Ursidae: The Undergraduate Research Journal at the University of Northern Colorado

Volume 4
Number 2 *McNair Special Issue*

Article 1

January 2014

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

Jesus Medrano

Jessica Brown

Daniel Shackelford

Corey Beebe

Alyse Brennecke

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

Jesus Medrano (Biological Sciences),
Jessica Brown, Daniel Shackelford, Corey Beebe, and Alyse Brennecke
Mentors: Brent Peterson, M.S. & Reid Hayward, Ph.D., Sport & Exercise Science

Abstract: There are more than 100 clinically distinct types of cancer, each having their own symptoms and requiring a different method of cancer treatment. Despite current advances, the positive effects from treatment are often matched and outweighed by negative effects. One of the most prevalently reported symptoms is chemotherapy-related cognitive impairment (CRCI). CRCI has been reported to negatively affect memory, concentration, reaction time, attention, cognition, organizational skills, linguistic abilities, executive function, and activities of daily living. **Purpose**: To examine the effects of a 12-week aerobic and cognitive training on cognitive function in cancer survivors who have undergone or are currently undergoing adjuvant treatment for cancer. **Methods**: A total of ten patients who either were going through chemotherapy or had just finished the treatment participated in this pilot study. Groups were composed of cancer-aerobic (n = 2), cancer- cognitive (n = 2), cancer-aerobic and cognitive (n = 2), cancer- flexibility (n = 2), and non-cancer controls (n = 2). Each subject completed an initial comprehensive physical assessment, cognitive assessment, Quality of Life (QOL) assessment, Piper Fatigue Inventory, and Beck Depression Inventory. Following these assessments, a 12-week computer-based aerobic training, cognitive training, and flexibility training intervention was completed by every participant. Upon completion of the intervention, all of the variables were reassessed. **Results**: Friedman's 2-way non-parametric ANOVA revealed significant ($p< 0.05$) differences in QOL, depression, Piper fatigue subtest-B, the plank test, and the Weschler Memory Scale LMII. However, follow-up dependent measures t-tests only confirmed significant decreases in fatigue in the cancer-cognitive group. **Conclusion**: Although results are preliminary and sample sizes are small, the data would suggest that both cancer survivors and non-cancer controls respond favorably toward aerobic and/or cognitive training and that cognitive training alone may be specifically beneficial for cancer survivors suffering from CRCI.

Keywords: *cancer, cancer rehabilitation, cognitive function, chemotherapy*

Cancer has been defined as being a class of diseases characterized by aberrant cellular growth, and has been reported to be a phenomena of increasing magnitude as time progresses (Proctor, 2003). In order to address the increasing incidences of cancer, treatments such as chemotherapy, radiation, surgery, and combinations of treatments may be necessary. Although the incidences of cancer are increasing, mortality rates following cancer diagnosis and treatment are continuing to decrease (Ward, DeSantis, Robbins, Kohler, & Jemal, 2014). Throughout the process; however, cancer survivors often experience many debilitating side effects following cancer treatments (Schneider, Hsieh, Sprod, Carter, & Hayward, 2007). These side effects may play a substantial role in the development of physiological and psychological damage, as well as decrease the independence and quality of life (QOL) in cancer survivors. Multiple studies have reported associations between chemotherapy treatments and cognitive dysfunction (Summers, 2012; Siegel, DeSantis, Virgo, Stein, Mariotto, & Smith, 2012; Jemal, Center, DeSantis, & Ward, 2010). The increased incidence of cancer, coupled with longer survival times, has resulted in larger numbers of cancer survivors who are experiencing cognitive dysfunction (Wefel & Schagen, 2012). Although, research has supported that exercise (Pinto, Dunsiger, & Waldemore, 2013) and cognitive training (Acevedo, 2012) may improve cancer survivors' cognitive functioning. Additionally, improving cognitive function may allow cancer survivors to perform daily activities to a greater extent, and may ultimately increase their overall QOL (Schuurs & Green, 2013).

The aforementioned studies were conducted individually and to our current knowledge we are the first to combine both cognitive and aerobic training together. Therefore, the purpose of this study was to examine the effects of a 12-week aerobic and cognitive training intervention on cognitive function in cancer survivors who had undergone or were currently receiving chemotherapy treatment for cancer with or without radiation treatment. This study is a portion of a larger study being conducted currently by my mentor and is being compared to the results of colleagues who are following a similar procedure with healthy individuals. It is hypothesized that the combination of aerobic and cognitive training would significantly improve aspects of cognitive function in cancer survivors following the intervention.

Background

Chemotherapy has been linked to cognitive dysfunction in multiple studies (Wefel & Schagen, 2012; Pinto et al., 2013); however, it was not until the mid-to-late 1990's that curiosity in the topic began to increase (Ahles, 2012). Cancer treatment may include numerous therapeutic processes such as surgery, chemotherapy, radiotherapy, and hormone therapy. Chemotherapeutic agents have been linked to negative bio-psychosocial side effects (Schneider & Hayward, 2013). With regard to the aforementioned side effects, researchers have aimed to create more effective chemotherapy drugs; however, Ahles (2012) indicated that there are still a vast amount of side effects that cancer survivors are experiencing during and following treatment regardless of improved efficacy. Over the past few years our group has developed a logical method of approaching the problem of chemotherapy-related cognitive impairment (CRCI). Pinto et al. (2013) reported that, individually, interventions of cognitive training and physical training have resulted in improvements in aspects of cognitive function in cancer survivors. However, our group is the first to combine cognitive and aerobic training into one intervention.

