MOTOR INTERVENTION FOR MEMORY ENHANCEMENT (MIME)

Principal Investigators:

Joe Verghese, MBBS (contact PI) & Helena Blumen, PhD

[1]Departments of Neurology and Medicine, Albert Einstein College of Medicine, Bronx, NY.

Supported by:

The National Institute on Aging
R21AG057586

ClinicalTrials.gov Identifier: NCT03475316

Version 1.2
September 17 2018

1) Background/Significance:

Social dancing is a complex sensorimotor rhythmic activity integrating physical, cognitive and social elements with the potential to ameliorate a wide range of physical and cognitive impairments in older individuals at risk of Alzheimer's disease (AD) and related dementias. We reported that social dancers had a 76% reduced risk of dementia compared to non-dancers.[1] The few extant studies report that dancing stimulates multiple cognitive processes, including attention, processing speed, and executive function, but these discoveries were made in small samples, lacking control conditions, and did not investigate the underlying biological mechanisms.[2-6]

Executive function (EF) is an umbrella term for the management of cognitive processes, including working memory, reasoning, task flexibility, and problem solving that are central to planning, goal-directed action, and coordination of daily activities. Impairment of EF and related processes such as processing speed and attention is seen in normal aging as well as early in dementia, and is associated with difficulty in performing daily activities and increased risk of adverse events such as falls. Encouragingly, aerobic exercise is reported to enhance cognition, especially EF.[7, 8] Cognitively impaired seniors fall more,[9] and have higher prevalence and severity of balance and gait problems than cognitively intact fallers.[10-12] Given social dancing's multimodal cognitive and physical benefits; it may help maintain mobility and reduce falls in individuals at risk for dementia. In support, we reported that older social dancers had better balance and gait than non-dancers.[13]

We propose a 6-month pilot single blind, randomized clinical trial (RCT) comparing social dancing (ballroom dancing) versus active control (walking) in 32 older adults at high risk of dementia. Our **overall hypothesis** is that social dancing in cognitively vulnerable seniors will induce neuroplasticity that will enhance cognitive processes and improving everyday behaviors. Our **objective** for this pilot trial is to examine feasibility as well as obtain preliminary data on intervention effects (trajectory and asymptote) on EF to design a full-scale RO1.

Aim 1: Obtain preliminary data regarding feasibility and effects on cognition of social dancing in seniors at risk for dementia. Dementia at-risk status is defined as cognition lower than expected for age (see 2.B for justification and criteria); similar approach was used in recent lifestyle interventions trials with cognitive outcomes.[14-17] While preliminary studies support a possible cognitive benefit of dancing, most studies have not targeted older individuals at high risk for dementia, a highly prevalent group with faster rates of cognitive decline. We will, hence, establish **feasibility** of conducting social dancing intervention in seniors at risk for dementia (see **Table 1** for feasibility parameters).

We will track changes in a **composite EF score** derived from a battery of standardized (Digit symbol substitution test: DSST),[18], computerized (Flanker test),[19, 20] and cognitive-motor (Walking While Talking: WWT) tests to capture various facets of this broad domain. Composite cognitive scores were used to define outcomes in many recent RCTs.[21-23] We will administer tests at baseline, month 2, month 4, month 6 (end of intervention) and month 9 (3 months post-intervention) to determine **trajectory** (**as well as any asymptote) on improvement** in both groups that will help plan optimal duration for our full-scale RO1. These highly reliable EF tests were used to show exercise effects on cognition,[8, 24-27] and predict cognitive (dementia) and non-cognitive outcomes (falls).[28-31] The composite EF score helps overcome limitations of single EF tests.[21-23]

Aim 2: Explore functional and structural neuroplasticity for cognitive benefits of social dancing in seniors at risk for dementia. We will explore neuroplasticity in functional activation/deactivation and structural connectivity patterns as a function of social dancing (pre-post intervention). We will use **functional Magnetic Resonance Imaging (fMRI)** to investigate neuroplasticity in functional activation/deactivation patterns with our validated 'imagined WWT' task[32]- as well as with DSST and Flanker tests, which are responsive to physical interventions.[25] *We predict that compared to walking, dancing will result in greater intervention-related changes in functional activation of supplementary motor, anterior cingulate and prefrontal regions during imagined WWT, DSST and Flanker tests*.

To investigate neuroplasticity in structural connectivity patterns, we will use **diffusion-weighted imaging**, which are responsive to social dancing and physical interventions.[33, 34] We predict that compared to walking, dancing will result in greater intervention-related changes in structural connectivity patterns, including fornix and cingulum.

Social dancing appeals to older adults, has intrinsic value, is enjoyable, and has high potential for sustainability. This R21 proposal is novel and high risk, but will provide the evidence base to develop a

definitive full-scale RCT to support or refute prescription of social dancing to prevent cognitive decline in older adults at high risk of AD and related dementias.

2) Study Design

Overview and Design. We propose a pilot single blind RCT of social dancing versus walking in 32 dementia at-risk seniors (16/group). For Aim 1, outcome is change in EF composite score measured with a comprehensive battery of conventional (DSST), computerized (Flanker test) and cognitive-motor (WWT) EF tests assessed at baseline, month 2, month 4, month 6 (immediate post-intervention), and 3 months post-intervention to derive trajectories to inform design of future R01. Feasibility is assessed through metrics described in Table 1. For Aim 2, outcome is neuroplasticity measured using our *validated fMRI iWWT protocol, DSST and Flanker Tests, and white matter integrity.*

a) **RECRUITMENT AND SCREENING:** We will enroll 32 dementia at-risk seniors over 2 years. **Our sample size is not based on demonstrating clinical efficacy but to obtain preliminary data and feasibility to plan our RO1**. We will contact a random sample of individuals age 65 and over identified from local population lists as well as from the large clinical population in our health system. Both sources were used to recruit ~3000 participants for our aging studies.[35-37] A letter explaining our study is followed by a telephone call. Those expressing interest on the telephone are screened with Memory Impairment screen **(MIS)**[38] and **AD-8**[39] to establish dementia-risk status. Potential recruits will be invited for an in-person visit where final eligibility is determined. Written consent and screening is at our research center. **An independent DSMB will be constituted prior to the start of the study.**

b) **ELIGIBILITY CRITERIA.** Our target population is dementia at-risk seniors. Patients will be evaluated by research assistants followed by the study clinician to assess eligibility for the trial.

   i) Inclusion criteria: **1**) Age 65 and older. **2**) 'At-risk for dementia' status defined as meeting cutscores on either MIS (≤ 6) or AD-8 (≥1) tests. The MIS is a 4-item dementia screener developed in our Bronx population.[38, 40] MIS accounts for various educational levels.[41-44] The AD-8 is a 2-minute screener with high validity for detecting dementia.[39, 45] AD-8 is less educationally biased as it does not test patients on acquired learning. AD-8 is culturally neutral as it focuses on changes in basic activities in which everyone engages. Both tests correlate highly with dementia pathology.[46, 47] We used these 2 screeners to enroll 3000 participants in 3 NIH funded studies.[38, 48, 49] We decided against MCI as a criterion, as its prevalence is low (<12% in our community-based cohort[50]); limiting generalizability. We examined validity of our **'dementia at-risk'** definition in 543 older adults in the Einstein Aging study;[48] 176 met dementia at-risk criteria (prevalence 32%). Over a mean follow-up of 1.5 years, 'dementia at-risk' status predicted incident cognitive impairment (any of MCI, Motoric cognitive risk syndrome (MCR)[51, 52] or dementia) (HR adjusted for age, sex, education and illnesses 2.0, 95%CI 1.1-3.8). Hence, our definition captures a high-risk yet highly prevalent group. **3**) Sedentary: exercises less than the CDC recommended level of 150 min moderate intensity activity/week.[53] **4**). Agree to neuroimaging: more efficient to enroll those who also meet imaging criteria for this pilot. We recruited >100 participants in the last 2 years for various imaging studies.

   ii) Exclusion criteria: **1**) Active medical or major psychiatric illnesses. **2**) Musculoskeletal/cardiovascular mobility limitations. **3**) Competitive dance or regular social dance (>1/month). As seniors may occasionally dance at social events (but not at dose for cognitive benefits), excluding all seniors who ever danced is not practical. **4**) Presence of dementia[106] (telephone or in-house evaluation). **5**) Standard imaging exclusions. It will not be feasible to obtain MRI or other biomarkers to screen and enroll participants. However, the pre-intervention MRI for Aim 2 will allow us to stratify the at-risk group into those with or without brain pathology (e.g. hippocampal atrophy[54]) for exploratory analyses.

c) **RANDOMIZATION.** Eligible participants are randomized for interventions at initial visit, stratified by gender and age (< or >80 years). Equal number of men and women will be enrolled. Group assignment is generated by Dr. Wang, who is not involved in subject testing or interventions. She will generate an encrypted file with the randomization order to assign participants to the study arms. She will be the only one with access to the list. To avoid attrition following enrollment, we will not wait to recruit all participants to start the interventions but will have rolling admission into the dance and walking classes.

i) **Social Dance (intervention arm):** 90-min dance sessions twice weekly for 6-months. The session includes warm-up, dance and cool down. The program includes Foxtrot, Waltz, and Latin dances. The choice of multiple dances is pragmatic since it mirrors the choice offered in senior centers and avoids tedium of only doing one dance form. Intensity will not be manipulated to mimic exercise training as in aerobic dance classes. Dance instructors are experienced in teaching seniors (see LOS from USA Dance). Progression to new dances will be gradual and take into account balance, cardiac and cognitive demands. Methodological structure is the same for all sessions. The instructor will demonstrate the dance sequence. Participants warm up with gentle stretches. The instructor will repeat dance sequence several times and the participants will try to reproduce it along with the instructor, until sequence is learned. When participants execute the dance sequence satisfactorily, they will reproduce it along with the music.
   (a) **Duration (6 months), frequency (2/wk) and intensity** based on earlier dance studies and pragmatic considerations. A review of dance interventions for various health outcomes (including cognition) concluded that dance programs should provide a minimum of one 45-minute session per week for 6 weeks (lower than our study).[55] The dose of exercise in both dancing and walking arms is higher than the CDC recommended exercise dose.[53]
   (b) **Pairing** at dances is at random and the instructor will ensure participants rotate partners.
   (c) Performance monitoring: Intensity measurement via **accelerometers** and cardiac monitoring during dance lessons.
   (d) Dancing integrates **physical, cognitive and social elements**. Our interventions may also improve **mood, self-esteem, and self-efficacy.**[56, 57] We will measure each of these components. However, a detailed mechanistic examination of which dance components contribute to cognitive benefits is beyond the scope of this pilot study, and will be done in our future RO1. Randomization is also a powerful tool to address biases due to confounders.

