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Effects of a Twelve-week Aerobic and Cognitive Training Intervention on Cognitive Function in Cancer Survivors

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EFFECTS OF A TWELVE-WEEK AEROBIC AND COGNITIVE TRAINING INTERVENTION ON COGNITIVE FUNCTION IN CANCER SURVIVORS

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ABSTRACT

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Chemotherapy-related cognitive impairment (CRCI) has been reported to negatively affect upwards of 75% of cancer patients. Decreased reaction times, cognitive and linguistic inabilities, decreased quality of life (QOL), decreased concentration and memory, and attentional difficulties may be due to CRCI. Exercise and cognitive training, independently, have been shown to improve functional capacity and aspects of cognitive function in various populations. However, to our knowledge there have been no studies that have examined the effects of aerobic and cognitive training on cognitive function in cancer survivors. **Purpose**: To examine the effects of a quasi-randomized, controlled 12-week or 36 session aerobic and cognitive intervention on cancer survivors (CAN) versus non-cancer participants (NC). **Methods**: CAN (n = 28) who were in treatment or had completed treatment within eight weeks and NC (n = 7) were included in this study. Pre and post physical and cognitive assessments, Beck Depression, QOL, and Piper fatigue inventories were completed. Following initial assessments, a 12-week computer-based cognitive training and flexibility training intervention was conducted. CAN participants were assigned to aerobic, flexibility, and cognitive training (CAN-AER-COG), aerobic and flexibility training (CAN-AER), flexibility training only (CAN-CON), or cognitive and flexibility (CAN-COG) training groups. The apparently healthy group completed aerobic, flexibility, and cognitive training (NC-CON). **Results**: No

significant ($p > 0.05$) main effects were observed between groups for all variables of interest. Wilcoxon sign ranks tests revealed significant improvements among within-group measures. The AER-CAN-COG significantly ($p < 0.05$) decreased (-33%) in the Piper B subcategory. The CAN-AER group significantly ($p < 0.05$) increased in measures of logical memory raw and scaled scores (28%, 33%, respectively), delayed recall raw and scaled scores (39%, 27%, respectively, $p < 0.05$), block design raw and scaled scores (20%, 19%, respectively, $p < 0.05$), and letter-number sequencing scaled scores (12%, $p < 0.05$). Piper S scores significantly (34%, $p < 0.05$) decreased while the Piper C subscale trended toward significant ($p = 0.06$) decreases (26%). The CAN-CON group significantly ($p < 0.05$) increased in gender, age, and education verbal fluidity scores (750%, 320%, and 205%, respectively). VO_{2peak} trended toward significant increased, while QOL significantly increased (16%, $p = 0.05$; and 26%, $p < 0.01$, respectively). The NC-CON group delayed recall scaled scores trended toward significant increases (12%, $p = 0.07$). The CAN-COG group failed to significantly ($p < 0.05$) increase in any measure of cognitive function. Beck depression significantly ($p < 0.05$) decreased (-59%) and QOL significantly ($p < 0.05$) increased (6%). **Conclusion**: Aerobic training impacted cognitive, physiological, and psychosocial measures the greatest. Individually, cognitive training and flexibility training resulted in notable cognitive, physiological, and psychosocial improvements. Yet, the combined cognitive, aerobic, and flexibility training failed to produce the synergistic and compounded results as hypothesized. Results suggest that, individually, aerobic, cognitive, and flexibility training are appropriate for addressing CRCI in this population, but combined training of this nature may actually be too demanding for those undergoing treatment.

DEDICATED IN MEMORY OF:

Dr. CAROLE M. SCHNEIDER, Ph.D.

Your perseverance, drive, and determination will always be carried with me as I move beyond this experience. You knew (even as I daily doubted myself) what I was capable of and pushed me to exceed all expectations. I am, and always will be, thankful and grateful to have been able to spend the years working next door to you and learning from you. Your infectious laugh and jovial spirit made working for you enjoyable. During the two years before your passing, I was blessed and honored to get to know you as not only my doctoral mentor and advisor, but during the times you had me fix things, hang up Christmas lights, carry things up from your basement, or mow your lawn every week, I had the opportunity to observe a different side of you. I was blessed to experience your genuine, heartfelt, care and compassion toward me as a person; not just your student. I will always cherish those moments and will be forever indebted to you for the skills you taught me, the ferocity at which you pushed me, and the opportunities you have made available to me, and now to my growing family for the future.

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As much more than an academic endeavor, this journey has been more of a test of my personal faith. The challenging academic times were significantly overshadowed by the arduously difficult, real-life, situations experienced outside of the classroom setting. Compared to many friends of mine who completed Ph.D.s across the country in a few short years, my circumstances were not typical by any means. In retrospect, I am extremely thankful and grateful for this experience, that I may carry the lessons I've learned and be much bolder in my faith wherever I am placed. Likewise, a project of this magnitude could have never been conducted without countless hours of help and guidance from many others who have sacrificed their time and resources to help me conduct this research. Therefore, this section is more lengthy than normal, but is absolutely necessary to properly address those who have helped me along the way. Hopefully, I haven't missed anyone!

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CHAPTER I

INTRODUCTION

Cancer patients experience a multitude of various physical, emotional, and psychological effects during and following chemotherapy. Despite the substantial methodological improvements, the positives are matched with sometimes debilitating negative side effects. Of the many different side effects that may occur with treatment, 4-75% of patients have been estimated to experience some form of cognitive dysfunction following treatment (Jackson, 2008; Konat, Kraszpulski, James, Zhang, & Abraham, 2008; Myers, 2009; Raffa & Tallarida, 2010). Staat and Segatore (2005) reported that cognitive impairment associated with chemotherapy treatment has been often described as "chemo-fog" or "chemo-brain;" however, it has more recently been defined as chemotherapy-related cognitive impairment (CRCI) (Myers, 2009; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). A formal definition of cognitive function is cognitive action in the everyday world. It is multifaceted, being composed of attention, language, learning and memory, visual-spatial processing, executive skills, and reasoning (La Rue, 2010). It (CRCI) has been described as presenting itself as impaired speed of processing information or reaction time, cognitive inability, and diminished organizational skills, as well as decreased linguistic abilities, and attention (Staat & Segatore, 2005). In addition, executive function, described as foresight, hindsight, and judgment may also be negatively impacted.

Chemotherapy-related cognitive impairment has been reported to negatively affect patients' quality of life (QOL), impact daily living activities, impair memory and concentration, and may persist long after completion of treatment (Carlsson, Strang, & Bjurstrom, 2000; Mitchell & Turton, 2011; Schilling, Jenkins, Morris, Deutsh, & Bloomfield, 2005). Patients have also described CRCI as forgetfulness, absentmindedness, and an inability to focus while performing daily tasks (Hess & Insel, 2007).

Three potential mechanisms have been proposed to help illuminate the mechanisms of CRCI. These are immunologic or inflammatory toxicity, direct neurotoxicity, or micro-vascular toxicity (Saykin & Ahles, 2003). Proliferating cells are targeted by chemotherapy, and these drugs (such as 5-fluorouracil) are able to cross the blood-brain barrier, and collect in cerebral-spinal fluid (Bourke, West, Cheda, & Tower, 1973; Kerr, Zimm, Collins, O'Neill, & Poplack, 1984). Chemotherapy-related cognitive impairment memory deficits may be due to direct toxicity on neurogenic zones such as the denate gyrus of the hippocampus (Mustafa, Walker, Bennett, & Wigmore, 2008). More recent evidence suggests that CRCI may be linked to cytotoxic agents releasing excessive cytokines contributing to toxic collateral damage to healthy tissue, potentially disrupting cognitive performance (Raffa, 2011).

In human and animal chemotherapeutic treatment models, investigators have demonstrated decrements in short-term memory and high order brain function (Konat et al., 2008), memory acquisition impairment (Liedke et al., 2009), learning and memory impairment (Schilling, Jenkins, Morris, Deutsh, & Bloomfield, 2005; Winocur, Vardy, Binns, Kerr, & Tannock, 2006), spatial memory, neutrotrophic protein, neurogenic

protein, vascular proliferating cell dysfunction (Mustafa et al., 2008), contextual memory dysfunction (Macleod et al., 2007), verbal and working memory impairment (Schilling, Jenkins, Morris, Deutsh, & Bloomfield, 2005), decreases in cerebral white matter, processing speed (Deprez et al., 2011), and decreases in attention/concentration scores (Yoshikawa et al., 2005).

It has been well established that exercise has been positively associated with increases in cardiopulmonary function, resting heart rate, pulmonary function, forced vital capacity (FVC), upper-body muscular endurance, lower-body muscular endurance, core muscular endurance and flexibility, as well as reductions in behavioral, sensory, affective, cognitive and mood, total fatigue scores, and reductions in inflammation in apparently healthy populations (Fairey et al., 2005; Hsieh et al., 2008; Schneider, Hsieh, Sprod, Carter, & Hayward, 2007a; Schneider, Hsieh, Sprod, Carter, & Hayward, 2007b; Schneider, Hsieh, Sprod, Carter, & Hayward, 2007c; Van Weert et al., 2010). Furthermore, investigators have also demonstrated that aerobic exercise and cognitive training may increase QOL and cognitive function in apparently healthy adults, cancer survivors, and Alzheimer's patients (Ferguson et al., 2007a; Potter, & Keeling, 2005; Wood, Alvarez-Reyes, Maraj, Metoyer, & Welsh, 1999), increase cognitive control and attention (Hillman et al., 2009), improve cognitive function and recall (Lautenschlager et al., 2008), and increase mental speed, memory, reaction time, attention, and cognitive flexibility (Masley, Roetzheim, & Gualtieri, 2009). In addition, during brain-based cognitive training studies using Posit-Science®, a commercially available home brain training software, investigators have demonstrated improvements on auditory processing speed, self-reported everyday cognitive skills, memory performance, increases in speed

and accuracy of central auditory system, and benefits potentially lasting well beyond the training interventions (Mahncke, Bronstone, & Merzenich, 2006; Mahncke et al., 2006; Smith, et al., 2009). However, to our knowledge, there were no current studies that had examined a combined exercise and cognitive intervention on measures of cognitive function in a cancer rehabilitation population.

Statement of Purpose

Therefore, the purpose of this study was to examine the effects of a quasi-randomized, controlled 12-week aerobic and cognitive intervention on cancer survivors (CAN) versus non-cancer participants (NC).

Research Hypotheses

H1 Aerobic training consisting of moderate intensity cycling on a stationary cycle ergometer would increase measures of cognitive function in CAN.

H2 Cognitive training using computer software consisting of brain training exercises would increase measures of cognitive function in CAN.

H3 The combined cognitive and aerobic training would have a synergistic effect on increases in cognitive function in CAN.

Significance of Study

Cancer is a staggering disease. Global estimates have revealed that approximately 12.7 million people were diagnosed with cancer as of 2008 (Jemal, Bray, Center, Ferlay, Ward, & Forman, 2011). The efforts to treat the disease are often times accompanied by varying degrees and severity to which treatment-related side effects may occur. In the war on cancer, the patient is often prescribed treatment modalities that may affect physical, psychological as well as cognitive abilities of the individual. The phenomenon of cognitive dysfunction related to chemotherapeutic treatment, commonly known as “chemo brain” or “chemo fog” may present considerably different among individuals.

Regardless, there is substantial information to suggest that certain areas of the brain are affected by current methods of treatment for cancer. The mission of cancer rehabilitation at The Rocky Mountain Cancer Rehabilitation Institute (RMCRI) is to relieve suffering, promote self-sufficiency, improve quality of life, and eliminate secondary cancers and cancer recurrence for cancer survivors through prescriptive exercise and nutrition evidence-based interventions. By implementing methods of aerobic exercise, flexibility, and cognitive training using a specifically designed software program to target areas of the brain most affected by treatment, not only will the mission be upheld, but this approach to cancer rehabilitation is completely novel. To our knowledge there were no other quasi-randomized or controlled studies conducted using specific cognitive training interventions combined with elements of exercise on cancer survivors in a cancer rehabilitation program.

Limitations

Although the novelty of this project was the major strong point of this study, much akin to many studies throughout history, many unforeseen limitations presented themselves throughout the course of data collection. The limitation with the most noteworthy influence on the process of data collection was the complexity of cancer itself. When clients are referred to the RMCRI, they may present at very different time points along the cancer continuum. We had participants who initially qualified for the study but presented at different stages, types of cancer, types of treatment, combinations of types of treatment and stages, and experienced a multitude of physiological and psychological responses to the treatment itself. Despite working with cancer survivors since 2008, having immersed myself in the literature, and having a modicum of

expectations, most participants presented with a combination of factors that forced reevaluation on an individual and frequent basis. For example, a particular participant (who was prescreened and met qualification standards for this study) was undergoing treatment for stage III brain cancer and would often have moments where she would randomly cease talking, slow or stop cycling, and appear to be awake, but not coherent. It was determined that because of her type of cancer, treatment, and being on frequently oscillating dosages of GABApentin that this was something that needed to be addressed on a daily basis, but did not fit the requirements for removal from the study. Throughout the study she continued to improve, but because of her particularities, we had to make appropriate adjustments in order to accommodate her needs. In addition, treatment-related side effects were also a source of difficulty. Since many were undergoing treatment, dosages and regimens often changed, and because many times participants, especially those who were undergoing treatment, often did not feel well enough to complete physical or cognitive training to the exact specifications of the study. When the study began in 2010, the process of referral from local oncologists predominantly included those that had just completed treatment or were upwards of eight weeks out of treatment. As the study progressed, the amount of referrals of clients that were currently undergoing treatment continued to increase to a point where those who were out of treatment were seldom observed. In light of the individual experiences with treatment, often times training had to be reduced to a comparable rate of perceived exertion (RPE) just so ambitious clients who were so worn out from treatment in the preceding days could complete the training without harming themselves. Medical emergencies, recurrence, inclement weather, holidays, or last minute appointment changes with

physicians were also significant factors in the delay of completing this study. For example, a particular client that, again was prescreened and qualified for the study, had a medical emergency where he contracted an infection near an incision site and consequently was admitted to the hospital for a month. Even though the requirements were explicitly conveyed prior to the start of the study, it is almost impossible with this population to expect perfect adherence. For example, all participants in the study had work or family-related situations which inhibited them from making all training sessions. In addition, participants included during the fall semesters were often the most difficult to complete because of the amount of family holidays that occur from late October until after January. Furthermore, clients dropping the study for health-reasons was also a factor that inhibited the completion of this study within the confines of the proposed timeline. Small sample sizes were a substantial limitation in this study for both the CAN and NC groups. Had the proposed amount of subjects refrained from withdrawal from this study, group differences may have been more pronounced. Yet, many participants did withdraw, which forced the alterations in statistical analyses. In fact, for the *N* of 35 that was completed and considered for this analysis, a total of 11 participants dropped the study at some point between 2010 and 2014. Furthermore, not all participants completed every single assessment variable of interest in this study. Consequently, data imputation methods were employed to explain approximately 1.3% of cognitive data and 3.6% of physiological and psychosocial data. This is reported in greater detail in the methods section. Finally, with the many other factors that acted as barriers to the completion of this study, death of participants because of cancer was also a factor that, sorrowfully, occurred for a couple of people directly following their involvement in the study. One

participant in particular passed away from brain cancer during the course of the study. Taken together, the results of this study should be interpreted with caution.

Assumptions

This study was based on the assumptions that participants would follow the instructions for maintaining normal activities of daily living (ADL) and not be involved with any other forms of physical exercise beyond what was administered during the study. With respect to the condition of each individual as cancer survivors, all participants were screened via a preliminary phone conversation for health-related conditions that would have been considered detrimental to the outcomes of the study and therefore were considered in relatively good health pending completion of a physical assessment. Participants were also prescreened for cognitive impairments and tested for sound mental status via Mini Mental Status Examination (MMSE) and were, therefore, considered mentally capable to participate in this study.

Definition of Terms

Cancer: A group of diseases characterized by uncontrolled growth and spread of abnormal cells (American Cancer Society, 2014).

Executive Control/Function: A subset of multiple procedures including: planning, working memory, scheduling, task coordination, and interference control (Hillman et al., 2006).

Non Matching to Sample testing: A series of paired sample and test trials focused on object recognition and non-spatial memory testing. The stimulus for the testing consists of a series of suspended cylinders above a water maze where rodents

must recognize familiar objects when placed in novel areas while being timed (Winocur et al., 2006).

Cognitive Function: Cognitive action in the everyday world. It is multifaceted, being composed of attention, language, learning and memory, visual-spatial processing, executive skills, and reasoning (La Rue, 2010).

Anisotropy: Diffusion that is dependent on direction (Beaulieu, 2002).

Morris Water Maze Test: Test of reference memory depending on functional integrity of rodent hippocampal tissue (Morris, Garrud, Rawlins & O'Keefe, 1982).

Brain derived neurotropic factor (BDNF): Reported to be involved in neurogenesis cultivation, learning, and memory (Mustafa et al., 2008).

Dentate Gyrus: Region of brain located within the hippocampus reported to be associated with neuronal proliferation and neurogenesis (Mustafa et al., 2008).

Ovariectomized: Surgical removal of one or both ovaries (Macleod et al., 2007)

Hippocampus: Limbic system component with the amygdala. The location of the hippocampus is composed of the medial aspect of the temporal lobe. Bilateral brain damage may inhibit new memory acquisition and retention; however, pre tissue insult memories may remain. Limbic structures have been reported to aid in the consolidation of memories but not storage (Marieb and Mallatt, 1997).

Praxis: The ability to carry out learned or purposeful action.

List of Abbreviations

WMS IV BCOG: Weschler Memory Scale (4th Ed.) general cognitive screener.

WMS IV LMI Raw: Weschler Memory Scale (4th Ed.) Logical Memory I raw score.

WMS IV LMI Scaled: Weschler Memory Scale (4th Ed.) Logical Memory I scaled score.

WMS IV LMII DR Raw: Weschler Memory Scale (4th Ed.) Logical Memory II delayed recall raw score.

WMS IV LMII DR Scaled: Weschler Memory Scale (4th Ed.) Logical Memory II delayed recall scaled score.

WMS IV LMIICP Raw: Weschler Memory Scale (4th Ed.) Logical Memory II cumulative percentage raw score.

TMT A Raw: Trail Making Test A raw score.

TMT B Raw: Trail Making Test B raw score.

WAIS IV BD Raw: Weschler Adult Intelligence Scale (4th Ed.) Block Design raw score.

WAIS IV BD Scaled: Weschler Adult Intelligence Scale (4th Ed.) Block Design scaled score.

WAIS IV LNS Raw: Weschler Adult Intelligence Scale (4th Ed.) Letter Number Sequence raw score.

WAIS IV LNS Scaled: Weschler Adult Intelligence Scale (4th Ed.) Letter Number Sequence scaled score.

WAIS IV CD Raw: Weschler Adult Intelligence Scale (4th Ed.) Coding raw score.

WAIS IV CD Scaled: Weschler Adult Intelligence Scale (4th Ed.) Coding scaled score.

COWAT Z G: Controlled Oral Word Association Test gender z-score.

COWAT Z A: Controlled Oral Word Association Test age z-score.

COWAT Z ED: Controlled Oral Word Association Test education z-score.

SBP: Systolic blood pressure.

DBP: Diastolic bold pressure.

RHR: Resting blood pressure.

VO_{2peak}: The highest rate of oxygen consumption measured during the exercise test, regardless of whether a VO_2 plateau is reached.

SANDR: Sit and Reach test.

PIPER I: Piper Fatigue Index overall score.

PIPER B: Piper Fatigue Index behavioral score.

PIPER A: Piper Fatigue Index affective score.

PIPER S: Piper Fatigue Index sensory score.

PIPER C: Piper Fatigue Index cognitive/mood score.

BECK: Beck Depression Inventory score.

QOL: Quality of Life score.

CHAPTER II

REVIEW OF LITERATURE

Cancer Overview

On a global scale, cancer is a substantial health concern. From a fiscal standpoint, by 2020 it is projected that direct annual costs of cancer will skyrocket from approximately $104 billion in 2006 to over $173 billion (Smith & Hillner, 2011). From an overall healthcare standpoint, cancer has been described as being multifaceted, having multiple, considerable factors to be aware of when approaching the topic. The American Cancer Society (ACS), in *Cancer Facts & Figures 2014,* described the postulated causes of cancer as being composed of potentially several internal and external factors. The internal factors may be composed of one or a combination of inherited and/or metabolic mutations, and compromised hormonal and/or immune function. External factors may include exposure to: chemicals, radiation, infectious organisms, and/or tobacco products. It is estimated that a total of 1,665,540 new cases of cancer were expected to be diagnosed in the United States in 2014 (ACS, 2014). The probability, in one's lifetime, of being diagnosed with some form of invasive cancer is 44% and 38% for males and females, respectively (Siegal, Naishadham, & Jemal, 2013). In addition, 585,720 people are also projected to succumb to the disease, with as many as 1600 people expected to perish each day.

Approximately one third (195,240) of the 585,720 deaths will be related to obesity, poor nutrition, and inactive lifestyles, which could be considered preventable occurrences. Behind heart disease, cancer is the second leading cause of death (ACS, 2014; Siegal et al., 2013). As disparaging as those numbers sound, Kohler et al. (2011) indicated that in data collected from 1975-2007, overall cancer incidence and mortality rates have decreased 1% across all races. More recent data (2005-2009) have indicated that incidence numbers across all races have maintained at 1% however, death rates have decreased 1.8% per year in men, and 1.5% per year in women, with the noted exception of Native Americans and Alaska Natives. These reductions have been attributable to, what was described as, "avoidances" of 1,180,000 deaths from cancer in the United States, since 1990 (Siegal et al., 2013). The five-year relative survival rate for all cancers diagnosed between 2002 and 2009 is 68%, up from 49% from 1975-1977 (ACS, 2014). In addition, our laboratory also found specifically individualized cancer rehabilitation interventions to be associated with significant increases in five-year survival rates (Peterson, Repka, Hayward, & Schneider, 2010). These witnessed reductions in death and increased five-year survival rates may be attributable to current progressive methods of prevention, detection, education, improved precision of treatment methods, as well as increased implementation of individualized cancer rehabilitation programs.

Effects of Chemotherapy on the Brain

In recent years, chemotherapeutic interventions have been instrumental in contributing to the survival and clinical outcomes of cancer patients. The positive effects that are witnessed with chemotherapy and associated cancer treatments are often matched or exceeded by the many different types of negative side effects. During the past two decades, notoriety has advanced within the body of literature regarding attention and memory decrements associated with chemotherapy treatment (Ferguson, Cassel, & Dawson, 2010). Approximately 77% of all cancer(s) diagnosed generally occur among those who are 55 years of age or older (ACS, 2014). With the combination of advances in detection and treatment methods, it is likely that more people will be either living with cancer, have been diagnosed and are residing within the treatment spectrum, or are beyond the process. Matsuda et al. (2005) reported that at least 10-40% of breast cancer survivors may experience various gradations of cognitive deficits when returning to their daily lives, negatively affecting QOL. With regards to cognitive difficulties witnessed during and following various chemotherapeutic treatments, there is an increasing demand to address this matter of survivorship and develop methods to better approach the issue, whether that be symptom management or rehabilitation to reduce, or offset some of the witnessed side effects, has yet to be determined.

Cognitive dysfunction or impairment that is associated with chemotherapy treatment has been reported in the literature as far back as the early 1980's. During various neuropsychological assessments, chemotherapy treatment has been indicated to negatively affect anxiety, stress, and depressive symptoms. Each having been observed in various extents in cancer patients, and have been suggested to adversely influence these

cognitive testing measures (Ferguson et al., 2010). In addition, during the early 1990's a substantial portion of the literature was focused on elements of sustained attention and working memory and how they are affected by various chemotherapeutic agents. Of the more prominent investigations on the topic, Van Dam et al. (1998) examined levels of cognition in high-risk breast cancer patients receiving standard or high dosages of chemotherapy. Thirty-two percent of the high dosage group and 17% of the standard dosage group exhibited significantly noticeable measures of cognitive dysfunction, as compared to 9% witnessed in the control group; this indicates a greater risk of cognitive impairment with increasing dosages of chemotherapy. However, the observed psychological and cognitive dysfunction by the investigators was attributed to emotional distress as opposed to direct or indirect effects of chemotherapy (Van Dam et al., 1998). In retrospect, Ferguson et al. (2010) elucidated that the compilation of CRCI literature during the 1990's could be considered an establishment of the functional relationship between chemotherapy dosage and observed cognitive dysfunction. When chemotherapy dosage increased, so did the level to which cognitive dysfunction was observed or experienced.

Chemotherapy and the intended toxicities on cancer cells, unfortunately have inadvertent effects on healthy cells (Raffa, 2011). In addition, these observed toxicities have been speculated to elicit extensive collateral damage to healthy tissue, as well as components of the central and peripheral nervous systems. Of those who have experienced chemotherapy-related side effects, an estimated 4-75% of patients experience some form of cognitive dysfunction following treatment (Jackson, 2008; Konat et al., 2008; Myers, 2009; Raffa & Tallarida, 2010). Therefore, understanding

CRCI is an important aspect to cancer rehabilitation. More recent evidence may suggest that these cognitive dysfunctions may be related to excessive cytokine release by cytotoxic agents, inflammatory issues, or direct neurotoxicity.

Cognitive Functioning

La Rue (2010) formally defined general cognitive functioning as daily cognition in action. Furthermore, language, executive functioning, learning, memory, visuo-spatial processing, and attention have been described as components of cognitive functioning. It is possible for individuals to classify as "fit" in certain areas like language and attention but may be less fit in other areas like learning or executive functioning (La Rue, 2010). Individuals with optimal brain fitness levels should be absent of brain disease or systemic illness that may critically disrupt normal brain function. Although, La Rue (2010) suggested that brain fitness may be impacted by genetic predispositions, endowments, lifestyle choices, and life experiences thereby making the task of monitoring brain fitness difficult to quantify.

In elderly breast cancer patients, Wefel, Saleeba, Buzdar, and Meyers (2010) examined the effects of pre-existing cognitive impairments prior to administration of treatment. The investigators measured affective status, QOL, and cognitive function before and after treatment. Wefel et al. (2010) determined that although 21% of patients were cognitively impaired prior to treatment, 65% of the sample exhibited significant declines in measures of learning, memory, executive function, and processing speed in analyses following treatment. Sixty-one percent experienced cognitive decline, with 30% displaying onset of previously unobserved cognitive impairments (Wefel et al., 2010).

Therefore, it may be worthwhile to consider that there may be a compounding effect of CRCI and pre-existing cognitive dysfunction witnessed in elderly cancer patients.

As of 2005, 925 million people across the globe were estimated to be 55 years of age or older. By 2015 this cohort is expected to increase to 1.4 billion people (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008). Research has indicated that age-related cognitive declines involving processing and working speed, and short and long-term memory are related to changes in brain structure and function (Hillman et al., 2006). In older adults, who have not had cancer, it is estimated that 3-19% will have experienced various elements of mild cognitive impairment which may be characterized by impaired performance on memory tasks and memory complaints (Belleville et al., 2006). Pre-dispositional engagement has been defined as the relatively stable mental disposition toward the enjoyment of a novel task, intellectual challenge, and creativity (Parisi, Stine-Morrow, Noh, & Morrow, 2009). In the investigation of relationships between the approaching of experiences in a mindful and creative way, cognition, and activity of participation in older adults, Parisi et al. (2009) administered a battery of neuro-psychological tests that evaluated processing speed, working memory, inductive reasoning, visuo-spatial processing, activity level, divergent thinking, and mental engagement predisposition. Factor analyses were then run on data collected from the neuropsychological tests to evaluate dimensions of engagement in various activities. These dimensions were also compared to overall cognition. The investigators found that performance on cognitive assessments could be explained, in part, by level of enjoyment and preference toward intellectually stimulating challenges. In particular, older adults who engaged in intellectually challenging activity tended to approach life experiences

with greater levels of creativity, thoughtfulness, and curiosity than their counterparts. Additionally, these older adults appeared to maintain healthy levels of lifetime cognitive functioning, which was a positive factor for cognitive vitality throughout life. Belleville et al. (2006) assessed a two-month cognitive training intervention with older adults experiencing mild cognitive impairment against older adults with normal levels of cognitive aging. The training included addressing episodic memory performance through mnemonics and semantic elaboration. The investigators found that the aforementioned cognitive training produced positive and long-lasting effects in healthy older adults' cognitive performance.

Age-associated cognitive losses may be substantially ameliorated by physical activity. Hillman et al. (2006) assessed primarily the executive control component of cognition function related to physical activity in 241 participants ranging from 15-71 years of age. The investigators evaluated physical activity by self-reported number of walked city blocks and estimated caloric expenditure. Executive control was defined as being a subset of multiple procedures including: planning, working memory, scheduling, task coordination, and interference control. These processes were reported to have an involvement in the intentional component of interaction with the environment, which may also decline with age. However, physical activity may serve to protect against losses, with the greatest benefits witnessed in some aspect of executive control. The results indicated that response accuracy (% correct) increased as amount of physical activity (days per week) increased across all conditions for older adults [(congruent condition) 0, 88%; 1, 92%, 2, 93%, 3, 95%, and 4, 97%, $p < 0.05$], [(incongruent condition) 0, 65%, 1, 81%, 2, 82%, 3, 86%, and 4, 88%, $p < 0.05$]. For the older adults, greater levels of

physical activity were associated with performance on tasks eliciting greater accuracy of responses. There were no significant (p >0.05) associations between physical activity and accuracy of responses for the younger adults [(congruent condition) 0, 97%, 1, 95%, 2, 97%, 3, 97%, and 4, 96%], [(incongruent condition) 0, 88%, 1, 90%, 2, 86%, 3, 91%, and 4, 85%]. No differences were observed between the groups for task conditions containing smaller executive control components, suggesting that aerobic fitness may selectively protect against cognitive aging on tasks requiring extensive executive control. The investigators concluded that physical activity may be beneficial to cognition during early and middle periods of the human life span and may continue to protect against age-related loss of cognitive abilities during older adulthood (Hillman et al., 2006).

In a review of literature, Angevaren et al. (2008) examined studies that incorporated fitness, cognitive functioning, and physical activity in sample populations reporting ages of participants greater than 55 years. The analysis of literature revealed significantly positive effects of exercise on cognitive speed, delayed memory functions, and visual attention as compared interventions other than listed [(SMD random effects-cognitive speed) 0.3, 95% CI (0.04, 0.5), $p < 0.05$, (SMD random effects-visual attention) 0.3, 95% CI (0.02, 0.5), $p < 0.05$). In studies that compared aerobic training interventions to balance or flexibility programs, the positive effects of aerobic exercise were significantly greater in delayed memory functions, than balance or flexibility alone. As compared to no intervention (controls) the effects of aerobic exercise on cognitive function yielded significant positive effects on auditory attention [(WMD random effects) 0.5, 95% CI (0.1, 0.9), $p < 0.01$) and motor function (WMD random effects 1.2, 95% CI (0.2, 2.2), $p < 0.05$). In a majority of the studies, improved VO_{2max} values of

approximately 14% were also linked to improvements in cognitive function; specifically, improvements in cognitive speed, delayed memory recall, observed motor function, and auditory and visual attention capabilities.

Mechanisms of Cognitive Dysfunction

In a review of literature, Ahles and Saykin (2007) stated that risk factors for the development of cancer and CRCI have been suggested as being composed of shared genetic risk factors which may include low efficiency efflux pumps, dysfunctional DNA repair mechanisms, and immune response incapacitation. The combined systemic effects of chemotherapy and the aforementioned shared genetic risk factors may pose as negatively compounding contributors to cognitive decline in patients following chemotherapy. Changes in cognitive abilities may present subtly and may occur at a range of gradations across various domains of cognition. Ahles and Saykin (2007) elaborated on the primary model of classical thought regarding cognitive dysfunction following chemotherapy. Treatment itself was suspected to be a secondary or tertiary factor originating from psychological complexities such as anxiety, fatigue, or depression. In studies implementing brain imaging techniques, the investigators indicated volumetric alterations in brain tissue have been associated with chemotherapy dosage. In addition, the investigators described that some studies have even shown that white matter integrity and volumes of brain constituencies profoundly involved in cognitive function have been observed to reduce in patients who have undergone chemotherapy. Ahles and Saykin (2007) also noted that within the realm of normal central nervous system function, cytokines play a substantial role in the modulation of glial and neuronal functioning, metabolism of dopamine and serotonin, and neural repair. The neurotransmitters

serotonin and dopamine play an important role in normal cognitive functioning, and have been associated with neurotoxicity and neurodegenerative disorders such as Parkinson's disease, Multiple Sclerosis, and Alzheimer's disease. Furthermore, cytokine induced "sickness behavior" is also associated with cognitive disturbance, fatigue and depression separate from cancer occurrence (Ahles & Saykin, 2007).

More recent literature has expanded on the concept that certain cytokines, specifically IL-1β, IL-6, and TNF-α play a significant role in complex cognitive processes, such as synaptic plasticity, neuro-genesis, and neuro-modulation. McAfoose and Baune (2009) indicated that cytokine-mediated cognitive processes may substantially facilitate the pathogenesis and long term development of specific neuropsychiatric disorders such as depression and dementia. Identification of this central role in various brain activities illuminates the mechanisms of brain function and elaborates on biological mechanisms, especially synaptic plasticity, memory, and cognition. McAfoose and Baune, (2009) referred to cognition as the combination of collective processes, such as attention, learning, executive function, memory, language, and consciousness. Of these cognitive processes, much of the research has centered on memory and learning. Depression may also represent an exaggerated form of cytokine-mediated behavior even in apparently healthy individuals. Individuals exhibiting "sickness behavior" are likely generating a hyper-expressed state of bioavailable cytokines similarly akin to disease models. In apparently healthy individuals, the investigators noted, these physiological modifications are adaptive and may be triggered by psychological stress.

Brain Structural Alterations

Phenotypic relationships between intelligence and brain volumes have been examined in many different studies. Wallace et al. (2010) examined the shared genetic and environmental factors between brain volumes and intelligence in a population sample composed of 649 adolescents, children, twins, and singletons. There were observed relationships between brain volumes and intelligence, however they were insignificant. Volumes of gray matter were uniquely affected by measured verbal perspicacity, whereas non-verbal skills were reported to have an association with gray and white matter brain regions. This would suggest that there are distinct mechanisms that may contribute to the relationships between brain volumes and verbal/non-verbal intelligence. There were no significant differences in brain volume means or variances between monozygotic (MZ) twins, dizygotic (DZ) twins, singletons, and siblings of twins (1172.5 ± 106.5cc, 1146.1 ± 105.9cc, 1164 ± 117.5cc, and 1165.8 ± 118.6cc, respectively), with the exception of significant volume differences in lateral ventricles among MZ and siblings of twins (11.5 ± 6.6cc, and 8.4 ± 4.1cc) ventricles. A majority of correlations (phenotypic) were significant (gray matter + white matter $p < 0.01$, r = 0.1; gray matter $p < 0.01$, r = 0.1; white matter $p < 0.05$, r = 0.1; frontal gray matter $p < 0.01$, r = 0.1; frontal white matter $p < 0.01$, r = 0.1; parietal gray matter $p < 0.01$, r = 0.1; temporal gray matter $p < 0.01$, r = 0.1; temporal white matter $p < 0.01$, r = 0.1; and the caudate nucleus $p < 0.01$, r = 0.2); however, they were small. A significant genetic correlation was also detected between the caudate nucleus volumes and vocabulary scores; however, after statistical correction, only unique environmental correlations for frontal gray matter, gray matter + white matter, and total gray matter remained significant (frontal gray matter $p < 0.01$, r = 0.1;

gray matter $p < 0.01$, r = 0.13; and total gray matter $p < 0.05$, r = 0.1). The findings suggest that different genetic and environmental influences may underpin the phenotypic relationship between brain volumes and verbal versus visual-spatial skills; however, Wallace et al. (2010) were unable to directly or succinctly model those shared contributions.

