STUDY PROTOCOL

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1. Aims/Objectives

Alzheimer's disease (AD) afflicts nearly 6 million Americans, a number projected to grow in coming decades (Hurd et al., 2013). AD is known to have a long preclinical phase in which pathophysiologic processes develop many years, even decades, before the onset of clinical symptoms (Langbaum et al., 2013; Caselli & Reiman, 2013). During this preclinical phase there is evidence of unremitting decline in cognitive function, particularly in episodic memory. Thus far, evidence of the efficacy of pharmacological interventions to slow this decline in cognitive function has been limited, leading to increasing interest in the utility of nonpharmacological interventions including exercise.

We propose to conduct a randomized, controlled trial of a novel home-based exercise intervention to improve episodic memory that uses resistance training coupled with real-time guidance delivered remotely in 60 individuals 50 years of age or older with mild cognitive impairment. The Rehab R&D SPiRE award mechanism is intended to fund small pilot projects that lack preliminary data. Our aim is to estimate the mean and standard deviation (SD) of within-person change in measures of episodic memory (Rey-Osterrieth Complex Figure Test, Wechsler Logical Memory Test) over 6 months separately in the intervention and control groups. These will provide estimates of the magnitude of the effect of the exercise intervention on changes in episodic memory as compared to a control group.

2. Background Information

2.1 Alzheimer's Disease

Alzheimer's disease (AD) afflicts nearly 6 million Americans, is considered to be the most expensive disease in the United States, and responds only marginally and briefly to currently available drugs (Hurd et al., 2013). AD is known to have a long preclinical phase in which pathophysiologic proceses develop many years, even decades, before the onset of clinical symptoms (Langbaum et al., 2013; Caselli & Reiman, 2013). During this preclinical phase there is evidence of unremitting decline in cognitive function, particularly in episodic memory, and higher rates of progression to clinically classified mild cognitive impairment (MCI) or dementia (Grober et al., 2008; Howieson et al., 2008; Lim et al., 2012).

2.2 Cognitive Impairment in VA Patients

There is only limited information regarding prevalence of MCI in the veteran population. In a recent study analyzing data from the Vietnam Era Twin Registry, the prevalence of amnestic MCI (aMCI), which includes memory impairment, in men 51 to 60 years of age was reported to be 38% (Jak et al., 2014). Slowing further decline in cognitive function and memory could have a tremendous public health impact, reducing the burden on veterans and their families. National estimates in the general population suggest that a 1-year delay in the onset and progression of AD would result in an estimated 9.2 million fewer AD cases in the year 2050 (Brookmeyer et al., 2007). In this context, lifestyle interventions including increased exercise appear to be promising strategies for reducing the progression of cognitive decline.

2.3 Exercise-related Improvements in Cognitive Function

Observational studies suggest that exercise reduces cognitive decline (Larson et al., 2006; Laurin et al., 2006; Yaffe et al., 2009; Yoshitake et al., 1995; Chang et al., 2010); however, those studies did not distinguish between the two main types of exercise: aerobic and resistance training. Intervention studies have shown protective but differential effects of aerobic and resistance training. A meta-analytic review of aerobic exercise interventions and neurocognitive performance indicated a striking lack of benefit on working memory, despite improvements in many other areas of cognitive function (Smith et al., 2010). This summary finding may be related to underlying mechanisms including exercise-related changes in growth factors

