were in a group that used the relaxation device. It is plausible that a more detailed introduction could have improved competence and confidence, and in turn, result in greater engagement. Participants also expressed a desire to have been able to use the device for "more than three sessions," which is a step in the right direction for designing a longer RCT and utilizing similar interventions. With respect to cognitive function and the relaxation device, a participant noted that:

> *"The study was a lot of fun. I felt energized by it and felt good about the mental tests because I feel like I did well on them. Sometimes I have trouble thinking of a name of someone famous or of an exact word I want to use in the circumstances, though the name/word will usually come to me if I give it a minute or two, and I find that worrisome since words are very important to me. I feel like it has benefited my experience of fatigue and my memory. The researcher and assistant were easy and congenial to work with. I am glad I got to participate. It was worth the time and I hope that this will continue to improve the way I remember things."*

Without disregarding the importance of objective testing, each individual's perceptions offer a richer description of the trial's impact on these women. There were strong positive opinions towards the experimental intervention and very few complaints. It is even more promising to read their statements reflecting a desire to continue training. Altogether, this evidence suggests that this form of intervention is worthy of continued investigation. That said, while participants felt as though the trial was beginning to help them improve their thinking processes, future research is warranted to better understand these relationships.

Perceived Fatigue

Participants across all conditions displayed fatigue improvement across a series of measurement inventories. Specifically, they averaged a very modest reduction in changes of fatigue on the *Piper Fatigue Scale* across all three days (Figure 9), a modest improvement in energy levels change on the *AD ACL Energy*and a small reduction in tiredness level changes on the *AD ACL Tired* subscale. As these changes reflect improvement across the sample, these findings were further supported by a .30-point reduction on the *PMFQ*, and a .13-point reduction on the fatigue portion of the *BFI*. The *AD ACL* only includes 4 possible response options, therefore a change of more than a quarter of a point is a seemingly important matter (Thayer, 1986). Furthermore, participants who took part in either of the interventions with the relaxation training displayed a larger decrease in perceived fatigue when compared to participants who only engaged in aerobic activity. As evidenced in Table 8, involvement in guided relaxation training, whether standalone or along with aerobic exercise, resulted in more favorable fatigue reduction.

The Piper Fatigue Scale is one of the most commonly used scales to assess symptoms of cancer patients (Piper et al., 1998), and it was believed that this scale would be best employed when scrutinizing perceptions of fatigue 10 minutes after the completion of each activity session. Importantly, only the COMBINED group showed scores that decreased over time and decreased from “moderate” levels of fatigue, to “mild” levels (see Figure 4). In partial support of the hypothesis, a large effect size ($\eta^2 = .17$) was found for the COMBINED. Although no significant difference was revealed between the RELAX and COMBINED groups, these findings do align with the literature, which again suggest that standalone aerobic exercise may also produce beneficial effects in these areas (J. K. Schneider, Mercer, Herning, Smith, & Prysak, 2004). The lack of difference between the RELAX and COMBINED groups suggests that the mindfulness component of these interventions are more effective at improving perceptions of fatigue in an acute sense when compared to the effects of aerobic exercise. Furthermore, these outcomes are supported by results from the *PMFQ*. While this questionnaire has not been validated among cancer populations, there was a significant group effect in favor of those in the COMBINED group, compared to both participants in the RELAX and AERO groups. The larger decrements in reported levels of fatigue on the *PMFQ* suggest that this measure is sensitive to intervention and correlates with other measures of fatigue.

Also in line with the fatigue hypothesis, the COMBINED group displayed more favorable levels of energy (another aspect of fatigue) relative to the AERO group on both the second and third appointments. The group difference at the third session in the *AD ACL Energy* subscale (after adjustment for theorized covariates) was moderate, and important ($\Delta = 0.49$). Although no significant difference was revealed between the RELAX and COMBINED groups, these findings do align with the literature. Again, this would suggest that being involved in interventions containing mindfulness training is more effective than aerobic activity, for reducing perceptions of fatigue (at least, after a 3-day training period). The findings are in agreement with existing literature indicating that relaxation methods are more effective at improving energy and reducing negative affect associated with cancer (Song et al., 2013).

It was reasonable to expect that the COMBINED group would have facilitated the most ideal energy scores reflecting the most favorable mental state across these measures. However, it is important to keep in mind that the relaxation training may have caused a ceiling effect or deflated any potentially larger increases in energy. Indeed, the RELAX group reported the lowest levels of energy. Intuitively, it makes sense that participants who focused on relaxing would not be filled with energy immediately after their session, as that would be completely counter to their efforts. It is interesting that the AERO condition did not drain the participants' energy and an intriguing question is whether the guided meditation instilled the women with any energy-regulation strategies, which, in theory, could translate into less accumulation of fatigue over time. It is reasonable to expect resilience to energy-draining and fatigue-inducing activities could be built up with continued commitment to regular relaxation training.

Fatigue improvement, as reflected by decreases in the *AD ACL Tired* subscale, was less clear (the graphical output was reverse coded to reflect high values being more desirable). Given that this construct represents an opposing state to the energy subscale, which is expected to increase following engagement in related activities (Rougeau, 2015), it was believed that one's sense of feeling tired would be best measured at the beginning of each appointment (e.g., baseline and following a minimum of 24-hours of rest since their last activity session). Although no statistically significant difference was found between groups, there was a trend suggesting data compatibility with hypotheses (p = .06). Due to the trending nature of this finding, an examination of Bonferroni corrected estimated marginal means was used and revealed a difference of -.57 points between the COMBINED and AERO groups, in favor of those in the COMBINED group. This finding emphasizes that the COMBINED group showed a change, which reflected less sensation of being tired by the end of the 3-session intervention period.

This suggests that brief engagement over the course of a week in both mindfulness and aerobic exercise training was more beneficial for decreasing levels of tiredness over the three scheduled sessions. It should be noted that the energy and tired scales were not designed to address the psychophysiological state of cancer patients or the survivorship population. In other words, these changes may have been more robust if the scale had been more population-specific or if it's phrasing reflected more state-like CRF changes rather than more general, trait-like changes. Since CRF is a chronic issue among this sample, it may require a very specific inventory that is sensitive to the persistent experience of fatigue among cancer survivors, across a variety of situations and circumstances (however subtle those variations may be). Finally, the randomized activities did not require vigorous intensity/effort or strain, which is known to have lag effects on perceived energy (DiLorenzo et al., 1999). Therefore, the prescribed activities may not have reached a threshold needed to invoke changes, but it is also possible that changes in perceptions may have occurred after the conclusion of the study. These findings agree with prior work by Rougeau (2015) exploring the effects of active and passive forms of exercise in the sense that the aerobic activity within the RACER trial was not intense enough to elicit more robust changes in a short period of time as observed by scores on the *AD ACL Energy* and Tired subscales.

Cognitive Functioning

This trial also aimed to explore the effects of the randomized interventions on higher order cognitive function among BCS. No statistically significant differences were observed across any of the measures of inhibition control, cognitive flexibility, or memory. However, the pattern of results, particularly for performance scores on the Picture Sequence task were compatible with the initial hypothesis. Although this has yet to have been shown among cancer populations, the literature does support the finding that relaxation training improves performance on attentional-based tasks (Semple, 2010). Other researchers studying meditation among college-aged samples have shown that relaxation training can improve executive functioning (Kaufman & Jensen, 2018). Although those researchers did not assess BCS, it should be noted that longer behavioral interventions conducted among BCS populations (Kesler et al., 2013) may be required to see more impact of aerobic exercise combined with adjuvant relaxation training on cognitive performance. Also, it is important to note that while some trials targeting BCS (Chen et al., 2018) have used the NIH toolbox, there is a dearth of literature reporting validated use for short-term cognitive change among women who have recently completed chemotherapy treatment. It is possible that engagement in such an acute intervention may have indeed had a positive cognitive effect, but the time between administration of the tasks and relatively low degree of cognitive and behavioral effort required by each group may have resulted in only fast-fleeting effects, as suggested by Roig and colleagues (Roig et al., 2016). It is also quite likely that practice effects over such a short period of time challenged the sensitivity of the tests to capture any potential differences in group performance. As such, time and type of cognitive function being assessed requires more in-depth evaluation among cancer survivors, as this is an area that may be dependent on neurophysiological components related to disease and treatment (Loprinzi, 2019).