Cancer Statistics

According to the American Cancer Society (2014) approximately 1,665,540 people will be diagnosed with cancer this year, and of this population 585,720 people are expected to succumb to the disease. This makes cancer the second most common cause of death in the US, exceeded only by heart disease, accounting for nearly 1 of every 4 deaths. Due to the increased effectiveness of early detection, treatment, and rehabilitation, survival rates are steadily increasing. Sadly, a vast majority of these cancer survivors experience one or more side effects during and following treatment, with the most commonly reported symptoms being fatigue, pain, CRCI, and/or some form of emotional distress (Siegel et al., 2012). There are multiple treatments in reducing the harmful effects of cancer; however, to this day researchers are striving to find the best method or combinations of treatment.

Chemotherapy

Chemotherapy drugs have been shown to reduce the size of cancerous tumors and decrease metastasis. This is an often administered form of treatment for specific types of cancers, such as cancers that arise from blood or bone marrow cells like leukemia, lymphoma, and multiple myeloma (Belvoir, 2010). Research has suggested that chemotherapy may adversely affect cognitive function by direct or indirect methods. Side effects such as cardio-toxicity, autonomic nervous system dysfunction, peripheral sensory and motor neuropathies, and long- and short-term cognitive deficits have been observed in cancer patients (Schmitz & Speck, 2010).

Cognitive Function

Cognitive decline among cancer survivors has been reported to range from 17% to 75% across various studies (Wefel & Schagen, 2012). These changes may profoundly affect cancer survivors' independence and activities of daily living. CRCI has been reported to negatively affect learning and working memory, executive function, and processing speed. The mechanisms of these declinations are multifaceted. It has been hypothesized that a combination of low-efficiency efflux pumps, deficits in DNA-repair mechanisms, and decreased immune response in conjunction with chemotherapy treatment may contribute to CRCI (Ahles & Saykin, 2007).

Functional magnetic resonance imaging (fMRI), electroencephalogram (EEG), and diffusion tensor imaging (DTI) methods have been utilized to measure structural and volumetric alterations in brain tissue. Imaging studies have helped scientists observe and document the structural damages to the brain as well as alterations in functional activity. Multiple studies using neuroimaging, with or without objective testing of chemotherapeutic agents have shown changes in brain function associated with chemotherapy treatment (Ahles, 2012; Grady, 2008; Conroy, McDonald, Smith, Moser, West, & Kamendulis et al., 2013).

Studies using voxel-based morphometry have allowed researchers to observe volume reductions of white and gray matter following standard or high-dose chemotherapy regimens (Wefel & Schagen, 2012). This phenomenon has been shown in an evaluation of 23 studies with patients who had received chemotherapy and other control groups who had not received chemotherapy. Koppelmans et al. (2011) reported significant decreases in brain matter volume and measures of cognitive functioning in 184 chemotherapy-exposed breast cancer patients compared to 368 aged-matched cancer-free subjects (-3.5 ml, p = 0.019 for TBV and -2.9 ml, p = 0.003 for gray matter). It was inferred that most of the changes within cognitive functioning may be associated with the disrupted white and gray matter integrity (Koppelmans et al., 2011). Additionally, the interruption of these information transferring tracts in the brain may substantially impair or block the performance of certain actions further impairing cognitive function (Koppelmans et al., 2011). Furthermore, this could affect their overall QOL and activities of daily living.

Rehabilitation

Cognitive Intervention. Many biological mechanisms for CRCI have been proposed, including excessive oxidative stress, DNA damage, and even compromised DNA repair (Conroy et al., 2013). Few studies have dealt with the observation of treatment-related neurological side effects; however, because of the need to administer these types of cancer treatments, interventions focused on the reduction of these side effects and the improvement of cognitive function are extremely important (Weis, Poppelreuter, & Bartsch, 2011). Weis et al. (2011) compared two types of neuropsychological interventions in a rehabilitation setting against a control group, which resulted in significant improvements in all three groups after completing a comprehensive neuropsychological test battery. Aspects of cognitive function that were measured in this study were basic information processing speed, metal flexibility, attention span, and memory (Weis et al., 2011).

Due to today's advancing technology, multiple types of interventions are beginning to be formulated by researchers to address decrements in learning and memory. For example, human versions of visual-spatial memory task, more commonly known as the Memory Island (MI) program, have been explored in research (Acevedo, 2012). As part of various interventions focused on the improvement of cognitive functioning, the MI program is a human spatial memory assessment modeled after the Morris water maze, which may be administered to middle age and older adults (Pieper, Acevedo, Craytor, Murray, & Raber, 2010). Cognitive interventions are useful in measuring variables such as motor coordination, working memory, picture recognition, and visual-spatial memory within the brain. Multiple studies have reported that cognitive training may increase the development of coping skills and overall improve their behavioral patterns by engaging greater brain activity in cancer survivors (Acevedo, 2012; Pieper et al., 2010).

