Official Protocol Title: **Motor Imagery Intervention for Improving Gait and Cognition in the Elderly**

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Motor Imagery: A Pilot Intervention for Improving Gait and Cognition in the Elderly

PROTOCOL AND MOP MODIFICATIONS/AMENDMENTS

Description of change	Date	Document name & Page #

Motor Imagery: A Pilot Intervention for Improving Gait and Cognition in the Elderly

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TABLE OF CONTENTS

Page

PRÉCIS

Study Title

Motor Imagery: A Pilot Intervention for Improving Gait and Cognition in the Elderly

Objectives:

Primary. Compared to a visual imagery intervention group, participants who are enrolled in the motor imagery intervention (MI) group will demonstrate:

P1: Significant improvements in gait speed during actual Walking and Walking While Talking

Secondary. Compared to a visual imagery intervention group, participants who are enrolled in the motor imagery intervention (MI) group will show:

P 2.1: Significant improvements in cognitive performance during Talking and Walking While Talking

P 2.2: Change in blood-oxygen-level dependent signal during Walking and Walking While Talking

Design and Outcomes

The investigators propose to conduct a single-blind randomized clinical trial to test the efficacy of a phone-based motor imagery intervention for improving gait and cognition in older adults between 65 and 85 years old

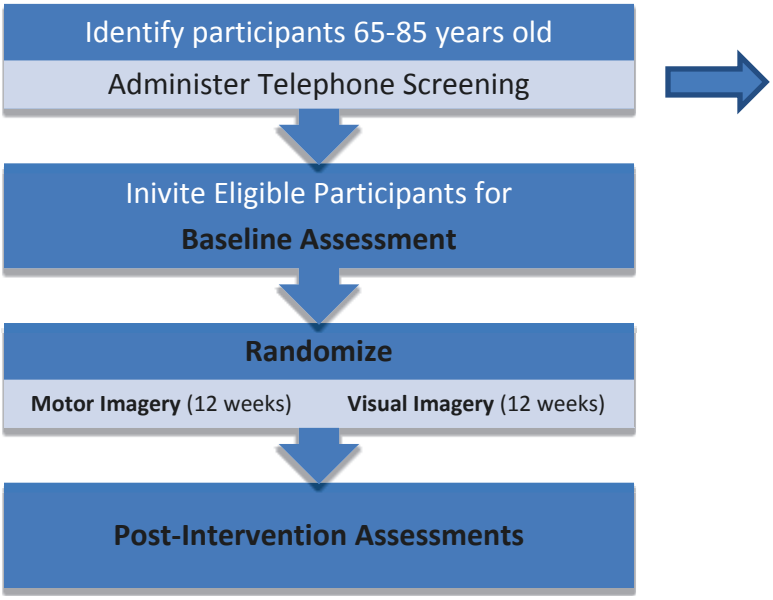

Figure 1. Participant Flow

Interventions and Duration

Participants will be randomized into either a 12-week phone-based motor imagery intervention or visual imagery intervention (active control condition). Both groups will complete 36 (15-minute) sessions (9 hours).

Participants will receive gait, mobility, cognitive and neuroimaging assessments at baseline and post-intervention (14-18 weeks after intervention). Baseline and post-intervention assessments will last about 3 hours over 1 day.

Sample Size and Population

We will enroll 48 cognitively-healthy older adults (24 in each group).

STUDY TEAM ROSTER

Principal Investigator:

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Main responsibilities/Key roles: She will coordinate efforts between team members, supervise implementation of study measures and supervise data collection. She will develop data analysis plans as well as scientific presentations and manuscripts based on the research findings.

Mentor:

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Main responsibilities/Key roles: Dr. Wang will provide statistical consultation and provide input regarding data management, security, and randomization processes for the clinical trial.

1 STUDY OBJECTIVES

1.1 Primary Objective

Compared to a visual imagery intervention group, the participants who are enrolled in the motor imagery intervention group will demonstrate significant improvements in gait speed (cm/s) during actual Walking and Walking While Talking using an instrumented walkway (GAITRite® electronic walkway system).

1.2 Secondary & Tertiary Objectives

Compared to a visual imagery intervention group, the participants who are enrolled in the motor imagery intervention group will show:

- Significant improvements in cognitive performance during Talking and Walking While Talking
- Changes in blood-oxygen-level dependent signal during Walking and Walking While Talking
- Improvement in executive function, and other mobility-related cognitive processes, such as speed of processing, memory and spatial navigation.
- Improved gait variability and other quantitative gait parameters during walking and walking while talking.

2 BACKGROUND AND RATIONALE

2.1 Background

Age-related gait decline is common among the elderly; with over a third of community-residing elders having clinically diagnosable gait abnormalities. Gait impairment in the elderly is associated with an increased risk of falls, morbidity, hospitalization, mortality, cognitive decline, and dementia (1-5). Physical exercise programs can be used to improve gait in the elderly, but long-term adherence to physical exercise programs is low, and particularly difficult to implement in the elderly (6-8). Determining the efficacy of motor imagery for improving gait and cognition may provide scientific support for a future large-scale randomized controlled trial to establish and contrast the independent and combined roles of physical and imagined exercises to prevent mobility disability.

2.1 Study Rationale

Motor imagery involves envisioning motor actions without actual execution, and has been successfully used by athletes to improve athletic performance for quite some time; for reviews see

(9-12). There is some evidence that *motor imagery* can be used to improve gait, gait-related and cognitive functions in Parkinson's disease (13-15) and post stroke (16-20), but the rehabilitative potential of motor imagery in relatively healthy elderly is currently unknown.

Recent research suggests that gait engages a distributed network of brain regions including motor, basal ganglia, cerebellar and supplementary motor regions. Based on recent findings by us (21) and others (22, 23), we hypothesize that imagined gait can be used as a rehabilitative tool for improving gait in the elderly because it engages and strengthens similar neural systems as actual gait. Age-related gait decline is particularly evident in dual-task situations that demand Executive Functions (EF) and engage the prefrontal cortex (24-31). We recently developed and validated an imagined gait protocol against an actual gait protocol that involves an ecologically-valid dual-task situation (walking while talking; WWT) that predicts falls, frailty, disability and mortality in the elderly (21, 31, 32). This imagined gait protocol involves: 1) imagined Walking (iW), imagined Talking (iT) and imagined Walking While Talking (iWWT), 2) is associated with actual WWT performance, and 3) permits us to examine the underlying neural systems of gait with functional magnetic resonance imaging (fMRI). We have identified a pattern of brain regions whose activation change as a function of imagery task difficulty (iW < iT< iWWT), and is associated with actual WWT performance (21). Increases were most notably observed in cerebellar, precuneus, supplementary motor and prefrontal cortex regions. These initial findings suggest that our imagined gait protocol engages similar neural systems as actual gait and EF and command the development of this protocol into a tool for improving gait and EF in the elderly.

The first aim of this research is to establish the efficacy of this imagined gait protocol to improve gait and EF in the elderly**.** We propose a pilot Randomized Clinical Trial (RCT) of 48 cognitively-healthy elderly adults who will be randomly assigned to an imagined gait intervention or an Active Control (AC; non-mobility related visual imagery) condition. The imagined gait (or AC) protocol will be administered during each study visit, and over the phone three times a week for three months (15 min/session, total of 36 sessions). Each participant will complete two study visits (pre and post). Pre-post intervention changes in gait velocity (cm/s) and cognitive performance (percent of correct letters provided; (correct/error x correct) x 100) during actual W, T and WWT will be our primary outcome measures. Age, Sex and Education will be covariates in all analyses. Other variables/covariates will be recorded (e.g. medical illnesses and history of falls), and carefully examined for potential inclusion as covariates in upcoming full-scale RCT.

The second aim is to determine neuroplasticity changes in response to our imagined gait intervention. To this end, participants will complete the imagined gait protocol (iW, iT and iWWT) during fMRI scanning at the pre and post-intervention study visits. We predict that our imagined gait protocol engages neural systems linked to actual gait and EF, while the AC condition engages neural systems linked to visual processing and imagery in general. We further predict that the neural systems engaged during our imagined gait protocol are strengthened following our imagined gait intervention.

3 STUDY DESIGN

Design: We propose a single-blind study of cognitively-healthy older adults randomized to a phone-based motor imagery or visual imagery (active control) intervention for 12 weeks (36 sessions)

Outcomes: The primary outcome is post-intervention change in gait speed during actual walking and walking while talking.

Secondary and tertiary outcomes include improvements in cognitive performance during Talking and Walking While Talking, changes in blood-oxygen-level dependent signal during Walking and Walking While Talking, improvement in executive function, and other mobility-related cognitive processes (speed of processing, memory and spatial navigation), and improved gait variability and other quantitative gait parameters during walking and walking while talking (see Clinicaltrials.gov-NCT02762604 for a comprehensive list).

Study population: 48 Bronx and Westchester county residents between 65 and 85 years old will be randomized into a phone-based motor imagery or visual imagery (control) intervention for 12 weeks (36 sessions)

Study location: Pre and post-intervention visits will be held at the Albert Einstein College of Medicine.

Approximate duration of enrollment period and follow-up: Potential recruits who meet eligibility criteria on the telephone are invited to baseline assessment and then randomized to motor imagery or visual imagery intervention. Baseline study assessments are limited to 180 minutes over 1 day to avoid fatigue. Telephone assessments are 15 minutes. Post-intervention assessments will be conducted within 4 weeks of the completion of the intervention.

We plan to enroll and randomize 48 participants over 36 months (1-2 per month). If necessary, we will ask for a no cost extension to allow for additional time to process and analyze the data, write manuscripts, and possibly apply for a follow-up grant.

Randomization and Blinding: We will include a number of methods to reduce bias.

