Spring 2013

The Effects of Cognitive Intervention Training and Exercise on Memory Efficacy of Alzheimer's Disease At-Risk Elders

Genna M. Losinski
John Carroll University, glosinski13@jcu.edu

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Genna M. Losinski

John Carroll University

Senior Honors Project

Spring, 2013

Abstract

The effects of cognitive and exercise intervention training in patients labeled as 'at-risk' for Alzheimer's disease were examined. Sixty-eight cognitively intact older adults between the ages of 60-85, with a positive family history of Alzheimer's disease, and reportedly not currently engaged in regular exercise, were recruited. In a 12-week controlled clinical trial, participants were randomly assigned to participate in one of three conditions: (a) cognitive intervention training, (b) exercise intervention training, or (c) control group. All participants were administered a standardized battery of neuropsychological tests of episodic memory and sustained attention at baseline and at the 12-week follow-up session. In addition, each week, the participants completed the Physical Activity Scale for the Elderly, PASE, a commonly used self-report outcome measure for assessing activities of daily life. Results indicated a statistically significant difference for the interaction between the cognitive intervention group and the control group for portions of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Brief Visuospatial Memory Test-Revised (BVRT-R) neuropsychological tests. However, there were no statistically significant interactions between the groups for the Letter Number Sequencing (LNS) or Symbol-Digit Modalities Test (SDMT) neuropsychological tests. In addition, results indicated that there were no significant differences among the groups and the PASE scores at the follow-up session. Findings are discussed in the context of the possibility that cognitive intervention programs could lead to increased memory skills in at-risk Alzheimer's disease adults and that exercise interventions must be reevaluated and refined before any definitive conclusion can be drawn concerning the efficacy of this treatment.

Keywords: exercise intervention, cognitive intervention, physical activity, Alzheimer's disease, at-risk elders

The Effects of Cognitive Intervention Training and Exercise on Memory Efficacy of Alzheimer's Disease At-Risk Elders

Older age is associated with cognitive decline, dwindling independence in activities of daily life, and mortality. Memory function deficiencies are the most common complaint among the elder population (Bruce-Keller et al., 2012). Age-related biological changes in the brain have been explored as potentially explaining the occurrence of these cognitive and memory deteriorations (Squarzoni et al., 2012, Trollor et al., 2012). Squarzoni et al. (2012) identified gray matter volume reduction in the orbital frontal cortex and the temporolimbic regions of the brain as relevant biomarkers of cognitive deficits in healthy aging individuals. Trollor et al. (2012) found that neuroinflammation was related to cognitive decline in an elderly, non-demented, community dwelling population independent of depression, cardiovascular or metabolic risk factors. The question to consider is whether these cognitive deficiencies and structural brain changes are just part of the biological aging process or should be considered subclinical disease activity for developing dementia-related diagnoses.

One of the most diagnosed dementia-related diseases is Alzheimer's disease, which affects approximately five million Americans today (Centers for Disease Control and Prevention, 2012). Numerous theories exist that attempt to explain the cause of Alzheimer's disease. Evidence for the amyloid hypothesis has found that an elevated load of the precursor to the protein in the brain called beta-amyloid can cause cell damage and interfere with cell communication when hard, insoluble plaques are formed (Rosenberg, 2002). Another theory states that a protein called tau, which is responsible for internal support and transport of brain cells, has been found to tangle, leading to the failure of the transport system. (Hardy & Selkoe, 2002). Another factor that has been examined in Alzheimer's disease and dementia research is the role of the Lewy body structure presence in the brain. It has been found that abnormal round structures termed “Lewy bodies” develop in regions of the brain involved in thinking and movement, possibly causing the symptoms associated with Alzheimer’s disease and dementia (Calderon et al., 2001).

