HUMAN SUBJECTS RESEARCH PROTOCOL

Project Title: Maintaining Cognitive Health in Aging Veterans

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Principal Investigator: Maureen K. O'Connor, Psy.D.

Co-Investigators: N/A

Institution(s): Bedford ENRM VA Hospital

1.0 Objective and Specific Aims:

The current study attempts to build upon previous work on cognitive intervention in healthy older veterans by investigating a multi-component intervention that more closely adhere to standards set forth by key regulatory agencies intended to capture real world gains in functioning and psychological wellness.

AIM 1: ***To determine whether our intervention increases knowledge about cognitive aging.*** Initial intervention sessions will provide information about the differences between normal and pathological cognitive aging to reduce misconceptions about cognitive aging (e.g., that significant cognitive loss is part of the normal aging process) that can contribute to psychological distress, cognitive difficulties, and functional loss. We hypothesize that our intervention will result in increased knowledge of cognitive aging.

AIM 2: ***To determine whether our intervention improves psychological wellness.*** The intervention will provide information about the relationship between cognitive aging and affective states (e.g., depression and stress), attitudes about aging, and lifestyle factors (e.g., diet, exercise, sleep, and cognitive stimulation). We hypothesize that our intervention will result in a reduction in anxiety about cognitive aging, improved well being, more positive attitudes toward aging, and increased perception of control over cognitive aging.

AIM 3: ***To determine whether our intervention improves cognitive and functional ability.*** Specific cognitive strategies to improve cognitive and functional ability will also be presented and practiced over three focused sessions. In-session practice and out-of-session homework is intended to improve generalization to day-to-day life. Sessions will begin with a thorough review of homework assignments and troubleshooting regarding the application of new skills. We hypothesize that our intervention will result in increased use of compensatory strategies, reduced functional difficulties, and improved cognitive functioning.

2.0 Background and Significance

2.1 Background

Understanding issues related to aging is a top priority of the Veterans Health Administration.

Issues related to aging are becoming critically important to consider as human longevity increases and the proportion of the older adult population grows. The first wave of baby boomers, those born between 1946 and 1964, have already reached age 65. By 2030 an estimated 1 in 5 Americans will be over age 65 and there will be more adults over age 85 than ever before (He et al., 2005). The aging veteran population has increased at a faster rate than the general US population, with the proportion of veterans over age 65 rising from 11% to 26% from 1980 to 1990, and estimated to rise to over 50% by 2030 (Hisnanik, 1994). Currently there are 9,166,281 Veterans over the age of 65, representing 68% of the veteran population (9/30/10 data; www1.va.gov/VETDATA/Demographics/Demographics.asp). In 2013 that number is predicted to rise to more than 9,600,000 Veterans over the age of 65, which will represent 82% of the predicted 2013 veteran population. Due to the growing number of older veterans, health issues specific to the aging veteran population is a primary concern for the Veterans Health Administration.

Cognitive aging is one of the most important age-related issues facing the older adult population.

Research suggests that declines in cognition may begin in early adulthood (Salthouse, Schroeder, & Ferrer, 2004; Salthouse, 2009) and accelerate with increasing age (Guillaume et al., 2009). A recent review of cognitive aging (Drag & Bieliauskas, 2010) describes central nervous system changes associated with aging. These include a decline in brain volume, especially frontal cortex. Changes in hippocampus are also observed but to a much lesser extent than in pathological conditions such as Alzheimer's disease. Cerebrovascular system changes include decreases in resting blood flow and the metabolic rate of oxygen consumption. Physiological changes such as decreased hemispheric asymmetry and a shift to recruitment of anterior brain regions are postulated to reflect compensation for age-related declines (Cabeza, 2002; Davis et al., 2008). Although central nervous system changes result in decrements in cognition, there are several cognitive abilities that remain preserved or even improve in healthy aging. Sustained attention, or the ability to maintain attention and vigilance over time, remains relatively unaffected by normal aging (Berardi, Parasuraman, Haxby, 2001). However, declines in processing speed, selective attention (focusing on task relevant stimuli while ignoring task irrelevant stimuli), divided attention (concurrently attending to and processing information from multiple sources), and working memory (the active manipulation and processing of information) are observed and can impact performance on other cognitive tasks. Similarly, decreases in executive functions such as planning and self-initiation of strategic processing can also interfere with performance in other cognitive domains. For example, episodic memory, or memory for events, declines with aging, but episodic memory is even more difficult when information is presented rapidly, attention is compromised, or strategic processes are required. On the other hand, retention of previously learned information is relatively spared. Procedural memory, or memory for actions and skills, also remains relatively unaffected by aging (Churchill et al., 2003). Prospective memory, or memory for events that need to be carried out in the future, declines with age, but importantly, event-based prospective memory (e.g., remembering to take medications with breakfast) remains more preserved than time-based prospective memory (e.g., remembering to take medications at 9am) (Maylor, 1990). Although retrieval difficulties make verbal information less accessible (Mortenson, Meyers, & Humphreys, 2006), semantic memory, or memory for facts and vocabulary, actually increases with age as older adults accrue knowledge over the lifespan (Caserta et al., 2009). Knowing which areas of cognition are impaired and which are spared can be helpful for designing cognitive interventions.

Cognitive changes should be a focus of clinical attention.

