Department of Veterans Affairs

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ATLANTA VA HEALTH CARE SYSTEM
Consent to be a Research Subject

TITLE: Effects of Aging on Cortical Excitability During Motor Learning

PRINCIPAL INVESTIGATOR: Joe Nocera, PhD

SPONSOR'S NAME: Department of Veterans Affairs

INTRODUCTION:
You are being asked to volunteer for a research study. Please carefully read this consent form. Before you decide to take part, discuss any questions or concerns with the research staff. If you agree to be in this study, you will need to sign this consent form and a HIPAA form before starting in the study.

PURPOSE
The purpose of this study is to look at changes in the brain as we age. We will use brain imaging along with cognitive and behavioral tests to study these changes. We will recruit 60 healthy adults ages 60-80 years old. We will also recruit 20 healthy adults ages 18-35 as a comparator group for the MRI scans. The results of this study should help improve our understanding of how the brain's inhibitory function changes as we age.

PROCEDURES:
This table is an overview of the study activities for the intervention group. A full description of the activities follows this table.

Study visits	Activity	Location	Time it will take
Assessment 1 (Baseline)			
Day 1–Test visit 1	· Consenting · Study tests: Questionnaires, Behavioral tests, Fitness test	Atlanta VA, GRECC, or through phone or video communication	· 3 hours
Day 2 –Test visit 2	· TMS	Atlanta VA	· 1 hour
Day 3 –Test visit 3	· MRI	Emory University Hospital	· 1.5hours
Intervention 1			
Months 1-3	· Aerobic Exercise **OR** Interval Exercise	Atlanta VA. GRECC, or remote monitoring	· 3 days a week, 60 minutes/session

Assessment 2			
Day 1- Test visit 5	· Study tests: Questionnaires, Behavioral tests, Fitness test	Atlanta VA, GRECC, or through phone or video communication	· 3 hours
Day 2 –Test visit 6	· TMS	Atlanta VA	· 1 hour
Day 3–Test visit 7	· MRI	EUH	· 1.5 hours

This table lists the study activities for the comparator group. A full description of the follows this table in the Assessment section within the Magnetic Resonance Imaging subsection.

Activity	Location	Time it will take
MRI scan	EUH	1.5 hours
MRI scan	EUH	1.5 hours

ASSESSMENTS

Day 1: Questionnaires and Behavioral Tests

All of the activities on Day 1 occur at the Atlanta VA and will take about two hours to complete.

- Questionnaires: about your medical history, physical and cognitive (memory, attention, processing speed) functioning.
- Cognitive (thinking) tests: These tests are designed to examine your memory, planning and language abilities.
- Hand movement tests: These test qualities of the neuromuscular system of your hand, such as dexterity, strength and coordination. You may request rest breaks between each task, and of course, may stop at any time.
- Physical fitness assessment: This assessment will be used to estimate your fitness level and will include the following:

    - 400 Meter Walk*:* You will be asked to walk at your usual pace, without over-exerting. You can stop for up to 1 min for fatigue or other symptoms. You will be allowed to use a cane if you feel unsafe.

    - Walking and Walking While Talking*:* Participants will be asked to walk across an electronic walk way which captures walking speed and foot placement in a quiet well-lit hallway wearing comfortable footwear. You will be asked to recite alternating letters of the alphabet while walking.

    - Short Physical Performance Battery (SPPB): The SPPB is based on a timed short distance walk, repeated chair stands and a balance test. The battery will be administered by a trained and certified examiner.

- The Activities-specific Balance Confidence (ABC) Scale*:* The questionnaire will ask you about perceived difficulties in general activities of daily living during the last month.

- *Sit and Reach Test:* This test assesses the flexibility of the lower back and hamstrings. Participants will sit on the floor and reach as far they can towards their toes. The test will be performed three times while measuring the distance reached.

- *Functional Reach Test:* This test will assess participants' balance and functional mobility by having them stand perpendicular to a wall and reach out as far as possible.

- *Leg Press*: An assessment of bilateral leg movement function will be completed using the Keiser Leg press.

- *Maximal Treadmill Exercise Test:* You will complete a maximal treadmill exercise test to determine peak oxygen uptake (VO2 max). You will wear a breathing apparatus to measure your oxygen, carbon dioxide, and ventilation. A registered nurse 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.

- *Submaximal Treadmill Exercise Test: (For participants unable to complete a maximal test)* This test will examine estimates VO2max using an "extrapolation" method. 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 heart rate increases above levels that are considered safe.

- Body Measurements: Height and body weight measurements will be taken.