Exercise Intervention. Side effects from various chemotherapy treatments may last for days, months, or even years (Schneider & Hayward, 2013). However, reports have shown that exercise increases muscular strength and endurance, as well as cardiovascular endurance within cancer survivors (Courneya & Karvinen, 2007). Individualized, prescriptive exercise interventions for cancer survivors have also been reported to alleviate the negative side effects of fatigue (Hsieh, 2008; Schmitz & Speck, 2010; Schneider & Hayward, 2013). A more recent meta-analysis has reported the positive effects of physical activity (PA) interventions on psychosocial functioning of cancer survivors (Pinto, Dunsiger, & Waldemore, 2013). The long-term effects from physical training interventions for cancer survivors have resulted in improvements in more than just brain activity, such as decreases in cancer-related fatigue (CRF) and increases in physical functioning (Pinto et al., 2013). Highlighting a dose-response relationship between PA and QOL, Pinto (2013) reported that cancer survivors who have habitually engaged in longer periods and intense physical activity experienced significantly ($p = 0.02$) greater improvements in QOL. Additionally, exercise interventions have been shown to improve muscular strength and mass (Courneya & Karvinen, 2007), and aerobic fitness and flexibility (Schmitz & Speck, 2010). For example, in an intervention evaluating the effects of history of previous PA on psychosocial variables of 192 breast cancer survivors, researchers found decreases in particular areas like psychological stress, social stress, and insomnia after a period of 12 months (Pinto et al., 2013). In a review of literature, Schneider and Hayward (2013) reported that among multiple studies, cancer survivors who continued to be physically active following interventions reported even greater results in QOL.

Purpose of Research

As mentioned before, a large population of cancer survivors are coping with the adverse side effects from cancer treatments, one being CRCI. Exercise and cognitive training alone have been shown to increase cognitive functioning. In addition, exercise has been shown to improve QOL, flexibility, and aerobic fitness among cancer survivors. However, no studies have conducted an evaluation of both aerobic and cognitive training simultaneously. Therefore, the purpose of this study was to examine the effects of a 12-week aerobic and cognitive training intervention on cognitive function in cancer survivors following chemotherapy treatment with or without radiation. It was hypothesized that with the combination of aerobic and cognitive training this would significantly improve the cognitive function of cancer survivors.

METHOD

Participants

Cancer survivors over the age of eighteen who were undergoing or had completed chemotherapy with or without radiation were recruited by the Rocky Mountain Cancer Rehabilitation Institute (RMCRI), housed in the Ben Nighthorse Campbell Center on the campus of the University of Northern Colorado. In addition, some patients were referred to this study by the local medical community. Lifestyle factors such as, tobacco, alcohol, and dietary intake were also evaluated through multiple surveys and phone interviews prior to the study. Participants were also screened for medical or physical limitations not specifically outlined in the inclusion/exclusion criteria, but that may have potentially altered the outcomes of the study. Following acceptance and completion of informed consent forms, an in-depth initial cognitive assessment was completed, along with an initial physical assessment afterwards. These assessments were completed again at the end of the intervention. They were informed of the procedures and purpose as explicitly delineated within the informed consent, and then asked to read and sign it with the leisure that they were able to terminate their involvement in the study at any time. During the exercise training intervention and each physical assessment, all physiological parameters and survivor symptoms were constantly assessed and evaluated (e.g. heart rate, blood pressure, rating of perceived exertion, survivor pallor, etc.). This study was approved by the University Institutional Review Board.

Experimental Design

The intervention consisted of 12 weeks of aerobic training, cognitive training, or a combination of both cognitive and aerobic training, followed by flexibility (stretching) afterwards inside the facility of RMCRI. Aerobic and cognitive training was conducted on an instrument called the Motion Fitness Brain-Bike®. Participation in this study was based on pre-determined inclusion and exclusion criteria, which included dynamics about ability status and mental conditions. These criteria's were important in determining if the patient was capable of performing the various exercises lined up for this study. A total of ten participants were selected and randomized into one of five groups as described in Figure 1.

