Water-based Activity to Enhance Recall in Veterans

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02. Specific Aims

Persons with Mild Cognitive Impairment (MCI) have essentially normal functional activities yet experience cognitive impairment, of which they are aware. They are ideal subjects for intervention because they are able to more fully participate in their treatment than individuals with greater cognitive impairment. Interventions at this juncture may prevent or delay additional cognitive impairment. Rates of conversion to Alzheimer's disease (AD) can range from 4.9% to 16% (Mitchell & Ahiri-Feshki, 2009), with a predicted global AD prevalence of 106.8 million by 2050. It has been suggested that an intervention that could delay the onset or conversion to AD by a little as 12 months would lead to 9.2 million fewer global AD cases (Brookmeyer et al., 2007).

Cognitive training (CT) programs have been established as an efficacious alternative to pharmacological treatments for the improvement of memory in nondemented older adults (Rebok et al., 2007); however, at higher levels of cognitive impairment beneficial effects were reduced (O'Hara et al., 2007). Nonetheless, our most recent work using an established CT program demonstrated some benefit for patients with MCI, albeit less than seen in healthy older adults (Yesavage et al., 2008). Efforts to develop augmentation strategies to further enhance the benefit those with cognitive impairment may gain from these treatments have had some success. Specifically, physical exercise has been shown to have both immediate and long-term effects on memory (Geda et al., 2010) and a possible protective effect against some neurodegenerative diseases (Pontifex et al., 2009). The majority of the physical exercise research has examined the cognitive effects of aerobic and resistance exercises using a combination of walking or gym-based activities. While these exercises are successful in reaching recommended cardiovascular training zone, many older adults, and particularly older veterans, are unable to participate in these weight-bearing exercises due to numerous medical conditions including rheumatoid and osteoarthritis, gait and balance disorders, and limited mobility. Water-based exercise is the fourth most popular sports activity in the United States and is frequently recommended for older adults (US Census Bureau, 2012); however, little is known about the impact it has on cognitive function. This is the first study to include a water-based exercise training program as a component of an intervention for veterans with MCI.

Few studies have examined the effectiveness of an exercise training program coupled with a memory training program. Given the success of exercise programs with healthy older adults and evidence of some positive effects of in MCI patients, it is important to determine if alternative approaches, such as water-based activity, will extend the benefit for those individuals in whom weight-bearing exercise is not possible. The knowledge gained from this proposal will lay the groundwork for a large-scale clinical trial testing hypotheses about the efficacy of nonpharmacological interventions that target cognitive impairment in persons with MCI. The goal of pilot work is to ascertain that the proposed methods are adequate for a large-scale clinical trial in terms of recruitment and retention of appropriate subjects, inclusion and exclusion criteria, appropriateness of treatment condition, and measures.

The aims listed below will be tested in a two-phase single-arm trial conducted at the VA Palo Alto Health Care System (VAPAHCS) that will include: 1) a physical exercise phase and 2) a cognitive training phase. The six-month exercise phase will consist of non-weight bearing water-based physical exercises. After the six-month exercise phase, veterans will complete a two-week cognitive training program. This two-year proposal will include 50 veterans with MCI aged 50 years to 90.

Specific Aim 1: To determine the feasibility of a randomized, controlled trial combining physical activity + cognitive training in persons with MCI as shown by good recruitment and retention rates.
Specific Aim 2: To evaluate the appropriateness of suggested inclusion and exclusion criteria for the aims of the proposed project.
Specific Aim 3: To evaluate appropriateness of the water-based physical exercise + cognitive training (WATER + CT) conditions for study goals.
Specific Aim 4: To assess the ability of selected outcome measurement techniques to determine the efficacy of WATER+CT.
Specific Aim 5: To examine outcome "moderator" and "mediator" measurement techniques to determine: a) in whom and under what conditions clinically relevant change occurs and b) the mechanisms through which clinically relevant change occurs.

2a. RESEARCH PLAN

BACKGROUND/SIGNIFICANCE

Veterans are at an Increased Risk of Cognitive Decline. Vietnam veterans are at an increased risk of cognitive decline due to multiple psychiatric and medical illnesses (Krishnan et al., 2005; Office of Quality and Performance VHA, 2000) such as Post-Traumatic Stress Disorder (Yaffe et al., 2010), sleep apnea (O'Hara et al., 2009), traumatic brain injury (Bazararian et al., 2009), vascular risk factors such as hypertension, hypercholesterolamenia, diabetes mellitus, smoking, and obesity (Richard et al., 2010), and lifestyle factors such as physical and cognitive inactivity (Yaffe et al., 2014). These risk factors account for a significant number of the cases of Alzheimer's disease (AD) in veterans. In 2020,it is estimated 75,000 veterans will develop AD due to hypertension; 63,000 to obesity; 55,000 to smoking; 51,000 to physical inactivity; 49,000 to dyslipidemia; and 19,000 to diabetes (Veitch et al., 2013). Clearly veterans are particularly vulnerable to cognitive decline, and thus are in need of methods to prevent or delay cognitive impairment.

Modifiable Risk Factors Are a Target for Intervention. Veterans have numerous risk factors for cognitive impairment; however some of these risk factors are modifiable thus may be a target for intervention. It has been estimated that a 25% reduction of modifiable risk factors could prevent 492,000 cases in the United States and up to 3 million cases globally. Modifiable risk factors include health-related and lifestyle factors like hypertension, obesity, depression, physical inactivity, smoking, diabetes, and cognitive inactivity (Yaffe et al., 2014T). These health-related and lifestyle factors are an opportunity for intervention to prevent or delay cognitive impairment in veterans.

Cognitive Training Has Limitations and Identification of Augmentation Strategies is Necessary. Several groups, including our own, have documented the efficacy of cognitive training (CT) in non-demented older adults (Ball et al., 2002; Fairchild & Scogin, 2010). A meta-analytic study of CT in healthy older adults revealed that compared to a control or treatment as usual, CT improved performance on measures of executive functioning (working memory; processing speed), measures of memory (face-name recall; immediate recall; and paired associates); and general composite of memory (Kelly et al., 2014). Efforts to extend these benefits to those with MCI have had modest success with effect sizes ranging from 0.00 to 2.52 (Jean et al., 2010). Persons with MCI have been shown ability to learn specific information such as new verbal information (Akhtar et al., 2006) and name-face pairs, and that this learning is aided by mnemonics that use visual imagery and nicknames (Hampstead et al., 2008). Yet even with these aids, the cognitive gains seen in persons with MCI are less than those seen in non-demented older adults (Fairchild et al., 2013, Stott et al., 2011).

