Running Head: LOW-INTENSITY EXERCISE AND DEMENTIA

Neuropsychological and Neurophysiological Effects of Low-Intensity Strengthening

Exercise on Cognition

By

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ABSTRACT

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With the growing aging population, it's becoming increasingly important to find ways to either deter or prevent dementia. To date, most research has concentrated on the effects of aerobic exercise on cognition. Unfortunately, a large portion of older adults are often contraindicated to perform aerobic exercise due to different risk factors, which increase with age. Alas, alternate ways of exercise are necessary. Low-intensity strengthening exercise is a type of exercise aimed at improving balance and strengthening muscles without requiring one to overstrain. The current 11-week long exercise study test neuropsychological effects of exercise with an electroencephalogram (EEG). We find that 11 weeks of low-intensity strengthening exercise significantly improves verbal and visual-spatial memory (as measured by the Fuld task and the Complex Figure task) and significantly increases N200 amplitude hemispherical asymmetry in the frontal lobe.

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INTRODUCTION

Cognitive impairment and dementia become an increasing concern with age. Alzheimer's disease is the sixth leading cause of death in elderly adults and it is estimated that by 2050 one in every 85 people will be affected by Alzheimer's disease, raising the current number affected to 106.2 million (Brookmeyer, 2007). Numerous scientific initiatives have been undertaken to identify risk factors involved and to propose possible pathways in which the deterioration takes place (Harwood, 2010). Although there is currently no cure for Alzheimer's disease, research has shown that one of the simplest and cheapest ways to deter cognitive decline is exercise. Specifically, it has been repeatedly found that exercise can have a significant impact on cognitive function in older adults (Colcombe et al., 2004; Kramer et al., 2005, etc.). It is also widely accepted that increases in cardiovascular fitness result in increased functioning of key aspects of the attention network during mental tasks. In the following three sections, I will describe three of the ways of gauging the condition of the brain and how these ways have been implicated in measuring deterioration during a disease as well as the effects that exercise has on the brain. I will then describe the motivation for and the methodology of the current study before presenting the obtained results.

Imaging:

One way of measuring cognitive state and pathway of deterioration is neuroimaging. The neuroimaging technology available today allows for minimally-invasive techniques that provide insight into the human brain. These imaging techniques have brought to light numerous observations not only about the path of deterioration of the brain that takes place with normal aging (Raz et al., 2005), but also the deterioration as the result of a disease (Thompson, 1998, Larson et al., 2006 etc.). Exercise has been shown to increase nutrient supply to capillaries, to

decrease neuronal death (Feske et al., 1988; Dierks et al., 1999; Dierks, 2000), induce neurogenesis of the hippocampus, which is thought to be most important in memory formation and implicated in cognitive aging (Pereira et al., 2007; Erickson et al., 2009, 2011, etc.). These important and direct anatomical effects have been captured using technology with advanced spatial resolution, such as MRI and fMRI (Erickson et al., 2009, 2011). Although they possess incredible spatial resolution, fMRI and MRI lack in temporal resolution. An alternate imaging technique used to capture cognitive state and dynamics is through Electroencephalogram (EEG). EEG provides a temporal resolution superior to what is present in MRI and fMRI. EEG provides a way of measuring the rates of neuronal firing, rather than direct blood flow. In this study, we evaluated two aspects of the collected EEG data: Band Power and the P300 marker.

Band Power:

One way to analyze EEG recording is by measuring the prevalence of frequencies across groups. For this study, brain waves were classified into the following groups frequencies: Alpha (8-14 Hz), Beta (14-35 Hz), Theta (4-7 Hz), Delta (0-4 Hz) and Gamma (30-100 Hz). Research shows that patients with Mild Cognitive Impairment (MCI) have higher powers of longer waves: Theta and Delta, and lower power of shorter waves: Alpha and Beta (Yerokhin et al. 2011; Adler et al. 1999; Kamp, 1978; Lardon, 1999). It has also been shown that patients with Alzheimer's disease show higher powers of Theta and/or Delta and lower powers of Alpha and/or Beta (Adler et al. 1999; Huang et al., 2000; Ponomareva et al. 2003; Babiloni et al. 2004; Jeong, 2004; Luckhaus et al. 2008). In another study performed by Lackhaus et al. 2008, it was found that Alzheimer's patients as well as patients with progressing mild cognitive impairment (defined as the change in the total ADAS-cog score of \geq 4 points within one year) expressed a significant decrease in the alpha power over posterior leads as well as an increase in the slow wave activity

as compared to the healthy control and the group with stable mild cognitive impairment. Additionally, an increase in variability of frequencies has also been implicated with cognitive decline (Koenig, 2005; Hogan et al., 2006).