ii) **Walking (active control):** We completed a pilot walking study in frail seniors supporting feasibility.[58] Participants meet twice weekly for 6-months matching frequency and intensity in the dance group. Recent reviews report minimal to no cognitive benefits from exercise programs in cognitively impaired seniors.[26, 59-61] Walking exercises was reported in another review to show modest EF benefits in healthy but not cognitively impaired seniors (our focus).[62] Dr. Verghese was part of the LIFE study that reported that moderate-intensity physical activity program (walking) in sedentary seniors did not improve global or domain-specific cognitive function (including EF) compared to those in a health education program.[63] A recent review by the National Academy of Medicine concluded that the evidence was encouraging but inconclusive regarding cognitive benefits of exercise, and further research was required.[64]
   (a) **Procedure:** The protocol is based on American College of Sports Medicine[65] and American Heart Association[66] recommendations for seniors. Additional details are in our published report.[58] Briefly, each session starts with 5-10 minutes of warm-up walking at comfortable speed. Speed is gradually increased to the level at which participants felt it is 'somewhat hard' (12-14 Borg scale[67, 68]) for two 35 minute sessions with breaks in between followed by 5-10 minute cool down period (total 90 min to match dance group). Training interval is gradually increased over the first 2 weeks.
   (b) **Environment:** The indoor environment that is less subject to weather and other barriers when walking outdoors.
   (c) **Social interactions:** To match the social aspect of dance, treadmills will be arranged in clusters. The proportion of men to women is the same as in the dance group. Music will be played during treadmill sessions to minimize variability.

d) **OUTCOMES Aim 1 (Cognition)**: As EF includes multiple cognitive processes; a single test is not sufficient. We will examine a **composite EF score** by summing standardized scores on the 3 tests. Composite cognitive scores were used in many RCTs.[21-23] We will also compare trajectories in individual tests to gain insights into study design of our full-scale RO1. Study outcomes will be assessed at baseline, month 2, month 4, post-intervention (end of month 6), and 3 months post-intervention (month 9).

i) **Digit Symbol Substitution test (DSST)** is a timed test that assesses speed of processing, visuo-spatial attention and EF. DSST predicts cognitive (dementia) and non-cognitive outcomes (falls). DSST is amenable to exercise.[69]

ii) **Flanker Test** is in the NIH toolbox.[19, 20] It measures attention and inhibitory control. The Flanker test was used to demonstrate exercise effects on EF.[8, 70]

iii) **Walking While Talking test (WWT)** is an EF-dependent everyday behavior measure developed by our group.[29, 30] Dual-tasking assessed by WWT is a defined facet of EF,[36, 71] and associated with increased prefrontal activation.[72] Participants walk on an instrumented walkway for 2 trials reciting alternate letters of the alphabet.[73] See our published papers for WWT procedures.[28-30, 72-74] WWT has excellent test-retest and inter-rater reliability.[28-30]
Blinding: While double-blinding both subjects and testers is not feasible, the following steps (besides randomization) are included: A. Selection bias reduced by concealing treatment allocation until subject enrolled.[75] B. Outcome is an objective endpoint and not subjective reports.[75] C. Dance and walking groups meet non-overlapping times. D. Each aspect of the RCT is supervised independently: interventions (Ayers), assessments (Verghese) and imaging (Blumen). E. Participants/staff instructed not to disclose group assignment or interventions.
Learning effects: We will utilize 4 complementary approaches to attenuate practice effects[76]: (1) Practice pre-baseline to reduce task familiarity effects; (2) Item-specific driven improvements minimized by using tasks with multiple similar items and standardized encoding; (3) We developed alternate forms for the WWT task,[74] and alternate forms of the DSST are available; and (4) use of control group.

e) **OUTCOME Aim 1 (Feasibility)**: Metrics below will identify barriers and refine design of our full scale RCT.[77]

Metric	Measurement	Comments
Recruitment	Analyze recruitment sources by PI.	Monitor to improve recruitment rates and identify barriers.
Implementation	Proportion completed successfully. Observe all phases to find bottlenecks	Compare completion rates by education. Testers feedback on non-completion and other barriers to develop solutions.
Retention	Retention rates to be reported. 20-25% attrition common in high-risk samples.	Dancing program implemented in frailty and dementia.[6, 15, 78-82] **Make-up sessions** provided. **Transportation and snacks** will be provided. **Dose/frequency** accounted in analyses. **Compensation** at $10/session consistent with IRB guidelines, and has been reported to promote adherence in exercise programs.[83]
Safety	Staff monitoring/DSMB oversight	DSMB and safety procedures
Practicality	PI, staff and subject observations	Extent to which intervention can be done with available resources
Acceptability	Post-study interviews of participants	Help refine RO design and enhance generalizability
Reporting	Report pilot study design and results	CONSORT guidelines will be followed: See ref[84] for details.

f) **OUTCOME Aim 2 (Neuroplasticity):** Encouragingly, pilot dance intervention trials have shown neuroplasticity with similar or smaller samples (12 to 48) over 6-months or less,[3, 85-89] including the FAST study[34]. Our primary neuroimaging measure is task-based fMRI because functional brain changes are a more sensitive biomarker of AD than gray matter volume. Our exploratory neuroimaging measure is DTI because it has been shown to be sensitive to aerobic exercise[33] and social dancing intervention.[34, 90] Furthermore, functional and structural changes may occur before the emergence of cognitive symptoms in dementia.[91-95]

i) **Task-Based fMRI (Primary):** We will examine functional activation/deactivation changes pre-post intervention in both groups during an imagined WWT (iWWT) protocol developed by our group.[32]

The iWWT is strongly correlated with actual WWT performance, and engages a distributed network of brain regions, including cerebellar, precuneus, supplementary motor and other prefrontal regions.[32] The iWWT protocol involves 5 repeated blocks of imagined walking (iW), imagined talking (iT), and iWWT, and takes 12 minutes to administer. We will also examine functional activation/deactivation changes during DSST and Flanker tests. We will use a DSST task adapted for use in an fMRI environment and validated in older adults.[96] This task takes about 10 minutes and has 2 practice and 5 testing blocks, with 18 items each (total 95 test items). We will also use a Flanker task optimized for fMRI environment, with a 4-minute practice block and three 4-minute test blocks for a total of 120 test items (60 congruent, 60 incongruent) presented with jittered inter-stimulus intervals (4-8 sec).[97] *We predict that dance will increase activation in supplementary motor, anterior cingulate and other prefrontal cortex regions during the iWWT, DSST and Flanker tasks to a greater extent than walking*. We expect treadmill training to increase activation in the somatosensory cortex and the cerebellum. Jovancevic et al noted differences in activation in response to DSST on fMRI in 5 women (mean age 55) in the left middle frontal gyrus, right inferior parietal lobule, and left angular gyrus following a 6-week video dance program.[98]

ii) ***Diffusion-Weighted Imaging (exploratory).*** We propose to examine **pre-post changes in structural connectivity** as a function of social dancing. Structural changes in white matter integrity have been observed following physical and social dancing interventions.[34] Based on these initial findings, we propose to monitor structural changes in white matter integrity (fractional anisotropy) using Tracts Constrained by Underlying Anatomy (TRACULA).[99] *We expect that dance will change white matter integrity in fornix, cingulum and over frontal integrity to a greater extent than walking.*

g) **Other measures:** We will collect other measures to explore the broader impact of dancing. Given R21 space limits, these measures are summarized in Table 1. We have administered 3-hour test batteries to over 3000 participants in our other aging studies with minimal attrition.

Table 1. Summary of secondary outcomes, covariates and process measures

Domains	Tests and procedures (refs)	Description (0,2,4,6, 9 months)	Time
Clinical	Study clinician evaluation[35, 100] of neurological and musculoskeletal systems including gait	Standardized examination and CDR rating. Clinicians Global Impression of Change[101, 102]	30 m
Cognitive	Neuropsychological battery[103]	Test of multiple cognitive domains.[103]	60 m
	CHAMPS[104]	Lifestyle changes baseline and post-intervention	15 m
	Gait variables	GAITRite	10 m
	Balance	Unipedal stance, trunk sway (covariate)	5 m
	ADL scales	Monitor changes in function	5 m
Mood	Geriatric depression scale[105]	Depressive symptoms (covariate)	5 m

3) DATA AND SAFETY MONITORING PLAN:

1.0 Particpants Safety

1.1 Potential Risks and Benefits for Participants

Potential Risks: We do not expect any serious adverse events during these non-invasive tests and training programs of attention and executive function. Answering health questionnaires and mental state examinations involve minimal psychological, social, or other risks.

Dance classes will be taught by certified dance instructors (with experience teaching seniors) at varying levels of complexity and the progression during the intervention period will be gradual. Progression to new dances will take into account the balance challenge, cardiovascular demand, degree of flexibility, coordination and cognitive demand. The instructor will ensure that the programs will not be manipulated to mimic exercise training as in aerobic dance classes.

The treadmill training walking intervention protocol will be based on recommendations of the American College of Sports Medicine (ACSM)[106] and American Heart Association (AHA) for older adults. A gradual approach will be applied to increase exercise intensity in participants with a low baseline level of physical activity and who

may be unfamiliar with treadmill walking. Pulse and blood pressure will be assessed before and after each session to assure that the values are not deviated by 10 or more from the values of initial assessment for pulse and systolic blood pressure. During exercise, participants are monitored with the subjective Borg scale[68] every 5 minutes and heart rate is tracked by a physical therapist. Participants are encouraged to increase the training velocity if the subjective rating of exercise intensity is low (fairly light, Borg score <12). The treadmill speed will be reduced or exercise aborted if there are any untoward symptoms such as cardiovascular symptoms or excessive fatigue. Heart rate will be measured during the break between training periods and the second period will only be initiated after the value is below the 70% of estimated maximum heart rate.[106] Similar procedures will also be followed in the dance intervention group.

Potential Benefits: Our previous experience, the non-invasive nature of most proposed procedures, the widespread prevalence of dance and exercise programs in the community, the general acceptance by practicing physicians of the procedures to be used, and the close supervision and monitoring of the subjects all minimizes the potential risks. Both dancing and walking may improve physical fitness, and involve minimal risks to the participant. Early diagnosis and treatment of disorders discovered as a result of screening done in these studies may impact beneficially on their health. In addition, understanding of the role of physical, mental, and social activities in ameliorating age-related cognitive decline could provide important insights into the aging process and age-related diseases that could ultimately have a positive impact on the length and quality of life for study subjects.

1.2 Adverse Event and Serious Adverse Event Collection and Reporting

Adverse Events (AEs): Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), 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. AEs encompass both physical and/or psychological harms.

Serious Adverse Events (SAEs): An adverse event that meets any of the following criteria:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires prolonged hospitalization
- Causes persistent or significant disability or incapacity
- Is another condition which investigators judge to represent significant hazards

Unanticipated Problem: Any event, deviation, or problem, that meets ALL of the following criteria:

a. Unexpected (see Expectedness definitions below) in terms of nature, severity, or frequency given (a) the research procedures that are described in the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
b. Related or possibly related (see Relatedness definitions below) to participation in the research; and
c. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Adverse Events versus Unanticipated Problems:

- The vast majority of adverse events occurring in human subjects are not unanticipated problems.
- A small proportion of adverse events are unanticipated problems.
- Unanticipated problems include other incidents, experiences, and outcomes that are not adverse events.

Reporting: All AEs are collected on an Adverse Event Form in electronic format and recorded in the RedCap database. All AEs experienced by the participant from the start of intervention through the end of the study intervention period (6-months) will be reported to the Safety Officer (SO) and NIA in Safety Reports sent twice a year.