Physical Activity is Beneficial to Cognition. It is widely accepted that regular physical activity leads to improved health outcomes (Sun et al., 2010) and these benefits have been found to extend to late life cognitive function. A recent meta-analysis reported that physical activity was associated with an 18% reduction of the risk of dementia (Blondell et al., 2014). Furthermore, there appears to be a dose response with the intensity of physical activity and cognitive functioning in older adults as moderate to vigorous intensity physical activity is associated with better cognitive function than low light intensity physical activity (Kerr et al., 2013). While exercising at mid-life reduced risk of MCI by 39%, exercising in late-life reduced risk of MCI by 33% (Geda et al. 2010), thus it would seem that exercise is an intervention that could be implemented throughout the lifespan.

Several possibilities exist as to how physical activity impacts cognition. Two primary mechanisms of change that have received increased attention are: 1) improvement in cardiorespiratory fitness with reduction in vascular risk factors (Richardson et al., 2001) and 2) increased expression of brain derived neurotropic factor (BDNF). BDNF induces hippocampal neurogenesis, which influences neural plasticity and results in improved learning and memory (Lista & Sorrentino, 2010). Both vascular risk factors and BDNF are modifiable through physical activity thus both present as potential mechanisms through which physical activity exerts its positive effect on cognition. It is plausible that by improving neural plasticity or reducing vascular risk factors prior to beginning cognitive training, we can augment the effects of a cognitive training program. Put a different, if we are able to improve cognitive mechanisms, such as working memory, PRIOR to cognitive training, persons with MCI may receive greater benefit from the cognitive training program due to improved neural plasticity. Please see the Preliminary Work section for supporting evidence from our Current Work.

Exercise Trials for Older Adults Show Promise as an Intervention. Clinical trials of physical exercise and its effects on cognition in older adults with and without cognitive decline have noted benefits ranging from significant gains in one-third of the studies of healthy older adults and to significant gains in two-thirds of the studies of cognitively impaired older adults (Colcombe et al., 2003; van Uffelin et al., 2008). There is also some evidence that exercise trials show promise as an intervention to prevent or delay cognitive impairment in persons with MCI (Baker et al., 2010) but this research is plagued by methodological issues including small *n* designs, lack

of adequate follow-up, and lack of objective measurement of physical activity (Blondell et al., 2014). Furthermore, virtually all exercise trials targeting cognitive impairment have used land-based and weight-bearing physical exercises. This effectively limits the generalizability of the results to those who are physically able to engage in those types of exercises. Yet, many older adults, and particularly older veterans, have injuries or illnesses that limit their mobility and their ability to participate in weight-bearing exercises at the recommended level. Given the possible dose-response between physical activity intensity and cognitive functioning (Kerr et al., 2014), it is imperative that we identify cognitively beneficial non-weight bearing physical exercises in which persons with limited mobility can fully participate.

What is the Relationship Between Non-Weight Bearing Exercises and Cognition? Older veterans experience mobility-limiting injuries and illnesses (i.e., obesity, diabetes, and degenerative disc and cartilage diseases) at high rates (Yaffe et al., 2014). For those with mobility issues, weight-bearing activities, such as walking, jogging, or running; are exceedingly difficult if not impossible. Non-weight bearing exercises are ideal for persons with mobility issues due to injury, illness, or advanced age. Water-based activity presents as an ideal form of non-weight bearing exercise as it allows for freedom of movement while increasing flexibility, cardiovascular endurance, and muscular strength. It has been shown to produce positive hypotensive effects and improved vascular functioning in formerly sedentary older adults (Nualnim et al., 2012). No study to date has used aquatic exercise as an intervention to improve cognitive function, yet there is some evidence that aquatic exercise is associated with better cognitive function. In a cross-sectional analysis, Abou-Dest and colleagues (2012) compared young adults, sedentary older adults, and self-identified older swimmers on measures of cardiorespiratory fitness and executive function. While young adults performed better than older adults on all measures of cognitive function, regular swimming in older adults was related to better performance on some tasks of executive functioning.

Combined Training Programs Have Mixed Effects. Given the beneficial effects of physical exercise and CT on cognition, the reasons for their inclusion in a combined trial are apparent. Recently, Barnes and colleagues (2013) published the findings of the MAX Trial, which was a RCT that examined the combined effects of physical activity plus mental activity on cognitive function in a group of older adults with cognitive complaints. The study compared four treatment conditions that combined different types of physical exercise (stretching vs. aerobic) with different types of mental activity (computer-based cognitive training vs. educational DVDs) over the course of 12 weeks. Results indicated that while all participants evidenced significant improvements on global measures of cognitive function, there were no group differences in performance. Prior research has documented that a minimum of six months of regular moderate intensity exercise is necessary to achieve meaningful cognitive change (Geda et al. 2010), thus it is possible with a longer intervention a different pattern of results may have emerged.

PRELIMINARY WORK

This work represents a collaborative effort between experts in the field of cognition and exercise training. We are currently conducting a Department of Defense (DOD) funded RCT of the effects of physical exercise and cognitive training in veterans with MCI. Based on our current work, we know that exercise training may augment the effects of CT, thereby increasing its benefit; however it is not known if non-weight bearing exercise, specifically water-based physical exercise, produces a similar effect. Data presented below highlight preliminary work relevant to the proposed project.

Studies Accomplished: Cognitive Training. With over 25 years' experience in CT, we have investigated the efficacy of a pharmacological augmentation strategy for nondemented older adults (Yesavage et al., 2008). This RCT compared two groups: 1) Donepezil + CT and 2) Placebo + CT. The overall results of the trial suggested that Donepezil did not augment the effect of CT as both groups demonstrated improvement from baseline to 52-week follow-up on delayed recall of a word-list (Donepezil + CT group: mean gain score = 4.5, SD = 4.0, $p < 0.001$; Placebo + CT group: mean gain score = 4.3, SD = 4.2, $p < 0.001$) and a name-face task (Donepezil + CT group: mean gain score = 1.2, SD =2.7; Placebo + CT group: mean gain score = 1.6, SD = 2.7).

Studies Accomplished: Exercise Training. Dr. Myers has studied and written extensively on exercise training and its benefits for cardiovascular disease patients. Most recently he and his colleagues at VAPAHCS published the results of a randomized prospective longitudinal study of the effects of supervised combined aerobic and resistance exercise training for persons with abdominal aortic aneurysm (Myers et al., 2014). Results indicated that these methods were safe and that participants on average, increased time spent in physical activity to approximately one hour daily of modest exercise which was an improvement of ~30 - 40%. These improvements were notably greater than in similar prior exercise training studies. The authors posited that these marked improvements were partially due to the rigorous activity surveillance and case-managed approach

used in that trial. The proposed project will employ these same methods of surveillance and a case-managed approach, though coupled with water-based physical exercise.

