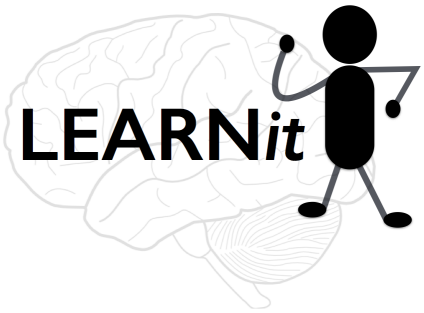
Lifestyle Enriching Activities for Research in Neuroscience – intervention trial



Study Protocol

NCT#:
NCT0272690

LEARNit Protocol
Version 3.0
April 26, 2024

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FULL PROTOCOL TITLE

Lifestyle Enriching Activities for Research in Neuroscience intervention trial (LEARNit), a randomized, single blind, 60 participant clinical trial examining the effect of aerobic exercise vs. health education on brain function and cognition in older adults with early mild cognitive impairment.

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Sponsor:
The National Institute on Aging
1R01AG046928 - 01A1

Investigational PET ligand F-AV-1451 Provided by:
Avid Pharmaceuticals

IND holder:
Dr. Peter Conti
IND # 129822

NCT#:
NCT02726906

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SUPPLEMENT / APPENDIX

PRÉCIS

Alzheimer's disease (AD) is the most common cause of cognitive impairment in older adults.[1] The need for effective treatments has become imperative, as 36 million people worldwide are affected.[2,3] The results from several large trials have been sobering with a lack of significant clinical outcomes, prompting a paradigm shift to initiate treatment earlier in the disease process and explore lifestyle interventions.[4-7] Exercise has emerged as an exciting, non-pharmacological approach to help remediate cognitive loss or delay onset of dementia.[8-13] However, to fully capitalize on the investments in exercise and to discover the full treatment potential of exercise, the brain mechanisms supporting exercise for older adults with MCI must be understood.

Using an aerobic walking intervention program, we will conduct an investigation of brain mechanisms supporting exercise, from localized function and structure of the hippocampus, to lower-level growth factors. This project will recruit 60 sedentary older adults between 55-80 years of age with early MCI. Based on the Surgeon General's recommendation for moderate-intensity aerobic in older adults,[14-15] participants will be randomly assigned to: aerobic walking for 30 mins, 5 days/week for 6 months OR health education non-active control for 6 months, with 30 participants in each arm. Primary outcome measurements include regional brain activity in the hippocampus and behavioral performance on the Mnemonic Similarity Task (MST).[16-17] Additionally, we will examine secondary outcomes of physical function, aerobic fitness, amyloid burden, and brain derived neurotrophic factor (BDNF) associated with exercise.[18-21] For exploratory purposes, all participants will be scanned with amyloid and tau PET tracers at baseline and follow-up to examine the contribution of amyloid and tau aggregation on brain function and to serve as an AD risk biomarker.

Study Title

Lifestyle Enriching Activities for Research in Neuroscience intervention trial (LEARNit)

Objectives

The purpose of this study is to examine the effects of modifiable lifestyle factors including exercise and healthy living education on brain health. The investigators will compare 2 types of interventions, moderate aerobic walking vs. healthy living education reading, over 6 months to evaluate changes in brain function, cognition, and physical function in older adults with cognitive concerns.

Our primary outcomes are neuroimaging measures of brain function after a 6--month exercise intervention, including regional BOLD activity and performance on a memory task, with secondary outcomes of brain derived neurotrophic factor, amyloid PET, physical function and aerobic fitness. We will link biological changes to meaningful clinical outcomes by examining

the relationship between enhanced brain function, improved memory performance and physical function after the intervention.

Primary outcomes. Based on the goals and innovation of this proposal, our primary outcomes are neuroimaging measure of brain function: fMRI BOLD signal in the hippocampus. Functional MRI has proven to be an effective non-invasive, in-vivo tool for measuring brain function. [22-24] Growing evidence supports that fMRI BOLD can detect neuronal changes that occur very early in the disease process. The hippocampus has been shown to be a selectively vulnerable region in AD, and several studies, including our own, identified a dysfunctional brain signal in the hippocampus in MCI patients.[25-27]

Secondary outcomes. The secondary outcomes consist of additional biological and clinical measures. The clinical outcomes were selected based on previous literature examining the effects of exercise and for enabling comparisons to the large ADCS exercise trial. The cognitive and functional outcome measures will be measured pre- and post-intervention (at baseline and 6 month follow-up).

Design and Outcomes

This trial is a single-blind, randomized controlled trial to test the efficacy of aerobic exercise on brain signal and memory function in individuals 55-80 years of age.

Interventions and Duration

There will be two arms:

Moderate aerobic walking OR Health education reading

Participants will engage in the arm specific intervention activities for the duration of the 6-month intervention. There will be two study visits, one at baseline and one at the end of the 6-month intervention.

Sample Size and Population

LEARNit will recruit 60 sedentary older adults ages 55-80 displaying early signs of cognitive impairment, as identified by the cognitive assessments administered at the screening visit via 1 SD or lower on one cognitive test from a neuropsychological battery. Subjects will be otherwise healthy older adults with no history of neurological disease or disorder who meet criteria to participate in the intervention and do not have any contraindications for MRI. Subjects will be randomized to one of the two arms, stratified by APOE4 status.

STUDY TEAM ROSTER

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1 STUDY OBJECTIVES

1.1 Primary Objective

The primary objective is to evaluate change in the outcomes of fMRI brain signal and behavioral performance during a mnemonic similarity memory task after a 6-month exercise intervention. We hypothesize that the exercise arm will have differences in hippocampal brain signal and performance relative to the health education control arm.

1.2 Secondary Objectives

Secondary objectives will examine change in outcomes of brain derived neurotrophic factor (BDNF), amyloid PET, physical function and aerobic fitness after a 6-month exercise intervention. We hypothesize that the exercise arm will have differences in amyloid PET accumulation, higher BDNF levels and improved aerobic fitness relative to the health education control arm.

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Alzheimer's disease (AD) is the most common cause of cognitive impairment in older adults and affects 36 million people worldwide.[1] Results from several large pharmacological trials prompted a paradigm shift to initiate treatment earlier in AD. [2-3] Mild cognitive impairment (MCI), a preclinical stage of AD, may be an optimal period for initiating treatment. Exercise has emerged as an exciting, lifestyle intervention to help remediate cognitive loss or delay onset of dementia.[8-10] However, to fully capitalize on the investments in exercise and to discover the maximum treatment potential of exercise, the brain mechanisms supporting exercise for older adults with MCI must be understood.[28-30] While a large body of literature has found that exercise enhances cognition, very few intervention studies have investigated the brain mechanisms responsible for these benefits.[31-36]

The positive effects of exercise on cognitive function in healthy older adults were first shown over a decade ago when aerobic walking improved executive function after 6 months, relative to stretching.[30] Increases in gray and white matter brain volume after a 6-month aerobic exercise intervention were later reported, and this finding was corroborated by a recent 12-month aerobic exercise study that showed increased hippocampal volume, improved memory function, and increased BDNF in healthy older adults.[28,37] Overall, the majority of studies on exercise that examined brain volume and cognition were in healthy older adults, leaving exercise effects on brain mechanisms in at-risk populations, such as MCI, largely unexplored. In a home-based exercise intervention, MCI patients were randomized to an exercise of choice, usually walking, or to a usual care control arm. The walking arm improved on the ADAS-Cog (Alzheimer's Disease Assessment Scale- cognitive subscale) by 0.26 points while the usual care arm actually

declined by 1.04 points.[9-10] Two studies to date, have examined the effects of exercise on brain function using fMRI in an intervention study.[37] These studies provided a glimpse into brain changes in MCI patients after exercise, but there is a need for a comprehensive study to understand how impaired brain mechanisms can be remediated with aerobic and strengthening exercise to support the cognitive benefits of exercise.