Unanticipated Problems Reporting: Unanticipated problems will be reported within 48 hours to NIA Program Officer and to the SO and will include a corrective plan and measures to prevent reoccurrence.

SAE Reporting: When SAEs occur that are unanticipated (i.e., events other than those described in the protocol, consent form and DSMP), and that are related to the intervention, they will be reported to NIA Program Officer and to the SO within 48 hours of study's knowledge of the SAE. The expedited report will be followed by a detailed, written SAE report as soon as possible. Follow up information may be required and asked for by the SO or the NIA.
Any anticipated AEs and SAEs will be reported in the bi-annual reports to the SO and NIA Program Officer.

Relatedness:
The potential event relationship to the study intervention and/or participation is assessed by the site investigator. The comprehensive scale to categorize an event is listed below:

- *Definitely Related*: The AE is clearly related to the investigational procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
- *Possibly Related:* An AE that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
- *Not Related:* The AE is clearly not related to the investigational procedure - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

Expectedness:
AEs must be assessed as to whether they were expected to occur or unexpected, meaning not anticipated based on current knowledge found in the protocol and the consent form. Categories are:

- *Unexpected:* The nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol or consent form.
- *Expected:* The event is known to be associated with the intervention or population under study.

Classification of AE Severity:

- *Mild:* Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient – i.e. no doctor visit or medical treatments were required.
- *Moderate:* Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning – i.e. minimal medical treatment was needed, possible doctor visit or physical therapy.
- *Severe:* Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating – i.e. medical attention was required, possible hospitalization.

Note: Severity is not synonymous with seriousness. SAEs are a subset of the reported AEs.

1.3 Protection Against Study Risks

Informed Consent Process:

1) The study interviewer will conduct the initial telephone-screening interview. Study interviewers will conduct an oral consent process over the telephone prior to asking any study related questions. Following the interview, potential subjects will be invited for further in-person evaluations. Study consent, evaluations, enrollment, and in-person interventions will be done at our research center.
2) The consent process will take place prior to initiating any study related evaluations or interventions and will inform a potential participant about the study. It indicates the participation is voluntary and he/she has the

right to stop at any time. Risks are enumerated in the informed consent form and described orally during the consent process.

Protection Against Risks:
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 participants express physical or mental tiredness or discomfort during any of the assessments or training procedures, the procedure will be terminated immediately. Drs. Verghese or Blumen will be available onsite or by cellular telephone at all times to address any safety concerns or clinical issues during the interventions.

i) Falls: Recent dance interventions using similar protocols in cognitively healthy and impaired participants report no or low rate of falls during dance sessions.[34, 107] The rate of falls was <1% among 5,500 participants from 11 diverse physical activity interventions participating in a trans NIH collaborative known as the Behavior Change Consortium. [108] A Cochrane review of interventions to promote physical activity reported that of the 8 physical exercise trials with information on adverse events, fall rates were only significantly different from controls in 1 out of these 8 studies.[109] Another Cochrane review that addressed the role of exercise programs (mostly walking but no dancing interventions) for people with dementia concluded that exercise was not harmful though the cognitive benefits were not proven.[110]

   Despite the low fall rate in these previous reviews, we take safety seriously, and have instituted a number of procedures to minimize fall risk in our pilot trail. Both the dance and walking groups are closely supervised. The groups are small so that instructors can pay attention to the participants, and intervene if balance problems are noted during the session. Participants will be instructed to wear sports shoes with good grip soles. Footwear and clothing will be inspected by the instructors prior to the start of sessions to ensure that they are appropriate for both intervention activities. Wooden complaint flooring used in our dance space is associated with lower risk of fall injury than hard flooring, though not as low as carpeted wooden flooring.[111, 112] However, carpets were reported to be associated with falls in a Cochrane review of studies.[113] It would not be practical to have safety harnesses on participants in the dance group, and this has not been the practice in the multiple previous dance intervention studies. Participants in both groups will be frequently asked about their comfort/discomfort levels. The intervention will be stopped if participants report any unsteadiness or balance problems, and will be examined by the study clinician. Our research center is located within a hospital complex, and referral to primary care physician or emergency room will be done as required.

ii) Musculoskeletal injuries: Given the sedentary nature of our participants, musculoskeletal symptoms or injuries may occur. Previous studies suggest that though musculoskeletal complaints are common in physical activity interventions, the majority of these issues are mild in nature.[108] Both the dance and walking groups are closely supervised. The groups are small so that instructors can pay attention to the participants. Participants are frequently asked about their comfort/discomfort levels including the Borg scale. The intervention will be stopped if participants report any discomfort, and will be examined by the study clinician. Our research center is located within a hospital complex, and referral to primary care physician or emergency room will be done depending on the severity of the problem.

iii) Neuroimaging results: Dr. Blumen will be immediately contacted in the event that an acute imaging finding requiring immediate action is discovered. She will review the reports of all MRI studies. Participants with normal studies will receive a letter to this effect. In the event that a non-urgent significant abnormality is discovered, Dr. Verghese will contact the participant by telephone to discuss the findings and advise that appropriate follow-up be obtained. A follow-up letter summarizing the discussion will be sent to the participant. If the participant wishes, the report will be sent to the primary care doctor.

iv) MRI Safety program: A comprehensive MRI safety program is in place including secure access to the MRI suite and ongoing surveillance for effectiveness of the safety program. A board certified subspecialty neuroradiologist will review each MRI scan for pathology and confirm that there are no clinically significant findings for any of the participants. All data are archived in the Picture Archival and Communication System (PACS) and if needed can be archived in DVD-R media and stored in a locked cabinet.

2.0 Data and Safety monitoring
All data collection in this clinical trial will be monitored to assure subject comfort, safety, and confidentiality. The clinical trial protocols, data collection instruments, subject recruitment letters, and consent forms will be reviewed and approved by the IRB. The NIA will also approve the creation and structure of the DSMP.

The PIs will be responsible for ensuring participants' safety on a daily basis. The SO will advise the NIA Program staff and the PIs regarding participant safety, participant risks and benefits, scientific integrity and ethical conduct of a study.

2.1 Frequency of Data and Safety Monitoring
Safety Reports will be sent to the SO twice a year and will include a detailed analysis of study progress, data and safety issues.

All deaths will be reported within 24 hours of study's knowledge of death. The report of death will be submitted to the NIA Program Officer and to the SO. When SAEs occur that are unanticipated and that are related to the intervention, they will be reported to NIA Program Officer and to the SO within 48 hours of the study staff's knowledge of SAE. The summary of all other SAEs will be reported in Safety Reports bi-annual reports.

2.2 Content Safety Report
At bi-annual intervals, the study team will prepare Safety Reports to be reviewed by the SO and NIA for recommendations for or against the trial's continuation, as well as any modification to the study. An open (i.e., not segregated by treatment) and closed (i.e., coded by treatment assignment (social dancing or treadmill walking)) report will be submitted to the SO. The contents of the reports will focus on patient accrual and demographics, data completeness, and other study performance measures. The closed report will additionally divide study participants according to treatment comparing participant demographics and baseline characteristics, rates and reasons for treatment discontinuation and loss to follow-up, and rates of serious adverse events. In addition, the PIs may prepare a section of the report addressing concerns they anticipate will have regarding the conduct of the study.

The reports will include:

- Monthly and cumulative accrual
- Baseline characteristics, overall and by treatment group
- Summary of completeness and quality of data collection forms
- Status of enrolled patients, 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
- Sample size assumptions
- Outcome rates, overall and by treatment group along with monitoring boundaries for efficacy and futility
- 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 adverse events

Only the closed report will include the comparisons by treatment group.

2.3 Safety Officer Description and Affiliation
The following individual has accepted position as SO. The SO will be reviewed and approved by the NIA. Should there be any questions regarding the independence of the SO, it will be addressed and corrected if necessary at that time.

Name: Preeti Raghavan, M.D.
Title, Organization: Associate Professor of Rehabilitation Research, Department of Rehabilitation Medicine, NYU Langone Hospital; Vice Chair for Research, Department of Rehabilitation Medicine, NYU Langone Hospital; Director, Division of Motor Recovery Research, NYU Langone Hospital

Brief Description of qualifications/reason for role as SO:
Dr. Raghavan specializes in rehabilitation for patients recovering from stroke and traumatic brain injuries, as well as people with neurological conditions. She also conducts research to investigate how neurological injuries affect motor skills in the upper extremities. Her experience in these roles has provided her with the qualifications and clinical expertise necessary to serve as the SO on this clinical trial involving complex sensorimotor activity.

2.4 Conflict of Interest for the SO
The SO has no direct involvement with the study investigators or intervention, and will sign a Conflict of Interest Statement which includes current affiliations, if any, with pharmaceutical and biotechnology companies (e.g., stockholder, consultant), and any other relationship that could be perceived as a conflict of interest related to the study and / or associated with commercial interests pertinent to study objectives.

2.5 Protection of Confidentiality
Data will be presented in a blinded manner in the open report for the SO, data and discussion are confidential. Participant identities will not be known to the SO.

2.6 SO Responsibilities
It is the responsibility of the SO to:
- 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.

4) Study Population
a) We will enroll 32 dementia at-risk seniors over 2 years. Our sample size is not based on demonstrating clinical efficacy but to obtain preliminary data and feasibility to plan our RO1.
b) General inclusion criteria:

i) Adults aged 65 and older. The age criterion is intended to maximize observed rates of age relate decline in executive function.
ii) At-risk for dementia defined as meeting cutscores on either the **MIS (≤ 6)[38] or AD-8 (≥ 1)**[39] tests administered by telephone.
iii) Plan to be in area for next year or more.
iv) Able to speak English at a level sufficient to undergo our interventions and cognitive assessment battery.
v) Willing to complete an MRI (exclusions relevant to neuroimaging are described below). Given our small sample size and budget limits of the R21 format we wanted to maximize study and budgetary efficiency by enrolling participants who not only agree to the study interventions but also agree to undergo neuroimaging.