Ongoing Study: Exercise Training + Cognitive Training. We have successfully collaborated on the current DOD-funded project, "A Combined Training Program for Veterans with Amnestic Mild Cognitive." This project represents the merging of our interests, namely cognitive training and exercise training, towards a new target problem. At completion in *September 2015*, this ongoing RCT will compare the effects of a combined aerobic and resistance exercise program + cognitive training (CARE + CT) program to a stretching exercise + cognitive training (SE+ CT) program. Interim results indicate that the intervention is relatively well received by participants, as recruitment and retention rates are positive. To date, fifty-five veterans have been randomized to either the CARE+CT or SE+CT condition. Approximately 8% of those randomized have been lost to follow-up. Reasons for discontinuing study participation were largely due to development of acute illness (i.e., CVA or cancer) or injury (i.e., concussion sustained after fall) that prevented further study participation. There are no group-based differential dropout rates. *The preliminary results of this trial suggest that physical exercise does augment the effect of cognitive training as the CARE+CT group, compared to the SE+CT group, demonstrated clinically significant improvements on measures of learning (CARE+CT group: mean gain score = 13.5, SD=11.21; SE+CT group: mean gain score = 9.5, SD=9.68) and delayed recall (CARE+CT group: mean gain score = 7.25, SD=4.11; SE+CT group: mean gain score = 5.83; SD=2.69).*

Over *1500* veterans have been screened study participation and approximately 15% of those were ineligible due solely to musculoskeletal injuries and illnesses (i.e., impaired gait, osteoporosis, degenerative disc and joint disease) that prevent full engagement in weight-bearing exercises. Given the prevalence of these illnesses and injuries in veterans coupled with the increased risk of cognitive impairment, it is vitally important that we investigate methods to extend the cognitive benefit of physical exercise and cognitive training to all

Proposed Study Strengths. This study has numerous strengths. First, the team of investigators includes experts in the field of cognitive impairment, CT, and exercise physiology who have successfully led a number of funded projects. The proposed project is a logical, and necessary, progression of the investigators current work. Thus, the infrastructure to support this feasibility study is already in place. Second, the facilities at VAPAHCS are uniquely well-suited to run a study of this nature. The CT classes will be conducted at MIRECC which has dedicated classroom space for Center staff. The VAPAHCS Exercise Testing Laboratory has state-of-the-art equipment to measure ventilatory gas exchange, hemodynamic and ECG responses to exercise. *The VAPAHCS has two aquatic facilities with lap pools and a therapy pool, so as to best meet the physical needs of veterans.* Third, the cognitive training intervention in this study has been successfully used in prior research studies (Yesavage et al., 2008) as have components of the exercise training (Myers et al., 2014) thus, we are applying a novel intervention (WATER) with proven treatments (CT) toward improvement of a growing problem for veterans (MCI).

Implications of this Research for Aging Research. Since this is the first study to evaluate a non-weight bearing exercise training augmentation for CT program, results should be informative as to the methodology of the proposed trial. We anticipate that this study will result in the preparation of a VA Rehab R&D Merit to test, on a larger scale, the efficacy of a combined training program, including non-weight bearing exercise and CT, to improve cognition in older veterans.

RESEARCH DESIGN

Proposed Study Design. The purpose of the proposed study to establish feasibility of a two-phase single-arm trial of water-based physical exercise (WATER) + cognitive training (CT) in veterans with MCI. Veterans *(*n = 50*)* will participate in a six-month water-based physical exercise program and then transition to a four-week CT program. Recruitment Site. Participants will be recruited via clinician referrals, media advertisements, local veteran agencies, outpatient clinics at VAPAHCS, and the greater Bay Area community. We will also recruit from the Stanford/VA Aging Clinical Research Center (ACRC), which provides diagnostic and referral services for persons experiencing cognitive impairment. Participants. Inclusion criteria are designed to identify persons with MCI based on criteria set forth Albert and associates (2011). Briefly, those criteria include: 1) cognitive complaint (self-report and/or informant); 2) cognitive impairment in one or more domains; 3) preserved independence of functional abilities; and 4) absence of dementia. We recognize variants of MCI may involve impairment in other cognitive domains than memory; however, for the purposes of this proposal, we will only include those with amnestic MCI. Rationale for Inclusion and Exclusion Criteria. The goal of these inclusion and exclusion criteria is to provide a well-characterized sample appropriate for participation in an exercise trial. To ensure that participants will be properly evaluated, rigorous inclusion and exclusion criteria will be applied as enumerated below. These inclusion and exclusion criteria are a combination of those used previously in our

CT(Yesavage et al., 2008) and exercise training (Myers et al., 2010) so as to ensure participants are appropriate for both aspects of the intervention. Inclusion or exclusion from the protocol will be based on veterans' responses to semi-structured clinical interviews, specific neuropsychological measures, functional assessment, approval of primary care provider, and a cardiopulmonary exercise test. Inclusion criteria: 1) veterans aged 50 – 90; 2) diagnosis of MCI; 3) available informant; 4) visual and auditory acuity to allow neuropsychological testing; 5) willingness to participate in exercise training + cognitive training program for eight months; *6) limited mobility due to musculoskeletal injury or illness;* and 7) approval by primary care provider. Exclusion criteria: 1) current severe psychiatric disorder; 2) diagnosis of dementia, CDR > 0.5; modified Hachinski score ≥ 4; or delirium; 3) history of neurological disorder or systemic illness affecting CNS function; 4) acute illness or unstable chronic illness; 5) current severe cardiac disease; 6) inability to participate in an exercise tress test; 7) morbid obesity (BMI > 39); 8) inability to read, verbalize understanding and voluntarily sign the Informed Consent. Please see the Human Subjects for greater detail regarding Inclusion and Exclusion criteria.

Enrollment and Study Implementation. Study staff will explain the study to veterans and, if interested, the consent form and a one page project description will be mailed. Appointments will then be made for three days of evaluation. Day 1: informed consent; cognitive, psychological and functional screening; Day 2: neuropsychological and self-report measures; and Day 3: cardiopulmonary testing and biological measures. When these evaluations are completed, eligible participants will be scheduled for the first exercise session within two weeks. The exercise training portion of intervention is approximately 24 weeks. After completion of the exercise training, participants will be re-assessed with the cardiopulmonary exercise testing, cognitive measures, biological measures, outcome measures, and measures of physical activity. Participants will then begin four weeks of thrice weekly cognitive training classes at VAPAHCS. At completion of the cognitive training, participants will undergo the post-treatment assessment: cardiopulmonary exercise testing, cognitive measures, biological measures, outcome measures, and measures of physical activity. Participants will receive payments of $50 for each set of assessments completed.

We plan to telephone screen 200 participants, based upon prior work (Myers et al., 2010; Yesavage et al. 2008), half or 100 are expected to proceed to an in-office evaluation (10 per month), half, or approximately 50 enrolled (5 per month). Dropouts will not be replaced as this is a feasibility study and an aim is to evaluate the appropriateness of the inclusion and exclusion criteria.

All in-house exercise sessions and activity surveillance will be supervised by exercise physiologists certified by the American College of Sports Medicine (ACSM). CT will be taught by the PI.