Ancillary Outcomes

Additional analyses of ancillary outcomes including mental engagement during the training sessions, perceived physiological and experiential changes, changes among self-efficacy for relaxation and stationary cycling, and variations in heart rate were conducted in order to better explain the findings herein. When comparing participants across the two groups taking part in aerobic exercise (AERO and COMBINED), the COMBINED group reported a lower mean Rating of Perceived Exertion across all three days ($M = 12.13$) when compared to the AERO group ($M = 14.01$). This may suggest that the additive engagement in mindfulness training allowed participants in the COMBINED group to feel as though they were not working as hard when exercising, in order to stay within their 50-70% targeted heart rate maximum zone. The *GEQ-M* contained four subscales (e.g., absorption, flow, presence, and immersion) for assessing activity engagement. Of these, only the presence subscale was trending for group differences ($p = 0.06$), with the largest levels of presence improvement being reported by individuals in the COMBINED group. This suggests that taking part in aerobic exercise as well as mindfulness training resulted in greater engagement in the sense that they reported higher degrees of experiencing automaticity, slower thoughts, and time zooming by. These findings are consistent (as they show improved engagement across the sample) with existing research addressing core components of mindfulness and other forms of relaxation training applications (Öst & therapy, 1987). This finding replicates and extends what is known within the cancer patient literature (Vasterling, Jenkins, Tope, & Burish, 1993) by showing that the combination of aerobic exercise and relaxation training is more effective than relaxation alone for combatting chemotherapy-related side effects through engagement components similar to those used by Vasterling and colleagues (i.e., novelty, and enjoyment).

Further, perceived changes as measured by the *EBCS* (see Table 6) show that greater improvement was found for participants in the COMBINED group, followed by the RELAX group, when compared to the AERO group. These changes reflect greater reductions in being out of breath and mental stress. These findings extend the literature addressing the impact of relaxation techniques among cancer populations (Ledesma & Kumano, 2009).

In order to better understand if self-efficacy beliefs can change as a function of these brief interventions, two types of self-efficacy were assessed at baseline and post-testing. Although no significant change was found, the literature lacks a clear understanding of the malleability of these levels among BCS. These findings are inconsistent with the negative affect literature, as work by Bodin and Martinsen (2004) suggest self-efficacy for aerobic exercise has been shown to be malleable to change. Albeit confidence-building strategies for engaging in each activity were not incorporated as part of the interventions.

This trial was designed to help understand how differences in heart rate levels occurred between groups over the three intervention sessions. Changes among average heart rates across each session revealed a significant effect of the weighted cancer treatment and date variable. This implies that individuals who went through more intensive chemotherapy treatments and had completed such treatment more proximally to study involvement, showed larger changes in their heart rate variations across the three appointments. This finding is extremely valuable as it agrees with the existing literature focused on the physiological effects of time and type of chemotherapy treatment (Carey & Burish, 1988) and supports the need for future research to incorporate such factors as to provide a deeper understanding into the effectiveness of behavioral interventions for improving CRF and related outcomes.

Strengths and Limitations

This acute pilot trial presented a number of strengths. Multiple established measures were used to assess a wide array of functioning and quality of life aspects. This trial shows specific effects and it used a rigorous research design (e.g., RCT) with time-matched control conditions in an attempt to control for known influential factors among BCS. This trial provides us with initial evidence to suggest that different aspects of fatigue perception, cognitive function, and evaluative opinions can be positively impacted following an acute bout of aerobic exercise along with technology-driven relaxation training. Until now, this had not been demonstrated among BCS. Additionally, feedback revealed favorable ratings of the COMBINED intervention, which further support evidence of feasibility and acceptability. This aligns with recent findings suggesting that survivors are interested in interventions incorporating technology, which address ease of use and focus on issues personally relevant to them (Phillips et al., 2019). These factors lend support to the notion that this type of intervention is promising and worthy of continued investigation. Maintaining a framework grounded in theory was imperative to the reliability of this trial, and will continue to guide future related work. Further, established measures were used amongst a relatively homogenous sample. Also, research assistants involved in the trial were highly trained and ensured the integrity and delivery of the planned intervention.

Aside from being effective and enjoyable, the COMBINED intervention is likely to be more cost-effective in comparison to engaging in other behavioral methods such as joining a yoga studio or fitness center (Sperandei, Vieira, Reis, & sport, 2016). This study represents an appealing modification of a mind-body approach when juxtaposed to a more strenuous and focused activity such as yoga, and offers an easy transition into aerobic activity for those who have not been regularly active. While this study used a stationary bike for the aerobic exercise portions of the trial, I believe that bicycling, or jogging would also result in similar benefit with or without pairing it with relaxation training. In other words, the aerobic intervention is most likely interchangeable with other fitness machines or physical activities, which widens its overall appeal. As for the relaxation-training device, it is relatively inexpensive when compared to other commercial apparatuses and different behavioral interventions required a paid membership. The experimental COMBINED intervention is therefore scalable. This device may be equally enjoyable and useful to the entire BCS population, and its portability and engaging biofeedback display may contribute to its appeal in conjunction with aerobic It may well be that this device is perceived as feasible, enjoyable and useful across the greater BCS population. These individuals may feel that it is easier to pick up and use whenever they deem necessary and perhaps it could contribute to a more approachable perception of the suggested exercise to go along with it.

As with any trial, there were several limitations, which were apparent in this study. Our strict inclusion and exclusion criteria resulted in interested participants being unable to be enrolled in the trial. For instance, while it was necessary for scientific purposes, to optimize homogeneity in the study sample by restricting the range of time since end of chemotherapy treatment to five years or less, it is possible that this specific criterion excluded participants who may have been just out of the time range and would have benefited from involvement. Expressly, this component accounted for 29.41% of all excluded individuals. To this point, it is possible that BCS who fell just short of the inclusionary criteria may have been good candidates for the trial (e.g., those who were only 6-10 years out), and may have ascertained meaning benefits from participation. However 70.17% of those whom contacted us initially were enrolled in the study and therefore, the results reported herein may generalize to those who have completed treatment in the last 5 years. Regarding sample size, although the final sample consisted of 40 women, it was ideal to enroll 41, or 45 for dropout purposes (no dropout occurred). Additionally, the majority of the included sample was Caucasian, with a college education, and were located to a large, Midwestern university. However, it's difficult to gauge external validity from these findings given the high level of supervision at the research site. Further, onsite research assistants available to answer questions may have given an extra sense of assurance to participants, which would not necessarily be available outside of academic or clinical settings. Consequently, generalizability to at home delivery would be low.