c) General exclusion criteria (one or more criteria):
i) **Presence of dementia** based on telephone interview, previous established physician diagnosis of dementia or dementia diagnosed by Dr. Verghese at initial visit.
ii) **Serious chronic or acute illness** such as cancer (late stage, metastatic, or on active treatment), chronic pulmonary disease on ventilator or continuous oxygen therapy or active liver disease. Individuals with recent cardiovascular or cerebrovascular event (MI, PTCA, CABG, or stroke) will not be excluded if they meet above inclusion criteria. *Many of these chronic conditions are very common in older adults. Hence, mere presence of these conditions will not be used to exclude subjects if well controlled or of mild severity and if subjects are able to complete the interventions*.
iii) **Mobility limitations solely due to musculoskeletal or cardiovascular conditions that prevent participation in the intervention programs.** Prevalence of arthritis is ~60% in the Einstein Aging Study[35], so mere presence of disease will not be used to exclude subjects if they can complete the mobility tasks. Screening clinician will assess and document presence of musculoskeletal diseases.
iv) Any **medical condition or chronic medication use** (e.g., neuroleptics) in the judgment of the screening clinician that will compromise safety or affect cognitive functioning.
v) **Terminal illness** with life expectancy less than 12 months.
vi) **Progressive, degenerative neurologic disease** (e.g., Parkinson's disease or ALS) diagnosed by Dr. Verghese and as per medical history that will restrict mobility and participation in interventions.
vii) **Severe auditory or visual loss**: Vision is screened using a Snellen chart by the psychological assistant. Also, the neurologist tests visual fields using confrontation perimetry and near vision using Jaeger test types. Significant loss of vision is defined as corrected vision (using reading glasses) less than 20/400 on the Snellen chart with both eyes and inability to read any test sentence on the Jaeger test card with both eyes. Hearing is initially evaluated as part of the screening telephone interview. Subjects who attend the clinic visit will be excluded only if they are unable to follow questions asked in a loud voice (even with hearing aid in place).
viii) **Active psychoses or psychiatric symptoms** (such as agitation) noted during the clinic visit that will prevent completion of study protocols. Past history of these symptoms or presence of psychiatric illness not used as exclusion criteria.
ix) **Either participation in competitive dancing or recreational dancing at a frequency >1/month in the past six months.** As seniors may dance at social events (but not at doses or frequency to have cognitive benefits), excluding all seniors who ever danced is not practical. We will examine all reports of participation in cognitive enhancement programs (as this covers a wide range of activities) to judge inclusion.
x) **Participation in other interventional study that overlaps with intervention period of this study.**

d) Specific Neuroimaging considerations: Additional exclusions relevant to neuroimaging include the presence of any surgically implanted metallic devices, such as aneurysm clips or pacemakers that would be a safety contraindication for MRI. Subjects with large amounts of dental or surgical hardware in the head and neck will be excluded because magnetic susceptibility effects will lead to severe image artifacts in these subjects' images. Due to the confined space of the MRI magnet, subjects with a known history of claustrophobia will also be excluded as will subjects with weight >350lbs or waist circumference >55 inches. Conditions that may confound the association between neuroimaging

cognition and mobility (normal pressure hydrocephalus or severe head trauma) will be excluded from analyses. We estimate that the prevalence of these conditions is very low based on other aging studies. Additional incidental findings that may be seen with a low prevalence in the elderly may include vascular anomalies or tumors. All scans will be reviewed by board-certified neuroradiologists. Abnormal results will be communicated to Dr. Verghese who will initiate follow-up with subjects and their physicians as has been our established procedure in other studies based in our center.

e) 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.

f) **Research material** obtained from human subjects will be the results of clinical and neuropsychological testing obtained from study assessments and telephone interviews. The subject and their primary care physician will be informed of all clinical results that are relevant to patient care. Phenotypic data will also include results of MRIs, questionnaires, and body composition tests.

5) Participant Recruitment

a) To achieve our study aims 32 participants will be recruited at random from commercially available lists of Bronx and Westchester County residents over the two-year funding period. We will also recruit participants from the Montefiore Medical Center Geriatrics and primary care clinics that have over 20,000 visits by patients, age 65 and older. We have had experience using both the community and clinic sources to recruit over participants for various aging studies in the past 10 years. Once telephone contact is achieved and the interview is complete, we assume that there will be a 20% loss due to lack of interest in the study and failure to meet general eligibility requirements and an additional 10% failure on the cognitive instruments (MIS or AD-8). There is an additional 10% loss in the remaining sample due to failure to meet eligibility requirements. Using telephone based recruitment instruments enables us to minimize loss due to not meeting criteria on in-person assessments.

A concern is that there might be attrition between the enrollment and start of the intervention in this high-risk group. To minimize this possibility, we will institute a rolling admission policy that we have successfully used in our ongoing cognitive remediation study.[114] A different dance is taught in each session. As soon as we have enrolled a pair into the dance group, they will start the dance program in the next available day. This modified rolling admission policy will help reduce delays between enrollment and the start of the dance intervention. In the walking group, the intervention is individualized though participants exercise in groups on the treadmill to simulate the social nature of dancing. Hence, participants randomized to the walking arm can join the walking program at any point during the 2-year study period. Participants randomized to the walking group will also start the program at the next available day.

6) Informed Consent

a) The study interviewer will conduct the initial telephone-screening interview. Potential subjects will be invited for further in-person evaluations. Study evaluations, enrollment, and in-person interventions will be done at our research center. Dr. Verghese and the research assistant and will diagnose and exclude cases following clinical and neuropsychological testing.

b) **Compensation** at $10/session consistent with IRB guidelines will be provided to participants. An additional $25 will be provided to participants for completing each MRI.

7) Risk/Benefit

a) **Potential risks:** We do not expect any serious adverse events during these non-invasive tests and training programs of attention and executive function. Answering health questionnaires and mental state examinations involve minimal psychological, social, or other risks.

i) Dance classes will be taught by certified dance instructors (with experience teaching seniors) at varying levels of complexity and the progression during the intervention period will be gradual. Progression to new dances will take into account the balance challenge, cardiovascular demand, degree of flexibility, coordination and cognitive demand. The instructor will ensure that the programs will not be manipulated to mimic exercise training as in aerobic dance classes.

ii) The treadmill training walking intervention protocol will be based on recommendations of the American College of Sports Medicine (ACSM)[106] and American Heart Association (AHA) for older adults. A gradual approach will be applied to increase exercise intensity in participants with a low baseline level of physical activity and who may be unfamiliar with treadmill walking. Pulse and blood pressure will be assessed before and after each session to assure that the values are not deviated by 10 or more from the values of initial assessment for pulse and systolic blood pressure. During exercise, participants are monitored with the subjective Borg scale[68] every 5 minutes and heart rate is tracked by a physical therapist. Participants are encouraged to increase the training velocity if the subjective rating of exercise intensity is low (fairly light, Borg score <12). The treadmill speed will be reduced or exercise aborted if there are any untoward symptoms such as cardiovascular symptoms or excessive fatigue. Heart rate will be measured during the break between training periods and the second period will only be initiated after the value is below the 70% of estimated maximum heart rate.[106] Similar procedures will also be followed in the dance intervention group.

Since there are no significant risks associated with the procedures, this study is justified because useful new scientific knowledge will be obtained.

b) **Protection against risk:** 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. Verghese, Blumen or the supervising investigator for each arm will be available onsite or by cellular telephone at all times to address any safety concerns or clinical issues during the interventions.

i) Fall safety: Recent dance interventions using similar protocols in cognitively healthy and impaired participants report no or low rate of falls during dance sessions.[34, 107] The rate of falls was <1% among 5,500 participants from 11 diverse physical activity interventions participating in a trans NIH collaborative known as the Behavior Change Consortium. [108] A Cochrane review of interventions to promote physical activity reported that of the 8 physical exercise trials with information on adverse events, fall rates were only significantly different from controls in 1 out of these 8 studies.[109] Another Cochrane review that addressed the role of exercise programs (mostly walking but no dancing interventions) for people with dementia concluded that exercise was not harmful though the cognitive benefits were not proven.[110]

Despite the low fall rate in these previous reviews, we take safety seriously, and have instituted a number of procedures to minimize fall risk in our pilot trail. Both the dance and walking groups are closely supervised. The groups are small so that instructors can pay attention to the participants, and intervene if balance problems are noted during the session. Participants will be instructed to wear sports shoes with good grip soles. Footwear and clothing will be inspected by the instructors prior to the start of sessions to ensure that they are appropriate for both intervention activities. Wooden complaint flooring used in our dance space is associated with lower risk of fall injury than hard flooring, though not as low as carpeted wooden flooring.[111, 112] However, carpets were reported to be associated with falls in a Cochrane review of studies.[113] It would not be practical to have safety harnesses on participants in the dance group, and this has not been the practice in the multiple previous dance intervention studies. Participants in both groups will be frequently asked about their comfort/discomfort levels. The intervention will be stopped if participants report any unsteadiness or balance problems, and will be examined by the study clinician. Our research center is located within a hospital complex, and referral to primary care physician or emergency room will be done as required. Our safety experience in this pilot trial will inform the design and conduct of our full scale RO1.

ii) Musculoskeletal injuries: Given the sedentary nature of our participants (new criterion included as suggested by reviewer), musculoskeletal symptoms or injuries may occur. Previous studies suggest that though musculoskeletal complaints are common in physical activity interventions, the majority of these issues are mild in nature.[108] Both the dance and walking groups are closely supervised. The groups are small so that instructors can pay attention to the participants. Participants are frequently asked about their comfort/discomfort levels including the Borg scale. The intervention will be stopped

if participants report any discomfort, and will be examined by the study clinician. Our research center is located within a hospital complex, and referral to primary care physician or emergency room will be done depending on the severity of the problem.

iii) Neuroimaging results: Dr. Blumen will be immediately contacted in the event that an acute imaging finding requiring immediate action is discovered. She will review the reports of all MRI studies. Participants with normal studies will receive a letter to this effect. In the event that a non-urgent significant abnormality is discovered, Dr. Verghese will contact the participant by telephone to discuss the findings and advise that appropriate PMD follow-up be obtained. A follow-up letter summarizing the discussion will be sent to the participant. If the participant wishes, the report will be sent to the PMD.

iv) MRI Safety program: A comprehensive MRI safety program is in place including secure access to the MRI suite and ongoing surveillance for effectiveness of the safety program. A board certified subspecialty neuroradiologist will review each MRI scan for pathology and confirm that there are no clinically significant findings for any of the participants. All data are archived in the Picture Archival and Communication System (PACS) and if needed can be archived in DVD-R media and stored in a locked cabinet.

v) Columbia Univerisity, NY: Yunglin Gazes, Ph.D. is an Assistant Professor of Neuropsychology in the Department of Neurology and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia University. She will be responsible for supervising the neuroimaging component of this RCT. She has considerable experience with forms of advanced neuroimaging analyses described in this project and has previously collaborated with Dr. Blumen (co-PI) on several projects using similar neuroimaging techniques. She will conduct and monitor neuroimaging analyses, assist in preparation of manuscripts and present findings at scientific meetings.

vi) **Benefits:** Our previous experience, the non-invasive nature of most proposed procedures, the widespread prevalence of dance and exercise programs in the community, the general acceptance by practicing physicians of the procedures to be used, and the close supervision and monitoring of the subjects all minimizes the potential risks. Both dancing and walking may improve physical fitness, and involve minimal risks to the participant. Early diagnosis and treatment of disorders discovered as a result of screening done in these studies may impact beneficially on their health. In addition, understanding of the role of physical, mental, and social activities in ameliorating age-related cognitive decline could provide important insights into the aging process and age-related diseases that could ultimately have a positive impact on the length and quality of life for study subjects.

c) 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 the statistician will have access. Randomization procedures were discussed previously. 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 Institutional Review Board (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.

i) Participants will be recorded as they walk on the gait mat. No sound will be recorded. The videos will not be destroyed. The tapes will be used by the research team to score the evaluations and refine measurements already collected. Participants will not receive any monetary compensation for being taped.

8) Data Analysis: Study outcomes will be assessed at baseline, month 2, 4, immediate post-intervention (month 6), and month 9. Attendance rates will be reported. The purpose of the analyses are to estimate effects that can be used for a larger confirmatory study.

a) **Aim 1:** Linear mixed effects models will be used to compare the trajectories of composite EF score at baseline and months 2/4/6/9. The optimal treatment period that yields the greatest treatment effect will

be identified. Estimates with 95% CI of dance effects at different time points as well as slope of change will be reported. The analysis will also be applied to **individual EF tests** to examine whether the dance effects differentiates among different aspects of EF.