P 300 and N200:

Another technique of collecting EEG data is by examining the ERP (Event Related Potentials). Two relevant components of ERP were used in this study: P300 and N200. P 300 was defined as the largest positive peak between 300-750 ms post stimulus. N200 was defined as most negative peak 0-350ms post-stimulus. Three components of each peak are typically analyzed: amplitude, latency and area under the curve (AUC). Increase in latency of P300, decrease in amplitude and a decrease of the AUC have been associated with a decline in cognitive state (Intriligator & Polich, 1994, 1995; Jasiukaitis, & Hakerem, 1988; Lardon & Polich 1996; McDowel et al. 2003). Relationship between the aforementioned N200 components and cognition is currently less explored. Studies have related N200 amplitude with stimulus inhibition, verbal production and executive functions (Folstein & Van Petten, 2008). *Neuropsychological Evaluation:*

An alternate way of gauging the cognitive state as well as cognitive dynamics is through neuropsychological testing. Neuropsychological testing allows for a different angle at viewing the brain, which may be more sensitive to specific aspects of cognition (especially executive functioning) than neuroimaging techniques, as neuropsychological examination provides a link between brain and behavior (Salmon & Bondi, 2009, Hall et al., 2001, etc.). Previous studies using neuropsychological evaluations have found significant improvement in executive functions (e.g. Anderson-Hanley, 2010; Colcombe & Kramer, 2003; Hall et al., 2001, Heyn et al., 2004, etc.) as the result of exercise.

Biological Evaluation:

In dementia, the brain begins to atrophy until its functions are no longer as efficient as they once were. While several biological markers have been associated with neurogenesis, decline in the amount of markers such as BDNF, has been linked to cognitive decline as well as dementia (Vaynman et al., 2004, Erickson, 2009, 2010, 2011, etc.). BDNF is thought to influence neurogenesis by promoting cellular development, differentiation, survival and plasticity (Egan et al., 2003). Furthermore, exercise has been shown to increase the secretion of BDNF and its receptor protein: tyrosine kinase trkB (Vaynman et al., 2004, Li, 2008), providing an important biological link for the pathway that potentially deters the disease.

Levels of BNDF in all previous neuropsychological studies have been measured using blood serum. Because blood collection can be invasive, frightening and also costly, it is imperative to search for other, less invasive and less expensive ways of measuring BDNF. In this study we used saliva to test for the levels of BDNF using ELISA (enzyme-linked immunosorbent assay). Previous attempts to measure salivary BDNF using SDS-PAGE have been promising (Mandel et al., 2009). While a most recent attempt to measure salivary BDNF using ELISA were inconclusive when compared to serum levels of BDNF (Mandal et al., 2011). *Motivation:*

Most psychophysiological research to date has concentrated on aerobic exercise (Erickson et al. 2009, 2011; Arent et al. 2000, etc.) However, aerobic exercise is often contraindicated and is at times unrealistic for older adults as a result of cardiovascular risks and other impairments (such as osteoporosis). Hence, a safer alternative to aerobic exercise is vital. Some researchers have already taken aim to look at the effects of low-intensity exercise on cognition and results are promising (Kramer et al., 2006, Anderson-Hanley et al., 2010).

Understanding the effects of this less-intensive exercise is especially important as the older population of baby-boomers is gradually increasing. One point of importance for research in the field is motivation. Specifically, amongst other factors that prevent exercise, older adults often believe that if they haven't exercised previously, it is too late to start now (Deeny, 2006). Although it has been shown that increased exercised in the earlier life does help decrease the risk of dementia (Hall et al., 2001; Hillman et al., 2004; Lardon & Polich, 1996), ample research suggests that it is not too late to start (Lautenschlager, 2009 ; Kramer et al., 2006 ; Kamijo et al., 2007 ; Streiner, 2009, etc.). Prior studies have already found significant neuropsychological benefits to low-intensity exercise (Kazmenski & Anderson-Hanley, 2007; Nimon & Anderson-Hanley, 2007). This study aims to test the effects of new low-impact exercise (e.g. chair exercises with small weights, see Appendix A) on cognition through neurophysiological (EEG), neuropsychological (neuropsychological battery) and biological (ELISA for BDNF) measures. Moreover, we plan on using a novel approach of biological testing and EEG data evaluation. *Hypotheses:*

It is expected that as a result of exercise,

- Executive functioning, visual and verbal memory, as measured by a neuropsychological battery will improve
- 2. Overall band power will increase, as measured by resting EEG
- Alpha and Beta powers will increase and Theta and Delta powers to decrease as measured by resting EEG
- 4. P300 latency will decrease and P300 amplitude will increase as the result of the exercise
- 5. N200 amplitude will increase

METHODS

Participants

The sample consisted of 11 older adults ages 60-95 (mean=79.31; SD=11.00) with mild cognitive impairment (MCI) and 8 normative older adults ages 55-78 (mean=62.91; SD=7.29) (See Table 1). All MCI participants were male. All but one volunteer were male. All normative older adults were either employees or volunteers at the Albany Stratton VA Medical Center (VAMC). Participants in the normative sample were recruited through fliers and posters in public locations (bulletin boards, elevators, etc.) at the Albany VAMC. MCI participants were patients at the Albany VAMC attending an adult day program, who were selected by adult day care program staff. Each participant was screened for inclusion during in-person appointment via questions about their brain health and past medical history pertinent to their cognition. They were also given a brief screening of their cognitive state in order to gauge their mental competence. MCI participants deemed unable to give their own consent were sent home with a surrogate consent form, which was approved by VAMC Human Research Board and explained in detail all of the possible study risks and benefits, to be signed by the caregiver. All other participants were informed of risks and benefits of the study and were asked to sign a consent form also approved by the Albany VAMC Human Research Board Physician consent to exercise was obtain from each of the participant's primary care physician. All participants had corrected to normal vision.