Using advanced brain imaging and key growth factor measures, the proposed study will take a cross-disciplinary approach to investigate the effects of exercise on brain mechanisms in individuals with MCI. Results from this study will provide critical insight into the brain mechanisms that drive the benefits of exercise on cognitive outcomes, will supply evidence of the intervention target and engagement, and will give neuroscientific support for public health interventions to increase exercise in older adults at risk for AD.

2.2 Study Rationale

Using an aerobic walking intervention program, we will conduct an unprecedented investigation of brain mechanisms supporting exercise, from large-scale connectivity, and localized function and structure of the hippocampus, to lower-level growth factors. This project will recruit 60 sedentary older adults between 55-80 years of age with early MCI. Based on the Surgeon General's recommendation for moderate-intensity aerobic in older adults, participants will be randomly assigned to: aerobic walking for 30 mins, 5 days/week for 6 months OR health education non-active control for 6 months, with 30 participants in each arm.[14-15] Primary outcome measurements include regional brain activity in the hippocampus and behavioral performance on the Mnemonic Similarity Task (MST). Additionally, we will examine secondary outcomes of brain volume, amyloid burden, cognition and brain derived neurotrophic factor (BDNF) associated with exercise. Importantly, all participants will be scanned with amyloid and tau PET tracers at baseline and follow-up to examine the contribution of amyloid and tau aggregation on brain function and to serve as an AD risk biomarker.

3 STUDY DESIGN

LEARNit is a single-site, single-blind, randomized controlled trial comparing the effects of moderate aerobic walking (55-80% target HR) versus healthy living education reading in older adults who perform at least 1 standard deviation below normative values for their age (N=60). Intervention is performed at home or in the participant's local community (e.g., home or neighborhood). Intervention duration is 6 months. Randomization for this single-blind study was achieved using a permuted block schema with block sizes of 2 and 4. Participants were randomized in a 1:1 allocation to either aerobic walking or healthy living education arms and stratified by APOE4 carrier status (yes/no) based on saliva APOE phenotyping.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

Selected and recruited participants were community-dwelling older adults between the ages of 55-80 years of age. Target enrichment of 20% underrepresented race/ethnic groups was a priority.

4.1 Inclusion Criteria

1. Male or female

2. English speaking

3. 55-80 years old

4. Exhibits sedentary behavior (defined as engaging in moderate intensity exercise, such as brisk walking for < 60 minutes total per week for the last 3 months)

5. MMSE score > 26

6. Perform 1 SD below normative values on neuropsychological tests

7. Absence of dementia

8. Ability to complete both fMRI and PET scans

9. Physical ability to complete exercise program as determined by performance on physical screen by certified PT indicating it is safe to participate in the intervention.

4.2 Exclusion Criteria

Candidates meeting any of the exclusion criteria at baseline will be excluded from study participation and then list each criterion.

1. Participants meet criteria for dementia (DSM-IV)

2. History of a neurological disorder

3. Head trauma with loss of consciousness > 10 minutes

4. Current psychiatric illness, including depression (GDS>7)

5. Severe sensory deficits

6. Current or substantial history of substance abuse

7. Diabetes

8. Inability to perform intervention (e.g., inability to walk without assistance)

9. Contraindications to MRI scan (e.g., pacemaker).

4.3 Study Enrollment Procedures

Recruitment:

Participants will be recruited from the community using local media outlets, like the newspaper, radio, flyers and local community groups, including senior centers, retirement communities and churches. The projected enrollment is 25 participants per year.

Screening and Eligibility Criteria:

All study candidates will first be telephone-screened for information on demographics, exercise level, medications, and MRI contraindications. If eligible after the telephone screening, participants will receive an in-person evaluation including a detailed history, neuropsychological screening battery assessing memory and executive function. Screening for depression will be done using the self-report 15-item Geriatric Depression Scale. Participants will be deemed eligible, meeting criteria for a diagnosis of cognitive decline, when performance on at least one measure of the neuropsychological battery is one standard deviation below age, education and gender matched norms.

Screening Records:

Detailed documentation for all subjects who are screened will be kept in the REDCap database including ineligibility documentation.

Eligibility Criteria:

A summary of each participant's in-person screening and eligibility data is included in the REDCap database in the Screening Key form.

Consenting:

Consent will be obtained from participants at the beginning of the Screening Visit prior to any testing. The Project Manager, Coordinator or PI will review the consent form (IFC) with participants. One of the collaborating MDs (e.g., Dr. Peter Conti) will be available to answer questions (by phone as necessary) and will sign the consent form.

A copy of the signed consent form will be offered to all participants for their records. The original signed consent form will be stored in a locked cabinet in the PI's office.

Randomization:

Randomization for this single-blind study was achieved using a permuted block schema with block sizes of 2 and 4. Participants were randomized in a 1:1 allocation to either aerobic walking or healthy living education arms and stratified by APOE4 carrier status (yes/no) based on saliva APOE phenotyping.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

At-home Walking Program: Participants enrolled in the at-home walking program will have a program tailored to them. A trained exercise therapist will assist them in designing this program to carry out for a period of 6 months. Over the first 6 weeks subjects will engage in walking exercises that gradually increase in duration up to 150 minutes/week. The interventionist will work closely with the subject during this period to ensure proper safety, positioning, and intensity. From week 6 and on, participants will continue walking at 150 minutes/week. At the end of the study, subjects will receive a packet of reading materials for the at-home health education program to independently engage in the other intervention program, if they wish.

At-home Health Education Program: Participants will be asked to participate in an at -home health education program for a period of 6 months that consists of a behavioral intervention packet of reading materials. Participants will be asked to read about two topics per month from the packet. The interventionist will work closely with them during the first 6 weeks to ensure understanding of the program and continue to visit them to ensure compliance through the duration of the intervention. Following the program, they will be offered the opportunity to attend an educational session on exercise with the interventionist and will receive materials on engaging in an at home walking program.

All participants will be asked to wear a physical activity-monitoring device for the intervention period of 6 months.
Participants will be asked to complete surveys, questionnaires, and keep an activity diary to be mailed in, collected by the interventionist, completed online or by phone.

5.2 Handling of Study Interventions

Aerobic Walking Arm:

The aerobic group will participate in aerobic walking for a total of 3-5 days/week for 6 months. There is a misconception of what constitutes beginner, intermediate and advanced levels of aerobics. It is exercise intensity level that determines heart rate. The target heart rate range for participants in the aerobic training group is 60 to 75% of their maximum heart rate. Since all participants are 55 years or older, simple walking activities will be all that is required to achieve this target heart rate range. All the participants in this study are inactive and may not have much, if any, prior aerobic experience. The aerobic walking program is detailed below. Each session will include warm-up, aerobic, and cool-down periods.

Components of Aerobic Training Exercise:

Warm-up (5 minutes) – Each exercise session will begin with an easy warm-up. Instruct the participant to use a heart rate zone of less than 50% of Max Heart Rate to guide your warm-up. As a general guideline, a warm-up can be something as simple as walking for 5 minutes at a slower pace.

Aerobic Segment (30 minutes) – The objective is to increase subjects' heart rates to 60% to 75% of their maximum. Subjects will measure their heart rate at 15 minutes into the walking period and at the end of walking. At the end of the aerobic training session, have subjects record their heart rates and perceived exertion in their Exercise Diaries.