- Pre-specified covariates[115-117] to account for **confounding** include age, gender, education and chronic illnesses.[118] Baseline distribution of covariates will be compared to assess adequacy of randomization. We do not discount residual/unmeasured confounding – though this is more of an issue in observational studies without randomization.
- **Intensity** (*actigraphy in-session*) and **dose** (*number of sessions*) of dance and walking will also be examined.

Power: The pilot sample size was based on pragmatics of recruitment and necessities for examining feasibility.[119] Based on previous studies, we expect correlations of at least 0.80 between repeated EF scores. With 16 in each group and assuming 20% drop out rate at post intervention, we can detect a difference of 0.075 SD per month in EF slope using measurements at baseline/2/4/6 months, between groups with 80% power using 2-sided tests with alpha level 0.05.

b) **Aim 2:** The comparison of imaging measures pre-post intervention (month 0 vs. 6) between study arms will be analyzed using multivariate covariance-based analyses, adjusting for age, gender and other covariates. Multivariate covariance-based analyses are particularly sensitive to detecting effects in the presence of between-subject variability and collinearity– issues particularly important to consider in aging populations and with neuroimaging data. Drs. Blumen and Gazes have considerable experience with these neuroimaging analyses.[96, 120-127] Mean and confidence intervals of imaging measures within each group as well as the difference between the two groups will be reported for performance at each time point of pre and post intervention, and for change at post from pre intervention.

- ***fMRI: WWT imagery task, DSST and Flanker Task.*** Standard pre-processing and first-level analyses will be performed with SPM12 (see Equipment). ***Group-Level Covariance Analyses***. Ordinal Trend Covariance Analyses (OrT-CVA; http://www.nitrc.org/projects/gcva_pca) will be used to analyze the imagined WWT, DSST and Flanker Tasks[128, 129]. OrT-CVA will be used to identify covariance patterns in the fMRI signal as a function of trial type (iT, iW and iWWT on the imagined WWT, task and rest blocks on the DSST, incongruent and congruent trials on Flanker Task) at each study visit (pre and post-intervention). OrT-CVA employs a 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 (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 & 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. Each intervention group will be split into two, and split half-reliability assessed by correlations on imaging measures.

Power: The sample of 16 per group is within the number recommended to conduct reliability studies[130] and to improve study design.[131] We will report estimates of imaging measures to improve study design of our full scale RCT.

c) **Potential pitfalls and solutions.** We recognize that despite all our efforts, there will be **missing data**. To address this issue we will identify contact persons. Flexible scheduling with makeup sessions is provided. We will not restrict participation in **outside activities** keeping with the pragmatic nature of the trial. We will track outside activities using validated leisure and activity scales (see Table 1) to see if it will explain durability of any observed effects.

9) Data quality control and database management

a) The content captured will consist of demographics, medical history, MRIs, laboratory data, clinical and biological safety outcomes and adherence data. Data management will incorporate the expertise of the Research Informatics Core (RIC), a component of the Einstein-Montefiore Institute for Clinical and Translational Research (ICTR) consisting of developers and database analysts who specialize in the management of research data. REDCap (Research Electronic Data Capture) is a mature, secure, web-based application for building and managing online surveys and databases developed by Vanderbilt

University to support the electronic collection and management of clinical research data. It has been available at Einstein-Montefiore since it became REDCap consortium member in 2010.

REDCap can be used to collect virtually any type of data (including 21 CFR Part 11 and FISMA-compliant environments), but it is specifically geared to support online or offline data capture for research studies and operations, being by design HIPAA-compliant. REDCap's streamlined process for rapidly developing projects helps to create and design projects using 1) the online method from a web browser using the Online Designer; and/or 2) the offline method by constructing a 'data dictionary' template file in Microsoft Excel, which can be later uploaded into REDCap. Both surveys and Data Collection Forms (or a mixture of the two) can be built using these methods. REDCap provides an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry. This system offers easy data management with audit trails for reporting, monitoring and querying participant records. REDCap provides automated export procedures for seamless data downloads to Excel and common statistical packages (SPSS, SAS, Stata, R), as well as a built-in project calendar, a scheduling module, ad hoc reporting tools, and advanced features, such as branching logic, file uploading, and calculated fields.

REDCap servers are housed in a data center at Einstein and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines. It currently supports 2394 academic/non-profit consortium partners and over 500,000 research end-users (www.project-redcap.org). A member of the study team will enter all data into this web-based system. The RIC will assist with the design of the data collection forms, implement protocols for data QA, access permissions, and production of customized reports and datasets for biostatistical analysis. All data collection procedures will be closely monitored to ensure that data integrity is maintained.

10) References

1. Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, et al. Leisure activities and the risk of dementia in the elderly. The New England journal of medicine. 2003;348(25):2508-16. doi: 10.1056/NEJMoa022252. PubMed PMID: 12815136.
2. Blasing B, Calvo-Merino B, Cross ES, Jola C, Honisch J, Stevens CJ. Neurocognitive control in dance perception and performance. Acta psychologica. 2012;139(2):300-8. Epub 2012/02/07. doi: 10.1016/j.actpsy.2011.12.005. PubMed PMID: 22305351.
3. Brown S, Martinez MJ, Parsons LM. The neural basis of human dance. Cereb Cortex. 2006;16(8):1157-67. Epub 2005/10/14. doi: 10.1093/cercor/bhj057. PubMed PMID: 16221923.
4. Brown S, Parsons LM. The neuroscience of dance. Scientific American. 2008;299(1):78-83. Epub 2008/07/16. PubMed PMID: 18623968.
5. Kattenstroth JC, Kalisch T, Kolankowska I, Dinse HR. Balance, sensorimotor, and cognitive performance in long-year expert senior ballroom dancers. Journal of aging research. 2011;2011:176709. Epub 2011/10/01. doi: 10.4061/2011/176709. PubMed PMID: 21961064; PMCID: PMC3179891.
6. Kattenstroth JC, Kolankowska I, Kalisch T, Dinse HR. Superior sensory, motor, and cognitive performance in elderly individuals with multi-year dancing activities. Frontiers in aging neuroscience. 2010;2. Epub 2010/08/21. doi: 10.3389/fnagi.2010.00031. PubMed PMID: 20725636; PMCID: PMC2917240.
7. Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, et al. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosomatic medicine. 2010;72(3):239-52. Epub 2010/03/13. doi: 10.1097/PSY.0b013e3181d14633. PubMed PMID: 20223924; PMCID: Pmc2897704.
8. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci. 2003;14(2):125-30. Epub 2003/03/29. PubMed PMID: 12661673.
9. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. New England Journal of Medicine. 1988;319(26):1701-7. PubMed PMID: 3205267.
10. Bueno-Cavanillas A, Padilla-Ruiz F, Jimenez-Moleon JJ, Peinado-Alonso CA, Galvez-Vargas R. Risk factors in falls among the elderly according to extrinsic and intrinsic precipitating causes. Eur J Epidemiol. 2000;16(9):849-59. Epub 2001/04/12. PubMed PMID: 11297228.
11. van Dijk PT, Meulenberg OG, van de Sande HJ, Habbema JD. Falls in dementia patients. Gerontologist. 1993;33(2):200-4. Epub 1993/04/01. PubMed PMID: 8468012.

12. van Doorn C, Gruber-Baldini AL, Zimmerman S, Hebel JR, Port CL, Baumgarten M, et al. Dementia as a risk factor for falls and fall injuries among nursing home residents. J Am Geriatr Soc. 2003;51(9):1213-8. Epub 2003/08/16. doi: 51404 [pii]. PubMed PMID: 12919232.
13. Verghese J. Cognitive and mobility profile of older social dancers. J Am Geriatr Soc. 2006;54(8):1241-4. Epub 2006/08/18. doi: 10.1111/j.1532-5415.2006.00808.x. PubMed PMID: 16913992; PMCID: PMC1550765.
14. Ngandu T, Lehtisalo J, Solomon A, Levalahti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015. Epub 2015/03/17. doi: 10.1016/s0140-6736(15)60461-5. PubMed PMID: 25771249.
15. Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. Jama. 2008;300(9):1027-37. Epub 2008/09/05. doi: 10.1001/jama.300.9.1027. PubMed PMID: 18768414.
16. Cyarto EV, Lautenschlager NT, Desmond PM, Ames D, Szoeke C, Salvado O, et al. Protocol for a randomized controlled trial evaluating the effect of physical activity on delaying the progression of white matter changes on MRI in older adults with memory complaints and mild cognitive impairment: the AIBL Active trial. BMC psychiatry. 2012;12:167. Epub 2012/10/12. doi: 10.1186/1471-244x-12-167. PubMed PMID: 23050829; PMCID: PMC3534144.
17. Lam LC, Chau RC, Wong BM, Fung AW, Tam CW, Leung GT, et al. A 1-year randomized controlled trial comparing mind body exercise (Tai Chi) with stretching and toning exercise on cognitive function in older Chinese adults at risk of cognitive decline. Journal of the American Medical Directors Association. 2012;13(6):568 e15-20. Epub 2012/05/15. doi: 10.1016/j.jamda.2012.03.008. PubMed PMID: 22579072.
18. Gershon RC, Cella D, Fox NA, Havlik RJ, Hendrie HC, Wagster MV. Assessment of neurological and behavioural function: the NIH Toolbox. Lancet Neurol. 2010;9(2):138-9. Epub 2010/02/05. doi: 10.1016/s1474-4422(09)70335-7. PubMed PMID: 20129161.
19. Zelazo PD, Anderson JE, Richler J, Wallner-Allen K, Beaumont JL, Conway KP, et al. NIH Toolbox Cognition Battery (CB): validation of executive function measures in adults. J Int Neuropsychol Soc. 2014;20(6):620-9. Epub 2014/06/25. doi: 10.1017/s1355617714000472. PubMed PMID: 24960301; PMCID: Pmc4601803.
20. Zelazo PD, Anderson JE, Richler J, Wallner-Allen K, Beaumont JL, Weintraub S. II. NIH Toolbox Cognition Battery (CB): measuring executive function and attention. Monographs of the Society for Research in Child Development. 2013;78(4):16-33. Epub 2013/08/21. doi: 10.1111/mono.12032. PubMed PMID: 23952200.
21. Chew EY, Clemons TE, Agron E, Launer LJ, Grodstein F, Bernstein PS. Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function: The AREDS2 Randomized Clinical Trial. Jama. 2015;314(8):791-801. Epub 2015/08/26. doi: 10.1001/jama.2015.9677. PubMed PMID: 26305649.
22. Henderson VW, Ala T, Sainani KL, Bernstein AL, Stephenson BS, Rosen AC, et al. Raloxifene for women with Alzheimer disease: A randomized controlled pilot trial. Neurology. 2015;85(22):1937-44. Epub 2015/11/06. doi: 10.1212/wnl.0000000000002171. PubMed PMID: 26537053; PMCID: PMC4664126.
23. Liu G, Weinger JG, Lu ZL, Xue F, Sadeghpour S. Efficacy and Safety of MMFS-01, a Synapse Density Enhancer, for Treating Cognitive Impairment in Older Adults: A Randomized, Double-Blind, Placebo-Controlled Trial. Journal of Alzheimer's disease : JAD. 2015;49(4):971-90. Epub 2015/11/01. doi: 10.3233/jad-150538. PubMed PMID: 26519439; PMCID: PMC4927823.
24. Ballesteros S, Kraft E, Santana S, Tziraki C. Maintaining older brain functionality: A targeted review. Neuroscience and biobehavioral reviews. 2015;55:453-77. Epub 2015/06/10. doi: 10.1016/j.neubiorev.2015.06.008. PubMed PMID: 26054789.
25. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, et al. Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci. 2006;61(11):1166-70. Epub 2006/12/15. doi: 61/11/1166 [pii]. PubMed PMID: 17167157.
26. Ohman H, Savikko N, Strandberg TE, Pitkala KH. Effect of physical exercise on cognitive performance in older adults with mild cognitive impairment or dementia: a systematic review. Dement Geriatr Cogn Disord. 2014;38(5-6):347-65. Epub 2014/08/30. doi: 10.1159/000365388. PubMed PMID: 25171577.