Hippocampal atrophy has been found to be one of the strongest predictors of Alzheimer’s disease (Henneman et al., 2009, Morra et al., 2009, Stoub, Rogalski, Leurgans, Bennett & Detaledo-Morrel, 2008). A study by Henneman et al. (2009) investigated the rate of hippocampal atrophy and the rate of whole brain volume atrophy within different population groups. A significant differentiation was found among three groups: patients with Alzheimer’s disease, patients with mild cognitive impairment, and elderly patients serving as controls. Hippocampal measures differed greatly between the controls and the mild cognitive impairment groups. Whole brain volume atrophy differed significantly between the mild impairment group and the Alzheimer’s disease group.

Research conducted by Morra et al. (2009) found similar results using the same three population groups from a larger participant pool and a more precise measurement method. A six year longitudinal study by Stoub et al. (2008) showed the rate of hippocampal and entorhinal cortex volume atrophy differed significantly among the same three population groups. At year six, 11 of the 33 patients labeled mildly cognitive impaired at baseline were diagnosed with Alzheimer’s disease and nine controls exhibited a decline in cognitive function (Stoub et al., 2008).

Factors have been studied that make individuals more susceptible to biological pre-cursers for Alzheimer’s disease. After years of research, scientists combined findings to identify the three most supported risk factors for developing Alzheimer’s disease. These three risk factors are age over 50, family history, and the presence of the apolipoprotein E (APOE) Ɛ4 allele on chromosome 19 (Donix, Small, & Bookheimer, 2012). Recognizing these factors can lead to improvements in diagnostic and therapeutic strategies for the at-risk population for Alzheimer's disease. For example, some of these therapeutic strategies include interventions that could slow the onset of the disease.

Physical exercise has been shown to be an effective intervention technique to delay dementia. A study first conducted using animals suggested that physical exercise affects brain function through calcium and calmodulin-dependent dopamine synthesis (Sutoo & Akiyama, 2003). In addition, recent research conducted on humans found that elderly adults who are physically active are 21% less likely to be diagnosed with dementia (Bowen, 2012). Epidemiological and biological research concluded that physical activity slows the course of Alzheimer's disease (Friedland, Fritsch & Smyth, 2001, Friedman & Tappen, 1991, Lindsay, Laurin & Verreqult, 2002, Logsdon, McCurry & Teri, 2005, Wilson, Mendes & Barnes, 2002). However, further research should be conducted to specify the type, duration, and intensity of physical exercise that proves most beneficial to Alzheimer's disease patients (Rolland, Abellan van Kan, & Vellas, 2008).

Another dementia intervention method receiving attention is cognitive training. In the Wilson, Scherr, Schneider, Tang, & Bennett (2007) longitudinal study, 700 elderly patients were measured for five years at annual clinical evaluations assessing their daily life participation in cognitively stimulating activities. Measurements were also recorded in eight regions of the brain for amyloid burden, density tangles, and presence of Lewy bodies. Results found that frequent participation in cognitively stimulating activities was associated with reduced incidence of Alzheimer's disease (Wilson et al., 2007).

No study has established the neural effects of physical exercise intervention or cognitive training intervention in individuals specifically considered at-risk for Alzheimer's disease. Therefore, the goal of this study was to examine the cognitive and memory efficacy of both exercise and cognitive training interventions in an at-risk elderly population. Neuropsychological testing and self-report surveys were utilized to measure outcomes.

Method

Participants

Participants were 68 adults between the ages of 68-85. All participants had a positive family history of Alzheimer's disease in a first or second degree relative. A first degree relative includes the individual's parents, full siblings, or children, while a second degree relative includes the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces or half-siblings. Recruitment took place in three domains: relatives of patients being treated in the Cleveland Clinic Lou Ruvo Center for Brain Health, relative support groups sponsored by the Alzheimer's Association-Cleveland Area Chapter, and advertisements in the local newspapers and on flyers on the property of the Cleveland Clinic.

Criteria for participant exclusion were neurological illnesses or conditions, medical illnesses or conditions that may affect brain function, and psychiatric disturbances meeting the Diagnostic and Statistical Manual for Mental Disorders 4^{th} edition (DSM-IV) Axis 1 criteria. Participants exhibiting severe depressive symptoms or substance abuse or dependence were excluded. Other exclusion criteria concerning drug usage included participants with current use of psychoactive medications except selective serotonin reuptake inhibitor (SSRI) and serotonin norepinephrine reuptake inhibitor (SNRI) antidepressants, and prior or current history of acetylcholinesterase inhibitor usage. Patients with any unstable or severe cardiovascular disease or asthmatic condition, history of transient ischemic attack, inability to walk unassisted, and diagnosis of Attention Deficit Disorder or any other learning disorder were also excluded. The study was approved by the Cleveland Clinic Institutional Review Board.

