Lifestyle Interventions for the Treatment of EOAD Study (LITES)

Dustin B. Hammers, PhD, Associate Professor
Indiana University School of Medicine
355 West 16th Street
Indianapolis, IN 46202

Co-Investigators:

Frederick Unverzagt, PhD, Professor
Indiana University School of Medicine
355 West 16th Street
Indianapolis, IN 46202

Liana G. Apostolova, MD, Professor
Indiana University School of Medicine
355 West 16th Street
Indianapolis, IN 46202

Support Provided by:
Alzheimer's Association

Version: 6/13/22

Table of Contents:

Abbreviations

AA	Alzheimer's Association
ACTIVE	Advanced Cognitive Training for Independent and Vital Elderly
AD	Alzheimer's Disease
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ANCOVA	Analysis of Covariance
ATRI	Alzheimer's Therapeutic Research Institute
BDI-2	Beck Depression Inventory - 2
CANTAB	Cambridge Neuropsychological Test Automated Battery
RVP	Rapid Visual Processing
MTS	Match To Sample
PAL	Paired Associates Learning
PRM	Pattern Recognition Memory
SWM	Spatial Working Memory
SOC	Stockings of Cambridge
VPA	Verbal Paired Associates
DGS	Digit Span
CSRQ	Cognitive Self-Report Questionnaire
DSMC	Data Safety Monitoring Committee
EOAD	Early-Onset Alzheimer's Disease
IU	Indiana University
LEADS	Longitudinal Early-Onset AD Study
MCI	Mild Cognitive Impairment
MOCA	Montreal Cognitive Assessment
PCQ	Perception of Change Questionnaire
RCT	Randomized Clinical Trial
SAE	Significant Adverse Event

1.0 Background & Rationale

EOAD is an Overlooked Condition

Despite the rapid expansion of research on interventions for Alzheimer's disease (AD), treatment for patients diagnosed at a younger stage of life (aged 40 to 64 years old) has been overlooked. This is likely due to the rareness of the condition – less than 5% of patients with AD have onset before 65 years old [1] – and also to challenges identifying disease modifying treatments in traditional-onset AD. These "early onset-AD" (EOAD) patients experience a unique set of complications related to their functioning, including cognitive declines while raising families and performing at the height of their careers. As a result of relatively preserved insight and this early decline, elevated rates of depression are common in EOAD [2]. Identification of successful treatments for this condition would lead to significant improvements for patients and families across multiple aspects of life.

EOAD and Traditional-Onset AD Present Differently

EOAD does not appear to be traditional-onset AD at an earlier age. EOAD tends to possess a more aggressive disease course [3] and greater cognitive severity [4] than traditional AD. Additionally, EOAD is proposed to manifest with greater relative involvement of non-memory cognitive domains, [5] and phenotypes associated with logopenic progressive aphasia, posterior cortical atrophy, progressive ideomotor apraxia, frontal variant AD, and corticobasilar syndrome are common [4]. Subgroups of EOAD

tend to have higher rates of neurological symptoms than traditional AD and decreased comorbidities such as diabetes, obesity, and circulatory disorders [6]. On magnetic resonance imaging, greater parietal and overall cortical atrophy is seen in EOAD, with less atrophy in the medial temporal lobe and hippocampus [7]. Relatedly, fluorodeoxy glucose positron emission tomography studies show greater parietal lobe hypometabolism in EOAD, [8] and diffuse tensor imaging studies indicate that white-matter degradation in EOAD patients is greater posteriorly (posterior cingulate and parietal), with less medial temporal involvement [9]. While recent studies have suggested some promise of monoclonal antibodies (i.e., Aduhelm) for the treatment of traditional AD, at present no attempts at pharmacological interventions in EOAD have been undertaken.

Lifestyle Interventions Offer Promising Results

Extensive research on the benefit of lifestyle interventions for older adults' functioning exists across a variety of cognitively intact and impaired samples. Computerized cognitive training, for example, has repeatedly shown benefit in a host of conditions impacting cognition, including brain injury [10] and healthy aging [11]. The largest study of its kind – a randomized controlled trial (RCT) of 2800 older adults in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study [12, 13] – showed that cognitive training improved cognitive performance in non-demented older adults upon completion of training, [12] and at 2-years, [12] 5-years, [14] and 10-years post-training [15]. *BrainHQ* (Posit Science) is a brain plasticity-based adaptive cognitive training program involving a suite of 29 online exercises that target several cognitive domains. Since 2019, >50 studies have been published on the use of *BrainHQ*, including those showing treatment benefits in cognitively intact participants, [16, 17] and those with schizophrenia, [18] Mild Cognitive Impairment (MCI), [19, 20] and mood disorders [21]. Training dosage effects have been observed in older adults with or without a cognitive disorder, with higher rates of training suggesting greater benefit from treatment [22]. Additionally, stronger cognitive training improvements have been suggested in participants with stronger baseline cognition, [22] and preliminary evidence in MCI suggests that women show greater treatment effects compared to men [23].