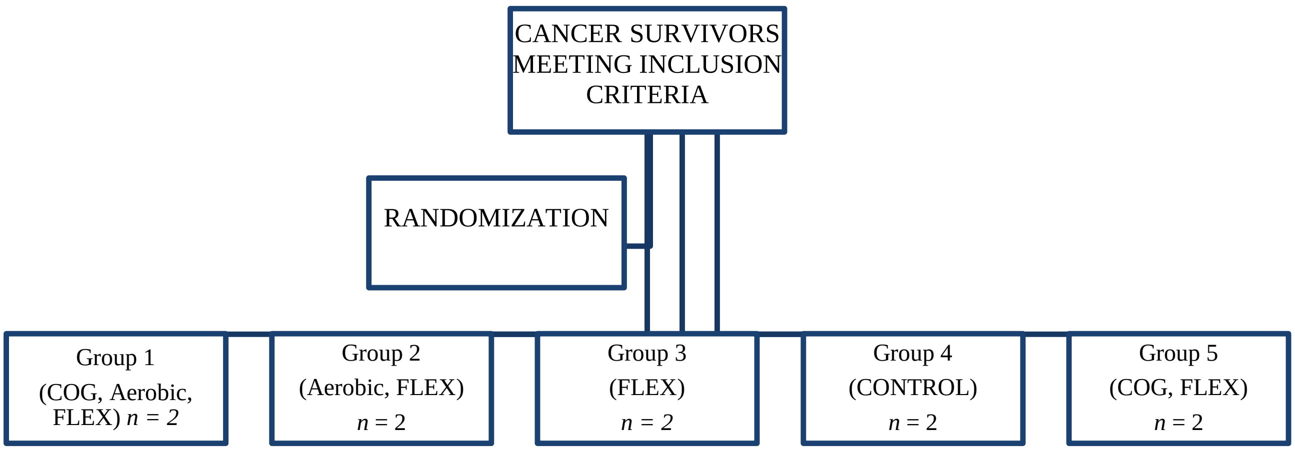

Figure 1. Participants and group randomization

Group 1 (*n* = 2) was composed of cancer survivors that participated in all interventions consisting of aerobic, cognitive, and flexibility training. Group 2 (*n* = 2) was composed of cancer survivors that participated in aerobic training and flexibility. Group 3 (*n* = 2) was composed of cancer survivors that participated in flexibility training, but did not participate in aerobic or cognitive training. Group 4 (*n* = 2) was the control group which consisted of participants who had not been diagnosed with any form of cancer. These participants completed aerobic, cognitive, and flexibility training. Group 5 (*n* = 2) was composed of cancer survivors who participated in cognitive training and flexibility. Cognitive, physical, and psychological variables were measured for each participant during the study using multiple measures for each variable (Tables 1 and 2). As stated, all cognitive and physical parameters were collected prior to and following the exercise intervention.

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 (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), Piper Fatigue Scale (Piper, Dibble, Dodd, Weiss, Slaughter, & Paul, 1998) and Ferrans & Powers (1985) Quality of Life Index Cancer Version III (Table 2). The Beck Depression Inventory is composed of 21 declarative statements corresponding to values ranging from 0 to 3. Statements that reflect values of 0 are indicative of the most extreme positive statement. Values of 3 indicate the most extreme negative statement. However, a neutral stance existed for the values represented by 1 and 2. At the end, values for all 21 items were added together. The scores range from 0 to 63, with 0 indicative of no depression and a score greater than 40 reflecting extreme depression (Salkind, 1969).

Table 1. Cognitive Parameters measured pre & post intervention.

Cognitive Parameters	**Test/Instrument**
General cognitive functioning	• Wechsler Memory Scale, 4th ed, (WMS-IV) • General Cognitive Screener
Processing Speed	• Trail-Making A
Working memory, executive function, & attention	• Wechsler Adult Intelligence Scale, 4th ed. (WAIS-IV) • Letter/Number Sequencing, Coding • Trail-Making B
Verbal learning & memory	• Wechsler Memory Scale, 4th ed. (WMS-IV) • Logical Memory I & II
Verbal fluidity	• Controlled Oral Word Association Test (COWAT)
Perceptual reasoning	• Wechsler Adult Intelligence Scale, 4th ed. (WAIS-IV) • Block Design

Table 2. Physical and psychological variables measured pre & post intervention.

Parameter	**Method of Assessment/Resources Offered**
Resting Measures	Telemetry, pulse oximetry, auscultation
Body Composition	Skinfolds, circumference measurements
Balance	Bertec™ Balance Screener, Unipedal stance test
Pulmonary Function	Spirometry
Cardiovascular Function	Graded maximal exercise test (RMCRI Treadmill Protocol)
Muscular Strength	Estimated 1-RM (upper and lower body), handgrip
Muscular Endurance	Chair/squat test, plank test
Flexibility and ROM	Modified Sit and Reach (lower back and hamstrings), goniometry/reaching tests
Function and Mobility	National Academy of Sports Medicine (NASM) squat test, anatomical plumb line evaluation
Psychological Values • Fatigue • Depression • Quality of Life (QOL)	Revised Piper Fatigue Scale, Beck Depression Inventory, Ferrans and Powers' Quality of Life Index Version III

The 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 by CRF are further demarcated using the calculated values obtained for cognitive/mood, behavioral, affective, and sensory subscales. There are 22 items in the inventory composed of a 4 subscale as previously mentioned; each possible score per subscale can range from 0 to 10. Scores ranging from 1-3, 4-6, and 7+ indicate mild, moderate and severe fatigue, respectively (Piper, Dibble, Dodd, Weiss, Slaughter, & Paul, 1998).

The Ferrans & Powers QOL assessment contains 66 questions which pertain to the significance and importance that the individual places on psychological, social, health, and family associated issues. This assessment is a criterion-based instrument, and was determined as such based on the correlational values between overall satisfaction with QOL and the instrument with dialysis patients ($r = 0.65$) and graduate students (r = 0.75). Total scorings that are high indicate a covenant between the importance on each dimension and an individual's satisfaction with that element, which is recognized as an overall condition of well-being (Ferrans & Powers, 1985).

Physiological Assessment

Participants received a physical examination for clearance to exercise during the physiological assessment. The variables measured included heart rate (HR), blood pressure (BP), oxygen saturation (SpO_2), height, weight, body composition, circumference measurements, cardiovascular fitness (CF) (VO_{2peak}, RMCRI protocol), balance (Bertec Balance Screener or Unipedal Stance Test), pulmonary function (Spirometry), estimated one repetition max (RM) (Brzycki equation), handgrip dynamometry, abdominal muscular endurance (plank test), and flexibility measures (modified sit and reach and shoulder reach behind back). In this study, the Bryzcki equation (1-RM = weight lifted (lb) / [1.0278 – (reps to failure x .0278)]) was used to estimate each individual's 1-RM using the number of repetitions at a given submaximal load to fatigue, assuming the repetitions do not exceed 10 repetitions. Handgrip was used to estimate muscular strength. Details about these variables are included in Table 2. Furthermore, relevant information regarding current existing medical conditions or medications was evaluated in the context of the study parameters.