2.4 Resistance Training and Cognitive Improvement

Cassilhas et al. (2007) conducted an RCT comparing the effects of 6 months of moderate-intensity resistance training, high-intensity resistance training, and stretching (control group) on cognitive function in 62 elderly men. Significant improvements were observed in cognitive function in both resistance training groups, as compared with the control group. In particular, improvements were found in episodic memory, as measured by the Rey-Osterrieth Complex Figure Test. Impairments in episodic memory, the ability to learn and retain new information, are most commonly seen in patients with MCI who subsequently progress to a diagnosis of AD dementia (Albert et al., 2011). The cognitive status of study participants at baseline was not presented in the article by Cassilhas et al. (2007). Further, results were only presented for participants attending 75% or more of the training sessions. In a 6-month clinical trial, 86 older women with probable MCI were randomized to twice-weekly resistance training, aerobic training, or balance training (Nagamatsu et al., 2012). As compared with the balance training group, the resistance training group, but not the aerobic training group, displayed significantly improved associative memory performance, a key contributor to episodic memory (Guez et al., 2015). According to the trial investigators (Nagamatsu et al., 2012), their estimate of the efficacy of resistance training on cognition may be conservative because of low exercise adherence. These two trials (Cassilhas et al., 2007; Nagamatsu et al., 2012) observed effects of resistance training on memory and emphasized the need to optimize exercise adherence. The study conducted by Cassilhas et al. (2007) was implemented in older men; however, it did not target those with cognitive impairment. The study by Nagamatsu et al. (2012) was implemented in a sample with probable MCI but was limited to women.

3. Rationale and Purpose

Amnestic MCI, often a prodromal phase of AD, may represent a critical time window to slow memory decline. Thus far, evidence of the efficacy of pharmacological interventions to slow this decline has been limited, leading to increasing interest in the utility of nonpharmacological interventions including exercise. Recent studies (Cassilhas et al., 2007; Westwood et al., 2014; Nagamatsu et al., 2012) provide evidence suggesting the benefits of resistance training on episodic memory, while indicating important insights into potential underlying mechanisms. However, the exercise interventions were implemented in clinical facilities, which increases participant burden and may have reduced exercise adherence. We propose to assess the feasibility of a home-based resistance training program to improve episodic memory that uses state-of-the-art information technology. The program has several notable features that overcome limitations of prior studies: 1) it does not require specialized clinical facilities; 2) it can be used in the home setting, eliminating the need to travel to a clinical facility; 3) it costs very little to set up and operate; 4) it can be sustained for an indefinite period of time; 5) it incorporates motivational and problem-solving strategies to promote increased adherence to exercise; 6) it can be implemented independent of certain external barriers such as weather or the season.

4. Relevance to Veterans Health

This study will assess the feasibility of a home-based strength training intervention coupled with voice response guidance to slow down progression of early memory impairment. This approach may offer an affordable way to continue to both instruct and encourage strength training by veterans virtually indefinitely through our remote access technology. Preliminary data collected during this feasibility study will be used for planning a future larger study, which may help VA clinicians provide optimal care for the many veterans with memory impairment.

5. Study Design

We will assess the feasibility of our home-based resistance training program (TLC-LIFT) to improve episodic memory in patients with aMCI. Sixty patients will be randomized to the TLC-LIFT program for 6

months or to a health education control program for 6 months. All evaluations will take place at the Jamaica Plain campus of the VA Boston Healthcare System.

5.1 TLC-LIFT

The Telephone-Linked Computer-based Long-term Interactive Fitness Trainer (TLC-LIFT uses advanced interactive voice response (IVR) technology, including speech-recognition software, to facilitate communication with TLC-LIFT. The TLC-LIFT program provides verbal instructions on which exercises to do and how to do them, guiding the participants through the exercises as they perform them in their home. The TLC-LIFT system asks the participant to begin a given exercise and to count each repetition out loud. Voice recognition of each counted repetition allows the system to monitor the number of repetitions for each exercise. Because TLC-LIFT is fully automated and administered by telephone in the participant's home, TLC-LIFT offers great flexibility and sufficiently low cost to continue indefinitely. To facilitate this approach, participants are supplied with a wireless headset (with microphone) that connects with their existing phone, thus allowing for hands-free communication with TLC-LIFT as they exercise. TLC-LIFT utilizes speech-recognition technology that we have customized to recognize wide variations in speech clarity in addition to variations in speech during exercise (e.g., variations counting repetitions out loud due to changes in breathing patterns). Furthermore, TLC-LIFT facilitates interactive communication (e.g., "Are you ready to set a higher goal for your next exercise?") tailored to each individual to optimize engagement and a person-centered approach. Participants are provided with an illustrated instructional booklet that converts to a desktop easel, allowing them to see the exercises while simultaneously listening to the audio instructions. Participants will be asked to call the TLC-LIFT system to initiate exercise sessions 3 days per week.