27. Voss MW, Prakash RS, Erickson KI, Basak C, Chaddock L, Kim JS, et al. Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. Frontiers in aging neuroscience. 2010;2. Epub 2010/10/05. doi: 10.3389/fnagi.2010.00032. PubMed PMID: 20890449; PMCID: Pmc2947936.
28. Ayers EI, Tow AC, Holtzer R, Verghese J. Walking while talking and falls in aging. Gerontology. 2014;60(2):108-13. Epub 2013/11/07. doi: 10.1159/000355119. PubMed PMID: 24192342; PMCID: PMC3944080.
29. Verghese J, Buschke H, Viola L, Katz M, Hall C, Kuslansky G, et al. 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.
30. 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; PMCID: PMC3470773.
31. 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. J Am Geriatr Soc. 2012;60(11):2093-8. Epub 2012/10/09. doi: 10.1111/j.1532-5415.2012.04193.x. PubMed PMID: 23039200; PMCID: PMC3498524.
32. Blumen HM, Holtzer R, Brown LL, Gazes Y, Verghese J. Behavioral and neural correlates of imagined walking and walking-while-talking in the elderly. Hum Brain Mapp. 2014. Epub 2014/02/14. doi: 10.1002/hbm.22461. PubMed PMID: 24522972.
33. Voss MW, Heo S, Prakash RS, Erickson KI, Alves H, Chaddock L, et al. The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: results of a one-year exercise intervention. Hum Brain Mapp. 2013;34(11):2972-85. Epub 2012/06/08. doi: 10.1002/hbm.22119. PubMed PMID: 22674729; PMCID: PMC4096122.
34. Burzynska AZ, Jiao Y, Knecht AM, Fanning J, Awick EA, Chen T, et al. White Matter Integrity Declined Over 6-Months, but Dance Intervention Improved Integrity of the Fornix of Older Adults. Frontiers in aging neuroscience. 2017;9:59. Epub 2017/04/01. doi: 10.3389/fnagi.2017.00059. PubMed PMID: 28360853; PMCID: PMC5352690.
35. Verghese J, LeValley A, Hall CB, Katz MJ, Ambrose AF, Lipton RB. Epidemiology of gait disorders in community-residing older adults. J Am Geriatr Soc. 2006;54(2):255-61. doi: 10.1111/j.1532-5415.2005.00580.x. PubMed PMID: 16460376; PMCID: PMC1403740.
36. Holtzer R, Wang C, Verghese J. Performance variance on walking while talking tasks: theory, findings, and clinical implications. Age (Dordrecht, Netherlands). 2014;36(1):373-81. Epub 2013/08/15. doi: 10.1007/s11357-013-9570-7. PubMed PMID: 23943111; PMCID: PMC3889876.
37. Verghese J, Mahoney J, Wang C, Ambrose A, Holtzer R. Cognitive remediation to improve mobility in sedentary seniors. Journal of Gerontology: Medical Sciences. 2010:in press.
38. Lipton RB, Katz MJ, Kuslansky G, Sliwinski MJ, Stewart WF, Verghese J, et al. Screening for dementia by telephone using the memory impairment screen. J Am Geriatr Soc. 2003;51(10):1382-90. Epub 2003/09/27. PubMed PMID: 14511157.
39. Galvin JE, Roe CM, Powlishta KK, Coats MA, Muich SJ, Grant E, et al. The AD8: a brief informant interview to detect dementia. Neurology. 2005;65(4):559-64. Epub 2005/08/24. doi: 10.1212/01.wnl.0000172958.95282.2a. PubMed PMID: 16116116.
40. Buschke H, Kuslansky G, Katz M, Stewart WF, Sliwinski MJ, Eckholdt HM, et al. Screening for dementia with the memory impairment screen. Neurology. 1999;52(2):231-8. Epub 1999/02/05. PubMed PMID: 9932936.
41. Milne A, Culverwell A, Guss R, Tuppen J, Whelton R. Screening for dementia in primary care: a review of the use, efficacy and quality of measures. Int Psychogeriatr. 2008;20(5):911-26. Epub 2008/06/06. doi: 10.1017/s1041610208007394. PubMed PMID: 18533066.
42. Cordell CB, Borson S, Boustani M, Chodosh J, Reuben D, Verghese J, et al. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting. Alzheimers Dement. 2013;9(2):141-50. Epub 2012/12/26. doi: 10.1016/j.jalz.2012.09.011. PubMed PMID: 23265826.
43. Holsinger T, Deveau J, Boustani M, Williams JW, Jr. Does this patient have dementia? JAMA. 2007;297(21):2391-404. Epub 2007/06/07. doi: 10.1001/jama.297.21.2391. PubMed PMID: 17551132.

44. Holsinger T, Plassman BL, Stechuchak KM, Burke JR, Coffman CJ, Williams JW, Jr. Screening for cognitive impairment: comparing the performance of four instruments in primary care. J Am Geriatr Soc. 2012;60(6):1027-36. Epub 2012/06/01. doi: 10.1111/j.1532-5415.2012.03967.x. PubMed PMID: 22646750.
45. 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: 10.1212/01.wnl.0000247042.15547.eb. PubMed PMID: 17159098.
46. Verghese J, Buschke H, Kuslansky G, Katz MJ, Weidenheim K, Lipton RB, et al. Antemortem memory impairment screen performance is correlated with postmortem Alzheimer pathology. J Am Geriatr Soc. 2003;51(7):1043-5. Epub 2003/07/02. PubMed PMID: 12834533.
47. Galvin JE, Fagan AM, Holtzman DM, Mintun MA, Morris JC. Relationship of dementia screening tests with biomarkers of Alzheimer's disease. Brain. 2010;133(11):3290-300. Epub 2010/09/09. doi: 10.1093/brain/awq204. PubMed PMID: 20823087; PMCID: PMC2965421.
48. Holtzer R, Mahoney JR, Izzetoglu M, Wang C, England S, Verghese J. Online fronto-cortical control of simple and attention-demanding locomotion in humans. NeuroImage. 2015;112:152-9. Epub 2015/03/15. doi: 10.1016/j.neuroimage.2015.03.002. PubMed PMID: 25765257; PMCID: PMC4408246.
49. Ayers E, Barzilai N, Crandall JP, Milman S, Verghese J. Association of exceptional parental longevity and physical function in aging. Age (Dordrecht, Netherlands). 2014;36(4):9677. Epub 2014/07/06. doi: 10.1007/s11357-014-9677-5. PubMed PMID: 24997018; PMCID: PMC4150888.
50. Katz MJ, Lipton RB, Hall CB, Zimmerman ME, Sanders AE, Verghese J, et al. Age-specific and sex-specific prevalence and incidence of mild cognitive impairment, dementia, and Alzheimer dementia in blacks and whites: a report from the Einstein Aging Study. Alzheimer disease and associated disorders. 2012;26(4):335-43. Epub 2011/12/14. doi: 10.1097/WAD.0b013e31823dbcfc. PubMed PMID: 22156756; PMCID: PMC3334445.
51. Verghese J, Annweiler C, Ayers E, Barzilai N, Beauchet O, Bennett DA, et al. Motoric cognitive risk syndrome: multicountry prevalence and dementia risk. Neurology. 2014;83(8):718-26. Epub 2014/07/18. doi: 10.1212/WNL.0000000000000717. PubMed PMID: 25031288; PMCID: PMC4150127.
52. Verghese J, Ayers E, Barzilai N, Bennett DA, Buchman AS, Holtzer R, et al. Motoric cognitive risk syndrome: Multicenter incidence study. Neurology. 2014;83(24):2278-84. Epub 2014/11/02. doi: 10.1212/WNL.0000000000001084. PubMed PMID: 25361778; PMCID: PMC4277675.
53. CDC. Physical Activity for Older Adults www.cdc.gov/features/activity-older-adults/index.html: Centers for disease control and prevention; 2016 [updated June 14, 2016; cited 2017 11/01/2017].
54. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):280-92. Epub 2011/04/26. doi: S1552-5260(11)00099-9 [pii]
10.1016/j.jalz.2011.03.003 [doi]. PubMed PMID: 21514248.
55. Hwang PW, Braun KL. The Effectiveness of Dance Interventions to Improve Older Adults' Health: A Systematic Literature Review. Alternative therapies in health and medicine. 2015;21(5):64-70. Epub 2015/09/24. PubMed PMID: 26393993; PMCID: PMC5491389.
56. Strassel JK, Cherkin DC, Steuten L, Sherman KJ, Vrijhoef HJ. A systematic review of the evidence for the effectiveness of dance therapy. Alternative therapies in health and medicine. 2011;17(3):50-9. Epub 2011/12/15. PubMed PMID: 22164813.
57. Puetz TW, Morley CA, Herring MP. Effects of creative arts therapies on psychological symptoms and quality of life in patients with cancer. JAMA internal medicine. 2013;173(11):960-9. Epub 2013/05/24. doi: 10.1001/jamainternmed.2013.836. PubMed PMID: 23699646.
58. Oh-Park M, Holtzer R, Mahoney J, Wang C, Verghese J. Effect of treadmill training on specific gait parameters in older adults with frailty: case series. Journal of geriatric physical therapy (2001). 2011;34(4):184-8. Epub 2011/11/30. doi: 10.1519/JPT.0b013e3182193165. PubMed PMID: 22124418; PMCID: PMC3226950.
59. Snowden M, Steinman L, Mochan K, Grodstein F, Prohaska TR, Thurman DJ, et al. Effect of exercise on cognitive performance in community-dwelling older adults: review of intervention trials and recommendations for public health practice and research. J Am Geriatr Soc. 2011;59(4):704-16. Epub 2011/03/29. doi: 10.1111/j.1532-5415.2011.03323.x. PubMed PMID: 21438861.