Initial resting values for BP were obtained from subjects via auscultation methods as outlined in Hayward (2006). In addition, percentage of oxygen (O_2) bound to hemoglobin, as well as the patient's heart rate, was measured via pulse oximetry. Both height and weight were measured using the Health-O-Meter® medical grade balance beam scale. Body fat percentage was determined by using the 3-site Jackson and Pollock (1978/1980) methods. Males were measured using chest, abdomen, and thigh skinfold regions. Females were measured using triceps, suprailiac (area on side of waist), and thigh skinfold regions. Measurements of anthropometric nature were implemented using a calibrated measuring tape. These measures were taken so that any peripheral, general or lymph associated edema may be observed and noted in the participants' medical charting. The RMCRI treadmill protocol was used to evaluate each participant's cardiovascular fitness. Each stage was one minute in length with intensity adjusted as a means of belt speed, incline, or both each successive minute.

The Bertec Balance Check Screener series of tests were used to assess the ability of the participant to maintain balance while standing. An assessment of pulmonary function was completed using a Spirolab III (MIR, Roma, Italy). Participants were then assessed for muscular endurance, flexibility, and range of motion as depicted in Table 2.

Cognitive Training Protocol

All of the tasks for cognitive testing were divided based on recommendations from the Brain Center International (BCI) located in Canada. 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. The division of time spent during each task was already pre-determined by BCI. Each of the cognitive training tasks (see Table 3) was composed of 5 minutes of training. Details of each cognitive session are outlined in Table 4. For the first five sessions, sessions 16-20, and sessions 31-36 participants completed only specific exercises (parking, driving, smart driving,

Ursidae: The Undergraduate Research Journal at the University of Northern Colorado, Vol. 4, No. 2 [2014], Art. 1

the policeman, and brain twister). For sessions 6-15, participants completed ten sessions of the pilot consecutively, until that exercise was completed. On session 20, participants were then required to complete ten sessions of the stock exchange consecutively until session 30. Then they returned to the first five brain exercises as previously mentioned. Upon completion of cognitive training, data was wirelessly transmitted from our databases to the BCI databases for analysis.

Table 3. Cognitive training exercises (corresponds to training schedule found in Table 4).

Number	Exercise	Trained Functions	Description
1	Parking	• Working Memory • Visio-Spatial Memory	Adaptation and classic visuospatial span task
2	Car Driving	• Processing Speed • Divided Attention • Selective Attention • Vigilance	Two simultaneous bi-conditional discrimination (S-R) tasks with a vigilance task
3	Smart Driving	• Processing Speed • Selective Attention • Attentional Flexibility • Useful Field of View (UFOV) • 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 response conflict and attention set-shift paradigm
6	The Pilot	• Divided Attention • Temporal Perception • Arithmetic Operations	Dual monitoring task
7	Stock Exchange	• Processing Speed • Divided Attention • Working Memory	Two simultaneous n-back tasks: one audio-verbal and the other visuospatial

Table 4. Cognitive training schedule (corresponds to cognitive exercises found in Table 3).

Week	Session	Training Exercises
1	1-3	1-5, 1-5, 1-5
2	4-6	1-5, 1-5, 6 (step 10)
3	7-9	6 (steps 9-7)
4	10-12	6 (steps 6-4)
5	13-15	6 (steps 3-1)
6	16-18	1-5, 1-5, 1-5

Week	Session	Training Exercises
7	19-21	1-5, 1-5, 7 (step 10)
8	22-24	7 (steps 9-7)
9	25-27	7 (steps 6-4)
10	28-30	7 (steps 3-1)
11	31-33	1-5, 1-5, 1-5
12	34-36	1-5, 1-5, 1-5

Table 5. Flexibility and stretching intervention.

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

Aerobic Training Protocol

The participants were randomized into the aerobic training group and seated on the Motion Fitness Brain-Bike®. Their leg-to-pedal distance was measured to allow optimal leg flexion and extension. For the purpose of consistency, their most favorable seat position was recorded and adjusted for the remainder of their training sessions. Each aerobic training group participant would exercise during each session, while his or her heart rate was recorded, in order to evaluate their percent of heart rate reserve (% HRR, Karvonen Method). Aerobic training sessions were progressive and began at 55% HRR for weeks 1-4, 60% HRR for weeks 5-8, and 65% HRR for weeks 9-12. Before each aerobic session, participants were required to attach a telemetric heart rate monitoring device (Polar®) around their chest or use a pulse oximeter for accurate heart rate and oxygen tracking and safety. Participants were asked to begin by warming up, which consisted of 5-minutes of low intensity, self-paced cycling. Following completion of the warm-up, each participant had a resistance applied to the Brain Bike® recumbent cycle ergometer in ordeto elevate heart rate to the training range associated with percent of HRR and weekly progression. Subjects who were randomized into the combined aerobic and cognitive group followed the cognitive exercises and regimen found in Tables 3 and 4. These participants were required to cycle at the prescribed intensity while completing the cognitive exercises.