The need to disseminate information related to brain health has recently been recognized by key agencies involved in promoting the welfare of older adults, including the National Institutes of Neurological Disorders and Stroke, Mental Health, and Aging (the Cognitive and Emotional Health Project; Hendrie et al., 2006) and the Centers for Disease Control and Prevention and the Alzheimer's Association (the Healthy Brain Initiative; 2007). Although cognitive aging is not the same as pathological aging, the impact of normal age-related changes warrants intervention since it can cause emotional distress and functional difficulties impacting occupational, recreational, and social pursuits. Cognitive decline in normally aging older adults has been associated with decreases in instrumental activities of daily living, such as grocery shopping, cooking, medication management, and financial management, and with social pursuits, such as reading and traveling (Royall et al., 2004, 2005; Dodge et al., 2008). The most common functional complaints from older adults include feeling mentally slower, misplacing items, difficulty multitasking, forgetting names, and not being able to come up with the right word when needed. Age-Associated Memory Impairment (AAMI) has been a term used to describe a decline in memory compared to younger adults, presenting at or after age 50, that does not reflect a pathological disease state (Crook & Larrabee, 1988). The Diagnostic and Statistical Manual of Mental Disorders (2000) also recognizes the clinical significance of cognitive aging, referred to as Age Related Cognitive Decline, as a condition that may be a focus of clinical attention (V-code 790.9) defined by "an objectively identified decline in cognitive functioning consequent to the aging process that is within normal limits given the person's age."

Understanding the difference between normal and pathological cognitive aging is important for older veterans.

Normal aging can be differentiated from pathological aging by brain changes observed through imaging techniques, cognitive profile, and types of complaints commonly described during clinical interview. Although the media has increased focus on Alzheimer's disease and dementia, the general public still has relatively limited understanding of dementia (Anderson et al., 2009). Increased awareness in the face of limited knowledge is not

without consequence. Fear of developing dementia is common among older adults (Commisseris, Ponds, & Jollees, 1998; Corner & Bond, 2004). Minor memory lapses that were previously of little concern may now be misinterpreted as signaling the beginning stages of dementia (Commissaris et al., 1994). Indeed, perceived forgetfulness in older adults is associated with lower quality of life (Mol et al., 2007). In addition, negative false beliefs about aging can have psychological and functional consequences for older adults. This is often referred to as "stereotype threat": the finding that membership in a group associated with a negative stereotype (such as "older adults are not able to remember things") often causes behavior consistent with that stereotype. Holding negative views about aging has been shown to be associated with reduced feelings of control over memory (Lineweaver & Hertzog, 1998) and decrements in actual cognitive performance (Chasteen et al., 2005). Understanding the normal aging process and improving attitudes about aging has the potential to enhance psychological well being and functioning in day-to-day life.

Increasing awareness of factors that contribute to successful aging can lead to healthier lifestyle choices.
While cognitive changes can be expected as we age, there is a growing body of literature demonstrating that modifiable lifestyle factors impact functioning and quality of life as one ages (Depp, Vahia, & Jeste, 2010; LaRue, 2010). Cognitive reserve refers to the notion that not only innate factors, like intelligence, but also life experiences and skills may serve as protection against cognitive decline and reduce the risk of dementia (Stern, 2009). Many factors have been implicated to play a role in the aging process, such as diet, exercise, sleep, and participation in cognitive and social activities. For example, diets rich in foods containing antioxidants and anti-inflammatory components such as fruits, vegetables, nuts, legumes, and fish are said to have a beneficial effect on cognitive aging, whereas diets containing high amounts of meat, dairy, refined sugars, cholesterol, and trans-fat are said to negatively impact cognitive aging (Frisardi et al., 2010; Roberts et al., 2010; Scarmeas et al., 2009). There is increasing evidence to suggest that physical activity has a protective effect on brain functioning for older adults and that exercise may promote the growth of new neurons in the aging brain (Voss et al., 2010; Barella, Etnier, & Chang, 2010). In contrast, inadequate sleep can lead to declines in cognitive functioning (Meerlo et al., 2009; Nebes et al., 2009). Importantly, evidence suggests that late life participation in cognitively stimulating activities may delay the onset of cognitive decline (Scarmeas & Stern, 2003; Hall et al., 2009). Providing older veterans with information about factors associated with cognitive aging can bring about lifestyle changes that will promote successful aging.

Cognitive interventions have shown gains on cognitive measures, but limited generalization to day-to-day life.
The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trials represent one of the largest longitudinal studies on cognitive rehabilitation in healthy older adults (Unverzagt et al., 2009). In addition to performance on cognitive measures, ACTIVE researchers included functional outcome measures to detect real-world gains. While domain-specific cognitive training (memory, reasoning, or processing speed) resulted in gains on analogous cognitive measures, only limited impact on functional outcome measures was observed. Other studies of cognitive interventions in older adults have demonstrated similar outcomes, with promising improvements on related tasks but little evidence of generalization to everyday life (see reviews Papp et al., 2009; Lustig et al., 2009). The majority of studies have been limited by several factors. Methodological issues such as non-random assignment to groups and lack of follow-up over time are common. Most studies use performance on cognitive measures as their main outcome of interest, but the ecological validity, or extent to which performance on cognitive measures reflects real-world functioning, has been debated and, while there is certainly a relationship between performance on cognitive measures and everyday functioning, the magnitude of this relationship is often modest (Chaytor & Schmitter-Edgecombe, 2003). When functioning has been evaluated, self-report measures have been used, which call into question the accuracy of reported functional gains. Perhaps most importantly, most studies have focused training on very specific tasks, but the specificity of training may have limited generalization to day-to-day life, where successful performance of complex tasks requires multiple cognitive skills and psychological resources, such as an individual's perception of their memory ability.

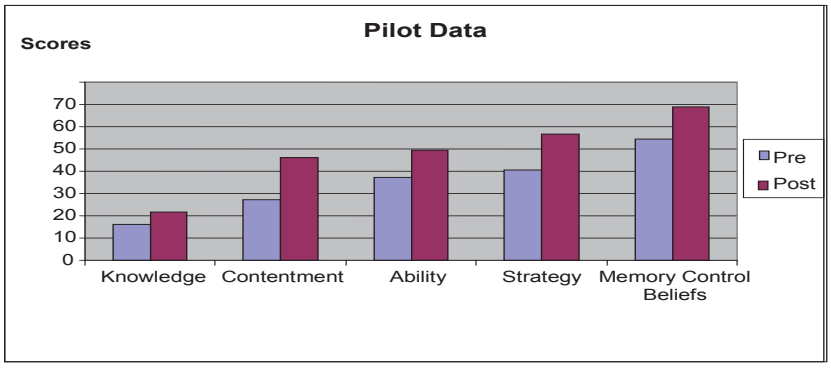
There is a continued need to develop cognitive interventions and evaluate their day-to-day impact.