- Selection bias will be reduced by concealing treatment allocation until the participant is entered into trial.
- Primary outcome is an objective endpoint (gait speed) and not subjective mobility complaints.
- Motor imagery and visual imagery interventions will be administered individually, and at non-overlapping times.
- Participants and study staff will be instructed not to disclose group assignment or details of interventions.
- Study staff that administers baseline and post-intervention assessments will be different from those that administer the phone-based motor imagery and visual imagery interventions.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

- Adults between 65 and 85 years and older, residing in the community.
- Able to speak English at a level sufficient to undergo study procedures.
- Plan to be in the area for the next 3 months.

4.2 Exclusion Criteria

- Presence of dementia (telephone-based memory impairment screen < 5 or AD-8 score > 1).
- Presence of gait disorder diagnosed by clinician (e.g. neuropathy).
- Any medical condition or chronic medication use (e.g. neuroleptics) that will compromise safety or affect cognitive functioning.
- Terminal illness with life expectancy <12 months.
- Progressive, degenerative neurologic disease (e.g. Parkinson's disease, ALS).
- Major psychiatric disorders such as Schizophrenia.
- Pacemaker or any permanent metal implants like hip prosthesis (other than tooth fillings) and claustrophobia.
- Participation in other intervention trial or observational studies during the intervention period.

4.3 Study Enrollment Procedures

Participants will be recruited from the Bronx and Westchester areas. A letter explaining our study will be sent and followed by a telephone call a few days later. Those expressing interest will be screened with the Telephone MIS (33) (sensitivity 85%, specificity 86%) and AD-8 (34, 35) (sensitivity 74%, specificity 86%).

Baseline visit: Eligible participants are invited for baseline assessments. Written consent and baseline assessments will occur in our research center. On arrival, potential participants will review study information and sign consent. Eligible subjects will be randomly assigned to an intervention group after completing baseline assessments.

All reasons for ineligibility and for non-participation will be documented in the database.

Following the completion of baseline assessments, participants will be randomly assigned to either the motor imagery or visual imagery interventions. Group assignment will be displayed to RAs from a generated list using sequential study numbers so that the assistant who enrolls the participants will be blinded to randomization assignment of the next participant until assigned.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

During **gait imagery training**, participants will be trained to iW, imagine talking (iT: reciting alternate letters of the alphabet out loud) and iWWT. They will be instructed to close their eyes during imagery, use both visual and kinesthetic imagery, and pay equal attention to both tasks in the iWWT condition. Seated at a desk, they will then complete two trials of imagery training in 16-seconds blocks for approximately 15 minutes. Imagery instructions will be presented auditorily, and the beginning and the end of a block will be initiated with a tone. During the first trial,

instructions will be detailed (i.e. "Imagine Walking: At the start of the next tone, close your eyes and imagine or envision yourself walking on the mat. At the start of the following tone, stop, and wait for further instructions"), but during the second trial they will simply prompted to begin at the start of the tone (e.g. "Imagine Walking"). Following each trial, participants will be asked to evaluate the quality of their visual and kinesthetic images on a scale from 1 (no image; no sensation) to 5 (image as clear as seeing; as intense as executing the action)**.** During **visual imagery training**, participants will be trained to imagine a set of concrete objects (e.g. giraffe) from a standardized set of pictures (36) that have been normed for name agreement, image agreement and visual complexity. Again, they will be instructed to close their eyes during imagery and will complete two trials of imagery training in 16 second blocks for approximately 15 minutes. Imagery instructions will be presented auditorily and the beginning and the end of a block will be initiated with a tone. Following each trial participants will be asked to evaluate the quality of their visual and kinesthetic images on a validated scale from 1 to 5 (37, 38).

During the **imagined gait protocol (in MRI),** imagery prompts (e.g. imagine walking) will be presented auditorily and volume will be adjusted to ensure instructions can be heard clearly in the presence of scanning noise. Imagery will occur in 16-second blocks (eyes closed). A tone will indicate the beginning and the end of a block, and each block will be repeated six times. Following the imagery task, participants will again be asked to evaluate the overall quality of their visual and kinesthetic images on a 1-5 scale. During the **visual imagery protocol (in MRI)**, imagery prompts (e.g. imagine a giraffe) will be presented auditorily and volume adjusted to ensure instructions could be heard clearly in the presence of scanning noise. Again, imagery will occur in 16-second blocks (eyes closed). A tone will indicate the beginning and the end of a block, and each block will be repeated six times.

During the **imagined gait intervention**, participants will be called by the experimenter three times a week and be asked to iW, iT and iWWT following the same protocol as during their study visit. They will also be asked to rate their visual and kinesthetic qualities of their images on a 1-5 scale (37, 38) following each trial. During the **active control intervention**, participants will be called three times a week by the experimenter and be asked to imagine concrete objects following the same protocol as during their study visit. Participants will be contacted over the phone on Monday, Wednesday and Friday mornings (before 12 noon), unless other times or days are preferred. Calls will be made to a landline (unless cellphone is the only option for a particular participant), and participants will be instructed to sit down comfortably, and turn down any distracting noise (e.g. music or TV). If a participant is unavailable at the scheduled time, we will try to reach them later in the day, but if we are still unsuccessful, we will skip that particular session and wait until the next scheduled session. Any unexpected distractions or missed sessions will be carefully recorded, and examined to inform the development of full-scale RCT.

Performance monitoring and dose: The imagined gait and active control interventions will be administered by a designated RA in our research center under controlled conditions to protect internal validity of the study and to ensure compliance with protocol. Participants will also be instructed to take a seat and turn down any distracting noise (such as the radio or TV) before beginning each session. Following each 15-minute session, the visual and kinesthetic qualities of the images will be tracked to ensure that participants are fully engaged during each session.

Tracking imagery performance in this manner will also be informative to assess dose response effects, which will help in the design of future studies.

Frequency and duration: We propose a 36 session phone-based motor imagery or active control intervention over 12 weeks. Our intervention is of longer duration and greater intensity than most prior studies. Each training session takes 15 minutes to complete. Total training time over 12 weeks is 540 minutes. We can track performance to assess dose response effects, which will help in the design of future studies.

5.2 Handling of Study Interventions

Both interventions will be administered in doses of approximately 45 minutes (three 15-minute sessions) per week for 12 weeks without crossover at our facilities. Each intervention session will be supervised by Drs. Blumen and/or Dr. Verghese.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

N/A

5.3.2 Required Interventions

N/A

5.3.3 Prohibited Interventions

Participants will not be allowed to participate in any other intervention or observational studies while enrolled in the intervention phase of this trial

5.4 Adherence Assessment

Sustaining adherence represents a major challenge in any RCT involving older adults. The phone-based delivery of the RCT improves likelihood of adherence. We have also incorporated multiple methods to promote adherence and reduce possibility of missing data.

- A permanent staff contact will be provided for each participant in the motor imagery and visual imagery intervention groups.
- Transportation and snacks will be provided on pre and post intervention assessment days.
- All participants will be compensated for attending in-house or telephone sessions ($50 for the baseline visit, $25 for the phone-based intervention, and $50 for the post-intervention visit, for a total of $125 for the study).

We propose to over-enroll by 20% to account for any attrition. Methods to account for non-compliance and missing data:

- Protocol violations. Subjects who miss 6 sessions due to any reason will be excluded from main analyses. We will explore dose response by adjusting number of sessions attended as a

covariate.

- We will identify 2 contact persons who do not live with the participant for when participant cannot be reached.
- Flexible scheduling with makeup sessions on alternate days.
- For each in-house study visit, we will allow a four-week window for completion.
- If the participant is acutely ill, is in the hospital, or has a temporary condition that interferes with walking (e.g. ankle sprain), we will attempt to complete the assessment at another time.
- Outcome adjudication. The research team will adjudicate events such as mobility disability in subjects who drop out based on medical interviews, contact interviews, and home assessments as required.

6 STUDY PROCEDURES

6.1 Schedule of Evaluations

			Pre-Intervention	During Intervention	Post-Intervention
Measures	**Test/Type**	**Visit**	Baseline week 0	weeks 1-12	Post week 12-16
Verbal consent	Consent	Phone ✓			
Demographic/Health Screen	Screen	Phone ✓			
Memory Impairment Screen	Screen	Phone ✓			
AD-8 Dementia Screening Interview	Screen	Phone ✓			
Handedness	Screen	Phone ✓			
MRI safety (verbal)	Screen	Phone ✓			
Informed Consent	Consent	Study Visit	✓		
MRI safety (paper)	Screen	Study Visit	✓		✓
Baseline Medical history	Survey	Study Visit	✓		
Sensory Screen	Physical	Study Visit	✓		
Medications	Survey	Study Visit	✓		
Height/Weight/BMI	Physical	Study Visit	✓		✓
Blood Pressure	Physical	Study Visit	✓		✓
SPPB	Physical/Gait	Study Visit	✓		✓
Maze	Cognitive/Gait	Study Visit	✓		✓
Berg Balance Scale	Physical/Gait	Study Visit	✓		✓
Unipedal Stance	Physical/Gait	Study Visit	✓		✓
Stair climbing	Physical/Gait	Study Visit	✓		✓
Grip Strength	Physical/Gait	Study Visit	✓		✓
WRAT & WTAR	Cognitive	Study Visit	✓		✓
RBANS figure copy & delay	Cognitive	Study Visit	✓		✓
Free Cued Serial Recall Test	Cognitive	Study Visit	✓		✓
Falls Questions	Survey	Study Visit/Phone	✓	✓	✓
Falls Efficacy Scale	Survey	Study Visit	✓		✓
Duke Activity Status Index	Survey	Study Visit	✓		✓
Trails A & B	Cognitive	Study Visit	✓		✓
Control Oral Word Association Test	Cognitive	Study Visit	✓		✓

Semantic Fluency	Cognitive	Study Visit	✓		✓
General Mobility Questionnaire	Survey	Study Visit	✓		✓
Geriatric Depression Scale (GDS-30)	Survey	Study Visit	✓		✓
Instrumental ADL Questionnaire	Survey	Study Visit	✓		✓
Flanker Interference	Cognitive	Study Visit	✓		✓
WAIS Digit Symbol Substitution Test	Cognitive	Study Visit	✓		✓
Stroop Interference	Cognitive	Study Visit	✓		✓
Activity Balance Confidence Scale	Survey	Study Visit	✓		✓
SF-12	Survey	Study Visit	✓		✓
CHAMPS	Survey	Study Visit/Phone	✓	✓	✓
Letter Number Sequencing	Cognitive	Study Visit	✓		✓
Social Network Index	Survey	Study Visit	✓		✓
Beck Anxiety Inventory	Survey	Study Visit	✓		✓
MOS Social Support Survey	Survey	Study Visit	✓		✓
Gait Rite	Physical/Gait	Study Visit	✓		✓
Imagery Protocol		Study Visit	✓		✓

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Consenting Procedure

A letter explaining our study will be sent and followed by a telephone call a few days later. Those expressing interest will be screened using a structured telephone interview to obtain verbal consent. Potential recruits will then be screened over the phone, and those who meet eligibility criteria will be scheduled for their first study visit. They will also be told that they will receive a phone call reminder the evening before their appointment. Written consent will occur in our research center and conducted by trained RAs. On arrival, potential participants will review study information and sign consent. Consenting will take place prior to any assessments.