Procedures

The intervention period lasted 11 weeks. All participants were asked to follow a lowintensity strengthening exercise routine designed by Tufts University for seniors for prevention

of osteoporosis (Suguin, Epping, Buchner, Bloch & Nelson, 2002), which primarily consisted of chair and standing exercises, involving small free weights (see Figure 1). Participants were guided by adult day care staff and while watching a DVD at least 3 times per week for the 11 weeks of the study. The exercise was aimed at strengthening muscles and improving balance (see Appendex A). Exercise frequency at the VAMC was recorded using a log sheet (see Appendix B); participants were also given log sheets and a copy of the exercise DVD to take home if they wished to exercise at home.

Measures

Neuropsychological Battery

FOME (Fuld Object Memory Evaluation; Fuld, 1981). FOME is aimed at evaluating episodic memory in older adults. In this task, a bag with 10 common objects is presented to a participant. The participant is asked to reach into the bag and feel for an object, but not pull it out. The participant is asked to identify the object by touch, without looking. Next, the participant is asked to pull it out and identify the object visually. When all 10 of the objects have been pulled out of the bag by the participant, they are replaced into the bag and the bag is left on the table for the remainder of the task. After a brief verbal production test (the participant is asked to name as many different names of the same gender as possible within 60 seconds), the participant is asked to recall the object. Objects that were left out by the participant are dictated at a rate of 1 object/5 seconds. The participant is then asked to recall the object.

Complex Figure: Rey-O (Rey, 1941; normalized by Osterrieth, 1944) *and Taylor* (Taylor, 1969) versions. Rey-O version was used for pre and Taylor version was used for post exercise. In this task, the participant was presented with a complex figure and asked to copy it onto a sheet of paper as completely and accurately as possible. 30 minutes later, the participant was

reminded of the figure and asked to draw it again, but this time from memory. Each complex figure (copy and recall, pre and post) was scored by two different graders on a scale from 0 to 36 with 0-2 points assigned for each component of the drawing.

Stroop C. The Stroop Test (Stroop, 1935; adapted by Van der Elst, 2006) measures selective attention, cognitive flexibility and processing speed. The test consists of three parts: 1) Colored blocks, 2) black words and 3) Interference (colored words). The three components are administered consecutively on three different sheets of paper. For each sheet of paper, participants are asked to name targets as quickly as possible without making mistakes. On the first page, participants are asked to read the color of the blocks as. On the second page, participants are asked to read the name of the colors (presented in black) and on the third page, participants are asked to ignore the written word and name the color of the word. Time to complete each of the components is recorded, with higher time indicating a decline in cognitive functioning. Only Stroop C was used in the analysis.

Color Trails 2 (D'Elia, Satz, Uchiyama, & White, 1996). Color Trails 2 was administered after Color Trails 1. In both tasks (which were administered consecutively on two separate sheets of paper), either pink or yellow colored circles with numbers inside the circles were presented. In Color trails 1, participants were asked to connect the circles in ascending order, paying attention to numbers only. In Color Trails 2, however, participants were asked to connect the circles in ascending numerical order and alternate colors. Time for completion was recorded with a decrease in time indicating an improvement in cognitive functioning. Alternate forms from the publisher were used at pre and post exercise evaluations.

Digit Span Backwards: The Digit Span Tests (Wechsler Memory Scale-III tests). In this task, a string of numbers was read by the administrator at a rate of one number per second. The

string of numbers was different each trial and increased in length by one digit every other trial. The participant is asked to repeat this string of numbers in the order it was announced by the administrator. In the digit span backwards, a different string of numbers is read, but this time the participant is asked to repeat the string in a reverse order (if the dictated numbers are "9-1-7", the participant would be expected to say "7-1-9"). For both Digit Span and Digit Span Backwards, dictation terminated when the participant made a mistake two consecutive strings of the same length. Scores ranged from 1-14 with a point awarded for a completion of one string.

Brunel Mood Scale (BRUMS; Terry & Lane, 2003). BRUMS is a questionnaire designed to provide quick mood assessment for adults. It's a 24-item questionnaire aimed at gauging 6 main aspects of mood: anger, confusion, depression, fatigue, tension and vigor. Participants filled out this questionnaire pre and post exercise.

Physical Activity Questionnaire (PAQ) (Aadahl, 2003). PAQ consisted of questions about participants' typical exercise habits. As with BRUMS, PAQ was administered before and after the exercise period.

