Official Study Title:

Acute Exercise Effects on Word Learning in Aging and Stroke-induced Aphasia

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Protocol

1. Acute Exercise Effects on Word Learning in Aging, Mild Cognitive Impairment and Stroke-induced Aphasia

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2. Abstract

Objective: Difficulty retrieving words, one of the most common language complaints in healthy older adults and those with mild cognitive impairment (MCI) stroke-induced language disorders (i.e., aphasia), can have a negative impact on communicative function. Consistent with studies in young adults, our pilot study in healthy older adults, demonstrates that acute exercise may improve word learning; however, more research is needed to optimize learning paradigms for healthy older adults and those with MCI and aphasia and to investigate the factors that contribute to exercise-induced improvements in learning in these populations. The objectives of this research are to: 1) identify an optimal novel word learning paradigm; 2) determine the acute effects of exercise (compared to stretching) on word learning; 3) investigate the influence of timing of exercise (exercise before vs. after learning); 4) investigate the influence of high vs. low working memory ability on exercise-enhance word learning; and 5) investigate the neurophysiological correlates of exercise-enhanced word learning.

Research Plan: Word learning performance will be compared in up to four conditions (before exercise, after exercise, before stretching, after stretching). Performance of individuals with high vs. low working memory will be compared and peripheral levels of brain-derived neurotrophic factor (BDNF) and dopamine will be measured to investigate correlates of immediate and one-week retention of learned words.

Methods: We will compare word learning in up to four conditions using a within-subjects crossover design. Individuals aged 65-89 years (healthy older adults and MCI) and 35-89 years (individuals with aphasia) who meet the eligibility criteria will be offered enrollment. In the exercise conditions, participants will engage in 30 minutes of moderate-intensity cycling (with a warm-up/cool-down) before or after word learning. In the stretching conditions, participants will engage in upper- and lower-limb stretching for 30 minutes before or after word learning. In the word learning task, participants will be asked to learn novel words (“flark”) for a familiar object (“cup”) and will engage in tests of recall and recognition. Each condition will last two weeks. In week 1, training /testing will take place on Monday, Wednesday and Friday of week 1 to measure immediate retention. In week 2, testing will take place on Friday to measure one-week retention. To measure serum levels of BDNF and dopamine, blood samples will be taken at baseline (every 15 minutes for one hour) and in the two training conditions when exercise/stretching occurs before word learning (immediately before exercise/stretching, immediately after exercise/stretching, immediately after word learning, and 15 minutes after word learning).

Clinical Relevance: The aging population of the US is expected to more than double by 2060, and a similar trajectory is expected within our aging veteran population.

Additionally, stroke affects 795,000 individuals per year, and up to 30% are left with chronic disability including language impairment. MCI can also have an impact across all cognitive domains, including language and memory (Arnaiz & Almkvist, 2003).The declines in communicative function that are present in healthy older adults and those with aphasia often result in reduced independence and psychosocial well-being, and they may contribute to poorer health outcomes. Investigating an exercise-based approach to improving word retrieval is clinically relevant and has the potential to have a significant impact on the functioning and well-being of thousands of aging veterans.

3. Introduction and Background

The onset of cognitive decline can begin before 30 years of age (Salthouse, 2004), but the potential for improving brain function remains throughout the lifespan. To combat the effects of aging on cognition, exercise-based programs aimed at taking advantage of reactive neuroplasticity (immediate, short term changes) to promote adaptational neuroplasticity (long term changes) have become increasingly popular. Engaging in physical exercise promotes neuroplasticity through increased cerebral blood flow, increased neurogenesis, and neurochemical release (Greenwood & Parasuraman, 2010). Meta-analyses have shown that acute exercise has small to moderate effects on working memory (McMorris et al., 2012; Roig et al., 2013) and large effects on long-term memory (Roig et al., 2013; Lambourne & Tomporowski, 2010).