Flexibility 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; further description is provided in Table 5. The regions include: neck, shoulders/chest, posterior upper arm, upper back, lower back, hips, torso, anterior thigh and hip flexor, posterior thigh, groin, and calf.

Statistical Analyses

Cognitive and psychological changes were analyzed for each subject pre-and-post intervention via a Friedman test. The Friedman test is a non-parametric statistical test that yields similar findings as the independent samples *t-test*. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, 20) software package (SPSS, Chicago, IL.) Significance was set at $p \leq 0.05$.

RESULTS

All training groups, except Group 1, improved in QOL pre-to-post intervention (Figure 2). All groups increased in Logical Memory II, with Group 2 eliciting the greatest improvements and Group 3 showing the least improvement of 2.2% (Figure 3). Figure 4 represents the changes in fatigue levels before and after the intervention. Group 5 showed statistically significant improvements in fatigue levels of 64.3% ($p<0.05$) and Group 3 improved by 69.7%, but was not statistically significant. The control group of apparently healthy subjects (Group 4) indicated little improvement of <1%.

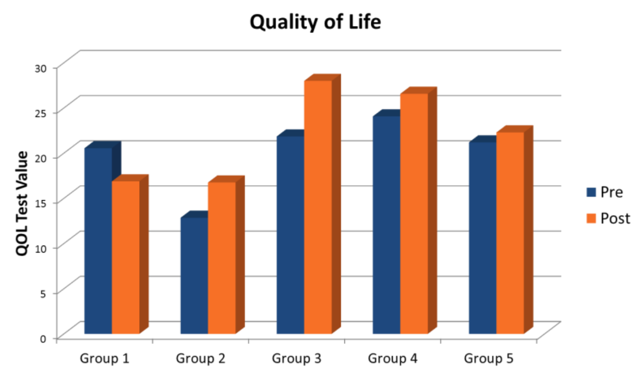

Figure 2. Quality of Life Assessment. *Note: Measured by Quality of Life-Cancer Version 3.*

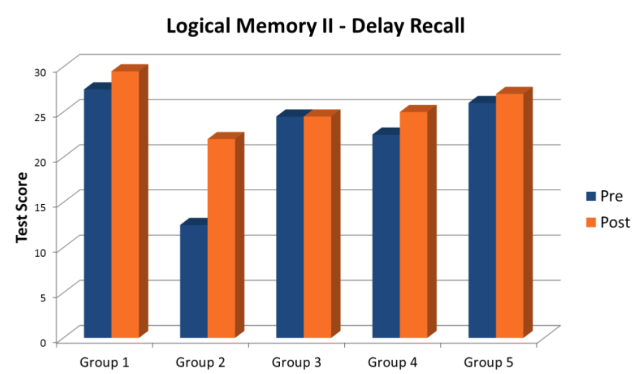

Figure 3. Logical Memory II-Delay Recall. *Note: Measured by Wechsler Memory Scale.*

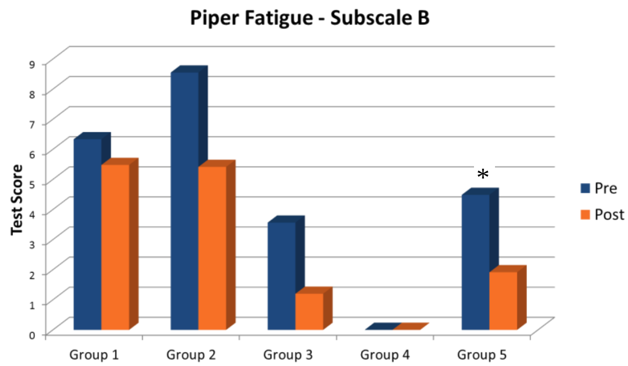

Figure 4. Piper Fatigue Scale – Subscale B.
Note: Measured by Revised Piper Fatigue Scale. Subscale B represents behavioral fatigue.
**statistically significant (p<0.05), Friedman test.*

DISCUSSION

This data is preliminary and marks the first study assessing both cognitive and aerobic training in cancer survivors. Due to the small sample sizes and novelty of this study, it was difficult to yield significance. We however, believe the findings of this study are beneficial in directing us in future interventions that may support cancer survivors experiencing CRCI. Group 1, which consisted of all three protocols (aerobic, cognitive, and flexibility) was the only group in which participants reported decreases in QOL following the intervention. This may have occurred because this group underwent the greatest amount of training and perhaps experienced too great a deal of stress while going through and finishing chemotherapy treatment. According to Schneider et al. (2003), there is an optimal dose of exercise during and following treatment and that when the intensity or amount becomes too high, immune function and QOL decrease.

All groups increased in Logical Memory II, which is a valid measure of cognitive function. Group 2 which included only aerobic and flexibility training yielded the greatest improvement, which was an anomaly since this group did not participate in any cognitive training. After careful review of the data, Group 2 started the study with a vastly lower baseline in Logical Memory II than the other four groups (a score of 12 versus 24.5). Since the n of each group is only 2, one individual performing poorly on the cognitive screening assessments, may have skewed the analysis post intervention. Fatigue was seen to improve in every cancer group and decreased significantly in Group 5 (cognitive and flexibility training). This indicates that physical activity in general may improve fatigue, but that cognitive training and flexibility training may play a pivotal role in reducing fatigue independently of exercise. Also of note, it comes with little surprise the least improvement occurred within the control group of the non-cancer subjects because they began the intervention with no fatigue.