Cool-down (5 min) – Aerobic activity should always be followed by a cool-down period. The participant will slow down walking speed in the last 5 minutes of the walking session. Instruct the participant to "slow down your movement and try to get your heart rate back down to less than 50% of Max Heart Rate. " Perceived exertion should be checked again to be sure everybody is recovering adequately

Progression of Aerobic Exercise:

Ideally participants will progress the walking program over the first 4 weeks with the following schedule: weeks 1-2 will consist of 40 minutes for 2 days/week (including 5 minutes warm-up, cool-down and 30 minutes of continuous walking). By weeks 3-4 subjects will have added the 3rd walking day at 40 minutes. Thus, by week 5 up to 6 months, subjects are participating fully in the aerobic component of the program (40 minutes total including 5 minutes warm-up, 30 minutes continuous aerobic walking and 5 minute cool-down for at least 3 days/week). However, it is likely that not all subjects in the aerobic group can progress at this rate. In these cases, the interventionist will tailor a program of increasing duration per session and increasing frequency per week to eventually achieve the complete walking program of 40 minutes.

Structure of aerobic exercise: minimum of 3 days per week (45 minutes each) walking, up to 5 days per week (30 minutes each).

If a subject has limited endurance and can only manage 10 minutes of continuous aerobic exercise during the first session before complaining of fatigue or RPE of 'very hard exertion,' the following adapted schedule may be used such that the subject is participating fully by Week 6.

<u>Health Education Arm</u>:

Interventionists will have equivalent contact with participants from the health education to that of the aerobic walking group. They will visit weekly for the first four weeks, biweekly at weeks

6 and 8, with a monthly visit thereafter. Additional bi-weekly phone calls will be made in between the monthly visits. The health education protocol will consist of a home-based behavioral intervention packet of reading materials and videos for lifestyle practices including nutrition, stress management and risk factors for negative health outcomes (e.g., smoking, etc).

At the Orientation Visit (Week 0), subjects will complete the Health Education Contract with the interventionist and select their preferred topic order. Participants will be given a binder for the reading materials. There will be approximately two topics per month to read and participants will answer 4-5 reflection questions per week via electronic journal or on paper, to measure adherence. Because providing 'choices' to the subjects has been shown to greatly impact adherence, the subjects will be given the choice to complete 13 out of 15 of the topics listed above. They may order the topics however they wish and select the educational topic they want to study for every two week period. Participants should be given the new topics at each home visit.

The topic choices for each participant will be recorded in REDCap using the Health Education Topic Order instrument. This form must be completed within a week of the Orientation Visit as it links the appropriate reflection questions to the reading journals.

Arm Visit Matrix

Visit	Aerobic Walking Arm	Health Education Arm
Week 0	**Home Visit**	**Home Visit**
Week 1	**Home Visit**	**Home Visit**
Week 2	**Home Visit**	**Home Visit**
Week 3	**Home Visit**	**Home Visit**
Week 4		
Week 5	**Home Visit**	**Home Visit**
Week 6		
Week 7	**Home Visit**	**Home Visit**
Week 8		
Week 9	**Phone Call**	**Phone Call**
Week 10		
Week 11	**Home Visit**	**Home Visit**
Week 12		
Week 13	**Phone Call**	**Phone Call**
Week 14		
Week 15	**Home Visit**	**Home Visit**
Week 16		

Week 17	**Phone Call**	**Phone Call**
Week 18		
Week 19	**Home Visit**	**Home Visit**
Week 20		
Week 21	**Phone Call**	**Phone Call**
Week 22		
Week 23	**Home Visit**	**Home Visit**
Week 24		
Week 25	**Phone Call**	**Phone Call**
	6-month Visit	**6-month Visit**

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

Participants are allowed to continue or begin any medications or treatments prescribed or recommended by their physicians. Other studies involving research intervention are not allowed.

5.3.2 Required Interventions

None

5.3.3 Prohibited Interventions

Other studies involving research intervention are not allowed.

5.4 Adherence Assessment

Adherence will be assessed using several strategies, including Exercise Journal entries, and adherence outcomes obtained during the interventionist visits that include completed days of activity, exercise duration, time in target HR zone, subjective ratings of perceived effort, and achieved HR.

The study team and interventionists will implement behavioral management strategies to support a positive exercise environment. The goal in LEARNit will be for participants to complete at least 80% of the prescribed exercise sessions. Participants who miss one or more exercise sessions each week will be contacted by their interventionist or a study team member to provide encouragement and help generate a plan to help the participant complete the training sessions the following week. In cases where adherence is an ongoing problem, the study team may meet with the interventionist to discuss strategies to increase adherence (e.g., goal setting, reinforcers identified and scheduled, etc.).

Theory and evidence-based approach to increase adherence. A challenge of employing a behavioral intervention is achieving program adherence and completion, particularly in

individuals with MCI. To increase the likelihood of meeting these goals, the interventionist will draw upon principles of social-cognitive and health belief models for personal and environmental factors and perceived barriers and benefits.[38-40] The interventionist will begin by establishing rapport and trust with the participant by gaining an understanding of the participant's perspective on the intervention and any perceived barriers to increasing self-efficacy.[41-43] This will be followed by an introduction and rationale for the intervention, education on the benefits of exercise, and addressing home-life challenges. The program steps of each intervention will be detailed in a manual for the interventionist to be performed by the interventionist with the participant during two 1-hour sessions during the first 2 weeks.

To encourage adherence and accountability, these steps will be followed: 1) The interventionist will develop a contract with the participant and identify motivating factors for compliance and increasing positive health outcomes during the first 2 home visits, and a contract copy will be kept in the behavioral modification packet for the participant. 2) The participant will complete an exercise journal of activity completion (start/stop time), heart rate during activity, and any adverse events. It has been highly successful for collecting confidential information for our current projects and will be used for the participants' journal. 3) The interventionist will conduct weekly phone calls for the first 6 weeks and bi-weekly calls thereafter to answer questions, reinforce safe practices, and probe any adverse events. Research staff will monitor journals for compliance and address any identified concerns. The interventionist will complete monthly home visits to provide encouragement and retrieve pedometer data as well as the exercise journal. 4) The study coordinator will mail monthly newsletters to the participants on the health benefits of exercise (or healthy lifestyles for the control arm). 5) The interventionist will perform a fidelity check during 2 of the home visits. Specifically, the interventionist will perform the program with the participant (walking, strengthening activities) to observe the participant's completion and use motivational techniques to provide feedback and additional instruction if needed. If the participant must travel away from the home during the intervention period of 12 months, the interventionist will work with the participant to establish a plan for maintaining activity during travel time. 6) To mitigate possible reduced motivation over time, we will conduct 2 "refresher course" at the midway point of the intervention. The steps of using a contract and journal to increase adherence in MCI have been used by Drs. Winstein and Fisher, Co-Investigators and are detailed in the Manual of Procedures (MOP).

5.5 SCHEDULE OF EVALUATIONS

Schedule of Evaluations			
	Screen	**BL**	**6 mo**
Study description / informed consent	•		
Neuropsychological Screening	•		
Physical Assessment for study inclusion	•		
Saliva Collection	•		
Accelerometer Tracking	•	•	•
Modified Physical Function Test		•	•
Treadmill walking test		•	•
Serum collection		•	•
Neuroimaging		•	•
-Task and resting state fMRI		•	•
-T1 anatomical		•	•
-Amyloid, Tau PET scan		•	•
Neuropsychological Testing		•	•
-Memory, Exec Function		•	•
Interventionist home visit (monthly)		•	•
Participant phone contact (bi-weekly)		•	•
Exit interview			•

6 Description of Evaluations

6.1 Screening Evaluation

Visit 1 (Screening Visit):

- Informed Consent (IFC Review): Review and sign the informed consent form. The study investigators will answer any questions participants may have about the study.
- Evaluation: Subjects will receive an in--person evaluation including a review of medical history, physical screen and a comprehensive neuropsychological screening battery assessing memory and attention. Subjects will be asked to provide a saliva sample.

30-Day Compliance Test

- Physical Activity Monitoring: Subjects will be given an accelerometer and asked to wear the device at home for a period of 30 days.