Simultaneously recruiting individuals who had previously taken part in BC focused trials on campus from similar circles as other researchers on campus served as a barrier to recruitment. Other factors such as seasonal effects (the trial was mostly conducted during the winter months in Central Illinois) may have influenced fatigue levels and related outcomes. Although, it's unlikely the season caused differences among groups, given that everyone faced the same effects of inclement weather. With respect to the primary outcome, we were reliant upon self-report measures, which are purely subjective in nature. Biomarkers such as lactic acid and salivary markers or stress, blood samples, and neurophysiological responses indicative of changes would help to cross validate some of the patterns that participants may or may not have perceived. Future research should consider the implementation of additional measurements to better understand mechanisms of change and analyzing the differences in performance and perceived outcomes between the randomized interventions. Since women who completed treatment more than 5 years were excluded, we did not test how this would affect women who may have lesser effects or experiences of fatigue would be impacted. As is reflected in the literature, similar symptomology is reported for multiple decades following the completion of treatment (Koppelmans et al., 2014). It should also be noted that participants were told the purpose of the study through the Informed Consent Document and telephone screening. Thus, findings may have been prone to bias effects (e.g., response bias or Hawthorne effect).

Future Directions for Research

Contrary to hypotheses, no robust effects were found on cognitive functioning. Future studies interested in the acute effects of aerobic exercise, relaxation training, or a combination thereof should consider using different cognitive assessments, and varied administration intervals. Additionally, researchers should test the effects of combined treatments over longer periods of time to assess the chronic effects of regular engagement in aerobic and relaxation training. Moreover, follow-up periods in the absence of any professional oversight or supervision should be implemented to test the potential for behavioral transfer. Specifically, it is possible that short-term mindfulness training facilitates greater self-regulatory strategies enabling one to become a more physically active person. On the other hand, engagement in short-term aerobic exercise could encourage one to become a regular meditator. Moreover, the practice of both behaviors could yield changes in both behaviors in an additive or synergistic fashion. Thus, these interventions could have real-world impact and improve chronic mental states (e.g., stress, anxiety, and depression) or tangible health outcomes (e.g., lower blood pressure, reduce stroke risk). Although it has been argued here that BCS are forced to deal with treatment and an abundance of disease-related stressors which make it more difficult to comply with physical activity guidelines for healthy adults, the addition of technology, as evidenced by prior work by Bird and colleagues (2015), and the preliminary results reported herein, may make exercise more enjoyable.

Indeed, traditional and technology-enhanced relaxation methods probably need to be given more attention and consideration as feasible and efficacious complementary therapies for addressing CRF and related symptoms. The opportunity to engage in relaxation training as a component of an intervention (or as a standalone) may present a more appealing option for survivors (relative to physical activity). In some cases, it may be unreasonable to expect one to engage in physical activity right away whereas relaxation training could be used as a “gateway” to changing one’s attitudes towards physical activity. Alternatively, engagement in moderately intense cycling followed by relaxation may be more advantageous and allow one to return to normal quality of life more quickly. When used in tandem, these methods appear to improve certain aspects of quality of life among BCS. Further assessment of physiological measures would improve our understanding of mechanisms underlying acute changes in fatigue. Lastly, continual study of aerobic exercise in combination with other behavioral interventions may contribute to the understanding of potential additive and synergistic effects that can optimize outcomes among BCS.

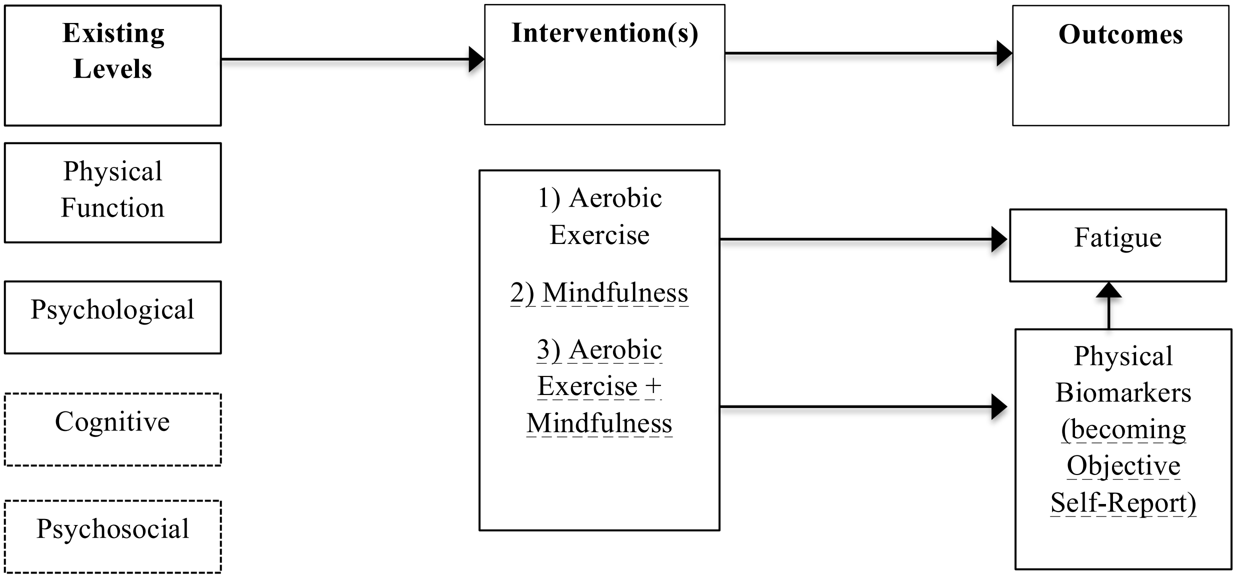
Conclusions

To date, this was the first RCT to test the feasibility and efficacy of aerobic exercise and technology-based relaxation training effects on fatigue in a sample of breast cancer survivors.

The results should be interpreted with caution, given the small sample, acute design, and preliminary findings. The trial was, however, grounded in theory and the results are promising and pave the way for replication and extension. Findings from this trial may appeal to clinicians, researchers, industry, caretakers and cancer survivors, as well as others in order to improve commonly experienced symptomologies among a growing population. While these results can be interpreted as a step in the right direction, researchers and tech-companies who look to capitalize on the technological innovation tested herein, further research is needed to replicate these preliminary findings, and to inform practical prescriptions for brief and longer-term behavioral interventions.

Chapter VI: Figures

Figure 1. Neuroendocrine-based Fatigue Model



Notes:

- New additions to the working model are under-scored or bordered by " ----"
- While existing levels in the original model reflected biological factors, the working model has replaced them with additional measurable, behaviorally-based components
- The intervention component of the original model now reflects the three randomly assigned interventions in the working model