In a case study examining cognitive function between one set of twins (one who had received chemotherapy and one who did not), Ferguson, McDonald, Saykin, and Ahles (2007b) examined how chemotherapy would elicit cognitive changes between siblings. The twin that underwent chemotherapy received four cycles of doxorubicin (DOX), cyclophosphamide, tamoxifen, and docetaxel. There were significantly greater amounts of verbal complaints of cognitive trouble reported for the twin who had undergone chemotherapy as compared to the untreated twin. The investigators reported that during structural image testing that there were no significant volumetric differences witnessed. However, the investigators also noted that the treated twin's cortical activity pattern was increased significantly greater than that of the untreated twin. Volumes of white matter lesions were observed to be greater in the treated twin in the left (6075 mm^3 vs. 3343.4 mm^3, respectively, and right cerebral hemispheres (3725.7 mm^3 vs. 2897.8 mm^3, respectively). The investigators noted that these observed increases in activation of cortical regions (as observed in functional magnetic resonance imaging) in the treated twin's brain may signify a compensatory adaptation of neural circuitry in unaffected regions of the brain to the toxic effects of chemotherapy on affected regions.

Examination of brain activity has yielded results for cancer survivors as far out as ten years. Silverman et al. (2007) administered positron emission tomography (PET)

testing on age-matched apparently healthy older adults and breast cancer patients who previously had undergone chemotherapy between five and ten years prior to examination. Regardless of the time since treatment, those who had undergone chemotherapy significantly differed from those who had not in neural activation patterns during short-term memory tasks. In particular, those who had undergone treatment exhibited a statistically significant, 2% increase in peak activation in the inferior frontal gyrus during recall tasks. Performance on delayed recall tasks by chemotherapy-treated patients also elicited 3.2 points less, or a 13% decrease when as compared to controls (20.6 ± 4.8 vs. 23.8 ± 6.3, respectively).The researchers noted that the areas that were significantly active were the inferior frontal gyrus, the contralateral posterior cerebellum near the midline, as well as the superior frontal gyrus. However, the most significant alterations in brain activity were witnessed in the basal ganglia. Metabolism was significantly decreased in patients who had received chemotherapy. The most substantial side-effects patients reported having difficulties with were diminished attention, memory, concentration, and processing speed disruption. The investigators also indicated that cognitive-related complaints have typically centered on their perception of mental slowness and diminished abilities to maintain attention, concentrate, and remember things. Abnormal activation in the inferior frontal cortex during performances of short-term memory tasks were witnessed in images taken from chemotherapy treated patients. Untreated patients, in contrast, demonstrated greatest cortical activation in the parietal and occipital cortices when performing the same task. Thus, overall, the altered cortical activation associated with performance of a memory task in chemotherapy treated patients could be characterized as involving greater recruitment of frontal cortical tissue.

Metabolism in the inferior frontal gyrus was significantly related to cognitive performance on short-term memory recall tasks, suggesting that the chemotherapy associated changes in cerebellar activation were related to cognitive deficits. The observed increases in frontal activation may represent a compensatory response to lower resting metabolism found in this region of the brain in chemotherapy treated, cognitively impaired patients.

Brain Imaging and Direct Entry of Chemotherapy

As previously stated, chemotherapeutic agents were classically thought to be unable to cross the blood-brain barrier. However, in various human and animal models, research has indicated that chemotherapeutic drugs have been observed in cerebrospinal fluid and brain tissue. Drugs, such as 5-flourouracil, have been observed to traverse by simple diffusion (Bourke et al., 1973; Kerr et al., 1984). Beaulieu (2002) described a method that may help explain the mechanisms involved in chemotherapy traveling across the blood brain barrier or traversing into other central nervous system structures. Direct neurotoxicity may disrupt brain parenchyma, producing demyelination and/or altered water content, resulting in white matter disruptions. Although this technical review outlined anisotropic mobility of water, the investigators noted literature that examined the effects of the methyl mercury and studies of vinblastine on nervous system components during in vitro and *in vivo* animal models. The investigators indicated that in each of the aforementioned models that anisotropy is a noticeable factor in the fluid mechanics of neurological microstructure. The investigators also noted that with simple diffusion there is a dependence on the interactions of the diffusing molecule which results in diffusion in all directions. In anisotropic diffusion, there is a directional movement based on

neurological structuring, much like the example of placing a cut portion of a flower or a stalk of celery in a colored aqueous solution. There is a distinct method of diffusion of color throughout the plant microtubules. Chemotherapeutic entry into central nervous system components may follow this same delivery method.

Micro-structural abnormalities have also been observed in chemotherapy-exposed brain white matter. Deprez et al. (2011) examined the cerebral white matter integrity of patients, who had undergone chemotherapy. The investigators used magnetic diffusion tensor imaging (DTI) as well as implemented measures of cognitive abilities. Decreased performance on attention and processing speed analyses were significantly correlated [(Attention) Bourdon-Wiersma Dot Cancellation Test-parietal $p < 0.01$, T = -5.5; Test of Everyday Attention-auditory elevator-parietal $p < 0.05$, T = 6.1; (Processing Speed) Nine-Hole Pegboard Test- parietal-temporal (3 measures) $p < 0.01$, $p < 0.05$, $p < 0.05$, T = -5.5,-4.2, and -4.6; WAIS-digit symbol temporal $p < 0.05$, T = 5.7, and Trail Marking Test-A- parietal $p < 0.01$, T = -5.3] with parietal and temporal white matter tracts, suggesting micro-structural damage to white matter may underlie CRCI. The results of this study indicated that there were significant differences witnessed in patients' brain volumes [(fractal anisotropy) .39 x $10mm^2 \cdot s^{-1}$ vs. .43 x $10mm^2 \bullet s^{-1}$ (mean diffusivity), .8 x $10mm^2 \bullet s^{-1}$ vs. .7 x $10mm^2 \bullet s^{-1}$, and (radial diffusivity) .6 x $10mm^2 \bullet s^{-1}$ vs. .5 x $10mm^2 \bullet s^{-1}$, that underwent chemotherapy within four months of starting data collection. The investigators concluded that the CRCI observed during cognitive assessments may be attributed to recent chemotherapy treatment exposure.

High resolution magnetic resonance imaging (Hi-res MRI) and cognitive function techniques conducted on breast cancer survivors and non-cancer patients have also been

utilized to examine soft tissue damage in brain tissue at one and three-year intervals post-treatment (Inagaki et al., 2007). No significant differences in soft tissue damage were observed between cancer survivors and apparently healthy non-cancer controls at one and three-year increments. Although, smaller right prefrontal and parahippocampal regions in the brain were reported for cancer patients whose time out of treatment was less than four months. The investigators noted that significantly smaller frontal regions of the brain may account for the decreases in score on attention/concentration and visual memory indices of the WMS-R cognitive assessments. The prefrontal cortex, including superior and middle frontal gyrus, has been reported to have roles in various functions including memory, planning, execution, monitoring and cognitive processing, behavior, inhibition, and change in circumstantial behavior. The investigators concluded that the current study showed significantly smaller regional brain volumes (right middle frontal gyrus $p < 0.05$, right superior frontal gyrus $p < 0.05$, right parahippocampal gyrus $p < 0.05$, left precuneus $p < 0.05$, left parahippocampal gyrus $p < 0.05$, right cingulate gyrus $p < 0.05$, and left middle frontal gyrus $p < 0.05$) in areas related to cognitive functions in cancer survivors who received adjuvant chemotherapy. However, at the three-year assessment there were no significant volumetric differences.

As speculated, the hippocampus plays a significant role in memory acuity, which may be profoundly affected by the decreases in brain volumes observed during chemotherapy. Yoshikawa et al. (2005) examined the effects of adjuvant chemotherapy on hippocampal volumes in Japanese breast cancer survivors via magnetic resonance imaging (MRI), and memory via WMS-R testing. Breast cancer patients included in the study had completed chemotherapy regimens which included: cyclophosphamide,

methotrexate, fluoruracil, DOX, tegafuracil, doxofluridine, and carmofur. There were no significant differences witnessed in memory function, including the delayed recall index and percent retention, or hippocampal volume observed between the treatment and non-chemotherapy group. There were, however, significant differences in the attention/concentration scores (95.7 ± 9.5 vs. 100.7 ± 9.9) for those in the chemotherapy group compared to those who did not receive chemotherapy. Some of the participants had been out of treatment for three years when data were being collected for this study. The investigators suggested that this may account for the lack of significance found between groups, and may be attributable to healing and repair of damaged areas in the brain following treatment.

In a review of literature, Myers (2009) stated that there are also a variety of potentially associated factors that have been identified as contributors to CRCI. These include: age, educational level, intelligence, social support, anxiety, depression, fatigue, disease site, stage, and co-morbidities; treatment regimen, timing, duration, and concomitant therapies; and hormonal levels, cytokine levels, damage to neural progenitor cells, and the presence of apolipoprotein E-4 allele. Patients have described the effects of cognitive dysfunction as forgetfulness, absentmindedness, and an inability to focus when performing daily tasks (Hess & Insel, 2007).

Chemotherapeutic Agents

In a combined *in vivo* and *ex vivo* animal model, Han et al. (2008) found that progenitor cells and oligodendrocytes were particularly vulnerable to clinically relevant dosages of 5-FU. A major cause of decreased cell numbers in 5-FU treated cultures was due to a reduction in progenitor cell division. When mice were treated *in vivo* with 5-FU,

significant induction of apoptosis in multiple CNS regions were noted. In the corpus callosum, there was also a significant increase in apoptosis at day one to approximately 70% above control values. However, six months following treatment, excessive apoptosis was reported to have normalized following treatment. Mice that were treated with chemotherapy were significantly deficient in delayed white matter. Midline longitudinal sections of corpus callosum displayed scattered foci of demyelinated axons, including partial or complete loss of the myelin sheaths and increases in interlaminar splitting of the myelin sheaths. In examination of transverse sections, there were significant amounts of degenerating axons with multi-laminated structures and collapsed centers, swelling of axons and altered axonal cytoskeleton and organelles. The usage of 5-FU in the treatment of many types of cancers is of concern considering the evidence of acute and delayed toxicity side effects. The investigators also noted that even transient exposure to 5-FU increased apoptosis by 2.5-fold in the subventricular zone and a 4-fold increase in the dentate gyrus in the hippocampus. The investigators also noted that the increasing amount of cells dying continued for 14 days, however was at normal values six months following administration of 5-FU.

Van Der Kooy, Zito, and Roberts (1985) examined the effects of DOX administration on brain tissue in Sprague-Dawley rats. The researchers separated the two halves of the brain by strategic incisions and administered DOX unilaterally. The protective effect of incisions against neurotoxicity was evidence to support the retrograde transport of DOX which led to neurotoxic effects in the treated portion of the brain. Administration of DOX was reported to have destroyed dopaminergic and thalamic neurons, which are afferent to the striatum, and damaged gamma-aminobuteric acid

(GABA) neurological interfaces via retrograde transport. The investigators concluded that DOX may have useful purposes for discriminatory destruction of afferent neurons localized to site of injection by way of retrograde transport.

Joshi et al. (2005) examined the effects of oxidative stress parameters in light of the knowledge that Adriamycin (ADR) has been shown to produce reactive oxygen species (ROS) upon administration. In addition, oxidative stress that is facilitated by free radicals has been associated with neurodegenerative disorders with aging (Butterfield & Kanski, 2001). The investigators measured protein carbonyls (protein oxidation), 3-nitrotyrosine levels, and 4-hydroxynonenal levels (lipid oxidation) in the brain tissue of mice that were injected 72 hours prior to excision. In the ADR treated brain tissue there was approximately a 60% increased expression of protein carbonyls, a 25% increased expression of 4-hydroxyneonenal, 220% increase in multidrug resistance protein-1, and a 55% increased expression of 3-nitrotyrosine which would suggest the susceptibility of the brain to oxidative stress (Joshi et al., 2005). The high levels of polyunsaturated fatty acids, low antioxidant capacity, presence of redox metal ions, and high utilization of oxygen, increases the vulnerability of the tissue. In addition, oxidative stress induced by ADR in the brain could cause damage to proteins critical for cell functioning, possibly leading to cell death. Finally, the investigators concluded that ADR, its metabolites or downstream sequelae is likely to enter the brain and increase oxidative stress, which is likely to contribute to CRCI.

Madhyastha, Somayaji, Rao, Nalini, and Laxminarayana-Bairy (2002) examined the effects of intracerebroventricular dosages of methotrexate on cognitive dysfunction in Wistar rats at various dosages; specifically 3, 4, 5, or 6 mg/kg of body mass depending on

group randomization for acute toxicity testing. Behavior during an avoidance task, as well as a dark/bright arena task was then observed follow four hours of monitoring for gross behavioral alterations. The acute observances were as follows: convulsions, hyperactivity, grooming, sedation, hypothermia, and increased respiration (Madhyastha et al., 2002). A 16% mortality rate was observed among rats that were administered 6mg/kg dosages of methotrexate. During task performance assessments, two groups were administered chemotherapy; one at 1.5mg/kg and the other at 2 mg/kg. Significant reductions in task performance [line crossings in dark area ($p < 0.01$), line crossings in bright area ($p < 0.05$), and time spent in dark area ($p < 0.01$)] were witnessed in rats that were treated with 2mg/kg of methotrexate as compared to the non-treated rats across five days of testing. The investigators noted that results suggest drug-related disruptions in exploratory and locomotor activity. Scores on task retention significantly increased as the dosages increased, indicating dose-dependent toxicities. There were significant declines in hippocampal brain amines, as quantified by high pressure liquid chromatography (HPLC). Dopamine was the most significant [1.5mg/kg (63.2 ±3.6ng/g), 2 mg/kg (61.5 ±1.8), $p < 0.01$] then serotonin [1.5mg/kg (150.7 ±4.9ng/g), 2 mg/kg (150.4 ±3.7ng/g), $p < 0.01$] followed by norepinephrine [1.5mg/kg (136.5 ±5.6ng/g), 2 mg/kg (136.0 ±6.7ng/g), $p < 0.01$] when compared to the control group. The investigators noted significant decreases in overall number of neuroglial cells and neurons in the CA-3 and CA-4 hippocampal regions of the brains. The loss of physical number of neurons, behavioral and learning impairment, and depletion of hippocampal brain amines led the investigators to suspect direct neurotoxicity as a strikingly likely factor. Foley, Raffa, and Walker (2008) examined the combined effects of 5-FU and methotrexate on memory and

learning acquisition in a mouse model. The greatest dosages administered were 32mg/kg for methotrexate, and 75 mg/kg for 5-FU across the two-day study. The results indicated that the 5-FU alone at 75mg/kg significantly ($p < 0.05$) increased latencies versus controls for retrieval of behavioral responses that were previously learned. The combined administration of 5-FU and methotrexate significantly increased adjusted latencies. The combination of administered drugs during this study elicited profoundly negative effects on retrieval and retention tasks. The effects appear to be a more selective disruption in learning and memory processes.

Determining the mechanisms that underlie the problem of CRCI has yet to be accomplished. Konat et al. (2008) reported that cognitive dysfunction, particularly attention and memory deficits, have been observed in upwards of 75% of cancer patients who have undergone chemotherapy. The investigators sought to determine whether CRCI was attributable to the malignancy itself or the chemotherapy. ADR was administered to rats four times (one per week) at a dosage of 2.5mg/kg, while cytoxan (CTX) was administered at 25mg/kg for a period of four total doses; again once per week. The rats were subjected to 30 minutes of open field testing comprised of hind leg rearing and line crossings within a lined black box. They were also subjected to a passive avoidance test in which they were placed in a lit box and were timed on their latency of entering the darkened box from the lit box. There were undesirable effects of chemotherapy on integrity of higher brain functioning. Chronic administration of commonly used chemotherapeutic agents and the combination of ADR and CTX significantly impaired short-term memory function. However, these ADR and CTX cocktails may not substantially hinder or impair long-term memory functioning (Konat et al., 2008). In a

study conducted on primates, Bourke, West, Cheda, and Tower (1973) examined the effects of 5-FU administration and diffusion into cerebral spinal fluid (CSF). Examination of bilateral perfusion in overexposed cerebral cortex or vertebral cisternal perfusion demonstrated that 5-FU crosses the blood brain barrier. In addition, the investigators explained that 5-FU may be a useful drug to combat tumors that invade central nervous system structures. Furthermore, because of the exceptional ability of 5-FU to access the brain, oncologists should demonstrate caution with administration.

Chemotherapy-related cognitive impairment has also been reported to be possibly affected mechanistically by altered primary sex hormones, telomere shortening, blood-brain barrier disruption, cytokine dysfunction, and genetic susceptibility (Ahles & Saykin, 2007). On a single-trial step-down inhibitory avoidance protocol, Liedke et al. (2009) examined the effects of a single bolus dosage of DOX in Wistar rats at increasing levels similar to those given to humans (.5mg/kg, 2mg/kg, and 8mg/kg). Prior to training, DOX was administered. Training consisted of a fear-motivated hippocampal memory dependent protocol where animals learned to associate training apparatus locations with electric shock to their feet. On day one and day seven, assessments of cognitive function were administered via retention test trials that were identical to training except for the lack of electric shocks to the feet. It was determined that a single dose of DOX did not cause permanent brain damage, which was indicated by improvements in the DOX group seven days later. In addition, the investigators suggested that a single dosage of DOX produces reversible memory acquisition impairment but not memory consolidation.

Winocur et al. (2006) examined the effects of a combination of two anticancer drugs, methotrexate and 5-FU on cognitive function in a mouse model. The investigators

used the Morris Water Maze Test of spatial memory, which has been reported to be sensitive to hippocampal dysfunction. Secondly, mice were also administered a non-spatial test of memory in which a discrete cue signaled the location of the submerged platform in the water. These were followed by a test of Non Matching to Sample rule learning, which is highly sensitive to frontal-lobe dysfunction. Mice were either injected with 37.5mg/kg methotrexate and 75mg/kg 5-FU or comparable amounts of saline solution and were comparable to human dosages and schedules. The results indicated that learning and memory impairment were significantly associated [trials 18.9 ± 7.7 (drug) vs. 14.2 ± 8.5 (control), $p < 0.05$, and errors 20.5 ± 10.1 (drug) vs. 14.9 ± 6.8 (control), $p < 0.05$] with treatment of 5-FU and methotrexate, a widely used combination of drugs in the treatment of breast cancer. Drug induced deficits were observed in tests of spatial memory and conditional rule learning. However, there were no significant differences between drug and control groups on cued memory or discriminate learning.

Vascular proliferating cells within the dentate gyrus in the hippocampus have been associated with neurogenesis, neuronal proliferation, differentiation, and have been reported to be involved in learning and memory. Mustafa et al. (2008) reported that these brain regions require brain-derived neutrotrophic factor (BDNF) to aid in the process of neurogenesis. The researchers examined the effect of 5-FU on spatial working memory as modeled by a location recognition test in rats. Vascular-associated proliferating cell numbers and changes in neutrotrophic and neurogenic proteins were also measured. The object location task was determined by the amount of exploratory time each rat spent licking, sniffing, chewing, or moving while directing their nose toward an object. Objects were then randomly rearranged. The rats received 5 injections of 5-FU at 20mg/kg over

the course of 12 days. Indicative of unaffected spatial working memory, control animals proceeded to explore novel locations of objects as much as 14% greater amounts of time than treated rats. There was no significant difference witnessed between exploratory times of novel and familiar locations in 5-FU treated rats. The investigators also suggested that treated rats were unable to discriminate between objects in novel locations and familiar ones when compared to controls. There were no significant alterations observed in proliferating cell counts. However, there was an approximately 50% reduction in BDNF. These deficits may suggest structural changes or alterations in the hippocampus and potentially alterations in neurogenesis.

In an examination of a standard breast cancer therapy protocol, Macleod et al. (2007) examined the effects a combined cyclophosphamide (40mg/kg) and DOX (4mg/kg) treatment regimen on ovariectomized rats for three weeks. Rats were treated once a week with chemotherapy. The investigators implemented a fear-type experiment which examined learning following treatment. The training consisted of a standard operant conditioning apparatus which audible tones were paired with mild shocks to their feet. The investigators noted that significant impairments in contextual fear memory were observed, suggesting detrimental effects on the hippocampal-related learning and memory (Macleod et al., 2007).

In a longitudinal study Schilling, Jenkins, Morris, Deutsh, and Bloomfield (2005) administered cognitive assessments on 50 patients who had undergone chemotherapy at six and 18 month intervals. A wide array of cognitive assessments were administered which included: measures of verbal memory (WMS logical memory, AVLT recall 1-7), visual memory (complex figure, copy, immediate and delayed recall), executive function

(Stroop Task), working memory (spatial span, letter/number sequencing, digital span), FSIQ estimate (national adult reading test), processing speed (letter cancellation task), and self-report [cognitive failures questionnaires, GHQ_{12}, FACTB, ES, F (patients only)]. The three measures that showed significant group by time interaction were: the AVLT supraspan, total recall, and the WMS letter number sequencing task. All three require a high degree of concentration and attention, precisely the function that patients complain about the most (Schilling et al., 2005).There were significant differences observed between patients who had undergone chemotherapy compared to apparently healthy non-cancer controls. The results also indicated a group by time interaction for three measures of verbal and working memory. The investigators speculated that the neurotoxic effects observed during cognitive assessments may be indicative of direct neurotoxicity.

In addition, female cancer survivors of menopausal age may be at greater risk of CRCI considering the modifications of hormonal levels. In particular, Schilling et al. (2005) indicated that menopausal females undergoing hormone therapy in addition to receiving chemotherapy may be at a significantly greater risk for CRCI. Lastly, the investigators noted that QOL, anxiety, and fatigue can be affective of cognitive functioning, although patients undergoing chemotherapy were 2.3 times more likely to show cognitive impairment than the control group. The investigators suggested that while low dosages of chemotherapy, as expressed in the self-report portion of the patient evaluation, may not induce noticeable impairment, it should be expected that greater doses may cause more severe and lasting impairments.

Life decisions regarding career and educational choices may be profoundly affected by the negative side-effects of chemotherapy on memory and concentration.

These decrements may also have an effect on general QOL (Mitchell & Turton, 2011). Four cancer patients were interviewed, and their experiences with CRCI and QOL measures were recorded. Reduction in the ability to make smooth transitions back to activities of daily living, such as returning to work, may persist long after treatment is completed (Carlsson et al., 2000; Schilling et al., 2005). With the difficulties that patients face along the cancer continuum, Mitchell and Turton (2011) suggested that on average, patients were significantly less likely to share their experiences with cancer to their healthcare provider than to fellow cancer survivors. In addition, they suggested that healthcare providers should educate their patients about the potential sequelae of side effects they may experience as they complete treatment, especially with the incidence of cognitive dysfunction. If patients were more aware of the negative effects of CRCI, they may be more encouraged to report incidences to their healthcare provider.

Exercise Benefits in a Cancer Population

Physical activity and cognitive function are important to QOL as well as overall health, and are vitally important to the reduction of disease impact and maintaining a healthy cognitive function. Wood, Alvarez-Reyes, Maraj, Metoyer, and Welsh (1999) investigated self-reported physical fitness, QOL, visual acuity, and cognitive function on two separate occasions within a two week period of time and determined that increased physical and cognitive function was significantly related to observed increases in QOL scores among older adults. In pre-adolescent school-based academic performance, Hillman et al. (2009) examined the effects of walking during a 20-minute Balke treadmill protocol on neurological and behavioral indices on aspects of cognitive control and attention. The investigators found that a single, moderately intense acute bout of aerobic

exercise may improve attention, cognitive control, and academic performance in pre-adolescent children.

During the past few decades, advances in health care and treatment of various diseases have been a factor in healthcare cost increases. Considering resource and financial limitations, interventions aimed at the improvement of overall health should lead to maximal health benefit utilizing as minimal of an amount of resources as possible. In oncology, advances in treatment have prolonged life expectancy. With increasing life expectancy for cancer survivors, the chances of increased amount of treatment-related side effects also become more pronounced. In a review of literature, Roine et al. (2009) examined 61 studies reporting on the cost effectiveness of exercise-based interventions and the treatment of various diseases. Although some of the research presented minor conflicting arguments as to the efficacy of certain exercise interventions, the overall results indicated that exercise is a cost effective method of healthcare.

It has been well established that exercise has been positively associated with increases in cardiovascular function, resting heart rate, pulmonary function, forced vital capacity (FVC), upper-body muscular endurance, lower-body muscular endurance, core muscular endurance and flexibility, improvements in body composition, as well as reductions in behavioral, sensory, affective, cognitive, mood, and total fatigue scores (Fong et al., 2012; Hsieh et al., 2008; Schneider, Hsieh, Sprod, Carter, & Hayward, 2007a; 2007b; 2007c; Van Weert, et al., 2010). In addition, exercise has been linked with reductions in inflammation (Fairey et al., 2005). Furthermore, individualized cancer rehabilitation interventions have been shown to increase five-year survival rates (Peterson, Repka, Hayward, & Schneider, 2010).

Cognitive Training

The term brain plasticity refers to the inherent capacity of the brain itself to respond to physical and functional changes (Mahncke et al., 2006). Brain function can be strengthened or degraded, depending on the circumstances. Manipulating learning context can alter plasticity that can be both positive and negative, which would imply that physical, environmental, and behavioral stimuli may strengthen or degrade brain function across the aging process. Manipulation of learning context can also alter plasticity. Stimuli leading to positive plastic changes may be a fundamental tenet of cognitive therapy to help restore memory, cognitive, motor, and sensory cognitive functions. In recent years, brain training software packages have gained momentum in sales and notoriety. One commercially available program, Brain Fitness® by Posit Science®, consists of progressive online cognitive exercises designed to enhance "brain plasticity" (Smith et al., 2009). Mahncke et al. (2006) reported that training brain plasticity utilizing appropriately designed training archetypes may substantially improve function and recovery from losses in sensation, cognition, memory, and motor control. In addition, this process should be initiated early in the aging process to enhance brain health and cognitive fitness before significant losses develop but also could be effective later in the aging process when significant losses have already emerged. Furthermore, the investigators noted that when a clinically validated model is available, this scientifically based approach unambiguously targets the primary causes of cognitive decline associated with aging, this could revolutionize therapeutic techniques for aging adults.

The demand for delaying or preventing age-associated declines in older adults has been steadily increasing. Designing and implementing cost effective alternatives to

standard care may be beneficial for the reduction of the need for home care, nursing homes, and hospital stays, and therefore reduce health care costs. Ball et al. (2007) evaluated the associations between three Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) interventions (memory, reasoning, and speed of processing training), in a sample of 2802 independently thriving older adults. This training was aimed to improve mental abilities as well as daily functioning. Research has indicated in human and animal populations that neural plasticity endures across the lifespan, and that cognitive stimulation in the environment is an important predictor of enhancement and maintenance of cognitive functioning. The investigators noted that limited education is a risk factor for dementia. Primary and secondary follow-up analyses indicated significant, immediate gains on cognitive outcomes in all groups except the no contact control. Eighty-seven percent of speed-trained, 74% of reasoning-trained, and 26% of ACTIVE-trained participants demonstrated reliable improvement on the pertinent cognitive composite immediately following intervention. Furthermore, the proximal effects occurred and continued throughout the following 24-months, further implying that cognitive training may have residual effects that may have prolonged improvements. Finally, those who participated in booster training showed improved gains (speed-92% vs. none-68%; reasoning-72% vs. none-49%) beyond normal cognitive training.

In breast cancer patients who were about to receive chemotherapy, Wefel, Saleeba, Buzdar, and Meyers (2010) examined cognitive functioning to gauge levels of preexisting dysfunction. In particular, measures of affective status, cognitive function, and QOL were measured prior to administration of treatment, during treatment, and directly following treatment. Prior to treatment, approximately 21% of the sample

displayed evidence of cognitive dysfunction. In addition, older patients appeared to be at a greater risk of displaying evidence of cognitive dysfunction. The investigators noted that approximately 65% (during and following treatment) of the sample exhibited acute declines in cognitive function. Learning, executive function, memory, and processing speed were domains of cognitive function that were most affected by chemotherapy treatment. There were no significant differences between patients exhibiting acute cognitive decline and those who did not decline on any clinical, demographic, or mood variable. Sixty-one percent of the sample exhibited late decline (one year) in cognitive function with 30% of the sample demonstrating new onset of cognitive dysfunction that was not present beforehand. The investigators concluded that the impact of diminished brain/cognitive reserve may play a substantial role in the vulnerability and failure to fully recover from acute treatment-related changes in cognition and/or the development of late cognitive decline of post chemotherapy patients.

Reduction of disease impact and conditions generally affecting older population has become increasingly important. Exercise and maintaining a healthy level of cognitive function have become methods that have been progressively more supported. Elements of cognitive functioning are considerably connected to overall health and QOL (Wood, Alvarez-Reyes, Maraj, Metoyer, & Welsh, 1999). Wood et al. (1999) tested pre versus post levels of physical fitness, cognitive function, visual acuity, and QOL during a two-week intervention in 44 older adults. The investigators then examined the relationships between values of physical fitness against the aforementioned variables. It was determined that there were significant relationships between QOL, physical fitness, and

cognitive function. It may be that greater levels of physical fitness and cognitive function lead to increased QOL scores in older adults.

Decrements in cognitive performance have also been observed in individuals undergoing treatment for high grade gliomas. Hassler et al. (2010), in a pilot study, examined the effects of ten weeks of cognitive training on 11 patients with high grade gliomas. The training intervention consisted of ten weekly group meetings consisting of 90 minutes of holistic mnemonic training that encompassed attention, memory, and verbal skills. Cognitive function testing was completed before and following completion of the training intervention. Specifically, the Controlled Oral Word Association Test (COWAT) for verbal acuity, Trail Making Tests A and B for executive function and visual motor speed, and the Hopkins Verbal Learning Test (HVLT) for verbal memory were implemented. Hassler et al. (2010) speculated that the location of the tumor in high grade glioma patients may compound the effect of CRCI because of the location of the tumor being located within the brain or spine. There were improvements observed in all cognitive measures however, significant improvements were only detected during the HVLT (score 19.6 ± 8.9- baseline, 23.6 ± 8.8-12 weeks, $p < 0.05$) assessments. The investigators also noted that this pilot work demonstrated that patients with central nervous system tumors can not only tolerate the stress of training, but they also can improve on measures of cognitive functioning.

In a combined assessment of Memory and Attention Adaptation Training (MAAT), Ferguson et al. (2007a) assessed cognitive function via assessment of multiple cognitive and behavioral components on 29 breast cancer survivors who had recently completed treatment. The MAAT was composed of education on memory and attention,

self-awareness, self-regulation focusing on reduction of arousal through relaxation training, activity scheduling and pacing, and training of cognitive compensatory strategies. The MAAT interventions were implemented once a month for four months. Prior to and following interventions participants were tested via the following for cognitive functioning: The California Verbal Learning Test-II, Logical Memory I and II from Weschler Memory Scale, Digit Symbol Subtest from the Weschler Adult Intelligence Scale III, Trail Making tests A and B, and the Stroop Color-Word Interference Test. The results indicated that participants significantly ($p < 0.05$) improved from pre to post for cognitive functioning in a daily life setting for all participants. Quality of life, as measured by the Quality of Life-Cancer Survivors Scale (QOL-CS), also revealed significant improvements from pre to post intervention.

In a sample population of cognitively healthy, well-educated older adults near the age of 75, Smith et al. (2009) evaluated the effects of cognitive training on cognitive function using the Posit Science® Brain Fitness® program. Participants were either randomized into the experimental cognitive training group or were randomized as active controls and were given content-oriented coursework that required an equivalent amount of time as the cognitive training group. The results indicated that there were significant improvements on auditory processing speed (3.9 points vs. 1.8 points, $p < 0.05$), and small but statistically significant benefits on memory performance for the group using the Posit Science® Brain Fitness® program (99.6 ± 14 to 103.8 ± 14). The investigators explained that this type of cognitive training software has been developed to focus improvement on central auditory system speed and accuracy. In addition, the training of neuromodulatory systems may positively impact generalized benefits in measures of

memory and attention greater than general cognitive simulation. Smith et al. (2009) added that brain plasticity-based training may develop information flow through language and auditory pathways in the brain that can possibly translate training benefits to non-trained tasks and that training based improvements may endure following training completion.

Wolinsky, Unverzagt, Smith, Jones, Stoddard, and Tennstedt (2006) examined the ability of three ACTIVE cognitive training interventions (memory, reasoning, and speed of processing). Health-related QOL (HRQOL) was measured using a test consisting of eight 36-item health surveys (SF-36). At two years' post training, 24% and 37% had clinically relevant drops on ≥ 4 and ≥ 3 SF-36 scales. At five years' post training, 33% and 47% had clinically relevant drops on ≥ 4 and ≥ 3 SF-36 scales. Participants in the speed of processing intervention were significantly less likely to have extensive HRQOL decline compared to participants in the control group regardless of the threshold or time period, whereas participants in the memory and reasoning intervention were significantly less likely to have HRQOL decline only at five-years post-training and only at the lower threshold. The effect of the speed of processing intervention was stronger and evident earlier than those for the memory and reasoning interventions. The result stems from the speed of processing intervention being the most procedural intervention, operating through sensory-motor elaboration and repetition, bringing about a broader pattern of regional brain activation. At five years' post-training, however, all three interventions were successful in protecting against a lower threshold of age-related extensive declines in cognitive function. Older adults face declining cognitive ability and increasing difficulty with activities of daily living.

Physical Activity and Cognitive Function

In a longitudinal study consisting of healthy older adults, Barnes, Yaffe, Satarino, and Tager (2003) examined cardiorespiratory fitness at baseline and compared the association between those values and cognitive function over the course of six years. Cardiorespiratory fitness may provide a means to bridging the gap between cognitive function and history of physical activity because it is largely determined by habitual physical activity and is based on objective physiological measurements (Barnes et al., 2003). The investigators hypothesized that baseline measures of cardiorespiratory fitness would be associated positively with maintenance of cognitive function over time and with levels of cognitive function at follow-up. The results indicated that cardiorespiratory fitness was positively associated with preservation of cognitive function over a six-year period. Participants with worse cardiorespiratory fitness at baseline experienced greater decline percentage on the MMSE over six years 95% CI [lowest 0.5 (0.8-0.3), global score-28.5 (28.3-28.7), middle-0.2 (0.5-0.0), global score-28.9 (28.7- 29.1), highest-0.0 (0.3-0.2), global score-29.2 (29.0-29.5) $p < 0.01$]. After adjustment for demographic and health-related covariates, baseline measures of cardiorespiratory fitness were also positively associated with performance on cognitive testing conducted 12 years later. The association between cognition and cardiorespiratory fitness was the most robust for measures of attention/executive function and global cognitive function. It is possible that fitness has a more pronounced effect on the frontal lobes, which the investigators suggested mediates attention/executive function (Barnes et al., 2003). It is also possible that cardiorespiratory fitness is a better marker of underlying health status, which is associated with cognitive function over time. The investigators concluded that

participants with greater baseline levels of cardiorespiratory fitness experienced cognitive decline to a lesser extent over the course of 12 years following completion of the study. This suggests that maintaining high levels of cardiorespiratory fitness may help provide long-term protection against cognitive dysfunction in older adults.

There appears to be a universal acceptance of the fact that exercise on a regular basis has benefits for muscular strength, cardiovascular fitness and function, management of weight, metabolic health, disease prevention, bone mineral density, disease management and prevention, as well as decreases in mortality; however, much less is known about the brain and the effect of exercise upon it (Zoeller, 2010). In a review of literature, Zoeller (2010) described aging as being accompanied by varying degrees of decline in cognitive function declination. In particular, processing speed, memory, and increases in risk of dementia and Alzheimer's disease have been linked to age-related cognitive decrements. Physical performance and speed of gait were indicated to be predictors of dementia in individuals with or without baseline levels of cognitive impairment. Large improvements in certain measures of cognitive function such as, auditory attention, delayed memory and motor function have been linked to interventions with results indicating improvements in aerobic training interventions. Lesser improvements in aerobic interventions have been associated with cognitive speed and visual attention improvements. Exercise was most significantly related to executive function improvements as opposed to any other measure of cognitive function. In addition, habitual exercise has been associated with neurogenesis, enhanced central nervous system metabolism, improvements in memory and angiogenesis, as well as attenuation of the age-related brain volume, structure, and density losses (Zoller, 2010).