Although studies to date have suggested that cognitive interventions for older adults hold promise, the cognitive training that has been done has been domain specific, rather than broad based. Additionally, study design has generally lacked randomization to conditions and follow-up over time, and outcome measures have not adequately captured real world gains. The lack of education on cognitive aging, lifestyle factors associated with successful cognitive aging, and psychological well being in many of these interventions may limit their effectiveness (West et al., 2004; Papp et al, 2009). Considering that the ultimate goal of cognitive interventions is to improve the lives of older adults, a multi-component intervention that more thoroughly evaluates the impact on day-to-day functioning and participant well-being is critical. The current intervention will provide education and broad cognitive skills training. Importantly, study design will focus on the necessity of capturing real world gains. Unfortunately, there are currently no agreed upon standards for evaluating the effectiveness of cognitive interventions. Using standards set forth by the Food and Drug Administration (FDA) and European Medicines Agency (EMeA), Solomon and Michalczuk (2009) provide guidelines for the evaluation of complementary and alternative medicines, such as ginkgo biloba, that are purported to enhance cognition in older adults. These same guidelines can provide an improved standard for judging the real world outcome of cognitive interventions. These guidelines include two key components: (1) random assignment to groups, and (2) outcomes that consist of both cognitive measures and measures that indicate that the treatment provides benefit to the individual and significant others in day-to-day life, as evidenced by self report, other report, and blinded clinician ratings. The current study attempts to build upon previous work on cognitive intervention in healthy older adults by investigating a multi-component intervention using a randomized controlled trial design, 3- and 6- month follow-up, and outcome measures that more closely adhere to standards set forth by key regulatory agencies intended to capture real world gains in functioning and psychological wellness.

2.2 Preliminary Studies

The proposed intervention was originally designed as a clinical service to meet the needs of the large number of veterans presenting with concerns about their memory despite normal cognitive performance on formal evaluation, and then refined over a period of four years. We originally collected data using a seven-item questionnaire we felt was pertinent to the goals of the intervention (see appendix). Using a within-subjects pre-post test design with a representative sample of nine veterans (mean age=78, SD=4.2) we found a reduction in anxiety about cognitive functioning (*How concerned are you about your memory, or potential memory problems, as you get older?*; $t(8)=2.50$, $p<.05$) and an increase in perceived knowledge about brain aging (*How much do you feel you know about what happens to your memory and your brain as you age?*; $t(8)=3.00$, $p<.05$) at immediate follow-up as compared to baseline (Kraft & Steadman-Wood, 2008). Qualitative comments collected at the end of the intervention also supported the veterans' view that the intervention was effective: "I was hoping to get tips about how to improve my memory and I did", "Through the group I found that we, my wife and I, are not alone", and "I didn't realize there was so much to learn."

Using a subset of the measures proposed in the current submission we recently collected within-subjects baseline and immediate follow-up pilot data (collected within two weeks from the end of the intervention) from a new group of four cognitively healthy veterans (mean age=61, SD=2.7) participating in the intervention (measures from left to right on the graph include the Knowledge of Memory Aging Questionnaire-Revised; Multifactorial Memory Questionnaire: contentment, ability, and strategy use subscales; and Memory Controllability Inventory: memory specific control beliefs subscale). Despite the small sample size, these pilot data show numerical trends, some reaching significance, in a repeated-measures ANOVA, $F(1,6)$, that provide support for a subset of our



predictions including improvement in knowledge of cognitive aging (p=.07), increased contentment with memory (p=.03), improved self- perceived memory ability (p=.05), increased strategy use in daily life (p=.00), and increased feelings of memory- specific (p=.01) control.

2.3 Significance

Along with the outcomes being measured that confer benefit to the individual veteran, other potential outcomes relevant to the VA include: decreases in veteran anxiety about aging which may reduce the need for mental health services, better recognition of early pathological aging which may improve early detection and treatment, reduced time that other VA providers such as primary care Patient Aligned Care Teams (PACT) may spend providing education about normal aging, improved preventative health behaviors which reduce the need for VA services, and improve compliance with medical management (i.e., strategies are taught that can help veterans remember to take their medications, attend medical appointments, and remember information presented at medical appointments). The context of a pilot study does not allow for full exploration of all of these constructs, but future research can incorporate measures intended to capture these additional outcomes.

3.0 Research Design and Methods

3.1 Drug/Device Information

N/A

3.2 Type of Study

Prospective, randomized, no treatment control

3.3 Study Procedures

a. Sub-Study Participation

N/A

b. Study Related Procedures

i. Bedford AgeWISE Course: The memory and aging course will take place in the building 5 solarium on the Bedford VA campus. The course will be run by neuropsychology staff under the supervision of Dr. Maureen O'Connor, a clinical neuropsychologist who has developed this manualized group, and has run the group for a number of years at the Bedford VA. Healthy older adults ages 50 to 90 will be recruited from the community at large and from advertisements on the Internet and local gathering places. Over the next year, we intend to enroll a maximum of 144 participants. Of the 144 participants, 72 of those will be older veterans, and 72 will be study partners, when study partners are identified, available, and willing to participate. Veterans without study partners will not be excluded from the study. Of the 72 veterans (with or without study partners), 36 will be assigned to the intervention group and 36 will be assigned to the control group. All veterans participating in the study will perform a standard battery of neuropsychological tests(attached). These tests will be administered in a separate study session. Veterans will be excluded if they display impairment on a cognitive screening measure, as determined using age corrected criteria (using criteria: Schretlen, Testa, and Pearlson, 2010) as follows:

Age	/ MMSE Cut-off
51-55	/ 26 and below
56-60	/ 25 and below
61-65	/ 25 and below
66-70	/ 25 and below
71-76	/ 23 and below
76-80	/ 23 and below
81-85	/ 23 and below
86 +	/ 22 and below