Figure 2. RACER Trial Study Flow Chart

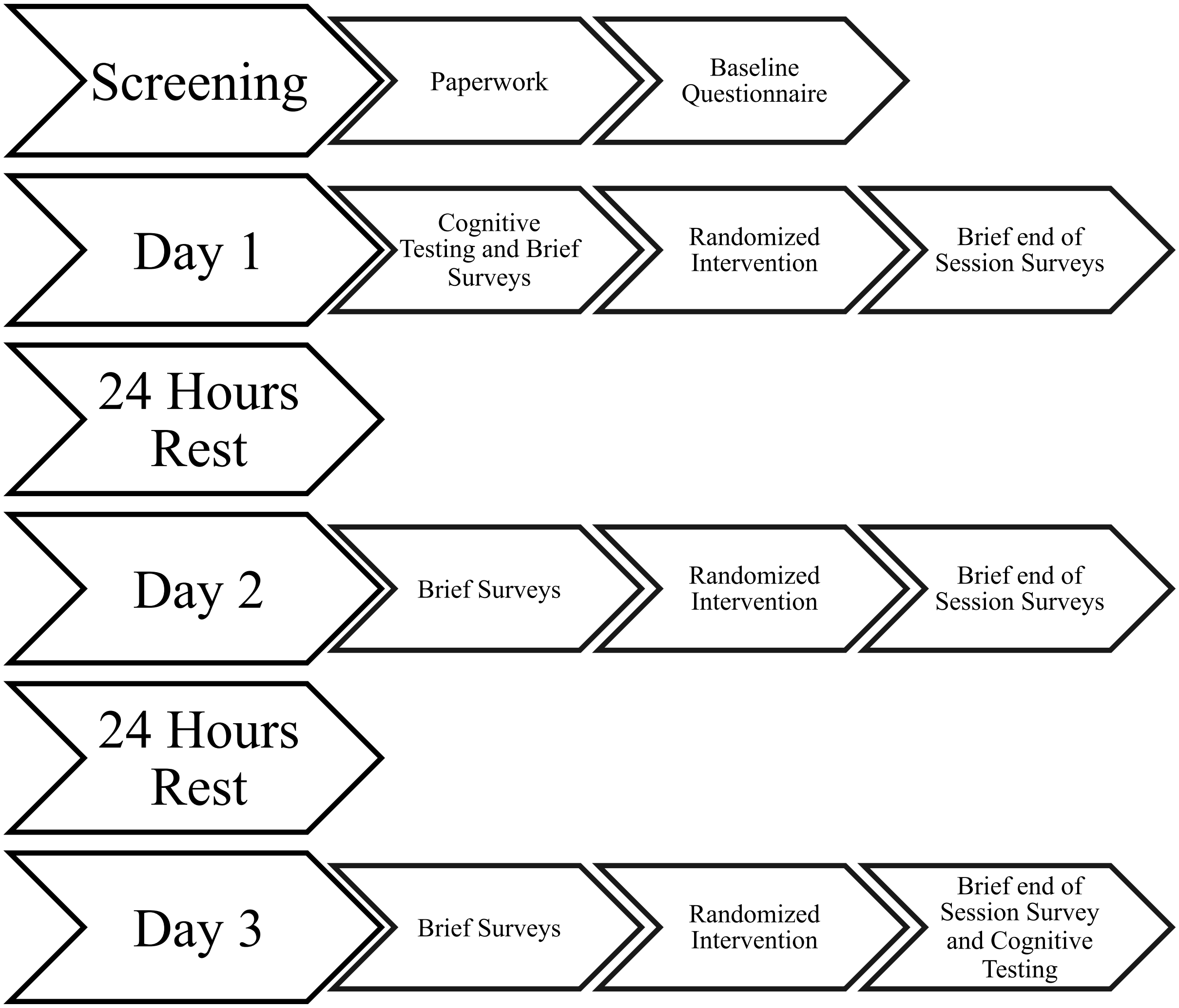


Figure 3. RACER Trial Final Consort

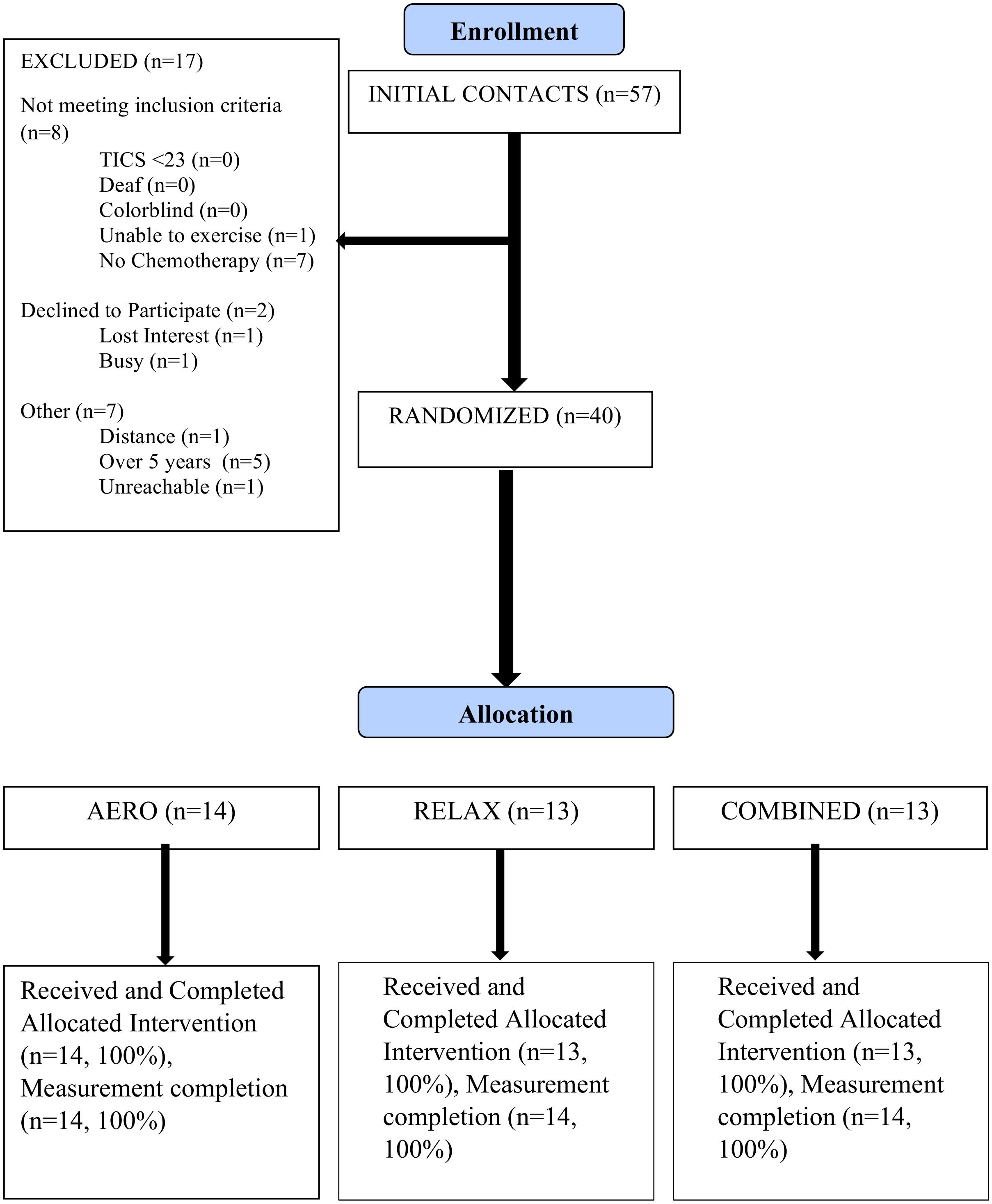
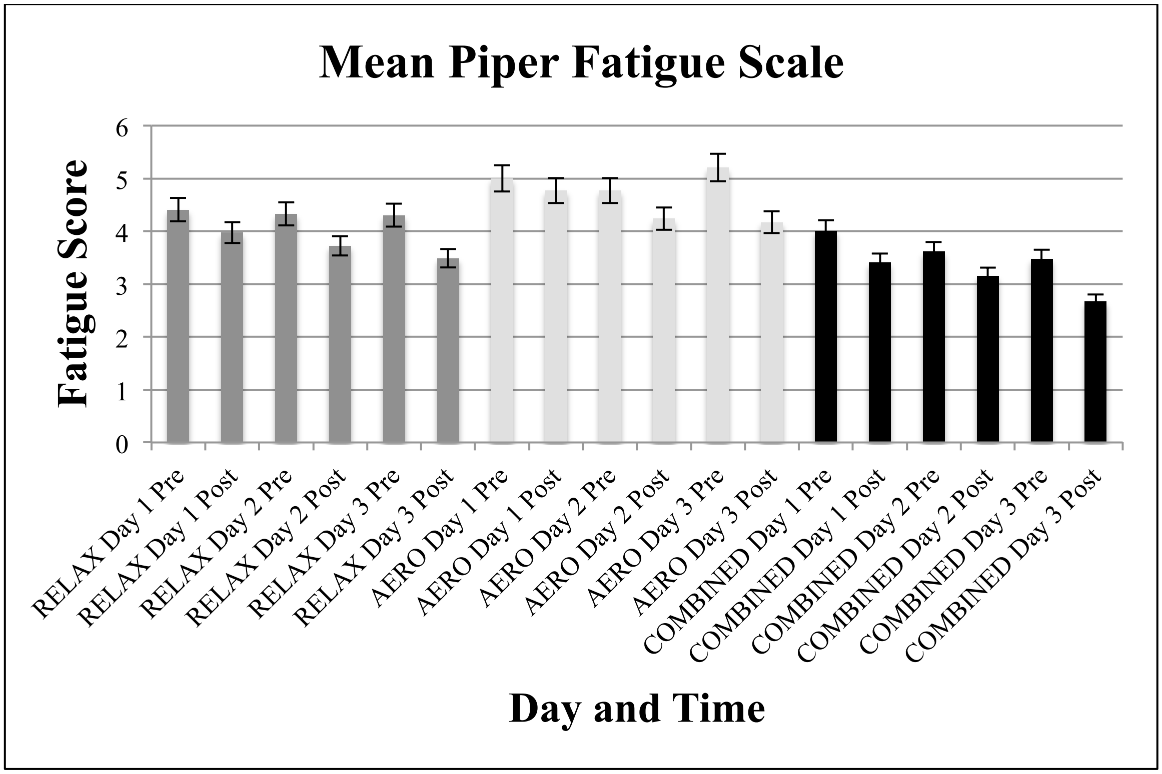
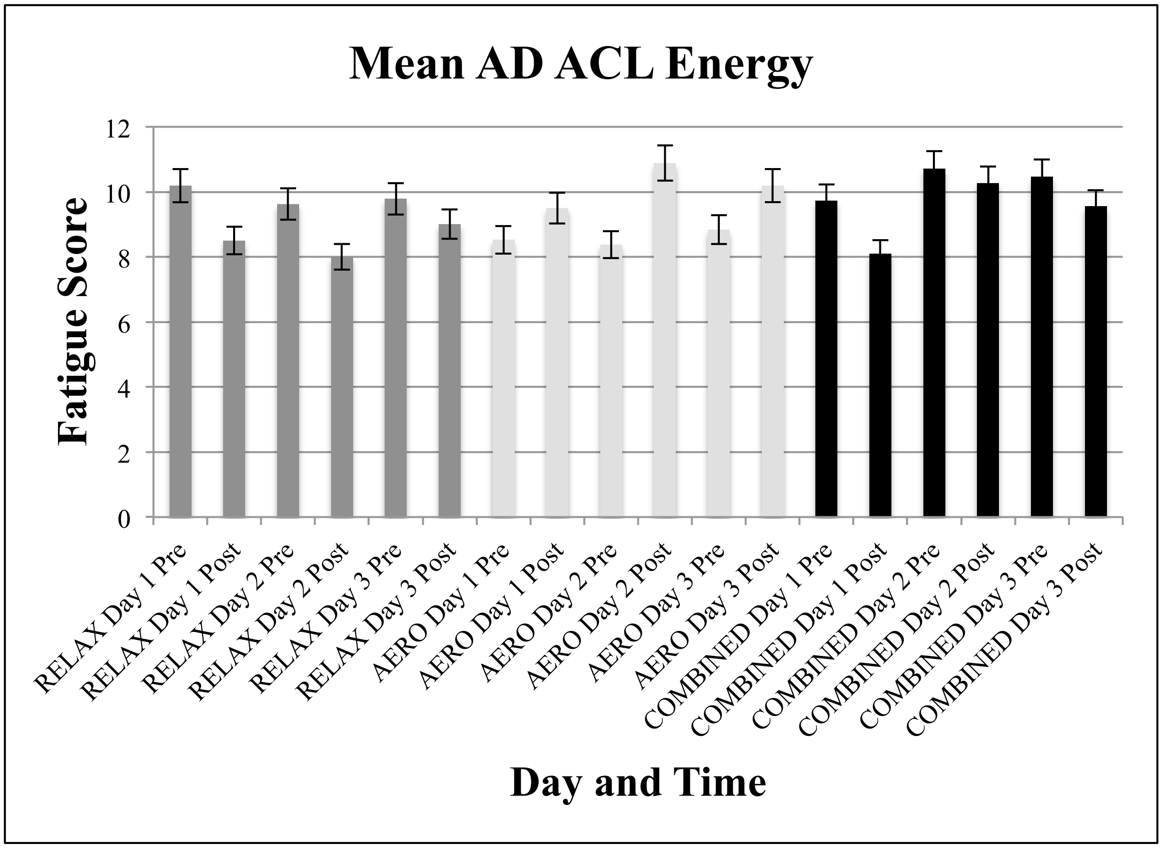