Physical exercise paradigms have additionally been shown to benefit cognition [24, 25]. A recent meta-analysis of 13 RCTs (*n* = 673) showed that physical exercise interventions improved performance in patients with AD on the Mini-Mental State Exam (*SMD*=1.12, *CI*: 0.66-1.59) compared to control groups [26]. A separate meta-analysis of 20 studies (*n*=2,553) of *Tai Chi* intervention in adults aged 60 and over found support for cognitive enhancement [27]. Specifically, effect sizes were large (*Hedge's g* =0.51; *p*=0.003) for executive functioning outcomes in cognitively healthy adults relative to controls, and moderate (*Hedge's g* =0.35; *p*=0.004) for global cognition outcomes in cognitively impaired adults [27]. A more recent systematic review (9 studies, *n*=456) suggested *Tai Chi* improved short-term cognitive function in the elderly, including for global cognitive functioning, visuospatial skills, semantic memory, verbal learning/memory, and self-perception of memory [28].

The unique benefits of cognitive training and physical exercise have led some researchers to combine these treatments into a single intervention. Meta-analytic findings of 10 RCTs (*n*=742) involving combined cognitive training and physical exercise suggest a small-to-medium positive effect of interventions on global cognitive function (*SMD*=0.32, *CI*: 0.17-0.47) in older adults with MCI and dementia, and a moderate-to-large positive effect for activities of daily living (*SMD* = 0.65, *CI*: 0.09-1.21) [29]. Additional research is underway to examine the efficacy of a cognitively-enhanced *Tai Chi* intervention on cognitive health delivered remotely to older adults with MCI ("*Tai Ji Quan: Moving to Maintain Brain Health*"; NIH 5R01AG059546), with preliminary data (*n*=69) suggesting feasibility, acceptability, and safety of the intervention [30]. The **synergistic effects** of using both interventions have been associated with "guided plasticity facilitation" [31-33]. Specifically, it is proposed that physical exercise facilitates synaptic plasticity and neurogenesis due to the release of neurotrophic factors like brain-derived neurotrophic factor (BDNF) and cytokine/hormonal factors, [34] and stimulation of synapses and neurons during cognitive training guides synapse formation and integration of new neuronal

structures in brain circuitry, resulting in enhanced gray matter/dorsolateral prefrontal lobe density [35, 36] and cognitive processing [32].

An Opportunity Exists for Lifestyle Interventions in EOAD

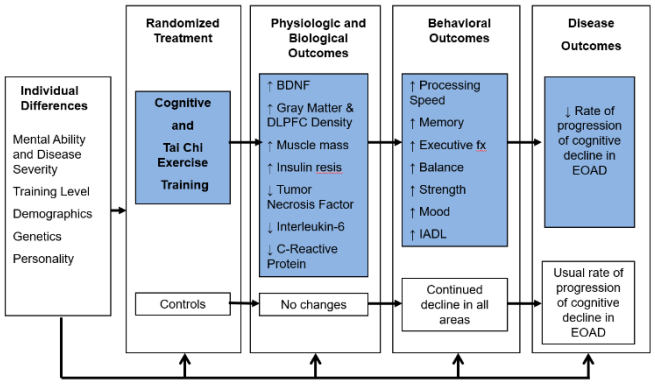


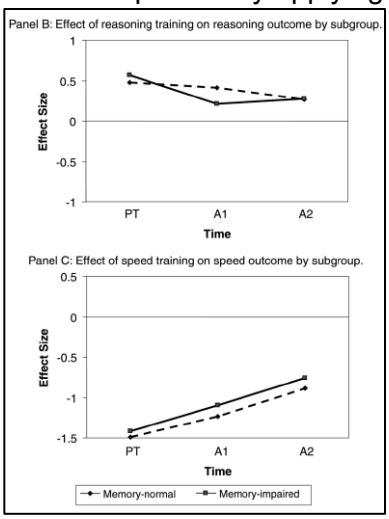
Figure 1. Proposed Conceptual Model of Intervention Effects in EOAD