Materials

In the present study, three intervention conditions were created.

Cognitive Intervention Condition: The cognitive training group completed a commercially available training program titled "Brain Fitness Program" for a total of 12 weeks. The program consisted of six computerized tasks aimed at improving speed and accuracy of auditory information processing.

Exercise Intervention Condition: The exercise training group completed a controlled, 50 minutes a day, four days a week, aerobic exercise program for a total of 12 weeks. The program consisted of a treadmill exercise at an intensity level of 60%-70% based on the patient's fitness level, including a warm-up and cool-down.

Control Condition: The control group completed 40 physical flexibility and education sessions for a total of 12 weeks. The 20 physical flexibility sessions included 30 minutes of structured stretching exercises. The 20 educational sessions included a viewing of DVD-based educational programs on history, art, and literature.

Measures

Standardized Battery of Neuropsychological Tests

Research assistants administered to the participants a standardized battery of neuropsychological tests of episodic memory and sustained attention at baseline and at the end of week 12. The battery consisted of the Repeatable Battery for the Assessment of

Neuropsychological Status (RBANS), Brief Visuospatial Memory Test-Revised (BVMT-R), Letter Number Sequencing (LNS), and Symbol-Digit Modalities Test (SDMT).

Physical Activity Scale for the Elderly (PASE)

Participants were advised to complete a ten minute self-report PASE survey each week during the course of the experiment. The survey measured the physical activity of a person in day-to-day life experiences considering frequency, duration, intensity, and type of activity. Questions were categorized under leisure time activities, household activities or work-related activities. The answers ranged from yes/no to generalized answers (seldom, sometimes, or often) to answers related to time (less than 1 hour, at least 1 hour but less than 2 hours, 2-4 hours, or more than 4 hours). Each question corresponded to a specific category of physical activity and each category was given a certain PASE weight. The categories and PASE weights used can be found in Table 1 and the PASE survey with the questions can be found in the appendix.

Table 1: Physical Activity Categories and Corresponding PASE Weight ("Physical Activity Scale for the Elderly and Paffenberger Physical Activity Scale," p. 4).

Question	Category	PASE Weight
2 **2a**	walking	20
4 **3b**	light sports	21
5 **4b**	moderate sports	23
6 **5b**	strenuous sports	23
7 **6b**	muscle strength	30
8	light housework	25
9	heavy housework	25
A	home repairs	30
B	lawn work	36
C	gardening	20
D	caring for others	35
11 **10a** **10b**	job involving standing/walking	21

To score each survey, the answer options were recoded as a number of days or hours spent on the activity. For example, the answer 'seldom' was appointed 1.5 days, the answer 'sometimes' was given 3.5 days, and the answer 'often' was appointed 6 days. 'Yes' answers were recoded as '1' and 'No' answers were recoded as '0.' The number of days or number of hours was then multiplied by the PASE weight to arrive at the final score for that question. The scores of all of the questions were added up to calculate the final PASE score for each participant each week ("Physical Activity Scale for the Elderly And Paffenberger Physical Activity Scale", p. 4).

Procedure

Potential candidates were contacted and a standardized telephone screen was conducted to review medical and psychiatric history, to determine if the candidate was fluent in English, and to confirm the candidate's ability to adhere to the time commitment of the study. If all of the inclusion and exclusion criteria were met, the potential candidate was scheduled for a screening evaluation at the Clinic. The psychometric examination ensured that the potential candidate met the mean requirements for the Rey Auditory Verbal Learning Test (RAVLT), Mini-Mental Status Exam (MMSE), Geriatric Depression Scale (GDS), and the Lawton and Brody Self-Maintaining and Instrumental Activities of Daily Living (ADL) Scale.