Acute bouts of moderate exercise have also been indicated to positively affect outcomes of memory in circadian rhythm altered shift workers. Potter and Keeling (2005) hypothesized that acute bouts of moderate intensity exercise would improve memory ability to encode and recall words in a 15-item list. The second portion of the study was to examine whether circadian rhythms in memory performance might interact with the exercise intervention to produce different levels of performance change at different time of day for 31 male shift workers, working at all hours of the day. Following each exercise trial there were significant increases (approximately 8, 10, 12, 13, 14 words per trial, $p < 0.01$) on overall number of words recalled. There was also a significant interaction with exercise and time of day, in addition to the exercise intervention and average number of recalled words. This would suggest that moderate, short term; intensity exercise may be beneficial for memory function and may significantly reduce the effects of daytime circadian rhythms on memory performance.

Lautenschlager et al. (2008) examined the effects of a 24-week physical activity intervention consisting of at least 150 minutes of moderate intensity activity per week in older adults exhibiting objective or mild cognitive impairment. Prior to the exercise intervention, all participants were assessed via Alzheimer Disease Assessment Scale (ADAS-Cog). This assessment consists of 11 brief cognitive tests assessing memory, language, and praxis. All participants chose to do walking or some other form of aerobic activity as well as some strength training. Participants were outfitted with a pedometer to help monitor progress each week. The results indicated during follow-up assessments of cognitive function that older adults in the exercise group performed to a greater extent during measures of delayed memory recall. In addition, those in the exercise group

showed better delayed memory recall. In summary, this study demonstrated that aerobic exercise improves cognitive function in older adults with subjective and objective mild cognitive impairment.

In a progressive aerobic only intervention, Masley, Roetzheim, and Gualtieri, (2009) examined the effects of a ten-week progressive aerobic intervention on cognitive function. The cognitive function measures were: mental speed, memory, reaction time, attention, and cognitive flexibility. The investigators indicated that those who were in the aerobic training groups had significantly ($p < 0.05$) greater percentage scores on memory (2.8), mental speed (5.2), reaction time (5.1), attention (45.9), and cognitive flexibility (31.7), which is a measure of executive function. Of interest is that the investigators mentioned that those individuals who were more aerobically active during the week had significantly greater scores than those who were less aerobically active during the week. The investigators suggested that these positive effects on neurocognition may be dose-response dependent.

In a 12-week mental and physical intervention, Barnes, Santos-Modesitt, Poelke, Kramer, Castro, Middleton, and Yaffe (2013) examined the combined effects of mental activity in addition to physical activity on measures of cognitive function in older adults who were considered inactive. Participants were assigned to groups that were involved with home-based mental activity (Posit Science®, or educational DVDs) and/or class-based physical activity, and the group combinations therein. A stretching and toning based control was also utilized to compare group differences. The investigators found that cognitive scores on a global scale significantly improved over time. However, those who participated in the mental activity training (Posit Science®) did not significantly

differ from those who were in the mental activity control group that watched educational DVDs. The results indicated that although the groups that participated in mental activity training improved on measures of cognitive function, there were no significant differences between those who used PositScience® or the educational DVD's. The investigators concluded that amount of mental activity may be a greater factor than the type of mental activities.

Within the literature it is apparent that cancer treatment(s) devastate not only cancerous cells in the body, but to varying degrees across treatments, cancer types, and stage of cancer have been observed to negatively and destructively affect healthy cellular tissue. Whether it be inflammatory toxicity, micro-vascular toxicity, or direct neuro-toxicity; the implementation of combative measures, with the purpose of treatment-related side-effect reduction, or alleviation is of importance. Cancer incidence has been reported to be increasing which may also signify an increasing amount of prescribed treatments. Although, following treatment people are also living longer, which suggests potentially greater incidence of treatment-related side-effects. Unaccompanied, research has indicated the benefits of exercise and cognitive training on physiological, psychological, and cognitive variables. Implementing combined regimens of aerobic and cognitive training may be a substantially greater method of treating the treatment

CHAPTER III

METHODS

Experimental Design

The intervention consisted of 12 weeks (or 36 sessions) of aerobic, cognitive, or a combination of aerobic and cognitive training on the Motion Fitness Brain-Bike®. This study provided allowance for the investigation of the implications of cognitive and aerobic training on physiological and psychological parameters in cancer survivors who were undergoing, or underwent treatment. Participation in this study was according to pre-determined inclusion and exclusion criteria. In addition, participants were screened for any secondary factors such as medication(s) or physical limitations not included in inclusion/exclusion criteria, but that could have potentially altered the outcomes of the study. Selection of CAN participants was conducted during or following initial physical assessment. Selection of NC participants was via email listserv and university-related recruitment websites. In certain circumstances where offsite recruiting resulted in participants expressing interest in this study, selection may have occurred prior to initial physical assessment. In depth cognitive and psychological assessment parameters included: general cognitive functioning, processing speed, working memory, executive function, attention, verbal learning and memory, verbal fluidity, perpetual reasoning, mood, anxiety, depression, fatigue, and QOL.

Medical history, fatigue, depression, mood, and anxiety information was collected prior to initial assessment. Comprehensive cognitive assessment data were gathered prior to and following the exercise intervention, and have been explained in detail in the cognitive assessment section. Physiological baseline measures were gathered prior to and following the exercise intervention, including the assessment of peak aerobic capacity (VO_{2peak}). Further details have been included in the subsequent physiological assessment section.

Participants

Participants in this study were males and females (56.9 ± 8.8 years of age), who had been diagnosed with cancer (CAN) (n = 28) and age-matched participants who had not been diagnosed with any type of cancer (NC) (n = 7). Individual group stratification abbreviations are listed in Table 1. Participants who had cancer, were either undergoing, or had underwent chemotherapy or chemotherapy and radiation treatment, and were referred to the RMCRI from local oncologists. Following physician referral to the RMCRI, participants were asked to read and complete the following paperwork required for pre-screening: complete medical history, cardiovascular disease risk assessment, cancer history, and a lifestyle/activity evaluation. All of the aforementioned paperwork items were evaluated prior to initial assessment for potential limitations or co-morbidities that might have affected the outcomes of the study. Lifestyle factors such as, tobacco, alcohol, dietary intake have been highlighted through questioning on the lifestyle/activity evaluation. Participants were informed on the overview of the procedures and purpose as explicitly delineated within the informed consent (Appendix A).

Participants were then asked to read and sign the informed consent form. Pending acceptance of terms and conditions of the study as well as complying with inclusion/exclusion criteria as described in the following paragraph, participants were then randomized into one of five groups as described in Table 1. The CAN-AER-COG (*n* = 9) group was composed of cancer survivors that participated in aerobic, cognitive, and flexibility training. The CAN-AER group (*n* = 7) was composed of cancer survivors and participated in aerobic and flexibility training; however, they did not participate in cognitive training. The CAN-CON group (*n* = 7) was composed of cancer survivors that participated in flexibility training, but did not participate in aerobic or cognitive training. The NC-CON group (*n* = 7) was the control group consisting of participants who had not been diagnosed with any form of cancer. The NC-CON group completed aerobic, cognitive, and flexibility training. The CAN-COG group (*n* = 5) was composed of cancer survivors who participated in cognitive training and flexibility training; however, they did not participate in aerobic training. This study followed and abided by guidelines established by University Institutional Review Board following approval (Appendix B).

Table 1

Group stratification

Group	Participants	Aerobic	Cognition	Flexibility
1 CAN-AER-COG	Cancer	Yes	Yes	Yes
2 CAN-AER	Cancer	Yes	No	Yes
3 CAN-CON	Cancer	No	No	Yes
4 NC-CON	No Cancer	Yes	Yes	Yes
5 CAN-COG	Cancer	No	Yes	Yes

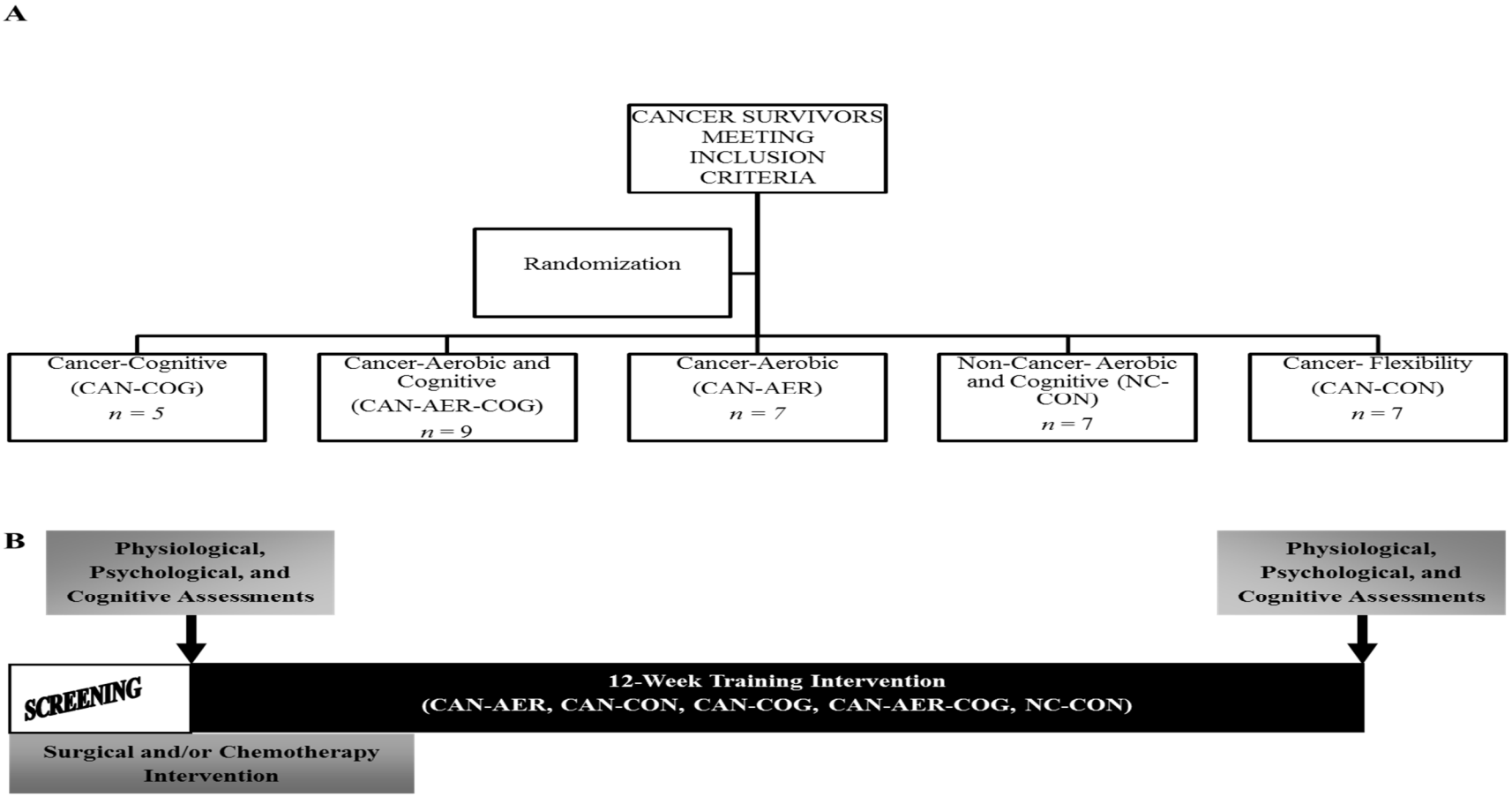


Figure 1. Experimental Design. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. CAN groups, $n = 28$; CON group, $n = 7$.

Inclusion/ Exclusion Criteria

Participants in the study were excluded from the study if they reported having any history of psychiatric diagnoses, neurological disease, past or present alcohol or substance abuse, difficulty with mobility, auditory dysfunction, and non-corrected visual issues. Participants were not allowed to partake in the study if they had undergone any type of software based cognitive training in the past 6 months including: Neuro-Active®, Posit-Science®, Mindfit®, Lumosity®, My Brain Trainer®, or any other brain fitness program. It was also a preliminary requirement that participants be right handed because the mechanical design of the original Brain Bike® mouse pad assembly only allowed for individuals who were right handed, however in 2013 our lab acquired a second Brain Bike® which had a detachable mouse pad assembly which could be moved from the right side of the Brain Bike® to the left side allowing for left hand dominant individuals to be included. Participants were told they could not have participated in any type of aerobic activity such as walking or running greater than two times per week for eight weeks prior to starting the study. Participants were also required to score greater than or equal to 26 on the MMSE, had been undergoing, or had completed chemotherapy within eight weeks of starting the study, or completed the combination of chemotherapy and radiation treatments, in upwards of six years.

Physiological Assessment

Following the completion of preliminary paperwork, participants completed a physical examination for clearance to exercise. Initial values for heart rate (HR), blood pressure (BP), oxygen saturation (SpO_2), height, weight, body composition, circumference measurements, cardiovascular fitness (VO_{2peak}, RMCRI protocol), balance

(Bertec Balance Screener or Unipedal Stance Test), pulmonary function (Spirometry), estimated 1RM (Brzycki equation), muscular endurance (plate loaded cable assisted machines), handgrip dynamometry, abdominal muscular endurance (plank test), and flexibility measures (Modified Sit and Reach and Shoulder Reach Behind Back) were determined and recorded as part of the standard RMCRI physical assessment protocol. Since this study was conducted over a period of nearly four years, certain procedural changes were introduced that altered some components of the overall RMCRI assessment. These include additions or removals of the following: Unipedal stance test, Bertec balance screening, circumference measures, crunch test, plank test, shoulder reach behind back test, muscular endurance via (plate loaded cable assisted machines), estimated 1RM and the waist-to-hip ratio measures and data collected had varying values for the aforementioned, and therefore could not be included in analyses. For the purposes of this evaluation, descriptions and analyses concerning anything other than measures of HR, BP, cognitive function, VO_{2peak}, and Modified Sit and Reach were conducted during pre and post assessments, but have been purposely excluded from this evaluation. Any other relevant information regarding currently existing medical conditions, over the counter, and prescription medications, was evaluated in the context of the study parameters.

Blood Pressure, Heart Rate, and Pulse Oximetry

Initial resting values of blood pressure (BP) were obtained from subjects via auscultation methods as outlined in Heyward (2006). Participants were asked to sit quietly for at least five minutes. With the participant's arm resting approximately at heart level the deflated blood pressure cuff was placed around the participant's bare arm and

attached via Velcro® strapping. The placement of the blood pressure cuff was secured approximately one inch above the antecubital fossa. The manometer was positioned so that the center of the dial was visible at the eye level of the assessor. The head of the stethoscope was placed approximately one centimeter medial and superior to the antecubital fossa over the brachial artery. Following the asking of each client what his or her typical systolic blood pressure was, the assessor closed the valve and steadily and rapidly inflated the cuff air bladder to approximately 30mmHg above the client reported values. If the values that the client reported were not sufficient to result in an accurate measure of blood pressure, the assessor re-inflated the cuff to a value great enough to produce accurate assessments of blood pressure. The assessor then slowly opened the valve to reduce air pressure and listened for phase I of the Korotkoff sounds. Phase I sounds have been reported to equate to systolic pressure (Hayward, 2006). Pressure reduction continued while listening for phase IV and V. Phase V is generally considered as equating to diastolic blood pressure. The assessor continued deflating the pressure in the cuff until the complete cessation of audible sounds occurred. A minimum of 30 seconds was allowed between each measure of BP as recommended by Heyward (2006). Measures of BP were recorded on assessment data collection sheets with the average of the two measures chosen as the final value. In addition, percentage of O_2 bound to hemoglobin was measured via pulse oximetry.

Assessment of Cardiorespiratory Fitness

The RMCRI treadmill protocol was administered to evaluate each participant's cardiorespiratory fitness (CF). In 2010, this progressive treadmill protocol was designed specifically for cancer survivors. Participants were made privy to all elements of the

pending treadmill testing prior to commencement. If health-related concerns presented themselves that would have inhibited the participant from executing an appropriate performance during the advancement of the initial assessment, then secondary measures of CF such as, submaximal cycle-ergometer testing measures would have been employed. However, no such circumstances presented themselves during the course of this study.

The RMCRI protocol was carefully monitored and administered. Each stage was one minute in length with the intensity adjusted as a means of belt speed, incline, or both each successive minute. Stage one walking speed started at 1.0 mph and was increased by 0.5 mph until the participant verbalized his/her commitment to aborting the continuation of the test. During stages one through four, grade consistency was maintained at 0% until stage five began. The first grade inclination was set to 2% and was maintained throughout the sixth stage. From stage seven until stage 21 or at the onset of volitional fatigue, grade and belt speed was increased 1% and 0.1 mph, respectively. HR and SpO_2 were recorded each minute while BP and RPE were recorded every third minute until test completion. Table 2 further details the staging, administration, and determination of VO_{2peak} for the RMCRI protocol. The test was terminated if the client reached volitional fatigue, asked to stop for any reason, HR or SBP did not increase as intensity increased, DBP fluctuated more than 10mmHg from baseline, SpO_2 dropped below 80 via pulse oximetery, and HR exceeded calculated maximum HR determined by the following formula (HRmax = 205.8 – (.685 x age). The test completion time was measured in conjunction with age, gender, and whether or not the participant used the handrails. VO_{2peak} was determined based on these variables. Lastly, table 3 describes how the classification of CF analogous to the aerobic capacity ($mL \cdot kg^{-1} \cdot min^{-1}$) was determined.

Table 2

Estimation of cardiorespiratory fitness ($mL \cdot kg^{-1} \cdot min^{-1}$)

S	mph	%	Estimated VO_2 peak (mL/kg/min)		METS	Estimated VO_2 peak (H) (mL/kg/min)		METS (H)
1	1.0	0	6.2 (walk)		1.7	6.2 (walk)		1.7
2	1.5	0	7.5 (walk)		2.1	7.5 (walk)		2.1
3	2.0	0	8.9 (walk)		2.5	8.9 (walk)		2.5
4	2.5	0	10.2 (walk)		2.9	10.2 (walk)		2.9
5	2.5	2	12.6 (walk)		3.6	12.1 (walk)		3.5
6	3.0	3	15.9 (walk)		4.5	14.4 (walk)		4.1
7	3.3	3	17.1 (walk)		4.9	15.2 (walk)		4.3
8	3.4	4	19.1(walk)		5.5	16.6 (walk)		4.7
9	3.5	5	21.3(walk)		6.1	18.1 (walk)		5.2
10	3.6	6	28.0 (run)	23.6 (walk)	8.0 / 6.7	22.8 (run)	19.7 (walk)	6.5 / 5.6
11	3.7	7	29.6 (run)	25.9 (walk)	8.5 / 7.4	23.9 (run)	21.3 (walk)	6.8 / 6.1
12	3.8	8	31.3 (run)	28.4 (walk)	8.9 / 8.1	25.0 (run)	23.0 (walk)	7.1 / 6.6
13	3.9	9	32.9 (run)	30.9 (walk)	9.4 / 8.8	26.2 (run)	24.8 (walk)	7.5 / 7.1
14	4.0	10	34.6 (run)	33.5 (walk)	9.9 / 9.6	27.3 (run)	26.6 (walk)	7.8 / 7.6
15	4.1	11	36.4 (run)	36.3 (walk)	10.4 / 10.4	28.6 (run)	28.5 (walk)	8.2 / 8.1
16	4.2	12	38.2 (run)	39.0 (walk)	10.9 / 11.1	29.8 (run)	30.4 (walk)	8.5 / 8.7
17	4.3	13	40.0 (run)	42.0 (walk)	11.4 / 12.0	31.1 (run)	32.5 (walk)	8.9 / 9.3
18	4.4	14	41.9 (run)	45.0 (walk)	12.0 / 12.9	32.4 (run)	34.6 (walk)	9.3 / 9.9
19	4.5	15	43.9 (run)	48.1 (walk)	12.5 / 13.7	33.8 (run)	36.7 (walk)	9.7 / 10.5
20	4.6	16	45.9 (run)	51.3 (walk)	13.1 / 14.7	35.2 (run)	38.9 (walk)	10.0 / 11.1
21	4.7	17	48.0 (run)	54.6 (walk)	13.7 / 15.6	36.6 (run)	41.2 (walk)	10.5 / 11.8

Note: (H) denotes the usage of handrails by the participant

Table 3

RMCRI cancer-specific cardiorespiratory fitness norms ($mL \cdot kg^{-1} \cdot min^{-1}$)

	Age	Low	Fair	Avg.	Good	Ex.	M ± SD
Women	19-39	< 22.2	22.2 - 25.0	25.0 - 26.6	26.6 - 28.3	> 28.3	26.0 ± 5.6
	40-49	< 18.6	18.6 - 22.3	22.3 - 24.5	24.5 - 27.6	> 27.6	23.5 ± 5.5
	50-59	< 17.6	17.6 - 21.1	21.1 - 23.4	23.4 - 27.8	> 27.8	22.5 ± 6.3
	60-69	< 15.4	15.4 - 17.6	17.6 - 21.3	21.3 - 23.6	> 23.6	19.7 ± 5.6
	70+	< 10.9	10.9 - 15.0	15.0 - 16.7	16.7 - 19.2	> 19.2	16.1 ± 5.1
Men	19-39	< 23.9	23.9 - 24.8	24.8 - 25.0	25.0 - 31.7	> 31.7	25.3 ± 5.4
	40-49	< 18.5	18.5 - 24.1	24.1 - 29.1	29.1 - 33.0	> 33.0	26.3 ± 6.9
	50-59	< 14.5	14.5 - 19.6	19.6 - 23.5	23.5 - 29.2	> 29.2	22.5 ± 7.4
	60-69	< 15.7	15.7 - 17.7	17.7 - 23.4	23.4 - 27.9	> 27.9	21.3 ± 6.7
	70+	< 13.6	13.6 - 17.1	17.1 - 21.3	21.3 - 24.3	> 24.3	19.2 ± 6.0

Flexibility

In the evaluation of flexibility, the modified sit and reach test was administered. The modified sit and reach test allows for the determination of flexibility while controlling for limb length differences between individuals. The participant began the assessment by first removing his or her shoes and seating themselves on the floor with his or her head, shoulders, and buttocks placed firmly against a wall, and with his or her legs positioned straight ahead of them. The sit and reach measurement apparatus was then placed against his or her shoeless feet with the "zero" end of the measurement arm facing toward the participant. The participant was instructed to hold his or her arms straight forward while keeping his or her back, head, and buttocks firmly placed against the wall. The measurement arm was then moved toward the fingertips of the participant's extended arms. Once that measure was secure, the participant was subsequently instructed to reach

forward as far as possible, pushing the sliding measurement tab as far as he or she could. The participant was also instructed to keep his or her hands together and knees fully extended during each trial. The furthest of three trials was considered the final measurement of flexibility.

Psychological Indices

Before preliminary assessment, and following the completion of the 12-week intervention, the following indices of psychological assessment were completed: Beck Depression Inventory, Piper Fatigue Scale, and Ferrans and Powers Quality of Life Index Cancer Version III. Following antineoplastic treatment, a commonly experienced side effect is depression.

Beck Depression Inventory

In this study, depression was measured using the Beck Depression Inventory. The Beck Depression Inventory is composed of 21 items which are declarative statements analogous to values ranging from zero to three. Statements that reflect values of zero are indicative of the most extreme positive position. Opposing assertions, valued as three, indicate the most extreme negative statement. A sense of neutrality exists for values represented by one and two, although either the three or the zero on the opposing ends of the continuum may be favored. Values for all 21 items are added; scores range from zero to 63 with zero indicative of no depression and > 40 reflecting extreme depression (Salkind, 1969).

Piper Fatigue Inventory

Piper fatigue Inventory results yield an inclusive score, indicating the overall extent of cancer-related fatigue (CRF). Aspects of participants' lives that may be

significantly impaired or hindered by CRF were further delineated using the calculated values obtained for cognitive/mood, behavioral, affective, and sensory subscales. There are 22 items in the inventory composed of four subscales as previously mentioned. Each possible score per subscale ranges from zero to ten. Overall measures of CRF range from zero to ten and is evaluated from the average of all subscales. A combined score of zero is redolent of a lack of perceived fatigue. Scores ranging from one-three, four-six, and seven+ indicate mild, moderate and severe fatigue, respectively (Piper, Dibble, Dodd, Weiss, Slaughter, & Paul, 1998).

Quality of Life Index

In cancer rehabilitation settings, outcomes on QOL assessments are ideal for determining efficacy and impact of rehabilitative programs (Ferrans, 2010). Utilizing Ferrans and Powers Quality of Life Index Cancer Version III, QOL measures were administered at baseline and at three months following the intervention. Sixty-six questions are included in this assessment which pertain to the significance and importance the individual places on psychological, social, health, and family associated issues. The Ferrans and Powers QOL assessment is a valid, criterion-based instrument, and was determined as such based on correlational values between overall satisfaction with QOL and the instrument with dialysis patients ($r = 0.7$) and graduate students ($r = 0.8$). Test-retest correlations substantiated the reliability of the instrument (graduate students, $\alpha = 0.9$, $r = 0.9$; dialysis patients, $\alpha = 0.9$, $r = 0.9$). Observed total scorings that are higher indicate an agreement between importance placed on each dimension and individual satisfaction with that element, which can be attributed to an overall condition of well-being (Ferrans & Powers, 1985).

Exercise Intervention

Prior to beginning the study, participants who were assigned to an aerobic activity group were seated and leg-to-pedal distance was measured to allow individual flexion and extension comfort while cycling in the recumbent position. Seat position was recorded on data collection sheets for the purpose of consistency during the following training sessions. Resting heart rate was recorded to evaluate % of heart rate reserve (HRR, Karvonen Method) intensity each aerobic training group participant exercised at during each training session. Aerobic training sessions were progressive and began at 55% HRR for weeks one-four, 60% HRR for weeks five-eight, and 65% HRR for weeks nine-12, as detailed in Table 4. Before each warm-up session, participants were initially required to attach a telemetric heart rate monitoring device (Polar®). However, during the Spring of 2012 when three similar studies were being conducted and multiple clients were being scheduled back-to-back, having participants wear heart rate monitors became a substantial disadvantage to collecting data on time within a tight schedule (for both the data collectors and the clients), and therefore necessitated the reliance on pulse oximetery and heart rate monitoring via handles of the Brain Bike® apparatuses. For example, under the assumption that the client arrived for training on time (rarely occurred), it often took upwards of ten extra minutes to have clients grab the heart rate monitor, walk to the bathroom, attach the monitor, stop to use the restroom, walk out of the restroom, and then (finally) sit down to begin warming up. If the participant did not have any problems adjusting the strap on the heart rate monitor and it was reading appropriately then training could start only slightly behind schedule. However, many times the participants had difficulty in putting their heart rate monitors on and an extra few minutes would have to

be spent in order to make proper adjustments and ensure that it was reading appropriately. In addition, because of the amount of participants training was chaotic between three studies, many times, participants left without removing their heart rate monitors which negatively affected the amount of heart rate monitors for clients of the RMCRI not participating in a study. When training began, participants were asked to seat themselves and commence their warm-up consisting of five minutes of low intensity, self-paced cycling. Following completion of warm-up, each participant had resistance applied to the Motion Fitness Brain Bike® recumbent cycle ergometer in order to stimulate elevations in heart rate to the training range associated with % of HRR and weekly progression for the duration of 30 minutes in addition to 30 minutes of flexibility training. Those who were in the CAN-AER-COG group cycled and completed cognitive training at the same time. In the event that the client was unable to maintain the prescribed percentages of HRR, RPE was utilized to maintain voluntary levels of exertion that were numerically (1-10 scale) equivalent to HRR intensities. The first Brain Bike® recumbent cycle ergometer we obtained was generously donated by Brain Center International (BCI) located in Quebec City, Canada. Upon completion of cognitive training, data were wirelessly transmitted to BCI databases for analysis.

Table 4

Aerobic training schedule and cognitive training exercises

Week	% HRR	Session	Training Exercises
1	.55	1 - 3	1 - 5, 1 - 5, 1 - 5
2	.55	4 - 6	1 - 5, 1 - 5, 6 (step 10)
3	.55	7 - 9	6 (step 9 - 7)
4	.55	10 - 12	6 (step 6 - 4)
5	.60	13 - 15	6 (step 3 - 1)
6	.60	16 - 18	1 - 5, 1 - 5, 1 - 5
7	.60	19 - 21	1 - 5, 1 - 5, 7 (step 10)
8	.60	22 - 24	7 (step 9 - 7)
9	.65	25 - 27	7 (step 6 - 4)
10	.65	28 - 30	7 (step 3 - 1)
11	.65	31 - 33	1 - 5, 1 - 5, 1 - 5
12	.65	34 - 36	1 - 5, 1 - 5, 1 - 5

Stretching Protocol

In order to differentiate between interventions, a total-body stretching protocol was implemented as the control for this study. The stretching session consisted of 30 minutes of static stretches designed to target major muscle regions throughout the body. The regions included: neck, shoulders/chest, posterior upper arm, upper back, lower back, hips, torso, anterior thigh and hip flexor, posterior thigh, groin, and calf (Baechle & Earle, 2008).

Table 5

Regional bodily areas covered with stretching

Body Region	Stretching Motion	Muscles Actuated	Time (min)
Neck	Look Right/ Left	-Sternocleidomastoid (SC)	1
	Flexion/ Extension	-SC, Suboccipitals, Spenae	1
Shoulders/ Chest	Straight Arms Behind Back	-Anterior Deltoid, Pectoralis Major	1
	Seated Lean-Back	- Deltoids, Pectoralis Major	1
Posterior Upper Arm	Behind-Neck Stretch	-Triceps Brachii, Latissimus Dorsi	2
Upper Back	Cross Arms In Front of Chest	-Posterior Deltoid, Rhomboids, Mid Trapezius	1
	Arms Straight Up Above Head	-Latissimus Dorsi	1
Lower Back	Spinal Twist	-Int/Ext Oblique, Piriformis, Erector Spinae	2
	Semi-Butterfly	-Erector Spinae	2
Hips	Forward Lunge	-Iliopsoas, Rectus Femoris	1
	Supine Knee Flex	-Gluteus Maximus, Hamstrings	1
Torso	Side Bend With Straight Arms	-External Oblique, Lattissimus Dorst, Serratus Anterior	1
			1
Anterior Thigh and Hip Flexor	Side Quadriceps Stretch	-Quadriceps, Iliopsoas	4
Posterior Thigh	Sitting Toe Touch-Hurdler	-Hamstrings, Erector Spinae, Gastrocnemius	2
	Semi-Straddle	- Hamstrings, Erector Spinae, Gastrocnemius	2
Groin	Straddle	-Gastrocnemius, Hamstrings, Erector Spinae	2
	Butterfly	-Hip Adductors, Sartorius	1
Calf	Wall Stretch	-Gastrocnemius, Soleus, Achiles Tendon	1
	Step Stretch	-Gastrocnemius, Soleus, Achiles Tendon	2
TOTAL TIME			30min

Cognitive Training Protocol

The cognitive training tasks were based on the recommendations from BCI. The tasks included exercises which emphasized training in working memory, visuo-spatial memory, processing speed, divided attention, selective attention, vigilance, attentional flexibility, useful field of view, verbal processing speed, cognitive control, temporal perception, and arithmetic operations. Division of time spent during each task was pre-determined by BCI. Each of the cognitive training tasks (parking, driving, smart driving, the policeman, brain twister, the pilot, and the stock exchange) was composed of five minutes of training. Details of each cognitive training component are included in Table 6. For the first five sessions participants completed parking, driving, smart driving, the policeman, and brain twister exercises. On session six, participants then completed five sessions of the pilot consecutively until session 16. During sessions 16-20 participants then returned to completing parking, driving, smart driving, the policeman, and brain twister. On session 21, participants were then required to complete five sessions of the stock exchange consecutively until session 30. Finally, during sessions 31-36, participants were again required to complete parking, driving, smart driving, the policeman, and brain twister. Screenshots have been provided in Appendix C.

Parking

The parking training segment consisted of a simulated “pay to park” parking lot where cars appeared on screen as either not paid, paid in full, or had accidentally paid double the fee. The simulated cars that had paid the full amount blinked with a single dollar sign encircled in red. The cars that paid double appeared on the screen as having two dollar signs encircled in red above the car. Those cars that had not paid appeared as

not having a dollar sign appear above them. The participant has to then memorize each car and how they presented their status of payment and click the mouse to designate that status. For example, the cars that appeared as not having paid required one mouse click, cars that appeared as having paid double required two mouse clicks, and cars that appeared to have paid the correct amount did not require any mouse clicks since they paid correctly. The five-minute segment was broken down into smaller segments that changed once the participant validated the set of parked cars.

Car Driving

During the car diving segment of training, the participant assumed the role of driving a car down a series of simulated intersections and was required to make decisions based on the appearance of oncoming street signs and lighted signals. At each intersection participants had to decide as soon as possible whether street signs that appeared were the same or different by inputting their response on a numerical keypad by pressing the "/" key for the designation of same street and the "*" for the designation of different street signs. Similarly, when each new intersection appeared, participants inputted whether the signal appeared red or green as quickly as possible on numerical keypad by pressing "2" for red and "3" for green. Throughout this training segment participants also needed to be aware of the sounds of honking horns from other drivers. Upon hearing each horn honking, participants were then required to press the "+" key on the numerical keypad as quickly as possible.

Smart Driving

Unlike the aforementioned car driving task, smart driving doesn't give the participant the feeling of driving throughout simulated intersections, but has the driver

sitting in their car during heavy, non-moving traffic. On the screen there are multiple interactive locations where objects such as kids crossing the street or the gas light on the dashboard that appeared randomly. Other on screen interactive areas included: the rearview mirror, a lighted street sign located at the top of the screen, and a large street sign in the middle of the screen. This large centrally located sign was different than the other interactive areas in that while participants were scanning the screen for the appearance of a lit gas can, or a child running out into the street, they needed to also observe what picture appeared and then clicked on one of two pictures that appeared immediately following the disappearance of the first picture. For example, the picture of a man lifting weights may have appeared on the first sign and upon disappearance, a sign with two picture choices appeared. Since the first picture was of a man lifting weights, the correct answer would have been for the participant to then click on the second picture that portrayed a man lifting weights.

The Policeman

In the policeman, the participant was given the simulated experience of being a police officer wielding a radar gun monitoring the speeds of passing vehicles. On the top of the screen a dialogue box indicated a number from one to five. These numbers were reflective of the difficulty of the task. Participants were then required to remember radar speeds that corresponded to each car and compare them against cars that followed behind them. For example, in beginning stages of training participants may have had to compare one car's speed to the next; however, in advanced stages, participants could potentially have had to compare every five cars. What makes this exceptionally difficult is that the

first car would be compared to the fifth car, the second car compared to the sixth car, the third car compared to the eighth car, and so on.

Brain Twister

During this task, participants are shown a light blue screen with various shapes and descriptor terms that must be compared to a central "consistent" or "inconsistent" banner that appears in the middle of the screen. If the central banner reads "consistent" then participants must choose shapes and descriptors that embody consistency. For example, among other shapes and descriptor terms, a red circle may appear with the word "red" inside it. If the banner reads "consistent," then the correct choice would be to choose the red circle as the only consistent choice. The task only allows for one correct answer, so there are no options for multiple correct answers.

The Pilot

This training task allows the participant the feeling that they are behind the cockpit of a helicopter, although there is no motion other than the "dials" portion and the "calculator" portion. The instructions dictate that the participant is flying a helicopter and must evaluate the dials against the calculation portion of training. The dials are composed of a block of six dials of equal sizes and are round shaped. The dials are stacked ion columns of two and correspond with three different times with "24 seconds", "12 seconds", and "8 seconds" appearing from left to right below the dials. The calculation panel consists of a keypad very similar to that of a standard calculator. During the training the participant is told which task to provide a greater amount of their attention to in conjunction with the other. For example, one segment of training may ask that the participant prioritize the dials portion of training over the calculations panel. In this case,

the participant must give a greater amount of their attention to the dials as opposed to the calculations. This training segment is broken down into three parts wherein each part will state a new training objective that the participant must prioritize. Prioritization is never only one or the other and may state that the participant prioritize both tasks equally.

