Study Protocol and Statistical Analysis Plan

Document Date: May 4, 2018

ID: NPSASA-14-321959
NCT: 02864069

Impact of Combined Behavioral Interventions on Cognitive Outcomes in MCI

SPECIFIC AIMS/HYPOTHESES: Primary Aim: Compare the efficacy of participating in singular [(walking *or* computer training (CT)] vs. combined (walking *and* CT) behavioral interventions in maintaining/ improving cognitive functioning, quality of life (QOL), and daily functioning, in 60 adults with mild cognitive impairment (MCI) or cognitive complaints, ages 55-80. Primary hypotheses: 1: The combined group will show greater cognitive benefits (objective neuropsychological and ecological measures of cognition) 0- and 3-months post-intervention than either singular intervention group. 2: The combined group will have greater QOL benefits (patient and informant self-report) and maintenance of independent functioning (Independent Living Scales; ILS, CDR) 0- and 3-months post-intervention than either singular intervention group. Secondary Aim: Compare any differential cognitive benefits of physical vs. cognitive interventions. Secondary hypothesis: Walking will result in greatest benefits to executive functioning while CT will result in greatest benefits to memory.

EXPERIMENTAL DESIGN AND METHODS: *Participants.* We will recruit 60 largely sedentary (< 1 hour/week of purposeful aerobic exercise for the past 6 months), though otherwise medically healthy, participants with MCI or cognitive complaints, ages 55-80. Participants will be randomized to the walking intervention (n=20), a CT program (n=20), or a combined walking and CT intervention (n=20). Participants will be recruited from the Memory and Aging Resilience Center (MARC), the Alzheimer's Disease Research Center (ADRC) and multiple existing studies of aging at the University of California, San Diego (UCSD) who consented to be contacted about other studies. We will over-recruit by 10% to account for subject attrition and to ensure a final sample size of 60. These sources should allow for realistic attainment of the desired sample size and recruiting from these extant sources is optimal given that many have already been screened for general health and gross cognitive status. Should these recruitment avenues be insufficient, however, additional community participants will be recruited. All participants will be screened and excluded if they have a history of significant head trauma, other neurologic or major psychiatric disorders, known dementia, current substance dependence, or any contraindication to increased physical activity. Participants must also be fluent in English, willing to commit to the time requirements of their assigned intervention, and be free of sensory or mobility deficits that would interfere with the interventions. Participants not showing sufficient adherence to their intervention protocol will be discontinued from the study. If not administered by the recruitment source in the last 6-weeks, the Montreal Cognitive Assessment (MoCA) and the Clinical Dementia Rating Scale (CDR) will be included in the screening; MoCA must be 18-30 and CDR of 0 or 0.5 at entry into the study. Participants cannot be engaged in another cognitive training or exercise trial during participation during this investigation. Individuals over age 80 will not be included due to increased risk of mobility difficulties and safety concerns in the oldest-old with the walking protocol.
Procedures: Appropriate individuals who agree to participate will provide informed consent. Although participants will be screened for inclusion/exclusion criteria prior to study entry, if during the course of any of the following assessments exclusionary information becomes available, that participant's data will not be analyzed. Dementia is exclusionary at baseline, however, if future assessments reveal that a participant has transitioned to dementia, their data will be utilized. We will reduce participant burden and practice effects and maximize use of data already available from our recruitment avenues; if participants have undergone neuropsychological testing within six weeks of their scheduled baseline assessment, we will request their prior test results to use as part of their baseline evaluation and only administer tests