60. van Uffelen JG, Chin APMJ, Hopman-Rock M, van Mechelen W. The effects of exercise on cognition in older adults with and without cognitive decline: a systematic review. Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine. 2008;18(6):486-500. Epub 2008/11/13. doi: 10.1097/JSM.0b013e3181845f0b. PubMed PMID: 19001882.
61. Young J, Angevaren M, Rusted J, Tabet N. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst Rev. 2015;4:Cd005381. Epub 2015/04/23. doi: 10.1002/14651858.CD005381.pub4. PubMed PMID: 25900537.
62. Scherder E, Scherder R, Verburgh L, Konigs M, Blom M, Kramer AF, et al. Executive functions of sedentary elderly may benefit from walking: a systematic review and meta-analysis. Am J Geriatr Psychiatry. 2014;22(8):782-91. Epub 2013/05/03. doi: 10.1016/j.jagp.2012.12.026. PubMed PMID: 23636004.
63. Sink KM, Espeland MA, Castro CM, Church T, Cohen R, Dodson JA, et al. Effect of a 24-Month Physical Activity Intervention vs Health Education on Cognitive Outcomes in Sedentary Older Adults: The LIFE Randomized Trial. Jama. 2015;314(8):781-90. Epub 2015/08/26. doi: 10.1001/jama.2015.9617. PubMed PMID: 26305648; PMCID: PMC4698980.
64. National Academies of Sciences E, and Medicine. Preventing Cognitive Decline and Dementia: A Way Forward. Press TNA, editor. Washington, DC2017.
65. Medicine ACoS. ACSM's Guidelines for exercise testing and prescription. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.
66. Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. Circulation. 2007;116(9):1094-105. Epub 2007/08/03. doi: CIRCULATIONAHA.107.185650 [pii] 10.1161/CIRCULATIONAHA.107.185650. PubMed PMID: 17671236.
67. Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med. 1970;2(2):92-8. Epub 1970/01/01. PubMed PMID: 5523831.
68. Borg G. Perceived exertion as an indicator of somatic stress. Scandinavian journal of rehabilitation medicine. 1970;2(2):92-8. Epub 1970/01/01. PubMed PMID: 5523831.
69. Williamson JD, Espeland M, Kritchevsky SB, Newman AB, King AC, Pahor M, et al. Changes in cognitive function in a randomized trial of physical activity: results of the lifestyle interventions and independence for elders pilot study. The journals of gerontology Series A, Biological sciences and medical sciences. 2009;64(6):688-94. Epub 2009/02/27. doi: 10.1093/gerona/glp014. PubMed PMID: 19244157; PMCID: PMC2679423.
70. Erickson KI, Colcombe SJ, Wadhwa R, Bherer L, Peterson MS, Scalf PE, et al. Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. Neurobiol Aging. 2007;28(2):272-83. Epub 2006/02/17. doi: 10.1016/j.neurobiolaging.2005.12.012. PubMed PMID: 16480789.
71. Holtzer R, Stern Y, Rakitin BC. Age-related differences in executive control of working memory. Mem Cognit. 2004;32(8):1333-45. Epub 2005/05/20. PubMed PMID: 15900927.
72. 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. J Gerontol A Biol Sci Med Sci. 2011;66(8):879-87. Epub 2011/05/20. doi: glr068 [pii]
10.1093/gerona/glr068 [doi]. PubMed PMID: 21593013.
73. Verghese J, Kuslansky G, Holtzer R, Katz M, Xue X, Buschke H, et al. Walking while talking: effect of task prioritization in the elderly. Arch Phys Med Rehabil. 2007;88(1):50-3. doi: 10.1016/j.apmr.2006.10.007. PubMed PMID: 17207675; PMCID: PMC1894901.
74. Brandler TC, Oh-Park M, Wang C, Holtzer R, Verghese J. Walking while talking: investigation of alternate forms. Gait & posture. 2012;35(1):164-6. Epub 2011/09/29. doi: 10.1016/j.gaitpost.2011.08.003. PubMed PMID: 21944476; PMCID: PMC3296479.
75. Day SJ, Altman DG. Statistics notes: blinding in clinical trials and other studies. BMJ. 2000;321(7259):504. Epub 2000/08/19. PubMed PMID: 10948038; PMCID: PMC1118396.
76. Goldberg TE, Harvey PD, Wesnes KA, Snyder PJ, Schneider LS. Practice effects due to serial cognitive assessment: Implications for preclinical Alzheimer's disease randomized controlled trials. Alzheimer's & dementia (Amsterdam, Netherlands). 2015;1(1):103-11. Epub 2015/03/01. doi: 10.1016/j.dadm.2014.11.003. PubMed PMID: 27239497; PMCID: PMC4876902.

77. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. American journal of preventive medicine. 2009;36(5):452-7. Epub 2009/04/14. doi: 10.1016/j.amepre.2009.02.002. PubMed PMID: 19362699; PMCID: PMC2859314.
78. de Mendonca A, Ribeiro F, Guerreiro M, Palma T, Garcia C. Clinical significance of subcortical vascular disease in patients with mild cognitive impairment. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2005;12(2):125-30. Epub 2005/02/01. doi: 10.1111/j.1468-1331.2004.00892.x. PubMed PMID: 15679700.
79. Baker LD, Bayer-Carter JL, Skinner J, Montine TJ, Cholerton BA, Callaghan M, et al. High-intensity physical activity modulates diet effects on cerebrospinal amyloid-beta levels in normal aging and mild cognitive impairment. Journal of Alzheimer's disease : JAD. 2012;28(1):137-46. Epub 2011/10/06. doi: 10.3233/jad-2011-111076. PubMed PMID: 21971406; PMCID: PMC3280092.
80. Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol. 2010;67(1):71-9. Epub 2010/01/13. doi: 10.1001/archneurol.2009.307. PubMed PMID: 20065132; PMCID: PMC3056436.
81. Hackney ME, Earhart GM. Social partnered dance for people with serious and persistent mental illness: a pilot study. The Journal of nervous and mental disease. 2010;198(1):76-8. Epub 2010/01/12. doi: 10.1097/NMD.0b013e3181c81f7c. PubMed PMID: 20061874.
82. Kim SH, Kim M, Ahn YB, Lim HK, Kang SG, Cho JH, et al. Effect of dance exercise on cognitive function in elderly patients with metabolic syndrome: a pilot study. Journal of sports science & medicine. 2011;10(4):671-8. Epub 2011/01/01. PubMed PMID: 24149557; PMCID: PMC3761497.
83. Mitchell MS, Goodman JM, Alter DA, John LK, Oh PI, Pakosh MT, et al. Financial incentives for exercise adherence in adults: systematic review and meta-analysis. American journal of preventive medicine. 2013;45(5):658-67. Epub 2013/10/22. doi: 10.1016/j.amepre.2013.06.017. PubMed PMID: 24139781.
84. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. Bmj. 2016;355:i5239. Epub 2016/10/26. doi: 10.1136/bmj.i5239. PubMed PMID: 27777223; PMCID: PMC5076380 http://www.icmje.org/coi_disclosure.pdf and declare support from the following organisations for the submitted work-Queen Mary University of London, University of Sheffield (ScHARR Research Committee Pump priming grant), NIHR Research Design Services London and South East, NIHR Statisticians Group, Chief Scientist Office Scotland. GAL is editor in chief of the new BioMed central journal Pilot and Feasibility Studies proposed by Daniel R Shanahan, which was created out of this work. Daniel R Shanahan is employed by BioMed Central, and Trish Groves is an editor of the BMJ. SME, CMB, MJC, and LT are on the editorial board of Pilot and Feasibility Studies and CLC is an associate editor. Frank Bretz works for Novartis. The authors declare no other competing interests. None of the listed people involved in either journal played any part in the peer review process or editorial decision making.
85. Bar RJ, DeSouza JF. Tracking Plasticity: Effects of Long-Term Rehearsal in Expert Dancers Encoding Music to Movement. PLoS One. 2016;11(1):e0147731. Epub 2016/01/30. doi: 10.1371/journal.pone.0147731. PubMed PMID: 26824475; PMCID: PMC4732757.
86. Giacosa C, Karpati FJ, Foster NE, Penhune VB, Hyde KL. Dance and music training have different effects on white matter diffusivity in sensorimotor pathways. Neuroimage. 2016;135:273-86. Epub 2016/04/27. doi: 10.1016/j.neuroimage.2016.04.048. PubMed PMID: 27114054.
87. Karpati FJ, Giacosa C, Foster NE, Penhune VB, Hyde KL. Dance and the brain: a review. Ann N Y Acad Sci. 2015;1337:140-6. Epub 2015/03/17. doi: 10.1111/nyas.12632. PubMed PMID: 25773628.
88. Olshansky MP, Bar RJ, Fogarty M, DeSouza JF. Supplementary motor area and primary auditory cortex activation in an expert break-dancer during the kinesthetic motor imagery of dance to music. Neurocase. 2015;21(5):607-17. Epub 2014/10/11. doi: 10.1080/13554794.2014.960428. PubMed PMID: 25301352.
89. Sacco K, Cauda F, Cerliani L, Mate D, Duca S, Geminiani GC. Motor imagery of walking following training in locomotor attention. The effect of "the tango lesson". Neuroimage. 2006;32(3):1441-9. Epub 2006/07/25. doi: 10.1016/j.neuroimage.2006.05.018. PubMed PMID: 16861008.
90. Chen G, Shu H, Chen G, Ward BD, Antuono PG, Zhang Z, et al. Staging Alzheimer's Disease Risk by Sequencing Brain Function and Structure, Cerebrospinal Fluid, and Cognition Biomarkers. Journal of Alzheimer's disease : JAD. 2016;54(3):983-93. Epub 2016/08/29. doi: 10.3233/jad-160537. PubMed PMID: 27567874; PMCID: PMC5055443.