All consent forms will be stored in a locked file with other study documents and records. See approved Consent form in Appendix I.

Screening

Potential recruits who meet eligibility criteria on the telephone are invited to schedule their first study session, and are told that they will receive a phone call reminder the evening before the appointment.

Telephone screening: A letter explaining our study will be sent, followed by a telephone call a few days later. Those expressing interest will be screened over the phone prior to enrollment. Telephone screening responses will also be reviewed and/or repeated (e.g. MRI safety) during the first study session to ensure eligibility prior to other study procedures. Inclusion criteria are: 1) age 65-85 years old 2) able to speak English at a level sufficient to undergo study procedures, and 3) plan to be in the area for the next 3 months. Exclusion criteria are: 1) Presence of dementia (telephone-based

memory impairment screen MIS < 5 or AD-8 score >, 2) Presence of gait disorder (e.g. neuropathy), progressive neurodegenerative disease (e.g. Parkinson's disease) or major psychiatric disorder (e.g. Schizophrenia), 3) MRI contraindication (e.g. pacemaker), 4) participation in other interventional or observational study during the study period, and 5) any medical condition or chronic medication use (e.g. neuroleptics) that will compromise safety or affect cognitive functioning.

6.2.2 Enrollment, Baseline, and Randomization

Enrollment

The enrollment date is defined as the date that the participants are randomized into either the motor imagery or visual imagery intervention, after they have met all screening criteria and agreed to participate.

Baseline Assessments

For participants who have successfully been screened for eligibility, baseline assessments are performed during their first study session.

Randomization

Randomization will be determined after completion of the baseline assessments. Initiation of the study intervention will take place in the week following the baseline assessment visit.

6.2.3 Follow-up Visits

Post intervention follow-up assessments will occur within 4 weeks of the completion of the intervention. In addition adverse events will be evaluated over the phone throughout the intervention and at the post-intervention visits. A 4-week window will be allowed for each of the post-intervention assessments.

6.2.4 Completion/Final Evaluation

Assessments to be completed at the final visit (12 months post-intervention) are listed in Table 5.1.

Losses to follow-up can be classified into non-informative (missing at random (MAR)) and informative censoring (drop out depends on the unobserved outcomes). No adjustment is necessary for non-informative censoring. However, for informative censoring, parameter estimates and resulting tests on hypotheses will be biased without further adjustment. The best way to handle missing data is to avoid it. However, we recognize that despite all our efforts there will be missing data.

Dropouts: We will follow-up with participants who dropped out of the study to determine both their mobility status and reasons for withdrawal. The research team will adjudicate events such as mobility disability in subjects who drop out based on medical interviews, contact interviews, and home assessments as required. Utilization of the telephone based

questionnaire to account for possible non-random drop-out will be administered. If the participant is acutely ill, is in the hospital, or has a temporary condition that interferes with walking (e.g. ankle sprain), we will attempt to complete the assessment at another time.

We also propose intention to treat (ITT) analysis, which includes all randomized participants in the groups assigned, regardless of their adherence with the entry criteria, whether motor imagery was received, and subsequent withdrawal or deviation from the protocol. ITT analysis is pragmatic because it admits noncompliance and protocol deviations, and gives an unbiased estimate of the intervention effect. Handling missing data is a major issue in ITT, and is dealt with by imputation or sensitivity analysis. Our statistician, Dr. Wang, is very experienced in these methods.

A rich set of telephone-based information will be collected even for those subjects who may drop out. We will utilize this auxiliary information to assess the MAR assumption and combine it into the main model through joint modeling and multiple imputation approaches. Dr. Wang has applied these approaches to eliminate or reduce bias in presence of informative censoring in our other aging studies.

7 SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

The research staff and investigators will be present during all testing. All questionnaire completion will be done at a slow enough pace so as not to tire individuals. If subjects express physical or mental tiredness or discomfort during any of the assessments or training procedures, the procedure will be terminated immediately. Drs. Blumen and Verghese will be available onsite or cell at all times to address any safety concerns or clinical issues during the interventions.

All abnormal findings from the clinical, mobility, neuroimaging, and neuropsychological assessments done on baseline, screening visits, and post-intervention visits will be documented and reviewed by the DSMB chair. Periodic audits from the Albert Einstein College of Medicine IRB ensure compliance with confidentiality guidelines and adverse events monitoring.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Answering health questionnaires and mental state examinations involve minimal psychological, social, or other risks. We do not expect any serious adverse events during these non-invasive tests and training programs of attention and executive function. The motor imagery and visual imagery interventions involve mental but no physical effort by the participants. Some people are bothered by feelings of confinement (claustrophobia), and by the noise made during MRI. Participants will be asked to wear earplugs or earphones while in the MRI machine. They may not participate in this study if they have a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices.

7.3 Adverse Events and Serious Adverse Events

An **adverse event (AE)** is defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse Events encompass both physical and/or psychological harms. AEs will be documented on forms (See Appendix II).

A **serious adverse event (SAE)** is 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. SAEs will be documented on SAE forms (Appendix II).

Unanticipated Problem (UP): Any event, deviation, or problem, that is unexpected; AND possibly, probably or definitely related to study participation; AND serious.

a. Unexpected: An event can be categorized as unexpected if it occurs in one or more subjects participating in a research protocol; and the nature, severity, or frequency of which is not consistent with either:

i. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in protocol-related documents such as: the IRB-approved research protocol; any applicable investigator brochure: the current IRB-approved informed consent document; or other relevant sources of information, such as product labeling and package inserts; or

ii. The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

b. Serious: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

i. death,

ii. a life-threatening adverse reaction,

i. inpatient hospitalization or prolongation of existing hospitalization,

ii. persistent or significant disability/incapacity,

iii. a congenital anomaly/birth defect,

iv. or based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Protocol Deviation (PD): Any change in the processes or procedures of research that were not approved by amendment of an IRB-approved protocol.

7.4 Reporting Procedures

An internal log of all AE, SAE, UP and PD events that come to the attention of the staff will be maintained.

Unanticipated Problems will be reported to the IRB using the Reportable Events Form within 5 business days of the identification of the event by the research staff.

RAs will maintain a daily attendance log throughout the intervention. If a participant is not in attendance at any of the sessions it will be recorded and they will attempt to get in touch with the participant. If it comes to their attention that an adverse even has taken place they will document this on the attendance log and fill out an AE form and/or SAE form if necessary. All adverse events will be compiled and reported on an ongoing basis and in summary form at the conclusion of the study to the IRB, the DSMB medical officer (Dr. Bean) and the NIA program officer (Dr. St. Hillaire-Clarke). Unanticipated (non-serious) adverse events will be reported within 30 days via submission of an Adverse Event Report. Serious adverse events will be reported within 24 hours by phone, email or fax. A completed Adverse Event Report will be submitted within 10 days of initial notification. All deaths will be reported within 24 hours.

If PIs become aware of issues that threaten the integrity of the trial or participant safety, they will alert the NIA representative to the DSMB who will consult with the DSMB Chair as to whether a special meeting or conference call of the DSMB should be held.

7.5 Follow-up for Adverse Events

AEs will be followed until resolved or considered stable.

7.6 Safety Monitoring

Prior to beginning data collection, Dr. Blumen and the DSMB Chair will reconfirm that our site has appropriate safety measures in place. The DSMB will meet with the entire research team to review the study protocols. Particular attention will be paid to outcome definition, study design, procedures for recording and reporting adverse events, and informed consent procedures and documentation.

At the initial meeting, the DSMB may recommend modifications or clarification of the protocol, and it will formulate its operating procedures (e.g., meeting schedule, reports due dates for the study statistician, unblinding policy, and what interim data may be released to the investigators). At the initial meeting the plans for interim monitoring for efficacy and futility will be presented to the DSMB as an aid for monitoring the trial.

We will train competent staff to conduct the interventions and assessments, ensure they understand the nature of the interventions, and understand adverse event reporting requirements. Trained clinical assistants, who will monitor the subject for any adverse events, will perform all assessments. We do not expect any serious adverse events during these non-invasive interventions. The clinical assistant will stop the testing procedures if subjects feel stressed or get embarrassed by their performance, and relay the information immediately to Dr. Blumen or Verghese. At least one investigator will be present onsite during all testing and intervention sessions. In addition Drs. Blumen and Verghese will be available by cellular telephone at all times to address any safety concerns or clinical issues.

Please see the Safety Monitoring Guidelines for further details (DSMP).

8 INTERVENTION DISCONTINUATION

Early study termination will occur in the event of any unanticipated serious adverse event determined to be possibly, probably or definitely related to study procedures, failure to recruit at least 50% of the projected number of subjects within 4 months, or failure to retain at least 75% of study subjects to the conclusion of the protocol.