WATER: Initially all participants in this condition will undergo supervised exercise sessions three times a week at *the Aquatic facilities located at the Palo Alto VA and Menlo Park VA.* These sessions will continue for a two-month period. During these group-based sessions, participants will begin their training program, demonstrate understanding of exercise prescription and use of activity monitoring devices and heart rate logs, and receive guidance and instruction on what is expected of them during the study. Participants will then have the option to transition to a self-paced program with VAPAHCS-based exercise sessions repeated every two weeks for the duration of this four-month phase. *For those veterans who do not wish to transition to a self-paced program, they will continue to attend group-based pool exercise at VAPAHCS. Those veterans who do transition to a self-paced program will have access to the VAPAHCS aquatic facilities during normal ''drop-in'' hours so that they may continue their thrice-weekly aquatic exercises*. All pool-based exercise sessions will include five-minute warm-up and cool-down sessions prior to and following a combination of land-based stretching and water-based exercises to achieve the targeted cardiovascular training zone. *These aquatic exercises will incorporate resistance training, functional exercise movements, and aquatic plyometric activities. Participants will use assistive devices such as water dumbbells, noodles, inflatable boards, and kickboards so as to engage their entire body in resistance exercise and provide needed support. They will also engage in aerobic activities such as aqua walking or jogging and plyometric activities such as skipping or single leg hopping while in the pool.* Exercise intensities will initially be targeted to achieve 60% of heart rate for 30 minutes with intensity documented every 5 minutes (heart rate and rate of perceived effort/RPE). This will progress according to established guidelines of the ACSM, with the goal to increase intensity and duration to 70% to 80% heart rate reserve and 45 minutes, respectively. Participants will be asked to document daily pedometer steps and heart rate/RPE at 5-minute increments during exercise sessions.

CT: All participants will complete a four-week CT course after the six-month exercise phase. The CT will follow the format of a "comprehensive extended" training developed in our earlier work (Fairchild et al., 2010; Yesavage et al., 2008). Training procedures include non-mnemonic "pre-training" combined with mnemonic training. This includes six hours of pre-training in a classroom-type setting (two hours/day) consisting of imagery training, semantic elaboration training, and relaxation training. Once pre-training is complete, all participants com-

plete ten hours of mnemonic training in: 1) list-learning mnemonic and 2) name-face mnemonic. **Method-of-Loci mnemonic**: This mnemonic involves associating a list of words to a fixed list of places (or "loci"). **Name/face mnemonic***:* This mnemonic involves learning faces and names through a three-step technique: 1) choosing a prominent feature of persons face, 2) developing a concrete high imagery transformation of person's name, and 3) forming a visual image that associates the facial feature with the name. Design Considerations. Selection of a single-arm trial was based upon the purpose of the study, which is to establish feasibility of the intervention. Thus a direct comparison group is not needed at this time; however, should this intervention be shown feasible, an active control would be appropriate for inclusion as a direct comparator. A parallel-groups design was chosen so the effect of water-based exercise could be determined separately from that of the CT, thus allowing for preliminary evaluation of water-based exercise alone as an augmentation strategy.

Sample size: One of the proposed project's aims is to examine recruitment and retention rates for a MCI population in a treatment study. No prior research has examined a water-based physical exercise + CT intervention. To guide power analyses for the current project, studies from both the exercise training and the CT literature were examined. A meta-analysis (Li et al., 2011) of cognitive interventions for persons with MCI reported a modest effect size (0.45). The literature on effect sizes for aerobic interventions for cognitive improvement is more limited and the effects reported are less consistent, hence we assume a small effect size of (0.35), less than that expected for the CT. Using the smaller of the two effect sizes (0.35), we would need 274 participants to test the efficacy of this treatment. In the proposed feasibility study, we will randomize 50 participants over the course of the trial, which we hope will generate more accurate estimates of expected effect sizes as well as demonstrate recruitment feasibility. Ultimately we hope to demonstrate that in a larger RCT over 5 years, recruiting at the same rate, we will be able to recruit the necessary 274 participants.

Measures. There are three primary time points (Time 1: Screening/Baseline, Time 2: End of Exercise Training, Time 3: End of CT) at which participants will complete cognitive, psychological, physiological, and biological assessments. Screening measures include measures of episodic memory (Logical Memory I and II from WMS-IV; Wechsler, 2008), mental health (MINI; Sheehan et al., 2002), activities of daily living (Functional Activities Questionnaire (FAQ); Pfeiffer, 1982), a semi-structured interview of cognitive impairment (Clinical Dementia Rating Scale (CDR); Morris, 1993), and assessment of risk factors for vascular dementia (modified Hachinski; Rosen et al., 1980). Measures collected during the cardiopulmonary exercise testing include the VA Prognostic Score, and Veterans Specific Activity Questionnaire (VSAQ; Myers et al., 1994), all of which will be used to estimate risk and assess suitability for exercise training (Gibbons et al., 2002; Morrow et al., 1993). The VSAQ will be used specifically to estimate exercise capacity and thus individualize the intensity during the cardiopulmonary exercise test. Veterans who are not eligible to participate because of cognitive, psychiatric, or medical issues will be referred for further diagnostic work-up or treatment to the Memory Disorders Clinic at VAPAHCS, which provides diagnostic services to older veterans. *Data collected regarding the reasons for exclusion will be analyzed to provide support for the appropriateness of the inclusion and exclusion criteria*. Feasibility will be assessed through examination of recruitment and retention rates. Participant adherence: Participants will wear heart rate monitors during exercise sessions and pedometers throughout the exercise phase of treatment. They will also log their activities on a 7-day activity recall questionnaire. Data from the pedometers, heart rate monitors and the 7-day activity recall will be collected from participants when they return for the VAPAHCS-based exercise sessions. During CT, participants will have homework and complete quizzes assessing their knowledge of the techniques. They will also complete logs tracking their use of mnemonic techniques. These quizzes and logs of homework completed will serve as measures of participant adherence during the cognitive training portion of the study. The proposed primary outcome measure is measure of delayed recall on a 16-item Word-List Task. Equivalent alternate lists of words will be used to counterbalance across time points. The proposed secondary outcome measure is recall of a 12-item Name-Face Pair Task. Both the Word-List Task and the Name-Face Pair Task have been used successfully in our prior research and have been shown to be sensitive to the mnemonics taught in the CT (i.e., Method of Loci and Name-Face Mnemonic) (Yesavage et al., 2008). Cognitive measures include measures of verbal learning and memory (Rey Auditory-Verbal Learning Test; Lezak, 2004), working memory (Digit Span from WAIS-IV; 2008), processing speed (Symbol Digit Modalities Test; Smith, 1991); attention (Stroop Color and Word Test; Golden 1978), and subjective memory impairment (Multifactorial Memory Questionnaire; Troyer and Rich, 2002). Self-report measures of physical activity include the Yale Physical Activity Survey (DiPietro et al., 1993). Finally, biological measures will be collected from participants. These include measures of DNA, which will be collected through blood collected at VAPAHCS. We will examine both APOE and BDNF genotypes. The APOE genotyping will be performed according to the restriction isotyping protocol of Hixson and Vernier (1990). BDNF genotyping will also be conducted in-house by Dr. Hallmayer's staff. Additionally, plasma concentrations of BDNF will be measured using

enzyme-linked immunosorbent assay (ELISA). These analyses will be conducted in-house by Dr. Hallmayer's staff.