Or self or informant reported diagnosis of a brain disorder affecting cognition such as Alzheimer's disease, Mild Cognitive Impairment, Parkinson's disease, other dementia, stroke, or brain injury or diagnosis of a major mental illness such as major depression, schizophrenia, or bipolar disorder; active alcohol or substance abuse. In addition to the standard neuropsychological tests, participants will be filling out questionnaires regarding their cognition and quality of memory. Veterans with a study partner (a spouse, family member, significant other, or adult child living with the veteran) will have the study partner complete a brief interview of participant functioning on three separate occasions. Interviews will be conducted prior to the study, within two weeks after the study is completed, and again at 6-months following the previous interview. Interview questions will ask study partners to list or describe any: notable recent events; medical problems; physical abilities; any concerns the participants might have; description of the participant's thinking abilities; description of the participant's feelings or behavior; descriptions about the participant's daily activities and social activities; and any other related information regarding the participant. Veterans (intervention and control) will complete protocol measures at baseline, within 2 weeks after the intervention is completed, and again at 6-months after immediate follow-up.

Once the group is underway, a manual will be provided to each veteran. The manual will include an overview of the topic discussed during the class as well as written strategy instructions, practice exercises, and homework (e.g., readings on the week's topic, questions, and additional practice exercises on the compensatory strategy of the week). Each of the sessions will begin with veterans reviewing the past week's homework assignments. The group leader(s) will then introduce a new topic along with a compensatory strategy following a scripted set of instructions. Veterans will be encouraged to ask questions and participate in general discussion. Attached please find a copy of the 12-week course outline that describes the content of each group session.

a.Qualitative Interview with Bedford AgeWISE Cohort: A portion of the Veteran participants randomly assigned to the Group B condition of the study will be recruited to participate in qualitative interviews about their perceptions of memory and aging. A non-veteran cohort will also be recruited for this portion to differentiate between Veteran-specific concerns and cognitive aging. The qualitative interviews will be audio-recorded for the purpose of maintaining accurate records and interpretation of Veteran responses to questions asked during the interview. Interviews will be recorded using the audio-recording function of VA issued webcams. The video function of these webcams will not be used. These audio recordings will only be obtained for research analysis and will not be disclosed beyond the VA.

ii. Telemental Health AgeWISE Course: This version of the AgeWISE course will be taught via the Telemental Health Service from the ENRM Bedford VA campus. Veteran participants will view the Telemental Health AgeWISE course at Community Based Outpatient Clinics. Veterans ages 50-90 will be recruited from the Telemental Health AgeWISE course. Over the next year, we intend to enroll 20 participants for this portion of the study. All Veterans participating in the Telemental Health AgeWISE course will be provided with questionnaires prior to and immediately after the 12-week course. There will be no participant screening for this portion of the study. This portion of the study will seek to understand the perceived impact of the memory and aging course on participants. Thus, no cognitive restrictions must be met. There will be no randomization for this portion of the study.

3.4 Data Collection

Instrumentation

The outcomes for this proposal were chosen to inform our specific aims concerning veteran's knowledge about cognitive aging (AIM 1), psychological wellness (AIM 2), and cognitive and functional ability (AIM 3). The following measures will be used at baseline and follow-up visits to test the hypotheses associated with each aim. A detailed description of each measure is provided below. In its entirety, it will take participants an average of 2 hours to complete the following measures (see below); sessions will be broken into two one-hour sessions to minimize any fatigue. A demographic questionnaire will be administered only at baseline that captures basic data including age, gender, race, educational history, and occupational history.

AIM 1: Knowledge of Memory Aging Questionnaire-Revised (KMAQ; Cherry et al., 2003) measures laypersons' knowledge of memory changes in adulthood for research or educational purposes using true/false/"don't know" questions, with half of the questions pertaining to normal memory aging and the other half covering pathological memory deficits due to non-normative factors, such as dementia. Test-retest reliability and convergent and discriminant validity were established at adequate levels (Cherry et al., 2000).

Qualitative interview questions taken from the Healthy Brain Study (Wilcox et al., 2009) measure laypersons' perceptions and knowledge of aging brain processes regarding cognitive health promotion. Respondents answer questions based upon life experience and information provided via various media entities. These questions will provide narrative structure to veteran perceptions of memory and aging.

AIM 2: Multifactorial Memory Questionnaire (MMQ; Troyer & Rich, 2002) will be used to measure psychosocial functioning (and also functional ability for AIM 3; see below). The MMQ is a measure constructed to reflect aspects of memory that are potentially amenable to clinical intervention. The MMQ-Contentment subscale assesses emotions and perceptions about current memory ability including anxiety, embarrassment, and irritability. The scale contains 18 statements rated on a 5-point scale (strongly agree, agree, undecided, disagree, strongly disagree). The MMQ has been shown to be have adequate content validity, test-re-test reliability (.86-.93), internal consistency (.83-.95) and convergent and discriminant validity. General and Memory Specific Control Beliefs Scale (Bielak et al., 2007) will be used to measure perceived control over cognitive health. The scale is composed of two sets of items focusing on general and memory-specific control beliefs. We are interested in examining changes in memory-specific control beliefs.

AIM 3: MMQ The MMQ-Ability subscale contains 20 items phrased as memory failures in everyday memory situations (e.g., forgetting an appointment). Respondents indicate the frequency with which they have made each mistake over a two-week period using a 5-point scale (all the time, often, sometimes, rarely, never). The MMQ-Strategy subscale measures the self-reported use of strategies designed to improve memory. This subscale contains 19 items describing different memory aids and strategies applicable to everyday memory tasks (e.g., writing appointments on a calendar). Respondents indicate the frequency with which each strategy was used over a two-week period using a 5-point scale (never, rarely, sometimes, often, all the time). A battery of neuropsychological measures will provide quantitative measurement of cognitive functioning and includes validated and standardized measures reflecting the cognitive domains of memory, attention, executive functioning, and language: California Verbal Learning Test – Second Edition (CVLT-II), Wechsler Memory Scale – Third Edition (Logical Memory and Visual Reproduction), Digit Span, Delis-Kaplan Executive Function System (Trail Making and Verbal Fluency). An overall score will be obtained by taking the average of the z scores for each individual test. Alzheimer's Disease Cooperative Study Global Impressions of Change Scales (ADCS-GICS; Schneider et al., 2006; Knopman et al., 1994) include self-rated and study partner-rated versions, which will be used as an index of global, real world changes in functional ability. Self rated and study partner rated versions were developed specifically for use with non-demented elderly.