Subjects may withdraw voluntarily from participation in the study at any time and for any reason. If the participant is acutely ill, is in the hospital, or has a temporary condition that interferes with walking (e.g. ankle sprain), we will attempt to complete the assessment at another time. We will follow-up with participants who dropped out of the study to determine both their mobility status and reasons for withdrawal. We will use intention to treat (ITT) analysis, which includes all randomized participants in the groups assigned, regardless of adherence with entry criteria, whether motor imagery was received, and subsequent withdrawal or deviation from the protocol. ITT analysis is pragmatic because it admits noncompliance and protocol deviations, and gives an unbiased estimate of the intervention effect. Handling missing data is a major issue in ITT, and is dealt with by imputation or sensitivity analysis. Our statistician, Dr. Wang, is very experienced in these methods.

A rich set of telephone-based information will be collected even for those subjects who may drop out. We will utilize this auxiliary information to assess the MAR assumption and combine it into the main model through joint modeling and multiple imputation approaches.

The research team will adjudicate events such as mobility disability in subjects who drop out based on medical interviews, contact interviews, and home assessments as required. For each study assessment, we will allow a 4-week window for completion.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Our goal in this preliminary single-blind RCT is to determine the efficacy of motor imagery for improving gait and cognition in older adults. Baseline distribution of covariates will be compared to assess adequacy of randomization to produce comparable groups of participants using appropriate graphical procedures and summary statistics.

9.1.1. *Primary outcome*

Gait speed was recommended to FDA as the preferred outcome for RCTs (39) because of its good validity, reliability, sensitivity to change, and predictive validity for multiple adverse outcomes.(39) We have reported that gait speed highly correlates with mobility related activities in our community.(40)

Reliability: We have reported excellent test-retest reliability of gait speed on GAITRite (Kappa >0.9).(41) Gait speed correlates highly with complaints of mobility limitations, falls and dementia in our studies.(41, 42)

Practice effects: Gait speed improved only by <2% when tested twice 8 weeks apart in controls in our pilot study suggesting that longer intervals between gait assessments may help minimize practice effects.

Walking while talking test (WWT) is a novel ecologically valid mobility measure developed by our group.(43, 44) Our studies establish the incremental validity of WWT speed over NPW speed for predicting adverse outcomes such as falls, frailty and disability.(44) Other investigators have shown that training older adults on WWT like tasks translates into clinically relevant outcomes such as reduced falls, better balance, or improved function.(45) Hence, establishing the efficacy of motor imagery on our co-primary outcome of WWT speed alone could be of high clinical impact and relevance (irrespective of its effect on NPW speed).

Reliability: We reported good inter-rater reliability (r = 0.602) on a previous WWT version.(43) In 31 EAS subjects, we had excellent test-retest (r = 0.935) and inter-rater reliability (r = 0.918) for WWT speed.

9.1.2. *Secondary and Tertiary outcomes.*

Cognitive performance during the WWT – number of correct letters generated during WWT will be the main cognitive outcome. Additional cognitive/executive function tasks, including the WAIS-III Letter Number Sequencing Test (46), Stroop Color and Word Test (47), Trail Making Test (48) and Flanker Interference Task (49) will also be administered to determine if there are any far-transfer effects of our imagined gait intervention, and to carefully identify appropriate outcome measures for upcoming studies. Improved performance on the Stroop test following motor imagery training has been shown in individuals with Parkinson's disease (13), and we have previously shown improved performance on the Letter Number Sequencing Task in cognitively-healthy older adults following a cognitive intervention (50). Additional neuropsychological measures of processing speed, language, and memory will also be examined (see ee Clinicaltrials.gov-NCT02762604 for a comprehensive list).

Change in blood-oxygen-level-dependent (BOLD) signal will be examined during single (imagined walking) and dual task (imagined walking-while-talking) walking conditions. Changes in BOLD signal has been shown following physical and cognitive interventions in the past (51-53).

Additional variables/potential covariates will be recorded and carefully examined for potential inclusion as covariates or outcome measures in upcoming full-scale RCT, including stride length (cm), double support time (s), cadence (steps/min), swing time (s), stance time, stride length variability (SD), swing time variability (SD), the Geriatric Depression Scale (54), Medical Illnesses and Medication questionnaires (26, 55), Cognitive and Physical leisure activity questionnaire (56-58), Falls (59), Obesity (assessed with weight, waist circumference, and BMI (kg/m^2)), Vision (Snellen's chart), Disability (7 ADLs using the scale developed by Gill and colleagues (60, 61), IADL (62, 63), Blood pressure (Sitting/Standing), Gray Matter Volume/Atrophy (T1-Weighted structural images) White Matter Integrity (Diffusion Tensor Imaging; DTI) and White Matter Hyper intensities (Fluid-Attenuated Inversion Recovery; FLAIR).

9.2 Sample Size and Randomization

The primary hypothesis examines change in gait speed (during NPW and WWT conditions). Setting an alpha level of .05, power of .80 and a medium effect size of defined as f =.25, the necessary sample size for detecting an interaction between time of test (pre and post), trial type (W or WWT) and imagery condition (Imagined gait or AC) is n = 34. Thus, our study completion goal of n = 48 (58 enrolled; 48 completed) is sufficient to detect our effects of interest and account for the 18% attrition rate expected during the study period (as observed in our previous studies (64)).

To detect a BOLD signal change at the individual subject level (i.e. first-level time-series modeling using SPM) at $p < 0.001$, a percent signal change of 0.34% is required using a published method and estimate of noise at a magnet strength of 3.0 Tesla (65). Based on this estimate, to detect a difference in contrast values between groups (i.e. second level analyses using SPM) at $p < 0.001$ and a power of at least .80, where the mean of one group's signal change is 50% of the other, 16 subjects per group are required. Thus, our study completion goal of n = 48 (24 in each condition) is sufficient to detect a main effect of imagery condition (imagined gait vs. AC) and leave room for the detection of interactions

9.2.1. Treatment Assignment Procedures

Group assignment randomization will be generated by Dr. Wang using sequential study numbers so that the assistant who enrolls the participants will be blinded to randomization assignment of the next participant until assigned. Dr. Wang will not be involved with subject testing or interventions.

Given the nature of our interventions, double-blinding both subjects and testers will not be feasible. But we will include a number of methods (besides randomization) to reduce bias.

- Selection bias will be reduced by concealing treatment allocation until the subject is entered into trial.
- Primary outcome is an objective endpoint (gait speed) and not subjective mobility complaints.

- Motor imagery and visual imagery interventions will be done at non-overlapping times.
- Participants and study staff will be instructed not to disclose group assignment or details of interventions.

9.3 Interim analyses and Stopping Rules

No interim analysis is planned for this pilot intervention of 48 volunteers. Early study termination will occur in the event of any unanticipated serious adverse event determined to be possibly, probably or definitely related to study procedures, failure to recruit at least 50% of the projected number of subjects within 4 months, or failure to retain at least 75% of study subjects to the conclusion of the protocol

9.4 Data Analyses

9.4.1 Primary outcome.

To examine gait speed during W and WWT we will use repeated-measures analyses that include time of test (pre and post), and trial type (W or WWT) as within subjects factors, and imagery condition (imagined gait or AC) as the between-subjects factor. Consideration of these analyses will focus on the three-way interaction between time of test, trial type, and imagery condition.

9.4.2. Secondary and tertiary outcomes.

Similar repeated-measures analyses will be used for our secondary outcomes measures/additional EF measures: Trail Making Test, the Letter Number Sequencing Test, the Stroop Color and Word Test, and the Flanker Interference Task. These measures include the time to complete Trails B corrected for Trails A from the Trail Making Test (Trails B-A), the raw score from the letter-number sequencing task WAIS-III, the raw response time to Color-Word (incongruent) trials corrected for Color (congruent) trials from the Stroop Color and Word Test (i.e., Stroop Interference) and the flanker interference response time measure (incongruent-congruent trials) from the Flankers interference task. Although three of these four measures are difference scores, our analyses will be completed on raw scores in order maximize power. More specifically, for these measures we will use repeated-measures analyses that included time of test (pre and post) and trial type as within subjects factors, and imagery condition (imagined gait or AC) as the between-subjects factor. Trial type for the Trail Making Test will be Trails A and Trails B. Trial Type for the Stroop Color and Word Test will be congruent trials and incongruent trials. Finally, trial type for the Flanker task will be congruous and incongruous trials. Consideration of these analyses will focus on the three-way interaction between time of test, trial type, and condition. Analyses will focus on the primary outcome variables during training and to the end of training period.

All behavioral analyses will be corrected for multiple comparisons using the Bonferroni correction.

We will use a whole-brain multivariate Ordinal Trend Covariance Analysis (OrT-CVA) to analyze the BOLD signal during imagined walking and walking while talking (66, 67). This is because we are interested in determining how the use of the entire locomotion and executive

function systems change as a function of our imagined gait versus the active control condition. This is also because changes in neural activation are often masked by between-subject variability, an issue that is particularly important to consider in aging populations (68, 69). Our multivariate analyses will be performed with software developed by my co-mentor in advanced neuroimaging analysis, Dr. Habeck: http://www.nitrc.org/projects/gcva_pca. OrT-CVA will be used to identify covariance patterns in the fMRI signal as a function of trial type (iT, iW and iWWT) at each study visit (pre and post-intervention) for each imagery condition (imagined gait or AC). OrT-CVA is similar to other covariance analyses such as partial least squares (70, 71) in that it employs a principal components analysis (PCA) to the data matrix that is then transformed to a matrix of the experimental design. Linear regression is then applied to detect a covariance pattern, or ordinal trend, in the fMRI signal as a function of task conditions that is based on a linear combination of a small set of principal components. An ordinal trend is a monotonic change in pattern expression as a function of task conditions, in this case as a function of trial type (iW, iT and iWWT). The expression of an ordinal trend is quantified in terms of a participant-specific expression score that is derived by projecting the covariance pattern onto a participant's scan for each task condition. These participant-specific (or pattern) expression scores can also be used for further analysis (e.g. to correlate with actual WWT performance). Note that the proposed multivariate analyses of fMRI data involve data reduction and therefore does not involve multiple comparisons.