Electroencephalography (EEG)

EEG recording was administered to each participant before and after the 11-week-long exercise intervention. For each of the EEG recording components, participants were seated comfortably in a slightly reclined position with lights dimmed. EEG data was recorded using a commercially available QuickCap (Compumedics, Inc.). Size of a cap was selected to accommodate the participants' heads. The cap consisted of 38 Ag/AgCl electrodes in the 10-20 system (Jasper, 1958) referenced to A1/A2 on the mastoid bones. The cap was fixed in place with a chin strap in order to minimize shifting. Each electrode was filled with Electr-Gel (Neumedical Supplies, Inc.) in order to reduce impedance. Data was collected from FP1/2,

FP3/4, FZ, F7/8, FT7/8, FC3/4, FCZ, T3/4, C3/4, CZ, TP7/8, CP3/4, CPZ, P3/4, PZ, T5/6, O1/2, OZ, FT9/10, PO1/2. Impedance was lowered below 10 k Ω for all electrodes included in the analysis. Signal was amplified using a commercially available amplifier, NuAmps (Compumedics, Inc.), and sampled at a rate of 1000Hz.

Resting EEG:

For the resting EEG component, participants were asked to lie comfortably in a chair with their eyes closed for 5 minutes, then open their eyes upon request and lie comfortably with their eyes open for 5 minutes during the EEG recording. Participants were asked to make sure to not fall asleep, to move as little as possible and to not cross their arms or legs.

ERP Tasks:

For both tasks, the presentation occurred on a screen about 0.50 meters away from the participant. Each participant was comfortably reclined at approximately 45° angle during both tasks.

Oddball Task:

Oddball paradigm was recreated similarly to Pontifex et al., 2009, where a target (5.5 cm diameter black circle with red outline on black background) and a distractor (3 cm white circle, black background) are presented for 100ms duration with 1000 ms inter-stimulus interval for two counter-balanced blocks of 200 trials. The target was presented with 0.20 probability and the distractor with 0.80 probability of occurring. Participants were asked to respond as quickly and as accurately as possible to the target only by pressing the left mouse button with their right index finger. One block of 300 trials of the oddball task was administered. The same random seed was used for each participant.

Three-stimulus Task:

Participants were once again asked to respond as quickly and as accurately as possible to the target randomly occurring on the screen. However, this time there was an added distractor (a 3 cm diameter green circle on a black background). The new distractor was presented with a probability of 0.20, the previous distractor with a probability of 0.20 and the target with a probability of 0.60. One block of 100 trials of the Three-Stimulus Task were administered. The same random seed was used for all of the participants.

Biomarkers

Salivary samples were collected from each participant once before, once during (week 5) and once after the study. All samples were stored at -18°C and will be analyzed via the ELISA technique.

RESULTS

A total of 8 patients and 4 controls were used for data analysis. The rest dropped, or were unable to make it to one of the testing times (pre and/or post).

Neuropsychological Data

Neuropsychological data was scored and entered by trained staff. Two scorers evaluated the complex figure and the average of the two scores was used for analysis. Same scorer was used for as many different batteries as possible in order to insure consistency. Significant improvement in verbal memory (p<0.05; as measured by the Fuld task) and visual-spatial memory (p<0.05; as measured by the complex figure task) was observed as a result of exercise in patients (See Figure 1). In the normative controls, however, only significant increase in visual-spatial skills was observed (p<.05; as measured by complex figure, copy task) with exercise (See Figure 4).

EEG Data

EEG data was analyzed using SCAN 4.3 software (Compumedics, Inc.). After application of a band pass filter between 0.5 and 30Hz, all major artifacts were manually rejected. Due to time constraints, the data from only the frontal lobe (FP1/2, FZ, F7/8) was analyzed. Additionally, an index of hemispherical asymmetry ([average of FP1 and F7] – [FP2 and F8]) was calculated. Group averages for controls and patients pre and post exercise were obtained. All data had to be decimated from 1000Hz to 250Hz because one of the times was recorded in 250Hz.

Resting EEG

After manual artifact rejection, data was epoched into 512ms segments. Segments with artifacts $\pm -100\mu$ V were rejected and baseline correction was imposed using the entire sweep. A paired, two sided t-test revealed significant decrease in Frontal asymmetry of the Beta band (p=0.01) was found in both patients and control post exercise. No significant differences were found in any of the other bands.

ERP

Due to time constraints, only the Oddball task data was analyzed. After manual rejection, the ERP data was epoched in -100ms pre-stimulus and 924ms post-stimulus. Baseline correction was performed using the pre-stimulus data (-100ms to 0ms) in order to minimize the noise in the ERP. Epochs containing \pm /- 100 μ V were rejected and the remaining epochs were averaged. Two peaks were assigned as follows: 1) N200 was assigned to be the most negative peak between -100 and 350 ms post-stimulus and 2) P300 was assigned to be the most positive peak 300-700ms post-stimulus.

A two-tailed paired t-test revealed a significant increase in the asymmetry index for N200 amplitude for both controls (p=0.04) and patients (p=0.03). Additionally, change in

asymmetry was significantly correlated with improvement in delayed recall (r=0.69; p=0.01). No significant differences were found in any of the other analyzed components.