3.5 Analysis Plan

To test the primary outcome we will run repeated measures ANOVAs with the factors of group x time. Follow-up analyses will be done as indicated.

4.0 Human Subjects

4.1 General Characteristics

We intend to enroll 164 participants, 92 older veterans, and a maximum of 72 study partners for participation in the study.

4.2 Inclusion of Vulnerable Subjects and Special Populations

N/A

4.3 Inclusion of Incompetent Subjects

N/A

4.4 Inclusion/Exclusion Criteria

a. Bedford AgeWISE Course (Veterans)

Inclusion Criteria:VETERANS: Veterans > 50 years old with subjective cognitive complaints who want to learn more about cognitive aging; English speaking as all intervention materials are written in English.

Exclusion Criteria: VETERANS:

Veterans with impairment on a cognitive screening measure, as determined using age corrected criteria (using criteria: Schretlen, Testa, and Pearlson, 2010) as follows:

Age / MMSE Cut-off
51-55 / 26 and below
56-60 / 25 and below
61-65 / 25 and below
66-70 / 25 and below
71-76 / 23 and below
76-80 / 23 and below
81-85 / 23 and below
86 + / 22 and below

Or self or informant reported diagnosis of a brain disorder affecting cognition such as Alzheimer's disease, Mild Cognitive Impairment, Parkinson's disease, other dementia, stroke, or brain injury or diagnosis of a major mental illness such as major depression, schizophrenia, or bipolar disorder; active alcohol or substance abuse.

Inclusion Criteria: STUDY PARTNER: Study partners will be identified by eligible veterans. Study partners can include spouses or significant others/partners, adult children, or other family members. Study partners must be 18 years of age or older. Study partners must have at least 10 hours per week of direct contact (in-person) with the veteran. Study partners must be English speaking as all materials are in English.

Exclusion Criteria: STUDY PARTNER: Study partners must not be diagnosed with a brain disorder affecting cognition such as Alzheimer's disease, Mild Cognitive Impairment, Parkinson's disease, other dementia, stroke, or brain injury or diagnosis of a major mental illness such as major depression, schizophrenia, or bipolar disorder; active alcohol or substance abuse, as indicated by self- and veteran-report.

b. Bedford AgeWISE Course (Non-Veterans)

Inclusion Criteria: NON-VETERANS:

Non-Veteran > 50 years old with subjective cognitive complaints who want to learn more about cognitive aging; English speaking as all intervention materials are written in English.

Exclusion Criteria: Non-Veterans:

Non-Veterans with impairment on a cognitive screening measure, as determined using age corrected criteria (using criteria: Schretlen, Testa, and Pearlson, 2010) as follows:

Age	/ MMSE Cut-off
51-55	/ 26 and below
56-60	/ 25 and below
61-65	/ 25 and below
66-70	/ 25 and below
71-76	/ 23 and below
76-80	/ 23 and below
81-85	/ 23 and below
86 +	/ 22 and below

Or self or informant reported diagnosis of a brain disorder affecting cognition such as Alzheimer's disease, Mild Cognitive Impairment, Parkinson's disease, other dementia, stroke, or brain injury or diagnosis of a major mental illness such as major depression, schizophrenia, or bipolar disorder; active alcohol or substance abuse.

c. Telemental Health AgeWISE Course
Inclusion Criteria: Veterans > 50 years old with subjective cognitive complaints who want to learn more about cognitive aging; English speaking as all intervention materials are written in English.
Exclusion Criteria: N/A

4.5 Recruitment Procedures

Bedford AgeWISE Course:
Healthy veterans ages 50 to 90 will be recruited from the VA. Veterans will be recruited through flyers posted around the hospital. Veterans will also be recruited through the Neuropsychology Service by being provided with a flyer about the study when they appear to be an appropriate study candidate; interested veterans would then be able to call study staff on their own and express interest. Veterans will also be recruited through local Veterans of Foreign Wars Posts, American Legion Posts, and Councils On Aging. Flyers will be provided to staff at these locations and recruitment protocol, determined by each location, will be followed for recruitment procedures. Enrolled veterans will be asked if they have a study partner that meets inclusion/exclusion criteria that they would like to participate. If a study partner is identified the veteran will be given a flyer to pass along to their potential study partner and the study partner will be responsible for contacting study staff if they agree able to learning about the study.

Qualitative Interview
Veteran cohort: Veterans randomly assigned to Group B will be offered the opportunity to participate in a qualitative interview. If Veterans decline to participate in the qualitative interview, this will not affect their participation in the rest of the study.
Veterans assigned to Group B who were enrolled in the study prior to the implementation of the qualitative interview portion of the study (and are still enrolled) will be provided the opportunity to participate in the qualitative interview. Study staff will contact each Veteran, assigned to group B, via telephone to inquire if they are interested in participating in the qualitative interview. During this time of contact Veterans will be informed that their participation in the study as a whole will not be affected by their decision to participate or not participate in the qualitative interview portion of the study.
Non-Veteran cohort: Non-Veterans will be recruited from Councils on Aging, libraries, and other public spaces. Flyers will be provided to staff at these locations and recruitment protocol, determined by each location, will be followed for recruitment procedures.