Age, sex and education will be covariates in all analyses. Given that is a pilot RCT on a fairly small sample of participants, it is not statistically feasible to control for more than the basic covariates listed above. Additional variables/potential covariates will be recorded and carefully examined for potential inclusion as covariates or outcome measures in upcoming full-scale RCT, including stride length (cm), double support time (s), cadence (steps/min), swing time (s), stance time, stride length variability (SD), swing time variability (SD), the Geriatric Depression Scale (54), Medical Illnesses and Medication questionnaires (26, 55), Cognitive and Physical leisure activity questionnaire (56-58), Falls (59), Smoking and alcohol consumption questionnaires, Obesity (assessed with weight, waist circumference, and BMI (kg/m^2)), Vision (Snellen's chart), Disability (7 ADLs using the scale developed by Gill and colleagues (60, 61), IADL (62, 63), Blood pressure (Sitting/Standing), Gray Matter Volume/Atrophy (T1-Weighted structural images) White Matter Integrity (Diffusion Tensor Imaging; DTI) and White Matter Hyper intensities (Fluid-Attenuated Inversion Recovery; FLAIR).

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Confidentiality will be preserved by use of ID code numbers for identification. ID and name associations will be password protected in an encrypted master file to which only the PIs and statistician will have access. Participant data, including computer data disks, will be kept in a locked room. Identifying information about a subject will not be used during the discussion or presentation of any research data. To ensure confidentiality and anonymity during the study, each subject will be assigned a confidential study number. Access to the subject study identification codes or other information will be restricted to the PIs, co-investigators, and study staff, and upon

written request, to the IRB or other regulatory agencies, or by written request of the subject, released to others. Paper records will be stored in locked file cabinets in the investigators' offices, and all computers used for data management and analysis will be password-protected and located in secure offices.

10.2 Data Management

Behavioral data will be entered, stored and maintained in a REDcap database (72). REDcap provides a secure web-based application for developing, and managing data bases, and is used by thousands of active institutional partners in more than one hundred countries. Our study site, Albert Einstein College of Medicine, provides on-site support for the development, upkeep, and maintenance of REDcap databases. Only trained RAs will be permitted to enter data in this database, and REDcap automatically records the date, time and the person who entered or changed data into a database. Neuroimaging data will be stored, maintained, processed and analyzed in a secure Linux server environment.

Participant confidentiality will be maintained by assigning each subject a unique study ID upon entry to identify and link subject data. ID and name associations will be password protected and only the data manager, PI and primary mentor will have access.

10.3 Quality Assurance

10.3.1 Training

All study staff have taken the Safety Training Class-an online training venue that provides an overview of human subjects safety surveillance and reporting requirements in clinical research studies. The intent of the course is to help clinical study investigators and staff understand and implement NIA and regulatory requirements for safe, high quality clinical research. The topics covered include Good Clinical Practice (GCP), Human Subject Protections, Adverse Events and Unanticipated Problems, Safety Monitoring and Reporting Requirements, Safety Monitoring and Oversight: DSMBs and Safety Officers, Regulatory Requirements and Responsibilities of PIs, and Data and Safety Monitoring Plans.

They have also all successfully completed the required CITI training courses.

10.3.2 Quality Control Committee

N/A

10.3.3 Metrics

We will train competent staff to conduct the interventions and assessments, ensure they understand the nature of the interventions, and understand adverse event reporting requirements. Trained clinical assistants, who will monitor the participant for any adverse events, will perform all assessments. The clinical assistant will stop the testing procedures if participants feel stressed or get embarrassed by their performance, and relay the information immediately to Drs. Blumen and Verghese. At least one member of the research team will be

present onsite during all testing and intervention sessions. In addition, Drs. Blumen and Verghese will be available by pager and cellular telephone at all times to address any safety concerns or clinical issues.

The PIs will monitor performance and safety issues on a day-to-day basis. In addition the DSMB will be responsible for the following which will ensure the quality, accuracy and efficiency of the study.

- Review the research protocol, informed consent documents and plans for data safety and monitoring;
- Recommend participant recruitment be initiated after receipt of a satisfactory protocol;
- Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that can affect study outcome;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- Review study performance, make recommendations and assist in the resolution of problems reported by the PIs;
- Protect the safety of the study participants;
- Report to NIA on the safety and progress of the trial;
- Make recommendations to the NIA and the PIs concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- Ensure the confidentiality of the study data and the results of monitoring; and,
- Assist the NIA by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

10.3.4 Protocol Deviations

Protocol deviations will be recorded and documented for each participant in the database calendar. All adverse event forms will be completed and reported as described above.

All protocol and MOP changes and/or amendments will be recorded on an ongoing basis and reported to the IRB as well as documented on the cover page of this protocol.

10.3.5 Monitoring

All data collection in this clinical trial will be monitored to assure participant comfort, safety, and confidentiality. The clinical trial protocols, data collection instruments, participant

recruitment letters, and consent forms will be reviewed and approved by the IRB prior to study initiation. We will also provide an annual progress report to the IRB and NIH. The study coordinator will be responsible for preparing these reports.

The DSMB will monitor participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses. The PI will monitor performance and safety issues on a day-to-day basis. Both closed and open meetings of the DSMB will be held on a biannual basis. In addition the DSMB will meet more or less frequently as study progress dictates.

If PIs become aware of issues that threaten the integrity of the trial or participant safety, they will alert the NIA representative to the DSMB who will consult with the DSMB Chair as to whether a special meeting or conference call of the DSMB should be held.

The open session report will focus on patient accrual and demographics, data completeness, and other study performance measures. Only aggregate data will be presented during the open session (i.e., not segregated by treatment). The closed session report will divide study participants according to coded treatment assignment, comparing participant demographics and baseline characteristics, rates and reasons for treatment discontinuation and loss to follow-up, and rates of serious adverse events. The PIs may prepare a report addressing concerns they anticipate the DSMB will have regarding the conduct of the study.

The data reports will include:

- Cumulative accrual
- Baseline characteristics, overall and by treatment group
- Summary of completeness and quality of data collection forms
- Status of enrolled participants, overall and by treatment group
- Assessments of whether study personnel have followed eligibility criteria and other protocol requirements
- Assessment of participant adherence, overall and by treatment group
- Outcome rates, overall and by treatment group along with monitoring boundaries for efficacy and futility (if the planned interim analysis is due)
- Listing of serious adverse events by participant ID number and a table of event-specific cumulative rates, overall and by treatment group
- A summary description of all serious adverse events

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol, the informed consent (Appendix I), all recruitment materials, assessments and scripts as well as any subsequent modifications to these documents will be reviewed by the IRB.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant (Appendix I). The consent form describes 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 and this fact will be documented in the participant's record.

11.3 Participant Confidentiality

Any data, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID) 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 and the NIA.

11.4 Study Discontinuation

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

12 ETHICAL CONSIDERATIONS

Recruitment, enrollment, and participation of participants in this project are not limited by gender, skin color, racial/ethnic group, or economic status. We will monitor recruitment and retention patterns to ensure adequate representation of women and minorities.

13 COMMITTEES

N/A

14 PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NIA prior to submission.

15 REFERENCES

1. Newman AB, Simonsick EM, Naydeck BL, Boudreau RM, Kritchevsky SB, Nevitt MC, Pahor M, Satterfield S, Brach JS, Studenski SA, Harris TB. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. Journal of the American Medical Association. 2006;295(17):2018-26. Epub 2006/05/04. doi: 10.1001/jama.295.17.2018. PubMed PMID: 16670410.
2. Verghese J, Wang C, Lipton RB, Holtzer R, Xue X. Quantitative gait dysfunction and risk of cognitive decline and dementia. Journal of Neurology, Neurosurgery, and Psychiatry. 2007;78(9):929-35. Epub 2007/01/24. doi: 10.1136/jnnp.2006.106914. PubMed PMID: 17237140; PubMed Central PMCID: PMC1995159.
3. Marquis S, Moore MM, Howieson DB, Sexton G, Payami H, Kaye JA, Camicioli R. Independent predictors of cognitive decline in healthy elderly persons. Archives of Neurology. 2002;59(4):601-6. Epub 2002/04/10. PubMed PMID: 11939895.