As a result of this support for lifestyle interventions, we offer a conceptual model (**Figure 1**) of cognitive and *Tai Chi* exercise training for improved cognition in EOAD individuals, moderated by individual differences in training and participant variables. To date, these interventions have had limited consideration in EOAD populations, due to its rareness and the severity/aggressive course commonly observed in EOAD [4]. Given the increased focus on EOAD by the Alzheimer's Association and leading AD scientists, this reflects a gap in knowledge in AD literature. This also overlooks a potential treatment option for patients with EOAD and their families. Consequently, we are undertaking an *NIH-defined Stage IB (NIH Stage Model)* study to collect preliminary data to investigate the feasibility and pilot testing of this combined lifestyle intervention on short-term and long-term cognition, functioning, and mood in participants with EOAD from the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS), relative to an Active Control group. Because LEADS is a multi-site study across the U.S., all aspects of this proposed study will be **conducted remotely**. Current LEADS participants classified as *amyloid-positive* EOAD (n = 60) will be recruited for our study. Our research team is uniquely positioned to examine this model, given our extensive experience with lifestyle interventions, access to the most well-characterized cohort of EOAD participants in the U.S., and the inclusion of several pre-eminent scholars in neurodegeneration, AD clinical trials, and EOAD. We are currently unaware of any other research attempting to identify the efficacy of lifestyle interventions in this population.

Preliminary Data: As the goal of this application is to generate preliminary data on the benefit of cognitive and *Tai Chi* training in participants with EOAD – which has previously been unexamined in the literature – little to no previous findings exist to directly support our proposal. As such, a brief review of related literature will be provided to support our Aims.

Aim 1. Evaluate feasibility of a lifestyle intervention and outcomes in participants with EOAD

In a recent pilot study applying *BrainHQ* cognitive training to patients with mild to moderate traditional-onset dementia, 8 of 10 participants studied were able to complete the 36 hours of cognitive training, with participant eagerness, rate of non-refusal, and attentiveness being strong (refusal rate for the 384 training sessions was only 3%) [37]. Cognitive screening scores on the Montreal Cognitive Assessment (MOCA) were notably low (M = 13.1 ± 1.6), suggesting that *BrainHQ* can be tolerated by severely-cognitively impaired populations. These results are relevant to our proposal as the mean MOCA score for our current EOAD cohort is 16.9 (± 5.6). Relatedly, both *BrainHQ* and *Tai Chi* have been found to be efficacious when administered remotely-to-home, [16, 38] consistent with the procedure planned for the current study. Together, these findings suggest that use of this lifestyle intervention remotely in our cognitively compromised EOAD cohort is **feasible**.



Aims 2 & 3. Efficacy and Moderation of a lifestyle intervention in EOAD

Dr. Unverzagt (Co-Mentor) has been centrally involved with lifestyle interventions – and cognitive training in particular – over the past 20 years. He has shown that memory impaired participants failed to benefit from memory training in the ACTIVE program, but did show expected training gains on domains of reasoning and processing speed [13] (**Figure 2**). Additionally, his work helped show the aforementioned benefit of cognitive training in ACTIVE immediately and after a delay [12, 14, 15]. Overall, his research into cognitive training **established empirical support for the paradigm** – paving the way for its application in EOAD – and suggests that severity of memory impairment may play a moderating role in treatment outcomes in our sample.

Figure 2. Improvements in cognition on reasoning/speeded training post-treatment (PT) and at follow-up years 1 (A1) and 2 (A2)

2.0 Objective(s)

2.1 Primary Objective

The Primary Objective is to **evaluate the feasibility of the combined lifestyle intervention and outcome assessments for use in future trials in participants with EOAD.** Hypothesis 1.a: We will monitor adherence to interventions and outcome assessments. Adherence to treatments and completion of outcome assessments will be ≥75% and ≥90%, respectively. Adherence will not differ among the two treatment arms. Hypothesis 1.b: We will monitor acceptability and attrition of the lifestyle intervention. At least 70% of participants will rate the intervention as enjoyable, and attrition will be <15%.

2.2 Secondary Objective

The Secondary Objective is to **investigate if the lifestyle intervention combining cognitive training and *Tai Chi* improves (2a) short-and long-term cognition and (2b) functioning and mood in participants with EOAD compared to an active control condition.** Hypotheses 2.a and 2.b: The EOAD participants in the experimental training condition will perform better on outcomes related to (2.a) cognition and (2.b) functioning and mood at follow-up compared to the EOAD participants assigned to the active control condition.

2.3 Tertiary/Exploratory/Correlative Objectives

The Tertiary Objective is to **explore potential moderators on the degree of benefit from a combined cognitive training and *Tai Chi* lifestyle intervention in EOAD.** Because of sample size limitations in this preliminary study, focus will be on determining effect sizes and sample-size magnitude needed for future work. Exploratory hypotheses include: Hypothesis 3.a: A greater treatment response will be seen in women with EOAD relative to men. Hypothesis 3.b: Better response will be related to increased hours of training and decreased disease severity.