Figure 4. Estimated Means of Post Session Piper Fatigue Scale Scores Over Time



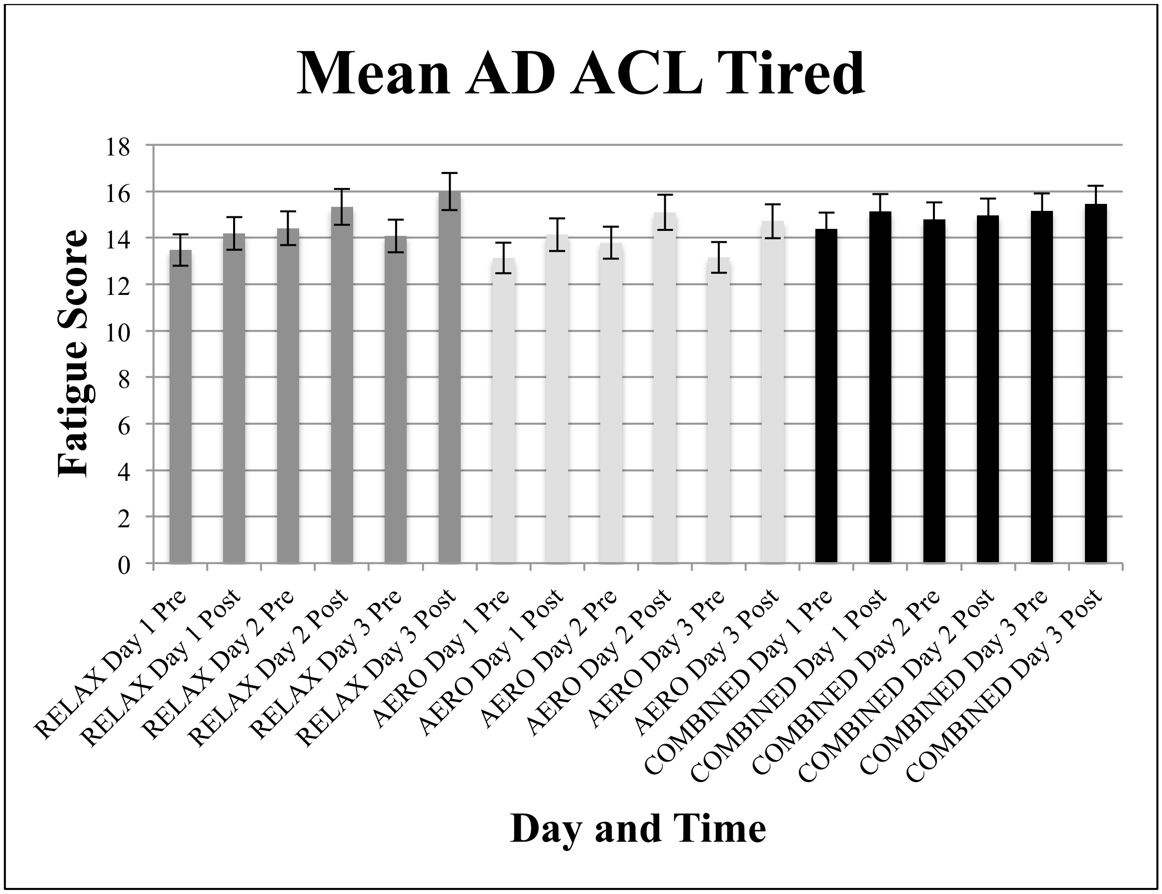
Note. Covariates appearing in the model are evaluated at the following values: BMI baseline = 27.3825, Age baseline = 57.3250, Godin Total = 33.8670, Total Anxiety Score = 5.0750, Total Depression Score = 7.9000.