A physical examination determined if the potential candidate was medically capable of exercise interventions. A blood sample was collected with no identifying information and sent away for APOE genotyping. The results were only given to patients who requested it and an appointment was scheduled with a genetic counselor if appropriate. If eligibility were confirmed at the conclusion of the evaluation, a Physician Consent form was sent to each of the participants' physicians. The consent asked for the permission of the patient to partake in the study, noting the exercise requirements.

The 68 participants were randomly assigned to participate in one of the three conditions: the exercise intervention training, the cognitive intervention training, or the control group. For 12 consecutive weeks, the participants were expected to visit the Clinic a total of 42 times to complete one of the three conditions. At each weekly visit, participants completed the PASE survey evaluating their physical activity performed during the past week. A maximal exercise test was administered to the participants once at baseline and again at the week 12 follow-up session. The assessment was conducted with three purposes: to determine if the participants were capable of participating in exercise training, to establish an appropriate starting point for exercising, and to assess the effect of exercise training in improving cardiorespiratory fitness. The participants completed the neuropsychological battery of tests at this same meeting at baseline and at the week 12 follow-up session. At the end of the experiment, all participants were fully debriefed and thanked for their time. Outcome data on the neuropsychological tests and the PASE survey were collected.

Statistical Measures

Using the R statistical program, several between subjects, repeated measure, ANOVAs were conducted on the PASE survey score from each participant each week to analyze baseline, improvement at midpoint (weeks 1-6) and overall improvement (weeks 1-12) for the incorporation of physical activity into daily life. In addition, the R statistical program was also used to conduct several between subjects, repeated measure, ANOVAs on the RBANS, BVMT-R, LNS and SDMT neuropsychological cognitive tests.

Results

The R statistical program, repeated measures ANOVA tests with a between subjects factor were run on the results of the RBANS, BVMT-R, LNS and SDMT neuropsychological cognitive tests. A test of simple effects with a Tukey correction indicated there was a statistical significance for the interaction between the results of the RBANS List Recall Test for the cognitive intervention and control groups, $F(2,65) = 4.49$, $p = .037$, $\eta_p^2 = 0.734$ (small effect), 95% CI [3.62, 9.13]. Participants who completed the cognitive intervention (M=7.17, SD=2.70) scored higher on the RBANS List Recall Test at follow-up than participants in the control group (M=5.32, SD=2.42). The results of the interaction are graphed in Figure 1.

In addition, the RBANS Digit Span Test showed the same result. A test of simple effects with a Tukey correction indicated that there was a statistical significance for the interaction between the cognitive intervention group (M=11.83, SD=2.69) and the control group (M=10.05, SD=2.15), $F(2,65) = 4.21$, $p = .032$, $\eta_p^2 = 0.689$ (small effect), 95% CI [0.13, 3.43] with the cognitive intervention group scoring higher than the control group. The results of the interaction are graphed in Figure 2.

Another test of simple effects with a Tukey HSD correction indicated there was a significant interaction between the results of the BVMT-R Test and the cognitive intervention group (M=8.865, SD=3.17) and control group (M=6.654, SD=2.16), $F(2,65) = 3.028$, $p = .006$, $\eta_p^2 = 0.689$ (small effect), 95% CI [0.58, 3.91] with again, the cognitive intervention group scoring higher than the control group. The results of the interaction are graphed in Figure 3. However, there was no main effect for the LNS Test at follow-up, $F(2,65)=3.563$, $p= 0.121$. In addition, no main effect for the SDMT Test was found, $F(2,65)=2.61$, $p= 0.109$.