3.0 Outcome Measures/Endpoints

3.1 Primary Outcome Measures

To not interfere with the NACC-UDS 3.0 battery being administered at annual LEADS visits, the current study will administer a novel and streamlined battery at Baseline, immediately Post-Treatment (approximately 14 weeks later), and at 6-months Follow-up.

Primary outcome measures will be post-treatment and 6-month follow-up improvements on **CANTAB Connect computerized cognitive measures** (Rapid Visual Processing [RVP], Match To Sample

[MTS], Paired Associates Learning [PAL], Pattern Recognition Memory [PRM], Spatial Working Memory [SWM], Stockings of Cambridge [SOC], and Verbal Paired Associates [VPA]), after controlling for baseline performance.

CANTAB measures were selected for their assessment of memory, executive functioning, and visuospatial working memory, with validation in AD samples (Barnett et al., 2016). Based on meta-analytic findings (Zhang et al., 2019), cognitive domains of episodic memory and executive/working memory were expected to result in the highest benefit from behavioral interventions. CANTAB Connect research has suggested that at-home testing is feasible (Maljkovic et al., 2019) and practice effects are generally low with repeat testing (Cacciamani et al., 2018), making it appropriate for use in this remote repeated assessment protocol.

3.2 Secondary Outcome Measures

Secondary outcomes include the following, assessed at Baseline, immediately Post-Treatment, and at 6-months Follow-up:

a. Cognitive Self-Report Questionnaire **(CSRQ)**, which is a 25-item self-report questionnaire of subjective cognitive difficulties [39]. This measure has been used in a variety of studies examining benefit from cognitive training [40, 41].
b. Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory [42] (**ADCS-ADL**) scale. This informant-based rating scale assesses the participant's ability to perform a variety of activities of daily living over the past four weeks, and has been shown to discriminate between healthy elderly controls and those with mild AD [42].
c. 21-item Beck Depression Inventory-2 (**BDI-2**) [43] was used as a measure of self-reported depression.

3.3 Tertiary/Exploratory/Correlative Outcome Measures

A brief self-reported Perception of Change Questionnaire (**PCQ**) will also be administered to gauge blinding procedures.

4.0 Eligibility Criteria

4.1 Inclusion Criteria

- Enrolled in the Longitudinal Early-Onset AD Study (LEADS), [44] and being classified via LEADS consensus criteria as having amyloid-positive EOAD
- Aged 40-64 years at the time of enrollment into LEADS
- Fluent in English
- In good general health and absent another neurological disorder
- Have a knowledgeable informant.
- Have had a Clinical Dementia Rating scale of 0.5 to 1.0 at the time of enrollment into LEADS.
- Have sufficient vision, hearing, comprehension, and manual dexterity to participate in the testing and training program