Figure 5. Estimated Means of AD ACL Energy Subscale over Time



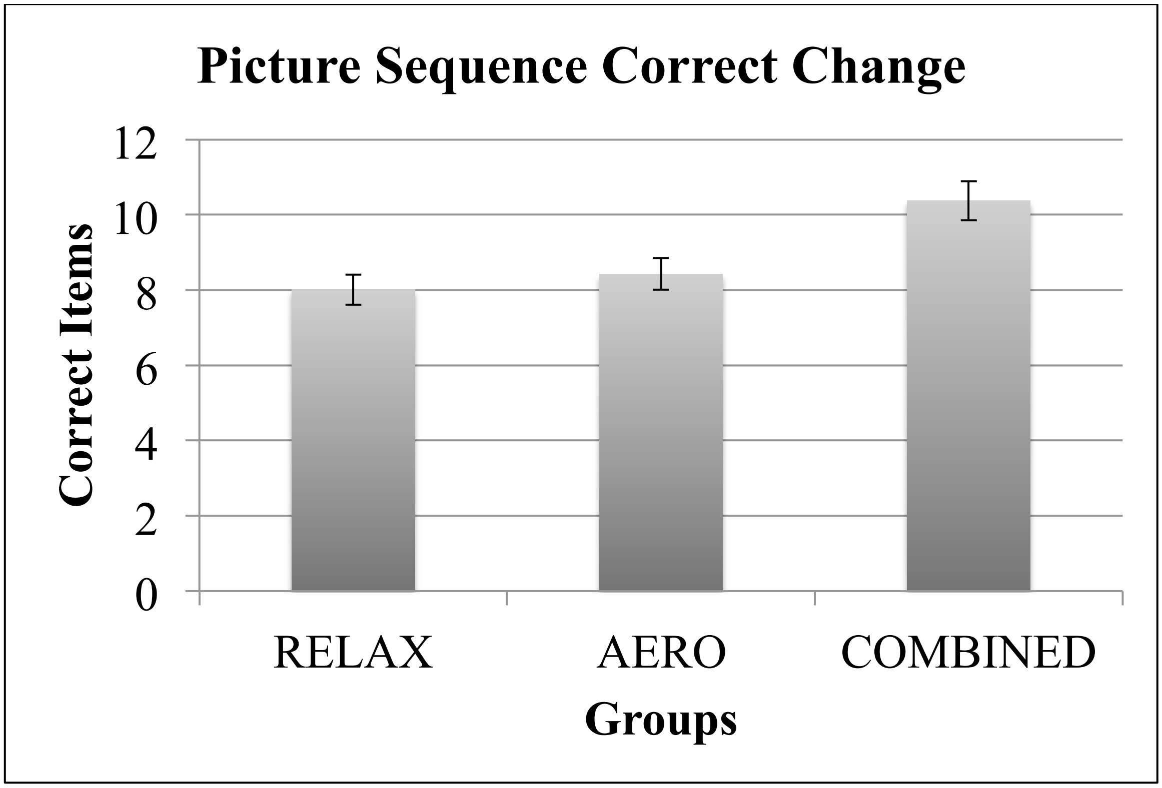
Note. AD ACL Energy = Activation Deactivation Adjective Check List Energy subscale total score. Covariates appearing in the model are evaluated at the following values: BMI baseline = 27.3825, Age baseline = 57.3250, Godin Total = 33.8670, Total Anxiety Score = 5.0750, Total Depression Score = 7.9000.

Figure 6. Estimated Means of Pre Session AD ACL Tired Subscale Over Time



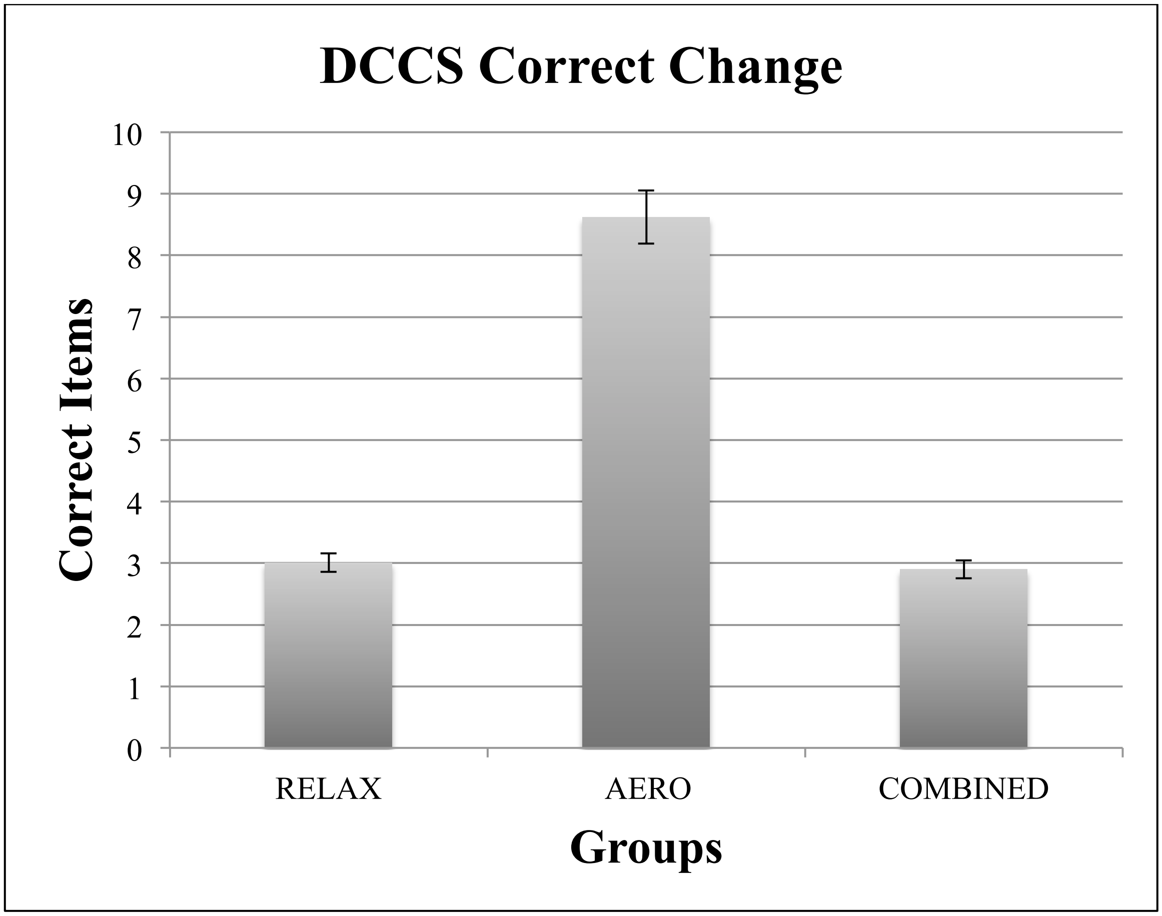
Note. AD ACL Tired = Activation Deactivation Adjective Check List Tired subscale total score. Covariates appearing in the model are evaluated at the following values: BMI baseline = 27.3825, Age baseline = 57.3250, Godin Total = 33.8670, Total Anxiety Score = 5.0750, Total Depression Score = 7.9000.