The tailored resistance exercise training program comprises three 60-minute sessions per week consisting of a warm-up phase (10 minutes), a stimulus phase (40 minutes), and a cool-down phase (10 minutes). The stimulus phase is made up of eight exercises to address the following key muscle groups: hip extensors, knee extensors, plantar flexors, trunk extensors, elbow flexors, elbow extensors, shoulder flexors and extensors. Exercises (e.g., biceps curls, front shoulder raises, heel raises) are performed with dumbbells (2 lb to 20 lb) to provide increased resistance and as a means of progressing the exercise program over time.

During each exercise session, participants are instructed to perform 2 sets of 12 repetitions of the 8 exercises. Each participant starts the program with the use of 2 lb vinyl-coated dumbbells. Weight is increased by 2 lb per limb (up to a maximum of 20 lb) each succeeding session for a given exercise as long as the participant is able to complete 2 sets of 10 or more repetitions. The TLC-LIFT system provides participants with detailed instructions on the proper technique for each of the 8 exercises.

The TLC-LIFT program includes dialogues that have a strong behavioral theoretical underpinning in social cognitive theory (Bandura, 1977; Bandura, 1986). At the conclusion of each exercise session, one interactive counseling module is delivered to the participant by the TLC-LIFT system. One important construct that is included in the counseling dialogues is self-efficacy, the expectation that one has the capacity to successfully perform a behavior required for a desired outcome to occur. Motivational messages aimed to increase self-efficacy are presented to participants regularly. These messages are designed to get participants to recognize their own exercise abilities, to reinforce good exercise performance, and to target areas of low confidence in order to promote self-confidence in exercise. Prior research indicates that level of self-efficacy predicts level of participation in physical activity promotion programs (Bandura, 1992; Marcus et al., 1992; Sallis et al., 1989; Ellis et al., 2011). Real-time monitoring of adherence permits continual reinforcement of goals and promotion of self-efficacy, motivational techniques known to increase adherence. Another important construct contained in the modules is outcome expectations, or the results that one would anticipate after performing a particular behavior (Bandura, 1997; Ellis & Motl, 2013). As expected, the extent to which individuals perceive they will be able to perform a behavior is related to the outcomes they anticipate. Three major forms of outcome expectations have been identified (Bandura, 1986): 1) positive and negative physical effects; 2) positive and negative social effects; and 3) positive and negative self-evaluative reactions to the change in behavior. Within each major form, positive expectations function as incentives and negative expectations as disincentives to changing behavior. Information is offered to participants about the typical

results that they could expect from participation in the TLC-LIFT exercise program in each of these three areas. Positive outcomes, for example, the known benefits of exercise, are highlighted often throughout the course of the program. Negative outcomes are discussed with an emphasis on how to overcome or resolve them; for example, if exercise is taking time away from social activities, participants are reminded about the benefits of exercise and the positive impact they can have on their social activities. Other important behavioral techniques that are incorporated into the dialogues are goal setting and reinforcement. Goal setting has been identified as an important construct for changing behavior and increasing compliance (O'Leary & Wilson, 1987). For TLC-LIFT, each week participants are prompted to set a goal in one of the exercise areas thus providing the participant with an endpoint on which to focus and helping to build self-efficacy when accomplished. The use of reinforcement techniques is also effective for behavior change and maintenance of the change (O'Leary & Wilson, 1987). Therefore, reinforcement, which can incorporate tangible rewards (such as purchasing a DVD movie or going out to dinner) and verbal rewards (praise, supportive comments), is another behavioral technique included in the TLC-LIFT dialogues.

Adherence to this intervention will be encouraged by intermittent newsletters, birthday cards, holiday greeting cards, and certificates of study participation. Participants will earn certificates of achievement, which will be mailed after completion of blocks of 12 sessions (approximately monthly if fully adherent).