Stock Exchange

This set of cognitive training tasks gives the participant the simulated feeling of being on the trading floor at the New York stock exchange. On the computer display, there is a central screen which will have a stock ticker symbol (BCI) that will move from location to location. The participant must also be aware of a vocalized numerical value as it pertains to the trading price of the BCI stock. During the training, the participant must prioritize either the location of the stock symbol (same or different location) or the value (higher or lower) by pressing corresponding keys on the keypad. This training task is composed of five levels which will alter the prioritization of tasks and speed of delivery as the participant increases in level of difficulty.

Table 6

Cognitive training exercises

Number	Exercise	Trained Functions	Description
1	Parking	Working Memory Visio-Spatial Memory	Adaptation and classic visuo-spatial span task
2	Car Driving	Processing Speed Divided Attention Selective Attention Vigilance	Two simultaneous biconditional discrimination (S-R) tasks with a vigilance task
3	Smart Driving	Processing Speed Selective Attention Attentional Flexibility Useful Field of View Divided Attention Vigilance	Derived from ACTIVE trial; with UFOV program
4	The Policeman	Working Memory Verbal Processing Speed	Standard *n*-back task with adaptable time limit
5	Brain Twister	Processing Speed Cognitive Control Attentional Flexibility	Stroop-like based on cue and reponse conflict and attentional set-shift paradigm
6	The Pilot	Divided Attention Temporal Perception Arithmetic	Dual monitoring task
7	Stock Exchange	Processing Speed Divided Attention Working Memory	Two simultaneous *n*-back tasks: one audio-verbal and the other visuo-spatial

Cognitive Testing

Prior to and following the 12-week exercise intervention, each participant underwent a comprehensive cognitive assessment (Appendix D) conducted by doctoral students from the University of Northern Colorado School of Psychological Sciences.

Table 7

Pre/post cognitive testing measures

Neuropsychological Construct	Instrument	Abbreviation
General cognitive functioning	-Wechsler Memory Scale, 4th ed. (WMS-IV) - General Cognitive Screener	BCOG
Processing speed	-Trail-Making A	TMT-A
Working memory, executive function, attention	-Wechsler Adult Intelligence Scale, 4th ed. (WAIS-IV) – Letter Number Sequencing, Coding.	LNS raw or scaled CD raw or scaled
	-Trail Making B	TMT-B
Verbal learning & memory	-Wechsler Memory Scale, 4th ed. (WMS-IV) – Logical Memory I and II - Wechsler Memory Scale, 4th ed. (WMS-IV) – Delayed Recall	LMI raw of scaled LMII raw or scaled LMII DR raw or scaled
Verbal fluidity	- Controlled Oral Word Association Test	COWAT-Age COWAT-Gender COWAT-Education
Perceptual reasoning	-Wechsler Adult Intelligence Scale, 4th ed. (WAIS-IV) – Block Design	BD raw or scaled

Statistical Analyses

Data Transformation and Imputation

Preliminary data frequency and descriptive analyses were run to visually represent the raw data set to address possible inconsistencies or anomalous numerical occurrences. When missing data occurred, a series mean imputation was conducted using the Statistical Package for the Social Sciences version 21 (SPSS, Armonk, NY) which is detailed in Appendix E. For the cognitive variables included in this study, approximately 1.3% of data were missing and replaced. For the physiological variables included in this study, approximately 3.6% of data were missing and replaced. In light of the fact that group sample sizes were small and unequal, this required analysis by non-parametric methodologies. Pre-to-post differences were then performed on all variables as a data reduction method resulting in singular data points, and were therefore considered for analysis.

Global Analyses

An omnibus Kruskal-Wallis Test of k independent samples [$T = \frac{1}{S^2}\left(\sum_{i=1}^{k} \frac{R_i^2}{n_i} - N\ \frac{N(N+1)^2}{4}\right)$] was conducted to assess group median differences between the four training interventions (aerobic, cognitive, and flexibility) against randomized controls for physiological, psychological, and cognitive measures (Conover, 1999). Elliot and Hynan (2011) reported that although the Kruskal-Wallis non-parametric analysis of variance is an equivalent substitution for a one-way Analysis of Variance (ANOVA), it is still an omnibus or global statistical procedure. This means that when rejection of the null hypothesis occurs (one or more groups differ significantly) that follow-up procedures

should be conducted to evaluate any pairwise comparisons that may be responsible for the significant main effects observed. Data utilized in these analyses were in direct violation of parametric one-way ANOVA assumptions and, precisely necessitated the adoption of non-parametric equivalents. The Kruskal-Wallis test does not provide any specific follow-up analyses; however, Elliot and Hynan (2011) reported that GraphPad PRISM® is a readily available statistical analysis software package that has the capability to appropriate run this analysis with post hoc testing (Conover, 1999; Elliot & Hynan, 2011). Therefore, Kruskal-Wallis analyses were employed using GraphPad PRISM® version 4.03 (GraphPad Inc., La Jolla, CA). Post hoc analyses are described in the adjustments and post hoc analyses section. Wilcoxon sign ranks tests and pre-to-post percentages were also conducted to address individual group pre-to-post changes for each dependent variable (Glass & Hopkins, 1996). Wilcoxon sign ranks tests were performed using Statistical Package for the Social Sciences version 21 (SPSS, Armonk, NY).

Assumptions

Data were assessed for adherence to four assumptions of Kruskal-Wallis testing (Conover, 1999). These are: independence of observation, mutual independence among various samples, the measurement scale is at least ordinal, and either the *k* observation distribution functions are identical, or else some observations may tend to yield greater values than other observations do.

Randomization

Randomization of groups was performed using the PROC PLAN protocol for the Statistical Analysis Software version 9.3 (SAS, Cary, NC). Given the number of proposed subjects and the amount of treatment groups, PROC PLAN randomly assigned

each subject to a treatment which was then utilized as a list to follow when recruiting and training subjects. The quasi aspect of this investigation pertained to individual discretion as to the placement of certain subjects who presented with particular health or cognitive issues that otherwise may have excluded them from participating in the study. For example, a particular participant presented as a stage III oligodendroma brain cancer patient. She expressed a profound interest in participating in the study, yet was randomized to the flexibility only group. In light of this situation, the ethical decision was made to allow her to participate in the aerobic and cognitive training group strictly because of her precarious position and recommendations from her physician.

Groups

As previously mentioned, participants were randomized into one of five groups as outlined in Table 1 and Figure 1.

Factors

Cancer status and treatment groups were the factors evaluated. Factor A was indicative of cancer status; being those who had cancer and those who did not have cancer. Factor B was indicative of the five training groups. In light of the fact that there are greater than three levels to Factor B, multiple comparison procedures were implemented.

Adjustments and Post Hoc Analyses

Although parametric post hoc analyses and adjustments such as a Bonferroni correction during multiple comparisons are employed to decrease the familywise error rate [$FW\alpha = 1-(1-\alpha)^c$] for the purposes of reducing Type I error risk or rejecting the null hypothesis when it may actually be true, these methods were not employed for

nonparametric analyses conducted (Vincent, 2005). As reported previously, the Kruskal-Wallis test does not provide specific post hoc pairwise comparisons (Conover, 1999). However, Kruskal-Wallis analyses were conducted using GraphPad PRISM® software (Elliot & Hynan, 2011). Although no significant ($p < 0.05$) main effects were observed between groups for each independent variable, any observed main effects, would have been followed up with a Dunn's post hoc assessment. For all analyses, a p-value of 0.05 was considered statistically significant.

CHAPTER IV

RESULTS

Participant Characteristics

This study comprised a total of 35 subjects which included 28 cancer survivors and seven apparently healthy age-matched adults who had never been diagnosed with cancer (10 males, 25 females). The percentage of adherence to this study was 76%. Cancer diagnoses included anaplastic oligodendroma of the left frontal lobe (1), breast (14), breast/colon (1), colon (1), Hodgkin's lymphoma (1), lung (1), lymphoma (1), multiple myeloma (1), non-small cell lung/brain (1), ovarian (2), ovarian/breast (1), prostate (1), supraglottic/laryngeal (1), and throat/tongue (1). All participants completed each of the required 36 training sessions; however, not one participant adhered to the requirements of completing their training within 12 weeks (average time to complete 36 sessions was approximately 20 weeks). All participants completed pre and post cognitive assessments. Assessments were conducted by cognitive assessors from the University of Northern Colorado School of Psychological Sciences. A total of eight different assessors worked on this project. Because of this turnover, there were some aspects of the battery of cognitive assessments that were unintentionally overlooked or forgotten. Therefore, series mean imputation methodologies were employed to statistically account for missing data (Appendix E). All participants, with the exception of one, completed pre and post physiological assessments. Specifically, this one participant who did not complete her post physiological assessment refused to come back because she verbally stated she was

feeling better and the demands of her work schedule was of much greater importance than continuing with her rehabilitation.

Physiological Assessment

Independent samples Kruskal-Wallis testing revealed no significant main ($p > 0.05$) effects between all five groups and all measures of physiological function, therefore nullifying the need for post hoc analyses (Figures 2 and 3). Pre-to-post Wilcoxon sign ranks tests revealed that SANDR increased by 39% in the CAN-AER-COG group (Table 9). VO_{2peak} and SANDR increased by 20% and 17%, respectively in the CAN-AER group (Table 11). SANDR increased by 22% and VO_{2peak} significantly ($p < 0.05$) increased (16%) from pre-to-post in the CAN-CON group (Table 13). RHR trended toward a significant ($p = 0.09$) decrease (-13%) in the NC-CON group (Table 15). There were no significant ($p > 0.05$) pre-to-post changes observed in the CAN-COG group. However, SANDR and VO_{2peak} increased by 24% and 12%, respectively (Table 17).

Psychological Indices

There were no significant ($p > 0.05$) main effects observed between all five groups and Piper fatigue (index and subcategories), Beck Depression Inventory, and QOL. Figures 4-10 graphically depict these comparisons. Pre-to-post percentage decreases were observed among Beck depression and all Piper fatigue subcategories ranging from -15 to -33% for the CAN-AER-COG group, and QOL increased by 9% (Table 9). Specifically, the CAN-AER-COG group significantly ($p < 0.05$) decreased from pre-to-post in the Piper behavioral subcategory. The CAN-AER group significantly ($p < 0.05$) decreased (-34%) from pre-to-post in the Piper sensory subcategory. All other Piper fatigue subcategories and Beck depression decreases ranged from -25% to -32%,

while QOL increased by 13% in the CAN-AER group (Table 11). There was a significant decrease (-55%, $p < 0.05$) in Beck depression, and a significant ($p < 0.05$) increase (26%) in QOL observed in the CAN-CON group. In addition, the CAN-CON group also decreased in all subcategories of Piper fatigue ranging from -40% to -67%, with the Piper cognitive/mood subcategory trending toward significance ($p = 0.09$) (Table 13). There were no significant ($p > 0.05$) pre-to-post differences observed in the NC-CON group. However, Beck depression scores did decrease (-42%) (Table 15). There was a significant ($p < 0.05$) decrease (-59%) and a significant ($p < 0.05$) increase (6%) in QOL observed in CAN-COG pre-to-post analyses. In addition, all Piper fatigue subcategories decreased with a range from -23% to -52% with the Piper index, affective, and cognitive/mood subcategories trending toward significance ($p = 0.08$) (Table 17).

Cognitive Function

There were no significant ($p > 0.05$) main effects observed between all 5 groups and for each cognitive variable (Figures 11-27). There were no significant ($p > 0.05$) differences observed in any measure of cognitive function in the CAN-AER-COG group. However, the CAN-AER-COG group did decrease from pre-to-post in measures of reaction time (-49%, TMT-A), and increase in verbal fluidity (675%, COWAT-Z-G and 280%, COWAT-Z-A) (Table 8). There were significant ($p < 0.05$) increases (28%-39%) observed among all Weschler Memory Scale (WMS-IV) raw and scaled scores, with the exception of WMS-IV-LMII cumulative percentage scores and BCOG scores in the CAN-AER group. In addition, there were significant ($p < 0.05$) increases in Weschler Adult Intelligence Scale (WAIS-IV) block design raw and scaled scores (20% and 19%, respectively). Furthermore, the CAN-AER group significantly ($p < 0.05$) increased (12%)

from pre-to-post in the WAIS letter number sequence scaled scores, and trended toward significance ($p = 0.07$). Finally, the CAN-AER group increased in 2 of the 3 measures of verbal fluidity (70%, COWAT-Z-A and 44%, COWAT-Z-ED) (Table 10). There were no significant pre-to-post increases in measures of cognitive function observed with the exceptions of significant ($p < 0.05$) increases (750%, COWAT-Z-G; 320%, COWAT-Z-A; and 205%, COWAT-Z-ED) in all COWAT verbal fluidity scores (Table 12). There were no significant ($p > 0.05$) pre-to-post differences observed in the NC-CON group. However, reaction time (TMT-B) decreased (-22%) and all 3 COWAT measures increased (420%, COWAT-Z-G; 71%, COWAT-Z-A; and 78%, COWAT-Z-ED) (Table 14). There were no significant ($p > 0.05$) pre-to-post differences observed for the CAN-COG group. However, all WMS-IV scores increased ranging from 6%-20% with the exception of WMS-IV cumulative percentage (CP) scores. Reaction times (TMT-B) also decreased (-26%). All measures of verbal fluidity increased (156%, COWAT-Z-G; 574%, COWAT-Z-A; and 60%, COWAT-Z-ED) (Table 16).

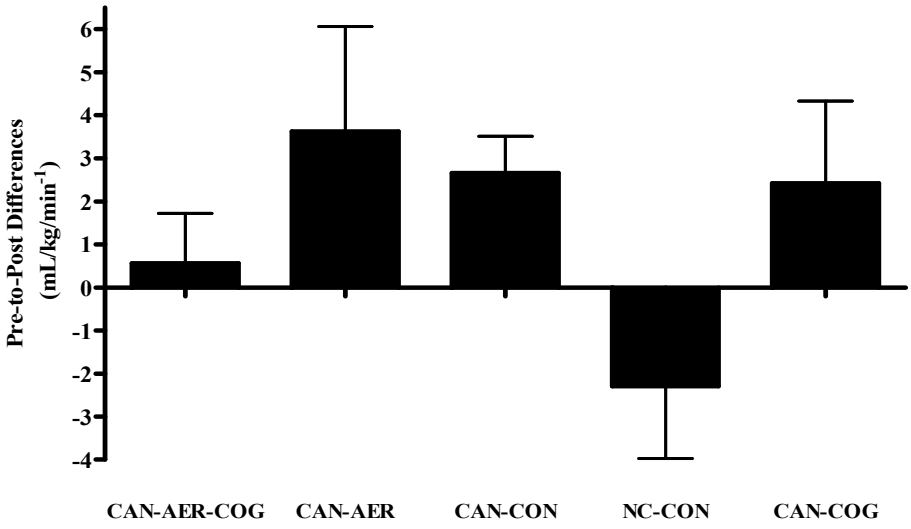


Figure 2. Group Comparisons of VO_{2peak}. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

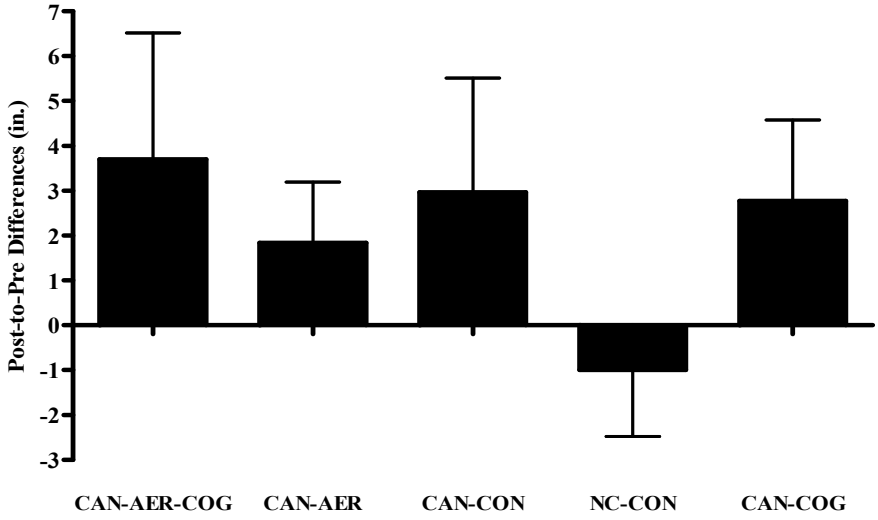


Figure 3. Group Comparisons of Sit and Reach Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

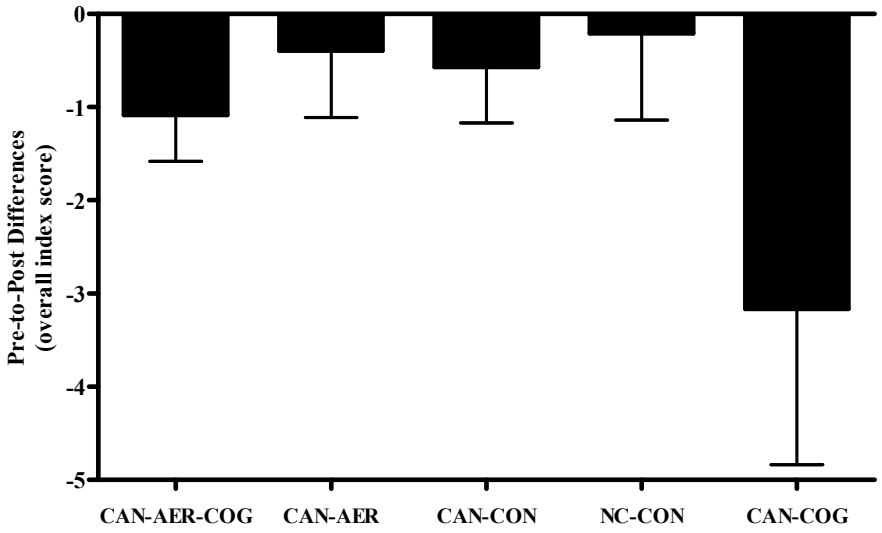


*Figure 4.*Group Comparisons of Piper Fatigue Index Overall Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

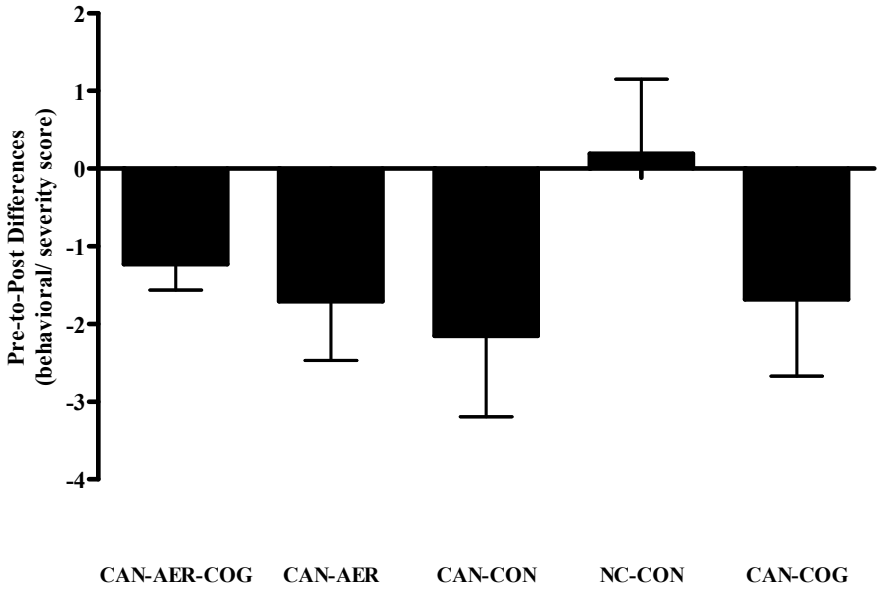


Figure 5. Group Comparisons of Piper Fatigue Index Behavioral Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

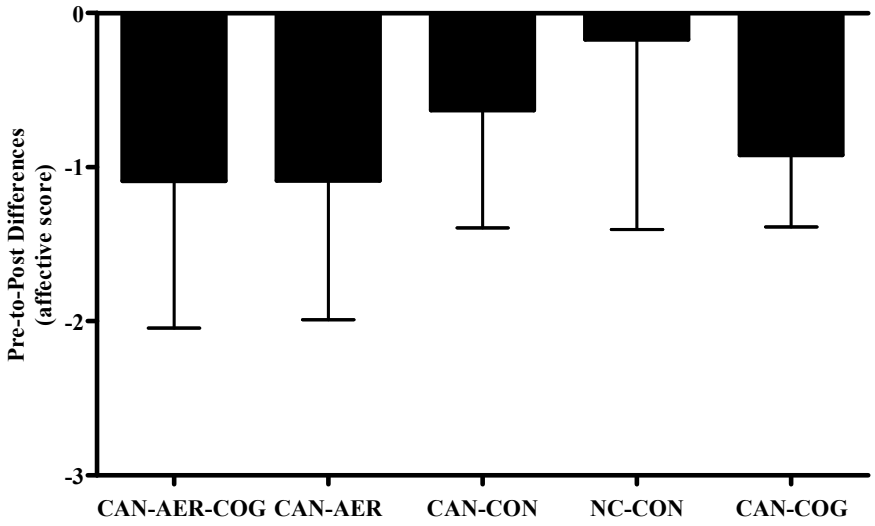


Figure 6. Group Comparisons of Piper Fatigue Index Affective Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

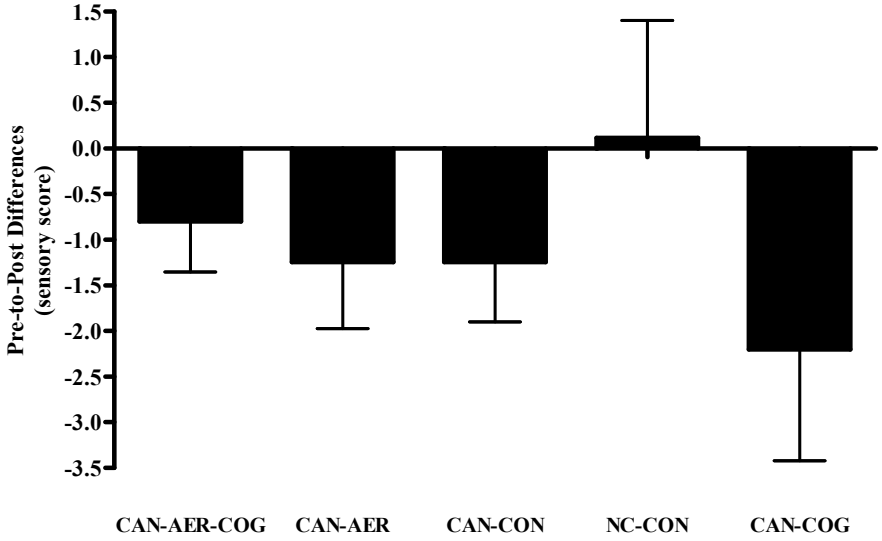


Figure 7. Group Comparisons of Piper Fatigue Index Sensory Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

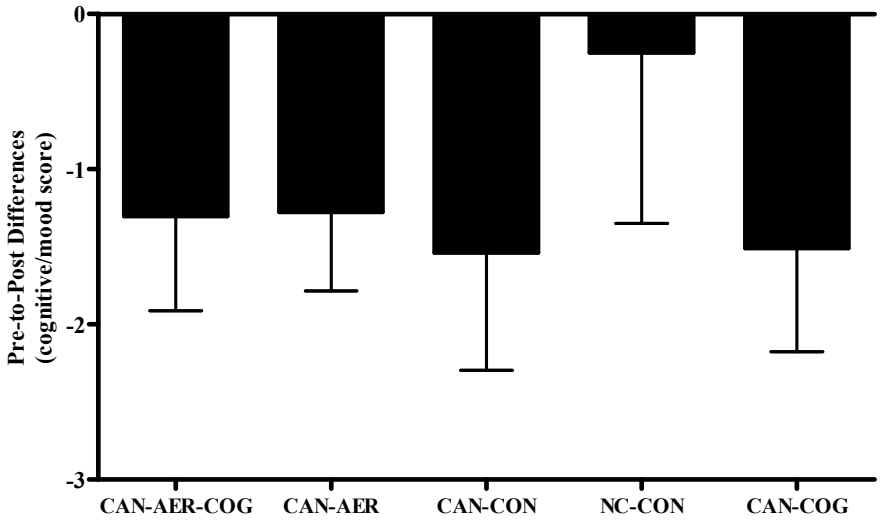


Figure 8. Group Comparisons of Piper Fatigue Index Cognitive Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

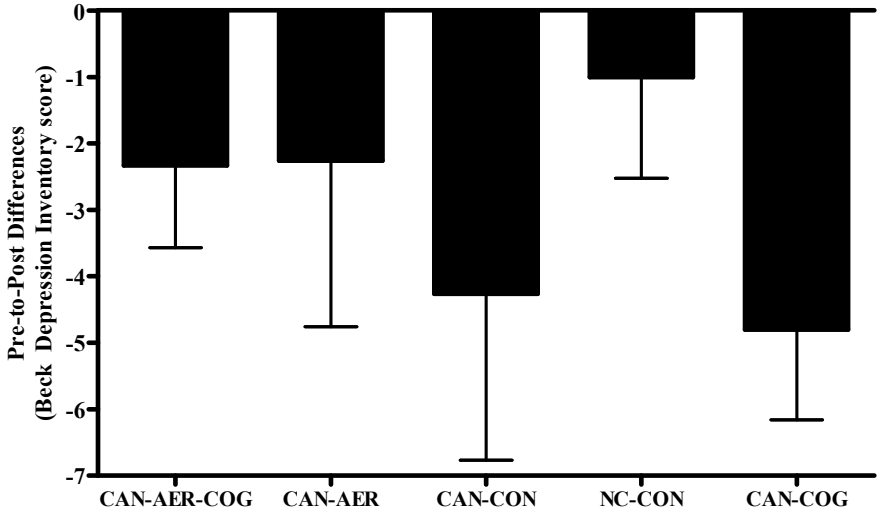


Figure 9. Group Comparisons of Beck Depression Inventory Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

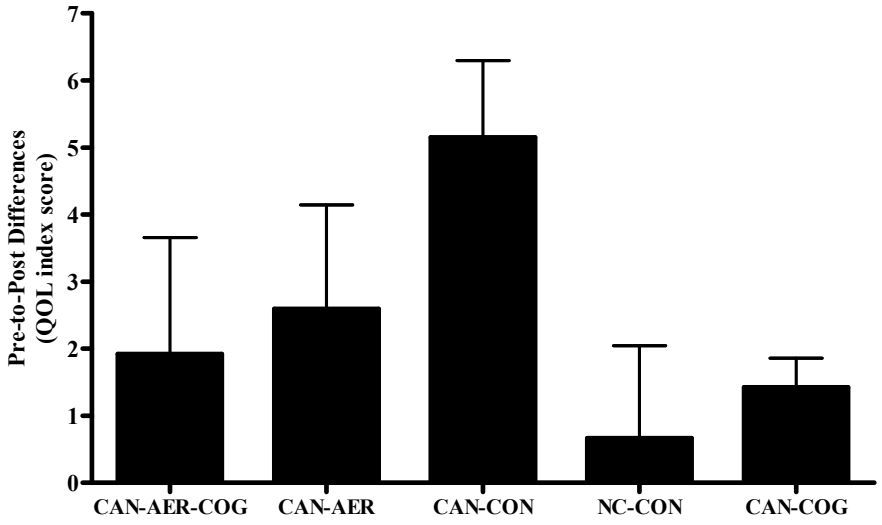


Figure 10. Group Comparisons of Ferrans and Powers Quality of Life Index Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

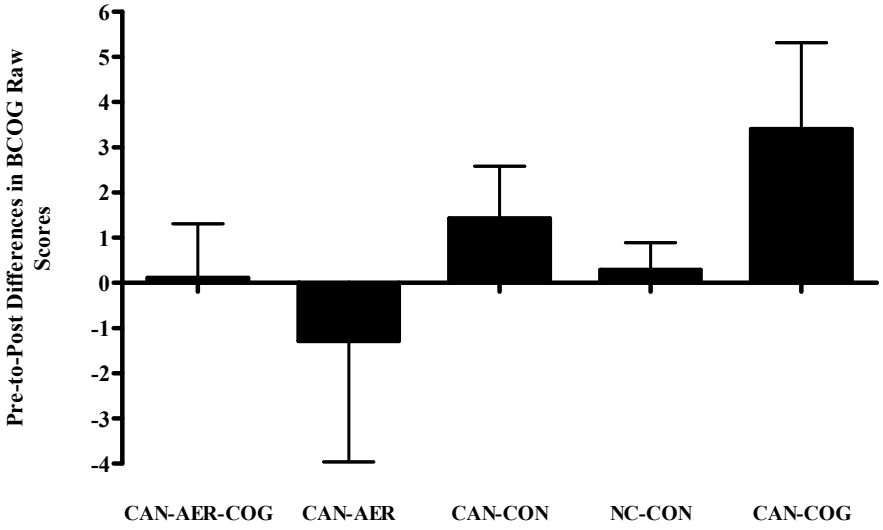


Figure 11. Group Comparisons of General Cognitive Screening. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

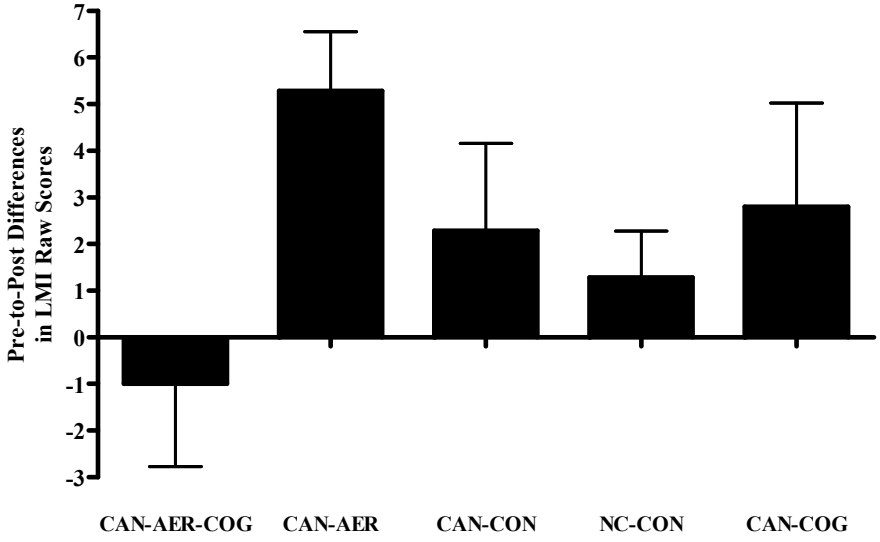


Figure 12. Group Comparisons of Logical Memory I Raw Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

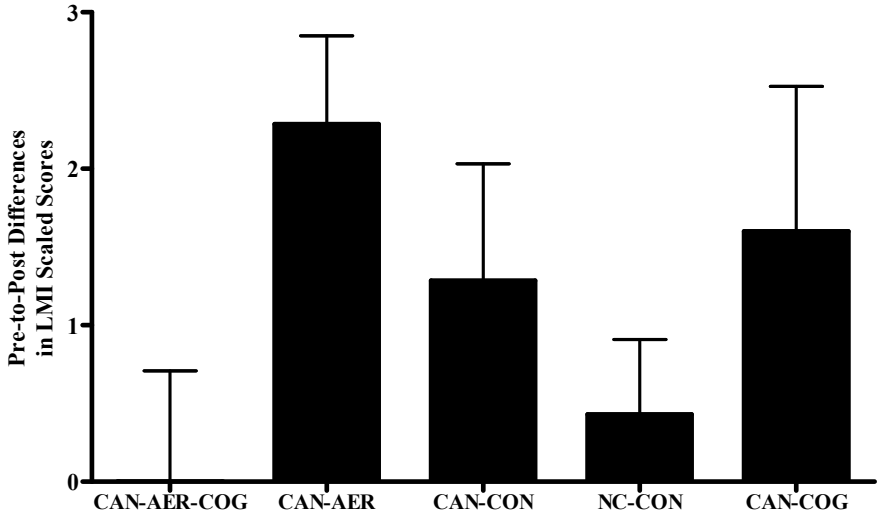


Figure 13. Group Comparisons of Logical Memory I Scaled Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

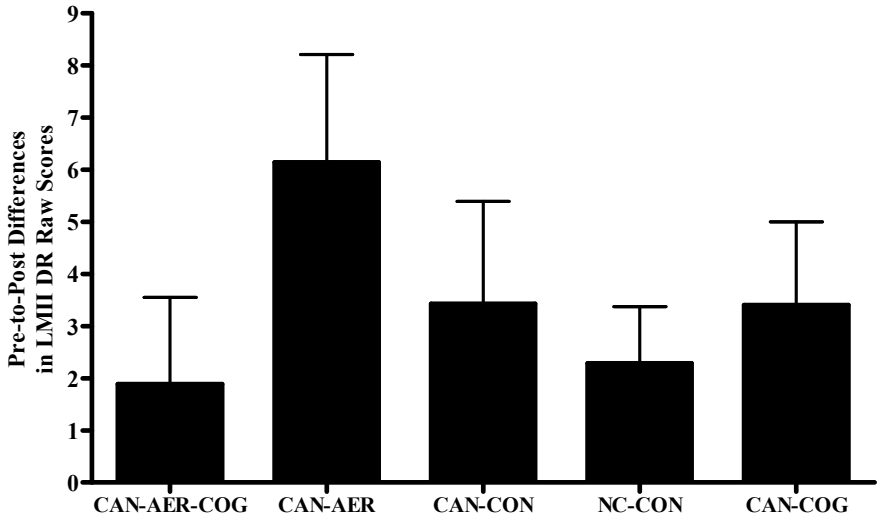


Figure 14. Group Comparisons of Logical Memory II Delayed Recall Raw Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

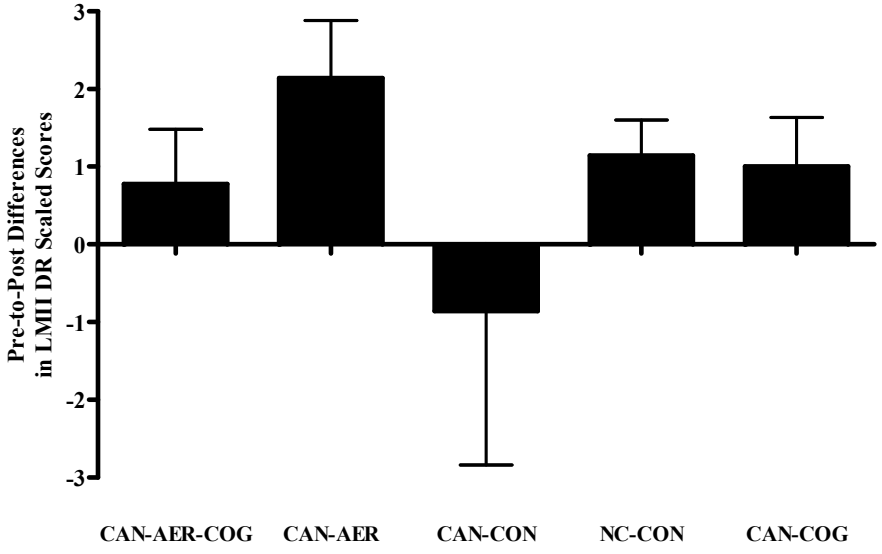


Figure 15. Group Comparisons of Logical Memory II Delayed Recall Scaled Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