Telemental Health AgeWISE Course
Veterans participating in the Telemental Health AgeWISE course will be recruited to participate in the research study via flyers that will be provided to staff at VA Community Based Outpatient Clinics; interested veterans would then be able to call study staff on their own and express interest.
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4.5.1 Subject Identification and Pre-Enrollment Screening: Subjects will be identified by providers.

4.5.1a HIPAA Authorization for Screening:
Bedford AgeWISE course subjects will sign a freestanding authorization form.

4.5.1b Consent to Screening:
Bedford AgeWISE course subjects will sign a screening ICF.

4.5.2 Enrollment: Enrollment is the responsibility of the research team approved by the IRB.

4.5.2a HIPAA Authorization:
Bedford AgeWISE course and Telemental Health AgeWISE course subjects will sign a freestanding authorization form.

4.5.2b Informed Consent:
Bedford AgeWISE course and Telemental Health AgeWISE course subjects will sign an ICF.

4.5.2c Audio-Video Consent:
Subjects recruited for the qualitative interview will sign an Audio-Video Consent form.

4.6 Risk/Benefit Ratio

4.6.1 Potential Risks and Methods to be Used to Minimize Risks:

There is a small risk that something about veterans from this study will become known to others. We will store data collection forms separate from signed consent forms and other identifying information. All study forms will be stored in locked cabinets. All electronic data will be stored on password protected computers. The code linking the study number on data collection forms and information that can identify subjects is stored in a separate password protected computer. See the confidentiality section for more information.

Other than a potential breach of confidentiality, there are no known risks for subjects participating in this study. Veterans will be immediately informed of any new findings during the course of the study that would influence their participation, including any information about unforeseen risks that arise. There are minimal potential discomforts and these include feeling frustrated or uncomfortable when completing study measures. Every effort will be made to minimize such discomforts. Veterans will be free to discontinue their participation at any time. During assessments, all instruments will be carefully explained.

4.6.2 Data and Safety Management Plan:

4.6.2.1 Data Security

In order to maintain the confidentiality of all veterans, informed consent forms and research data will be kept in two separate folders, in separate locked filing cabinets. Informed consent forms will not be included in the medical record. Identifiable information, such as the veteran's consent form, medical history, and reimbursement form (which contains their address and social security number) will be placed in an identifiable folder and placed in a locked filing cabinet. All veterans will be assigned codes and a folder will be made with their research code

on it and all study data will be placed in these folders with only the research code on it. The research data will be placed in a separate locked filing cabinet from the identifiable information. The only people who will have access to this identifiable information will be the Principal Investigator and the research study staff. Identifiable information will be kept in folders in one locked filing cabinet on the Bedford Veterans Hospital campus. Research data will be kept in folders with the participant's code on it in another (separate) filing cabinet and the database that links the identifiable information and the research codes will only be able to be accessed by the PI and research coordinator.

4.6.2.2 Data Safety Monitoring

The Principal Investigator and the research coordinator will be responsible for reporting Adverse Events to the IRB and, when required, to ORO, ORD, and other Federal Agencies or Sponsors.

4.6.3 Potential Benefits: There may be direct benefits to those participating including an increase of knowledge about memory aging, improved psychological wellness, and improved cognitive and functional ability, but this has yet to be shown and it is possible that there will be no direct benefit to participants or limited benefit. Benefits to the veteran population include increased knowledge about interventions that help to improve the odds of successful cognitive aging.

4.6.4 Alternative Procedures: There are no alternatives to participation. You may choose not to participate in this study.

4.7 Costs and Payments

Bedford AgeWISE: Veterans will be paid $10 an hour for their time. Assessments at baseline, initial follow-up, and 6-month follow-up are expected to take an estimated 4 hours each. Therefore, veterans will be paid a total of $40 per assessment, or $120 over the course of the study. In addition, if veterans have a study partner, the study partner will receive $10 for 1 hour at each of the 3 assessments (study partner time estimated to be one hour per assessment), for a total of $30 over the course of the study.

Qualitative Interview: Veteran and Non-Veteran participants will be paid $10 an hour for their time. Interviews will last approximately 1.5 hours. Therefore, participants will be paid a total of $15 dollars for their time. If the interview lasts longer than 1.5 hours, participants will continue to be paid at a rate of $10 per hour.

Telemental Health Group: Veterans will be paid $10 dollars an hour for their time. Assessments at baseline and immediate follow-up, are expected to take two hours each. Therefore, veterans will be paid a total of $20 per assessment or $40 over the course of the study.

5.0 Resources

The Bedford VA has all needed resources including a group room, photocopiers, students, needed to run the group intervention.

6.0 Collaborations

N/A

7.0 Qualifications of the Investigators

The principal investigator for the proposed study is Maureen O'Connor, Psy.D., Director of Neuropsychology at the Bedford VA, Instructor in Neurology at Boston University School of Medicine. Dr. O'Connor specializes in evaluation and treatment of older adults. She conducts intervention-based research and most recently served as the PI of an Alzheimer's Association funded project aimed at helping caregivers manage neuropsychiatric symptoms.

REFERENCES:*

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed.,

text revision). Washington, DC: Author.

Anderson, L.A., Day, K.L., Beard, R.L., Reed, P.S., Wu, B. (2009). The public's perceptions about cognitive health and Alzheimer's disease among the US population: A national review. *The Gerontologist,* 49(S1), 3-11.

Barella, L.A., Etnier, J.L., Chang, Y.K. (2010). The immediate and delayed effects of an acute bout of exercise on cognitive performance of healthy older adults. *Journal of Aging and Physical Activity*, 18(1), 87-98.

Berardi, A., Parasuraman, R., Haxby, J., (2001). Overall vigilance and sustained attention decrements in healthy aging. *Experimental Aging Research*, 27(1), 19-39.

Bielak, A.A., Hultsch, D.F., Levy-Ajzenkopf, J., MacDonald, S.W.S., Hunter, M.A., Strauss, E. (2007). Short-term changes in general and memory-specific control beliefs and their relationship to cognition in younger and older adults. *International Journal Aging and Human Development*, 65, 53-71.