6.1.1 Enrollment, Baseline, and/or Randomization

Baseline Assessments (2-day Visit):

The following procedures will take place over 2 days at the baseline visit. Total participation during the 2--day period is not anticipated to exceed 10 hours. (For example, baseline participation may be 6 hours on day one and 4 hours on day two).

- Cognitive Tasks: Subjects will be asked to perform one or more memory or attention task(s). They may be presented with images, videos, words, numbers, or sounds. The cognitive testing session should last no more than two hours.
- Questionnaires: Subjects will be asked to complete one or more surveys or questionnaires on paper or in electronic format. Completing these documents should take no more than 30 minutes.
- fMRI Scan: Subjects will be asked to perform cognitive tasks while we use magnetic resonance imaging (MRI) to measure changes in activity in the brain. Estimated time in the MRI machine will be about 60 to 90 minutes. The entire session should last no more than 3.5 hours including said cognitive tasks.
- PET/CT Scan: Subjects may be asked to participate in 2 positron emission tomography (PET/CT) scans per visit (2 at Baseline and 2 at 6-month visit). After a delay of about 75 minutes to allow the tracers to be absorbed, you will be moved into the PET/CT scanner for about 30 minutes.
- Blood Draw: Subjects will be asked to have a blood draw. This will be a fasting blood draw. We will collect about 50 mL of blood.
- Physical Assessment: Subjects will be asked to complete a physical function test. Subjects will be asked to perform a number of everyday activities. The second assessment is a treadmill walking test performed at the clinical exercise research center

(CERC) while we monitor heart rate. Subjects will be monitored by trained study staff. Finally, body composition and body weight will be measured at the same time on the Biospace InBody 520 device. Subjects will stand on the scale-like device while grasping two handles, one in each hand. The device works by sending a very low- voltage electrical signal through the body to determine water content and body fat percentage. The voltage is so low that subjects cannot feel it. The testing will take about 45 minutes.

- Randomization: Subjects will be assigned randomly, much like tossing a coin, to a study group. They will be randomized into one of two health programs, and will have a 50% chance of being placed in either group. One group will participate in an at-home walking program and the other an at-home health education program.

6.1.2 Follow-up Visits / Completion/Final Evaluation

Follow-up 6-month Visit (2-day Visit):

The following procedures will take place over 2 days at the follow-up visit. Total participation during the 2-day period is not anticipated to exceed 10 hours. (For example, participation may be 6 hours on day one and 4 hours on day two).

- Cognitive Tasks: Subjects will be asked to perform one or more memory or attention task(s). They may be presented with images, videos, words, numbers, or sounds. The cognitive testing session should last no more than two hours.
- Questionnaires: Subjects will be asked to complete one or more surveys or questionnaires on paper or in electronic format. Completing these documents should take no more than 30 minutes.
- fMRI Scan: Subjects will be asked to perform cognitive tasks while we use magnetic resonance imaging (MRI) to measure changes in activity in the brain. Estimated time in the MRI machine will be about 60 to 90 minutes. The entire session should last no more than 3.5 hours including said cognitive tasks.
- PET/CT Scan: Subjects may be asked to participate in 2 positron emission tomography (PET/CT) scans per visit (2 at Baseline and 2 at 6-month visit). After a delay of about 75 minutes to allow the tracers to be absorbed, you will be moved into the PET/CT scanner for about 30 minutes.
- Blood Draw: Subjects will be asked to have a blood draw. This will be a fasting blood draw. We will collect about 50 mL of blood.
- Physical Assessment: Subjects will be asked to complete a physical function test. Subjects will be asked to perform a number of everyday activities. The second assessment is a treadmill walking test performed at the clinical exercise research center (CERC) while we monitor heart rate. Subjects will be monitored by trained study staff. Finally, body composition and body weight will be measured at the same time on the Biospace InBody 520 device. Subjects will stand on the scale-like device while grasping

two handles, one in each hand. The device works by sending a very low- voltage electrical signal through the body to determine water content and body fat percentage. The voltage is so low that subjects cannot feel it. The testing will take about 45 minutes.

7 SAFETY ASSESSMENTS

Adverse events are recorded via electronic recording directly into REDCap by the participant in the form of "Have there been any changes in your health status?" Any reporting of an AE triggers an alert to the study team in the REDCap system.

7.1 Adverse Events and Serious Adverse Events

An **adverse event (AE)** is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recording regardless of their relationship to the study intervention.

A **serious adverse event (SAE)** is generally defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

7.1.1 Evaluation of Safety Measures

Event and participant count of the following will be summarized overall and by treatment group for the entire cohort:

- AE: Overall and by MedDRA System Organ Class
- AE: MedDRA Preferred Term
- SAE: Overall and by MedDRA System Organ Class
- SAE: MedDRA Preferred Term
- SAE Definitely Related to Intervention: Overall and by System Organ Class
- Hospitalization
- Deaths

Comparisons of the number of participants with at least one AE, SAE, SAE definitely related to Intervention and Death will be examined between Intervention groups using the Fisher's Exact test.

7.2 Reporting Procedures

AEs will be reported to the IRB according to the timing specifications laid out by the governing body. SAEs will be reported within 24 hrs of reporting to the Safety Monitor and the IRB.

7.3 Follow-up for Adverse Events

The follow-up of adverse events occurs while the participant is actively engaged in the study through electronic inquiry.

7.4 Safety Monitoring

This trial was monitored by an NIH-approved Data and Safety Monitoring Officer, Dr. Sharon Sha, MD, Chief of Memory Disorders Division at Stanford University.

Sharon J. Sha, MD, MS
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8 INTERVENTION DISCONTINUATION

Investigators will make every effort to maximize participant retention. If a participant expresses a desire to stop the intervention, the study team will meet to discuss the participant's existing challenges and possible approaches to reduce burden to encourage continued participation if at all possible (e.g., adapt exercise routine to reduce pain or increase interest, problem-solve regarding adherence issues, etc.).

If a participant continues to decline further participation, or if an investigator discontinues the intervention, an exit interview should be completed as soon as possible immediately following intervention discontinuation.

All early intervention discontinuation participants will be strongly encouraged to complete the month 6 assessment visit.

Reasons for Early Discontinuation

Participants are allowed to voluntarily discontinue participation in this trial at any time. Due to the low safety risk of this intervention, we do not anticipate early discontinuation due to safety concerns.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Hypotheses regarding the primary cognitive outcome, and secondary and exploratory outcomes will be tested using a linear mixed model for repeated measures (MMRM) including indicator variables for time, intervention, time-by-intervention interaction term, and additional covariates meeting confounding criteria below. A participant-level random intercept will be specified; significance of random slopes will be tested and included in the model if significant. Age and sex/gender will be treated as potential confounders. Potential confounders will be identified from randomization imbalance and based on their effect on the magnitude of treatment. A variable will be treated as confounder if adding it to the model changes the value of treatment estimate by more than 15%. APOE4 will be included in all models because it was a randomization stratification factor. For fMRI hippocampal BOLD analysis, within subject changes in activity will be calculated for each individual subject in those with both baseline and follow-up fMRI data. Subject data will be normalized to group template space which is comprised of timepoint 1 and 2 to reduce measurement error or individual subject bias. Analyses will be performed by staff blinded to the treatment group.

9.2 Sample Size and Randomization

Given the planned sample size of 30 participants per group, the magnitude of effect observable for this analysis are described below:

This study was powered based on the fMRI primary outcome. Group sample sizes of 30 achieve 80% power for each test to detect an effect size of at least 0.736 and a type I error of 0.05 using a two-sided two-sample equal-variance t-test. There are 2 primary outcomes (cognition, imaging), but because they are very different measures, the alpha level will remain at 0.05 for each primary outcome test. There will be no alpha-level correction for secondary or exploratory outcomes. Preliminary data provide an estimated standard deviation of 0.25 z-score units for fMRI network

function, indicating that we will be able to detect differences of 0.184 z-score units in brain function between groups. The effect sizes for fMRI BOLD activity and network function reported in previous physical activity intervention studies in older adults ranged from 1.17-1.24, thus we have high power to detect significant differences in brain function.