Difficulty retrieving the right word at the right time is one of the most common complaints in healthy older adults and those with MCI and stroke-induced language impairment (i.e., aphasia). The consequences of word retrieval deficits include reduced independence and psychological well-being (Llewellyn et al., 2008) as well as poor health outcomes. Novel word learning paradigms have been used to investigate a variety of behavioral and neuromodulatory approaches to word retrieval deficits in these populations. We are using a novel word learning paradigm to investigate the acute (or immediate) effects of exercise on word recall with a long-term goal of developing targeted interventions for word retrieval impairment. In a pilot study, we demonstrated that engaging in moderate-intensity exercise can improve long-term *recognition* of novel words (e.g., flark) for familiar objects (e.g., ball) in healthy older adults (Rodriguez et al, in prep); however, evidence regarding acute exercise effects on novel word *recall* and the potential mechanisms that support these effects is required.

Moreover, despite the known declines in language, learning and working memory in the aging population, no studies have investigated the influence of baseline working memory ability on exercise-enhanced word learning. Additionally, other factors, such the influence of timing of exercise in relation to learning have also not been investigated in older adults. As not all cognitive functions are likely to be enhanced by exercise (Lambourne & Tomporowsk, 2010; Roig et al., 2013), and individual differences in baseline cognitive function have been shown to influence outcomes in younger adults (Sibley & Beilock, 2007; Schmidt-Kassow et al. 2013), this line of inquiry is an important step in developing effective exercise-based interventions.

Similarly, there has also been very little research on the neural correlates of exercise-enhanced word learning, and the results of two studies in younger adults yielded contrasting results. Winter and colleagues (2007) found that increased levels of serum brain-derived neurotrophic factor (BDNF) and dopamine were related to short- and long-term learning success (respectively) in young male athletes who engaged in high intensity prior to learning; however, Schmidt-Kassow et al (2013) failed to find a link between serum BDNF and learning in healthy young females who engaged in light to moderate exercise during learning. Although a recent review by Coelho and colleagues (2013) suggests that moderate-intensity exercise is most effective in promoting increased BDNF levels in the elderly, no studies have investigated the relationship between BDNF and word learning in aging populations.

Our research aims to address these gaps in the literature in order to inform the development of targeted, exercise-based interventions for word retrieval impairments in healthy older adults and those with stroke-induced aphasia.

3. Objectives/Hypothesis/Research Questions

1) To identify an optimal novel word learning paradigm for investigation of acute exercise effects on word recall
2) To determine the effect of moderate-intensity aerobic exercise (compared to a stretching control) on word learning
3) To investigate factors known to modulate acute exercise effects such as:
    a. Timing of exercise (exercise before vs. after learning)
    b. Individual differences (high vs. low working memory ability)
4) To investigate the neurophysiological correlates of exercise-enhanced word learning

Research Question 1: Does acute, moderate-intensity exercise (compared to gentle stretching) enhance novel word learning in healthy older adult and neurologic populations? Based on our pilot work, we hypothesize that with an optimal paradigm both recall and recognition will be significantly better in the moderate-intensity exercise condition (compared to gentle stretching).

Research Question 2: Modulating Factors

a. Does timing of exercise in relation to word learning moderate the effect of acute exercise on novel word learning in healthy older adults and individuals with MCI or aphasia?
b. Do individual differences in baseline working memory moderate the effect of acute exercise on novel word learning in healthy older adults and individuals with MCI or aphasia?

Based on our pilot data, the findings that acute exercise benefits low performers at baseline (Schmidt-Kassow et al., 2013; Sibley and Beilock; 2007), and the findings that acute exercise improves processing efficiency (McMorris et al., 2012), we hypothesize

that exercise (compared to gentle stretching) before learning will significantly enhance immediate and long-term retention of words in the low working memory group (compared to the high working memory group). Furthermore, based on findings that exercise improves long-term retention (Rodriguez et al., in prep; Roig et al., 2013), we hypothesize that exercise (compared to gentle stretching) after learning will significantly enhance long-term retention of words (compared to immediate retention) with no significant difference in the change between the high and low working memory groups.