5.2 Health Education Control

The group randomized to receive health education will serve as an attention control. Participants will be asked to call the health education control system 3 times per week to receive general information about a variety of health topics including content on exercise. This system, similar to the TLC-LIFT system, provides auditory instructions/content via the participant's home telephone. The health education control system uses advanced IVR technology, including speech-recognition software, to facilitate communication with the system. There are opportunities for participant interaction while the content is delivered by the system, for example, the participant can request subtopics about which they desire more information while skipping others of less interest. Near the end of the baseline visit, the initial health education session is completed with a staff member who has experience working with older adults with cognitive impairment. During the first four weeks of the intervention, content on stretching exercises to increase flexibility, based on the VA's MOVE! Program, will be sequentially presented to the participants. The content will be delivered across 12 sessions focusing on the benefits of stretching (session 1); principles of stretching: how much and how often (session 2); safety tips with stretching (session 3); getting started and staying on track (session 4); tips for getting up and down from the floor (session 5); instruction in stretching hamstrings and calves (session 6); instruction in stretching of quadriceps and hip rotators (session 7); instruction in stretching of neck and trunk (session 8); instruction in stretching of triceps and biceps (session 9); instruction in stretching of wrists and hands (session 10); and overcoming barriers to exercise and sticking to it (session 11 and 12). Participants will be provided with illustrations of the exercises with written instructions from the MOVE! booklet to accompany the auditory content. All the exercises are low intensity and performed in a supine, side lying, sitting, or standing (hands on a wall for support) position. Subsequently, during each session, participants will select a topic from three content areas: common symptoms, medical conditions, and preventive medicine topics. A similar approach as described above (see Section 5.1) will be used in the control group to encourage and maintain study participation.

6. Study Subject Selection

6.1 Sample Description

Patients with aMCI will be identified from VISN1 with the use of the Corporate Data Warehouse (CDW). This approach will involve searching the CDW to identify patients in the New England area with evidence indicating aMCI. To access electronic medical records we will use the CAPRI system, which provides one

interface into the VISTA systems within VISN 1. We will review these data to confirm specific eligibility criteria.

6.2 Subject Inclusion Criteria

1. aMCI based on published criteria (Petersen, 2004)
2. 50 years of age or older
3. Ability to use a telephone without assistance

6.3 Subject Exclusion Criteria

1. Angina pectoris (unless symptomatically resolved post-revascularization)
2. History of myocardial infarction (MI) within 6 months, or remote (>6 months) MI with current ischemia on an exercise stress test
3. History of ventricular dysrhythmia requiring current therapy, or current atrial fibrillation without adequate rate control (resting HR <90)
4. Participation in a regular exercise program (2 or more times weekly for 30 minutes or longer per session) during the previous 2 months
5. Other conditions limiting the ability to participate or associated with poor short-term prognosis, for example, severe degenerative joint disease, cerebrovascular accident with severe residual deficits, severe peripheral neuropathy, severe depression, advanced cancer, or renal failure on renal dialysis

7. Data Collection/ Study Measures

7.1 Baseline Evaluation

Two episodic memory tests will be administered: the Auditory Verbal Learning Test (Ivnik et al., 1992) and the Wechsler Memory Scale Visual Reproduction-II (delayed recall) (Wechsler, 2009). In addition, the Mini-Mental State Examination (MMSE), the Functional Activities Questionnaire (Pfeffer et al., 1982), the Community Healthy Activities Model Program for Seniors (CHAMPS) physical activity questionnaire (Stewart et al., 2001), and the Clinical Dementia Rating (CDR) (Morris, 1993) will be administered. The diagnosis of aMCI will be based on published criteria (Petersen, 2004) including the following: a subjective memory complaint; an Auditory Verbal Learning score or Visual Reproduction score ≥1.5 SD below an age- and education-adjusted norm; a CDR score of 0.5; a score of 24 to 30 on the MMSE; no or mild difficulties in functional activities as assessed by the CDR and the Functional Activities Questionnaire (Pfeffer et al., 1982). Participants who do meet the criteria for aMCI will be withdrawn and therefore, will not complete any further evaluations or participate in the interventions. Participants with confirmed aMCI will then complete the Wechsler Logical Memory Test and the Rey-Osterrieth Complex Figure Test, which will be repeated later as study outcomes.

After completion of the baseline evaluation, half of the 60 participants will be randomized to each study arm (TLC-LIFT, health education control).