9.2.1 Treatment Assignment Procedures

We used a randomized, single-blind study design where randomization was achieved using a permuted block schema with block sizes of 2 and 4. Participants were randomized in a 1:1 allocation to either aerobic walking or healthy living education arms and stratified by APOE4 carrier status (yes/no) based on saliva APOE phenotyping. Research suggests that APOE4 status may affect response to exercise, thus carriers were balanced across groups.

9.3 Interim analyses and Stopping Rules

No interim analyses or stopping rules were applied for this clinical trial.

9.4 Outcomes

Hypotheses regarding the primary cognitive outcome, and secondary and exploratory outcomes will be tested using a linear mixed model for repeated measures (MMRM) including indicator variables for time, intervention, time-by-intervention interaction term, and additional covariates meeting confounding criteria below. A participant-level random intercept will be specified; significance of random slopes will be tested and included in the model if significant. Age and sex/gender will be treated as potential confounders. Potential confounders will be identified from randomization imbalance and based on their effect on the magnitude of treatment. A variable will be treated as confounder if adding it to the model changes the value of treatment estimate by more than 15%. APOE4 will be included in all models because it was a randomization stratification factor.

For fMRI hippocampal BOLD analysis, within subject changes in activity will be calculated for each individual subject in those with both baseline and follow-up fMRI data. Subject data will be normalized to group template space which is comprised of timepoint 1 and 2 to reduce measurement error or individual subject bias. Analyses will be performed by staff blinded to the treatment group.

9.4.1 Primary outcome

The primary outcome measures will be collected during fMRI acquisition at baseline and 6-month follow-up. Participants will complete the mnemonic similarity test (MST) during the fMRI scan to provide both primary outcome measures of hippocampal BOLD signal and MST performance, which is assessed using the Lure Discrimination Index.

- Hippocampal BOLD signal: change in hippocampal BOLD signal during the MST task defined as differences in activity between baseline and 6-month as the outcome measure. Change can be in either direction.

- Lure Discrimination Index (LDI): change in the LDI score, defined as 6-month – baseline, as the outcome measure will be analyzed using the MMRM approach. Higher change scores indicate improvement in LDI performance.

9.4.2 Secondary outcomes

Secondary analyses will be conducted using the same MMRM statistical approach described above for the analysis of all secondary outcomes.

- Single-stage treadmill test: change in the VO2 max score from the single-stage treadmill test defined as 6-month – baseline as the outcome measure. Higher change scores indicate improvement.
- Physical function test score: change in the Physical Function test score defined as 6-month – baseline as the outcome measure. Higher change scores indicate improvement.
- Brain-derived neurotrophic factor (BDNF) level: change in total plasma BDNF defined as 6-month – baseline level as the outcome measure. Higher change scores are better.
- Amyloid PET SUVR: change in global amyloid composite score including the mean of frontal, temporal, parietal cortex SUVRs defined as 6-months – baseline will be the outcome measure. Lower change scores are better.

9.5 Data Analyses

Hypotheses regarding the primary cognitive outcome, and secondary and exploratory outcomes will be tested using a linear mixed model for repeated measures (MMRM) including indicator variables for time, intervention, time-by-intervention interaction term, and additional covariates meeting confounding criteria below. A participant-level random intercept will be specified; significance of random slopes will be tested and included in the model if significant. Age and sex/gender will be treated as potential confounders. Potential confounders will be identified from randomization imbalance and based on their effect on the magnitude of treatment. A variable will be treated as confounder if adding it to the model changes the value of treatment estimate by more than 15%. APOE4 will be included in all models because it was a randomization stratification factor.

For fMRI hippocampal BOLD analysis, within subject changes in activity will be calculated for each individual subject in those with both baseline and follow-up fMRI data. Subject data will be normalized to group template space which is comprised of timepoint 1 and 2 to reduce measurement error or individual subject bias.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Data is collected using REDCap forms. Outcome assessments are collected by blinded assessors from study staff, the USC Memory and Aging Center, the Clinical Exercise Research Center and the USC PET Imaging Center. Subject data is collected using only their study ID, for which the key is kept separate and inaccessible by the blinded assessors. Physical copies of the IFC will be kept separately from all other study forms in a locked file cabinet, within in a secure office.

Data acquired during the intervention period for completion of intervention tasks was entered remotely via REDCap with assistance from the interventionists, as the intervention was home-based.

10.2 Data Management

This was a single site randomized clinical trial. Screening, Baseline and Follow-up visit data was collected on site at USC, by the study team, the USC Memory and Aging Center, as well as the Clinical Exercise Research Center and the USC PET imaging center. Data was scored when needed by the assessor collecting the outcome measures. Imaging data was acquired and transferred to the USC NIIN Computer cluster. Clinical report forms were used on paper or electronic entry. All paper data were entered into the online digital database, REDCap. REDCap data forms were created with built-in value controls and double entry from independent data managers was used to ensure accuracy.

10.3 Quality Assurance

10.3.1 Training

Data entry staff were trained on all REDCap forms and cognitive tests as needed. Accuracy of data entry was ensured via double entry from 2 independent data managers familiar with the forms. Double data entry was used for all paper to electronic transfer scoring. Any discrepancies were discussed by the quality control group described below.

10.3.2 Quality Control Committee

A committee of study staff was formed to review the cognitive testing and physical function tests for consistency and accuracy of scoring. The group met at three separate time frames to review data together. Any discrepancies were reviewed and adjudicated by the group for consensus on accuracy and scoring values.

10.3.3 Metrics

REDCap data forms were created with built-in value controls and double entry from independent data managers was used to ensure accuracy.

10.3.4 Protocol Deviations

Protocol deviations will be captured in REDCap using a protocol deviation form to record details and timeline of the deviations. Deviations will be reviewed in real time by the study team to determine appropriate action.

10.3.5 Monitoring

Consent forms were collected during the initial screening visit, signed by the PI and uploaded to the clinical trials portal within 2-4 weeks, before the baseline assessment visit. Outside review was conducted by the University to ensure completion at the baseline visit. Participants submitted weekly activity reports to the study team using REDCap. Reports were monitored weekly and contact was made by the study team or interventionist to ensure completion and accuracy.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document (Appendix I) and any subsequent modifications will be reviewed and approved by the IRB.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. Participants who cannot consent for themselves will be excluded from this study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant.

11.3 Participant Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIA, and the OHRP. Any data with subject identifiers will be kept in a separate locked file cabinet from the Participant Study ID.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12 ETHICAL CONSIDERATIONS

Good Clinical Practice
This study will be conducted in accordance with Good Clinical Practice (GCP) guidelines, as defined by the International Conference on Harmonisation (ICH) Guideline, Topic E6, the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) – Protection of Human Subjects and Part 56 – IRBs, HIPAA, State and Federal regulations and all other applicable local regulatory requirements and laws.

Study personnel involved in conducting this study will be qualified by education, training and experience to perform their respective task(s) in accordance with GCP.

No study document shall be destroyed without prior written agreement from the investigator. Should the investigator wish to assign study records to another party or move them to another location, he/she may do so only with the prior written consent from USC regulatory bodies.

Participant Confidentiality | HIPAA
Information about study participants will be kept confidential and managed according to the requirements of HIPAA. HIPAA regulations require a signed HIPAA Authorization informing the participant of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. The PI, under the guidance of the local IRB, is responsible for ensuring that all applicable HIPAA regulations and State laws are met.