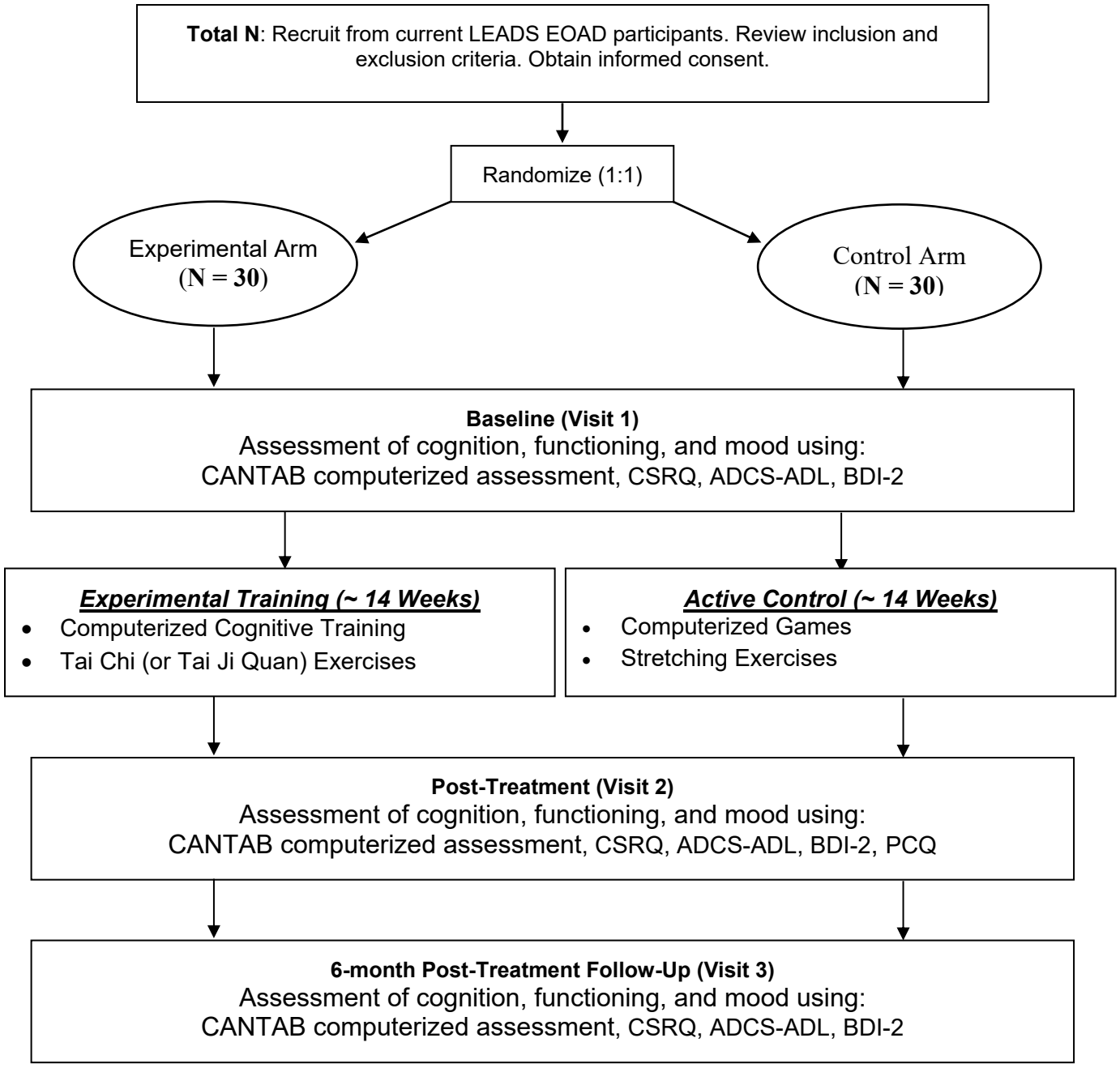
4.2 Exclusion Criteria

- Have access to the internet (e.g., home, family, public library, etc.) for **less than 4 hours per week**.

5.0 Study Design

This research study aims to generate preliminary data regarding the efficacy of a combined cognitive-training and *Tai Chi* exercise lifestyle intervention in participants diagnosed with EOAD. Participants will complete a series of cognitive, functional, and mood assessments at a remotely-assessed baseline visit, and then be randomized into one of two conditions: (1) **Computerized Cognitive Training + *Tai Chi* Exercise** or (2) **Active Control**. Outcome measures will be repeated immediately Post-Treatment and at 6-months post-treatment Follow-Up. Specific Aim 1 will examine the feasibility of this lifestyle intervention and outcome assessments when applied to participants with EOAD. Specific Aim 2 will investigate if this lifestyle intervention improves short- and long-term cognition, functioning, and mood. Specific Aim 3 will be exploratory to assess whether individual differences in training or clinical/ demographic characteristics moderate the degree of benefit from this intervention; owing to sample size limitations in this feasibility study, focus of this latter aim will be on determining effect sizes and sample-size magnitude needed for future work.

The following schematic provides an overview of the study procedures:



6.0 Enrollment/Randomization

Recruitment

The proposed study will recruit 60 participants with amyloid-positive Early Onset Alzheimer's Disease through the ongoing NIH-funded multi-center Longitudinal Early-Onset Alzheimer's Disease Study

(LEADS). To date, LEADS has enrolled 200 EOAD participants, along with 62 early-onset non-AD and 91 control participants. New participants will be added to LEADS on a rolling basis until final enrollment numbers reach 400 EOAD participants, 200 early-onset non-AD participants, and 100 control participants.

The LEADS sites for recruitment include Indiana University (IU), Massachusetts General Hospital, University of California – San Francisco, Mayo Clinic – Rochester, Mayo Clinic Jacksonville, John Hopkins Medicine, Georgetown University, and Houston Methodist Hospital. Recruitment of participants into the proposed study can be expanded to the other 10 LEADS sites, if necessary.

Individuals will be recruited by LEADS study members during ongoing LEADS appointments. When participants arrive to these already-scheduled LEADS appointments, a research member will let them know that they are eligible for a research study that examines the benefit of a combined lifestyle intervention for EAOD. Site researchers will provide potential participants with study information and Dr. Hammers/Study Coordinators contact information, but should not send potential participants contact information directly to Dr. Hammers/Study Coordinator. Those interested in participating will be scheduled for the informed consent process at a convenient time, and informed consent will be obtained through the IU IRB-approved *e-consent process* (given the remote nature of this study). Study procedures will immediately follow written consent if they decide to participate. Despite the low risk of this study, there is the possibility that some participants with EOAD will have limited capacity to provide informed consent. In those instances, consent will be obtained from a care partner and assent will be obtained from the participant with EOAD. First name, telephone number, and email addresses will be obtained to confirm the scheduled visit, but will be destroyed immediately following their participation in the study.