A repeated measure ANOVA test run with the R statistical program found no significant main effect for the PASE score at baseline, $F(2,65) = 7.92$, $p = .457$, meaning the groups were matched on physical activity at Week 1. At the time of follow-up, there was no significant main effect for the PASE score either, $F(2,65) = 1.307$, $p = .280$. Participants in the exercise group (M=111.88, SD = 81.15) showed no significant amount of more physical activity at week 12 compared to participants in the cognitive group (M = 203.80, SD = 67.99) or participants who were in the control group (M = 77.50, SD = 35.62). The results are graphed in Figure 4. It was discovered that many participants had not completed the survey up to week 12 and data were missing. Therefore, a repeated measure ANOVA test was run with the main effect for the PASE score at mid-program, defined as Week 1-Week 6, when all participants had completed the survey each week. ANOVA tests for midpoint improvement showed no significant main effect for PASE scores among the three groups, $F(2,65) = .867$, $p = .425$.

Discussion

The major finding in this study indicated that a statistically significant interaction existed between the cognitive intervention group and the control group for the List Recall and Digit Span portions of the RBANS and the BVMT-R test. However, no statistically significant interactions between the groups were found for the LNS or SDMT tests. Although these findings vary, practical and applied implications can still be identified within the significant results. Recent studies have found similar results with cognitive training in a comparable population (Herrera et al., 2012, Kueider, Parisi, Gross, & Rebok, 2012). These studies suggest the use of cognitive training as preventative therapeutic measures for Alzheimer's disease and as a potential early-intervention strategy. In conclusion, this study adds to the growing body of research for cognitive training as a beneficial intervention to the onset of Alzheimer's disease.

The physical exercise intervention group did not significantly show any improvements on the neuropsychological tests in comparison to the other groups. In regard to the PASE survey, as expected, at baseline the three groups began with matched levels of reported physical activity in everyday life. However, no significant improvements in reports of physical activity were found in any of the groups at the end of 12 weeks.

Limitations and Suggestions for Future Research

There are several limitations with the current study. As noted in the Results, there was a large incidence of missing observations in the PASE data set and a less appropriate, weaker, statistical analysis of the findings had to be conducted. Many participants did not complete a survey each week, resulting in multiple absent scores for many weeks. To compensate for this problem, an analysis of completed scores without missing data from week 1 to week 6 was run, yet no significant results were found. Due to the incomplete data set, a MANOVA could not be run to analyze the overall improvement over the full 12 weeks, leading to a less appropriate and weaker statistical analysis of the findings. Closer monitoring of the distribution and collection of the completed PASE survey should have been enforced.

A second limitation to consider is the scoring of the PASE survey. This scoring system should be reevaluated, since certain questions may have been weighted unreasonably. For example, 'lawn work' received the highest PASE weight. However, there are many non-physical activities that can be considered as 'lawn work,' such as holding a hose to water plants. In addition, 'light housework' was given a heavier PASE weight than strenuous sports. Light housework, such as doing the dishes, should not be measured as a more physical activity than strenuous sports such as swimming laps. Reevaluation of the scoring or a more specific scoring process should be considered in future research.

Results from the current study indicate that exercise intervention needs to be reexamined. Future research should consider finding and incorporating the most beneficial types of exercise in regard to type, intensity, and duration. Specifically, research should focus on the type of exercise that stimulates and enhances the parts of the brain that have been shown to deteriorate in Alzheimer’s disease, such as hippocampal atrophy. Exercise interventions are so vast in today’s culture that an explicit regimen should be researched to apply to at-risk Alzheimer’s disease adults. Once this type of exercise has been established, a possible improvement in cognitive functions of at-risk Alzheimer’s disease elders due to exercise intervention may be determined.