*Research Question 3***:** Does exercise-enhanced novel word learning correlate with increases in peripheral levels of BDNF or dopamine in healthy older adult and individuals with MCI or aphasia? Based on previous exercise and word learning research, we hypothesize that significantly better short-term retention (immediately after learning) will correlate with increased BDNF levels and that significantly better long-term retention (at one-week follow-up) will correlate with increased levels of dopamine.

4. Description of Relevance to VA

It is anticipated that by 2060 the aging population in the United States will more than double to 92 million (United States Census Bureau, 2012). A similar trajectory is expected within our aging veteran population over the next decade. Aging can significantly impact cognitive functions including language, learning and memory (Burke & Mackay, 1997). Difficulty retrieving words is one of the most common complaints in healthy older adults and individuals with MCI and stroke-induced aphasia. Consequences of word retrieval deficits include reduced independence and psychosocial well-being (Llewellyn et al., 2008), as well as poor health outcomes. Safe, cost-effective, accessible approaches for enhancing word retrieval in older adult populations are needed. Exercise is one approach that has yielded positive effects on the ability to remember new words, but more research is required so that exercise-based interventions for word retrieval can be optimized. That is the focus of this line of research. Due to the pervasiveness of word retrieval difficulty in aging populations, and the negative consequences associate with it, this research has the potential to significantly impact veterans in our rapidly aging nation.

6. Overview of Design/Methods

The study will enroll up to 100 healthy older adults and up to 50 older adults with MCI and stroke-induced aphasia. A crossover design will be used to compare two novel word learning paradigms and/or the additive effect of moderate-intensity exercise vs. stretching on novel word learning.

Study procedures

<u>Assessment:</u>

The subject's cognitive and physical function will be assessed at the start of the study. Some assessments may be audio-recorded for scoring and reliability assessment.

Cognitive Assessment:

a) Reading Span (RSPAN) and Operation Span (OSPAN): assesses working memory capacity. These two tests will allow us to categorize subjects into high vs low working memory, which will allow us investigate how acute exercise effects vary as a function of individual differences in baseline working memory ability (Objective 3b).

b) Digit Span: assesses the central executive component of working memory

c) Verbal fluency (semantic and letter): assesses the verbal component of executive function

d) Color-word Interference Test: assesses the inhibition component of executive function

e) Hopkins Verbal Learning Test: assesses verbal learning and memory (immediate recall, delayed recall, delayed recognition)

f) Brief Visuospatial Memory Test- Revised: assesses visuospatial memory (immediate recall, delayed recall, delayed recognition)

g) Digit Symbol Substitution: sensitive to the effect of brain damage, dementia, age and depression on task completion

h) American National Adult Reading Test- Revised: estimates intelligence in based on reading of words with irregular grapheme-to-phoneme conversion.

i) Edinburgh Handedness Inventory: assesses handedness

j) *Task practice:* Subjects will be administered a practice word learning task at baseline to familiarize them with the novel word learning paradigm.

k) Discourse production: Subjects will be asked to answer two open-ended questions in order to get a measure of their connected speech.

The following measures will be administered to participants with aphasia:

a) Comprehensive Aphasia Test- assesses general language ability
b) Philadelphia Naming Test- assesses confrontation naming ability
c) Pyramids and Palm Trees- assesses semantic processing ability

Physical Assessment:

Submaximal Treadmill Exercise Test (participants not on beta blockers): The YMCA test, which estimates maximal volume oxygen uptake (VO2max) using an "extrapolation" method, will be administered. This test will provide an indication of aerobic capacity and will be used to set subjects' individual target training zone for exercise training. Heart rate monitors will be used to ensure subjects are maintaining their target heart rate and to prevent hear rate increases above levels that are considered safe.