not previously given. All participants will obtain medical clearance by a physician to participate in the protocol and provide basic medical information (including medical history, basic health and fitness variables, stroke risk factors, blood pressure, height, weight, and body mass index). All participants will undergo neuropsychological assessment on three occasions: a baseline assessment, immediately post-intervention (0-month post), and extended follow-up at 3-months post-intervention (3-month post). Based on prior research, the assessment measures were chosen to cover executive functioning and memory, daily functioning, and informant report of functioning, in particular. Ecological measures of cognition are also included to be able to determine generalizability and impact on everyday functional skills. The baseline assessment will entail a comprehensive neuropsychological exam consisting of measures of global cognitive functioning and estimated premorbid intellectual functioning (American National Adult Reading Test; ANART) the Wechsler Abbreviated Scale of Intelligence (WASI), language (the Boston Naming Test (BNT), memory (Hopkins Verbal Learning Test (HVLT), executive functioning [selected subtests from the Delis Kaplan Executive Functioning System (DKEFS)], attention/working memory from WAIS-IV: Symbol Search, and Digit Span, Symbol-Digit Modalities Test (SDMT), the CDR, and an ecologically valid assessment of cognitive functioning (Rivermead Behavioural Memory Test; RBMT) that will test some skills specifically trained in the CT condition (e.g., name learning, and story learning) but also additional untrained skills such as prospective memory. We will also administer the ILS, a practical measures of functional living skills (Loeb, 1996), the Everyday Cognition Scale (ECog), an informant-based questionnaire of everyday cognitive skills with multiple scales covering memory, language, visuospatial abilities, executive functioning, and divided attention (Farias et al., 2008), a self-report measure of mood (the Geriatric Depression Scale), a measure of QOL, the Quality of Life Interview-Brief Version [QOLI-Brief (Lehman, Kernan, & Postrado, 1994)], and a self-report assessment of current and past physical activity including the Community Health Activities Monitoring Program for Seniors (Stewart et al., 2001).

The walking intervention will begin following baseline assessments and will be continued for 12 weeks. The walking group will be given a pedometer (a small, unobtrusive device, clipped to a waistband or put in a pocket that saves step data for one week, and should not impede normal daily activities) to use daily and log their daily steps, with an identified goal of increasing step counts by 3000 steps a day over the course of the intervention. After obtaining a weeklong baseline step count, individuals in the intervention group will be placed on a program to progressively increase their step counts by 100 steps daily each week for the first three weeks, by 200 steps daily for weeks four through six, by 300 steps daily for weeks seven through nine, and by 400 steps daily for weeks ten through twelve. These are cumulative step increases so that participants will increase average daily step counts by 3000 steps over the course of the intervention. Mean baseline step counts for sedentary older adults in our pilot work were 4150 per day; therefore, most participants will almost double their daily activity by the end of the intervention. To guide participants and maintain adherence to the study protocol, the study coordinator will contact the participants weekly to discuss activity logs and adjust step goals. The study coordinator will also be available via phone throughout the study to answer questions that may arise.

In the CT condition, participants will use Brain HQ, a computer cognitive training program (Posit Science Corporation,San Francisco, CA), shown to be well tolerated by older adults with positive short and long-term cognitive outcomes (Rebok et al., 2014; Smith et al., 2009). Participants will complete 6 Brain HQ modules: 'To Do List Training,' dedicated to verbal

memory, 'Syllable Stacks,' a working memory module, 'Divided Attention,' 'Mixed Signals,' targeting inhibition, 'In the Know,' for story learning, and 'Face Facts,' for name learning. Participants will use the program 60 minutes/day, 5 days/week for 12 weeks. They will receive a brief introduction to the program on site at the MARC (log-in, which modules to complete, and how long to spend each day on CT). These instructions will then be repeated via phone once the participant is on their home computer and can be supplemented by an in-home visit if significant technological difficulties exist. If participants do not have a home computer/internet access, they can complete the modules at another location such as a public library, senior center, or at the MARC, but training will still be self-directed. Brain HQ offers a secure clinician portal that allows for monitoring of usage and progress of participants but the study coordinator will still be in weekly phone contact with participants to discuss activity logs and answer any questions.

The combined condition will concurrently follow both the walking and the CT programs as described above.

STATISTICAL ANALYSES: Assuming a one tailed test, a medium effect size with power of .7 can be obtained with the sample size of 20 per group. The groups will be compared on baseline characteristics, including program adherence, using t-tests and χ^2 and analyses will be adjusted to account for any observed group differences. Lifestyle covariates such as health, prior physical activity, mood, and education will also be explored and used as appropriate. We will employ reliable change analyses to take into account change in neuropsychological test scores over the course of the intervention while also accounting for predicted practice effects. To address the primary hypothesis, group comparisons of changes in neuropsychological test scores and measures of daily functioning between the groups will be determined via ANCOVA and repeated measures analyses. For the CT condition in particular, we will examine whether any cognitive benefits generalize beyond the trained task. To address the secondary hypothesis, we will use logistic regression to determine the degree to which intervention group predicts differential cognitive outcomes. Correlations between neuropsychological test scores and health and fitness variables will also be explored.