Database Management and Planned Statistical Analyses

Data Collection and Database Management. There are three proposed testing time points in this study: prior to randomization (T1), at the end of the exercise program and prior to beginning CT (T2), and at the end of the CT (T3). All identifying information will be removed as data are coded by a unique subject number/identifier. Only the PI and her designee will have access to the identifying information linking subject number to name. All data will be checked for completeness and every effort made to obtain missing data. Data storage will be on computerized password protected databases that are backed up nightly. Additionally, our MIRECC and associated laboratories are familiar with the relevant security and confidentiality issues pertaining to genetic materials and take extra safeguards to protect this information.

Data Analyses. Descriptive analyses of categorical variables will include frequency tables; we will compute measures of central tendency (mean, median, standard deviation, and interquartile range) for those continuous variables. Additionally we will examine the distribution of scores on dependent measures to test assumptions of normality and homogeneity of variance and thus make appropriate transformations when necessary.

Specific Aim 1: WATER+CT will be feasible as shown by good recruitment and retention rates. *Statistical Analyses:* To test feasibility of the proposed project, the ratio of enrolled to completed participants will be calculated; ≥ 80% will be considered good retention. Specific Aim 2: To evaluate the appropriateness of suggested inclusion and exclusion criteria for the aims of the proposed project. *Statistical Analyses:* We will examine the reported adverse events for participants as well as reasons for screening failures (i.e., those who are consented but excluded from participation prior to randomization). Descriptive analyses of these data will include frequency tables and be used to provide justification for the proposed inclusion and exclusion criteria or to modify them appropriately. Specific Aim 3: To evaluate appropriateness of the WATER+CT for study goals. *Statistical Analyses:* Appropriateness of treatment conditions will be determined through examination of the participant adherence data. Adherence data will include information from pedometers, heart rate monitors, 7-day activity logs, and cognitive training homework logs. Adequate adherence to exercise prescriptions and CT homework will be defined as completion of ≥80% of assignments as defined by self-report and trainer observation. Specific Aim 4: To assess outcome measurement techniques for participant rate of response in WATER+CT. *Statistical Analyses:* As this is a single-arm trial, a direct comparison between the WATER + CT condition and a comparative condition is not possible. Participants response rate will be determined by examining the percentage of participants who evidence clinically relevant change after study participation. To determine what a clinically relevant difference in the primary outcome measure (delayed recall of a Word List) would be, we reanalyzed data from our initial clinical trial (Yesavage et al., 2008). Our strategy was to look in that study at the difference in baseline scores between 60 year olds and 70 year olds on the same measure as the proposed work. We found that the difference was 1.7 words. We believe that showing such a difference would be clinically meaningful insofar as it represents a decade of aging's effects on memory. This will be an intent-to-treat analysis, thus all data will be analyzed. Specific Aim 5: To examine outcome "moderator" and "mediator" measurement techniques to determine: a) in whom and under what conditions clinically relevant change occurs and b) the mechanisms through which clinically relevant change occurs. Here we are referring to within subjects effects. *Statistical Analyses*: Multiple regression modeling will be performed in a preliminary manner to examine individual differences in treatment response depending or baseline (T1) characteristics (age, level of education, APOE and BDNF genotypes). A significant Response Rate X Moderator interaction indicates a differential response rate, e.g., the response rate depends upon age. Such measures are "moderator" variables, i.e., they are used to determine on whom or under what conditions improvement occurs. Additional analyses will be performed to examine the extent to which individual differences in the efficacy of CT treatments depend upon changes in cardiovascular functioning, BDNF plasma levels, and changes in efficiency of working memory (Digit Span) during combined aerobic and resistance exercise training (T1 to T3). These analyses use changes in these two measures as "mediator" variables, i.e., they are used to determine how or why improvement occurs.

Project Management. To support the Specific Aims stated above, the investigators will perform appropriate tasks within the funding period. The first two months of the funding period (Start-Up Phase) will be devoted to hiring and training of research staff and purchasing activity monitoring devices. The Data Collection Phase will begin in Month 3 and continue through Month 20 to allow adequate time for participants to complete the 8-month long intervention. We will randomize five veterans a month through Month 13. Finally, the Study Close-out Phase will begin in Month 21 with Data Analysis and Manuscript Preparation. These will activities will be completed within Month 24.

Human Subjects Involvement and Characteristics. Involvement of human subjects in the proposed study includes participation in a feasibility study of an water-based physical exercise plus cognitive training adjunctive treatment for Mild Cognitive Impairment (MCI) in older veterans. We expect to enroll a total of 50 veterans, age 50 years old to 90, in this study. Using the criteria put forth by Alberts et al (2011), all veterans will be classified as having amnestic MCI. These veterans will be recruited through clinician referral, media advertisement, and local veteran agencies. Participants will also be recruited from the outpatient clinics of the VA Palo Alto Health Care System (VAPAHCS) as well as the Stanford / VA Aging Clinical Research Center (ACRC).

Inclusion:

- Veterans, aged 50 to 90, of any racial or ethnic group
- Diagnosis of amnestic MCI based on Logical Memory of the Wechsler Memory Scale-IV (WMS-IV) and Functional Activities Questionnaire (FAQ)
- Available informant
- Visual and auditory acuity to allow neuropsychological testing
- Willingness to participate in exercise training + cognitive training program for 8 months duration
- *Musculoskeletal illness or injury (i.e., osteoporosis, degenerative disc or joint disease, arthritis) that would make weight-bearing exercise difficult*
- Approval by Primary Care Provider to participate in water-based physical exercise

Exclusion:

Psychiatric Exclusions

- Current, uncontrolled severe psychiatric disorder, such as Bipolar I, Schizophrenia, or Major Depressive Disorder as determined by the Mini International Neuropsychiatric Interview (MINI)
- Diagnosis of dementia, Clinical Dementia Rating Scale (CDR) > 0.5; modified Hachinksi score ≥ 4; or delirium. Those veterans with scores indicative of dementia (CDR > 0.5, modified Hachinski ≥ 4) will be referred to the Memory Disorders Clinic at VAPAHCS for a full diagnostic work-up.