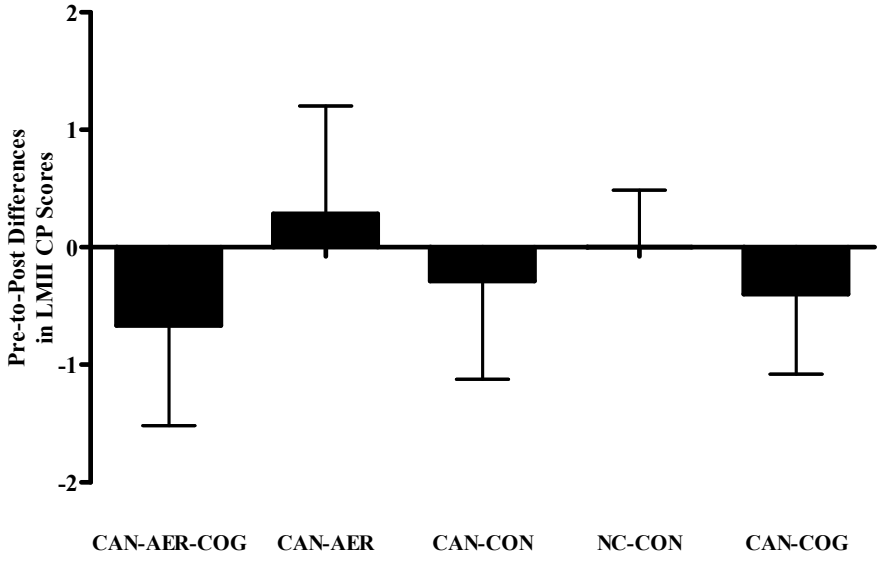


Figure 16. Group Comparisons of Logical Memory II Cumulative Percentage Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

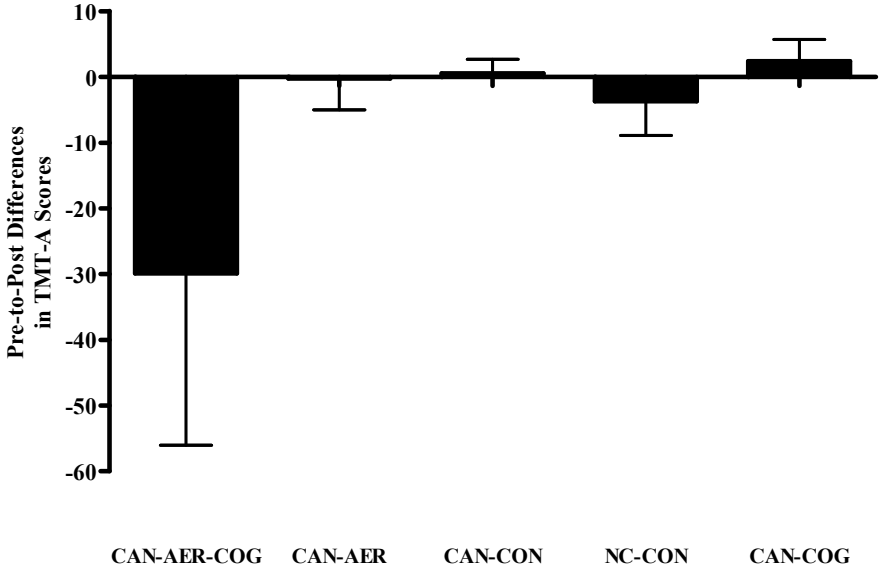


Figure 17. Group Comparisons of Trail Making Test-A Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

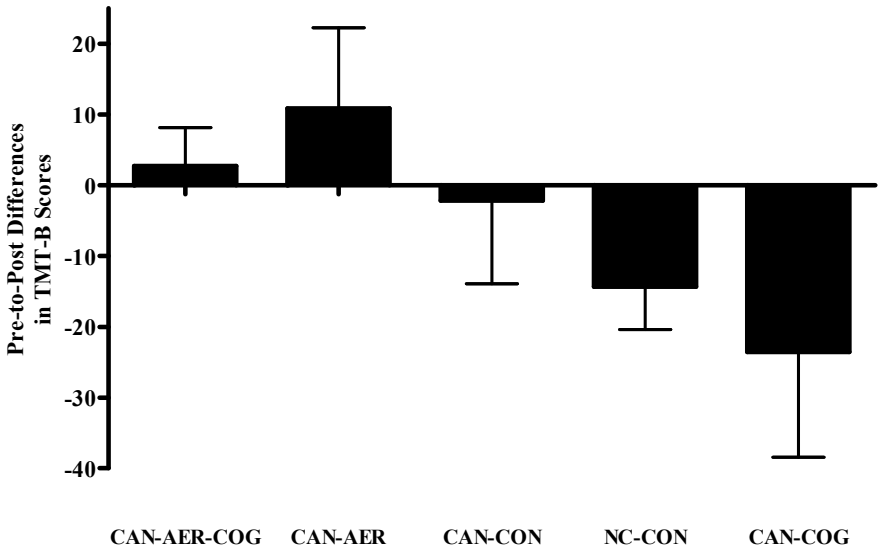


Figure 18. Group Comparisons of Trail Making Test-B Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

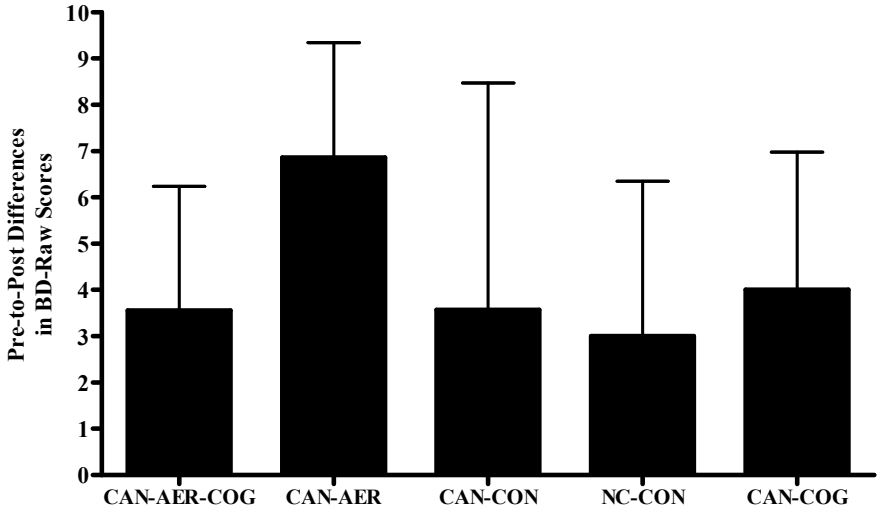


Figure 19. Group Comparisons of WAIS Block Design Raw Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

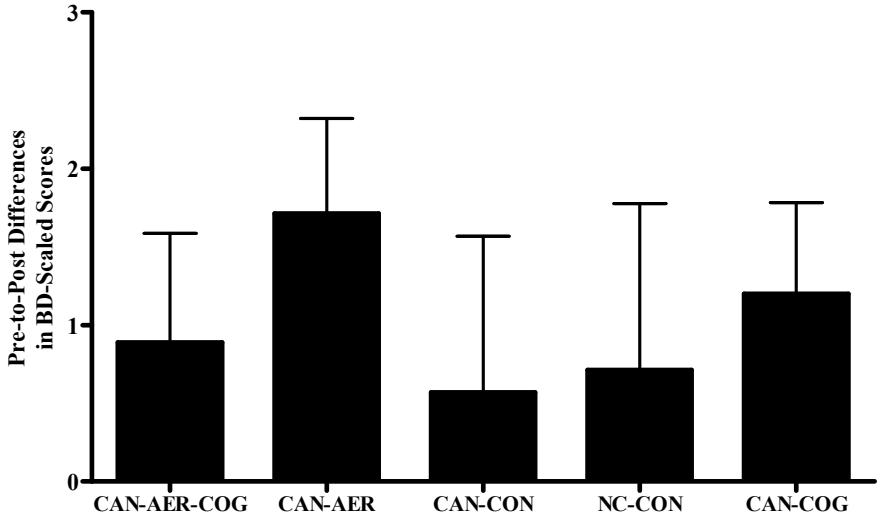


Figure 20. Group Comparisons of WAIS Block Design Scaled Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

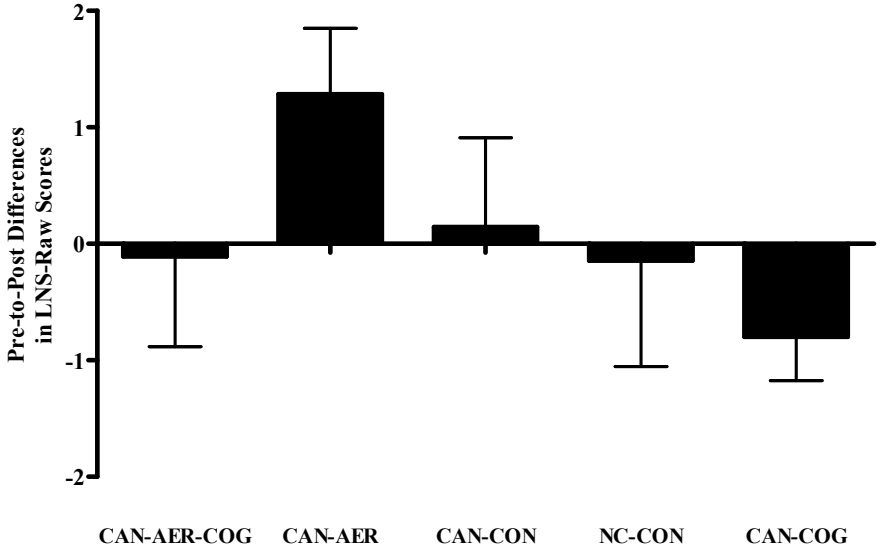


Figure 21. Group Comparisons of WAIS Letter Number Sequencing Raw Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

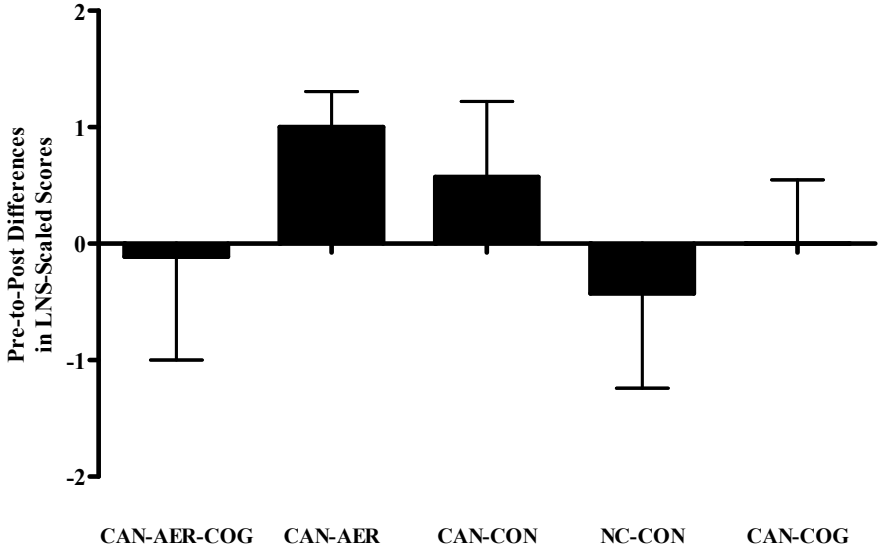


Figure 22. Group Comparisons of WAIS Letter Number Sequencing Scaled Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

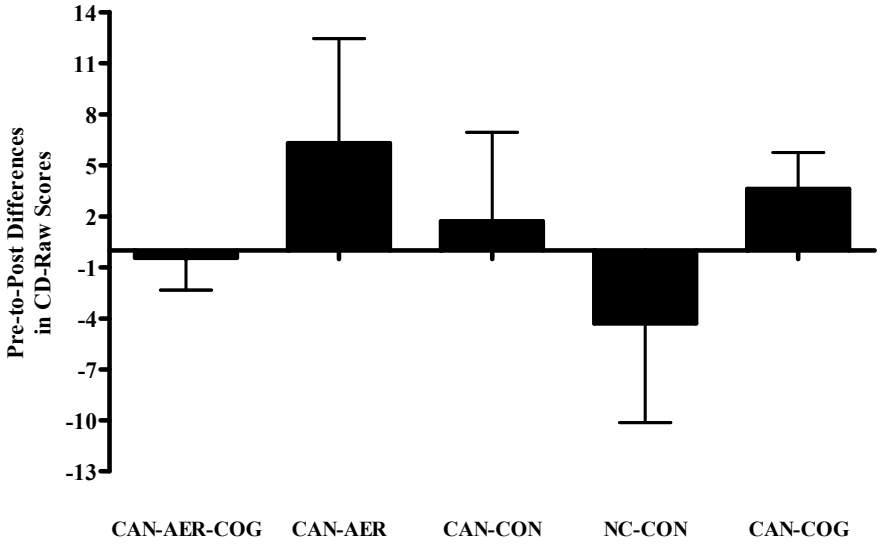


Figure 23. Group Comparisons of WAIS Coding Raw Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

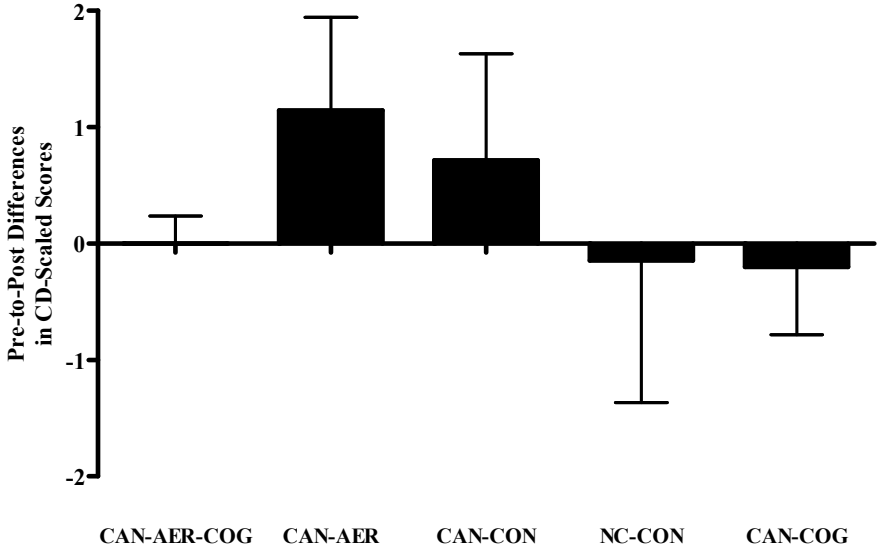


Figure 24. Group Comparisons of WAIS Coding Scaled Scores. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

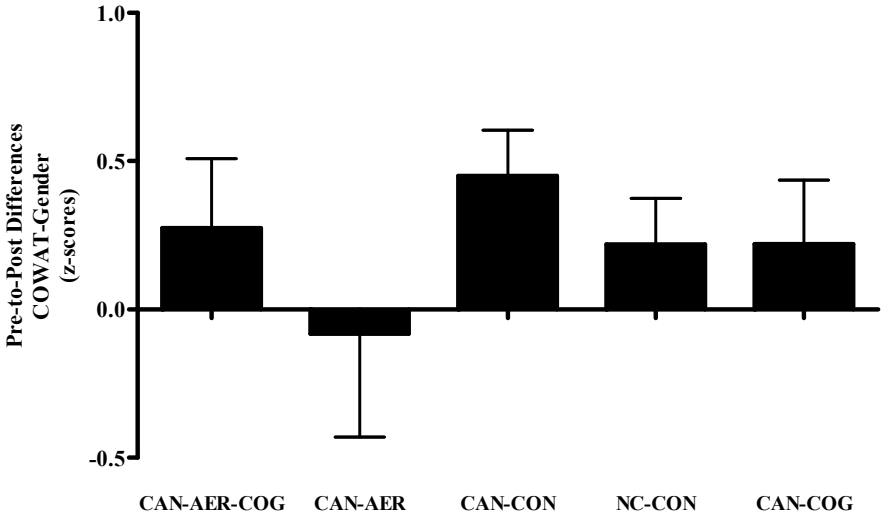


Figure 25. Group Comparisons of Controlled Oral Word Association Test-Gender. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

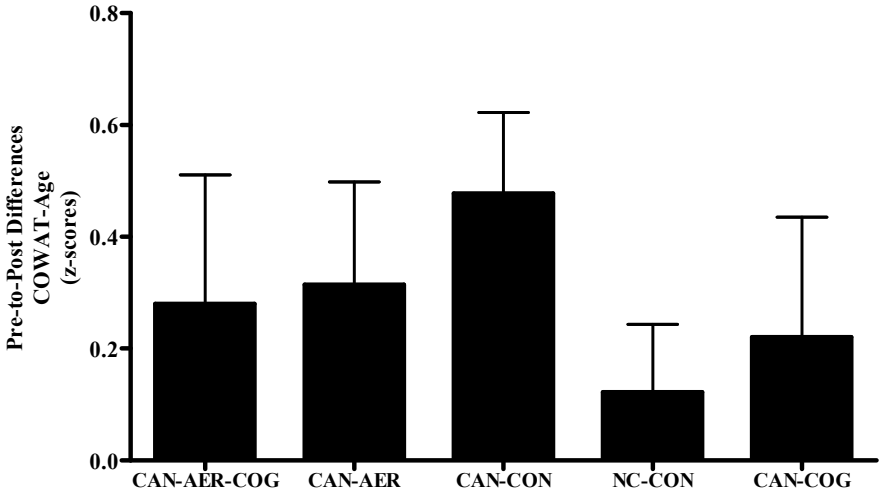


Figure 26. Group Comparisons of Controlled Oral Word Association Test-Age. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

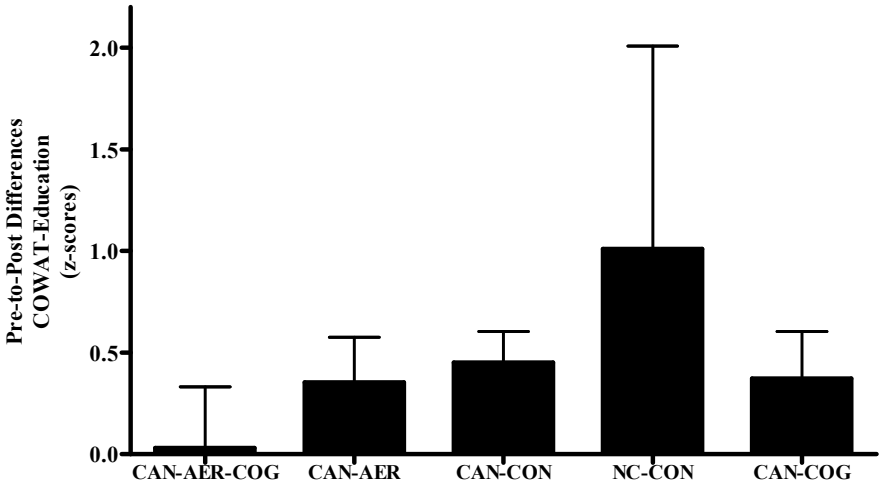


Figure 27. Group Comparisons of Controlled Oral Word Association Test-Education. CAN, cancer; COG, cognitive training; AER, aerobic training; CON, non-cancer controls. Data are mean ± SD.

Table 8

CAN-AER-COG wilcoxon sign ranks test: cognitive variables and percentage changes

Variable	Pre Mean	Pre SD	Post Mean	Post SD	SIG.	% Change
WMS_IV_BCOG	54.55	3.64	54.67	3.54	0.93	0.22
WMS_IV_LMI_RAW	26.89	7.90	25.89	4.54	0.57	-3.72
WMS_IV_LMI_SCALED	10.33	3.00	10.33	2.00	0.87	0.00
WMS_IV_LMII_DR_RAW	24.33	6.56	26.22	4.97	0.26	7.77
WMS_IV_LMII_DR_SCALED	11.44	2.74	12.22	2.17	0.27	6.82
WMS_IV_LMIICP_RAW	26.89	2.47	26.22	1.20	0.40	-2.49
TMT_A_RAW	60.44	80.02	30.67	10.00	0.14	-49.26
TMT_B_RAW	69.44	20.34	72.22	29.75	0.95	4.00
WAIS_IV_BD_RAW	32.00	12.34	35.56	12.00	0.27	11.13
WAIS_IV_BD_SCALED	9.00	2.96	9.89	2.89	0.26	9.89
WAIS_IV_LNS_RAW	20.67	3.16	20.56	2.79	0.89	-0.53
WAIS_IV_LNS_SCALED	11.56	3.43	11.44	2.88	1.00	-1.04
WAIS_IV_CD_RAW	68.78	19.57	68.33	24.00	0.87	-0.65
WAIS_IV_CD_SCALED	11.78	3.87	11.78	4.06	1.00	0.00
COWAT_Z_G	-0.04	1.60	0.23	1.80	0.31	675.00
COWAT_Z_A	0.10	1.57	0.38	1.78	0.26	280.00
COWAT_Z_ED	-0.20	1.52	-0.17	1.75	0.86	15.00

Note: WMS IV, Weschler Memory Scale (4th Ed.) (BCOG, general cognitive screener; LMI & LMII, Logical Memory delayed recall (DR), or cumulative percentage (CP)); TMT A or B, Trail Making Test version A or B, WAIS IV, Weschler Adult Intelligence Scale (4th Ed.) (BD, block design; LNS, letter number sequence; CD, coding); COWAT, Controlled Oral Word Association Test (Z, z-score; G, gender; A, age; ED, education).

Table 9

CAN-AER-COG wilcoxon sign ranks test: physiological and psychosocial variables with percentage changes

Variable	Pre Mean	Pre SD	Post Mean	Post SD	SIG.	% Change
SBP	122.67	13.56	120.22	10.89	0.40	-2.00
DBP	74.78	6.00	72.56	7.92	0.41	-2.97
RHR	73.78	10.45	70.89	12.33	0.31	-3.92
VO_{2PEAK}	21.07	8.35	21.62	8.48	0.95	2.61
SANDR	9.58	2.28	13.28	8.52	0.31	38.62
PIPER_I	4.60	1.39	3.52	2.35	0.07	-23.48
PIPER_B	3.81	2.71	2.57	2.48	*0.01	-32.55
PIPER_A	5.02	2.06	3.93	3.25	0.25	-21.71
PIPER_S	5.18	1.06	4.38	2.22	0.24	-15.44
PIPER_C	4.78	0.73	3.48	2.16	0.07	-27.20
BECK	9.78	4.76	7.44	6.15	0.10	-23.93
QOL	20.87	2.01	22.79	6.00	0.09	9.20

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure; RHR, resting heart rate; VO_{2PEAK}, the highest rate of oxygen consumed measured regardless of reaching VO_2 plateau; sit and reach test; PIPER, piper fatigue index (B, behavioral; A, affective; S, sensory; C, cognitive/mood subscales); BECK, beck depression inventory; QOL, quality of life. * denotes results were significant ($p < 0.05$).

Table 10

CAN-AER wilcoxon sign ranks test: cognitive variables and percentage changes

Variable	Pre Mean	Pre SD	Post Mean	Post SD	SIG.	% Change
WMS_IV_BCOG	54.00	5.26	52.71	4.54	0.61	-2.39
WMS_IV_LMI_RAW	19.00	4.16	24.29	5.25	*0.03	27.84
WMS_IV_LMI_SCALED	7.00	1.73	9.29	2.29	*0.03	32.71
WMS_IV_LMII_DR_RAW	15.57	6.43	21.71	5.09	*0.04	39.43
WMS_IV_LMII_DR_SCALED	7.86	3.13	10.00	2.31	*0.05	27.23
WMS_IV_LMIICP_RAW	24.00	2.94	24.29	3.15	0.79	1.21
TMT_A_RAW	36.86	7.60	36.43	14.19	0.75	-1.17
TMT_B_RAW	87.29	9.79	98.14	34.19	0.50	12.43
WAIS_IV_BD_RAW	33.57	8.60	40.43	7.13	*0.03	20.43
WAIS_IV_BD_SCALED	9.00	1.83	10.71	1.11	*0.03	19.00
WAIS_IV_LNS_RAW	16.86	1.07	18.14	1.35	0.07	7.59
WAIS_IV_LNS_SCALED	8.14	0.69	9.14	0.90	*0.04	12.29
WAIS_IV_CD_RAW	51.14	17.23	57.43	8.52	0.35	12.30
WAIS_IV_CD_SCALED	9.14	1.46	10.28	1.38	0.20	12.47
COWAT_Z_G	-0.54	0.31	-0.63	1.10	0.74	-16.67
COWAT_Z_A	-0.46	0.37	-0.14	0.61	0.13	69.57
COWAT_Z_ED	-0.80	0.56	-0.45	0.81	0.13	43.75

Note: WMS IV, Weschler Memory Scale (4th Ed.) (BCOG, general cognitive screener; LMI & LMII, Logical Memory delayed recall (DR), or cumulative percentage (CP)); TMT A or B, Trail Making Test version A or B, WAIS IV, Weschler Adult Intelligence Scale (4th Ed.) (BD, block design; LNS, letter number sequence; CD, coding); COWAT, Controlled Oral Word Association Test (Z, z-score; G, gender; A, age; ED, education. * denotes results were significant ($p < 0.05$).

Table 11

CAN-AER wilcoxon sign ranks test: physiological and psychosocial variables with percentage changes

Variable	Pre Mean	Pre SD	Post Mean	Post SD	SIG.	% Change
SBP	129.14	21.87	128.77	23.4	0.46	-0.29
DBP	78.71	8.18	78.8	14.05	1.00	0.11
RHR	76.86	8.45	69.69	11	0.24	-9.33
VO_{2PEAK}	18.67	5.43	22.4	8	0.09	19.98
SANDR	10.64	4.44	12.48	2.83	0.25	17.29
PIPER_I	4.62	3.61	3.39	3.26	0.18	-26.62
PIPER_B	5.39	3.7	3.69	3.53	0.08	-31.54
PIPER_A	5.66	4.21	4.1	2.83	0.09	-27.56
PIPER_S	5.26	2.78	3.49	2.54	*0.04	-33.65
PIPER_C	5.02	2.83	3.74	2.68	0.06	-25.5
BECK	10.86	7.86	7.8	7	0.18	-28.18
QOL	19.45	6.68	22.04	4.12	0.12	13.32

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure; RHR, resting heart rate; VO_{2PEAK}, the highest rate of oxygen consumed measured regardless of reaching VO_2 plateau; sit and reach test; PIPER, piper fatigue index (B, behavioral; A, affective; S, sensory; C, cognitive/mood subscales); BECK, beck depression inventory; QOL, quality of life. * denotes results were significant ($p < 0.05$).

Table 12

CAN-CON wilcoxon sign ranks test: cognitive variables and percentage changes

Variable	Pre Mean	Pre SD	Post Mean	Post SD	SIG.	% Change
WMS_IV_BCOG	54.29	3.20	55.71	4.27	0.28	2.62
WMS_IV_LMI_RAW	25.14	6.79	27.43	6.13	0.24	9.11
WMS_IV_LMI_SCALED	9.43	2.88	10.71	2.21	0.14	13.57
WMS_IV_LMII_DR_RAW	20.43	7.81	23.86	6.54	0.13	16.79
WMS_IV_LMII_DR_SCALED	12.14	5.27	11.29	2.36	0.83	-7.00
WMS_IV_LMIICP_RAW	25.14	3.48	24.87	3.63	0.93	-1.07
TMT_A_RAW	29.43	7.96	30.00	11.11	0.93	1.94
TMT_B_RAW	74.71	22.51	72.43	46.84	0.50	-3.05
WAIS_IV_BD_RAW	37.14	9.60	40.71	8.14	0.60	9.61
WAIS_IV_BD_SCALED	10.43	2.51	11.00	1.91	0.91	5.47
WAIS_IV_LNS_RAW	20.38	1.83	20.10	2.04	0.92	-1.37
WAIS_IV_LNS_SCALED	10.60	2.21	10.76	2.86	0.67	1.51
WAIS_IV_CD_RAW	65.00	5.42	66.71	17.34	0.40	2.63
WAIS_IV_CD_SCALED	10.71	1.63	11.43	3.31	0.29	6.72
COWAT_Z_G	0.06	0.83	0.51	0.84	*0.04	750.00
COWAT_Z_A	0.15	0.86	0.63	0.85	*0.03	320.00
COWAT_Z_ED	-0.22	0.91	0.23	1.00	*0.05	204.55

Note: WMS IV, Weschler Memory Scale (4th Ed.) (BCOG, general cognitive screener; LMI & LMII, Logical Memory delayed recall (DR), or cumulative percentage (CP)); TMT A or B, Trail Making Test version A or B, WAIS IV, Weschler Adult Intelligence Scale (4th Ed.) (BD, block design; LNS, letter number sequence; CD, coding); COWAT, Controlled Oral Word Association Test (Z, z-score; G, gender; A, age; ED, education. * denotes results were significant ($p < 0.05$).

Table 13

CAN-CON wilcoxon sign ranks test: physiological and psychosocial variables with percentage changes

Variable	Pre Mean	Pre SD	Post Mean	Post SD	SIG.	% Change
SBP	123.00	9.71	121.14	7.36	0.74	-1.51
DBP	74.00	7.67	77.14	7.19	0.35	4.24
RHR	92.71	10.56	100.29	17.26	0.24	8.18
VO_{2PEAK}	16.93	8.25	19.59	7.59	*0.05	15.71
SANDR	13.19	2.49	16.15	7.37	0.24	22.44
PIPER_I	2.43	2.51	1.42	1.44	0.40	-41.56
PIPER_B	3.20	3.28	1.05	1.11	0.12	-67.19
PIPER_A	2.74	2.83	1.64	1.48	0.35	-40.15
PIPER_S	3.63	3.01	1.86	1.58	0.13	-48.76
PIPER_C	2.92	2.81	1.39	1.76	0.09	-52.40
BECK	9.29	7.43	4.20	3.20	*0.04	-54.79
QOL	19.76	4.80	24.91	3.13	*0.02	26.06

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure; RHR, resting heart rate; VO_{2PEAK}, the highest rate of oxygen consumed measured regardless of reaching VO_2 plateau; sit and reach test; PIPER, piper fatigue index (B, behavioral; A, affective; S, sensory; C, cognitive/mood subscales); BECK, beck depression inventory; QOL, quality of life. * denotes results were significant ($p < 0.05$).

Table 14

NC-CON wilcoxon sign ranks test: cognitive variables and percentage changes

Variable	Pre Mean	Pre SD	Post Mean	Post SD	SIG.	% Change
WMS_IV_BCOG	56.66	1.46	56.86	1.46	0.50	0.35
WMS_IV_LMI_RAW	24.71	3.73	26.00	3.92	0.34	5.22
WMS_IV_LMI_SCALED	10.00	1.83	10.43	1.81	0.33	4.30
WMS_IV_LMII_DR_RAW	20.57	3.87	22.86	4.98	0.10	11.13
WMS_IV_LMII_DR_SCALED	9.42	1.40	10.57	1.99	0.07	12.21
WMS_IV_LMIICP_RAW	25.73	1.76	25.57	2.44	0.69	-0.62
TMT_A_RAW	37.57	12.50	33.86	7.43	0.35	-9.87
TMT_B_RAW	66.14	16.15	51.86	6.62	0.06	-21.59
WAIS_IV_BD_RAW	40.86	14.60	43.86	14.72	0.40	7.34
WAIS_IV_BD_SCALED	10.71	4.11	11.43	3.31	0.52	6.72
WAIS_IV_LNS_RAW	20.14	1.95	20.00	1.41	0.83	-0.70
WAIS_IV_LNS_SCALED	10.57	1.99	10.14	0.69	0.52	-4.07
WAIS_IV_CD_RAW	74.00	9.38	69.71	15.68	0.89	-5.80
WAIS_IV_CD_SCALED	11.57	1.81	11.43	2.07	0.72	-1.21
COWAT_Z_G	0.05	0.67	0.26	0.48	0.35	420.00
COWAT_Z_A	0.17	0.62	0.29	0.49	0.53	70.59
COWAT_Z_ED	-1.30	2.71	-0.29	0.53	0.35	77.69

Note: WMS IV, Weschler Memory Scale (4th Ed.) (BCOG, general cognitive screener; LMI & LMII, Logical Memory delayed recall (DR), or cumulative percentage (CP)); TMT A or B, Trail Making Test version A or B, WAIS IV, Weschler Adult Intelligence Scale (4th Ed.) (BD, block design; LNS, letter number sequence; CD, coding); COWAT, Controlled Oral Word Association Test (Z, z-score; G, gender; A, age; ED, education).* denotes results were significant ($p < 0.05$).

Table 15

NC-CON wilcoxon sign ranks test: physiological and psychosocial variables with percentage changes

Variable	Pre Mean	Pre SD	Post Mean	Post SD	SIG.	% Change
SBP	127.86	14.31	127.34	10.25	0.55	-0.41
DBP	77.71	12.35	76.80	12.91	0.93	-1.17
RHR	88.14	14.72	77.12	12.95	0.09	-12.50
VO_{2PEAK}	31.25	8.83	28.96	6.47	0.17	-7.33
SANDR	11.67	3.68	10.68	3.89	0.61	-8.48
PIPER_I	2.58	1.80	2.37	1.94	0.87	-8.14
PIPER_B	1.24	1.26	1.42	2.64	0.72	14.52
PIPER_A	2.69	2.84	2.51	2.29	0.92	-6.69
PIPER_S	3.54	2.49	3.66	2.37	0.87	3.39
PIPER_C	2.63	2.34	2.38	1.84	0.83	-9.61
BECK	5.40	2.72	3.14	5.37	0.18	-41.85
QOL	24.18	3.77	24.84	3.46	0.50	2.73

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure; RHR, resting heart rate; VO_{2PEAK}, the highest rate of oxygen consumed measured regardless of reaching VO_2 plateau; sit and reach test; PIPER, piper fatigue index (B, behavioral; A, affective; S, sensory; C, cognitive/mood subscales); BECK, beck depression inventory; QOL, quality of life. * denotes results were significant ($p < 0.05$).

Table 16

CAN-COG wilcoxon sign ranks test: cognitive variables and percentage changes

Variable	Pre Mean	Pre SD	Post Mean	Post SD	SIG.	% Change
WMS_IV_BCOG	53.20	5.31	56.60	1.67	0.13	6.39
WMS_IV_LMI_RAW	21.60	7.92	24.40	3.91	0.41	12.96
WMS_IV_LMI_SCALED	8.00	3.39	9.60	1.67	0.13	20.00
WMS_IV_LMII_DR_RAW	18.40	8.56	21.80	6.72	0.08	18.48
WMS_IV_LMII_DR_SCALED	9.20	3.70	10.20	2.95	0.16	10.87
WMS_IV_LMIICP_RAW	24.40	2.30	24.00	2.35	0.58	-1.64
TMT_A_RAW	29.20	10.99	31.69	9.92	0.47	8.53
TMT_B_RAW	92.60	33.65	68.98	20.50	0.14	-25.51
WAIS_IV_BD_RAW	27.40	5.98	31.40	3.97	0.23	14.60
WAIS_IV_BD_SCALED	7.80	1.64	9.00	1.41	0.10	15.38
WAIS_IV_LNS_RAW	20.00	1.22	19.20	1.10	0.10	-4.00
WAIS_IV_LNS_SCALED	9.60	0.89	9.60	0.55	1.00	0.00
WAIS_IV_CD_RAW	66.20	10.40	69.80	8.29	0.14	5.44
WAIS_IV_CD_SCALED	12.00	1.58	11.80	1.92	0.71	-1.67
COWAT_Z_G	-0.14	0.78	0.08	0.66	0.35	155.56
COWAT_Z_A	-0.04	0.75	0.18	0.67	0.28	573.68
COWAT_Z_ED	-0.62	0.63	-0.25	0.60	0.23	59.68

Note: WMS IV, Weschler Memory Scale (4th Ed.) (BCOG, general cognitive screener; LMI & LMII, Logical Memory delayed recall (DR), or cumulative percentage (CP)); TMT A or B, Trail Making Test version A or B, WAIS IV, Weschler Adult Intelligence Scale (4th Ed.) (BD, block design; LNS, letter number sequence; CD, coding); COWAT, Controlled Oral Word Association Test (Z, z-score; G, gender; A, age; ED, education).