4. Waite LM, Grayson DA, Piguet O, Creasey H, Bennett HP, Broe GA. Gait slowing as a predictor of incident dementia: 6-year longitudinal data from the Sydney Older Persons Study. Journal of the Neurological Sciences. 2005;230:89-93.
5. Wang L, Larson EB, Bowen JD, van Belle G. Performance-based physical function and future dementia in older people. Archives of Internal Medicine. 2006;166(10):1115-20. Epub 2006/05/24. doi: 10.1001/archinte.166.10.1115. PubMed PMID: 16717174.
6. Singh MAF. Exercise Comes of Age: Rationale and Recommendations for a Geriatric Exercise Prescription. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2002;57(5):M262-M82. doi: 10.1093/gerona/57.5.M262.
7. Elsawy B, Higgins K. Physical Acitivity Guidelines for Older Adults. American family physician. 2010;81(1):55-9.
8. Dishman RK, Sallis JF, Orenstein DR. The Determinants of Physical Activity and Exercise. Public Health Reports (1974-). 1985;100(2):158-71. doi: 10.2307/20056432.
9. Martin KA, Moritz SE, Hall CR. Imagery use in sport: A literature review and applied model. The Sport Psychologist. 1999;13(3):245-68.
10. Murphy SM. Models of imagery in sport psychology: A review. Journal of Mental Imagery. 1990;14(3-4):153-72.
11. Guillot A, Collet C. Construction of the Motor Imagery Integrative Model in Sport: a review and theoretical investigation of motor imagery use. International Review of Sport and Exercise Psychology. 2008;1(1):31-44. doi: 10.1080/17509840701823139.
12. Feltz DL, Landers DM. The effects of mental practice on motor skill learning and performance: A meta-analysis. Journal of Sport Psychology. 1983;5(1):25-57.
13. Tamir R, Dickstein R, Huberman M. Integration of motor imagery and physical practice in group treatment applied to subjects with Parkinson's disease. Neurorehabilitation & Neural Repair 2007;21(1):68-75. Epub 2006/12/19. doi: 10.1177/1545968306292608. PubMed PMID: 17172556.
14. Heremans E, Feys P, Nieuwboer A, Vercruysse S, Vandenberghe W, Sharma N, Helsen W. Motor imagery ability in patients with early- and mid-stage Parkinson disease. Neurorehabilitation & Neural Repair 2011;25(2):168-77. Epub 2011/01/18. doi: 10.1177/1545968310370750. PubMed PMID: 21239707.
15. Schlesinger I, Benyakov O, Erikh I, Nassar M. Relaxation guided imagery reduces motor fluctuations in Parkinson's disease. J Parkinsons Dis. 2014;4(3):431-6. Epub 2014/04/02. doi: 10.3233/jpd-130338. PubMed PMID: 24685702.
16. Dunsky A, Dickstein R, Marcovitz E, Levy S, Deutsch JE. Home-based motor imagery training for gait rehabilitation of people with chronic poststroke hemiparesis. Archives of Physical Medicine and Rehabilitation. 2008;89(8):1580-8. Epub 2008/08/05. doi: 10.1016/j.apmr.2007.12.039. PubMed PMID: 18674992.
17. Kim JS, Oh DW, Kim SY, Choi JD. Visual and kinesthetic locomotor imagery training integrated with auditory step rhythm for walking performance of patients with chronic stroke. Clinical Rehabilitation 2011;25(2):134-45. Epub 2010/10/15. doi: 10.1177/0269215510380822. PubMed PMID: 20943715.
18. Verma R, Arya KN, Garg RK, Singh T. Task-oriented circuit class training program with motor imagery for gait rehabilitation in poststroke patients: a randomized controlled trial. Topics in Stroke Rehabilitation. 2011;18 Suppl 1:620-32. Epub 2011/11/29. doi: 10.1310/tsr18s01-620. PubMed PMID: 22120031.

19. Dunsky A, Dickstein R, Ariav C, Deutsch J, Marcovitz E. Motor imagery practice in gait rehabilitation of chronic post-stroke hemiparesis: four case studies. Int J Rehabil Res. 2006;29(4):351-6. Epub 2006/11/16. doi: 10.1097/MRR.0b013e328010f559. PubMed PMID: 17106356.
20. Cho H-y, Kim J-s, Lee G-C. Effects of motor imagery training on balance and gait abilities in post-stroke patients: a randomized controlled trial. Clinical Rehabilitation. 2013;27(8):675-80. doi: 10.1177/0269215512464702.
21. Blumen HM, Holtzer, R., Brown, L.L., Gazes, Y, Verghese, J. Behavioral and neural correlates of imagined walking and walking while talking in the elderly. Human Brain Mapping. 2014;35(8):4090-104. doi: 10.1002/hbm.22461.
22. la Fougere C, Zwergal A, Rominger A, Forster S, Fesl G, Dieterich M, Brandt T, Strupp M, Bartenstein P, Jahn K. Real versus imagined locomotion: a [18F]-FDG PET-fMRI comparison. Neuroimage. 2010;50(4):1589-98. Epub 2009/12/26. doi: 10.1016/j.neuroimage.2009.12.060. PubMed PMID: 20034578.
23. Zwergal A, Linn J, Xiong G, Brandt T, Strupp M, Jahn K. Aging of human supraspinal locomotor and postural control in fMRI. Neurobiology of Aging. 2012;33(6):1073-84. Epub 2010/11/06. doi: 10.1016/j.neurobiolaging.2010.09.022. PubMed PMID: 21051105.
24. Beurskens R, Bock O. Age-related deficits of dual-task walking: a review. Neural Plast. 2012;2012:131608. doi: 10.1155/2012/131608. PubMed PMID: 22848845; PubMed Central PMCID: PMC3403123.
25. Buracchio T, Dodge HH, Howieson D, Wasserman D, Kaye J. The trajectory of gait speed preceding mild cognitive impairment. Arch Neurol. 2010;67(8):980-6. doi: 10.1001/archneurol.2010.159. PubMed PMID: 20697049; PubMed Central PMCID: PMC2921227.
26. Holtzer R, Verghese J, Xue X, Lipton RB. Cognitive processes related to gait velocity: results from the Einstein Aging Study. Neuropsychology. 2006;20(2):215-23. Epub 2006/04/06. doi: 10.1037/0894-4105.20.2.215. PubMed PMID: 16594782.
27. Holtzer R, Mahoney JR, Izzetoglu M, Izzetoglu K, Onaral B, Verghese J. fNIRS study of walking and walking while talking in young and old individuals. Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2011;66(8):879-87.
28. Holtzer R, Wang C, Lipton R, Verghese J. The protective effects of executive functions and episodic memory on gait speed decline in aging defined in the context of cognitive reserve. Journal of the American Geriatrics Society. 2012;60(11):2093-8. doi: 10.1111/j.1532-5415.2012.04193.x. PubMed PMID: 23039200; PubMed Central PMCID: PMC3498524.
29. Lindenberger U, Marsiske M, Baltes PB. Memorizing while walking: increase in dual-task costs from young adulthood to old age. Psychology and Aging. 2000;15(3):417-36.
30. Neider MB, Gaspar JG, McCarley JS, Crowell JA, Kaczmarski H, Kramer AF. Walking and talking: dual-task effects on street crossing behavior in older adults. Psychol Aging. 2011;26(2):260-8. doi: 10.1037/a0021566. PubMed PMID: 21401262.
31. Verghese J, Buschke H, Viola L, Katz M, Hall C, Kuslansky G, Lipton R. Validity of divided attention tasks in predicting falls in older individuals: a preliminary study. Journal of the American Geriatrics Society. 2002;50(9):1572-6. Epub 2002/10/18. PubMed PMID: 12383157.
32. Verghese J, Holtzer R, Lipton RB, Wang C. Mobility Stress Test Approach to Predicting Frailty, Disability, and Mortality in High-Functioning Older Adults. Journal of the American Geriatrics Society. 2012. Epub 2012/09/26. doi: 10.1111/j.1532-5415.2012.04145.x. PubMed PMID: 23002714.

33. Lipton RB, Katz MJ, Kuslansky G, Sliwinski MJ, Stewart WF, Verghese J, Crystal HA, Buschke H. Screening for dementia by telephone using the memory impairment screen. J Am Geriatr Soc. 2003;51(10):1382-90. Epub 2003/09/27. doi: 51455 [pii]. PubMed PMID: 14511157.
34. Galvin JE, Roe CM, Powlishta KK, Coats MA, Muich SJ, Grant E, Miller JP, Storandt M, Morris JC. The AD8: a brief informant interview to detect dementia. Neurology. 2005;65(4):559-64. doi: 10.1212/01.wnl.0000172958.95282.2a. PubMed PMID: 16116116.
35. Galvin JE, Roe CM, Xiong C, Morris JC. Validity and reliability of the AD8 informant interview in dementia. Neurology. 2006;67(11):1942-8. Epub 2006/12/13. doi: 67/11/1942 [pii] 10.1212/01.wnl.0000247042.15547.eb [doi]. PubMed PMID: 17159098.
36. Snodgrass JG, Vanderwart M. A standardized set of 260 pictures: Norms for name agreement, image agreement, familiarity, and visual complexity. Journal of Experimental Psychology: Human Learning and Memory. 1980;6(2):174-215. doi: 10.1037/0278-7393.6.2.174.
37. Marks DF. Visual imagery differences in the recall of pictures. British Journal of Psychology. 1973;64(1):17-24. Epub 1973/02/01. PubMed PMID: 4742442.
38. Marks DF. New directions for mental imagery research. Journal of Mental Imagery. 1995;19(3-4):153-67.
39. Bhasin S, Espeland MA, Evans WJ, Ferrucci L, Fried LP, Gill TM, Pahor M, Studenski S, Guralnik J, Nayfield S, Romashkin S, Perlstein R, Burke L, Parks M. Indications, labeling, and outcomes assessment for drugs aimed at improving functional status in older persons: a conversation between aging researchers and FDA regulators. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2009;64(4):487-91. Epub 2009/03/10. doi: gln042 [pii] 10.1093/gerona/gln042 [doi]. PubMed PMID: 19270182.
40. Verghese J, Wang C, Holtzer R. Relationship of clinic-based gait speed measurement to limitations in community-based activities in older adults. Archives of physical medicine and rehabilitation. 2011;92(5):844-6. Epub 2011/05/03. doi: 10.1016/j.apmr.2010.12.030. PubMed PMID: 21530734; PubMed Central PMCID: PMCPMC3086725.
41. Verghese J, Katz MJ, Derby CA, Kuslansky G, Hall CB, Lipton RB. Reliability and validity of a telephone-based mobility assessment questionnaire. Age Ageing. 2004;33(6):628-32. doi: 10.1093/ageing/afh210. PubMed PMID: 15501841.
42. Holtzer R, Verghese J, Wang C, Hall CB, Lipton RB. Within-person across-neuropsychological test variability and incident dementia. JAMA. 2008;300(7):823-30. Epub 2008/08/21. doi: 10.1001/jama.300.7.823. PubMed PMID: 18714062; PubMed Central PMCID: PMCPMC2736784.
43. Verghese J, Buschke H, Viola L, Katz M, Hall C, Kuslansky G, Lipton R. Validity of divided attention tasks in predicting falls in older individuals: a preliminary study. J Am Geriatr Soc. 2002;50(9):1572-6. Epub 2002/10/18. PubMed PMID: 12383157.
44. Verghese J, Holtzer R, Lipton RB, Wang C. Mobility stress test approach to predicting frailty, disability, and mortality in high-functioning older adults. J Am Geriatr Soc. 2012;60(10):1901-5. Epub 2012/09/26. doi: 10.1111/j.1532-5415.2012.04145.x. PubMed PMID: 23002714; PubMed Central PMCID: PMC3470773.
45. Schwenk M, Zieschang T, Oster P, Hauer K. Dual-task performances can be improved in patients with dementia A randomized controlled trial. Neurology. 2010;74(24):1961-8. PubMed PMID: WOS:000279281700008.
46. Wechsler D. Wechsler Adult Intelligence Scale - III. San Antonio, TX: Psychological Corporation; 1997.
47. Golden C. Stroop Color and Word Test. Chicago, IL: Stolting; 1978.