Storage of Biospecimen Samples

All biospecimens banked for future AD biomarker research will be stored in freezers at USC. Sample tubes are bar-coded and linked to PID only and banked without personal identifiers. The presence of the sample is recorded into a computerized inventory database that is managed in RedCap and is encrypted and password-protected.

MRI Data Storage

MRI scans will be labeled with PID. All imaging data will be de-identified using a separate 8 digit identifier to maintain blinding and are checked by the imaging staff to confirm the absence of participant identifying information.

13 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures set forth by the sponsor, the National Institutes of Health - National Institute on Aging.

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SUPPLEMENT / APPENDICES

Appendix I - Informed Consent Form

Appendix II - Covid - 19 Required Safety Protocols

Appendix I – LEARNit Informed Consent

Study Title: Lifestyle Enriching Activities for Research in Neuroscience intervention trial (LEARN*it*)

Principal Investigator: Judy Pa, PhD
Phone #: 323-442-7246

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

You have been asked to participate as a subject in a medical experiment. Before you decide whether you want to participate in the experimental procedure, you have a right to the following information:

CALIFORNIA LAW REQUIRES THAT YOU MUST BE INFORMED ABOUT:

1. The nature and purpose of the study.
2. The procedures in the study and any drug or device to be used.
3. Discomforts and risks reasonably to be expected from the study.
4. Benefits reasonably to be expected from the study.
5. Alternative procedures, drugs, or devices that might be helpful and their risks and benefits.
6. Availability of medical treatment should complications occur.
7. The opportunity to ask questions about the study or the procedure.
8. The ability to withdraw from the study at any time and discontinue participation without affecting your future care at this institution.
9. Be given a copy of the signed and dated written consent form for the study.
10. The opportunity to consent freely to the study without the use of coercion.

I have carefully read the information contained above and I understand fully my rights as a potential subject in this study.

Date: _____ Time: _____

Signature: _____
(Research Participant)

INFORMED CONSENT

TITLE: Lifestyle Enriching Activities for Research in Neuroscience intervention trial (LEARN*it*)

PRINCIPAL INVESTIGATOR: Judy Pa, PhD
Phone #: 323-442-7246

DEPARTMENT: Neurology

We invite you to take part in a research study. Please take as much time as you need to read the consent form. You may want to discuss it with your family, friends, or your personal doctor. You may find some of the language difficult to understand. If so, please ask questions. If you decide to participate, you will be asked to sign this form.

WHY IS THIS STUDY BEING DONE?

There are currently no clear methods for improving brain health. In this study, we will examine two programs that may impact the effects of aging on the brain. You have been asked to participate in this study because you are an adult between ages of 55-80 and have mild concerns about your memory or attention. We hope to learn how health programs impact memory, attention, and the brain.

About 100 study participants will take part at USC.

WHAT IS INVOLVED IN THE STUDY?

If you decide to take part, the total length of participation is anticipated to be up to 13 months. This is what will happen:

First, you will participate in a "screening" visit to find out if you can participate in the study. If the screening exam shows that you are eligible and you choose to continue, then you will have 2 study visits, 6-months apart. At these visits, you will be asked to perform memory and attention tasks while participating in some or all of the procedures described in detail below at the USC Health Sciences campus. In the 6-month period between the 2 study visits, you will be asked to participate in *one* of two at-home health programs under the guidance of an interventionist who, in the context of this research, is a certified physical therapist trained in delivering the two health programs. You will be randomly assigned (like the flip of a coin) to *one* of the two at-home programs.
At 6-months, after finishing the health program, you will have one follow-up visit. At the end of the study, you will receive information about the health program to which you were *not* assigned.

Study Visits and Procedures

Visit 1 (Screening Visit)

Informed Consent: We will ask you to review and sign the informed consent form. The study investigators will answer any questions you may have about the study.

Evaluation: You will receive an in-person evaluation including a review of medical history, physical screen, and comprehensive neuropsychological screening tests to assess memory and attention. As part of the evaluation you will be asked for a saliva sample.

30-Day Compliance Test

Physical Activity Monitoring: You will be given an accelerometer and be asked to wear the device at home for a period of 30 days. The device should be worn on your wrist. The device is waterproof and should be worn 24 hours a day.

Visit 2 (Baseline Visit) and Visit 3 (6-month Visit)

The following procedures will take place over 2 days at both baseline and 6-month visits. Your total participation during the 2-day period is not anticipated to exceed 10 hours. (For example, at baseline you may participate for 6 hours on day one and 4 hours on day two).

- **Cognitive Tasks:** You will be asked to perform one or more memory or attention task(s). You may be presented with images, videos, words, numbers, or sounds. These may be presented to you on a computer monitor, through headphones, or on paper. Audio/Video recordings may be conducted during testing for fidelity purposes. The cognitive testing session should last no more than two hours.

- **Questionnaires:** You will be asked to complete one or more surveys or questionnaires on paper or in electronic format. Completing these documents should take no more than 30 minutes.

- **fMRI Scan:** You will be asked to perform cognitive tasks while we use a magnetic resonance imaging (MRI) to measure changes in activity in your brain. We use the fMRI to study which parts of your brain are most active while you do different cognitive tasks. You will be asked to lie on your back on a table and we will place a plastic imaging coil around your head. You will not come into contact with the coil during the scan. Foam pads will be placed around your head to limit head movement during the scan. We will then slide you into the MRI machine for about 60 to 90 minutes. While you are in the MRI machine, you will be asked to do the same cognitive tasks that you practiced earlier. The entire session should last no more than 3.5 hours including the cognitive tasks. Although you will be asked to hold still for the duration of the scanning session, you will be allowed to take breaks if

necessary. Study personnel, including the MRI technician, will be able to communicate with you throughout the MRI scan.

- **PET/CT Scan:** You will be asked to participate in 2 positron emission tomography (PET/CT) scans per visit (2 at Baseline and 2 at 6-month visit). We use PET/CT imaging to measure the binding of different radioactive tracers to disease risk biomarkers in the brain, which cannot be seen without these tracers. The scans involve radioactive tracers. The tracers will be injected intravenously. After about 75 minutes, to allow the tracers to be absorbed, you will be moved into the PET/CT scanner for approximately 30 minutes of PET/CT imaging. You may also choose to stop the scan for any reason.

- **Blood Draw:** You will be asked to have a blood draw. We will collect about 50 mL of blood. We will use the blood to test for relevant biomarkers. Biomarkers are substances in your body that tell us about your biological state or condition.

- **Physical Assessment:** You will be asked to perform two physical assessments and be weighed on an impedance scale at our exercise laboratory. The first assessment is a treadmill walking test, during which we will measure your heart rate using a heart rate monitor to get an estimate of how efficiently your body utilizes oxygen. The second assessment is a physical function test. We will ask you to perform a number of everyday activities. Finally, your body composition and body weight will be measured at the same time on the Biospace InBody 520 device. You will stand on the scale-like device while grasping two handles, one in each hand. The device works by sending a very low-voltage electrical signal through your body to determine water content and body fat percentage. The voltage is so low that you cannot feel it. This test takes about 2 minutes. The total testing time will take about 45 minutes.

- **Randomization:** You will be assigned randomly, like the toss of a coin, to a study group. You will be randomized into one of two health programs, and will have a 50% chance of being placed in either group. One group will participate in an at-home walking program and the other in an at-home health education program.

Health Program Activities:

- **At-home Physical Activity Program:** You may be asked to participate in an at-home walking program tailored individually to your walking environment, physical health, and capability. The interventionist, who is a trained exercise therapist, will assist you in designing this program to carry out for a period of 6 months. Over the first 6 weeks you will engage in walking exercises that gradually increase in duration up to 150 minutes/week. The interventionist will work closely with you during this period to ensure proper safety, positioning, and intensity. From week 6 onward, you will continue walking for 150

minutes/week and the interventionist will schedule a monthly visit to your home to walk with you. The interventionist will be in contact with you regularly (about once every 2 weeks) to answer any questions you may have. At the end of the study, you will receive a packet of reading materials for the at-home health education program to independently engage in the other intervention program, if you wish.