DISCUSSION

The effects of low-intensity strengthening 11-week exercise on cognition were assessed with EEG and a Neuropsychological battery. Resting EEG results were in accordance with current literature, showing an increase in the Beta band post-exercise. Improvement in Visual-Spatial and verbal memory was observed post-exercise, as measured by the Complex Figure and Fuld Object Memory Examination. Although P300 components did not seem to respond significantly to exercise, N200 amplitude assessed through hemispheric asymmetry of the frontal lobe appeared to increase with exercise. N200 amplitude hemispheric asymmetry index significantly correlated with the delayed recall components of the neuropsychological evaluation. These findings suggest that the N200 asymmetry may be more sensitive to cognitive change as a result of exercise and in general. This hypothesis is partially supported by previous findings, which indicate a distortion in coordination of neural activity with cognitive decline (Hogan et al., 2003; Jelic et al., 2000; Jiang et al., 2005)

The neuropsychological effects of the exercise program were in parallel with Anderson-Hanley et al. (2010) in the sense that neuropsychological improvement was observed. Anderson-Hanley et al. (2010) tested the effects of the same exercise technique program for 4 weeks on 16 older normative adults. They found that strengthening exercise appears to improve executive functions, as demonstrated by improvement in Digits Backwards (p=0.018) and Stroop C (p=0.041). The fact that our study did not show any significant differences in executive functions tests (such as the two above) may indicate that this type of exercise affects cognitively declined individuals differently than normative controls. This hypothesis is complicated

however, by the fact that the current control group did not experience a significant difference in either of the tasks, but only in the visual-spatial skills (see Figure 4). This brings to light the possibility that the visual-spatial and verbal memory may play an increasingly important role in cognitive change.

In the context of the current methodology, the asymmetry index calculated in this study is, to our knowledge, a novel approach at N200 evaluation. Previous studies have found evidence that N200 components were sensitive to 1) mismatch/novelty of the stimulus (Breton et al., 1988; Courchesne et al., 1975; Comerchero & Polich, 1998; Polich & Comerchero, 2003), responding to rare non-targets in the context of frequent standards, and 2) cognitive control (Bruin & Wijers, 2002; Azizian et al., 2006; Bartholow, 2005). In contrast, the current study was designed specifically in such a way as to control for the mismatch sensitivity, as both targets and distractors were simple circles, and not complex designs. Hence, in accordance with current literature, this design allowed for a more direct measurement of cognitive control (Folstein & Van Petten, 2008). Nevertheless, with improvement in cognitive control, we would have expected to see an improvement in Stroop C and Trails 2 of the neuropsychological examinations. When evaluating Figure 3, we can see that there was, in fact, improvement in those tasks, granting the lack of significance. Relatively similar dilemma was encountered by Kamijo et al. (2007), who looked at the effects of a 12-week walking program on cognition. Kamijo et al., 2007 found that P300 latency and amplitude were affected by the walking program, while behavioral measures (reaction time and error rate) were not. This finding suggests that P300 may be more sensitive to physical activity than behavioral measures. Generalizing this finding to our results, it may be that N200 was also more sensitive to exercise than Stroop C, Digit Span and Color Trails. Nonetheless, explanation for why Anderson-Hanley

et al. (2010) found effects from the same type of exercise (and especially shorter exercise duration) on the above tasks still remains unclear.

Further investigation is necessary to clarify and generalize the role of N200 and N200 asymmetry in cognitive change. Future studies should aim at increasing the sample size, introducing random assignments and incorporating different behavioral measures. Additionally, because N200 is implicated in mismatch/novelty, as described above, it would be interesting to evaluate the N200 in the context of the three-stimulus task.

Nevertheless, the current study adds to the ample evidence for the cognitive benefits of exercise for aging adults. The results indicate that electrophysiological approach to gauging cognitive decline can serve a more sensitive tool for diagnosis, prognosis and investigation. Current findings also suggest promise in the above method of incorporating the asymmetry index when assessing the effects of short-term non-aerobic exercise.

References

- Aadahl M, Jørgensen T. (2003). Validation of a new self-report instrument for measuring physical activity. *Med Sci Sports Exerc*, 35(7) : 1196-202
- Adler, G., Bramesfeld, A., Jajcevic, A. (1999). Mild cognitive impairment in older-age depression is associated with increased EEG slow-wave power. *Neuropsychobiology*, 40, 218-222.
- Anderson-Hanley, C., Arciero, P., & Nimon, J. (in review). Effects of videogame-enhanced exercise for older adults: Results from the Cybercycle Study. To be submitted for publication in *Health Psychology*.
- Anderson-Hanley, C., Nimon, J., & Westen, S. (2010). Cognitive Health Benefits of Strengthening Exercise for Community Dwelling Older Adults: A Controlled Clinical Trial. JCEN, iFirst, 1-6.
- Azizian A, Freitas AL, Parvaz MA, Squires NK. (2006) Beware misleading cues: Perceptual similarity modulates the N2/P3 complex. *Psychophysiology* 43:253–260
- Babiloni, C., Binetti, G., Cassetta, E., Cerboneschi, D., Dal Forno, G., Del Percio, C. et al.(2004). Mapping distributed sources of cortical rhythms in mild Alzheimer's disease.
 Amulticentric EEG study. *NeuroImage*, 22(1), 57–67.
- Babiloni, C., Frisoni, G., Vecchio, F., Lizio, R., Pievani, M. et al. (2009). Global functioning coupling of resting EEG rhythms is abnormal in mild cognitive impairment and Alzheimer's disease. Journal of Psychophysiology, 23(4), 224-234.
- Bartholow, B., Pearson, A., Dickter, C., Sher, K., Fabiani, M., Gratton, G. (2005) Strategic control and medial frontal negativity: Beyond errors and response conflict. *Psychophysiology* 42:33–42