Medical Exclusions

- History of neurological (e.g., multiple sclerosis, seizure disorder, stroke,) or system illness affecting CNS function (e.g., liver failure, kidney failure, congestive heart failure, systemic cancer)
- Acute illness or unstable chronic illness, e.g., history of severe liver disease (cirrhosis, esophageal varices, ascites, portal hypertension, hepatic encephalopathy)
- Current severe cardiac disease (e.g., uncontrolled atrial fibrillation, defined as mean 24 hour heart rate >85 beats/min, or 24 hour maximal ventricular rate >150 beats/min; uncontrolled ventricular arrythmias, defined as recurrent ventricular tachycardia >3 beats in succession, or 24 hour PVC count >20%; active pericarditis or myocarditis; Class III/IV heart failure and / or ejection fraction < 20%; thrombophlebitis; pulmonary disease with a drop in O_2 Sat with exercise to 90% without oxygen; embolism within past 6 months)
- Inability to participate in an exercise stress test
- Morbid obesity (BMI > 39)
- Inability to read, verbalize understanding and voluntarily sign the Informed Consent

Justification of Inclusion / Exclusion Criteria. The purpose of the inclusion and exclusion criteria is to provide a well-defined sample of older veterans with amnestic MCI that are appropriate for participation in both an

exercise training and cognitive training trial. The criteria chosen were based upon those used in prior studies of cognitive training with older adults with MCI (Yesavage et al., 2008) and those recommended by the American College of Sports Medicine (2006). Prior studies have used these criteria to successfully recruit veterans for cognitive training interventions (Yesavage et al., 2008) and exercise training interventions (Myers et al., 2010). Determination of inclusion and exclusion criteria will be based on veterans' responses to semi-structured clinical interviews (MINI and CDR), specific neuropsychological measures (Logical Memory of WMS-IV; CDR), functional assessment (FAQ), assessment of risk for vascular dementia (modified Hachinski score), a physical examination by a clinician, and a cardiopulmonary exercise test.

Recruitment Procedures. Participants will be recruited through clinician referral, media advertisement, and local veteran agencies. Other sources of recruitment include the ACRC and VAPAHCS outpatient clinics. Specifically, these outpatient clinics include but are not limited to those within the Sierra Pacific MIRECC (Geriatric Memory Clinic) and the VAPAHCS Psychology Service. Recruitment will be the responsibility of the PI and the exercise physiologists. Dr. Fairchild and staff will work closely with providers in these clinics and centers to identify potential participants as well as be available to speak with the veterans should they have questions about the study. Researchers in our center have a successful track record of recruiting subjects for cognitive training studies (Fairchild & Scogin, 2010; Yesavage et al., 2008) as well in exercise trials (Myers et al., 2010). We have strong ties with VA and community providers. These funds will be used to purchase "air time" on radio stations as well as print media to be used around the larger Bay Area community.

Study Procedures. Once recruited and successfully screened (i.e., Time 1 assessments), participants will meet with the study staff to develop an exercise prescription based upon the information obtained during the screening process. For the first two months of the exercise training, participants will attend thrice weekly exercise sessions at the VAPAHCS Aquatic Therapy Center. These training sessions will feature a combination of land-based stretching and water-based exercises to achieve the targeted cardiovascular training zone. *All pool-based exercise sessions will include five-minute warm-up and cool-down sessions prior to and following a combination of land-based stretching and water-based exercises to achieve the targeted cardiovascular training zone. These aquatic exercises will incorporate resistance training, functional exercise movements, and aquatic plyometric activities. Participants will use assistive devices such as water dumbbells, noodles, inflatable boards, and kickboards so as to engage their entire body in resistance exercise and provide needed support. They will also engage in aerobic activities such as aqua walking or jogging and plyometric activities such as skipping or single leg hopping while in the pool.* After the initial two months, participants may transition to a self-paced program with study staff-led exercise sessions repeated every 2 weeks for the duration of this 4-month phase. *For those veterans who do not wish to transition to a self-paced program, they will continue to attend group-based pool exercise at VAPAHCS. Those veterans who do transition to a self-paced program will have access to the VAPAHCS aquatic facilities during normal ''drop-in'' hours so that they may continue their thrice-weekly aquatic exercises*. After completion of the exercise-training portion of the intervention, participants will undergo a second series of assessments (i.e., Time 2 assessments). They will then transition to the cognitive training portion of the intervention. The "comprehensive extended" cognitive training program was selected because it has demonstrated efficacy in improvement of delayed recall of the proposed outcome measures (Yesavage et al., 2008). Veterans will participate in 4 weeks of cognitive training before completing the third and final series of assessments (i.e., Time 3 assessments).

Participant safety is of the utmost importance. As such, ACSM-certified exercise physiologists will conduct all exercise sessions and cardiopulmonary testing. During pool-based work, exercise physiologists will be in the water with the veterans, guiding them through the exercises. All staff to veteran ratio will be in dictated by current ACSM standards. In addition to the ACSM-certified exercise physiologists, both Aquatic facilities are fully staffed with lifeguards certified in CPR for Professional Rescuers and Standard First Aid. Lifeguards will be on the pool deck and present during all pool-based exercises. Both Aquatic facilities feature fully operational crash carts that undergo regular inspections. All study and pool staff are trained in basic life support as well as fully knowledgeable of all safety procedures for the facility. Study and pool staff undergo regular facility led safety drills.

Cognitive training classes will be taught by Dr. Fairchild, who is a board certified geropsychologist with considerable expertise in cognition and cognitive training.

Sources of Materials. Data will come from multiple sources:

1. Semi-structured interviews

2. Cognitive Assessments
3. Participant self-report of demographic information, medical history, memory complaints, and physical activity
4. Collateral interviews
5. Physical examination
6. Cardiopulmonary exercise testing
7. Laboratory work-up
8. Biological and Genetic Measures

Only research staff that have completed appropriate training in protection of human subjects at VAPAHCS and Stanford University will have access to the data. Data will be collected using paper-and-pencil measures and by computer. Hard copies of data will be kept in a locked cabinet in locked offices at the MIRECC at VAPAHCS. Electronic data will be stored on a secure computer on password-protected files and coded by subject identifier/ number so that participants cannot be identified by their research record.

Potential Risks

Exercise Testing. Exercise treadmill or bicycle tests will be performed to determine whether interested veterans are eligible for participation. There are rare instances of serious complications such as a heart attack, rhythm disturbance, or death. These occurrences are rare; however, happening in approximately 1 in 10,000 tests. There is also a slight risk of trauma secondary to falling. Additionally, participants may become fatigued or short of breath.

Psychiatric Testing. Psychiatric screening will be performed to determine whether the participant meets inclusion and exclusion criteria for the study. From past experience, potential risk to veterans is expected to be minimal. However, some questions asked during the interview or in the written questionnaires may be potentially distressing to the veterans or may cause them to think about traumatic events or problems that may be anxiety-provoking or upsetting. Veterans who develop suicidal intent will be treated following established procedures of VAPAHCS.