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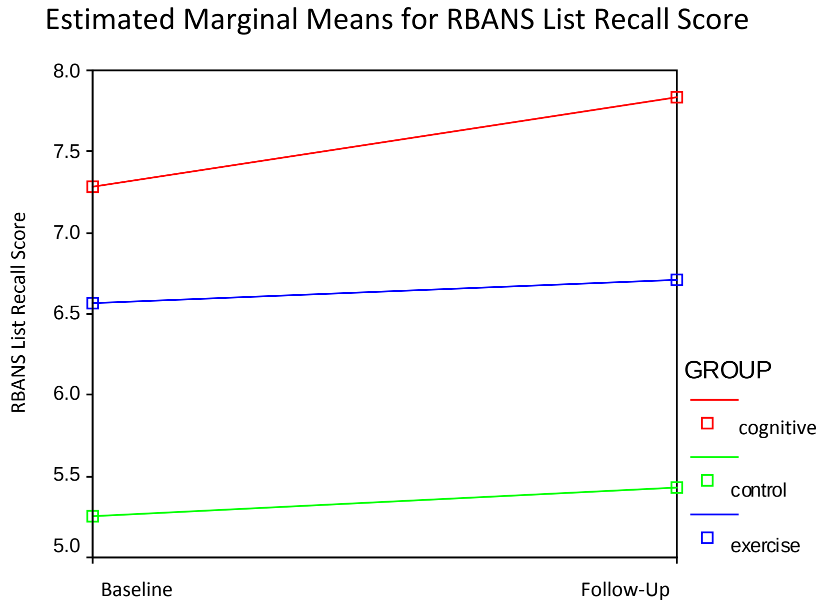

Figure 1: The interaction between the score on the RBANS List Recall Test and the three groups: exercise training, cognitive training and the control.

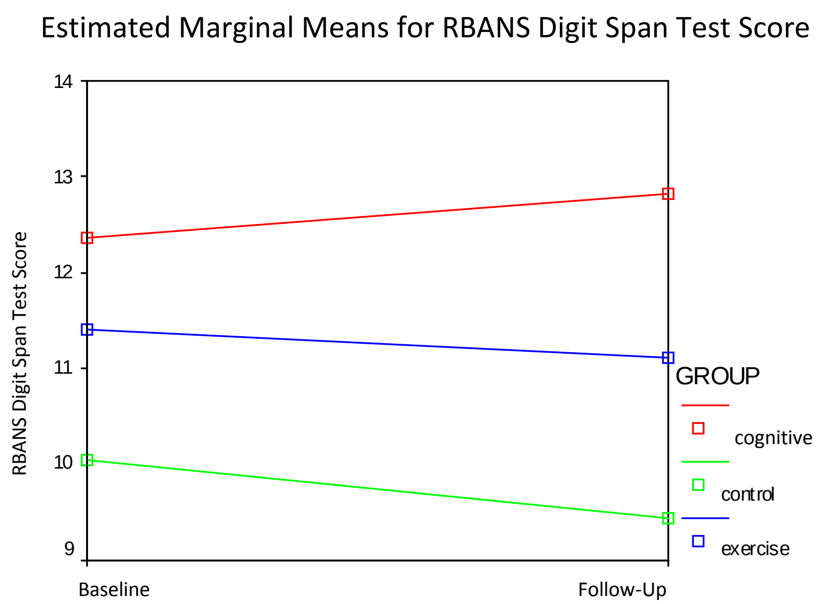

Figure 2: The interaction between the score on the RBANS Digit Span Test and the three groups: exercise training, cognitive training and the control.

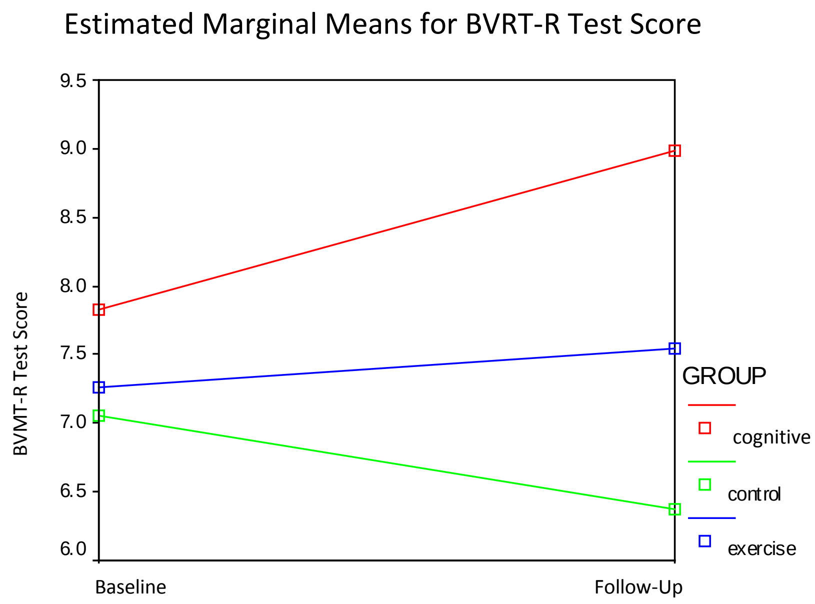

Figure 3: The interaction between the score on the BVMT-R Test and the three groups: exercise training, cognitive training and the control.