- Breton, F., Ritter, W., Simson, R., Vaughan, H. (1988) The N2 component elicited by stimulus matches and multiple targets. *Biological Psychology*, 27:23–44.
- Bruin, K., Wijers, A. (2002) Inhibition, response mode, and stimulus probability: A comparative event-related potential study. *Clinical Neurophysiology*, *113*:1172–1182.
- Comerchero, M., Polich, J. (1988) P3a, perceptual distinctiveness, and stimulus modality. *Cognitive Brain Research*, 7:41–48
- Colcombe, SJ., Kramer, A.F., McAuley, E., Erickson, K.I., Scalf, P. (2004). Neurocognitive Aging and Cardiovascular Fitness: Recent Findings and Future Directions. *Journal of Molecular Neuroscience*. 24(1), 9-14.
- Courchesne, E., Hillyard, S., Galambos, R. (1975) Stimulus novelty, task relevance and the visual evoked potential in man. *Electroencephalography & Clinical Neurophysiology*, 39:131–143
- Deeny, S. (2006). Exercise behavior and maintenance of cerebral cortical activity during cognitive challenge in middle-aged men and women genetically at risk for dementia: A magnetoencephalographic study. *Dissertation Abstracts International: Section B: The Sciences and Engineering, 66(12-B),* 6451.
- Dierks, T., Ihl, R., Frolich, L., & Maurer, K. (1993). Dementia of the Alzheimer type: effects on the spontaneous EEG described by dipole sources. *Psychiatry Research*, *50*(3), 51–162.
- Dierks, T., Jelic, V., Pascual-Marqui, R.D., Wahlund, L.O., Julin, P., Linden, D.E.J. et al. (2000). Spatial pattern of cerebral glucose metabolism (PET) correlates with localization of intracerebral EEG-generators in Alzheimer's disease. *Clinical Neurophysiology*, 111, 1817–1824.

- Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, et al. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*, *112*(2), 257-269.
- Erickson, K.I., Prakash, R.S. et al. (2009). Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus, 19(10), 1030-1039.
- Erickson, K.I., Prakash, R.S., Voss, M., Chaddock, L., Heo, S. McLaren, M., Pence, B.D.,
 Martin, S.A., Vieira, V.J., Woods, J.A., McAuley, E., Kramer, A.K. (2010). BrainDerived Neurotrophic Factor Is Associated with Age-Related Decline in Hippocampal
 Volume. Journal of Neuroscience, 30(15), 5368-5375.
- Erickson, K.I., Prakash, R.S., Voss, M., Chaddock, L., Heo, S. McLaren, M., Pence, B.D.,
 Martin, S.A., Vieira, V.J., Woods, J.A., McAuley, E., Kramer, A.K. (2011). Exercise
 training increases size of hippocampus and improves memory. *PNAS*, 108(7), 3017-3022.
- Feske, W., et al. (1988) Arterial Vascular Compliance Response to Exercise in Hypertension, *Biomedical Sciences Instrumentation*, 24, 161-165.
- Folstein, J., Van Petten, C. (2008). Influence of cognitive control and mismatch on the N200 component of ERP: A Review. *Psychophysiology*, *45*(*1*): 152-157.

Fuld PA. 1981. Fuld Object Memory Evaluation Instruction Manual. Stoelting: Wood Dale, IL.

- Hall, C. D., Smith, A. L., & Keele, S. W. (2001). The impact of aerobic activity on cognitive function in older adults: A new synthesis based on the concept of executive control. European Journal of Cognitive Psychology, 13(1-2), 279-300.
- Harwood, D., Kalechstein, A., Barker, W., Strauman, S., St. George-Hyslop, P. et al. (2010). The effect of alcohol and tobacco consumption, and apolipoprotein E genotype, on the

age of onset in Alzheimer's disease. *International Journal of Geriatric Psychiatry*, 25(5), 511-518.