Cognitive Testing. There do not appear to be any significant risks associated with cognitive testing other than the commitment of significant time for participation. Some participants may experience some anxiety during and after the cognitive testing. Those veterans found to have significant cognitive impairment, and thus are excluded from participation in the proposed study, will be referred to the ACRC for a full diagnostic evaluation.

Laboratory Work-Up and Collection of Genetic Data. There is minimal risk of bruising, infection, or fainting from the blood draw to collect laboratory and genetic data. On very rare occasions there may be mild bleeding or bruising at the sampling site.

2. Adequacy of Protection Against Risks

Recruitment and Informed Consent. Participants will be recruited via clinician referrals, media advertisements, and local veteran agencies. Depending on the referral source, potential participants will either call the Center or research staff will send a letter to interested participants informing them of the current study, providing them with a description of the study and with a contact number to volunteer for the study or to obtain further information. Those who volunteer will be invited to join the project and the nature of the experiment will be explained to them. Interested parties will be scheduled for a screening office visit during which informed consent process will be initiated. This will entail a discussion between the veteran and a trained clinician and / or research assistant. This discussion will highlight important aspects of the informed consent form such as details of the project, voluntary participation, and the risks and benefits of participation. Signatures will be obtained only after all questions have been adequately addressed. All participants will be treated in an ethical manner. The following sections describe the measures we will take to minimize risk to participants.

Exercise Testing. All exercise tests will be conducted in the state of the art VAPAHCS Exercise Testing Laboratory which is staffed by the Co-I (Dr. Myers), who is an expert in exercise physiology, as well as two research associates who each have extensive experience in exercise testing. The laboratory is located in the Cardiology division of the main hospital at VAPAHCS, thus if any emergency were to occur, appropriate staff

would be able to respond immediately. Additionally, if a participant becomes fatigued, short of breath, has chest pain, or desires to stop, the exercise treadmill test will be discontinued. All participants will be closely monitored by qualified staff during exercise treadmill testing and thus help can be provided immediately, if needed.

Exercise Training. Complications during exercise training are rare, even among individuals with existing heart disease. The American Heart Association has summarized the literature in this area and has suggested that a complication related to exercise (e.g., serious rhythm disturbance or myocardial infarction) occurs at a rate of once in every 62,000 hours of exercise. All exercise training will be performed using individualized prescriptions in accordance with established guidelines and overseen by trained exercise physiologists.

Psychiatric Screening. For both the psychiatric screening and cognitive testing, confidentiality is assured through the use of study participant ID numbers, and all files are kept in locked cabinets. Any computerized data will be identified by a study participant number. Any documents that obtain both the study participant identification number and the participant's name will be kept in a locked file cabinet separate from the study data. Participants may have their results forwarded to their physician or other health care provider at the participant's request. In the event of discomfort experienced during the psychiatric screening and/or cognitive testing, all participants will be informed that they are free to decline to answer any questions they do not wish to answer, or to stop the interview or testing at any time. Psychiatric screens will be done by psychiatry fellows at the MIRECC who are experienced and sensitive to clinical issues. Clinicians will be available in the case of an adverse event to debrief with the participant. Referrals to the outpatient mental health clinic will be available in the case of an adverse event.

Cognitive Testing. Same procedures as Psychiatric Screening (above).

Laboratory Work-up and Collection of Genetic Data. Because disclosure of genetic information could have psychological consequences, as well as affecting insurability and employment status of participants and/or their relatives, extreme caution is taken to prevent the inadvertent disclosure of genetic information. The consent form states that we do not divulge genetic information to participants, their caregivers, relatives, or their physicians. The actual clinical utility of all genetic testing which we perform at present is unknown. For this reason, it is impossible to provide genetic counseling as to the meaning of results to any individual subjects. Participants are, however, given free access to aggregate genetic data as it appears in publications. Participants are informed that if in the future it becomes possible to provide meaningful genetic counseling based on our results this service will be provided. We plan to follow the special genetic security procedures established at our Center for handling genetic information pertaining to dementia. We take these issues very seriously and will have all procedures followed under this project integrated with the established Center procedures that are summarized below.

Enhanced Security for Genetic Data. The purpose of these procedures is to ensure confidentiality of participant data, with particular reference to genetic information collected on all Center participants. Currently the number of genetic markers of interest to clinicians and researchers is limited but is expected to increase rapidly. Extra safeguards are provided so that this very private and potentially damaging information is carefully managed. We are sensitive to the potential impact of this information on medical insurability of participants and their children. Therefore, each Center participant is assigned a Patient ID number (PATID), and the following steps are taken:

1) The PATID is co-located with a participant's name only where absolutely necessary, e.g., on clinical charts and clinical scheduling records.
2) The Database Manager generates a Biosample ID number for each PATID.
3) The Biosample ID is used to identify biological samples for testing in independent laboratories, but no sample also contains the PATID, participant's name or social security number.
4) Laboratory results are provided to the Database Manager with the Biosample ID but not with the name. Participants' names or social security numbers are not in the central database. Only the Database Manager can match the Biosample ID with the PATID, and the Database Manager does not have access to participant's names.
5) Data analyses and print outs are provided by the Database Manager with PATIDs only in cases where original data are sent back to the investigator who collected it for verification of data integrity.

6) Typical data analyses, such as correlations that span multiple datasets, and printouts provided to investigators other than those who directly collected the data, are provided without PATIDs only after they complete the standard data request forms and the request has been approved.

Genetic data security meetings are held periodically for the Center. All PIs, collaborating investigators, and staff involved in the acquisition, handling, storage, or analysis of genetic data are required to attend. The following topics are discussed:

- Information contained in DNA samples.
- Informed consent for DNA samples and genotyping.
- How disclosure of genotypes could affect subjects.
- How disclosure of genotypes could affect relatives of subjects.
- How to respond to inquiries about genetic data.
- Security measures to prevent disclosure of genetic information.
- Transmission of genetic data among components of the Center.

All personnel collecting, managing, interpreting or receiving genetic data are required to sign a statement that they attended this meeting where the above topics were discussed.

In addition, we have created a formal Data Security Policy document which is followed by all researchers. All protected health information (PHI) can only be stored and accessed from a secure server.

Adverse Events and Serious Adverse Events. An Adverse Event (AE) is defined by the ICH for Clinical Safety Data Management as any untoward physical or psychological occurrence in a human subject participating in research. The AE does not necessarily have to have a causal relationship with the pharmacological product, study intervention or assessment. An AE can, therefore, be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medicinal (investigational) product. All AEs that commence during the treatment phase will be collected and followed until resolution OR for thirty days after the veterans participation in the study ends.