Maximal Treadmill Exercise Test (participants on beta blockers). Participants will undergo maximal treadmill exercise until exhaustion using the modified Balke protocol

to determine peak oxygen uptake (VO2 max). The protocol consists of a series of 3-minute stages in which speed and incline are increased in a stepwise manner. Levels of mixed expired oxygen, carbon dioxide, and ventilation are recorded at rest and every 30 seconds during exercise using a breathing apparatus with metabolic cart (Sensormedics). The VO2 max is defined as the highest VO2 rate observed during maximal exercise. A registered nurse (RN) will be present for the entire test and manually monitor blood pressure at baseline and during each stage of exercise, as well as monitor continuous EKG recordings. This same protocol is being by Co-I Nocera in other exercise-based studies that involving older adults.

Word learning paradigm:

A Dell laptop computer running EPrime 2.0 software and paired with a response box will be used to standardize stimuli presentation in the learning task and record the speed and accuracy of responses to the word recall and recognition tasks. Familiar objects will be paired with two-syllable nonwords that are 5-6 letters in length and phonologically plausible in the English language. Sets of stimuli will be balanced on the frequency and familiarity. The order of stimuli sets will be counterbalanced across subjects and conditions. During the word learning task, familiar objects will be randomly presented along with the target nonword, which will also be heard through headphones. Following the learning task, subjects will be administered a recognition task and a cued recall task. Verbal responses will be audio-recorded for scoring and reliability assessment. The number of stimuli, duration and number of exposures to stimuli, and feedback during testing will be manipulated to identify the optimal learning paradigm for investigation of acute exercise effects on word recall (Objective 1).

Exercise/Stretching:

a) Exercise: Subjects will engage in supervised moderate-intensity cycling for 30 minutes with a warm-up and cool-down. They will be asked to reach and maintain their individual physiological training target (i.e., heart rate at which 50-75% of maximal oxygen uptake would be achieved as predicted by sub-maximal test administered during the baseline assessment).

b) Stretching: Participants will participate in an upper- and lower-extremity stretching program for 30 minutes. The stretching program will provide the opportunity for 30 minutes of interaction without increasing heart rate.

Exercise and/or stretching will be paired with a novel word learning paradigm to determine the effect of moderate-intensity aerobic exercise (compared to a stretching control) on word recall (Objective 2). The exercise/stretching will be administered before and/or after word learning to better understand how acute exercise effects vary as function of timing (Objective 3a).

Subjects will be asked to avoid any exercise that is not part of the study on training days and to avoid exercise before testing on the testing only days. No other restrictions will be placed on subjects regarding their exercise routines.

Mood and arousal measures:

Bond and Lader's Mood Rating Scale will be administered to assess the effect of moderate-intensity exercise and gentle stretching on mood and arousal. Ratings will be obtained prior to the second word recall and recognition test in each session. As heart rate is physiological marker of arousal, we will also take heart rate measurements after subjects complete of the rating scale. These data will be used in secondary analyses to investigate the relationship between mood and arousal and performance on the recall and recognition tests.

Post-session and post-study questionnaires:

Post-session questionnaires will be used to explore how subjects feel physically and psychologically after a session. A rating scale to measure current level of motivation to learn novel words, current stress level, perceived difficulty of learning the words, and quality of the previous night's sleep will also be administered at each session. The post-study questionnaire will be used to explore the subject's perception of difficulty of the experimental conditions and any expectations regarding ease of learning.

Daily Diary:

To monitor exercise and sleep during the experimental conditions, subjects will be asked to keep a daily diary of any exercise outside of the training sessions (type, intensity, duration) as well as the amount of sleep.

Blood draws:

To explore the neurophysiological correlates of exercise-enhanced word learning (Objective 4), fasting whole blood will be collected from some subjects during a baseline blood draw and during subsequent training conditions. Samples will be collected by a certified phlebotomist, via venipuncture or peripheral venous line into pre-cooled plasma EDTA tubes and serum separator tubes (~40 ml per visit). The time line for collection of blood samples is as follows:

Baseline: every 15 minutes for one hour to demonstrate reliability.