Table 17

CAN-COG wilcoxon sign ranks test: physiological and psychosocial variables with percentage changes

Variable	Pre Mean	Pre SD	Post Mean	Post SD	SIG.	% Change
SBP	99.60	47.14	126.28	11.35	0.23	26.79
DBP	79.20	13.75	72.93	8.45	0.27	-7.92
RHR	84.60	15.11	85.37	14.43	0.69	0.91
VO_{2PEAK}	20.08	4.88	22.50	5.21	0.35	12.05
SANDR	11.62	5.01	14.39	2.88	0.23	23.84
PIPER_I	6.07	2.68	2.91	1.44	0.08	-52.06
PIPER_B	3.41	2.06	1.73	1.70	0.23	-49.27
PIPER_A	4.00	1.98	3.08	1.67	0.08	-23.00
PIPER_S	5.80	1.33	3.60	2.31	0.14	-37.93
PIPER_C	4.73	0.56	3.23	1.30	0.08	-31.71
BECK	8.20	1.79	3.40	1.52	*0.04	-58.54
QOL	22.12	1.47	23.54	1.47	*0.04	6.42

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure; RHR, resting heart rate; VO_{2PEAK}, the highest rate of oxygen consumed measured regardless of reaching VO_2 plateau; sit and reach test; PIPER, piper fatigue index (B, behavioral; A, affective; S, sensory; C, cognitive/mood subscales); BECK, beck depression inventory; QOL, quality of life. * denotes results were significant ($p < 0.05$).

CHAPTER V

DISCUSSION

Cancer is a multifaceted phenomenon that negatively affects millions of people worldwide (Jemal et al., 2011). It requires the development of scientifically-based tactics that are of holistic and multi-faceted in nature for not only the treatment of the disease, but for the rehabilitation process. Current progressive methods of prevention, detection, education, and treatment, along with increased implementation of individualized cancer rehabilitation programs have played a substantial role in the current estimates of increased survival rates (ACS, 2014). However, incidences of cancer continue to increase therefore, unequivocally, calls for continued research that aims to holistically address the specific, multifaceted, needs of this growing population.

Chemotherapy-related cognitive impairment has gained traction in the lay and scientific literature as being an ever increasing, disruptive, and frustrating phenomenon which negatively affects cancer survivors undergoing treatment. This project addressed factors that may play a role in the reduction or attenuation of CRCI, a side effect of treatment that has been reported to negatively affect the lives of upwards of 75% of those who have undergone treatment (Jackson, 2008; Myers, 2009; Konat et al., 2008; & Raffa & Tallarida, 2010). The purpose of this study was to examine the effects of a quasi-randomized, controlled 12-week aerobic and cognitive intervention on cancer survivors (CAN) versus non-cancer participants (NC).

It was hypothesized that aerobic cycling on a recumbent cycle ergometer would increase measures of cognitive function in CAN. Second, cognitive training using computer software consisting of brain training exercises was hypothesized to increase measures of cognitive function in CAN. Finally, it was hypothesized that the combined cognitive and aerobic training would have a synergistic effect on increases in cognitive function in CAN. Despite global analyses revealing no significant ($p > 0.05$) differences between each of the groups for physiological, psychosocial, or cognitive measures, the within group results suggest that aspects of these types of modalities may be effective at targeting CRCI. Although the methodology needs refinement to better focus the efforts on CRCI, the results of this investigation has provided fertile groundwork for research investigations in the future. For example, at home cognitive training using commercially available programs such as Posit-Science® and Lumosity® may actually remove the combined difficulty and cognitive demand observed in the groups that had the combined cognitive and aerobic training, thereby allowing participants better focus on aerobic training.

Aerobic, Cognitive, and Flexibility Training (CAN-AER-COG)

Although the hypothesis that the combined CAN-AER-COG group would generate the greatest overall increases in measures of aerobic and cognitive function, this group produced the least amount of improvements compared to any other group from pre-to-post. Yet, there were still aspects of this treatment group that deserve mention. Increases in TMT-A speed suggest that training may have an impact on their ability to reproduce the task with greater speed and efficiency. The TMT-A test has been reported to be utilized in multiple population samples as a test of mental processing speed and

executive function (Park & Larson, 2015). Processing speed has been roughly defined as being the speed of completing a task with a relative or reasonable accuracy (Jacobson et al., 2011). In addition, Lezak, Howieson, Bigler, and Tranel (2012) defined executive function as individual capacitance to engage successfully in self-directed, purposive, independent, and self-serving behavior. Part "A" of the Trail Making Test A and B is focused on the former being the processing speed. In this case, the CAN-AER-COG group increased in their speed of processing by 49% (pre 60.4 ± 80.0 vs. post 30.7 ± 10 seconds, $p = 0.14$) from pre-to-post. Although insignificant, a 49% increase in processing speed among cancer survivors may be a factor in the gaining of confidence in abilities or capabilities that had been reduced or abandoned while undergoing treatment. For example, a particular client in this group was told she absolutely should not drive her vehicle, (A) because of the high dosages of chemotherapy and radiation she was undergoing, and (B) because of how unwell she felt on a daily basis. Following the completion of chemotherapy and radiation treatment and at the discretion of her physician, she was then allowed to drive. This increase of 49% increase in the ability of the brain to process signals may appear as statistically insignificant, but to a cancer survivor, who is beginning to drive again after three months of not driving, a 49% increase in processing speed may be quite important.

Controlled Oral Word Association Test gender and age scores also improved by 675% and 275%, respectively (pre -0.04 ± 1.6 vs. post 0.2 ± 1.8; pre 10 ± 1.6 vs. post 0.4 ± 1.8) for the CAN-AER-COG group, suggesting that improvements were made for word association following training. Foster et al. (2013) noted that the COWAT test requires participants to come up with as many words as they possibly can within the given time

limit for a specified letter. These particular assessments make an adjustment for gender and age. However, regardless of the insignificance, it is important to note that the sheer number of word associations (or verbal fluidity) increased following the intervention.

Fatigue significantly decreased in the CAN-AER-COG group (-33%) (pre 3.8 ± 2.7 vs. post 2.6 ± 2.5, $p < 0.05$) in the Piper Fatigue Index Behavioral subcategory and there was a trend toward significant decreases (-24%) (pre 4.6 ± 1.4 vs. post 3.5 ± 2.4, $p = 0.07$) in the overall Piper Fatigue Index score. There was a trend toward a significant decrease (-27%) (pre 4.8 ± .7 vs. 3.5 ± 2.2, $p = 0.07$) in the Cognitive subcategory, and there were decreases (-22%, -15%, -24%) in the Piper Fatigue Index Affective and Sensory subcategories. This is still a matter of importance for the cancer survivor. Fatigue has been reported to manifest itself much differently in cancer survivors than apparently healthy adults. Finsterrer and Mahjoub (2014) described CRF as being overwhelming resting tiredness that may inhibit activities of daily living, decrease vigor and endurance, and may persist for long periods of time, ultimately affecting QOL in a negative manner. In addition, CRF may also negatively impact psychosocial aspects of function such as those measured in this study, consequently acting as a disabling factor to the individual's life (Finsterer & Mahjoub, 2014). It is important to note that depression and fatigue are all factors that play a substantial role in not only activities of daily life, but more importantly, overall QOL.

Quality of Life only improved by 9% in the CAN-AER-COG group suggesting that this type of training may not be the preferred method of intervention for cancer survivors going through treatment. Anecdotal information received from multiple clients helped to substantiate this. Many clients would state that they would have to reduce their

pedal rate in order to focus on the extremely difficult games, suggesting a neurological conflict of sorts may have been occurring such that the ability of the brain to appropriate the amount of processing capability between two difficult tasks. In addition, there were many times where clients had actually broken down in tears because they were so incredibly frustrated with the difficulty of not only their current treatment regimens, but how hard it was for them to concentrate with CRCI. Among the non-pharmacological approaches to addressing CRCI, these results suggest that combined training may not be the most appropriate for this particular population.

Aerobic and Flexibility Training (CAN-AER)

Recently it was reported that among apparently healthy males that exercise of a moderate intensity (65% HRR) for 20 minutes significantly ($p < 0.05$) increased accuracy and speed as a measure of cognitive performance (Stroop test) when compared to ten or 45 minutes of cycling, suggesting a dose-response relationship between aerobic exercise and cognitive function (Chang et al., 2015). Although the aforementioned comparison is a much different group, it is important to state that among all treatment groups, those that were randomized to the CAN-AER group were by far the most significantly improved group among pre-to-post measures of cognitive function. Measures of WMS-LMI raw and scaled scores significantly (pre 19.0 ± 4.2 vs. post 24.3 ± 5.3, $p < 0.05$; pre 7.0 ± 1.7 vs. post 9.3 ± 2.3, $p < 0.05$) increased (28%, 33%, respectively). WMS-LMII DR raw and scaled scores significantly (pre 15.6 ± 6.4 vs. post 21.7 ± 5.1, $p < 0.05$; pre 7.9 ± 3.1 vs. post 10.0 ± 2.3, $p < 0.05$) increased (39%, 27%, respectively). The WMS-LMI has been reported by the British Psychological Society (2012) to be a measure of narrative

working memory, while the WMS-LMII-DR has been reported to be a measure of narrative delayed recall, or longer term memory (BPS, 2012).

Various structures in the brain are associated with memory; of particular importance to this investigation, in the hippocampus. A particular study evaluating the effects of seven weeks of aerobic training (50-75% HRR) on brain volumetric changes in apparently healthy older adults revealed significant increases in hippocampal volumes and increases in cognitive tests of memory (Erickson et al., 2011). Results from the current investigation corroborate those observations: (A) aerobic training does increase aspects of memory, but for cancer survivors undergoing treatment, it may necessitate reductions in training percentages of HRR to account for the added physical and cognitive demand of chemotherapy treatment, and (B) increases of memory observed within the CAN-AER group during this study may have been due to volumetric increases in the hippocampus.

Weschler Adult Intelligence Scale Block Design raw and scaled scores both significantly increased (pre 33.5 ± 8.6 vs. post 40.4 ± 7.1, $p < 0.05$; pre 9.0 ± 1.8 vs. post 10.7 ± 1.1, $p < 0.05$) by 20% and 19%, respectively. The WAIS block design test has been reported to be a visual test of perceptual reasoning and visual processing (Benson, Hulac, & Kranzler, 2010; Ward, Bergman, & Hebert, 2012). Cognitive assessors show participants various shapes that the participant is encouraged to reproduce using their own set of multi-colored blocks. These results suggest that perceptions and processing of the visual components increased potentially as a result of aerobic exercise. WAIS LNS scaled scores significantly (pre 8.1 ± .7 vs. post 9.1 ± .9, $p < 0.05$) increased (12%). WAIS CD raw and scaled scores were statistically insignificant ($p > 0.05$) yet increased

by 12% and 13%, respectively. Both the LNS and CD tests are visual assessments of executive function and working memory (Benson et al., 2010; Ward et al., 2012) again suggesting that aerobic exercise corroborates with findings of previous studies.

Finally, measures of COWAT age and education scores, although statistically insignificant ($p > 0.05$) increased by 70% and 44%, respectively. Whether this was a function of the intervention itself or a recovery of previously attained levels of verbal fluidity, is yet to be determined. Yet, COWAT gender scores decreased by 17%, suggesting that there may have been a different response between males and females in verbal fluidity. Formulating a judgment on this particular result is difficult because (A) this group was disproportionately composed of females ($n = 5$) vs. males ($n = 2$), and (B) one of the female participants in this group had stage III brain cancer and had significant difficulties with verbal tasks due to the removal of large portions of her temporal lobe. This circumstance may have potentially affected the results which suggested that this group decreased in measures of verbal fluidity. For example, words that began with "s" were particularly difficult to say.

Chang et al. (2015) suggested that cognitive improvements as a function of moderate intensity (65% HRR) aerobic exercise may in fact follow the inverted U paradigm such that an optimal intensity and time may be necessary to yield the greatest amount of intervention-related cognitive changes, at least in apparently healthy males. When data collection commenced for the current study, some of the first participants had been out of treatment for a few weeks and the appropriate HRR values for each corresponding segment of training were accomplished. However, following a shift in oncologist referring, most participants from that point forward were still undergoing

treatment. During this study, 30 minutes of aerobic cycling was attempted at 55%, 60%, and 65% (HRR), however, maintaining each exact HRR was often times difficult to accomplish during many training sessions throughout data collection because subject functional capacity often changed from day-to-day with treatment. For example, a particular participant who was undergoing chemotherapy and radiation would often complete training at the required intensities, but on the one day per week that followed her chemotherapy infusions, she often could only complete a few minutes at the prescribed intensity due to overwhelming fatigue. This aspect of training transcended all of the CAN groups with the exception of the CAN-CON group and necessitated the implementation of the RPE scale to better equalize the training and allow participants to complete the session.

In light of the prevalence of this issue among those in groups that trained aerobically (who were undergoing treatment), it should be noted that intensities proposed in this study could not be strictly adhered to. In addition, intensities proposed in this study may have very well been appropriate for those who had completed treatment weeks prior, but not for those undergoing treatment. Furthermore, even though the results do suggest that this model of aerobic training produced significant increases in measures of cognitive function in this sample, a more appropriate level of intensity, perhaps between 40% and 55% HRR may more appropriately reflect the specific needs of the population.

Piper sensory subscale significantly (pre 5.3 ± 2.8 vs. post 3.5 ± 2.5, $p < 0.05$) decreased (34%). The Piper cognitive subscale trended toward significance (pre 5.0 ± 2.8 vs. post 3.7 ± 2.7, $p < 0.05$) and decreased by 26%. Piper behavioral and affective scores both trended toward significant decreases (pre 5.4 ± 3.7 vs. post 3.7 ± 5.5, $p = 0.08$; pre

5.7 ± 4.2 vs. post 4.1 ± 2.8, $p = 0.09$) (-32% and -28%, respectively). Piper index scores and Beck depression also decreased -27% and -28%, respectively. VO_{2peak}, sit and reach, and QOL scores, although statistically insignificant, increased by 20%, 17%, and13% from pre-to-post. Overall increases in measures of cognitive function, VO_{2peak}, sit and reach, decreases in fatigue, depression, and increases in QOL all suggest that the combination of aerobic and flexibility training should be further examined to better understand how best to implement this type of training in cancer survivors.

Flexibility Training (CAN-CON)

Multiple studies have indicated the impact of various types of flexibility training on cancer survivors. For example, in a review of literature composed of 25 studies evaluating the effects of yoga as a component of cancer interventions, Culos-Reed et al. (2012) found that among various interventions that implemented yoga that this type of training may be quite effective as a rehabilitative modality for cancer survivors. Furthermore, Culos-Reed et al. (2012) noted that yoga was associated with increases in QOL and spiritual well-being, decreases in anxiety, depression, and fatigue. Although, the CAN-CON group did not participate in yoga, the participants did complete 36 sessions of whole-body static stretching. Results from this study do, somewhat, corroborate findings from studies that evaluated the effects of yoga. VO_{2peak} trended toward significant increases (pre 16.9 ± 8.3 vs. post 19.6 ± 7.6, $p = 0.05$; 16%). Quality of life significantly increased (pre 19.8 ± 4.8 vs. post 24.9 ± 3.1, $p < 0.05$) (26%) for the CAN-CON group. The Piper behavior and cognitive subscales decreased (pre 3.2 ± 3.3 vs. post 1.1 ± 1.1, -67%; pre 2.9 ± 2.8 vs. post 1.4 ± 1.7, -52%). Beck depression significantly decreased (pre 9.3 ± 7.4 vs. post 4.2 ± 3.2, $p < 0.05$) (-55%).

Finally, Piper index, affective, and sensory subscales all decreased (-41.6, -40.5, and -48.8, respectively), and sit and reach increased by 22% in the CAN-CON group. These pre-to-post changes reflect an important component of cancer rehabilitation that may have been overlooked or underrated, which may actually be a substantial tool in the arsenal of cancer exercise specialists who are training clients that are currently undergoing treatment and may not be able to fully tolerate exercise. This area of cancer rehabilitation lacks a significant amount of research regarding physiological changes that may explain the results obtained during this study. However, other studies have implemented the Chinese therapeutic method of Qi-gong, which is not technically flexibility training or yoga. However, Qi-gong may be a much closer modality for comparison considering the subtlety of movements are slow-paced, require a modicum of active muscle stretch during each movement, and aid in breathing techniques which are mildly similar to static stretching (Yeh, Lee, Chen, & Chao, 2006; Lee, Loh, & Murray, 2011). Of the few studies that have evaluated physiological alterations following Qi-gong interventions in cancer patients undergoing treatment, Yeh et al. (2006) reported the effects of Qi-gong on multiple blood parameters. The investigators concluded that following the intervention white blood cell count and platelet count significantly increased among those undergoing treatment for cancer. Although no definitive explanation can be given for the results obtained from the current study, it bears importance that future investigations include delving into potential mechanistic actions that may better elucidate the benefits of flexibility training on functional capacity and CRCI in cancer survivors.

Little research exists that has evaluated the effects of a static-stretching, yoga, or Qi-gong on measures of cognitive function. In addition, those reviewed had cognitive assessment batteries that were completely different from what was conducted in this study. Furthermore, there was even less research that evaluated the aforementioned in a cancer survivor population. However, in an investigation of the effects of a six-month yoga-based intervention on measures of cognitive function among apparently healthy adults over 60 years of age, Hariprasad et al. (2013) found that following the intervention, significant increases were observed among delayed recall of visual and verbal memory, executive function, working memory and attention, processing speed, and verbal fluency. In this study no other measure of cognitive function significantly increased for the CAN-CON group except the COWAT gender (pre .06 ± .8 vs. post .5 ± .84, $p < 0.05$), age (pre .15 ± .9 vs. post .6 ± .85, $p < 0.05$), and education scores (pre -.2 ± .9 vs. post .2 ± 1.0, $p < 0.05$), which partially substantiates the results presented in the Harisprasad et al. (2013) study suggesting that verbal fluency significantly increased following the intervention.

Although not entirely understood, the main differences between the studies may have been responsible for the outcomes that were observed. These were: (A) apparently healthy older adults, (B) the intervention consisted of yoga as opposed to static stretching, and (C) the duration of the yoga intervention was six months as opposed to three in this study. It may very well be that because a vast majority of the participants in this study were undergoing chemotherapy and/or radiation treatment, that the targeted flexibility protocol was ineffective in the reduction of CRCI. However, measures of

verbal fluency significantly improved in this group from pre-to-post suggesting that a factor of training played a role in these observed improvements.

Due to the nature of the flexibility protocol being very socially interactive, the one-on-one personal training administered during training may have played a role in increased verbal fluency. In addition, it would be near impossible to have implemented this type of training intervention without a modicum of social interaction or facilitation of the individual stretches, and regularly attending clients of RCMRI often report how they enjoy the time they get to spend interacting with their trainers. This suggests that participants are positively affected by this type of training which may explain the increases in measures of word association.

Aerobic, Cognitive, and Flexibility Training (NC)

The apparently healthy control group appeared to increase the least when compared to pre-to-post changes among the CAN groups. This may be due to the fact that many of the age-matched, apparently healthy adults who were included in this study were actually more actively engaged in daily living activities of both physical and cognitive demand than they perceived. However, some aspects of cognitive function did increase following the completion of the study. WMS-LMII DR scaled scores trended toward significant increases (pre 9.4 ± 1.4 vs. post 10.6 ± 2.0, $p = .07$) (12%) which would indicate that aspects of long-term memory increased as a result of the training, which although beneficial, these results are not impactful enough to conclude that the cognitive training was responsible for outcomes observed. In addition, TMT-B scores trended toward significant decreases (pre 66.1 ± 12.2 vs. post 51.9 ± 6.6, $p = 0.06$) in speed of processing for TMT-B (-22%). All COWAT gender, age, and education scores increased

(420%, 71%, and 78%, respectively). No pre-to-post changes in physiological or psychosocial variables produced significant changes following the completion of the study. However, RHR trended toward a significant decrease (pre 88.14 ± 14.7 vs. post 77.12 ± 13.0, $p = 0.09$) (-13%). Finally, Beck depression decreased by (-42%). This could be explained in part because of the married couple who participated together in the study. The husband was a Greeley police officer who was part of a cyber team that investigated computer equipment of individuals that were suspects in cases where there were crimes against children. The wife was in the middle of completing her Master's degree at UNC in chemistry. Both the husband and wife were adamantly vocal about their levels of stress at their occupations. Near the completion of their training both the husband and wife were in totally different occupations, which were much less stressful and may have accounted for the decreases observed in depression. They both expressed how much happier they were that those chapters in their lives had closed.

The lack of significant increases in measures of cognitive function do not agree with multiple research investigations showing significant increases in measures of cognitive function following a cognitive training protocol (Ball et al., 2007; Cherrier et al., 2013; Ferguson et al., 2007b; Hassler et al., 2010; Kawashima, 2013; Kesler et al., 2013; Mahncke et al., 2006; Smith et al., 2009; & Wolinsky et al., 2006) and aerobic exercise at similar intensities as presented in this study (Barnes et al., 2003; Barnes et al., 2013; Lautenschlager et al., 2008; Masley et al., 2009; Potter & Keeling, 2005; & Zoeller, 2010). This, similar to the CAN-AER-COG group did not support the hypothesis that this type of training would produce synergistic increases observed in measures of cognitive function. Yet, like the CAN-AER-COG group the results suggest that there may

be other factors responsible for the lack of substantial and significant increases. Perhaps, the results of the combined training suggest a neurological conflict of sorts which, like the equivalent CAN-AER-COG group, may have played a role in the lack of ability of the brain to appropriate the amount of processing capabilities between two difficult tasks.

Cognitive and Flexibility Training (CAN-COG)

The results of this study for the CAN-COG group do not fully corroborate with other studies that have shown increases in aspects of cognitive function with multiple interventions consisting of various populations (Ball et al., 2007; Cherrier et al., 2013; Ferguson et al., 2007b; Hassler et al., 2010; Kawashima, 2013; Kesler et al., 2013; Mahncke et al., 2006; Smith et al., 2009; & Wolinsky et al., 2006). It was hypothesized that cognitive training would elicit increases in cognitive function, yet the CAN-COG group showed no significant increases in any measure of cognitive function. A few reasons to explain the lack of juxtaposition between the specifically designed training software and the outcomes observed may be (A) the level of difficulty was consistently high and may not be entirely appropriate for those who are undergoing treatment for cancer, (B) the type of games may not have been engaging or stimulating enough to encourage full cognitive involvement from the participants, or (C) the software itself fails to accurately train cognitive processes that its designers suggested it would.

A factor that should be considered, but was excluded from this evaluation because of low sample size and a wide variety of completed education levels, was how education played a role as a covariate in these analyses. Although insignificant, LMI scaled, LMII DR raw, COWAT gender, age, and education all increased (20%, 19%, 156%, 574%, 60%, respectively) from pre to post. TMT-B reaction time to completion also decreased

(-26%). These results may suggest that cognitive training, especially in this population does have a place with regards to the reduction of CRCI; however, it would appear that the training itself may have been far too difficult for those who were undergoing treatment for cancer, and potentially the NC-CON group as well.

Psychosocial measures of Beck depression significantly (pre 8.2 ± 1.8 vs. post 3.4 ± 1.5, $p < 0.05$) decreased (-59%) and QOL significantly (pre 22.1 ± 1.5 vs. post 23.5 ± 1.5, $p < 0.05$) increased (6%). All measures of Piper fatigue (index, behavioral, affective, sensory, and cognitive) also decreased (-52%, -49%, -23%, -38%, -32%, respectively), which may actually be attributable to the flexibility component of this intervention. The results do not suggest that the cognitive training alone using NeuroActive® software was responsible for the results observed for this group. Again, anecdotally, multiple participants who were in this group reported that they felt like the tasks were far too difficult to process while undergoing treatment. Participants also mentioned that they often times felt overwhelmed and frustrated by the complexity of the tasks, which many times resulted in a tearful participant.

Summary

Taken together, it appears that for the purpose of this study that aerobic training at an often self-reported (RPE) moderate intensity was the most effective intervention to increase measures of cognitive function, flexibility, VO_{2peak}, and QOL, and reduce fatigue and depression in cancer survivors.

Conclusion

To our knowledge, there have been no studies examining the effects of a combined cognitive and aerobic training intervention on cognitive function in cancer

survivors, specifically, a majority of those undergoing treatment. Although results of this current study failed to show significant differences between each of the training groups in cognitive, physiological, or psychosocial function, there are five important outcomes that were observed.

First, it is imperative that cognitive and aerobic training at a moderate intensity not be overlooked with regards to CRCI reduction methodologies. For the CAN-AER-COG group, there were no significant increases observed in measures of cognitive function, yet there were observed pre-to-post increases observed among each of the individual treatment groups, with the exception of controls. This may imply that combined training of this nature may be too demanding for the individual to do well at both cognitive and aerobic training, simultaneously.

Second, among individual treatment groups, 30 minutes of aerobic cycling at an often self-reported (RPE) moderate intensity was observed to produce the overall greatest number of pre-to-post increases in measures of cognitive, physiological, and psychosocial function. For those who are working with cancer survivors in a rehabilitative setting, these results should further reinforce the importance of this type of activity during training. Specifically, those following intensity-based programming can readily follow the aerobic training conducted in this study. Intensities that were mostly tolerable for those undergoing treatment are adaptable in cases where side effects of treatment overwhelmed the client (e.g., fatigue, depression, nausea, diarrhea). Upon occurrence, the reduction of revolutions per minute or resistance applied to the flywheel of the ergometer, may be appropriately substituted with RPE. In addition, for emerging rehabilitation

programs, a cycle ergometer is a cost-effective, durable apparatus that should not be excluded when developing a program.

Third, 30 minutes of flexibility training as detailed in this investigation should also not be overlooked. During the development of this project, it was thought that flexibility training would serve as an ethically appropriate control group that would not force our lab to require cancer survivors to be subjected to the "wait list." Results obtained following this intervention that verbal measurements of cognitive function, VO_{2peak}, Sit and Reach, all Piper fatigue scores, Beck depression scores, and QOL all improved were unexpected. Although the mechanisms are not currently known, flexibility training as presented in this investigation should (A) be further investigated to identify mechanisms of action, (B) be incorporated to a greater extent in cancer rehabilitation, (C) to be considered as a more ethically appropriate control group for studies conducted in cancer survivors as opposed to the "wait list" control group, and (D) investigated further to see if similar results are obtained in other studies.

Fourth, cognitive training alone should be considered when developing cancer rehabilitation programs that are aiming to address CRCI. Multiple studies presented in this investigation have corroborated the efficacy of cognitive training interventions in many different populations, but few have aimed to address CRCI in cancer survivors. It appears that cognitive training using NeuroActive® software may be mild-to-moderately beneficial, but may not be the most appropriate type of cognitive training software for this population. Many anecdotal comments included frustration with the level of difficulty of this program. In addition, the design of the BrainBike® itself with computer

interfaces that are grossly elevated and force participants to be in a constant state of neck extension may have compounded the level of frustration among this sample.

Finally, despite small sample sizes, replacement of missing data, treatment adjustments by subject, and attrition issues this investigation still breaks ground on multiple levels considering the novelty of designing an intervention that is addressing an issue in cancer survivors that is just beginning to come to light from two respected and substantiated intervention methods. This investigation was an attempt to evaluate how these two methods may be best utilized to reduce CRCI, thereby increasing QOL in cancer survivors. These results, although not revolutionary or conclusive, do provide fertile ground for future studies.

Future Research

Research in this field is just surfacing in regards to the effectiveness of cognitive training among the general apparently healthy population and even less in a cancer survivor population. Translational research should be the next avenue of focus to evaluate further how aerobic and cognitive training may best affect volumetric and functional aspects of brain physiology for both animal and human models. Methods such as fMRI, CT scan, and EEG technology should be employed to better elaborate upon possible mechanisms behind changes in measures of cognitive function and the relationship to volumetric alterations in brain tissue.

The least effective intervention was observed to be the CAN-AER-COG group; however, the individual treatment groups produced a myriad of differing but positive increases in cognitive, physiological, and psychosocial function. At this time, it would be unwise to abandon cognitive and aerobic training altogether, but rather modify the levels

of physical and cognitive difficulty. NeuroActive® software was designed to address multiple aspects of cognitive function, but was anecdotally reported to be far too difficult for both CAN and NC participants to do while cycling. It was evident during training that those who were undergoing cancer treatment experienced the greatest amount of difficulty. The next phase of this type of research should be to compare at-home types of cognitive training programs against the results of this study. In addition, the creation of a blocked schedule that would maintain three days a week of aerobic and flexibility training, but incorporate cognitive training between each of the aerobic and flexibility training sessions should be the next logical course of action.

Treatment-related differences in outcomes with cognitive and aerobic training need to be further developed. Our group has also evaluated the effects of cognitive and aerobic training on participants who underwent radiation treatment only. Research has indicated that radiation treatment for cancer may result in cognitive and/or psychosocial deficits similar to those undergoing chemotherapy (Attia, Page, Lesser, & Chan, 2014; Kim et al., 2009; Noal et al., 2011). Therefore, by evaluating response differences between both types of broad treatment groups this may better elucidate methods of rehabilitation that are more focused on the individual needs of the participant.

Finally, dose-related treatment responses to cognitive and aerobic training need to be evaluated. Multiple reports have suggested that with a greater dosage of chemotherapy and/or radiation that aspects cognitive dysfunction become much more apparent Collins, Mackenzie, Tasca, Scherling, & Smith, 2013; Lawrence et al., 2010).

REFERENCES

American Cancer Society. *Cancer Facts & Figures 2014.* Atlanta: American Cancer Society; 2014.

American College of Sports Medicine's guidelines for exercise testing and prescription (8th ed.). (2010). Philadelphia, PA: Lippincott-Williams & Wilkins.

Ahles, T.A., & Saykin, A.J. (2007). Candidate mechanisms for chemotherapy-induced cognitive changes. *Nature, 7,* 192-201. doi:10.1038/nrc2073

Angevaren, M., Aufdemkampe, G., Verhaar, H.J.J., Aleman, A., & Vanhees, L. (2008). Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database of Systematic Reviews, 3,* 1-56. doi: 10.1002/14651858.CD005381.pub3

Attia, A., Page, B.R., Lesser, G.J. & Chan, M. (2014). Treatment of radiation-induced cognitive decline. *Current Treatment Options in Oncology, 15*, 539-550. doi:10.1007/s11864-014-0307-3

Ball, K., Berch, D.B., Helmers, K.F., Jobe, J.B., Leveck, M.D., Mariske, M., … Willis, S.L. (2007). Effects of cognitive training interventions with older adults: a randomized controlled trial. *Journal of the American Medical Association, 288(18),* 2271-2281. doi:10.1001/jama.288.18.2271

Baechle, T.R., & Earle, R.W. (Eds.). (2008). Essentials of Strength Training and Conditioning (3rd Ed.) Human Kinetics: Champaign, IL. ISBN: 978-0-7360-5803-2

Barnes, D.E., Yaffe, K., Satarino, W.A., & Tager, I.B. (2003). A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. *Journal of the American Geriatric Society, 51,* 459-465. doi: 10.1046/j.1532-5415.2003.51153.x

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system: a technical review. *Radiology Nuclear Medicine & Medical Imagining in Biomedicine, 15,* 435-455. doi:10.1002/nbm.782

Belleville, S., Gilbert, B., Fontaine, F., Gagnon, L., Menard, E., & Gauthier, S. (2006). Improvements of episodic memory in persons with mild cognitive impairment and healthy older adults: evidence from a cognitive intervention program. *Dementia and geriatric Cognitive Disorders, 22,* 486-499. doi: 10.1159/000096316

Benson, N., Hulac, D.M., & Kranzler, J.H. (2010). Independent examination of the weschler adult intelligence scale-fourth edition (wais-iv): what does the wais-iv measure? *Psychological Assessment, 22(1),* 121-130. doi:10.1037/a0017767

Bourke, R.S., West, C.R., Chheda, G., & Tower, D.B. (1973). Kinetics of entry and distribution of 5-fluorouracil in cerebrospinal fluid and brain following intravenous injection in a primate. *Cancer Research, 33,* 1735-1746.

British Psychological Society. *Psychological Testing Center:Test Review, 2012.*Leicester: The British Psychological Society; 2014.

Butterfield, D.A., & Kanski, J. (2001). Brain protein oxidation in age-related neurodegenerative disorders that are associated with aggregated proteins. *Mechanisms of Aging and Development, 122,* 945-962. doi:10.1016/S0047-6374(01)00249-4

Carlsson, M., Strang, P., & Bjurstrom, C. (2000). Treatment modality affects long-term QOL in gynaecological cancer. *Anti-cancer Research, 20,* 563-568.

Chang, Y., Chu, C., Wang, C., Wang, Y., Song, T., Tsai, C., … Etnier, J.L. (2015). Dose-response relation between exercise duration and cognition. *Medicine & Science in Sports and Exercise, 47(1),* 159-165. doi:10.1249/MSS.0000000000000383

Cherrier, M.M., Anderson, K., David, D., Higano, C.S., Gray, H., Church, A., …Willis, S.L. (2013). A randomized trial of cognitive rehabilitation in cancer survivors. *Journal of Life Sciences, 93,* 617-622. doi:10.1016/j.lfs.2013.08.011

Collins, B., MacKenzie, J., Tasca, G.A., Scherling, C., & Smith, A. (2013). Cognitive effects of chemotherapy in breast cancer patients: a dose-response study. *Psycho-oncology, 22,* 1517-1527. doi:10.1002/pon.3163

Conover, W.J. (1999). *Practical nonparametric statistics* (3rd. Ed.). New York, NY: John Wiley & Sons, Inc.

Culos-Reed, S.N., Mackenzie, M.J., Sohl, S.J., Jesse, M.T., Zahavich, A.N.R., & Danhauer, S.C. (2012). Yoga and cancer interventions: a review of the clinical significance of patient reported outcomes for cancer survivors. *Evidence-Based Complementary and Alternative Medicine, ID:642576,*1-17. doi:10.1155/2012/642576

Deprez, S., Amant, F., Yigit, R., Porke, K., Verhoeven, J., Van den Stock, J., … Sunaert, S. (2011). Chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning in breast cancer patients. *Human Brain Mapping, 32,* 480-493. doi: 10.1002/hbm.21033

Elliot, A.C., & Hynan, L.S. (2011). A sas micro implementation of a multiple comparison post hoc test for a Kruskal-Wallis analysis. *Computer Methods and Programming in Biomedicine, 102,* 75-80. doi:10.1016/j.cmpb.2010.11.002

Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., …Kraemer, A.F. (2011). Exercise training increases size of hippocampus and improves memory. *Procedings of the National Academy of Sciences of the United States, 108(7),* 3017-3022. doi:10.1073/pnas.1015950108

Fairey, A.S., Courneya, K.S., Field, C.J., Bell, G.J., Jones, L.W., St. Martin, B., & Mackey, J.R. (2005). Effect of exercise training on c-reactive protein in post-menopausal breast cancer survivors: a randomized controlled trial. *Brain, Behavior, and Immunity, 19(5),* 381-388. doi:10.1016/j.bbi.2005.04.001

Ferguson, R.J., Ahles, T.A., Saykin, A.J., McDonald, B.C., Furstenburg, C.T., Cole, B.F., & Mott, L.A. (2007a). Cognitive-behavioral management of chemotherapy-related cognitive change. *Psycho-Oncology, 16,* 772-777. doi:10.1002/pon.1133

Ferguson, R.J., McDonald, B.C., Saykin, A.J., & Ahles, T.A. (2007b). Brain structure and function differences in monozygotic twins: possible effects of breast cancer chemotherapy. *Journal of Clinical Oncology, 25(25),* 3866-3870. doi: 10.1002/pon.1133

Ferguson, R.J., Cassel, A.G., & Dawson, R.F.S. (2010). Cognitive effects of cancer chemotherapy in adult cancer survivors: cognitive-behavioral management. *Journal of Rational-Emotive Cognitive-Behavioral Therapy, 28(1),* 25-41. doi: 10.1007/s10942-010-0108-y

Ferrans, C.E. (2010). Advances in measuring quality of life outcomes in cancer care. *Seminars in Oncology Nursing, 26(1),* 2-11. doi:10.1016/j.soncn.2009.11.002

Ferrans, C.E., & Powers, M.J. (1985). Quality of life index: development and psychometric properties. *Advances in Nursing Science, 8(1),* 15-24.