- Heyn, P, Abreu, B. C., & Ottenbacher, K. J. (2004). The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. <u>Archives Of Physical</u> <u>Medicine And Rehabilitation</u>, 85(10), 1694-704.
- Hogan, M., Carolan, L., Roche, R., Dockree, P., Kaiser, J., Bunting, B. et al. (2006).
 Electrophysiological and information processing variability predicts memory decrements associated with normal age-related cognitive decline and Alzheimer's Disease (AD).
 Brain Research, 1119, 215-226.
- Hillman, C., Belopolsky, A., Snook, E., Kramer, F., McAuley, E. (2004). Physical activity and executive control: implications for increased cognitive health during older adulthood. *Research Quarterly For Exercise And Sport*, 75(2), 176-185.
- Huang, C., Wahlund, L.O., Dierks, T., Julin, P., Winblad, B., & Jelic, V. (2000). Discrimination of Alzheimer's disease and mild cognitive impairment by equivalent EEG sources: A cross-sectional and longitudinal study. *Clinical Neurophysiology*, 11, 1961–1967.
- Intriligator, J., Polich, J. (1994). On the relationship between background EEG and the P300 event related potential. *Biological Psychology*, *37*(*3*), 207-218.
- Intriligator, J., Polich, J. (1995). On the relationship between EEG and ERP variability. International Journal of Psychophysiology, 20, 59-74.
- Jasiukaitis, P., & Hakerem, C. (1988). The effect of prestimulus alpha activity on P300. *Psychophysiology*, 25, 157-165.
- Jasper H. H. (1958) The ten-twenty electrode system of the international federation. Electroencephalography. *Clinical Neurophysiology*. 10:371–375.

- Jelic, V., Johansson, S.E., Almkvist, O., Shigeta, M., Julin, P., Winblad, B., Wahlund, L.O.,
 (2000). Quantitative electroencephalography in mild cognitive impairment: longitudinal changes and possible prediction of Alzheimer's disease. *Neurobiology of Aging*, 21:533-540.
- Jeong, J. (2004). EEG dynamics in patients with Alzheimer's disease. *Clinical Neurophysiology*, *115*, 1490–1505.
- Jiang, Z. (2005). Study on EEG power and coherence in patients with mild cognitive impairment during working memory task. *Journal of Zhejiang University* 6(12), 1213-1219.
- Kamijo, K., Nishihira, Y., Sakai, T., Higashiura, T., Kim, S., & Tanaka, K. (2007). Effects of a 12-week walking program on cognitive function in older adults. Advancements in Exercise Sport Physiology, 13(2), 31-39.
- Kamp, A., Troost, J. (1978). EEG signs of cerebrovascular disorder, using physical exercise as a provocative method. *Electroencephalography and Clinical Neurophysiology Volume 45, Issue 2*, August 1978, Pages 295-298
- Kazmerski, D. & Anderson-Hanley, C. (2005). The neuropsychological and mood effects of an osteoporosis exercise program for older adults. Poster presentation at the annual meeting of the Society of Behavioral Medicine, Boston, MA.
- Kramer, A.F., Colcombe, S.J., McAuley, E., Scalf, P.E., Erickson, K.I. (2005). Fitness, Aging, and Neurocognitive Function. *Neurobiology of Aging* 26 Suppl 1:124-7
- Koenig, T., Prichep, L., Dierks, T., Hubl, D., Wahlund, L.O., John, E.R. et al. (2005). Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment. *Neurobiology of Aging*, 26, 165–171.

- Lardon, M.T., Polich, J. (1996). EEG Changes from Long term physical exercise. Biological Physiology. September 27;44(1):19-30.
- Larson, E.B., Wang, L., Bowen J.D., McCormick W., C., Teri, L., Crane, P.(2006). Exercise is associated with reduced risk for incident dementia with persons 65 years of age and older. *Annuals of Internal Medicine*. 144, 73-81.
- Lautenschlager, N., Cox, K., Flicker, L. et al. (2009). Effects of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer's Disease: A Randomized Trial. Journal of American Medical Association. 300(9), 1027-1037.
- Li Y, et al. (2008) TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. *Neuron* 59:399–412.
- Luckhaus, C., Grass-Kapanke, B., Blaeser, I., Ihl, R., Supprian, T., Winterer, G., Zielasek, J., Brinkmeyer, J. (2008). Quantitative EEG in progressing vs. stable mild cognitive impairment (MCI): results of a 1-year follow up study. *International Journal of Geriatric Psychiatry*, 23, 1148-1155.
- Mandel, A., Ozdener, H., Utermohlen, V. (2009). Identification of pro- and mature brain-derived neurotrophic factor in human saliva. *Archives of Oral Biology*, *54*(7), 689-695.
- Mandel, A., Ozdener, H., Utermohlen, V. (2011). Brain-derived neurotrophic factor in human saliva: ELISA optimization and biological correlates. *Journal of Immunology and Immunochemistry*, 32(1), 18-30.
- McDowell, K., Kerick, S., Santa Maria, D., Hatfield, B. (2003). Aging, physical activity and cognitive processing: an examination of P300. *Neurobiology of Aging*, *24*(*4*), *597*.