Experimental: Immediately prior to exercise and stretching, immediately post exercise and stretching, immediately post word learning, and 15 minutes post word learning. The blood draws will occur on two days during the training conditions.

Following collection, tubes will be transferred in sealed biohazard bags. Plasma volume will be measured as described by Dill and Costill (1974). Lactate will be measured by an Accusport Lactate Analyzer (Roche Molecular Biochemicals, Mannheim, Germany).

7. Patient Evaluation and Data Collection Timeline

<table>
<tr><th>Study Visit</th><th colspan="4">Activity</th><th># of hours</th></tr>
<tr><td colspan="6">Pre Training</td></tr>
<tr><td>Assessment I</td><td colspan="4">· Consenting
· Screening Tests
· Study Tests</td><td>2</td></tr>
<tr><td>Assessment II + Blood draw (if applicable)</td><td colspan="4">· Study Tests
· Blood sample taken every 15 minutes for 1 hour</td><td>2</td></tr>
<tr><td>Assessment III</td><td colspan="4">· Study Tests</td><td>2</td></tr>
<tr><td colspan="6">Training Conditions (in random order)</td></tr>
<tr><td rowspan="4">Exercise + Word Learning
+
Blood draw**
(if applicable)</td><td>M</td><td>W</td><td>F</td><td rowspan="4">**Before exercise, after exercise, after word learning, 15 min after word learning</td><td rowspan="4">2</td></tr>
<tr><td>test/train/test</td><td>test/train/test</td><td>test/train/test</td></tr>
<tr><td></td><td></td><td>test</td></tr>
<tr><td colspan="3">One week break</td></tr>
<tr><td rowspan="4">Stretching + Word Learning
+
Blood draw**
(if applicable)</td><td>M</td><td>W</td><td>F</td><td rowspan="4">**Before stretching, after stretching, after word learning, 15 min after word learning</td><td rowspan="4">2</td></tr>
<tr><td>test/train/test</td><td>test/train/test</td><td>test/train/test</td></tr>
<tr><td></td><td></td><td>test</td></tr>
<tr><td colspan="3">One week break</td></tr>
</table>

8. Participant Selection

The study will enroll up to 100 healthy older adults and up to 50 older adults with MCI and stroke-induced aphasia.

Recruitment

Individuals will be recruited from the Atlanta VA Rehab R&D Subject Registry (IRB00000159) based on the inclusion and exclusion criteria. The Subject Registry study staff will query the data base of all patients meeting the inclusion and exclusion criteria who have consented to be contacted for research purposes and will print out their contact information. The Principal Investigator or study staff will contact these individuals and summarize the study procedures.

Additionally, participants may be recruited from VA's Information and Computing Infrastructure (VINCI) to enhance recruitment goals within the VISN. Potential Veteran subjects will be mailed an IRB approved recruitment letter, as well as an opt in/opt out response form to be returned using a postage paid envelope. This will allow for potential subjects to indicate whether they would like to be contacted in the future related to the study. If no response is received within two weeks, we will follow up with a phone call to gauge subject interest.

Finally, VA healthcare providers, Emory Alzheimer's Disease Research Center, Emory Rehabilitation Hospital, StrokeNet, other investigators, word of mouth and via advertisements.

Individuals who indicate interest in participating will undergo a phone screen comprised of questions about cognitive and physical function. Those who "pass" the phone screen will be provided a copy of the informed consent and will be scheduled for an orientation session. The PI/Co-PI or their trained study staff will go over and describe the consent in a quiet room. Prior to providing written consent, potential subjects will be given the chance to ask questions and the PI/Co-PI or study staff will ask questions to ensure the potential subject understands what the study entails.