Figure 7. Mean Change Scores of NIH Picture Sequence Memory Task



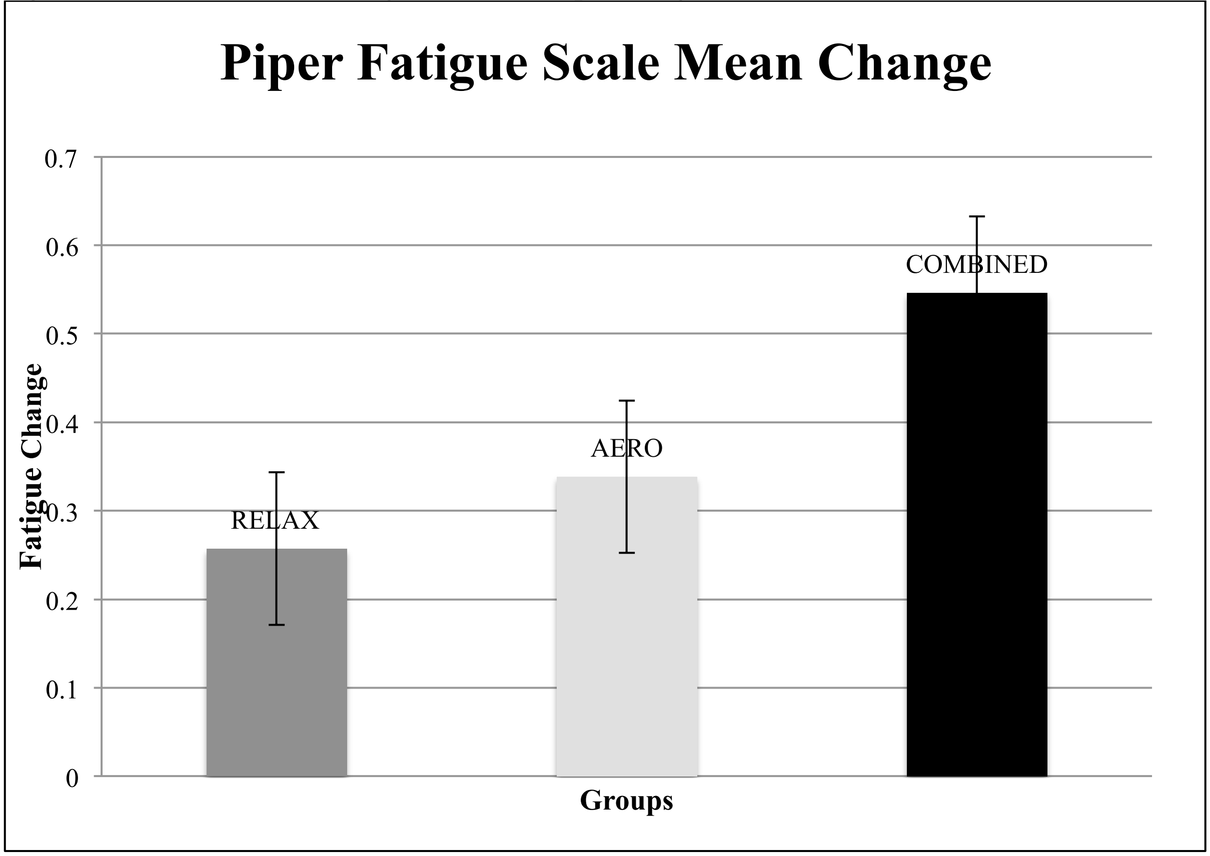
Note. Change score is calculated by subtracting pre-test scores from post-test scores, therefore, a higher score is indicative of a greater improvement

Figure 8. Mean Scores of NIH Dimensional Change Card Sort Task Accuracy Change



Note. Change score is calculated by subtracting pre-test scores from post-test scores, therefore, a higher score is indicative of a greater improvement

Figure 9. Mean Session Change Scores of Piper Fatigue Scale



Chapter VII: Tables

Table 1. Randomized Group Participant Characteristics

	Pooled	RELAX	AERO	COMBINED
	N/ M (*SD*)	*N/ M* (*SD*)	*N/ M* (*SD*)	*N/ M* (*SD*)
Race				
Caucasian	38	13	13	12
Black	1	1	-	-
Asian	1	-	-	1
College				
Yes	33	13	10	10
No	7	1	3	3
Age	57.33 (8.75)	59.71 (6.99)	58.56 (10.41)	53.62 (8.03
BMI[a]	27.38 (5.27)	28.21 (5.39)	26.04 (3.91)	27.93 (6.35)
BFP[b]	35.67 (7.24)	37.81 (6.77)	34.16 (6.38)	34.88 (8.44)
Height[c]	64.01 (2.45)	64.00 (1.93)	63.46 (2.78)	64.58 (2.64)
Weight[d]	153.65 (35.65)	158.24 (40.65)	140.28 (23.07)	162.08(38.90)
RHR[e]	80.00 (17.87)	80.43 (13.49)	82.00 (26.20)	77.54(53.85)
CRF[f]	26.16 (2.84)	21.88 (1.87)	22.70 (2.96)	21.93 (2.41)

Note. No significant differences were found at baseline across the groups, [a]=Body Mass Index, [b]=Body Fat Percentage, [c]=Measured in inches, [d]=Measured in pounds, [e]=Resting Heart Rate beats per minute, [f]=Estimate through the Non-exercise testing cardiorespiratory fitness model

Table 2. Baseline Correlations of Primary and Secondary Outcomes across Participants

	M (*SD*)	1	2	3	4	5	6
1. Piper Fatigue	4.47 (1.54)	--	-.77*	-.65*	-.13	.01	-.34*
2. Tired	3.01 (0.73)	--	--	-.50*	.17	.06	.37*
3. Energy	2.14 (0.75)	--	--	--	.08	-.16	.31
4. Flanker	7.37 (1.03)	--	--	--	--	.43*	.78*
5. Picture	535.09 (100.20)	--	--	--	--	--	.42*
6. Card Sort	7.29 (1.25)	--	--	--	--	--	--

Note. * = *p* < .05; Tired = Activation Deactivation Adjective Check List-State Anxiety Inventory Tired subscale; Flanker = Flanker Computed Score; Picture = Picture Sequence computed score; Card Sort = Dimensional Change Card Sort accuracy score

Table 3. Average Scores for all Primary Fatigue Measures

Measure	*PFS M* (*SD*)	*Energy M* (*SD*)	*Tired M* (*SD*)
RELAX Group			
Pre Day 1	4.40 (1.71)	2.39 (0.74)	2.89 (0.79)
Post Day 1	3.91 (1.51)	2.16 (0.73)	2.71 (0.78)
Pre Day 2	4.19 (1.38)	2.17 (0.64)	3.10 (0.79)
Post Day 2	3.67 (1.35)	2.10 (0.54)	2.94 (0.83)
Pre Day 3	4.21 (1.77)	2.40 (0.75)	3.01 (0.67)
Post Day 3	3.54 (1.56)	2.43 (0.67)	3.17 (0.68)
AERO Group			
PFS Pre Day 1	5.02 (1.64)	1.83 (0.82)	2.82 (0.79)
PFS Post Day 1	4.78 (1.05)	2.28 (0.54)	2.89 (0.53)
PFS Pre Day 2	4.94 (1.53)	1.97 (0.73)	2.86 (0.80)
PFS Post Day 2	4.36 (1.62)	2.54 (0.72)	3.22 (0.64)
PFS Pre Day 3	5.30 (1.27)	1.78 (0.65)	2.55 (0.57)
PFS Post Day 3	4.15 (1.62)	2.57 (0.69)	3.11 (0.64)
COMBINED Group			
PFS Pre Day 1	4.00 (1.13)	2.18 (0.62)	3.34 (0.49)
PFS Post Day 1	3.47 (1.16)	2.12 (0.69)	3.20 (0.69)
PFS Pre Day 2	3.59 (1.41)	2.71 (0.80)	3.42 (0.67)
PFS Post Day 2	3.09 (1.40)	2.82 (0.83)	3.58 (0.54)
PFS Pre Day 3	3.48 (1.87)	2.57 (0.74)	3.48 (0.74)
PFS Post Day 3	2.65 (1.20)	2.75 (0.60)	3.31 (0.76)