- Nimon, J. & Anderson-Hanley, C. (2007). Exercise in later life: Neuropsychological and physiological effects. Poster presentation at the annual meeting of the Society of Behavioral Medicine, Washington, DC.
- Osterrieth, P.A. (1944). "Filetest de copie d'une figure complex: Contribution a l'etude de la perception et de la memoire [The test of copying a complex figure: A contribution to the study of perception and memory]". Archives de Psychologie 30: 286–356.
- Pereira, A. et al. (2007). An in-vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *PNAS*, 104(13), 5638-5643
- Polich, J., Comerchero, M. (2003) P3a from visual stimuli: Typicality, task, and topography. Brain Topography, 15:141–152
- Ponomareva, N.V., Selesneva, N.D., & Jarikov, G.A. (2003). EEG alterations in subjects at high familial risk for Alzheimer's disease. *Neuropsychobiology*, *48*, 152–159.
- Raz N, et al. (2005) Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. Cereb Cortex 15:1676–1689.
- Rey, A. (1941). "L'examen psychologique dans les cas d'encephalopathie traumatique (Les problems.)". Archives de Psychologie 28: 215–285. Retrieved 2008-05-08.
- Salmon, D., Bondi, M. (2009). Neuropsychological assessment of dementia. *Annual Reviews of Psychology*, (60), 257-282.
- Schmajuk M., Liotti M., Busse L., Woldorff M.G. (2006). Electrophysiological activity underlying inhibitory control processes in normal adults. *Neuropsychologia* 44: 384–395.
- Seguin, R. A., Epping, J. N., Buchner, D. M., Bloch, R., & Nelson, M. E. (2002). Growing stronger: Strength training for older adults. Boston, MA: Tufts University.

Streiner, D. (2009) Clinical Journal of Sport Medicine. 19(5), 438

- Stroop , J. (1935). Studies of interference in serial verbal reactions. Journal of Experimental Psychology, 18, 643-662.
- Terry, P. C., Lane, A. M., & Fogarty, G. J. (2003). Construct validity of the POMS-A for use with adults. Psychology of Sport and Exercise, 4, 125-139.
- Thompson, P. M., Moussai, J., Zohoori, S., Goldkorn, A., Khan, A.A., Mega, M.S., Small, G.W.,
 Cummings, J.L., Toga, A.W. (1998). Cortical variability and asymmetry in normal aging
 and Alzheimer's disease. Laboratory of Neuroimaging, Department of Neurology,
 Division of Brain, Mapping and Alzheimer's Disease Center, UCLA School of Medicine,
 Los Angeles, CA, USA
- Thompson, P. M. & Toga, A. W. 2000 Warping strategies for inter-subject registration.
 Handbook of medical image processing (ed. Isaac Bankman), pp. 569-601. San Diego,
 CA: Academic Press.
- Vaynman S, Ying Z, Gomez-Pinilla F (2004) Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur J Neurosci 20:2580–2590
- Yerokhin, V., Anderson-Hanley, C., Dunnam, M., Huber, D., Osborne, S., Shulan, M. (2011). *Neurophysiological and Neuropsychological Effects of Strengthening Exercise for Cognitive Impairment*. Presented at the annual meeting of the American Academy of Clinical Neuropsychologists, Washington DC.

Table 1. Participant Demographics

		Age		Education							
		Standard			Standard						
	Mean	Deviation		Mean	Deviation						
Patients	78.6		11.2	11.4		2.7					
Controls	62.3		0.81	12		0.8					



Figure 1. Strengthening Exercises (Seguin, Epping, Buchner, Bloch & Nelson, 2002)

Figure 2. On-site participation log

Exercise Participation Log (VA Adult Day Program Strengthening Exercise Classes) January 2010

Name of Participant (last name, first name) M T W Th F M T W <th></th> <th colspan="4">1/3</th> <th colspan="6">1/10</th> <th></th> <th></th> <th></th> <th></th> <th colspan="5">1/24</th>		1/3				1/10										1/24					
	Name of Participant (last name, first name)	м	Т	W	Th	F	м	Т	W	Th	F	М	Т	W	Th	F	м	т	W	Th	F
Image: Sector of the sector																					
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Figure 3. At-home participation log sheet

Exercise Participation Log (for at-home strengthening exercise practice) January-March 2010

please indicate a " $\!\!\sqrt{}$ " for each date exercise is completed

	1/3					1/10					1/17					1/24				
Name of Participant (last name, first name)	м	т	w	Th	F	м	т	w	Th	F	м	т	w	Th	F	м	т	w	Th	F
	1/31					2/7					2/14					2/21				
	м	т	w	Th	F	м	т	w	Th	F	м	т	w	Th	F	м	т	w	Th	F
	2/28					3/7					3/14					3/21				
	м	т	w	Th	F	м	т	w	Th	F	м	т	w	Th	F	м	т	w	Th	F

Figure 4. Neuropsychological Effects of Exercise. Significant improvement was seen in

complex figure copy and delay as well as Fuld task immediate recall and delay.



Figure 5. Neuropsychological effects of exercise in controls. Significant improvement in the

Complex figure copy task is observed. * indicates a p value < 0.05





Figure 6. Map of controls only - pre and post exercise spectral averages during ERP tasks.