You may be asked to complete cognitive, motor, and physical function (fitness) assessments. If you have participated in Dr. Krishnamurthy's study, "Effects of Acute Exercise on Functional Magnetic Resonance Spectroscopy Measures of GABA in Aging and Chronic Stroke" (IRB00001334), we may obtain your data from your assessments. We will only share this data to decrease participation burden.

Day 2: Transcranial Magnetic Stimulation (TMS)

We will use TMS to determine what areas of your brain control the muscles of the arm. TMS is safe (FDA approved) and non-invasive. It is done by passing a weak magnetic current over your head. When the magnetic current makes contact with the area of your brain that controls a certain muscle, an electric signal is made. This signal is measured in the muscle using small surface electrodes. These electrodes are about the size of a dime and made of smooth plastic. Electrodes will be placed on the surface of your skin with an adhesive sticker.

You will be seated comfortably in the TMS chair. Your chin will rest in a "chin rest" to make sure your head is in the correct position. A camera attached to the TMS computer will be

used to record correct placement of the magnetic coil.

The magnetic coil, which looks like a figure-8, will be positioned over the target area of your head. A magnetic pulse will pass through your skull into your brain under the target area. As we locate the exact spot, it will feel like a tap on your head. You also may feel twitches in the muscles of the face. When the correct area of brain is identified, you will feel a twitch in the muscles of your leg or arm. The researchers will first find the lowest setting on the TMS unit that will make your muscles twitch, called the "threshold." Then, additional magnetic pulses will be presented at increasing levels. Finally, the researchers will use sites around threshold site to identify all of the parts of the brain that make those muscles twitch. This is called the "area of representation."

After this procedure, the researcher will ask you to squeeze a pinch grip while magnetic pulses are delivered to your brain.

Days 3 and 4: Magnetic Resonance Imaging (MRI)
If you are in the comparator group, this is the only assessment you will complete. You will complete two MRI scans.

The MRI test takes place at Emory University Hospital, 1364 Clifton Road, Atlanta, GA 30322. You will complete an MRI screening evaluation before you are put in the MRI scanner.

For MRI, you lie down on a special table that slides inside the MRI scanner. You will be asked to stay very still during the scan. The space within the magnet is small. If you feel claustrophobic (uncomfortably confined), you can stop at any time. The MRI scanner makes loud repetitive tapping sounds when in use. You will be required to wear earplugs and protective ear coverings for hearing protection. You may be fitted for a bite bar in order to keep your head from moving during the scans.

During the MRI, you will be asked to do memory tests. These tests will examine your memory as well as your thinking and language ability.

Blood Draws
At Week 1 and Week 12 you will be asked to come to the laboratory after an overnight fast and have your blood drawn.

Saliva Collection
We will ask you to provide 3mL of saliva. We will collect them in a 15mL sterilized tube and immediately placed on ice and stored at -80 degrees for subsequent analysis. We will collect saliva at week 1 and week 12 at the blood draw visit.

INTERVENTIONS

At the beginning of this study, you will be randomized (like the toss of a coin) to an exercise group for the study. The aerobic and stretch sessions will meet at the Exercise Lab of the Atlanta VA Rehab R&D Center or at the GRECC. You can also choose to have your sessions held remotely.

Intervention Groups

Aerobic Exercise

You will participate in an aerobic exercise program using a stationary bicycle 3 times a week, for 12 weeks. Over the 12-week period, you will gradually progress in your exercise difficulty and time. Generally, you will start with about 20 minutes per session and increase to a maximum of 60 minutes per session. Trained staff members will give you instructions throughout each exercise session. Before each exercise session, you will do a warm-up activity for your legs. You may request rest breaks and you may stop at any time.

Interval Exercise Group

You will participate in an interval exercise group 3 times a week, for 12 weeks. Over the 12-week period you will do progressive whole body stretching, toning and balance exercises designed for individuals 65 years and older. You will start with 20 minutes per session and increase to a maximum of 60 minutes per session. Trained staff members will give you instructions throughout each exercise session. Before each exercise session, you will do a warm-up activity for your legs. You may request rest breaks and you may stop at any time.

Remote Exercise Monitoring

As an alternative, participants that are uncomfortable with receiving face-to-face training within the hospital will be given the option to continue their exercise intervention visits remotely. For participants that have been randomly assigned to the 'spin' exercise training program, will be provided a stationary cycle ergometer that has been sanitized properly to use during the 12-week period. All subjects will be monitored and trained through VA and Emory approved remote access sites.

Control Group

A random subset of participants will be in a 12-week waitlist control. These participants will undergo the same pretesting procedures as described above. After 12-weeks of no activity with the study team, these participants will return and repeat the pre-assessment, 12-week exercise intervention and post assessment as described above.

We will ask you to return after the exercise period to complete the final assessments for this study.