Randomization and Blinding

Participants will be randomly assigned to the experimental or active control group via a computer-generated schedule. Randomization will occur after the Baseline visit in permuted blocks of six with random variation of blocking number. Group membership will be coded and blinded until analyses are complete. Participants will be informed that the intervention involves “cognitive and physical exercises” to enhance face validity of all groups and blind participants to group assignment. They will be told that two different types of training programs are being studied to see which one works best. Relatedly, assessors at post-treatment and follow-up visits will be blinded. The effectiveness of participant blinding will be evaluated by administering a questionnaire at post-treatment to compare the groups on self-reported perception of change in cognitive function (PCQ). We will also compare the proportions of voluntarily withdrawals from each group.

7.0 Study Procedures

The Appendix includes materials that participants will receive regarding BrainHQ, CANTAB, Cognitive Self-Report Questionnaire, ADCS-ADL, BDI-2, PCQ.

Procedures:

1. **Informed Consent**. Informed consent will be sought from all individuals that will participate in the proposed projects, including participants (and their informants). In most cases, when a potential participant has been identified at their regularly-scheduled LEADS visit, s/he will be presented with a brief overview of the study, as well as a brochure that further describes the study and its procedures. If interested, the participant will be instructed to contact one of the research assistants or the Principal Investigator if questions need to be answered. If still

interested, a virtual visit will be scheduled to review the informed consent document with the potential participant (and informant), answer additional questions, and obtain written consent (through the *e-consent process*). Since many of our potential participants will be cognitively impaired, we will also make a determination about capacity to provide informed consent. Following presentation of the informed consent document, participants will be asked questions about the study (e.g., purpose, procedures, risk and benefits). If these questions are adequately answered, then the participant will be judged to have capacity to provide informed consent. However, if these questions are not adequately answered, the participants will be judged to not have this capacity. In these latter cases, assent will be obtained from the participant and informed consent will be obtained from the participant's legally authorized representative (e.g., spouse, adult child).

2. **Baseline (Visit 1)**. During this visit, participants will complete measures of baseline functioning pertaining to cognition (CANTAB and CSRQ), daily functioning (ADCS-ADL), and mood (BDI-2). This visit should take approximately 75-90 minutes.

3. **Lifestyle Intervention**

    a. **Experimental Training Program**:

    i. Remote Computerized Cognitive Training from Posit Science's BrainHQ Program. This web-based application [45] was designed to improve the speed and accuracy of memory, executive functioning, and visual processing skills. Exercises will continually adjust difficulty levels to maintain an 85% correct rate. A set of computerized cognitive training exercises have been selected based on their validation in lifestyle intervention programs for older adults. Users will be expected to play 18 levels per session, 5 sessions per week for 14 weeks. Below are examples of the cognitive exercises that will appear in their schedule: 1) A divided attention and visual tracking task that requires the monitoring of a select number of moving objects upon a backdrop filled with identical moving objects. As the task continues the number of objects the participant must track increases ("Target Tracker"). 2) A visual precision exercise that emphasizes the ability to spot targets that appear on screen for increasingly brief amounts of time. As levels increase, peripheral vision is further utilized as the distance between targets is increased ("Hawk Eye").

    To use the experimental treatment program, a participant opens an Internet-browser and navigates to a general log-in screen or clicks on the BrainHQ app downloaded onto their mobile device from the App Store or Google Play store. The participant then logs into the experimental treatment program server using an anonymized email address and password created on their behalf by a staff member. This will allow us to track their progress through the program and provide personalized reminders for training. A game-like experience begins, where the participant is encouraged to earn stars and in-game rewards to advance. To do so, the participant completes the cognitive exercises scheduled for the day, and must achieve 10 stars to advance to the next exercise in their queue (stars are derived from normalized z-score performance). Notification of session completion is achieved when the user finishes at least 18 levels. The exercise itself contains the core therapeutic exercise task built into a game-like experience. Participants perform tens to hundreds of trials over the course of a session, with auditory and visual feedback and rewards to indicate if the trial was performed correctly or

incorrectly. Within each session, target frequency is titrated according to performance to maintain ~80% target accuracy across training session. Also, after each session, the difficulty of the next session is updated (e.g., less inter-stimulus-interval jitter) to ensure that each participant is appropriately challenged. Summary screens including game metrics (stars, scores) and exercise metrics (usage, progress) are shown to the participant at the end of each session. All usage and progress data is encrypted then transmitted to a central server. In a research study such as this one, no personally identifiable information is stored on the server (including internet protocol addresses). On the server, the data are available for review by the un-blinded research coordinator through a secure web portal. The research coordinator will use the secure web portal to regularly check on usage and progress of each active participant to customize their weekly emails to provide helpful guidance and coaching, if needed, outside of the automated email reminders.