Finsterer, J. & Mahjoub, S.Z. (2014). Fatigue in healthy and diseased individuals. *American Journal of Hospice & Palliative Medicine, 31(5),* 562-575. doi:10.1177/1049909113494748

Foley, J.J., Raffa, R.B., & Walker, E.A. (2008). Effects of chemotherapeutic agents 5-fluorouracil and methotrexate alone and combined in a mouse model of learning and memory. *Psychopharmacology*, *199,* 527-538. doi: 10.1007/s00213-008-1175-y

Fong, D.Y.T., Ho, J.W.C., Hui, B.P.H., Lee, A.M., Macfarlane, D.J., Leung, S.S.K., … Cheng, K. (2012). Physical activity for cancer survivors: meta-analysis of randomized controlled trials. *British Medical Journal, 344(70)*, 1-14. doi: 10.1136/bmj.e70

Foster, P.S., Drago, V., Yung, R.C., Pearson, J., Stringer, K., Giovanneti, T., …Heilman, K.M. (2013). Differential lexical and semantic spreading activation in alzheimer's disease. *American Journal of Alzheimer's Disease & Other Dementias, 28(5),* 501-507. doi:10.1177/1533317513494445

Glass, G.V., & Hopkins, K.D. (1996). *Statistical methods in education and psychology* (3rd Ed.). Needham Heights, MA: Allyn and Bacon.

Han, R., Yang, Y.M., Dietrich, J., Luebke, A., Mayer-Proschel, M., & Noble, M. (2008). Systemic 5-fluorouracil treatment causes a syndrome of delayed myelin destruction in the central nervous system. *Journal of Biology, 7(12),* 1-22. doi: 10.1186/jbiol69

Hariprasad, V.R., Koparde, V., Sivakumar, P.T., Varambally, S., Thirthalli, J., Varghese, M., …Gangadhar, B.N. (2013). Randomized clinical trial of yoga-based intervention in residents from elderly homes: effects on cognitive function. *Indian Journal of Psychiatry, 55,* 357-363. doi:10.4103/0019-5545.116308

Hassler, M.R., Elandt, K., Preusser, M., Lehrner, J., Binder, P., & Dieckmann, K., … Marosi, C. (2010). Neurocognitive training in patients with high grade glioma: a pilot study. *Journal of Neurooncology, 97,* 109-115. doi: 10.1007/s11060-009-0006-2

Hess, L.M., & Insel, K.C. (2007). Chemotherapy-related change in cognitive function: a conceptual model. *Oncology Nursing Forum, 34(5),* 981-994. doi:10.1188/07.ONF.981-994

Heyward, V. (2006). *Advanced fitness assessment and exercise prescription* (5th Ed.). Champaign, IL: Human Kinetics.

Hillman, C.H., Pontifex, M.B., Raine, L.B., Castelli, D.M., Hall, E.E., & Kramer, A.F. (2009). The effect of acute treadmill walking on cognitive control and academic achievement in preadolescent children. *Neuroscience,* 159(3); 1044-1054. doi: 10.1016/j.neuroscience.2009.01.057

Hillman, C.H., Motl, R.W., Pontifex, M.B., Posthuma, D., Stubbe, J.H., Boomsma, D.I., & DeGeus, E.J.C. (2006). Physical activity and cognitive function in a cross section of younger and older community-dwelling individuals. *Health Psychology, 25(6),* 678-687. doi:10.1037/0278-6133.25.6.678

Hsieh, C., Sprod, L.K., Hydock, D.S., Carter, S.D., Hayward, R., & Schneider, C.M. (2008). Effects of a supervised exercise intervention on recovery from treatment regimens in breast cancer survivors. *Oncology Nursing Forum, 35(6),* 909-915. doi: 10.1188/08.ONF.909-915

Inagaki, M., Yoshikawa, E., Matsuoka, Y., Sugawara, Y., Nakano, T., Akechi, T., …Wada, N. (2007). Smaller regional volumes of brain gray and white matter demonstrated in breast cancer survivors exposed to adjuvant chemotherapy. *Cancer, 109,* 146-156. doi:10.1002/cncr.22368

Jackson, G.E. (2008). Chemo brain: a psychotropic phenomenon? *Medical Hypotheses, 70,* 572-577. doi: 10.1016/j.mehy.2007.06.019

Jacobson, L. A., Ryan, M., Martin, R. B., Ewen, J., Mostofsky, S. H., Denckla, M. B., & Mahone, E. M. (2011). Working memory influences processing speed and reading fluency in ADHD. *Child Neuropsychology*, *17*, 209-224.

Jemal, A., Bray, F., Center, M.M., Ferlay, J., Ward, E., & Forman, D. (2011). Global cancer statistics. *Cancer: A Cancer Journal for Clinicians, 61(2),* 69-90. doi:10.3322/caac.20107

Joshi, G., Sultana, R., Tangpong, J., Cole, M.P., St. Clair, D.K., Vore, M., …Butterfield, D.A. (2005). Free radical medicated oxidative stress and toxic side effects in brain induced by the anti-cancer drug adriamycin: insight into chemobrain. *Free Radical Research, 39(11),* 1147-1154. doi:10.1080/10715760500143478

Kawashima, R. (2013). Mental exercises for cognitive function: clinical evidence. *Journal of Preventative Medicine & Public Health, 46,* 22-27. doi:10.3961/jpmph.2013.46.S.S22

Kerr, I.G., Zimm, S., Collins, J.M., O'Neill, D., & Poplack, D.G. (1984). Effect of intravenous dose and schedule on cerebrospinal fluid pharmacokinetics of 5-FU in the monkey. *Cancer Research. 44,* 4929-4932.

Kessler, S., Hosseini, S.M.H., Heckler, C., Janelsins, M., Palesh, O., Mustian, K., …Morrow, G. (2013). Cognitive training for improving executive function in chemotherapy-treated breast cancer survivors. *Clinical Breast Cancer, 13(4),* 299-306. doi:10.1016/j.clbc.2013.02.004

Kim, E., Jahan, T., Aouizerat, B., Dodd, M., Cooper, B., Paul, S., …Miaskowski, C. (2009). Changes in symptom clusters in patients undergoing radiation therapy. *Support Care Cancer, 17*, 1383-1391. doi: 10.1007/s00520-009-0595-5

Kohler, B.A., Ward, E., McCarthy, B.J., Schymura, M.J., Ries, L.A.G, & Eheman, C. et al. (2011). Annual report to the nation on the status of cancer, 1975-2007, featuring tumors of the brain and other nervous system. *Journal of National Cancer Institute, 103,* 1-23. doi:10.1093/jnci/djr077

Konat, G.W., Kraszpulski, M., James, I., Zhang, H.T., & Abraham, J. (2008). Cognitive dysfunction induced by chronic administration of common cancer chemotherapeutics in rats. *Metabolic Brain Disease, 23,* 325-333. doi: 10.1007/s11011-008-9100-y

La Rue, A. (2010). Healthy brain aging: role of cognitive reserve, cognitive stimulation and cognitive exercises. In A.K. Desai (Ed.), The healthy aging brain: evidence based methods to preserve brain function and prevent dementia. *Clinics in Geriatric Medicine, 26,* 99-111.

Lautenschlager, N.T., Cox, K.L., Flicker, L., Foster, J., Bockxmeer, F.M.V., & Xiao, J. et al. (2008). Effect of physical activity on cognitive function in older adults at risk for alzheimer's disease. *Journal of the American Medical Association, 300(9),* 1027-1038. doi:10.1001/jama.300.9.1027

Lawrence, Y.R., Li, A., Naqa, I.E., Hahn, C.A., Marks, L.B., …Dicker, A.P. (2010). Radiation dose-volume effects in the brain. *International Journal of Radiation Oncology, Biology, and Physics, 76(3),* 20-27. doi:10.1016/j.ijrobp.2009.02.091

Lee, S.Y., Loh, S.Y., & Murray, L. (2011). Study protocol in investigate the efficacy of participation in qi-gong by breast cancer survivors. *Journal of Cancer Therapy, 2,* 715-724. doi:10.4236/jct.2011.25097

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological assessment* (5th ed.). New York, NY: Oxford University Press.

Liedke, P. E. R., Reolon, G.K., Kilpp, B., Brunetto, A. L., Roesler, R., & Schwartsmann, G. (2009). Systemic administration of doxorubicin impairs aversively motivated memory in rats. *Pharmacology, Biochemistry, and Behavior, 94,* 239-243. doi: 10.1016/j.pbb.2009.09.001

Macleod, J.E., DeLeo, J.A., Hickey, W.F., Ahles, T.A., Saykin, A.J., & Bucci, D.J. (2007). Cancer chemotherapy impairs contextual but not cue-specific fear memory. *Behavioral Brain Research. 181(1),* 168-172. doi:10.1016/j.bbr.2007.04.003

Madhyastha, S., Somayaji, S.N., Rao, M.S., Nalini, M.S., & Laxminarayana-Bairy, K. (2002). Hippocampal brain amines in methotrexate-induced learning and memory deficit. *Canadian Journal of Pharmacology, 80,* 1076-1084. doi:10.1016/j.bbr.2007.04.003

Mahncke, H.W., Bronstone, A., & Merzenich, M.M. (2006). Brain plasticity and functional losses in the aged: scientific bases for a novel intervention. *Progress in Brain Research, 157,* 81-109. doi:10.1016/S0079-6123(06)57006-2

Mahncke, H.W., Connor, B.B., Appelman, J., Asanuddin, O.N., Hardy, J., & Wood, R.A., et al., (2006). Memory enhancement in healthy older adults using a brain plasticity-based training program: a randomized, controlled study. *Proceedings of the National Academy of Sciences, 103(33),* 12523-12528. doi:10.1073/pnas.0605194103

Marieb, E.N., & Mallatt, J. (1997). *Human anatomy.* (2nd Ed.). Menlo Park, CA: Benjamin Cummings.

Masley, S., Roetzheim, R., & Gualtieri, T. (2009). Aerobic exercise enhances cognitive flexibility. *Journal of Clinical Psychology in Medical Settings, 16,* 186-193. doi:10.1007/s10880-009-9159-6

Matsuda, T., Takayama, T., Tashiro, M., Nakamura, Y., Ohashi, Y., & Shimozuma, K. (2005). Mild cognitive impairment after adjuvant chemotherapy in breast cancer patients: evaluation of appropriate research design and methodology to measure symptoms. *Breast Cancer. 12(4),* 279-287. doi:10.2325/jbcs.12.279

McAfoose, J., & Baune, B.T. (2009). Evidence for a cytokine model of cognitive function. *Neuroscience and Biobehavioral Reviews, 33(3),* 355-366. doi:10.1016/j.neubiorev.2008.10.005

Mitchell, T. & Turton, P. (2011). 'Chemobrain': concentration and memory effects in people receiving chemotherapy- a descriptive phenomenological study. *European Journal of Cancer Care, 20,* 539-548. doi: 10.1111/j.1365-2354.2011.01244.x

Morris, R.G., Garrud, P., Rawlins, J.N., & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature*, *297,* 681- 683.

Mustafa, S., Walker, A., Bennett, G., & Wigmore, P.M. (2008). 5-fluorouracil chemotherapy affects spatial working memory and newborn neurons in the adult rat hippocampus. *European Journal of Neuroscience. 28,* 323-330. doi: 10.1111/j.1460-9568.2008.06325.x

Myers, J.S. (2009). Chemotherapy-related cognitive impairment: neuroimaging, neuropsychological testing, and the neuropsychologist. *Clinical Journal of Oncology Nursing. 13(4)*, 413-421. doi:10.1188/09.CJON.413-421

Noal, S., Levy, C., Hardouin, A., Rieux, C., Heutte, N., Segura, C.,… Joly, F. (2011). One-year longitudinal study of fatigue, cognitive functions, and quality of life after adjuvant radiotherapy for breast cancer. *Int. J. Radiation Oncology Biol. Phys., 81*(3), 795-803. doi: 10.1016/j.ijrobp.2010.06.037

Parisi, J.M., Stine-Morrow, E.A.L., Noh, S.R., & Morrow, D.G. (2009). Predispositional engagement, activity engagement, and cognition among older adults. *Aging, Neuropsychology, and Cognition, 16(4),* 485-504. doi:10.1080/13825580902866653

Park, S.K., & Larson, J.L. (2015). Cognitive function as measured by trail making test in patients with copd. *Western Journal of Nursing Research, 37(2),* 236-256. doi:10.1177/0193945914530520

Piper, B. F., Dibble, S.L., Dodd, M. J., Weiss, M. C., Slaughter, R.E., & Paul, S.M. (1998). The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. *Oncology Nursing Forum, 25*, 677-684. pmid:9599351

Peterson, B.M., Repka, C.P., Hayward, R., & Schneider, C.M. (2010). Five-year survival rates at an exercise based cancer rehabilitation institute. *Medicine Science in Sports and Exercise, 42(5),* 345. doi:10.1249/01.MSS.0000384626.61126.ea

Potter, D., & Keeling, D. (2005). Effects of moderate exercise and circadian rhythms on human memory. *Journal of Sport and Exercise Psychology, 27(1),* 117-125.

Raffa, R.B. (2011). A proposed mechanism for chemotherapy-related cognitive impairment (‘chemo-fog’). *Journal of Clinical Pharmacy and Therapeutics, 36,* 257-259. doi: 10.1111/j.1365-2710.2010.01188.x

Raffa, R.B., & Tallarida, R.J. (2010). Effects on the visual system might contribute to some of the cognitive deficits of cancer chemotherapy-induced "chemo-fog." *Journal of Clinical Pharmacy and Therapeutics, 35,* 249-255. doi: 10.1111/j.1365-2710.2009.01086.x

Roine, E., Roine, R.P., Rasanen, P., Vuori, I., Sintonen, H., & Saarto, T. (2009). Cost-effectiveness of interventions based on physical exercise in the treatment of various diseases: a systematic literature review. *International Journal of Technology Assessment in Health Care, 25(4),* 427-454. doi:10.1017/S0266462309990353

Salkind, M. R. (1969). Beck depression inventory in general practice. *Journal of the Royal College of General Practice, 18(88),* 267-271. pmcid: PMC2237076

Saykin, A.J., Ahles, T.A., & McDonald, B.C. (2003). Mechanisms of chemotherapy induced cognitive disorders: neuropsychological, pathophysiological, and neuroimaging perspectives. *Seminars in Clinical Neuropsychiatry. 8(4),* 201-216. pmid:14613048

Schilling, V., Jenkins, V., Morris, R., Deutsh, G., & Bloomfield, D. (2005). The effects of adjuvant chemotherapy on cognition in women with breast cancer- preliminary results of an observational longitudinal study. *Breast, 14(2),* 142-150. doi:10.1016/j.breast.2004.10.004

Schneider, C.M., Hsieh, C.C., Sprod, L.K., Carter, S.D., & Hayward, R. (2007a). Cancer treatment-induced alterations in muscular fitness and quality of life: the role of exercise training. *Annals of Oncology, 18,* 1957-1962. doi:10.1093/annonc/mdm364

Schneider, C.M., Hsieh, C.C., Sprod, L.K., Carter, S.D., & Hayward, R. (2007b). Exercise training manages cardiopulmonary function and fatigue during and following cancer treatment in male survivors. *Integrative Cancer Therapies, 6(3),* 235-241. doi: 10.1177/1534735407305871

Schneider, C.M., Hsieh, C.C., Sprod, L.K., Carter, S.D., & Hayward, R. (2007c). Effects of supervised exercise training on cardiopulmonary function and fatigue in breast cancer survivors during and after treatment. *Cancer, 110(4),* 918-925. doi: 10.1002/cncr.22862

Segal, R.J., Reid, R.D., Courneya, K.S., Sigal, R.J., Kenny, G.P., Prud'Homme, D.G., … D'Angelo, M.E.S. (2009). Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *Journal of Clinical Oncology, 27(3),* 344-351. doi:10.1200/JCO.2007.15.4963

Segal, R.J., Reid, R.D., Courneya, K.S., Malone, S.C., Parliament, M.B., Scott, C.G., … Wells, G.A. (2003). Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *Journal of Clinical Oncology, 21(9),* 1653-1659. doi: 10.1200/JCO.2003.09.534

Siegel, R., Naishadham, D., & Jemal, A. (2013). Cancer statistics, 2013. *Cancer Journal for Clinicians, 63,* 11-30. doi: 10.3322/caac.21166

Silverman, D.H.S., Dy, C.J, Castellon, S.A., Lai, J., Pio, B.S., Abraham, L., …Ganz, P.A. (2007). Altered frontocortical, cerebellar, and basal ganglia activity in adjuvant-treated breast cancer survivors 5-10 years after chemotherapy. *Breast Cancer Research Treatment, 103,* 303-311. doi:10.1007/s10549-006-9380-z

Smith, G.E., Housen, P., Yaffe, K., Ruff, R., Kennison, R.F., Mahncke, H.W., & Zelinski, E.M. (2009). A cognitive training program based on the principles of brain plasticity: results from the improvement in memory with plasticity-based adaptive cognitive training (IMPACT) study. *Journal of the American Geriatrics Society, 57(4),* 594-603. doi: 10.1111/j.1532-5415.2008.02167.x

Smith, T.J., & Hillner, B.E. (2011). Bending the cost curve in cancer care. *The New England Journal of Medicine, 364(21),* 2060-2065. pmid:21612477

Staat, K., & Segatore, M. (2005). The phenomenon of chemo brain. *Clinical Journal of Oncology Nursing, 9(6),* 713-721. doi:10.1188/05.CJON.713-721

Van Dam, F.S.A.M, Schagen, S.B., Muller, M.J., Boogerd, W., Van Der Wall, E., Droogleever-Fortuyn, M.J., & Rodenhuis, S. (1998). Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. *Journal of the National Cancer Institute, 90(3),* 210-218. doi: 10.1093/jnci/90.3.210

Van Der Kooy, D., Zito, K.A., & Roberts, D.C.S. (1985). Evidence of retrograde neurotoxicity of doxorubicin. *Neuroscience Letters, 53,* 215-219. doi:10.1016/0304-3940(85)90188-0

Van Weert, E., May, A.M., Korstjens, I., Post, W.J., Van der Schans, C.P., Van den Borne, B., … Hoekstra-Weebers, J.E.H.M. (2010). Cancer-related fatigue and rehabilitation: a randomized controlled multi-center trial comparing physical training combined with cognitive-behavioral therapy with physical training only and with no intervention. *Physical Therapy, 90(10),* 1413-1425. doi:10.2522/ptj.20090212

Vincent, W.J. (2005). *Statistics in Kinesiology.* (3rd Ed.). Champaign, IL: Human Kinetics.

Yeh, M.L., Lee, T.I., Chen, H.H., & Chao, T.Y. (2006). The influences of chan-chuang qi-gong therapy on complete blood cell counts in breast cancer patients treated with chemotherapy. *Journal of Cancer Nursing, 29(2),* 149-155.

Wallace, G.L., Lee, N.R., Prom-Wormley, E.C., Medland, S.E., Lenroot, R.K., Clasen, L.S., … Giedd, J.N. (2010). A bivariate twin study of regional brain volumes and verbal and nonverbal intellectual skills during childhood and adolescence. *Behavioral Genetics, 40,* 125-134. doi:10.1007/s10519-009-9329-1

Ward, C.L., Bergman, M.A., & Hebert, K.R. (2012). Wais-iv subtest covariance structure: conceptual and statistical considerations. *Psychological Assessment, 24(2),* 328-340. doi:10.1037/a0025614

Wefel, J.S., Lenzi, R., Theriault, R.L., Davis, R.N., & Meyers, C.A. (2004). The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. *Cancer, 100(11),* 2292-2299. doi: 10.1002/cncr.20272

Wefel, J.S., Saleeba, A.K., Buzdar, A.U., & Meyers, C.A. (2010). Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. *Cancer, 116,* 3348-3356. doi:10.1002/cncr.25098

Winocur, G., Vardy, J., Binns, M.A., Kerr, L., & Tannock, I. (2006). The effects of anti-cancer drugs, methotrexate and 5-fluorouracil, on cognitive function in mice. *Pharmacology, Biochemistry, and Behavior, 85,* 66-75. doi:10.1016/j.pbb.2006.07.010

Wolinsky, F.D., Unverzagt, F.W., Smith, D.M., Jones, R., Stoddard, A., & Tennstedt, S.L. (2006). The ACTIVE cognitive training trial and health-related quality of life: protection that lasts for 5 years. *Journal of Gerontology, 61(12),* 1324-1329.

Wood, R.H., Alvarez-Reyes, R., Maraj, B., Metoyer, K.L., &Welsh, M.A. (1999). Physical fitness, cognitive function, and health-related quality of life in older adults. *Journal of Aging and Physical Activity, 7,* 217-230.

Yoshikawa, E., Matsuoka, Y., Ienagaki, M., Nakano, T., Akechi, T., Kobayakawa, M., …Uchitomi, Y. (2005). No adverse effects of adjuvant chemotherapy on hippocampal volume in Japanese breast cancer survivors. *Breast Cancer Research and Treatment, 92,* 81-84. doi:10.1007/s10549-005-1412-6

Zoeller, R.F. (2010). Exercise and cognitive function: can working out train the brain, too? *American Journal of Lifestyle Medicine, 4(5),* 397-409. doi:10.1177/1559827610374413

APPENDIX A

Informed Consent Form

ROCKY MOUNTAIN
CANCER REHABILITATION INSTITUTE
at the UNIVERSITY *of* NORTHERN COLORADO

Name_____ Date_____

CAROLE M. SCHNEIDER, PH.D.

REID HAYWARD, PH.D.

KURT DALLOW, M.D.

BEN NIGHTHORSE
CAMPBELL CENTER

19TH STREET & 10TH AVENUE

CAMPUS BOX 6

GREELEY, CO 80639

PHONE 970-351-1876

FAX 970-351-1720

INFORMED CONSENT

The RMCRI and the School of Sport and Exercise Science support the practice of protection of human subjects participating in research. The following information is provided for you to decide whether you wish to participate in the present study. You should be aware that even if you agree to participate, you are free to withdraw at any time without affecting opportunities for participation in other projects offered by this department.

This project is involved with the assessment of your cardiovascular endurance, muscular strength and endurance, range of motion, and body composition. Measuring oxygen consumption on a motor-driven treadmill will assess your cardiorespiratory capacity. Assessment of muscular strength and endurance will occur through the use of weights, dumbbells, a handgrip dynamometer, and abdominal crunches. Flexibility and range of motion are measured by an instrument called a goniometer and by the sit-and-reach test. The pulmonary function test requires maximum exhalation into a sterile mouthpiece. Skinfold calipers are used to measure body composition (body fat percentage). Heart rate, blood pressure, height, weight, and circumference measurements are also taken. Forms to be completed include cancer history, medical history, cardiovascular risk profile, lifestyle/activity questionnaire, and fatigue and psychological tests such as depression scales, quality of life, fatigue and cognitive functioning. Blood will be drawn with your permission pre exercise and following your exercise intervention.

Once all of the tests are completed, the results will be analyzed and an exercise prescription written. The expected benefits associated with your participation in this program include information regarding your level of physical fitness and recommended fitness and lifestyle changes necessary to improve the quality of your life.

The project will be under the direction of the RMCRI Director and Clinical Coordinator but other persons will be associated or assist with the data collection. Your participation is solicited, although strictly voluntary. The obtained data may be used in reports or publications but your identity will not be associated with such reports.

This research should not result in physical injury, however, some soreness may occur and some of the fitness tests can be uncomfortable. Additionally, with the blood draws you may feel temporary discomfort. The duration of the discomfort is short. Please give your consent with full knowledge of the nature and purpose of the procedures, the benefits that you may expect, and the discomforts and/or risks which may be encountered. We appreciate your assistance. You will be given a copy of this consent form.

"Participation is voluntary. You may decide not to participate in this study and if you begin participation, you may still decide to stop and withdraw at any time. Your decision will be respected and will not result in loss of benefits to which you are otherwise entitled. Having read the above and having had an opportunity to ask any questions, please sign below if you would like to participate in this research. A copy of this form will be given to you to retain for future reference. If you have any concerns about your selection or treatment as a research participant, please contact the Office of Sponsored Programs, Kepner Hall, University of Northern Colorado Greeley, CO 80639; 970-351-2161".

_____ _____ _____

Signature of Subject Agreeing to Participate — Signature of Researcher — Date

By signing this consent you certify you are at least 18 years of age.

_____ _____

Signature of Physician — Date

9/9/2011

APPENDIX B

Institutional Review Board Approval

Request for IRB Change

Submit this request and all attachments to Sherry May, IRB Administrator, Office of Sponsored Programs, Kepner Hall, Suite #25

UNIVERSITY of NORTHERN COLORADO

e of Original UNC IRB Approval: May 4, 2010

Project Title: Exercise and Physical Therapy Interventions at the Rocky Mountain Cancer Rehabilitation Institute

Lead Investigator
Name: Carole M. Schneider
School: Sport and Exercise Science, RMCRI
Email: carole.schneider@unco.edu
Phone: 970-351-2676

Research Advisor (if applicable)
Name:
School:
Email:
Phone:

On a separate page, describe and provide justification for the changes being proposed. Be concise and specific in describing methodological changes that affect the experience of participants and/or relate to the risks/benefits of participation. Explain why these changes are necessary.

(●) Yes ( ) No The proposed changes in protocol will necessitate changes in documents such as recruitment flyers, consent forms, debriefing forms, or other project-related documents.

Yes ( ) No If yes, copies of the revised documents with changes highlighted are attached to this request.

CERTIFICATION OF LEAD INVESTIGATOR
I certify that information contained in this request is complete and accurate.

Carole M. Schneider 9-8-11
Signature of Lead Investigator Date

CERTIFICATION OF RESEARCH ADVISOR (If Lead Investigator is a Student)
I certify that information contained in this request is complete and accurate.

Signature of Research Advisor Date

Approved by:

Chairperson, Institutional Review Board 9/14/11 Date

SPONSORED PROGRAMS SEP 12 2011

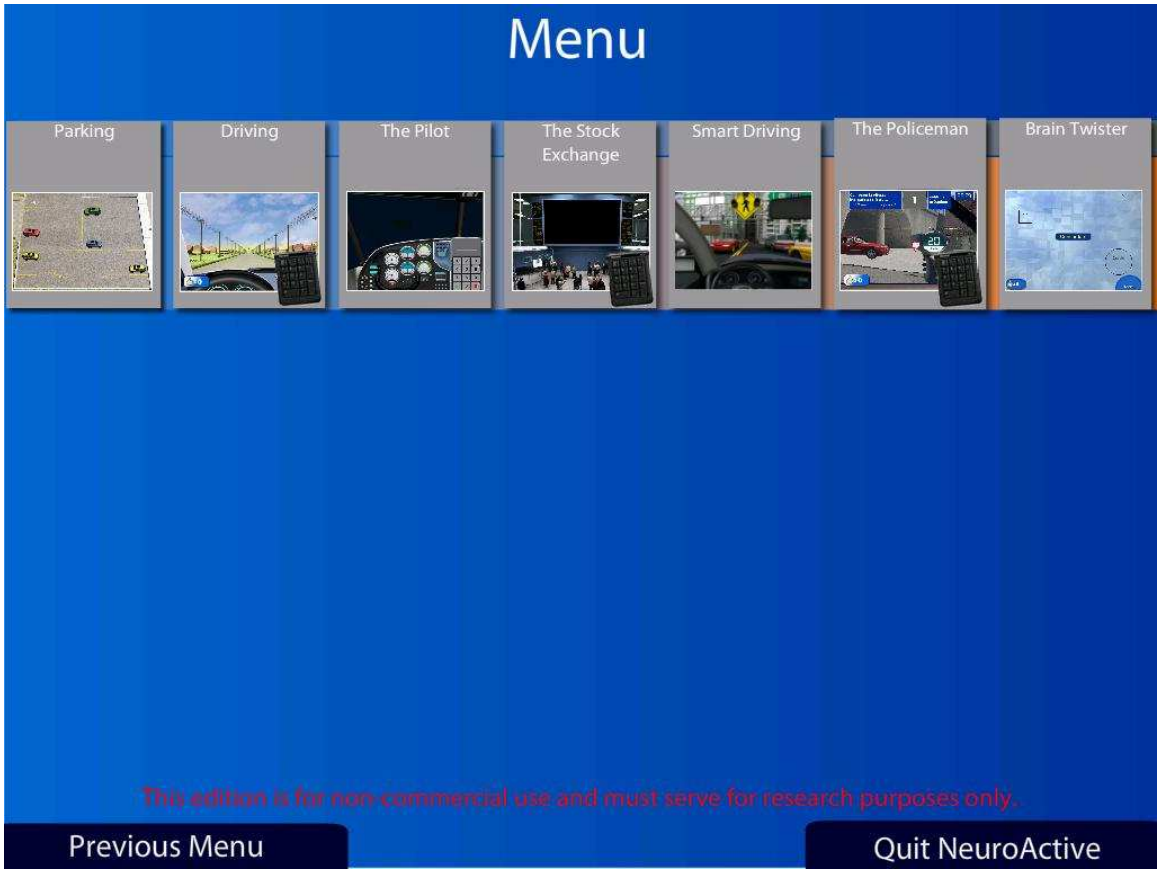
Clear Form

Date Request Received by OSP:

APPENDIX C

Cognitive Training Tasks

Menu


Menu
Parking
Driving
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The Policeman
Brain Twister
This edition is for non-commercial use and must serve for research purposes only.
Previous Menu
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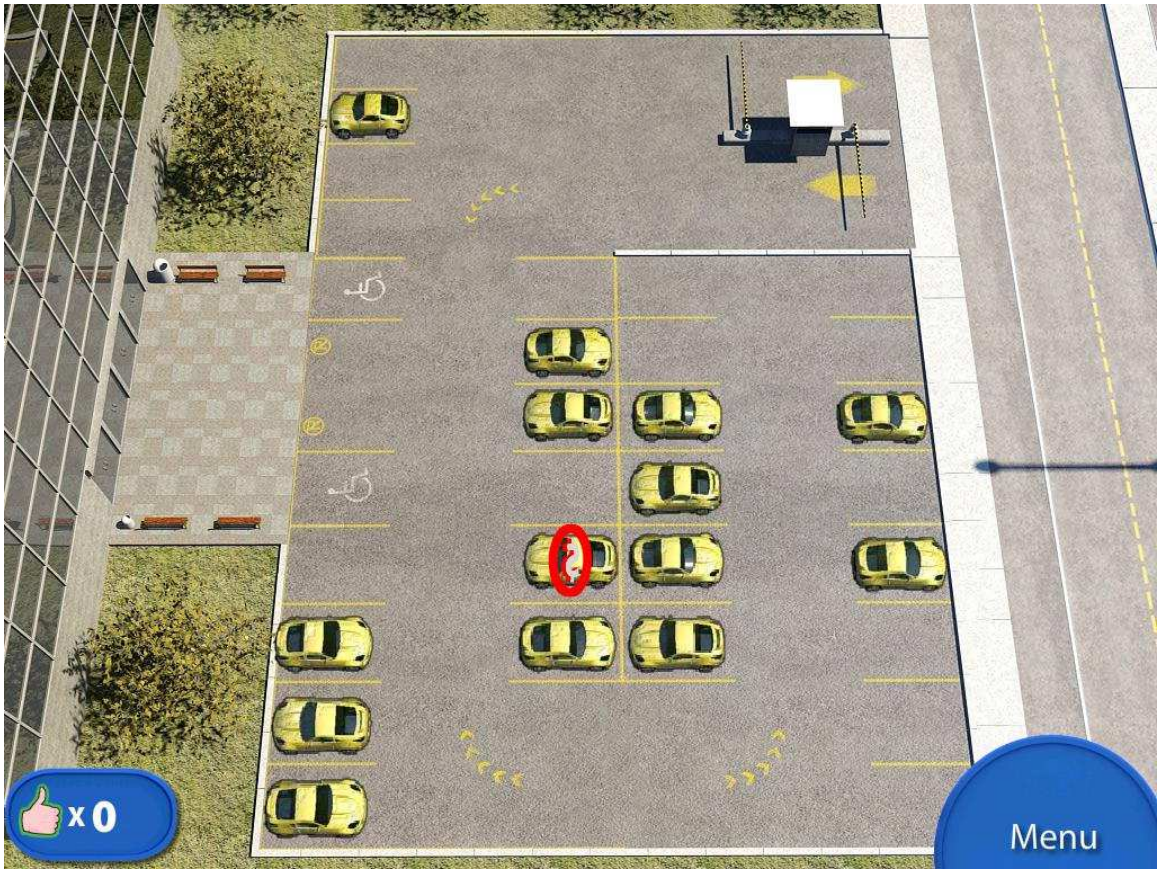
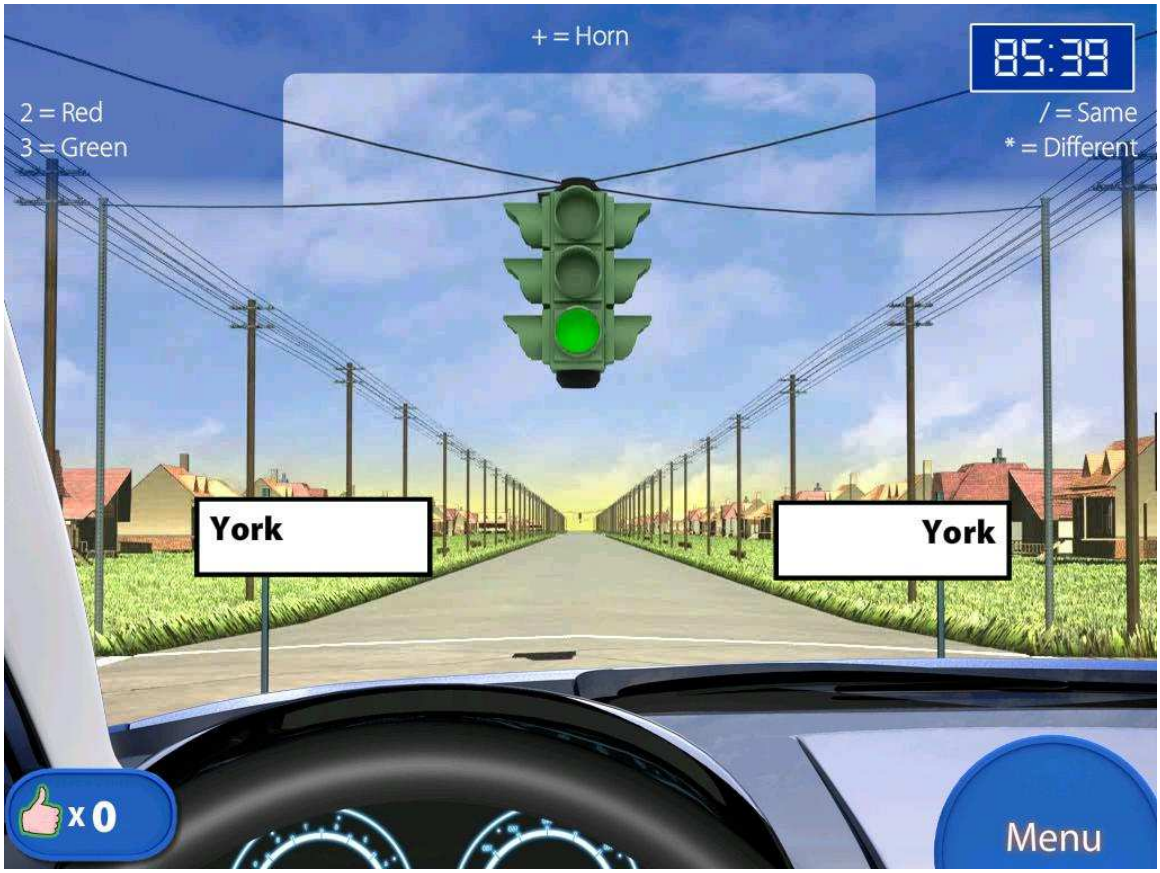
Parking