Note. PFS=Piper Fatigue Scale, Energy= Activation Deactivation Adjective Check List Energy Subscale, Tired=Activation Deactivation Adjective Check List Tired Subscale

Table 4. Baseline Uncorrected Cognitive Scores

Measure	*M* (*SD*)	Min	Max
RELAX Group			
Picture Sequence Score	53.71 (12.78)	37.00	88.00
Flanker Reaction Time Score	36.21 (10.12)	22.00	55.00
Flanker Accuracy Score	4.96(0.06)	4.88	5.00
DCCS Score	45.00(10.03)	32.00	60.00
AERO Group			
Picture Sequence Score	54.62 (11.18)	43.00	83.00
Flanker Reaction Time Score	35.69 (7.54)	28.00	53.00
Flanker Accuracy Score	4.95(0.10)	4.75	5.00
DCCS Score	41.08(11.08)	23.00	65.00
COMBINED Group			
Picture Sequence Score	57.53 (15.13)	38.00	87.00
Flanker Reaction Time Score	42.15 (10.67)	23.00	66.00
Flanker Accuracy Score	4.98(0.05)	4.5	5.00
DCCS Score	46.85(9.64)	26.00	68.00

Note. DCCS = Dimensional Change Card Sort Task

Table 5. Means of Enjoyment for Randomized Intervention

Measure	*M* (*SD*)	Min	Max
RELAX Group			
Enjoy	6.79 (0.43)	6	7
Recommend	6.07 (0.83)	5	7
Satisfied	5.64 (1.15)	3	7
Worthwhile	6.71 (0.61)	5	7
AERO Group			
Enjoy	6.31 (1.03)	4	7
Recommend	6.23 (1.01)	4	7
Satisfied	5.62 (1.26)	3	7
Worthwhile	6.46 (0.97)	4	7
COMBINED Group			
Enjoy	7.00 (0.00)	7	7
Recommend	6.31 (0.95)	5	7
Satisfied	5.54 (1.13)	4	7
Worthwhile	6.92 (0.28)	6	7

Note. Enjoy = “Overall I enjoyed taking part in my activities”; Recommend = “I would recommend these activities to friends who are experiencing similar symptoms”; Satisfied = “I was satisfied with the effectiveness of my activities for reducing fatigue”; Worthwhile = “I found this to be worthwhile”

Table 6. Baseline Assessments of Ancillary Measures

Measure	*M* (*SD*)	Min	Max
RELAX Group			
HADS Anxiety	4.43 (1.91)	2	8
HADS Depression	8.86 (2.24)	4	11
BAI	26.71 (5.09)	21	40
Expectancy-FR	5.79 (1.05)	4	8
Expectancy-CC	6.57 (1.60)	4	10
Expectancy-AF	6.57 (2.03)	3	10
BFI	33.57 (18.41)	9	68
ANAQ	4.54 (1.10)	3.20	6.80
FOF	44.93 (8.31)	36	66
MSEQ Grocery	6.71 (2.62)	3.6	10.6
MSEQ Maps	7.00 (2.76)	3	11
MMQ Ability	2.50 (0.43)	1.50	2.95
MMQ Contentment	2.47 (0.63)	1.17	3.61
AERO Group			
HADS Anxiety	6.54 (3.18)	3	13
HADS Depression	7.92 (5.04)	1	22
BAI	29.92 (4.27)	24	37
Expectancy-FR	6.85 (2.61)	1	11
Expectancy-CC	6.77 (2.74)	1	10
Expectancy-AF	6.62 (2.79)	1	11
BFI	49.00 (19.85)	11	73
ANAQ	4.89 (1.03)	3.60	6
FOF	44.15 (14.02)	20	62
MSEQ Grocery	6.86 (2.32)	4.20	10.40

Table 6. (cont.)

MSEQ Maps	7.92 (2.38)	4.20	10.80
MMQ Ability	2.55 (0.57)	1.75	3.40
MMQ Contentment	3.25 (0.81)	1.94	4.39
COMBINED Group			
HADS Anxiety	4.31 (2.66)	2	12
HADS Depression	6.84 (2.91)	2	11
BAI	29.69 (7.71)	22	53
Expectancy-FR	5.46 (1.51)	2	7
Expectancy-CC	5.15 (1.57)	2	7
Expectancy-AF	5.15 (1.86)	1	7
BFI	29.77 (17.80)	11	69
ANAQ	5.72 (1.35)	2.40	7
FOF	47.08 (9.71)	25	61
MSEQ Grocery	6.15 (2.70)	2	10.40
MSEQ Maps	6.65 (2.48)	3	10.80
MMQ Ability	2.70 (0.66)	2.05	4.35
MMQ Contentment	2.85 (0.93)	1.50	4.78

Note. HADS = Hospital Anxiety and Depression Scale, BAI = Beck Anxiety Inventory, Expectancy-FR= Expectation for Fatigue Reduction, Expectancy-CC = Expectation for Cognitive Change, Expectancy-AF=Expectation for Affective Improvement, BFI = Brief Fatigue Inventory, ANAQ= Anticipated Negative Affect Questionnaire, FOF = Frequency of Forgetting, MSEQ = Memory Self Efficacy Questionnaire, MMQ Multifactorial Memory Questionnaire

Table 7. Ancillary End of Study and Change Values

Measure	*M* (*SD*)	Min	Max
RELAX Group			
EBCS Change	0.90 (0.99)	-0.20	3.20
PMFQ Change	-0.11 (0.56)	-1.29	0.71
MAEQP	2.36 (1.50)	0	5
AERO Group			
EBCS Change	1.23 (1.33)	-0.20	4.40
PMFQ Change	0.01 (0.42)	-0.71	0.71
MAEQP	2.08 (1.38)	0	5
COMBINED Group			
EBCS Change	-0.49 (1.08)	-1.40	2.40
PMFQ Change	-0.23 (0.34)	-0.29	0.71
MAEQP	3.46 (1.71)	1	6

Note. EBCS = Modified Experienced Bodily Changes Scale; PMFQ = Perceived Mental Fatigue Questionnaire; MAEQP = Modified Activity Engagement Questionnaire-Presence Subscale

Table 8. Comparison of Fatigue Reduction in Relaxation vs. Non-Relaxation Conditions

Group	Measure	N	Minimum	Maximum	*M*	*SD*
AERO	AD ACL Energy	13	-1.00	1.20	-0.25	0.69
	AD ACL Tired	13	-1.20	1.00	-0.13	0.55
	PFS	13	-2.90	2.10	-0.59	1.17
RELAX and COMBINED	AD ACL Energy	27	-1.00	2.00	-0.34	0.95
	AD ACL Tired	27	-2.00	.80	-0.26	0.80
	PFS	27	-3.40	1.50	-0.63	1.48

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