The scheduling mechanism ensures that a participant progresses through the exercises in an optimally defined order, generally moving from simple (e.g., easy to discriminate stimulus types, moderate pacing) exercises to complex (e.g., greater self-pacing required, greater rule complexity) exercises over the course of the 14-week experience.

Participants will be asked to complete 18 levels per session (approximately 45 minutes), 4-5 sessions per week for 14 weeks (corresponding to approximately 40 hours of training total).

ii. Tai Chi (or Tai Ji Quan) Exercises.
This remote training of *Tai Chi* exercises will be modeled after the virtually-administered *Tai Ji Quan: Moving for Better Balance* program [46]. Specifically, it will involve practice of a core of 8 therapeutically-modified exercise forms aimed at stimulating and integrating musculoskeletal, sensory, and cognitive systems [47]. These self-initiated *Tai Chi* exercises will additionally incorporate synchronized breathing, center of gravity displacement, and unilateral weight-bearing and weight-shifting movements (of the trunk, pelvis, ankle, head, and hands). Participants will be asked to complete 14 hours of training total (in 30-minute sessions, 2 days per week for 14 weeks). Initial sessions will focus on learning and engaging in *Tai Chi* movements across multiple positions (e.g., seating, standing only, stepping) as necessary, with later sessions honing skills. Because participants will live in multiple time zones, pre-recorded videos will be available to watch online individually.

b. **Active Control Training Program**:

i. Computerized Games Through the BrainHQ Web Portal.
A set of computerized games have been selected that are engaging, but have not been empirically validated to improve cognition. In each training session, a pre-determined set of three exercises will be presented for approximately 15 minutes each. Participants will be asked to complete 40 hours of training total (in 45-minute sessions, 4 to 5 days per week for 14 weeks).

ii. Stretching Exercises.

Active Control participants will also be provided video-instructional materials on a stretching routine, consisting of activities related to breathing, stretching, and relaxation

activities. The central aspect of the exercise will involve progressive stretching of the upper and lower body, and trunk. Deep breathing exercises will additionally be included. Participants will be asked to engage in these stretching/breathing exercises twice per week, for approximately 30 minutes per session. This will total 14 hours over the course of 14 weeks.

Of note, all participants will receive a unique username for Posit Science/*BrainHQ*, which will determine the specific cognitive training content that they can access. For example, participants randomized into the Active Control arm will only have access to the active control training through the *BrainHQ* web portal. A separate username will be created for access to the respective online video-instruction for physical exercise. The amount of time spent on each of these websites will be tracked based on participant login/logout, which will be paired with a paper-and-pencil "training log" for each participant to record the date and start/stop times of their sessions. These variables may be used in the proposed moderation analyses in Specific Aim 3.

Remote coaching and technical support. Both computer programs through the *BrainHQ* portal will be accompanied by a centralized coaching and technical support service by *BrainHQ*, to provide ongoing participant support and ensure that any technical issues are resolved promptly and successfully. Assistance will also be available by IU staff familiar with BrainHQ. Staff will conduct remote 15-minute check-ins with participants to discuss progress and answer questions. This remote support system is consistent with existing lifestyle interventional trials, such as EXERT, US POINTER, PACT, among others.

4. **Post-treatment (Visit 2)**. Approximately 14 weeks after the Baseline visit, the outcome measures (CANTAB, CSRQ, ADCS-ADL, BDI-2) will be repeated for all participants. The **PCQ** will also be administered to gauge blinding procedures. This visit should take approximately 75-90 minutes.

5. **Follow-up (Visit 3**). Approximately 6 months after the completion of training, outcome measures (CANTAB, CSRQ, ADCS-ADL, BDI-2) will again be repeated for all participants. This visit should take approximately 75-90 minutes.