- **At-home Cognitive Activity Program:** You will be asked to participate in an at-home health education program for a period of 6 months that consists of a behavioral intervention packet of reading materials. You will be asked to read about healthy lifestyle factors weekly, covering about two topics per month from the packet. Planned topics include sleep behavior, diet, stress reduction, among others. The interventionist will work closely with you during the first 6 weeks to ensure understanding of the program. From week 6 onward, you will continue reading the materials weekly and the interventionist will schedule a monthly visit to your home to discuss your readings with you. The interventionist will be in contact with you regularly (about once every 2 weeks) to answer any questions you may have. At the end of the study, you will receive a packet of information for an at-home walking program, to independently engage in the other intervention program, if you wish.

- **Wearable Activity Monitor** *(All participants)*: You will be asked to wear a physical activity-monitoring device for a period of 6 months. The device should be worn on your wrist or arm. The device is waterproof and should be worn 24 hours a day for the duration of the intervention.

- **Questionnaires** *(All participants)*: You may be asked to complete surveys, questionnaires, and keep an activity diary to be mailed in, completed on-line, collected by the interventionist, or completed by phone.

Visit 4 (12-month Follow-up)

Cognitive Tasks: You will be asked to perform one or more memory or attention task(s). You may be presented with images, videos, words, numbers, or sounds. These may be presented to you on a computer monitor, through headphones, or on paper. Audio/Video recordings may be conducted during testing for fidelity purposes. The cognitive testing session should last no more than three hours.

Blood Draw: You will be asked to have a blood draw. We will collect about 50 mL of blood. We will use the blood to test for relevant biomarkers. Biomarkers are substances in your body that tell us about your biological state or condition.

Physical Assessment: You will be asked to perform two physical assessments and be weighed on an impedance scale at our exercise laboratory. The first assessment is a treadmill walking test, during which we will measure your heart rate using a heart rate monitor to get an estimate of how efficiently your body utilizes oxygen. The second assessment is a physical function test. We will ask you to perform a number of everyday activities. Finally, your body composition and body weight will be measured at the same time on the Biospace InBody 520 device. You will stand on the scale-like device while

grasping two handles, one in each hand. The device works by sending a very low-voltage electrical signal through your body to determine water content and body fat percentage. The voltage is so low that you cannot feel it. This test takes about 2 minutes. The total testing time will take about 45 minutes.

The maximum amount of time you will participate in any particular session of the study is detailed in the table below:

Visit	Session	Session duration
Screening Visit		
	Informed Consent Review	30 minutes
	Evaluation	1 hour
Baseline 2-day Visit		
	Blood draw	10 minutes
	Cognitive Tasks	2 hours
	fMRI	3.5 hours
	PET/CT (2 Scans)	1.5 hour (per scan)
	Physical Assessments	45 minutes
6-Month 2-day Visit		
	Blood draw	10 minutes
	Cognitive Tasks	2 hours
	fMRI	3.5 hours
	PET/CT (2 Scans)	1.5 hour (per scan)
	Physical Assessments	30 minutes
	Exit Interview	30 minutes
12-Month Visit		
	Blood draw	10 minutes
	Cognitive Tasks	3 hours
	Physical Assessments	45 minutes

WHAT ABOUT PREGNANCY?

We do not know if fMRI procedures will harm an unborn baby, however radiation from PET/CT scans is associated with risks to an unborn baby. If you are pregnant or become pregnant, you will not be allowed to participate in the study. If you are a woman who could become pregnant, a pregnancy test will be performed before each fMRI and PET/CT procedure to make sure you are not pregnant. If you are pregnant, you will not have the fMRI and PET/CT procedure performed.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

PET/CT:

Risks of Radiation: As a result of your participation in this study you will be exposed to radiation from up to 4 PET/CT scans. Please note that this radiation is for research purposes only. There is a small risk of cancer from exposure to radiation. Each

PET/CT scan procedure will expose you to an amount of radiation more than most routine diagnostic x-ray procedures. Exposure to radiation can increase one's risk of developing cancer. The risk of developing cancer from the dose of radiation received in this study is known to be low.

The doctor performing this study will explain these risks to you as any risks of the test in relation to your overall health situation.

Since the effects of radiation can be cumulative, it is important to know of your past radiation exposure. If you have taken part in other studies or tests in the past 12 months that have involved radiation exposure, please inform the Investigators or study staff. If it is determined that your past radiation exposure exceeds our current guidelines, it is possible that you will not be allowed to take part in this study.

Risks of Radioactive Tracers:

Potential risks with ^{18}F-AV-1451: ^{18}F-AV-1451 is a new compound that is being studied in clinical trials. In clinical studies, 273 subjects received Flortaucipir (18F). The following adverse events were reported in at least 1% of subjects: diarrhea, headache, muscle spasm, altered taste, and injection site pain. All reported events were mild or moderate in severity and all subjects recovered.

Potential risks with Florbetaben: Neuraceq (florbetaben F18 injection) is an FDA-approved PET/CT tracer. Common side effects include injection site reactions consisting of injection site rash, irritation, or pain.

Pain at the site of injection/IV catheter: There is also minor risk associated with the venipuncture and radioisotope injection (pain and bruising or painful infiltration of a failed injection).

Incidental Findings: We are performing the PET/CT and fMRI scans in this study to answer research questions, not as part of your medical care. These PET/CT and fMRI scans are not the same as one that your own doctor would order. They may or may not show problems that would be found on a standard PET/CT or fMRI scan. If we do see something that looks like a medical problem, we will ask a radiologist who specializes in results of this sort to review the results. If the radiologist thinks there might be a problem, we will tell you and help you get follow-up care.

fMRI: MRI is not invasive, and it does not expose you to treatments with energy such as X-rays or CT scans do. Many people have been safely studied using MRI techniques. While there are no significant risks from fMRI as it is to be performed, the fMRI procedures are not appropriate for people with pacemakers or metal in their bodies. We will not ask you to participate in the fMRI if you have a pacemaker or any metal in your body that cannot be easily removed. The space inside the bore of the MRI machine is just large enough for an average adult. Because the space is so confined, some people feel claustrophobic once inside the MRI machine. If you have a history of claustrophobia, we will not ask you to participate in the fMRI study. Because the fMRI scan makes loud noises, we will give you ear plugs to dampen the sound. You may also experience peripheral stimulation, which will

feel like a gentle tap or sensation of mild muscle tremor. If you do not like being in the scanner for any reason, we will immediately stop the experiment.

Blood draw: The risks associated with taking blood from the arm with a needle include temporary discomfort or bruising at the point where the blood is taken, and swelling or infection of the vein. There is a rare risk of fainting during or shortly after the blood draw.

Physical Assessments: You perhaps may feel common effects from mild exertion, including heavy breathing, and perhaps muscle soreness and strain. Although the impedance scale works by sending a very low-voltage electrical signal through your body, the voltage is so low that you cannot feel it.

Cognitive Tasks: You may become tired due to the duration of the study. You may become frustrated or embarrassed while completing the cognitive tasks.

Surveys: There is a risk of becoming tired due to the duration of the study. There is also a potential risk of feeling uncomfortable responding to some questions. Some of the questions may make you feel uneasy or embarrassed. You can choose to skip or stop answering any questions that make you uncomfortable.

Wearable Activity Monitor: There is a potential risk of mild discomfort of the skin that is in contact with the device.