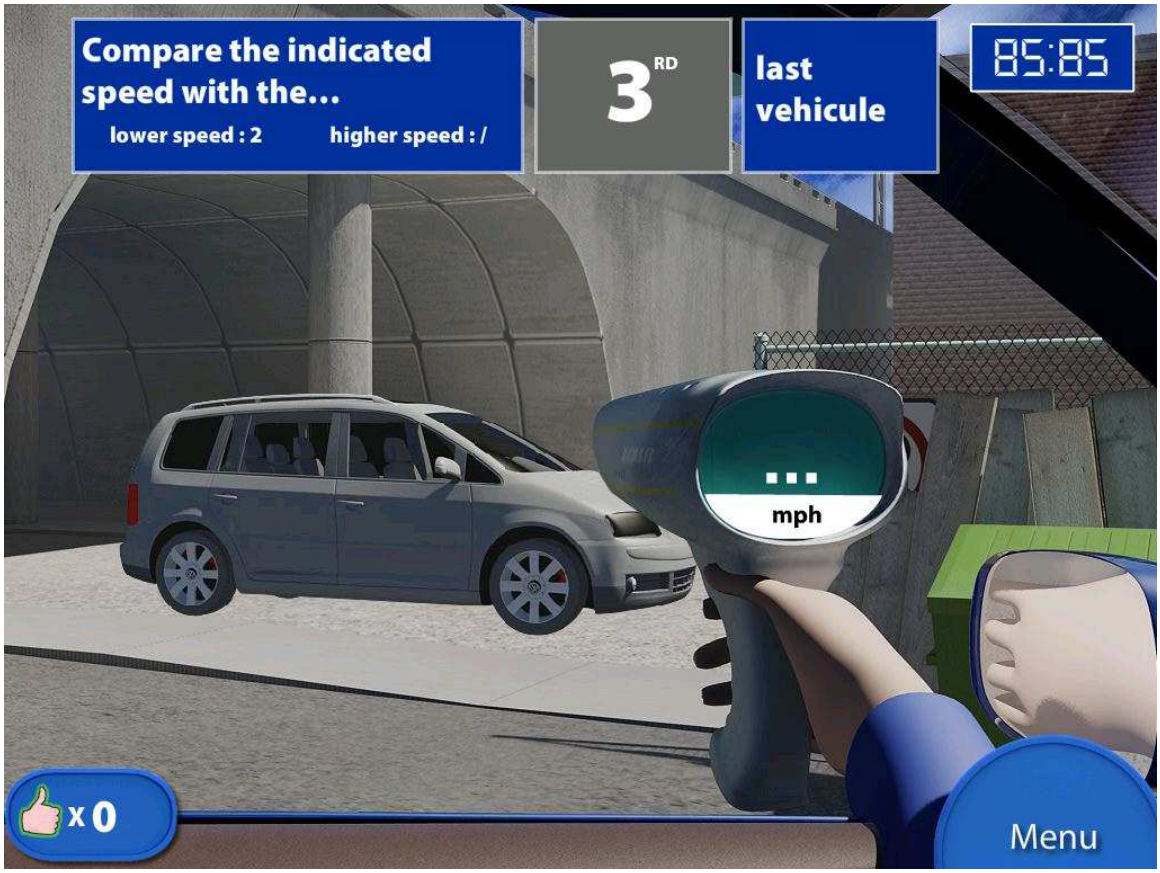


Driving

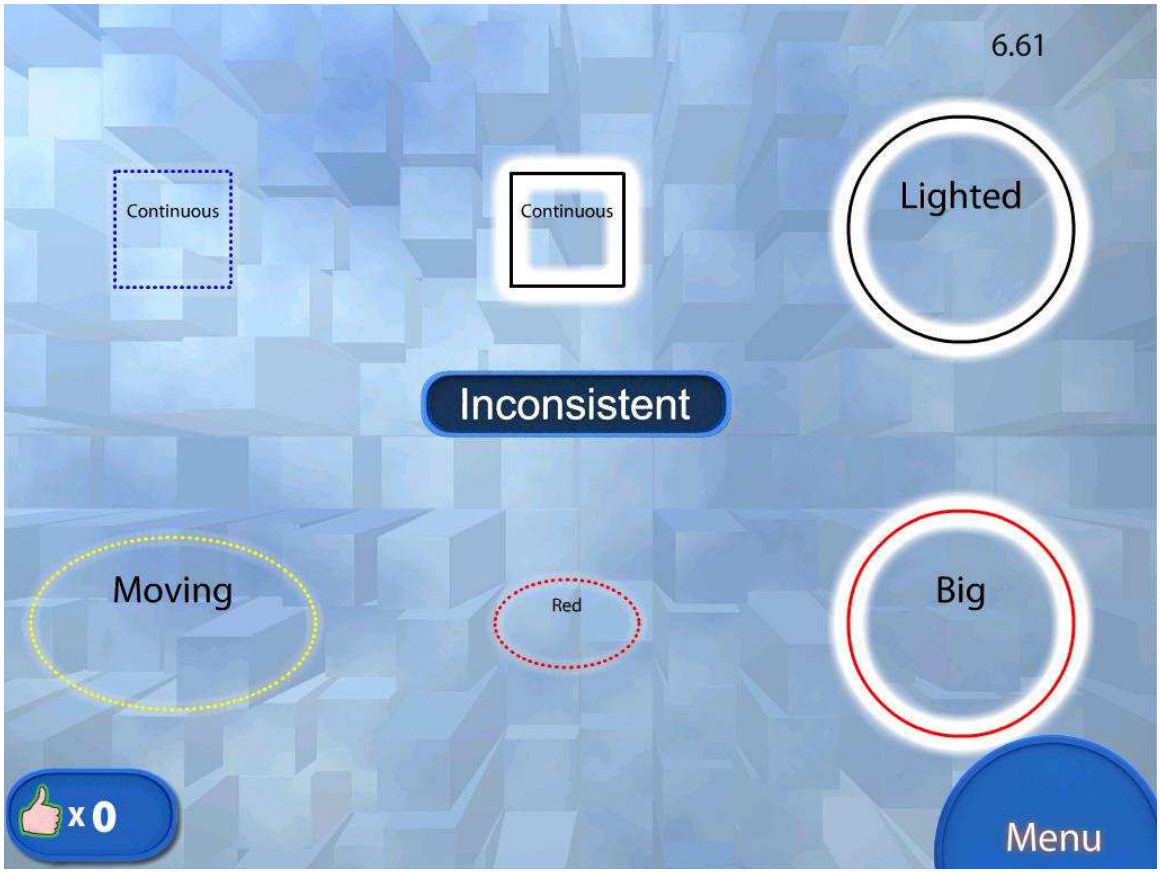


Smart Driving

The Policeman



Brain Twister



The Pilot

The Stock Market

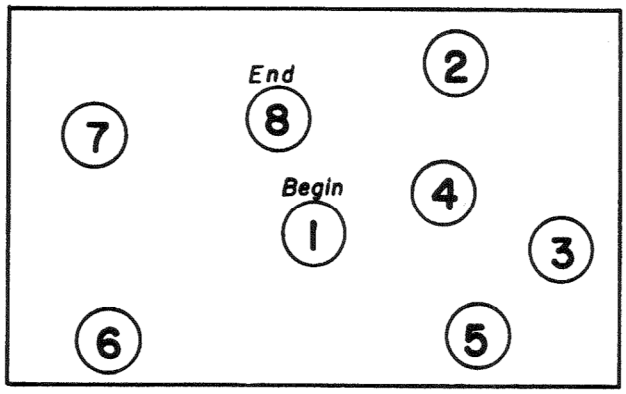
APPENDIX D

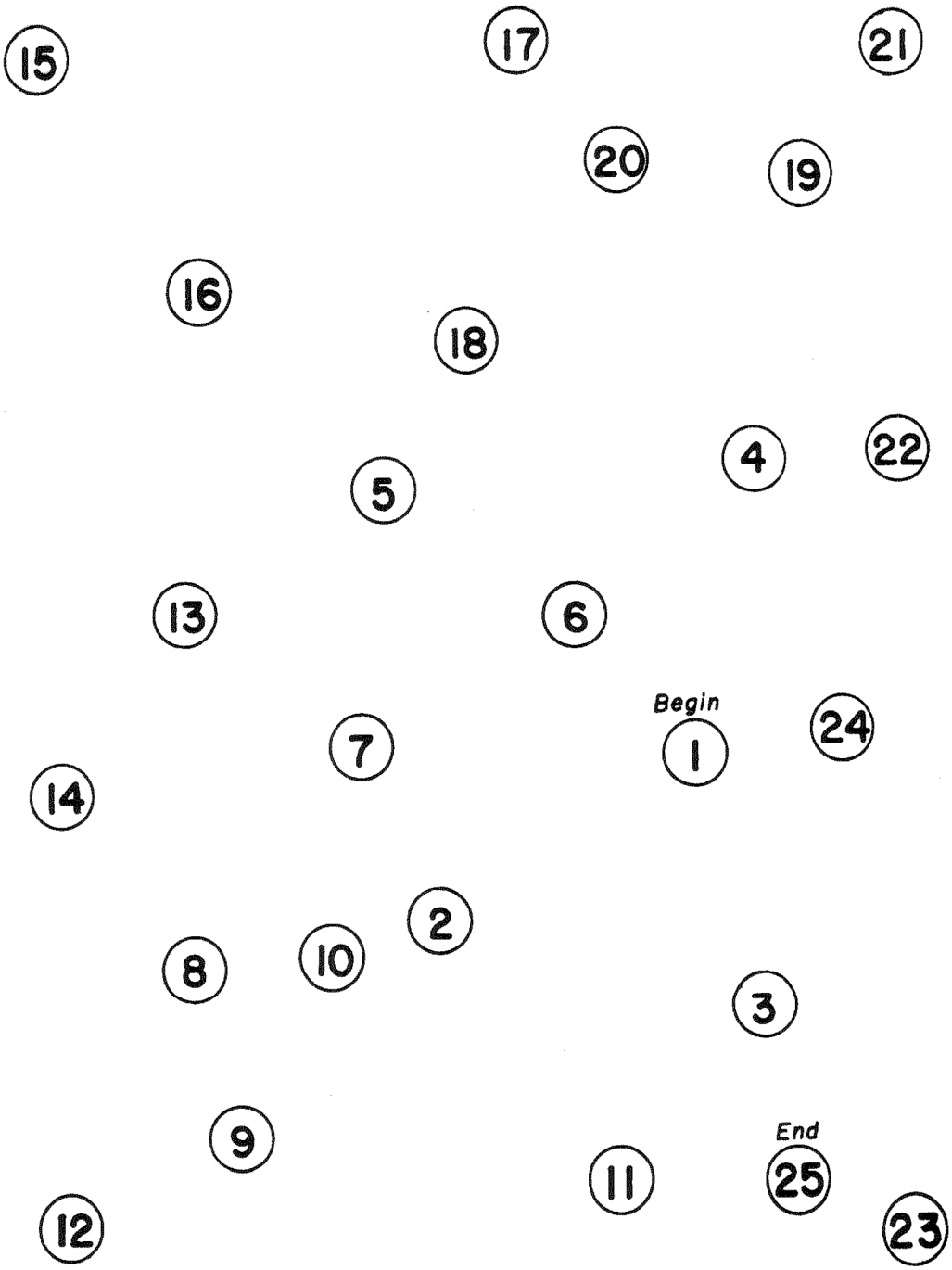
Cognitive Testing

TRAIL MAKING

Part A

SAMPLE

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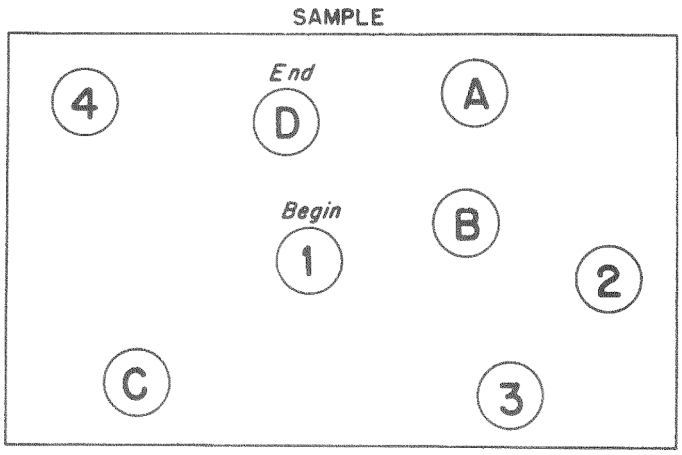
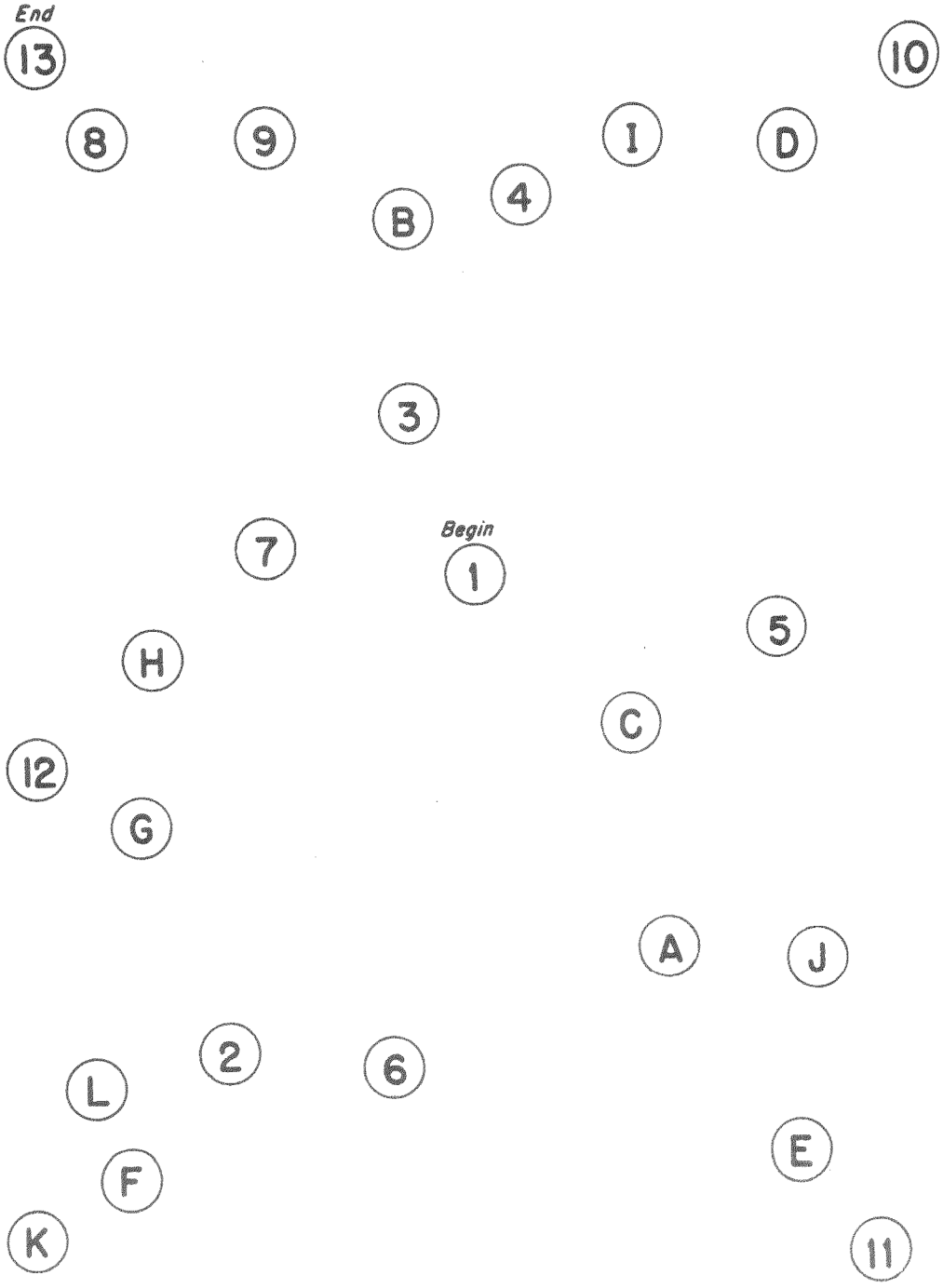
TRAIL MAKING

Part B

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WAIS-IV Record Form

WECHSLER ADULT INTELLIGENCE SCALE®–FOURTH EDITION

Examinee Name:

Examiner Name:

Calculation of Examinee's Age	Year	Month	Day
Test Date			
Birth Date			
Test Age			

Total Raw Score to Scaled Score Conversion

Subtest	Raw Score	Scaled Score	Rel. Group Scaled Score
Block Design			
Similarities			
Digit Span			
Matrix Reasoning			
Vocabulary			
Arithmetic			
Symbol Search			
Visual Puzzles			
Information			
Coding			
Letter–Number Seq.*		( )	( )
Figure Weights*		( )	( )
Comprehension		( )	( )
Cancellation*		( )	( )
Picture Completion		( )	( )
Sum of Scaled Scores			

*16–69 only

Verbal Comp.	Perc. Reas.	Work. Mem.	Proc. Speed	Full Scale

Sum of Scaled Scores to Composite Score Conversion

Scale	Sum of Scaled Scores	Composite Score	Percentile Rank	Confidence Interval* 90% or 95%
Verbal Comprehension		VCI		
Perceptual Reasoning		PRI		
Working Memory		WMI		
Processing Speed		PSI		
Full Scale		FSIQ		

*For *SEMs* used to calculate confidence intervals, refer to Table 4.3 of the Technical and Interpretive Manual.

Subtest Scaled Score Profile

	Verbal Comprehension				Perceptual Reasoning					Working Memory			Processing Speed		
	SI	VC	IN	CO	BD	MR	VP	FW	PCm	DS	AR	LN	SS	CD	CA
19	•	•	•	•	•	•	•	•		•	•	•	•	•	•
18	•	•	•	•	•	•	•	•		•	•	•	•	•	•
17	•	•	•	•	•	•	•	•		•	•	•	•	•	•
16	•	•	•	•	•	•	•	•		•	•	•	•	•	•
15	•	•	•	•	•	•	•	•		•	•	•	•	•	•
14	•	•	•	•	•	•	•	•		•	•	•	•	•	•
13	•	•	•	•	•	•	•	•		•	•	•	•	•	•
12	•	•	•	•	•	•	•	•		•	•	•	•	•	•
11	•	•	•	•	•	•	•	•		•	•	•	•	•	•
10	•	•	•	•	•	•	•	•		•	•	•	•	•	•
9	•	•	•	•	•	•	•	•		•	•	•	•	•	•
8	•	•	•	•	•	•	•	•		•	•	•	•	•	•
7	•	•	•	•	•	•	•	•		•	•	•	•	•	•
6	•	•	•	•	•	•	•	•		•	•	•	•	•	•
5	•	•	•	•	•	•	•	•		•	•	•	•	•	•
4	•	•	•	•	•	•	•	•		•	•	•	•	•	•
3	•	•	•	•	•	•	•	•		•	•	•	•	•	•
2	•	•	•	•	•	•	•	•		•	•	•	•	•	•
1	•	•	•	•	•	•	•	•		•	•	•	•	•	•

Composite Score Profile

	VCI	PRI	WMI	PSI	FSIQ
160					
155					
150					
145					
140					
135					
130					
125					
120					
115					
110					
105					
100					
95					
90					
85					
80					
75					
70					
65					
60					
55					
50					
45					
40					

PEARSON

ISBN 0154980900

WAIS®-IV

Response Booklet 1

Symbol Search

Coding

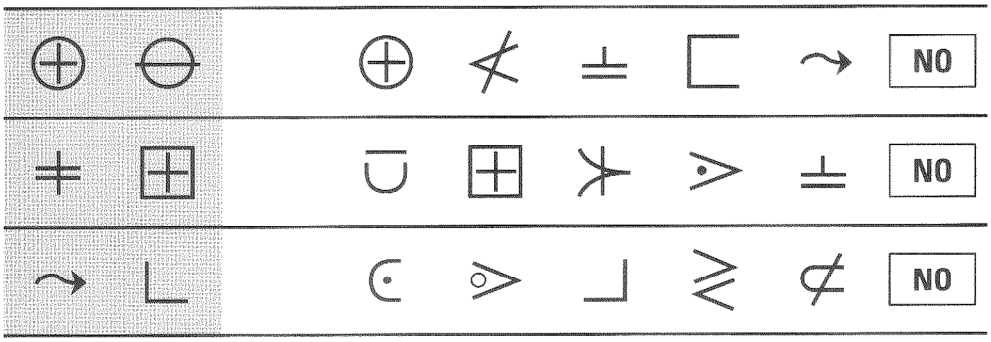
Examinee Name: _____ Age: _____

Examiner Name: _____

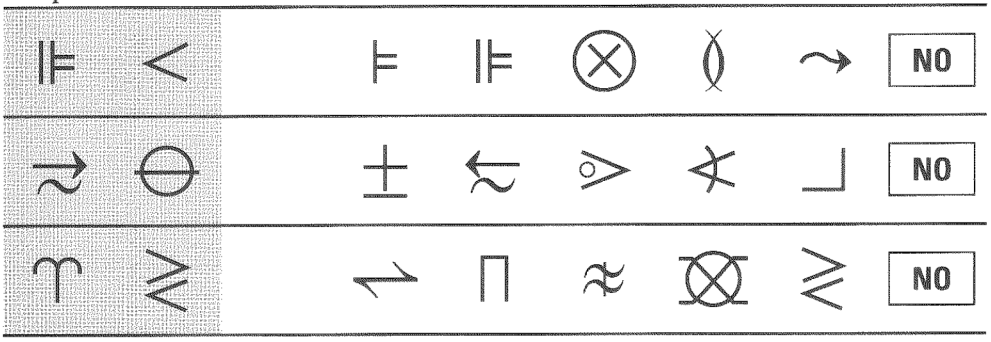
Test Date: _____

Symbol Search

Demonstration Items



Sample Items



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PEARSON PsychCorp

ISBN 015-4980-87-0

9 780154 980878

WMS®-IV

WECHSLER MEMORY SCALE®– FOURTH EDITION

Adult Battery (Ages 16–69) Record Form

Examinee Name:

Examiner Name:

Calculation of Examinee's Age	Year	Month	Day
Test Date			
Birth Date			
Test Age			

Total Raw Score to Scaled Score Conversion

Subtest	Raw Score	Scaled Score
Logical Memory I		
Logical Memory II		
Verbal Paired Associates I		
Verbal Paired Associates II		
CVLT–II Trials 1–5	T Score	( )
CVLT–II Long-Delay	T Score	( )
Designs I		
Designs II		
Visual Reproduction I		
Visual Reproduction II		
Spatial Addition		
Symbol Span		

Sum of Scaled Scores to Index Conversion

	Auditory Memory (AMI)	Visual Memory (VMI)	Visual Working Memory (VWMI)	Immediate Memory (IMI)	Delayed Memory (DMI)
Sum of Scaled Scores					
Index Score					
Percentile Rank					
90% or 95% Confidence Interval					

Index Score Profile

AMI	VMI	VWMI	IMI	DMI

160, 155, 150, 145, 140, 135, 130, 125, 120, 115, 110, 105, 100, 95, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 40

Primary Subtest Scaled Score Profile

Auditory Memory						Visual Memory				Visual Working Memory		
LM I	LM II	VPA I	VPA II	CVLT–II 1–5	CVLT–II LD	DE I	DE II	VR I	VR II	SA	SSP	
19	19											
18	18											
17	17											
16	16											
15	15											
14	14											
13	13											
12	12											
11	11											
10	10											
9	9											
8	8											
7	7											
6	6											
5	5											
4	4											
3	3											
2	2											
1	1											

Subtest	Abbreviation
Logical Memory I	LM I
Logical Memory II	LM II
Verbal Paired Associates I	VPA I
Verbal Paired Associates II	VPA II
CVLT–II Trials 1–5	CVLT–II 1–5
CVLT–II Long-Delay	CVLT–II LD
Designs I	DE I
Designs II	DE II
Visual Reproduction I	VR I
Visual Reproduction II	VR II
Spatial Addition	SA
Symbol Span	SSP
Brief Cognitive Status Exam	BCSE

PEARSON

PsychCorp
Product Number: 0154895857

APPENDIX E

Series Mean Imputation Outpu

	Result Variable	N of Replaced Missing Values	Case Number of Non-Missing Values		N of Valid Cases	Creating Function
			First	Last		
1	WMS_IV_Brief_Cog_RAW_PRE_1	1	1	35	35	SMEAN(WMS_IV_Brief_Cog_RAW_PRE)
2	WMSIV_Brief_Cog_RAW_POST_1	0	1	35	35	SMEAN(WMSIV_Brief_Cog_RAW_POST)
3	WMS_IV_LMI_RAW_PRE_1	0	1	35	35	SMEAN(WMS_IV_LMI_RAW_PRE)
4	WMS_IV_LMI_RAW_POST_1	0	1	35	35	SMEAN(WMS_IV_LMI_RAW_POST)
5	WMS_IV_LMI_SCALED_PRE_1	0	1	35	35	SMEAN(WMS_IV_LMI_SCALED_PRE)
6	WMS_IV_LMI_SCALED_POST_1	0	1	35	35	SMEAN(WMS_IV_LMI_SCALED_POST)

	Result Variable	N of Replaced Missing Values	Case Number of Non-Missing Values		N of Valid Cases	Creating Function
			First	Last		
7	WMS_IV_LMII_DR_RAW_PRE_1	0	1	35	35	SMEAN(WMS_IV_LMII_DR_RAW_PRE)
8	WMS_IV_LMII_DR_RAW_POST_1	0	1	35	35	SMEAN(WMS_IV_LMII_DR_RAW_POST)
9	WMS_IV_LMII_DR_SCALED_PRE_1	0	1	35	35	SMEAN(WMS_IV_LMII_DR_SCALED_PRE)
10	WMS_IV_LMII_DR_SCALED_POST_1	0	1	35	35	SMEAN(WMS_IV_LMII_DR_SCALED_POST)
11	WMS_IV_LMIICP_RAW_PRE_1	3	1	35	35	SMEAN(WMS_IV_LMIICP_RAW_PRE)
12	WMS_IV_LMIICP_RAW_POST_1	1	1	35	35	SMEAN(WMS_IV_LMIICP_RAW_POST)

	Result Variable	N of Replaced	Case Number of	N of Valid	Creating Function

	Result Variable	N of Replaced Missing Values	Case Number of Non-Missing Values		N of Valid Cases	Creating Function
			First	Last		
13	TMT_A_RAW_PRE_1	0	1	35	35	SMEAN(TMT_A_RAW_PRE)
14	TMT_A_RAW_POST_1	1	1	35	35	SMEAN(TMT_A_RAW_POST)
15	TMT_B_RAW_PRE_1	0	1	35	35	SMEAN(TMT_B_RAW_PRE)
16	TMT_B_RAW_POST_1	1	1	35	35	SMEAN(TMT_B_RAW_POST)
17	WAIS_IV_BD_RAW_PRE_1	0	1	35	35	SMEAN(WAIS_IV_BD_RAW_PRE)
18	WAIS_IV_BD_RAW_POST_1	0	1	35	35	SMEAN(WAIS_IV_BD_RAW_POST)
19	WAIS_IV_BD_SCALED_PRE_1	0	1	35	35	SMEAN(WAIS_IV_BD_SCALED_PRE)

	Result Variable	N of Replaced Missing Values	Case Number of Non-Missing Values		N of Valid Cases	Creating Function
			First	Last		
20	WAIS_IV_BD_SCALED_POST_1	0	1	35	35	SMEAN(WAIS_IV_BD_SCALED_POST)
21	WAIS_IV_LNS_RAW_PRE_1	1	1	35	35	SMEAN(WAIS_IV_LNS_RAW_PRE)
22	WAIS_IV_LNS_RAW_POST_1	1	1	35	35	SMEAN(WAIS_IV_LNS_RAW_POST)
23	WAIS_IV_LNS_SCALED_PRE_1	1	1	35	35	SMEAN(WAIS_IV_LNS_SCALED_PRE)
24	WAIS_IV_LNS_SCALED_POST_1	1	1	35	35	SMEAN(WAIS_IV_LNS_SCALED_POST)
25	WAIS_IV_CD_RAW_PRE_1	0	1	35	35	SMEAN(WAIS_IV_CD_RAW_PRE)

	Result Variable	N of Replaced Missing Values	Case Number of Non-Missing Values		N of Valid Cases	Creating Function
			First	Last		
26	WAIS_IV_CD_RAW_POST_1	0	1	35	35	SMEAN(WAIS_IV_CD_RAW_POST)
27	WAIS_IV_CD_SCALED_PRE_1	0	1	35	35	SMEAN(WAIS_IV_CD_SCALED_PRE)
28	WAIS_IV_CD_SCALED_POST_1	0	1	35	35	SMEAN(WAIS_IV_CD_SCALED_POST)
29	COWAT_Z_G_PRE_1	0	1	35	35	SMEAN(COWAT_Z_G_PRE)
30	COWAT_Z_G_POST_1	0	1	35	35	SMEAN(COWAT_Z_G_POST)
31	COWAT_Z_A_PRE_1	0	1	35	35	SMEAN(COWAT_Z_A_PRE)
32	COWAT_Z_A_POST_1	0	1	35	35	SMEAN(COWAT_Z_A_POST)

	Result Variable	N of Replaced Missing Values	Case Number of Non-Missing Values		N of Valid Cases	Creating Function
			First	Last		
33	COWAT_Z_ED_PRE_1	1	1	35	35	SMEAN(COWAT_Z_ED_PRE)
34	COWAT_Z_ED_POST_1	0	1	35	35	SMEAN(COWAT_Z_ED_POST)
35	SBP_PRE_1	0	1	35	35	SMEAN(SBP_PRE)
36	SBP_POST_1	3	1	35	35	SMEAN(SBP_POST)
37	DBP_PRE_1	0	1	35	35	SMEAN(DBP_PRE)
38	DBP_POST_1	3	1	35	35	SMEAN(DBP_POST)
39	RHR_PRE_1	0	1	35	35	SMEAN(RHR_PRE)
40	RHR_POST_1	3	1	35	35	SMEAN(RHR_POST)
41	HEIGHT_IN_1	0	1	35	35	SMEAN(HEIGHT_IN)
42	WEIGHT_LBS_1	0	1	35	35	SMEAN(WEIGHT_LBS)

	Result Variable	N of Replaced Missing Values	Case Number of Non-Missing Values		N of Valid Cases	Creating Function
			First	Last		
43	FVC_L_PRE_1	0	1	35	35	SMEAN(FVC_L_PRE)
44	FVC_L_POST_1	3	1	35	35	SMEAN(FVC_L_POST)
45	FVC_PRED_PRE_1	3	1	35	35	SMEAN(FVC_PRED_PRE)
46	FVC_PRED_POST_1	6	1	35	35	SMEAN(FVC_PRED_POST)
47	FEV1_PRE_1	1	1	35	35	SMEAN(FEV1_PRE)
48	FEV1_POST_1	4	1	35	35	SMEAN(FEV1_POST)
49	FEV1_PRED_PRE_1	3	1	35	35	SMEAN(FEV1_PRED_PRE)
50	FEV1_PRED_POST_1	6	1	35	35	SMEAN(FEV1_PRED_POST)
51	VO2PEAK_PRE_1	0	1	35	35	SMEAN(VO2PEAK_PRE)

	Result Variable	N of Replaced Missing Values	Case Number of Non-Missing Values		N of Valid Cases	Creating Function
			First	Last		
52	VO2PEAK_POST_1	2	1	35	35	SMEAN(VO2PEAK_POST)
53	LAT_PD_PRE_1	3	1	35	35	SMEAN(LAT_PD_PRE)
54	LAT_PD_POST_1	3	1	35	35	SMEAN(LAT_PD_POST)
55	SPRESS_PRE_1	6	1	35	35	SMEAN(SPRESS_PRE)
56	SPRESS_POST_1	5	1	35	35	SMEAN(SPRESS_POST)
57	CPRESS_PRE_1	3	1	35	35	SMEAN(CPRESS_PRE)
58	CPRESS_POST_1	4	1	35	35	SMEAN(CPRESS_POST)
59	SROW_PRE_1	3	1	35	35	SMEAN(SROW_PRE)

	Result Variable	N of Replaced Missing Values	Case Number of Non-Missing Values		N of Valid Cases	Creating Function
			First	Last		
60	SROW_POST_1	3	1	35	35	SMEAN(SROW_POST)
61	LCURL_PRE_1	0	1	35	35	SMEAN(LCURL_PRE)
62	LCURL_POST_1	3	1	35	35	SMEAN(LCURL_POST)
63	LEXT_PRE_1	2	1	35	35	SMEAN(LEXT_PRE)
64	LEXT_POST_1	3	1	35	35	SMEAN(LEXT_POST)
65	LPRESS_PRE_1	1	1	35	35	SMEAN(LPRESS_PRE)
66	LPRESS_POST_1	3	1	35	35	SMEAN(LPRESS_POST)
67	STWRU_PRE_1	0	1	35	35	SMEAN(STWRU_PRE)

	Result Variable	N of Replaced Missing Values	Case Number of Non-Missing Values		N of Valid Cases	Creating Function
			First	Last		
68	STWRU_POST_1	2	1	35	35	SMEAN(STWRU_POST)
69	STWRL_PRE_1	1	1	35	35	SMEAN(STWRL_PRE)
70	STWRL_POST_1	2	1	35	35	SMEAN(STWRL_POST)
71	PLANK_PRE_1	6	1	35	35	SMEAN(PLANK_PRE)
72	PLANK_POST_1	4	1	35	35	SMEAN(PLANK_POST)
73	HGR_PRE_1	1	1	35	35	SMEAN(HGR_PRE)
74	HGR_POST_1	2	1	35	35	SMEAN(HGR_POST)
75	HGL_PRE_1	1	1	35	35	SMEAN(HGL_PRE)
76	HGL_POST_1	2	1	35	35	SMEAN(HGL_POST)

	Result Variable	N of Replaced Missing Values	Case Number of Non-Missing Values		N of Valid Cases	Creating Function
			First	Last		
77	SANDR_PRE_1	1	1	35	35	SMEAN(SANDR_PRE)
78	SANDR_POST_1	3	1	35	35	SMEAN(SANDR_POST)
79	PIPER_I_PRE_1	0	1	35	35	SMEAN(PIPER_I_PRE)
80	PIPER_I_POST_1	1	1	35	35	SMEAN(PIPER_I_POST)
81	PIPER_B_PRE_1	0	1	35	35	SMEAN(PIPER_B_PRE)
82	PIPER_B_POST_1	1	1	35	35	SMEAN(PIPER_B_POST)
83	PIPER_A_PRE_1	0	1	35	35	SMEAN(PIPER_A_PRE)
84	PIPER_A_POST_1	2	1	35	35	SMEAN(PIPER_A_POST)

	Result Variable	N of Replaced Missing Values	Case Number of Non-Missing Values		N of Valid Cases	Creating Function
			First	Last		
85	PIPER_S_PRE_1	0	1	35	35	SMEAN(PIPER_S_PRE)
86	PIPER_S_POST_1	2	1	35	35	SMEAN(PIPER_S_POST)
87	PIPER_C_PRE_1	0	1	35	35	SMEAN(PIPER_C_PRE)
88	PIPER_C_POST_1	2	1	35	35	SMEAN(PIPER_C_POST)
89	BECK_PRE_1	1	1	35	35	SMEAN(BECK_PRE)
90	BECK_POST_1	2	1	35	35	SMEAN(BECK_POST)
91	QOL_PRE_1	0	1	35	35	SMEAN(QOL_PRE)
92	QOL_POST_1	4	1	35	35	SMEAN(QOL_POST)