Inclusion criteria:

- age 65-89 years (healthy older adults and individuals with mild cognitive impairment) and 35-89 years (individuals with aphasia)
- English as first and primary language
- "low physical activity" on the International Physical Activity Questionnaire
- *physician's written medical approval for participation in moderate-intensity exercise*

Exclusion criteria:

- any comorbid condition with exercise contraindications
- current use of hormone replacement therapy or dopaminergic drugs
- use of anti-depressant or anti-psychotic drugs for less than 3 months
- current use of illicit drugs
- consumption of >14 standard alcoholic drinks/week
- consumption of > 1pack of cigarettes/day
- uncorrected hearing or vision impairments that could interfere with study procedures
- < 26 on the Montreal Cognitive Assessment (healthy older adults only)
- low mood or depression as indicated by > 10 on the Beck Depression Inventory

Potential Benefits

Subjects who participate in the study may benefit from an improved awareness of their cardiovascular fitness level and greater confidence in knowledge of their cardiovascular fitness level.

Protection Against Risk

Fatigue, frustration or anxiety during testing will be managed by PI Rodriguez who is an experienced speech-language pathologist with expertise in managing emotional reactions to performance on assessments. Management may include verbal encouragement or short rest breaks, as necessary. In our experience, frustration or anxiety that cannot be managed by study personnel is rare. Additionally, we will decrease testing burden for participants, when possible.

That is, Dr Krishnamurthy's study entitled "Beyond lesion-language mapping in aphasia: A novel imaging-based prediction model" (IRB#104270) and Dr. Rodriguez's study entitled "Transcranial Direct Current Stimulation (tDCS) as an Adjuvant to Phonomotor Treatment for Aphasia" (IRB#102536) also investigate stroke and aphasia. While the question for this study is different, the framework is in place to use assessment data collected in Dr. Krishnamurthy's and Dr. Rodriguez's study to reduce the number of assessments in this study. Specifically, we may obtain a participant's data on the *Western Aphasia Battery-Revised (WAB-R), Comprehensive Aphasia Test (CAT), Hopkins Verbal Learning Test-Revised (HVLT-R), Brief Visuospatial Memory Test-Revised (BVMT-R), Beck Depression Inventory-II*, and *Boston Naming Test (BNT).*

Several precautions will be made to reduce the risk of exercise-related injuries:

- Warm-up and cooling down components are included to minimize injuries;
- At each exercise session, subjects will be questioned about the presence of musculoskeletal symptoms;
- Study staff will be instructed to be alert for the emergence of symptoms of angina and shortness of breath;
- Subjects will be instructed to discontinue exercise if there is significant pain, weakness, or joint swelling after exercise;
- We will ensure that that the site has immediate access to a phone and that provision of interventions and evaluations are undertaken in the immediate vicinity of a phone. Study staff will be encouraged to carry cell phones during testing and training;
- All testing and training activities will occur inside an air-conditioned facility because environmental extremes are poorly tolerated;
- Subjects will be provided fluids and the opportunity to rest, if necessary.

9. Adverse event reporting

In the case of a reportable event, the Principal Investigator will submit the form "Reportable Protocol Event Form for VA sites" along with supporting documentation and to the VA Science Information Office. The SIO will then route the report to the Emory IRB. The Emory IRB will be notified within five days of any adverse event occurring.

10. Data Security Plan

Information about subjects, including all research records created, will be held strictly confidential. Study files will be kept in a locked filing cabinet in the private office of the Principal Investigator at the Atlanta VA Medical Center (Room 12C-118). A study number rather the subject's name will be used on study records whenever possible. The data collected with special software on the study laptops during the word learning tasks will be de-identified (subject number, visit number). The data will be exported to Excel spreadsheets and transferred from the password-protected laptop to password-protected files on the secure VA network using a VA-issued USB drive. Audio-

recordings will also be stored on the secure VA network in password-protected files. Blood samples will be stored in a de-identified manner. Collection tubes will be labeled with subject number, visit number and draw number. Samples may be temporarily stored at Emory University in the locked office of Mike Iuvone (TEC B5601) while undergoing analyses. We will not use subjects' names or other identifying information when the study is presented or when the results are published. All research records and/or identifiers will be destroyed in accordance with the VA record retention schedule.

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