48. Reitan R. Manual for Administration of Neuropsychological Test Batteries for Adults and Children: Tucson, AZ: Reitan Neuropsychology Laboratories
1978.
49. Eriksen B, Eriksen C. Effects of noise letters upon the identification of a target letter in a nonsearch task. Perception & Psychophysics. 1974;16(1):143-9. doi: 10.3758/BF03203267.
50. Stern Y, Blumen HM, Rich LW, Richards A, Herzberg G, Gopher D. Space Fortress game training and executive control in older adults: a pilot intervention. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2011;18(6):653-77. Epub 2011/10/13. doi: 10.1080/13825585.2011.613450. PubMed PMID: 21988726.
51. Duchesne C, Gheysen F, Bore A, Albouy G, Nadeau A, Robillard ME, Bobeuf F, Lafontaine AL, Lungu O, Bherer L, Doyon J. Influence of aerobic exercise training on the neural correlates of motor learning in Parkinson's disease individuals. Neuroimage Clin. 2016;12:559-69. Epub 2016/10/01. doi: 10.1016/j.nicl.2016.09.011. PubMed PMID: 27689020; PubMed Central PMCID: PMCPmc5031470.
52. Randomized trial on the effects of a combined physical/cognitive training in aged MCI subjects: the Train the Brain study. Sci Rep. 2017;7:39471. Epub 2017/01/04. doi: 10.1038/srep39471. PubMed PMID: 28045051; PubMed Central PMCID: PMCPmc5206718.
53. Wagner G, Herbsleb M, Cruz F, Schumann A, Kohler S, Puta C, Gabriel HW, Reichenbach JR, Bar KJ. Changes in fMRI activation in anterior hippocampus and motor cortex during memory retrieval after an intense exercise intervention. Biol Psychol. 2017. Epub 2017/01/26. doi: 10.1016/j.biopsycho.2017.01.003. PubMed PMID: 28119067.
54. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982;17(1):37-49. Epub 1982/01/01. PubMed PMID: 7183759.
55. Verghese J, Wang C, Lipton RB, Holtzer R, Xue X. Quantitative gait dysfunction and risk of cognitive decline and dementia. Journal of Neurology, Neurosurgery & Psychiatry. 2007;78(9):929-35.
56. Hall C, Lipton RB, Sliwinski M, Katz MJ, Derby CA, Verghese J. Cognitive activities delay onset of memory decline in persons who develop dementia. Neurology. 2009;73(5):356-61. Epub 2009/08/05. doi: 10.1212/WNL.0b013e3181b04ae3. PubMed PMID: 19652139; PubMed Central PMCID: PMC2725932.
57. Verghese J, LeValley A, Derby C, Kuslansky G, Katz M, Hall C, Buschke H, Lipton RB. Leisure activities and the risk of amnestic mild cognitive impairment in the elderly. Neurology. 2006;66(6):821-7. Epub 2006/02/10. doi: 10.1212/01.wnl.0000202520.68987.48. PubMed PMID: 16467493; PubMed Central PMCID: PMC1415273.
58. Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, Ambrose AF, Sliwinski M, Buschke H. Leisure Activities and the Risk of Dementia in the Elderly. New England Journal of Medicine. 2003;348(25):2508-16. doi: doi:10.1056/NEJMoa022252.
59. Tinetti ME, Franklin Williams T, Mayewski R. Fall risk index for elderly patients based on number of chronic disabilities. The American Journal of Medicine. 1986;80(3):429-34. doi: http://dx.doi.org/10.1016/0002-9343(86)90717-5.
60. Gill TM, Baker DI, Gottschalk M, Gahbauer EA, Charpentier PA, de Regt PT, Wallace SJ. A prehabilitation program for physically frail community-living older persons. Archives of Physical Medicine & Rehabilitation. 2003;84(3):394-404. PubMed PMID: 12638108.
61. Gill TM, Murphy TE, Barry LC, Allore HG. Risk factors for disability subtypes in older persons. J Am Geriatr Soc. 2009;57(10):1850-5. Epub 2009/08/22. doi: JGS2443 [pii]

10.1111/j.1532-5415.2009.02443.x [doi]. PubMed PMID: 19694870.
62. Katz S. Assessing self maintenance: Activities of daily living, mobility and instrumental activities of daily living. Journal of the American Geriatrics Society. 1983;31(12):721-6.
63. Lawton M, Brody E. Assessment of older people: Self maintaining and instrumental activities of daily living. Gerontologist. 1969;9:179-86.
64. Verghese J, Holtzer R. Walking the walk while talking: cognitive therapy for mobility in dementia? Neurology. 2010;74(24):1938-9. Epub 2010/05/07. doi: 10.1212/WNL.0b013e3181e3d97d. PubMed PMID: 20445148.
65. Smith S, Jenkinson M, Beckmann C, Miller K, Woolrich M. Meaningful design and contrast estimability in FMRI. Neuroimage. 2007;34(1):127-36. doi: 10.1016/j.neuroimage.2006.09.019. PubMed PMID: 17070706.
66. Habeck C, Rakitin BC, Moeller J, Scarmeas N, Zarahn E, Brown T, Stern Y. An event-related fMRI study of the neural networks underlying the encoding, maintenance, and retrieval phase in a delayed-match-to-sample task. Brain Res Cogn Brain Res. 2005;23(2-3):207-20. doi: 10.1016/j.cogbrainres.2004.10.010. PubMed PMID: 15820629.
67. Habeck C, Stern Y. Neural network approaches and their reproducibility in the study of verbal working memory and Alzheimer's disease. Clin Neurosci Res. 2007;6(6):381-90. doi: 10.1016/j.cnr.2007.05.004. PubMed PMID: 18978933; PubMed Central PMCID: PMC2329589.
68. Cabeza R, Anderson ND, Locantore JK, McIntosh AR. Aging Gracefully: Compensatory Brain Activity in High-Performing Older Adults. NeuroImage. 2002;17(3):1394-402. doi: http://dx.doi.org/10.1006/nimg.2002.1280.
69. Colcombe SJ, Kramer AF, Erickson KI, Scalf P. The implications of cortical recruitment and brain morphology for individual differences in inhibitory function in aging humans. Psychology and aging. 2005;20(3):363-75. doi: 10.1037/0882-7974.20.3.363. PubMed PMID: 16248697.
70. Worsley KJ, Poline JB, Friston KJ, Evans AC. Characterizing the response of PET and fMRI data using multivariate linear models. Neuroimage. 1997;6(4):305-19. doi: 10.1006/nimg.1997.0294. PubMed PMID: 9417973.
71. McIntosh AR, Bookstein FL, Haxby JV, Grady CL. Spatial pattern analysis of functional brain images using partial least squares. Neuroimage. 1996;3(3 Pt 1):143-57. doi: 10.1006/nimg.1996.0016. PubMed PMID: 9345485.
72. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics. 2009;42(2):377-81. Epub 2008/10/22. doi: 10.1016/j.jbi.2008.08.010. PubMed PMID: 18929686; PubMed Central PMCID: PMCPMC2700030.

16 SUPPLEMENTS/APPENDICES

I. Informed Consent Form

II. Adverse Event Log and Serious Adverse Event Form

Appendix I-Informed Consent

IRB NUMBER: 2014-3633
IRB APPROVAL DATE: 12/05/2016
IRB EXPIRATION DATE: 12/04/2017

ALBERT EINSTEIN COLLEGE OF MEDICINE

DOCUMENTATION OF INFORMED CONSENT AND HIPAA AUTHORIZATION

Introduction

You are being asked to participate in a research study called **Motor Imagery: A Pilot Intervention for Improving Gait and Cognition in the Elderly.** Your participation is voluntary -- it is up to you whether you would like to participate. It is fine to say "no" now or at any time after you have started the study. If you say "no," your decision will not affect any of your rights or benefits

The researcher in charge of this project is called the "Principal Investigator." Her name is **Dr. Helena Blumen**. You can reach Dr. Blumen at:
Office Address:
1225 Morris Park Avenue, # 313 B
Bronx, NY 10461
Telephone: 718 430 3810

For questions about the research study, or if you believe you have an injury, contact the Principal Investigator or the IRB.

Support for this research study is provided by the **National Institute of Health**

The Institutional Review Board (IRB) of the Albert Einstein College of Medicine and Montefiore Medical Center has approved this research study. The IRB # is in the stamp in the upper right hand corner. If you have questions regarding your rights as a research subject you may contact the IRB office at 718-430-2253 or by mail:

Einstein IRB
Albert Einstein College of Medicine
1300 Morris Park Ave., Belfer Bldg #1002
Bronx, New York 10461

Why is this study being done?

The goal of this study is to evaluate whether walking and cognitive (learning, understanding and remembering) difficulties among senior citizens is a potentially preventable condition rather than an irreversible consequence of aging and disease. This study aims to determine if seniors show improved mobility (the ability to walk or move freely and easily) and/or cognition following imagery (visualization) training.

This study compares two interventions, both include imagery. One group will participate in motor imagery (visualizing themselves walking). The other group will participate in visual imagery (visualizing an octopus)

This study will provide important information regarding the usefulness of imagery interventions to prevent walking and cognitive disabilities.

Why am I being asked to participate?