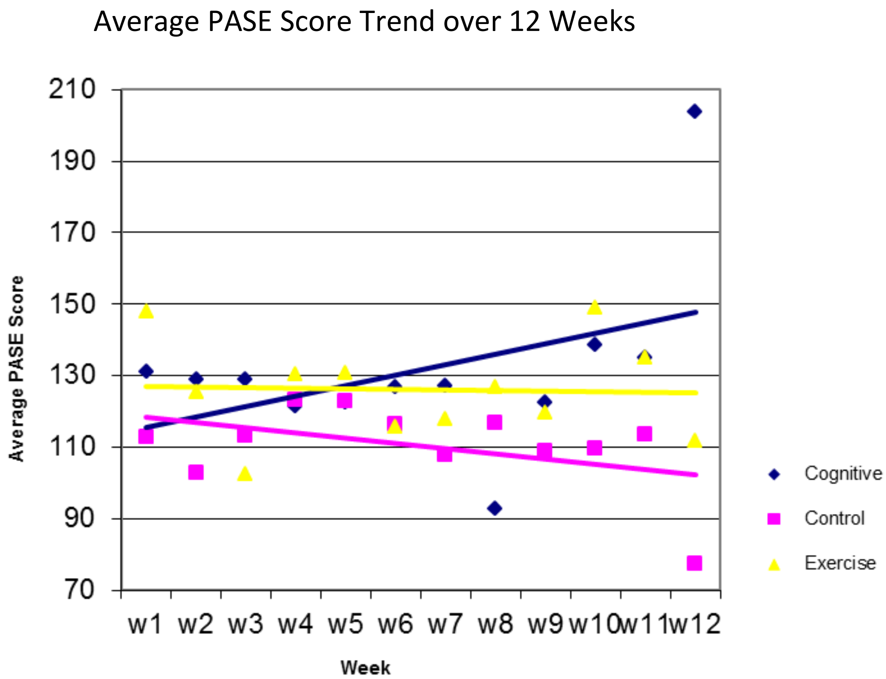

Figure 4: Average PASE Score Trend Over 12-Weeks by groups: exercise training, cognitive training and the control.

Appendix

Name : ______________________
Date : ______________________
☐ baseline ☐ _______ months

Physical Activity Scale for the Elderly
And Paffenbarger Physical Activity Index

LEISURE TIME ACTIVITIES

1. Over the past 7 days, how often did you participate in sitting activities such as reading, watching TV or doing handcrafts?

[0] never → Go to Q.2
[1] seldom (1-2 days)
[2] sometimes (3-4 days)
[3] often (5-7 days)

1a. What were these activities?
____

1b. On average, how many hours per day did you engage in these sitting activities on these days?
[1] less than 1 hour
[2] 1 but less than 2 hours
[3] 2 – 4 hours
[4] more than 4 hours

2. Over the past 7 days, how often did you take a walk outside your home or yard for any reason? For example for fun or exercise, walking to work, walking the dog etc?

[0] never → Go to Q.3
[1] seldom (1-2 days)
[2] sometimes (3-4 days)
[3] often (5-7 days)

2a. On average, how many hours per day did you spend walking on these days?
[1] less than 1 hour
[2] 1 but less than 2 hours
[3] 2 – 4 hours
[4] more than 4 hours

b) What was the **total** distance (kms/miles/blocks) that you walked in the past 7 days? (1 mile = 12 blocks: 1km = 0.625miles).