Limitations

Interventions similar to this protocol are common ways to address the adverse side effects from chemotherapy treatment. However, there were some limitations within this intervention. Some of these gaps include limited physical capabilities, limited mental capabilities, weight, the effort put forward by the cancer survivor, and even medication taken by participants. These variables created some problems within our research because if a cancer survivor had any of these limitations then they could not perform some of the tasks required during this intervention. For example, weight was a major set-back during this study because it limited some participants from doing certain physical activities. Also most of the participants coming into this study were on several types of medications in order to recover from their pervious chemotherapy treatments, which could have manipulated their heart rates, breathing, etc. In addition, the efforts put forward by every cancer survivor was critical in being that we needed them to be in a positive mood and trying their best during each session, which was not always the case. When a cancer survivor was not focused or feeling depressed, then he or she most likely did not perform at his or her highest exertions.

Conclusion

The number of people diagnosed with cancer has increased over the years, along with the survival rate from cancer, which has resulted in a higher number of cancer survivors within the population. A large fraction of cancer survivors are coping with the adverse side effects from cancer treatments like chemotherapy, radiation therapy, hormonal therapy, and even surgery. These treatments have been found to primarily affect cognitive function within cancer survivors, slowly removing them from their own independence due to the loss of active neurons slowing down brain function. However, researchers have found a way to simulate neurological activity, using various types of cognitive and aerobic training interventions. All of these interventions have been found to increase the cognitive function of cancer survivors, as well as provide additional benefits within QOL, bodily functions, and in mental and physical states. It is unclear whether or not life expectancy and QOL will improve within cancer patients responding to treatment, which is why interventions play a key role in increasing those chances and alleviating those side effects. To our knowledge, there are no current studies that have examined exercise and cognitive training simultaneously within an intervention, in a cancer rehabilitation population. Again, the purpose of this study was to examine the effects of a 12-week aerobic and cognitive training intervention on cognitive function in cancer survivors following chemotherapy treatment with or without radiation. In addition, this group (doing both aerobic and cognitive training) was compared with either a non-cognitive, non-aerobic, or flexibility protocol. Overall, it was hypothesized that the combination of aerobic and cognitive training would significantly improve the cognitive function of cancer survivors' during and post chemotherapy treatments. After review of the data, we fail to accept our hypothesis and can only conclude that a combination of cognitive training and flexibility training reduces fatigue. Our preliminary findings do suggest there is a valuable role for cognitive training in conjunction with other modes of physical activity on QOL, fatigue, and cognitive function, but there were not a sufficient number of subjects to support this research.

Future Directions

There have been assuring results from the studies of cognitive and physical interventions that have shown an increase in cognitive function for cancer survivors. This is important because there have been major decreases in cognitive functions from the adverse side effects of cancer treatment. Since researchers have looked at each of these variables individually, the next step would be combining the variables of cognitive and physical training, while monitoring their psychosocial levels, into one experiment and observing for an even higher increase in cognitive function within a group of cancer survivors.

The first way we could set up this experiment utilizes the method of parallel activity. This technique will be able to look at these combined variables all in the same period of time. For example, we might have a subject pedal on a bike while completing various brain exercises and measure their cognitive function all at once via computer software analyses. It could be that multitasking might significantly improve the cognitive functions of cancer survivors within a shorter amount of time.

Another way for this experiment to be set up can utilize the method of sequences of activities. This technique will measure all of the variables as well, but in different periods of time. This will have each subject go through the same activities of brain exercises and aerobic exercises; however, this subject will be taking breaks in between each sequence. This might take more time to complete, but could be necessary in allowing for the brain to adjust for the cancer survivor.

A major focus should be paying attention to what brain exercises are being used and the level of difficulty of each exercise performed. This could also prevent a subject from performing at his or her highest level because the exercises are either too hard or easy. Also it is important for further research to find out what specific brain exercises and physical exercises are the most beneficial to a cancer patient. This could also lead into many other directions for this type of research in future interventions.

Effects of Aerobic and Cognitive Training Intervention on Cognitive Function

REFERENCES

Acevedo, S.F. (2012). Why, after chemotherapy, is it necessary to assess memory using translational testing? *Breast Cancer: Basic and Clinical Research, 6*, 181-190.

Ahles, T.A. (2012). Brain vulnerability to chemotherapy toxicities. *Pshyco-Oncology, 21*, 1141-1148. doi: 10.1002/pon.3196

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

American Cancer Society. (2014). Cancer facts and figures 2014. Retrieved from http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014

Arnold, R., Rinke, A., Schmidt, Ch., & Hofbauer, L. (2005). Chemotherapy. *Best Practice & Research Clinical Gastroenterology, 19*, 649-656.

Baker, F., Denniston, M., Smith, T., & West, M.M. (2005). Adult cancer survivors: how are they faring? *Cancer, 104*, 2565-2576.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, *4*, 561-571.