Apple Watch

Some study participants will be asked to wear an Apple Watch. Some individuals will also be loaned an iPhone. Before taking home the Apple Watch (and iPhone, if applicable), you will be

asked to sign a form indicating that you understand the item(s) is/are being loaned to you and must be returned. A member of the study team will setup the Apple Watch for your use and will explain how to use the Watch. Setup will include entering your height, weight, and year of birth. The Watch will collect your daily total activity level. During Assessment 1 we will also schedule when you will return the Watch/iPhone to the study team. While you are in possession of the Watch we ask that you wear it every day.

RISKS:

Risks with Behavioral Tests
You may experience some frustration during the cognitive testing. You will be given breaks during testing and allowed to express any frustration.

Risks with Exercise and Physical Fitness Assessments
During any type of exercise, your heart rate and blood pressure will change. Because of these changes, there is a minimal risk of cardiac event or heart attack. Although any exercise program carries the possibility of a cardiac event, we minimized this risk by requiring you to be cleared by a doctor. We will instruct you in proper exercise procedure. While at the VAMC, you will be monitored throughout all exercise activity by research staff trained in cardiopulmonary resuscitation (CPR). Furthermore, when at the VA Health Care System, there is access to a full medical code response should an untoward event occur.

Some participants will experience exercise-related injuries and possibly muscle soreness and fatigue as a result of the testing and the intervention. There is a small risk for loss of balance and injury from a fall while walking and during balance testing. Research personnel will be with you at all times.

Risks with Transcranial Magnetic Stimulation (TMS)
There may be some discomfort with the skin preparation and removal of the sensors. Although steps are taken to reduce the chance of this happening, slight irritation is possible but should disappear in a few days. Subjects sometimes report low level but easily tolerable scalp discomfort from TMS. Occasionally, subjects report headaches from TMS that are relieved by common over-the-counter pain medications. Possible effects on hearing have been described so participants will wear earplugs during TMS. As with any electronic device, there is a possibility of electric shock. While this is very unlikely, we will ask you to remove any metal objects on your body prior to TMS testing.

Risks with Magnetic Resonance Imaging (MRI)
An MRI scan exposes you to strong magnetic fields. There is no evidence that this is directly harmful to you. Strong magnetic fields are capable of moving metal objects. Therefore, if you have any metal objects or fragments in your body, other than dental work, or you have a cardiac pacemaker, you must let us know so we can cancel this test. The MRI scan is conducted like a CT scan but the area in which you lie is quite confining and some people experience claustrophobia, that is discomfort in enclosed spaces. If you are affected in this way, it will be important for you to let us know, as this could adversely affect the results of the study and would lead us to discontinue our research with you.

The MRI scanner produces a loud hammering noise, which has produced hearing loss in a very small number of individuals. You will be given hearing protection to reduce this risk. You may experience a temporary decrease in your hearing abilities accompanied by a ringing in the ears. This should stop within 48 hours from the time you were scanned. If this does not stop within 48 hours please contact Dr. Joe Nocera, Principal Investigator of this study at 404-321-6111, ext. 201662.

You should stay away from loud noise environments for 24 hours after you have been scanned. Examples of a loud noise environment include mowing the lawn, riding on a motorcycle, and attending a music concert or sporting event. If you must be in a loud noise environment you should use hearing protection. We will provide you with foam earplugs for this purpose and we will show you how to use them.

Risks with Blood Draw

The risks of drawing blood from a vein include discomfort at the site of injection; possible bruising and swelling around the injection site; rarely an infection; and, uncommonly fainting from the procedure. A trained phlebotomist will collect all blood samples following standard protocol.

Risks with Apple Watch

People with skin sensitivities could experience skin irritation from wearing an Apple Watch. This risk can be reduced by keeping the watch band clean and dry. Anyone with a nickel or methacrylate allergy should confirm when first wearing an Apple Watch that it does not irritate his or her skin. Please stop wearing the Apple Watch if you experience any redness, itching, swelling, or other signs of skin irritation. Continuing to wear the Watch could worsen these symptoms.

Electromagnetic fields coming from the Apple Watch can interfere with pacemakers, defibrillators, and other medical devices. Please keep the Watch, band, and charger a safe distance from any medical devices (as specified by the medical device manufacturer), including others' medical devices. Stop using the Watch and its accessories if you suspect they are interfering with a medical device.

Information on safe handling of the Apple Watch can be found here:
http://help.apple.com/watch/#/apdcf2ff54e9

BENEFITS:

There may be no direct benefit to you from taking part in this study. You will receive information on your physical fitness levels and the results will be discussed with you. You also will have the opportunity to participate in a physical activity program with professional supervision.