At-Home Physical Activity Program: Older, formerly sedentary participants are especially susceptible to falls, worsening of underlying diseases, cardiac events during training (chest pain, irregular heartbeat, changes in blood pressure outside of target range, clinically significant electrocardiogram (ECG) changes/abnormal heart rhythm), fatigue and muscle soreness, soft tissue (muscle, tendon, cartilage) injury, and orthopedic injury (foot, leg, and knee injuries).

There is a small risk that people who are not connected with this study will learn your identity or your personal information.

WILL YOUR INFORMATION BE KEPT PRIVATE?

We will keep your records for this study confidential as far as permitted by law. However, if we are required to do so by law, we will disclose confidential information about you. The University of Southern California's Institutional Review Board (IRB) may review your records. The IRB is a research review board that is made up of professionals and community members who review and monitor research studies to protect the rights and welfare of research participants. We may publish the information from this study in journals or present it at meetings. If we do, we will not use your name.

Personal identifiers (such as name, telephone number, address) will be not be obtained in any audio/video recording. Audio/Video recordings will be assigned a code number that does not directly identify you. The digital files will be stored on our password-protected computing cluster (USC LONI). Once recordings are collected, they will be transferred from the data collection laptop to the computing cluster within 30 days. The data collection laptop is password-protected.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART IN THIS STUDY?
You may not receive any direct benefit from taking part in this study. However, your participation in this study may help us learn more about how the brain changes as we get older.

WHAT OTHER OPTIONS ARE THERE?
An alternative is to not take part in this study.

ARE THERE ANY PAYMENTS TO YOU FOR TAKING PART IN THE STUDY?
You will be paid about $580 total for the research visits if you participate in all assessments. Payments will be disbursed as follows: $150 at visit 2, $150 at visit 3, and the remainder at visit 4, $280 if all study assessments are completed.

WHAT ARE THE COSTS?
The study will pay for all research tests and procedures. You and/or your insurance plan will not be billed for tests and procedures that are done in this research.

WHAT HAPPENS IF YOU GET INJURED OR NEED EMERGENCY CARE?
If you think you have been hurt by taking part in this study, tell the study doctor immediately. If you require treatment because you were injured from participating in this study, treatment will be provided. You and/or your health plan/insurance will be billed for this treatment. The study sponsor will not pay for this treatment. There are no plans to offer any type of payment for injury. However, by signing this form you have not given up any of your legal rights.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT, AND WHAT WILL HAPPEN IF YOU DECIDE NOT TO PARTICIPATE?
Your participation in this study is voluntary. Your decision whether or not to take part will not affect your current or future care at this institution. You are not giving up any legal claims or rights. If you do decide to take part in this study, you are free to change your mind and stop being in the study at any time.

WHOM DO YOU CALL IF YOU HAVE QUESTIONS OR CONCERNS?
You may contact Judy Pa, PhD, Principal Investigator, at 323-422-7246 with any questions, concerns, or complaints about the research or your participation in this study. If you feel you have been hurt by taking part in this study, please contact Judy Pa, PhD at 323-422-7246. If you have questions, concerns, or complaints about the research and are unable to contact the research team, contact the Institutional Review Board (IRB) Office at 323-442-0114 between the hours of 8:00 AM and 4:00 PM, Monday to Friday. (Fax: 323-224-8389 or email at irb@usc.edu).

If you have any questions about your rights as a research participant, or want to talk to someone independent of the research team, you may contact the Institutional Review Board Office at the numbers above or write to the Institutional Review Board at 1640 Marengo Street, Suite 700, Los Angeles CA. 90033-9269.

You will get a copy of this consent form.

AGREEMENT:
I have read (or someone has read to me) the information provided above. I have been given a chance to ask questions. All my questions have been answered. By signing this form, I am agreeing to take part in this study.

Name of Research Participant	Signature	Date Signed (and Time*)

I have personally explained the research to the research participant and answered all questions. I believe that he/she understands the information described in this informed consent and freely consents to participate.

Name of Person Obtaining Informed Consent	Signature	Date Signed (and Time*)

Appendix II – COVID-19 Required Safety Protocols

Research staff (Interventionist) practices in the field

- Prior to engaging in research activities in any community/field settings, research staff must be tested and confirmed negative for COVID-19 in accordance with local testing guidelines / requirements.

- Research staff must provide attestation in their USC istar account that they have reviewed and understand the plan for completing a daily log of contacts with whom they have had direct in-person interaction, including research participants and staff.

- Before traveling to community/field research site(s) each day, all research staff must complete the *Trojan Check* university health screening protocol that is required of persons when requesting access to USC campuses and buildings.
- https://trojancheck.usc.edu/login

- In traveling to/from local community/field research sites, researchers must wear face coverings, ensure no more than two people occupancy per vehicle, and/or that local public health guidelines are followed when mass transit (bus/metro) is used. Researchers must wash hands (or use hand sanitizers) immediately upon departing the vehicle. High touch areas (e.g., keys, door handles, steering wheels, seat belt buckle) must be disinfected before and after the field day.

- Research staff must enter the community/field setting each day prepared with a sufficient number of face coverings and hand sanitizer for all research participants.

- Researchers at each off-campus study setting must complete a daily log of contacts with whom they have had direct in-person interaction, including research participants and staff, for purposes of participant notification. Contact information must be collected for the purpose of participant notification in all of the following cases: 1) any interactions occurring at fewer than 6 feet of distance and for more than a period of briefly passing by someone, whether indoors or outdoors; and 2) interactions occurring indoors for more than a period of 10 minutes. These rules apply regardless of whether PPE / facial coverings are worn during the interaction.

- Hand washing is required of research staff every 30 minutes and at the beginning and end of each visit to a community or field site. When hand-washing is not possible, hand sanitizer may be used.

- If a research staff member feels ill at any point while in the community/field setting, he/she/they must discontinue data collection and other research activities immediately,

report illness to the field supervisor and the USC health office, and self-quarantine.

- If a research staff member is diagnosed with COVID-19, they must contact USC Student Health to discuss and be prepared to share participant notification data with Student Health.

- Community/field research activities including data collection should be conducted in sparsely populated, low-density spaces and settings – preferably outdoors if at all possible.

- Research staff must ensure that research participants and prospective participants in field and community settings are assembled and/or seated in a manner that adheres to COVID-19 safety and risk mitigation standards, including a minimum of 6 feet of physical distancing.

- Research staff must provide to each participant an information sheet that explains the collection of data for the purpose of participant notification in the case of infection.

- Disinfectant wipes must be used in community/field settings to clean pens, clipboards, tablets, laptops, and any other equipment or devices immediately before and after sharing among research staff or between participants, or every 30 minutes, whichever is more frequent. Hand washing or sanitizing must also be done at these times.

- Disinfectant wipes must be used to clean cases, bags, or other containers immediately before they are provided to the participant and after they are returned, or every 30 minutes, whichever is more frequent. Hand washing or hand sanitizing must also be done at these times.

- Physical incentive items (e.g., gift cards) must first be cleaned using disinfectant wipes.

- Research participants who do not have a facial covering should be provided with masks (paper or cloth as directed by current public health guidelines) and hand sanitizer by the research staff prior to engaging in any research activity including study screening.

- Research participants who refuse to wear facial coverings or practice risk mitigation steps necessary to protect themselves and others will not be allowed to participate in USC research. (Exceptions for wearing masks shall be granted for children under two years of age and persons with disabilities, as recommended by current public health guidelines.)

- Research participants must be provided with information about COVID-19 risk mitigation and safety practices (i.e., information sheet available through OPRS).

- Research participants should be provided information on when and how to access health

care services (http://www.publichealth.lacounty.gov/media/Coronavirus/FAQ.pdf), and a list of available social services and resources such as food and domestic violence assistance (e.g., https://www.211la.org/ and https://www.1degree.org/).

- As with all aspects of community/field research, research participants' culture, language, and health literacy should be considered when communicating COVID-19 safety and risk mitigation information and practices.