91. Burggren A, Brown J. Imaging markers of structural and functional brain changes that precede cognitive symptoms in risk for Alzheimer's disease. Brain imaging and behavior. 2014;8(2):251-61. Epub 2013/12/10. doi: 10.1007/s11682-013-9278-4. PubMed PMID: 24317680; PMCID: PMC4012007.
92. Ewers M, Sperling RA, Klunk WE, Weiner MW, Hampel H. Neuroimaging markers for the prediction and early diagnosis of Alzheimer's disease dementia. Trends in neurosciences. 2011;34(8):430-42. Epub 2011/06/24. doi: 10.1016/j.tins.2011.05.005. PubMed PMID: 21696834; PMCID: PMC3275347.
93. Mondadori CR, Buchmann A, Mustovic H, Schmidt CF, Boesiger P, Nitsch RM, et al. Enhanced brain activity may precede the diagnosis of Alzheimer's disease by 30 years. Brain. 2006;129(Pt 11):2908-22. Epub 2006/10/03. doi: 10.1093/brain/awl266. PubMed PMID: 17012294.
94. Ranasinghe KG, Hinkley LB, Beagle AJ, Mizuiri D, Dowling AF, Honma SM, et al. Regional functional connectivity predicts distinct cognitive impairments in Alzheimer's disease spectrum. NeuroImage Clinical. 2014;5:385-95. Epub 2014/09/03. doi: 10.1016/j.nicl.2014.07.006. PubMed PMID: 25180158; PMCID: PMC4145532.
95. Smith CD. Structural imaging in early pre-states of dementia. Biochimica et biophysica acta. 2012;1822(3):317-24. Epub 2011/07/23. doi: 10.1016/j.bbadis.2011.07.002. PubMed PMID: 21777674; PMCID: PMC3223541.
96. Stern Y, Habeck C, Steffener J, Barulli D, Gazes Y, Razlighi Q, et al. The Reference Ability Neural Network Study: motivation, design, and initial feasibility analyses. Neuroimage. 2014;103:139-51. Epub 2014/09/24. doi: 10.1016/j.neuroimage.2014.09.029. PubMed PMID: 25245813; PMCID: PMC4312259.
97. Smith S, Jenkinson M, Beckmann C, Miller K, Woolrich M. Meaningful design and contrast estimability in FMRI. Neuroimage. 2007;34(1):127-36. Epub 2006/10/31. doi: 10.1016/j.neuroimage.2006.09.019. PubMed PMID: 17070706.
98. Jovancevic J, Rosano C, Perera S, Erickson KI, Studenski S. A protocol for a randomized clinical trial of interactive video dance: potential for effects on cognitive function. BMC geriatr. 2012;12:23. Epub 2012/06/08. doi: 10.1186/1471-2318-12-23. PubMed PMID: 22672287; PMCID: PMC3404007.
99. Yendiki A, Panneck P, Srinivasan P, Stevens A, Zollei L, Augustinack J, et al. Automated probabilistic reconstruction of white-matter pathways in health and disease using an atlas of the underlying anatomy. Frontiers in neuroinformatics. 2011;5:23. Epub 2011/10/22. doi: 10.3389/fninf.2011.00023. PubMed PMID: 22016733; PMCID: PMC3193073.
100. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993;43(11):2412-4. Epub 1993/11/01. PubMed PMID: 8232972.
101. Schneider LS, Clark CM, Doody R, Ferris SH, Morris JC, Raman R, et al. ADCS Prevention Instrument Project: ADCS-clinicians' global impression of change scales (ADCS-CGIC), self-rated and study partner-rated versions. Alzheimer Dis Assoc Disord. 2006;20(4 Suppl 3):S124-38. Epub 2006/12/01. doi: 10.1097/01.wad.0000213878.47924.44. PubMed PMID: 17135806.
102. Schneider LS, Olin JT, Doody RS, Clark CM, Morris JC, Reisberg B, et al. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 1997;11 Suppl 2:S22-32. Epub 1997/01/01. PubMed PMID: 9236949.
103. Holtzer R, Goldin Y, Zimmerman M, Katz M, Buschke H, Lipton RB. Robust norms for selected neuropsychological tests in older adults. Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists. 2008;23(5):531-41. Epub 2008/06/24. doi: 10.1016/j.acn.2008.05.004. PubMed PMID: 18572380; PMCID: PMC2610426.
104. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, et al. Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol. 2009;8(2):165-74. Epub 2009/01/24. doi: 10.1016/S1474-4422(09)70013-4. PubMed PMID: 19161908; PMCID: PMC3414436.
105. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. 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.
106. ACoS M. ACSM's Guidelines for exercise testing and prescription. 2005.
107. Doi T, Verghese J, Makizako H, Tsutsumimoto K, Hotta R, Nakakubo S, et al. Effects of Cognitive Leisure Activity on Cognition in Mild Cognitive Impairment: Results of a Randomized Controlled Trial. Journal

of the American Medical Directors Association. 2017;18(8):686-91. Epub 2017/04/12. doi: 10.1016/j.jamda.2017.02.013. PubMed PMID: 28396179.
108. Ory M, Resnick B, Jordan PJ, Coday M, Riebe D, Ewing Garber C, et al. Screening, safety, and adverse events in physical activity interventions: collaborative experiences from the behavior change consortium. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine. 2005;29 Suppl:20-8. Epub 2005/06/01. doi: 10.1207/s15324796abm2902s_5. PubMed PMID: 15921486.
109. Hillsdon M, Foster C, Thorogood M. Interventions for promoting physical activity. Cochrane Database Syst Rev. 2005(1):Cd003180. Epub 2005/01/28. doi: 10.1002/14651858.CD003180.pub2. PubMed PMID: 15674903; PMCID: PMC4164373.
110. Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S. Exercise programs for people with dementia. Cochrane Database Syst Rev. 2015(4):Cd006489. Epub 2015/04/16. doi: 10.1002/14651858.CD006489.pub4. PubMed PMID: 25874613.
111. Knoefel F, Patrick L, Taylor J, Goubran R. Dual-stiffness flooring: can it reduce fracture rates associated with falls? Journal of the American Medical Directors Association. 2013;14(4):303-5. Epub 2013/02/05. doi: 10.1016/j.jamda.2012.12.077. PubMed PMID: 23375479.
112. Simpson AH, Lamb S, Roberts PJ, Gardner TN, Evans JG. Does the type of flooring affect the risk of hip fracture? Age Ageing. 2004;33(3):242-6. Epub 2004/04/15. doi: 10.1093/ageing/afh071. PubMed PMID: 15082428.
113. Cameron ID, Gillespie LD, Robertson MC, Murray GR, Hill KD, Cumming RG, et al. Interventions for preventing falls in older people in care facilities and hospitals. Cochrane Database Syst Rev. 2012;12:Cd005465. Epub 2012/12/14. doi: 10.1002/14651858.CD005465.pub3. PubMed PMID: 23235623.
114. Verghese J, Ayers E, Mahoney JR, Ambrose A, Wang C, Holtzer R. Cognitive remediation to enhance mobility in older adults: The CREM Study. Neurodegenerative disease management. 2017;In Press.
115. Holtzer R, Friedman R, Lipton RB, Katz M, Xue X, Verghese J. The relationship between specific cognitive functions and falls in aging. Neuropsychology. 2007;21(5):540-8. Epub 2007/09/06. doi: 10.1037/0894-4105.21.5.540. PubMed PMID: 17784802; PMCID: PMC3476056.
116. Verghese J, Robbins M, Holtzer R, Zimmerman M, Wang C, Xue X, et al. Gait Dysfunction in Mild Cognitive Impairment Syndromes. J Am Geriatr Soc. 2008. Epub 2008/05/17. doi: JGS1758 [pii] 10.1111/j.1532-5415.2008.01758.x [doi]. PubMed PMID: 18482293.
117. Verghese J, Wang C, Lipton RB, Holtzer R, Xue X. Quantitative gait dysfunction and risk of cognitive decline and dementia. J Neurol Neurosurg Psychiatry. 2007;78(9):929-35. doi: 10.1136/jnnp.2006.106914. PubMed PMID: 17237140; PMCID: PMC1995159.
118. Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am J Cardiol. 1989;64(10):651-4. Epub 1989/09/15. PubMed PMID: 2782256.
119. Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. J Psychiatr Res. 2011;45(5):626-9. Epub 2010/11/03. doi: 10.1016/j.jpsychires.2010.10.008. PubMed PMID: 21035130; PMCID: PMC3081994.
120. Blumen HM, Holtzer R, Brown LL, Gazes Y, Verghese J. Behavioral and neural correlates of imagined walking and walking-while-talking in the elderly. Hum Brain Mapp. 2014;35(8):4090-104. Epub 2014/02/14. doi: 10.1002/hbm.22461. PubMed PMID: 24522972; PMCID: PMC4106989.
121. Blumen HM, Gazes Y, Habeck C, Kumar A, Steffener J, Rakitin BC, et al. Neural networks associated with the speed-accuracy tradeoff: evidence from the response signal method. Behav Brain Res. 2011;224(2):397-402. Epub 2011/06/28. doi: 10.1016/j.bbr.2011.06.004. PubMed PMID: 21699922; PMCID: 3159733.
122. Gazes Y, Bowman FD, Razlighi QR, O'Shea D, Stern Y, Habeck C. White matter tract covariance patterns predict age-declining cognitive abilities. NeuroImage. 2016;125:53-60. Epub 2015/10/20. doi: 10.1016/j.neuroimage.2015.10.016. PubMed PMID: 26477658; PMCID: PMC4691375.
123. Gazes Y, Habeck C, O'Shea D, Razlighi QR, Steffener J, Stern Y. Functional network mediates age-related differences in reaction time: a replication and extension study. Brain and behavior. 2015;5(5):e00324. Epub 2015/04/16. doi: 10.1002/brb3.324. PubMed PMID: 25874162; PMCID: PMC4389056.
124. Gazes Y, Rakitin BC, Habeck C, Steffener J, Stern Y. Age differences of multivariate network expressions during task-switching and their associations with behavior. Neuropsychologia. 2012;50(14):3509-

18. Epub 2012/10/02. doi: 10.1016/j.neuropsychologia.2012.09.039. PubMed PMID: 23022432; PMCID: PMC3518579.
125. Gazes Y, Rakitin BC, Steffener J, Habeck C, Butterfield B, Ghez C, et al. Performance degradation and altered cerebral activation during dual performance: evidence for a bottom-up attentional system. Behav Brain Res. 2010;210(2):229-39. Epub 2010/03/02. doi: 10.1016/j.bbr.2010.02.036. PubMed PMID: 20188768; PMCID: PMC3531229.
126. Habeck C, Steffener J, Barulli D, Gazes Y, Razlighi Q, Shaked D, et al. Making cognitive latent variables manifest: distinct neural networks for fluid reasoning and processing speed. J Cogn Neurosci. 2015;27(6):1249-58. Epub 2014/12/30. doi: 10.1162/jocn_a_00778. PubMed PMID: 25539045; PMCID: PMC4416986.
127. Steffener J, Brickman AM, Rakitin BC, Gazes Y, Stern Y. The impact of age-related changes on working memory functional activity. Brain imaging and behavior. 2009;3(2):142-53. Epub 2009/06/19. doi: 10.1007/s11682-008-9056-x. PubMed PMID: 19536354; PMCID: PMC2697064.
128. Habeck C, Rakitin BC, Moeller J, Scarmeas N, Zarahn E, Brown T, et al. 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. Epub 2005/04/12. doi: 10.1016/j.cogbrainres.2004.10.010. PubMed PMID: 15820629.
129. Habeck C, Stern Y. Neural network approaches and their reproducibility in the study of verbal working memory and Alzheimer's disease. Clinical neuroscience research. 2007;6(6):381-90. Epub 2008/11/04. doi: 10.1016/j.cnr.2007.05.004. PubMed PMID: 18978933; PMCID: PMC2329589.
130. Hupe JM. Statistical inferences under the Null hypothesis: common mistakes and pitfalls in neuroimaging studies. Frontiers in neuroscience. 2015;9:18. Epub 2015/03/10. doi: 10.3389/fnins.2015.00018. PubMed PMID: 25745383; PMCID: PMC4333770.
131. Mumford JA. A power calculation guide for fMRI studies. Social cognitive and affective neuroscience. 2012;7(6):738-42. Epub 2012/05/30. doi: 10.1093/scan/nss059. PubMed PMID: 22641837; PMCID: PMC3427872.

Amendments

- 9/17/2018 – The Data and Safety Monitoring Plan (DSMP) section is revised to be consistent with the DSMP approved by the NIA.
    - A DSMB is not required, but a SO is named.
    - Definitions and reporting guidelines for AEs are described per NIA policy.