Cabeza, R. (2002). Hemispheric asymmetry in older adults: The Harold model. *Psychology and Aging*, 17(1), 85-100.

Caserta, M.T., Bannon, Y., Fernandez, F., Giunta, B., Schoenberg, M.R., Tan, J. (2009). Normal brain aging clinical, immunological, neuropsychological, and neuroimaging features. *International Review of Neurobiology*, 84(1), 1-19.

Center for Disease Control and Prevention & Alzheimer's Association. (2007). The Healthy Brain Initiative. A National Public Health Road Map to Maintaining Cognitive Health. Chicago, IL: Alzheimer's Association. http://www.alz.org/national/documents/reporthealthybraininitiative.pdf

Chasteen, A.L, Bhattacharyya, S., Horhota, M., Tam, R., Hasher, L. (2005). How feelings of stereotype threat influence older adults' memory performance. *Experimental Aging Research*, 31(3), 235-60.

Chaytor, N., Schmitter-Edgecombe, M. (2003). The ecological validity of neuropsychological tests: A review of the literature on everyday cognitive skills. *Neuropsychology Review*, 13(4), 181-97.

Churchill, J., Stanis, J., Press, C., Kushelev, M., Greenough, W.T. (2003). Is procedural memory relatively spared from age effects? *Neurobiology Aging*, 24(6), 883-892.

Cherry, K.E., West, R.L., Reese, C.M., Santa Maria, M.P., Yassuda, M. (2000). The Knowledge of Memory Aging Questionnaire. *Educational Gerontology*, 26(3), 195-219.

Cherry, K. E., Brigman, S., Hawley, K. S., & Reese, C. M. (2003). The Knowledge of Memory Aging Questionnaire: Effects of adding a "don't know" response option. *Educational Gerontology, 29,* 427-446.

Commissaris, C.J., Verhey, F.R. Jr., Ponds, R.W., Jolles, J., Kok, G.J. (1994). Public education about normal forgetfulness and dementia: Importance and effects. *Patient Education Counseling,* 25, 163-67.

Commisseris, C.J., Ponds, R.W., Jolles, J. (1998). Subjective forgetfulness in a normal Dutch population: Possibilities for health education and other interventions. *Patient Education Counseling,* 34, 25-32.

Corner, L. (2004). Being at risk of dementia: Fears and anxieties of older adults. *Journal of Aging Studies*, 18(2), 143-155.

Crook, T., Larrabee, G.J. (1988). Age-associated memory impairment: Diagnostic criteria and treatment strategies. *Psychopharmacology Bulletin*, 24(4), 509-14.

Davis, S.W., Dennis, N.A., Daselaar, S.M., Fleck, M.S., Cabeza, R. (2008). Que PASA? The posterior-anterior shift in aging. *Cerebral Cortex*, 18(5), 1201-09.

Depp, C., Vahia, I.V., Jeste, D. (2010). Successful aging: Focus on cognitive and emotional health. *Annual Review of Clinical Psychology,* 6, 527-50.

Dodge, H.H., Kita, Y., Takechi, H., Hayakawa, T., Ganguli, M., Ueshima, H. (2008). Healthy cognitive aging and leisure activities among the oldest old in Japan: Takashima study. *The Journals of Gerontology*, 63(11), 1193-200.

Drag, L.L, Bieliauskas, L.A. (2010). Contemporary Review 2009: Cognitive Aging. *Journal Geriatric Psychiatry and Neurology*, 1-19.

Frisardi, V., Panza, F., Seripa, D., Imbimbo, B.P., Vendemiale, G., Pilotto, A., Solfrizzi, V. (2010). Nutraceutical properties of Mediterranean diet and cognitive decline: Possible underlying mechanisms. *Journal of Alzheimer's Disease*, 22(3), 715-40.

Guillaume, C., Clochon, P., Denise, P., Rauchs, G., Guillery-Girard, B., Eustache, F., Desgranges, B. (2009). Early age-related changes in episodic memory retrieval as revealed by event-related potentials.

Neuroreport, 20, 191-196.

Hall, C.B., Lipton, R.B., Sliwinski, M., Katz, M.J., Derby, C.A., Verghese, J. (2009). Cognitive activities delay onset of memory decline in persons who develop dementia. *Neurology*, 73(5), 356-61.

He, W., Sengupta, M.,Velkoff, V.A., DeBarros, K.A. (2005). U.S. Census Bureau, Current Population Reports, P23-209, 65+ in the United States: 2005, U.S. Government Printing Office, Washington, DC.

Hendrie, H.C., Albert, M.S., Butters, M.A., Gao, S., Knopman, D.S. (2006). The NIH Cognitive and Emotional Health Project: Report of the Critical Evaluation Study Committee. *Alzheimer's Dementia,* 2, 12–32.

Hisnanik, J.J. (1994). Changes over time in the ADL status of elderly US veterans. *Age and Ageing,* 23, 505-11.

Kraft, M., Steadman-Wood, P. (June 19, 2008). Preliminary Results of a Psychoeducational Group on Age-Related Cognitive Changes. American Academy of Clinical Neuropsychology 2008 Annual Conference, Poster Session. Boston, MA.

Knopman, D.S., Knapp, M.J., Gracon, S.I., Davis, C.S. (1994). The clinician interview-based impression (CIBI): A clinician's global change rating scale in Alzheimer's disease. Neurology, 44(12), 2315-21.

Laditka, S. B., Corwin, S. J., Laditka, J. N., Liu, R., Tseng, W., Wu, B., ... & Ivey, S. L. (2009). Attitudes about aging well among a diverse group of older Americans: implications for promoting cognitive health. *The Gerontologist*, *49*(S1), S30-S39.