This research study will ultimately lead to a better understanding of how the brain works as well as the impact of exercise on brain function. We hope that one day this knowledge will in turn lead to improvement of rehabilitation techniques for older adults, neurological impairment, or after brain injury and spinal cord injury.

CONFIDENTIALITY:
We will keep information about you, including any research records we create, strictly confidential to the extent required by law. We may be required to release your record if we receive a subpoena or a court order. The study staff will keep your study files locked in a file cabinet in a private office. We will use a study number rather than your name on study records when we can. Your name and other facts that might point to you will not appear when we present this study or publish its results. People other than those doing this research study may have access to your medical and study records including:

- The sponsor of the study: Department of Veterans Affairs
- The Office for Human Research Protections
- The Government Accountability Office (GAO)
- The Office of Research Oversight (ORO)
- The Inspector General
- The Emory University Institutional Review Board and other offices in Emory University that help run and/or oversee studies
- The Atlanta VA Research Compliance Officer
- VA research staff with the VA Hospital or at Emory University (when data is stored at Emory)
- Any appropriate state or federal government agencies that make rules and policy about how research is done that are not listed above

If you are participating in a study where a test and/or procedure may be performed at Emory and you are not and have never been an Emory patient, you do not have an electronic medical record. Please note that an Emory medical record will be created if you have any services or procedures done by an Emory provider or facility for this study.

All research records and/or identifiers will be destroyed in accordance with the VA record retention schedule.

If you are a veteran who is a patient in the Atlanta VA Health Care System, a copy of your signed and dated consent and HIPAA forms may be placed in your medical record(s). If you are a non-veteran receiving clinical services (i.e., use of the laboratory, radiology, audiology, etc.) as part of this study, you will have an electronic medical record created for you. You will also be given a VA Notice of Privacy Practices (NOPP) and we will ask you to sign a form saying that you have received this notice.

If you are in an FDA sponsored clinical trial: A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

COMPENSATION:
You will be compensated $50 for your time after completion of each visit during the initial assessments (Assessment 1). You will receive $50 per visit during the follow up testing

(Assessment 2). If you are in the comparator group you will receive $50 per visit for your time. A check will be mailed to you 4 – 6 weeks after each assessment period.

You will get emergency medical care if you get injured from being in this study. Under Federal Law, you will qualify for follow-up treatment if the injury was related to the research study. You may or may not get further compensation if you are injured in this study. This rule would not apply if you do not follow study procedures. If you believe you have been injured by this research, you should contact **Dr. Joe Nocera, the Principal Investigator, at 404-321-6111, ext. 201662.**

CONFLICT OF INTEREST:
None

COSTS:
Some Veterans are required to pay co-payments for medical care and services provided by the VA. These co-payment requirements will continue to apply to medical care and services that are not part of this study.

CONTACT PERSONS:
If you have any questions, concerns, or complaints about this study or if you have been harmed from being in this study, call **Dr. Joe Nocera at 404-321-6111, ext. 201662.**

If you want to speak to someone who is not a member of the study to discuss problems, ask questions or voice concerns, you can call:

- The Emory Institutional Review Board (404) 712-0720 or toll free at 1-877-503-9797,
- The VA Research Compliance Officer at (404) 321-6111 ext. 206964, or
- The VA Clinical Studies Center Director at (404) 321-6111 ext. 206933.

If you have any questions about your rights as a participant in this research study, call the Emory University Institutional Review Board at (404) 712-0720 or toll free at 1-877-503-9797.

VOLUNTARY PARTICIPATION AND WITHDRAWAL:
Participation in this study is voluntary. You have the right to refuse to be in this study. You can stop at any time after giving your consent. Whatever you decide, you will not lose any benefits to which you are entitled, nor are there any medical consequences associated with your non-participation. The study investigator and/or sponsor may stop you from taking part in this study at any time if they decide it is in your best interest, or if you do not follow study instructions. You may be withdrawn from the study for other reasons, for example:

- if you are unable to understand directions for the study
- if you are unable to fit into the MRI scanner
- if you show signs of significant discomfort from the procedures
- if your medical history indicates scanning is not safe for you
- if your performance on tasks administered outside the scanner does not meet established enrollment criteria

We will give you a copy of this consent form to keep. If you are willing to volunteer for this research, please sign below.

Research Participant's Signature and Date

_____
Research Participant's Name (Print)

_____ _____ _____
Research Participant's Signature **Date** **Time**
(to be entered by Participant)

_____
Name of Approved Individual Obtaining Consent (Print)

_____ _____ _____
Signature of Approved Individual Obtaining Consent | Date | Time
(to be entered by Approved Individual)

An Approved individual is one who has completed HRPP training and is officially approved to consent subjects for this specific study. The signature and date of this individual certifies that this is the most current approved consent document for this study.