7.2 Outcome Measures

A staff member, who is blinded to group assignment, will assess the following outcome measures at baseline and at approximately 6 months at the Jamaica Plain campus of the VA Boston Healthcare System. The Logical Memory task, a subtest from the Wechsler Memory Scale-IV (Wechsler, 2009), will be administered. Two short stories (Story A and B) will be read aloud to the participant. The participant will then be instructed to recall details of the stories immediately and after 30 minutes according to the manual guidelines. Gomar et al. (2014) reported that the Logical Memory Test was significantly associated with

conversion from MCI to AD in an American Alzheimer's Disease Neuroimaging Initiative (ADNI) sample.

The Rey-Osterrieth Complex Figure Test will be administered following the guidelines of the Meyers and Meyers manual (1995). Participants will be given a complex figure stimulus card and asked to copy this figure by hand. After 3 minutes the participant will be asked to draw the figure from memory. Then, 30 minutes later the participant will be asked to again draw the figure from memory. This test has been shown to be predictive of MCI conversion to AD in an ADNI sample (Borroni et al., 2006) and to improve following 24 weeks of resistance exercise training (Cassilhas et al., 2007).

8.3 Data Management and Security

For the purposes of this study, each subject will be assigned a unique randomly generated ID number, which will be used on all electronic data stored locally. A walk across file will be maintained to link the subject with the random ID number and stored in a separate location from all other data extracted. Only the study coordinator and PI will have access permissions to this file.

All electronic databases related to this protocol will be stored locally on a VA server in an entry controlled, locked room at the Jamaica Plain campus of the VA Boston Healthcare System. There are multiple levels of security to ensure the integrity and confidentiality of all data. The computer system operates entirely within the VA network, which is protected by a firewall maintained by the VA Office of Information Technology. Part of the maintenance of the VA server is that it is backed up regularly; therefore, all data related to this protocol will be routinely backed up and stored behind the VA firewall. Only authorized users can log on to the server. An additional layer of restrictions is at the file and directory level. Users can only access portions of the data to which they are entitled. Access to all data on the server is password protected. Once study team members are no longer a part of the research team, their access to data and research materials will be terminated and passwords will be changed. Data will not be removed from the VA protected environment at any time. If data needs to transmitted within the VA, it will be securely transmitted using VA approved methods.

All paper forms will be secured in a locked fireproof study cabinet. Only the PI will have keys to the study cabinet. All data will be kept indefinitely or until the law allows their destruction in accordance with the VA Record Control Schedule. Records will be destroyed, when allowed, in the following manner: paper records will be shredded and electronic records will be destroyed in a manner in which they cannot be retrieved. Suspected information security and privacy incidents will be reported within one hour to the Information Security and Privacy Officers and Research Administration.

To minimize data entry errors, all data collected on paper forms will be entered twice by a staff member using software that allows specification of valid responses for each entry field. Upon second entry of each record, the software will analyze each field to check for discrepancies in the two entries. Entry errors will be corrected on the spot and any errors requiring more extensive review will be deleted and re-keyed after the errors are resolved. In addition, the study coordinator will perform a careful quality assessment of all measures through logic and consistency checks and distributional assessment of overall distributions of responses. Data at follow-up exams will be compared to previous data for longitudinal consistency. Any patterns in missing or erroneous data will be discussed with the research assistants collecting the data to determine the cause of the problem and what corrective measures will be taken. Databases will be carefully versioned so that all analyses can be clearly audited.

8. Statistical Analysis Plan

We will estimate the mean and SD of within-person change in episodic memory (Rey-Osterrieth Figure Test, Wechsler Logical Memory Test) over 6 months in the intervention and control groups. We will estimate the difference between the intervention and control groups on change in these two variables from baseline to 6 months and will estimate the effect size given by Cohen's d, which equals $(M_1 - M_2)/SD_{pooled}$, where M_1 is the mean change in the intervention group, M_2 is the mean change in the control group, and SD_{pooled} is the pooled within-group SD of change. These effect size measures will be used as a basis for sample size calculations for

a proposed larger study.

9. References

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