Total number of blocks walked in the past **week** _____, or km _____, or miles _____

[1] less than 1 mile
[2] One but less than 2 miles
[3[two to 4 miles
[4] more than 4 miles

3. How many flights of stairs did you **climb up** in the past 7 days? (one flight = 10 steps)
Total number of steps climbed in the past **week** _______, or flights of steps _______
[1] less than 1 flight
[2] One but less than 2 flights
[3] two to 4 flights
[4] more than 4 flights

4. Over the past 7 days, how often did you engage in **light** sport or recreational activities such as 'light' cycling on an exercise bike, lawn bowls, bowling, water aerobics, golf with a cart, yoga, tai chi, fishing from a boat or pier or other similar activities?

[0] never → Go to Q.4
[1] seldom (1-2 days)
[2] sometimes (3-4 days)
[3] often (5-7 days)

3a. What were these activities?

____

3b. On average, how many hours per day did you engage in these light sport or recreational activities on these days?
[1] less than 1 hour
[2] 1 but less than 2 hours
[3] 2 – 4 hours
[4] more than 4 hours

5. Over the past 7 days, how often did you engage in **moderate** sport or recreational activities such as doubles tennis, ballroom dancing, golf without a cart, softball or other similar activities?

[0] never → Go to Q.5
[1] seldom (1-2 days)
[2] sometimes (3-4 days)
[3] often (5-7 days)

4a. What were these activities?

____

4b. On average, how many hours per day did you engage in these moderate sport or recreational activities on these days?
[1] less than 1 hour
[2] 1 but less than 2 hours
[3] 2 – 4 hours
[4] more than 4 hours

6. Over the past 7 days, how often did you engage in **strenuous** sport and recreational activities such as jogging, swimming, cycling, singles tennis, aerobic dance, skiing (downhill or cross country) or other similar activities?

[0] never → Go to Q.6
[1] seldom (1-2 days)
[2] sometimes (3-4 days)
[3] often (5-7 days)

5a. What were these activities?

____

5b. On average, how many hours per day did you engage in these strenuous sport or recreational activities on these days?
[1] less than 1 hour
[2] 1 but less than 2 hours
[3] 2 – 4 hours
[4] more than 4 hours

7. Over the past 7 days, how often did you exercise specifically to increase muscle strength and endurance such as lifting weights or pushups etc?

[0] never → Go to Q.7

[1] seldom (1-2 days)

[2] sometimes (3-4 days)

[3] often (5-7 days)

6a. What were these activities?

____

6b. On average, how many hours per day did you engage in exercise to increase muscle strength/endurance <u>on these days</u>?

[1] less than 1 hour   [2] 1 but less than 2 hours

[3] 2 – 4 hours   [4] more than 4 hours

HOUSEHOLD ACTIVITIES

8. During the past 7 days, have you done any light housework such as dusting or washing dishes?

[1] No   [2] Yes

9. During the past 7 days, have you done any heavy housework or chores such as vacuuming, scrubbing floors, washing windows or carrying wood?

[1] No   [2] Yes

10. During the past 7 days, did you engage in any of the following activities?

	No	Yes
a. Home repairs like painting, wallpapering, electrical etc	0	1
b. Lawn work or yard care including snow or leaf removal, wood chopping etc	0	1
c. Outdoor gardening	0	1
d. Caring for another person such as a dependent child, dependent spouse or another adult	0	1

WORK-RELATED ACTIVITIES

11. During the past 7 days did you work for pay or as a volunteer?

[1] No   [2] Yes

10a. How many hours per week did you work for pay and/or as a volunteer? __________hours

10b. Which of the following categories best describes the amount of physical activity required on your job and /or volunteer work?

(1) Mainly sitting with light arm movements (eg. Office work, watch maker, seated assembly line worker, bus driver etc)

(2) Sitting or standing with some walking (eg. Cashier, general office worker, light tool and machinery worker)

(3) Walking with some handling of materials generally weighing less than 50 pounds (eg. Mailman, waitress, construction worker, heavy tool and machinery worker)

(4) Walking and heavy manual work often requiring handling of materials weighing over 50 pounds (eg. Lumberjack, stone mason, farm or general labourer.