You are being asked to participate in this study because you are 65-85 years old and have responded to recruitment fliers posted around Albert Einstein College of Medicine, Montefiore

EINSTEIN IRB NUMBER: 2014-3633
IRB APPROVAL DATE: 12/05/2016
IRB EXPIRATION DATE: 12/04/2017

University Hospital, Internet sites, or have been contacted via market mailing to a Bronx and Westchester County Registered Voter List. A total of 58 participants will be enrolled in this study.

What will happen if I participate in the study?

If you agree to participate in this study you will be randomly assigned into either a 12-week telephone-based motor imagery intervention or a 12-week telephone-based visual imagery intervention. Both interventions consist of 3 **(15-minute) phone calls per week for 12 weeks.** Total training time is 45 minutes per week. In one group, the training will consist of motor imagery specifically design to improve attention and mobility. In the second group, the training will consist of visual imagery. If you agree to participate in this study, you will be invited to **two study visits** (one before and one after the 12-week intervention). During these study visits, the study interviewer will ask you questions about your medical history, education, daily activities and occupation. You will receive test of cognitive functions such as memory and attention. You will also receive neurological and mobility evaluations of gait (the way you walk), balance, coordination, vision, sensation and the strength and tone of muscles.

During the two study visit you will also undergo **Magnetic Resonance Imaging (MRI).** MRI permits us to examine how the brain responds to our interventions. MRI is a test that uses magnets and radio waves to make pictures of organs and structures inside the body. For an MRI test, the area of the body being studied is placed inside a special machine that contains a strong magnet. Pictures from an MRI scan are saved and stored on a computer for more study. Although the MRI you will have in this study is being done for research purposes only, it is possible that doctors may notice something that could be important to your health. If so, we will contact you to explain what was seen and tell you whether you should consult your doctor. We will make the MRI report available to your doctor, and if you want, we will talk with your private physician or refer you to someone for follow-up.

How many people will take part in the research study?

You will be one of 58 people who will be participating in this study.

Will there be audio and/or video recording?

Your auditory responses will be recorded during some evaluations and used only to determine the timing and accuracy of your responses. Only the principal investigator and her research team will have access to your recording. Your auditory recording will be given a code number and separated from your name. Your auditory recording will be kept as long as they are useful for this research.

Information Banking (Future Use and Storage)

We will store information about you in a "bank", which is a library of information from many studies. This information cannot be linked to you. In the future, researchers can apply for permission to use the information for new studies to prevent, diagnose, or treat disease. Your information may be kept for a long time, perhaps longer than 50 years. If you agree to the future use, some of your de-identified health information (not linked to you) may be placed into one or more scientific databases. These may include databases maintained by the federal government.

You can choose not to participate in the bank and still be part of the main study

IRB NUMBER: 2014-3633
IRB APPROVAL DATE: 12/05/2016
IRB EXPIRATION DATE: 12/04/2017

INITIAL ONE (1) OF THE FOLLOWING OPTIONS

_____ I consent to have my information used for future research studies.

_____ I do NOT consent to have my information used for future research studies. The information will be destroyed at the end of the study.

Some researchers may develop tests, treatments or products that are worth money. You will not receive payment of any kind for your information or for any tests, treatments, products or other things of value that may result from the research.

Will I be paid for being in this research study?

You will receive **$50 for the first study visit, $25 for the phone-based intervention, and $ 50 for the second study visit, for a total of $125** for the study. We will also provide **free transportation** to and from each study visit. If you choose to withdraw from the study before all study visits or the phone-based intervention are completed, you will be paid only for the parts you completed.

Will it cost me anything to participate in this study?

There will be no cost to you to participate in the study.

Are there any risks to me?

- You may be embarrassed if you have some difficulties with some of the cognitive and or motor evaluations that you will be asked to perform.
- Some people may experience mild temporary distress after taking cognitive evaluations. If any distress is experienced, you will have the opportunity to have your questions answered by the investigators.

Confidentiality

We will keep your information confidential. Your research records will be kept confidential and your name will not be used in any written or verbal reports. Your information will be given a code number and separated from your name or any other information that could identify you. The form that links your name to the code number will be kept in a locked file cabinet and only the investigator and study staff will have access to the file. All information will be kept in a secure manner and computer records will be password protected. Your study information will be kept as long as they are useful for this research.

Medical information collected during the research, such as test results, may be entered into your Montefiore electronic medical record and will be available to clinicians and other staff at Montefiore who provide care to you.

The only people who can see your research records are:

- the research team and staff who work with them
- the organization that funded the research: The National Institute of Health
- groups that review research (the Einstein IRB, and the Office for Human Research Protections)

IRB NUMBER: 2014-3633
IRB APPROVAL DATE: 12/05/2016
IRB EXPIRATION DATE: 12/04/2017

These people who receive your health information, may not be required by privacy laws to protect it and may share your information with others without your permission, if permitted by laws governing them. All of these groups have been asked to keep your information confidential.

Questionnaires
You may feel uncomfortable answering questions about your medical history, education, occupation, and daily activities. You can choose not to answer questions that make you feel uncomfortable.

MRI
Some people are bothered by feelings of confinement (claustrophobia), and by the noise made by the machine during the test. You will be asked to wear earplugs or earphones while in the machine. You may not participate in this study if you have a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices. It is important for you to tell the MRI staff if you have had brain surgery for a cerebral aneurysm, or if you have implanted medical or metallic devices, shrapnel or other metal, such as metal in your eye.

New Findings
If we learn any significant new findings during the study that might influence your decision to participate, we will contact you and explain them.

Unknown Risks
We have described all the risks we know. However, because this is research, there a possibility that you will have a reaction that we do not know about yet and is not expected. If we learn about other risks, we will let you know what they are so that you can decide whether or not you want to continue to be in the study.

Are there possible benefits to me?

You will not experience any direct benefit personally from participating in this study. We hope you will participate because the study will generate important information about the treatment of mobility cognition and provide information needed for rehabilitation of mobility and cognitive disability. The information learned from this study may, in the future, help advance scientific knowledge about cognitive and mobility performance in aging.

What choices do I have other than participating in this study?

You can refuse to participate in the study.

Are there any consequences to me if I decide to stop participating in this study?

No. If you decide to take part, you are free to stop participating at any time without giving a reason. However, some of the information may have already been entered into the study and that will not be removed.

Can the study end my participation early?

We will not let you participate in the study any more if any unanticipated serious adverse events determined to be possibly, probably or definitely related to study procedures occur. In addition,

IRB NUMBER: 2014-3633
IRB APPROVAL DATE: 12/05/2016
IRB EXPIRATION DATE: 12/04/2017

your participation will end if the investigator or study sponsor stops the study earlier than expected.

CONSENT TO PARTICIPATE

I have read the consent form and I understand that it is up to me whether or not I participate. I know enough about the purpose, methods, risks and benefits of the research study to decide that I want to take part in it. I understand that I am not waiving any of my legal rights by signing this informed consent document. I will be given a signed copy of this consent form.

Printed name of participant	Signature of participant	Date
Printed name of the person conducting the consent process	Signature	Date

Appendix II-Adverse Event Log

IRB #: 2014-3633				PI: Helena Blumen								
Subject ID#	Date of Onset	Date Resolved	Outcome *	Seriousness**	Relationship***	Unanticipated (Y/N)	Action with Study Treatment****	Reportable to Sponsor (Y/N)	Date Sent to NIH & DSMB	Reportable to IRB (Y/N)	Date Sent to IRB	PI Initials and date
	Event Description:											
	Event Description:											
	Event Description:											
	Event Description:											
	Event Description:											
	Event Description:											

Key

***Outcome**
1. Resolved
2. Resolved with sequelae
3. Recovering
4. Not Recovered/Not Resolved
5. Fatal
6. Unknown

****Seriousness**
1. Fatal
2. Life-threatening
3. Serious
4. Not Serious

*****Relationship**
1. Definite
2. Possible
3. Probable
4. Unlikely

******Action with Study Treatment**
1. No Action
2. Interrupted
3. Discontinued

Serious Adverse Event (SAE) Report Form

Protocol Title: Motor Imagery: A Pilot Intervention for Improving Gait and Cognition in the Elderly.

Protocol Number: 2014-3633

Pt_ID: [Enter participant id]

1. SAE Onset Date: [enter SAE onset date] (dd/mmm/yyyy)

2. SAE Stop Date: [enter SAE stop date] (dd/mmm/yyyy)

3. Location of serious adverse event (e.g. at study site or elsewhere):
   [Enter location of SAE]

4. Was this an unexpected adverse event?
   ☐ Yes ☐ No

5. Brief description of participant with no personal identifiers:
   Sex: ☐ Female ☐ Male Age: [Enter participant age]

6. Adverse Event Term(s):

   [Enter adverse event terms]

7. Brief description of the nature of the serious adverse event (attach description if more space needed):

   [Enter brief description of the nature of the SAE]

8. Category of the serious adverse event:

   ☐ death – date [Enter death date](dd/mmm/yyyy)
   ☐ life-threatening
   ☐ hospitalization - initial or prolonged
   ☐ disability / incapacity
   ☐ congenital anomaly / birth defect
   ☐ required intervention to prevent permanent impairment
   ☐ other:[other category of SAE]

9. Intervention type (circle one):

   Motor Imagery training Visual Imagery training

10. Relationship of event to intervention:

- ☐ Unrelated (clearly not related to the intervention)
- ☐ Possible (may be related to intervention)
- ☐ Definite (clearly related to intervention)

11. Was study intervention discontinued due to event? ☐ Yes ☐ No

12. What medications or other steps were taken to treat serious adverse event?

[Medications or other steps were taken to treat SAE]

13. List any relevant tests, laboratory data, history, including preexisting medical conditions

[List any relevant tests, lab data, history, including preexisting medical conditions]

14. Type of report:

- ☐ Initial
- ☐ Follow-up
- ☐ Final

Signature of Principal Investigator: [Signature of PI] Date: [sign date] (dd/mmm/yyyy)