Serious Adverse Events (SAEs) are a subset of adverse events and are defined by the ICH for Clinical Safety Data Management as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly / birth defect or
- Any other condition that, based upon medical judgment, may jeopardize the subject and require medical or surgical treatment to prevent one of the above outcomes

All SAEs will be recorded, regardless of cause. Collecting and recording of SAEs will begin at randomization and will continue throughout the treatment phase. For a veteran who ends study participation prior to the study's completion date, SAEs will be monitored and reported 30 days after the "End of Study" date for that veteran or until the SAE is resolved.

Expedited Reporting of Serious Adverse Events (SAEs). Serious Adverse Event reports will be provided to the PI within 24 hours and the PI will review the SAE report to assess completeness of documentation and to determine whether the SAE requires that a safety report be filed (rare). If the SAE is not resolved at the time the event is reported, the study personnel must monitor and provide SAE follow-up information to the PI at least every 30 days OR until the SAE resolves. The study personnel must handle requests for SAE follow-up information in the same prompt manner the original SAE reports are handled. The PI will be responsible for

evaluating all SAEs for veteran safety concerns. Tables of AEs and SAEs will be generated and presented to the PI on a schedule set by the IRB and PI.

3. Potential Benefit of the Proposed Research

The potential benefits of participating in the proposed pilot study clearly outweigh the risk. These include: 1) participants will have their psychiatric symptoms evaluated by a trained mental health professional; 2) previously undetected medical conditions could be detected during the baseline and post-treatment evaluations; 3) participants may experience improvement in cognitive symptoms and 4) participants' quality of life may be improved. This study will contribute to our understanding of factors affecting cognition in older veterans and the techniques that may maximize treatment outcomes for veterans with MCI. Should this project be shown to be feasible, we anticipate the submission of a VA Rehab R&D Merit proposal to test the efficacy of WATER-VET for older veterans with MCI. If this augmentation strategy were later shown to be an efficacious treatment for MCI, the investigators are uniquely positioned to disseminate these results. The investigators are uniquely positioned to disseminate these results should exercise be found to be an effective augmentation to cognitive training for veterans with MCI. The VISN 21 MIRECC is the primary point of point of development for the "roll-out" of evidenced based treatments nationwide for the VA. Over 800 providers have been trained since December of 2010. Given this established training program, there is a natural pathway for the results to be disseminated and available to providers, should this program have demonstrated efficacy through future RCTs.

4. Importance of the Knowledge

As seen in Figure 1, Vietnam veterans are now approaching an age at which they are vulnerable to cognitive decline. Unfortunately, Veterans, particularly Vietnam Veterans, experience a larger burden of psychiatric and medical illnesses than non-Veterans, which may place them at higher risk for developing significant cognitive decline (Krishnan et al., 2005). Thus, the VA will soon be faced with large numbers of Vietnam veterans who have cognitive impairment. Additionally, large numbers of recent returnees from the current conflict have concussive syndromes which are a risk factor for future cognitive impairment. As many veterans are at risk for developing cognitive impairment, treating memory disturbances has the potential of reducing distress caused by this condition, prolonging independence, and improving quality of life.

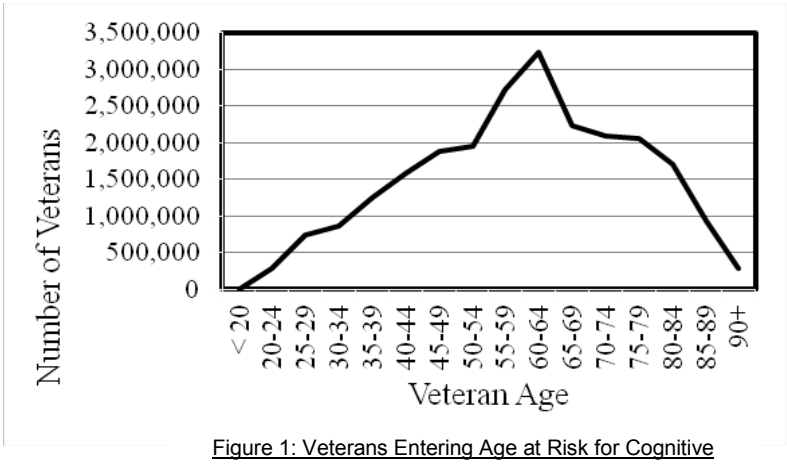

Figure 1: Veterans Entering Age at Risk for Cognitive Decline
(VA, 2013)

Current research suggests that physical activity levels are associated with cognitive function (Andrade et al., 2013; Kerr et al., 2013). Consequently, researchers have worked to develop physical exercise programs to improve cognition; however, the vast majority of that research has used land-based weight-bearing exercises. Unfortunately, many older veterans are not able to participate in those sorts of exercises due to the same health conditions and medical illnesses that have placed them at greater risk for dementia. For those veterans who are able participate in weight-bearing exercises, their health may prevent them from reaching the targeted training zone, and thus receiving the intended physiological and cognitive benefits. As weight-bearing and non-weight bearing activities produce different physiological responses, it is not known if non-weight bearing exercises, such as water-based activities, produce similar cognitive benefits as their weight-bearing counterparts. Can the cognitive benefits of physical exercise be extended to older veterans through non-weight bearing exercises? That question is the impetus of this application.

Should this project be shown to be feasible, we anticipate the submission of a VA Rehab R&D Merit proposal to test the efficacy of WATER-VET for older veterans with MCI. Additionally, this approach could lead to widely available safe treatments for older persons with cognitive impairment. There are minimal risks to this investigation, and a significant knowledge gap to fill. There appears reasonable hope that we will learn important information regarding exercise and cognition in the aging veteran, which may contribute to future

research, funding, and treatment interventions for veterans with MCI as well as to research in the broader field of cognitive impairment.

5. Data Safety and Monitoring Plan

All data collected for this study will be handled and used in compliance with VAPAHCS data security plans. All patient level data will be treated as protected health information. Study personnel will be required to complete annual training courses in data security and human subjects' protection as required by VAPAHCS and Stanford IRB. These courses cover good clinical practices, human subjects' protection, cyber security, and privacy policy. Any data security breaches will be immediately reported. File protections will be used to limit access to members of the study group. Patient level data will never be stored on portable storage devices unless it is encrypted, explicitly authorized, and use specific. We have previously described the procedures in place for genetic data. We also plan to have this study monitored annually for safety and data quality by a Data and Safety Monitoring Board (DSMB) of three individuals not connected to the project, including a clinician and a statistician, recruited from VAPAHCS and Stanford University School of Medicine staff.

As previously described, we will recruit veterans from multiple sources including: clinician referrals, media advertisements, local veteran agencies, and outpatient clinics at VAPAHCS. Our Center has an excellent track record of recruitment of study participants for cognitive training trials. We work closely with the ACRC which provides diagnostic and referral services for persons experiencing cognitive impairment.

Inclusion of Women and Minority

We will actively recruit women and minorities for participation in this study. We have included a detailed planned enrollment table seen below. As this study is concerned with late-life memory loss, the research topic is not relevant to children.

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