LaRue, A. (2010). Healthy brain aging: Role of cognitive reserve, cognitive stimulation, and cognitive exercises. *Clinics in Geriatric Medicine,* 26(1), 99-111. Lawton, M.P. (2003), Lawton's PGC Morale Scale [Morale Scale created by M. Powell Lawton (1923-2001) while at the Polisher Research Institute of the Philadelphia Geriatric Center (now known as the Abramson Center for Jewish Life)]. Retrieved 6-1-10 from http://www.abramsoncenter.org/PRI/ (Scales page).

Lineweaver, T.T,, Hertzog, C. (1998). Adults' efficacy and control beliefs regarding memory and aging: Separating general from personal beliefs. *Aging, Neuropsychology, and Cognition*, (5), 264–296.

Lustig, C., Shah, P., Seidler, R., Reuter-Lorenz, P.A. (2009). Aging, training, and the brain: A review and future directions. *Neuropsychology Review*, 19, 504-22.

Maylor, E. (1990). Age and prospective memory. *Quarterly Journal of Experimental Psychology*, 42(3), 471-93.

Mathews, A. E., Laditka, S. B., Laditka, J. N., & Friedman, D. B. (2009). What are the top-circulating magazines in the United States telling older adults about cognitive health?. *American journal of Alzheimer's disease and other dementias*.

Meerlo, P., Mistlberger, R.E., Jacobs, B.L., Heller, H.C., McGinty, D. (2009). New neurons in the adult brain: The role of sleep and consequences of sleep loss. *Sleep Medicine Review*, 13(3), 187-94.

Mol, M., Carpay, M., Ramakers, I., Rozendaal, N., Verhey, F., Jolles, J. (2007). The effect of perceived forgetfulness on quality of life in older adults: A qualitative review. *International Journal of Geriatric Psychiatry,* 22, 393-400.

Mortenson, L., Meyers, A., Humphreys, G. (2006). Age-related effects on speech production: A review. *Language and Cognitive Processes*, 21(1), 238-90.

Nebes, R.D., Buysse, D.J., Halligan, E.M., Houck, P.R., Monk, T.H. (2009). Self-reported sleep quality predicts poor cognitive performance in healthy older adults. *Journals of Gerontology*, 64(2), 180-7.

Papp, K.V., Walsh, S.J., Snyder, P.J. (2009). Immediate and delayed effects of cognitive interventions I n healthy elderly: A review of the current literature and future directions. *Alzheimer's and Dementia*, 5, 50-60.

Roberts R.O., Geda, Y.E., Cerhan, J.R., Knopman, D.S., Cha, R.H., Christianson, T.J., Pankratz, V.S., Ivnik, R.J., Boeve, B.F., O'Connor, H.M., Petersen, R.C. (2010). Vegetables, unsaturated fats, moderate alcohol intake, and mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders*, 29(5), 413-23.

Royall, D.R., Palmer, R., Chiodo, L.K., Polk, M.J. (2004). Declining executive control in normal aging predicts change in functional status: The Freedom House study. *Journal of the American Geriatrics Society*, 52(3), 346-52.

Royall, D.R., Palmer, R., Chiodo, L.K., Polk, M.J. (2005). Normal rates of cognitive change in successful aging: The Freedom House study. *Journal of the International Neuropsychological Society*, 11(7), 899-909.

Salthouse, T.A., Schroeder, D.H., Ferrer, E. (2004). Estimating retest effects in longitudinal assessments

of cognitive functioning in adults between 18 and 60 years of age. *Developmental Psychology, 40,* 813-822.

Salthouse, T.A. (2009). When does age-related cognitive decline begin? *Neurobiology of Aging, 30,* 507-514.

Scarmeas, N., Stern, Y. (2003). Cognitive reserve and lifestyle. *Journal of Clinical and Experimental Neuropsychology,* 25(5), 625-33.

Schneider, L.S., Clark, C.M., Doody, R., Ferris, S.H., Morris, J.C., Raman, R., Reisberg, B., Schmitt, F.A. (2006). ADCS prevention instrument project: ADCS-clinicians' global impression of change scales (ADCS-CGIC), self-rated and study partner-rated versions. *Alzheimer's Disease and Associated Disorders*, 20(4Suppl3), 124-38.

Schretlen, D.J., Testa, S.M., & Pearlson, G.D. (2010). *Calibrated neuropsychological normative system (CNNS)*. Lutz, FL: PAR.

Solomon, P.R., Michalczuk, D.E. (2009). Toward establishing guidelines for evaluating cognitive enhancement with complementary and alternative medicines. *Evaluation and the Health Professions*, 32(4), 370-92.

Stern, R.A., White, T. (2003). *Neuropsychological Assessment Battery*. Lutz, FL: Psychological Assessment Resources.

Stern, Y (2009). Cognitive Reserve. *Neuropsychologia,* 47, 2015-2028.

Troyer, A.K., Rich, J.B. (2002). Psychometric properties of a new metamemory questionnaire for older adults. *Psychological Sciences*, 57B, 19-27.

Unverzagt FW, Smith DM, Rebok GW, Marsiske M, Morris JN, Jones R, Willis SL, Ball K, King JW, Koepke KM, Stoddard A, Tennstedt SL. Cognitive training in older adults: Lessons from the ACTIVE study. *Current Alzheimer's Research*, 6(4), 375-83.

Voss, M.W., Prakash, R.S., Erickson, K.I., Basak, C., Chaddock, L., Kim, J.S., Alves, H., Heo, S., Szabo, A.N., White, S.M., Wojcicki, T.R., Malley, E.L., Gothe, N., Olson, E.A., McAuley, E., Kramer, A.F. (2010). Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Frontiers Aging Neuroscience*, 26(2), 32-41.

West, R.L. & Yassuda, M.S. (2004). Aging and memory control beliefs: Performance in relation to goal setting and memory self-evaluation. *The Journals of Gerontology*, 59, 56-65.

Wilcox, S., Sharkey, J. R., Mathews, A. E., Laditka, J. N., Laditka, S. B., Logsdon, R. G., ... & Liu, R. (2009). Perceptions and beliefs about the role of physical activity and nutrition on brain health in older adults. *The Gerontologist*, *49*(S1), S61-S71.