Belvoir Media Group, LLC, (2010). Chemotherapy. *Harvard Health Publication, Health Topics A-Z.*

Conroy, S.K., McDonald, B.C., Smith, D.J., Moser, L.R., West, J.D., Kamendulis, L.M.,… & Saykin, A.J. (2013). Alterations in brain structure and function in breast cancer survivors: effect of post-chemotherapy interval and relation to oxidative DNA damage. *Breast Cancer Research and Treatment*, *137,* 493-502.

Courneya, K.S., & Karvinen, K.H. (2007). Exercise, aging, and cancer. *Applied Physiology, Nutrition, and Metabolism*, *32,* 1001-1007.

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

Grady, C.L. (2008). Cognitive neuroscience of aging. *Annals of the New York Academy of Sciences, 1124*, 127-144.

Hsieh, C.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*, 909-915.

Jackson, A. S., & Pollock, M. L. (1978). Generalized equations for predicting body density of men. *British Journal of Nutrition, 40*, 497-504.

Jackson, A. S., & Pollock, M. L. (1980). Generalized equations for predicting body density of women. *Medicine and Science in Sports and Exercise, 12*, 175-181.

Jemal, A., Center, M. M., DeSantis, C., & Ward, E. M. (2010). Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiology Biomarkers & Prevention*, *19*, 1893-1907.

Koppelmans, V., de Ruiter, M.B., van der Lijn, F., Boogerd, W., Seynaeve, C., van der Lugt, A., & Schagen, S. B. (2011). Global and focal brain volume in long-term breast cancer survivors exposed to adjuvant chemotherapy. *Breast Cancer Research and Treatment*, *132*, 1099-1106.

Mackenzie, L.J., Carey, M.L., Sanson-Fisher, R.W., & D'Este, C.A. (2013). Psychological distress in cancer patients undergoing radiation therapy treatment. *Support Cancer Care, 21*, 1043-1051.

Maggio, M., Dall'aglio, E., Lauretani, F., Cattabiani, C., Ceresini, G., Caffarra, P., & Ceda, G.P. (2012). Hormonal dysregulation and cognition in the elderly: The hormonal pathway to cognitive impairment in older men. *The Journal of Nutrition, Health & Aging, 16*(1), 40-54.

Piper, B.J., Acevedo, S.F., Craytor, M.J., Murray, P.W., & Raber, J. (2010). The use and validation of the spatial navigation memory island test in primary school children. *Behavioral Brain Research*, 210, 252-262.

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

Pinto, B. M., Dunsiger, S., & Waldemore, M. (2013). Physical activity and psychosocial benefits among breast cancer patients. *Psycho-Oncology*, 22, 2193–2199. doi:10.1002/pon.3272

Proctor, R.N., (2003). Cancer. *Dictionary of American History*. 2 (3rd ed.), 34-35.

Quist, M., Rorth, M., Zacho, M., Andersen, C., Moeller, T., Midtgaard, J., and Adamsen, L., (2006). High-intensity resistance and cardiovascular training improve physical capacity in cancer patients undergoing chemotherapy. *Scandinavian Journal of Medicine and Science in Sports*. 16, 349-357.

Salkind, M. R. (1969). Beck depression inventory in general practice. *The Journal of the Royal College of General Practitioners, 18*, 267.

Schneider, C.M., & Hayward R. (2013). Cancer rehabilitation and cancer-related fatigue. Journal of Clinical Exercise Physiology, 2(1), 1-7.

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

Schmitz, K.H., & Speck, R.M. (2010). Risks and benefits of physical activity among breast cancer survivors who have completed treatment. *Future Science Group*, *6*, 221-238.

Schuurs, A., & Green, H.J., (2013), A feasibility study of group cognitive rehabilitation for cancer survivors: enhancing cognitive function and quality of life. *Psycho-Oncology*, 22, 1043-1049.

Siegel, R., DeSantis, C., Virgo, K., Stein, K., Mariotto, A., Smith, T.,… & Ward, E. (2012). Cancer treatment and survivorship statistics, 2012. *CA: A Cancer Journal for Clinicians, 62*, 220-241.

Summers, L. E. Effects of chemotherapy on patients' cognitive function. *Cancer Nursing Practice, 11*, 27-31.

Ward, E., DeSantis, C., Robbins, A., Kohler, B., & Jemal, A. (2014). Childhood and adolescent cancer statistics, 2014. *CA: A Cancer Journal for Clinicians, 64*, 83-103.

Wechsler, D. (2009). *Wechsler Memory Scale—Fourth Edition (WMS-IV) technical and interpretive manual*. San Antonio, TX: Pearson.

Wechsler, D. (2008). *Wechsler Adult Intelligence—Fourth Edition (WAIS-IV)*. San Antonio, TX: Pearson.

Wefel, J.S., & Schagen, S.B. (2012). Chemotherapy-related cognitive dysfunction. *The Canadian Veterinary Journal, 50*, 665-668.

Weis, J., Poppelreuter, M., & Bartsch, H. H. (2011). Rehabilitation of therapy-related cognitive deficits in patients with breast cancer. *Psicooncología, 8*, 371-384.

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: Medical Science*, *61A* (12), 1324-1329.

Wolman, R.L., Cornall, C., Fulcher, K, & Greenwood, R. (1994). Aerobic training in brain-injured patients. *Clinical Rehabilitation, 8*, 253-257.