8.0 Study Calendar

	Baseline (Visit 1)	Lifestyle Training Intervention	Post-Treatment (Visit 2)	6-month Post-Treatment Follow-Up (Visit 3)
	Week 1	Week 2 – Week 15	Week 16	Week 42
STUDY PROCEDURES				
Cognitive Assessment	X		X	X
Functional Assessment	X		X	X
Mood Assessment	X		X	X
Cognitive Training		X		
Exercise Training		X		

	Baseline (Visit 1)	Lifestyle Training Intervention	Post-Treatment (Visit 2)	6-month Post-Treatment Follow-Up (Visit 3)
	Week 1	Week 2 – Week 15	Week 16	Week 42
Perception of Change Questionnaire			X	
*Variations of +/- 3 weeks from the scheduled visit are permitted				

9.0 Reportable Events

There are no expected adverse events. As described in the Protection of Humans subjects, it is possible that participants will experience distress related to cognitive training, but there are no other known side effects anticipated. All adverse events that are related or possibly related to the protocol will be reported to the IU IRB as soon as possible, no more than 10 days from the event. Any serious adverse event will be reported within 24 hours of event, in accordance with the standard IU IRB reporting guidelines.

Participants will be informed in the consent document for Specific Aims 1-3 of circumstances under which licensed psychologists might be required to break confidentiality due to mandated reporting laws. These cases include: concerns for participants' risk to self (suicidality) or others (homicidality), or information that suggests a child, older adult, or dependent adult are being abused. If a participant described an intent or inability/unwillingness to develop and follow a safety plan, Dr. Hammers will be immediately located for additional assessment and intervention, and will work in conjunction with the respective LEADS site-PI given the remote nature of the data collection.

10.0 Data Safety Monitoring

This data safety monitoring plan was developed based on prior studies using similar types of cognitive training and *Tai Chi* exercises (including *BrainHQ*), where no adverse events have been reported (i.e., relatively low risk to participants). This plan will monitor the collected data for accuracy and completeness. The Principal Investigator and the Research Assistant will review the study data and files for accuracy and completeness after the first six participants' data are collected. If procedures are not accurately or completely capturing study data, then procedures will be modified to allow for more accurate and complete data capture. If any changes in the procedures will be necessary, then the IRB be informed in an amendment. If these changes are approved by the IRB, then the Alzheimer's Association will be informed of these changes in our annual progress report. All research data will be stored on encrypted Indiana University (IU) servers as well as encrypted external hard drives that will be kept in a locked cabinet in the PI's office. Additionally, participant identifiers will be stored separately from the coded test data.

A Data and Safety Monitoring Committee (DSMC) has been established to review on an ongoing basis the safety of all subjects enrolled in this clinical trial. Meetings will be held approximately quarterly – as necessary – after the first subject is enrolled and will be held via virtual conference. The frequency of meetings may change at the discretion of the chair. The DSMC will be regularly informed of the occurrence of any significant adverse event (SAE) and immediately notified of any fatal or life-threatening event. After reviewing the safety data, the DSMC will make recommendations regarding the conduct of the study. These recommendations include amending the safety monitoring procedures, modifying the protocol or consent, performing additional analyses, terminating the study, or continuing the study as designed. Given the co-enrollment of the proposed study's participants with the LEADS

study, the DSMC utilized by LEADS will also oversee data safety for the proposed study. Specifically, the Alzheimer's Therapeutic Research Institute (ATRI) at the Keck School of Medicine of the University of Southern California serves as the DSMC for LEADS, and as the Director of ATRI, Dr. Paul Aisen has offered ATRI's services as DSMC for the project as well. ATRI's DSMC is made up of the individuals with significant experience in geriatric neurology, clinical trials, and cognition, and will include Paul Aisen, MD. Any DSMC reports will be filed in the regulatory binder at IU, with a copy also being sent to the LEADS Executive Committee and the IRBs at all participating sites.

The following will be monitored as part of the Data Safety Monitoring Plan: data quality, subject recruitment, accrual, retention, outcome and adverse event data, assessment of scientific reports or therapeutic development, results of related studies that may impact subject safety, and procedures designed to protect the privacy of subjects. No pre-planned stoppage analyses will be conducted given the preliminary nature of the data collection.

11.0 Study Withdrawal/Discontinuation

Withdrawal from the study will occur by the participant (or care partner) contacting the PI or study team to report a desire for study discontinuation. Withdrawal prior to the completion of the lifestyle interventions will result in a discontinuation of access to *BrainHQ* and the *Tai Chi* exercise programs.

12.0 Statistical Considerations

All statistical hypothesis tests will be performed on a comparison-wise basis, using a 2-sided α=0.05 without adjustment for multiple comparisons. The risk of inflated Type 1 error due to multiple comparisons will be limited in the current aims by designating 1-2 primary analyses for each Specific Aim. A total sample size of n = 60 (n = 30 per arm) is being used in this study.

Specific Aim 1: Evaluate feasibility of a lifestyle intervention in participants with EOAD.

Analysis: Hypothesis 1.a: Successful adherence will be defined as participants completing 75% of training visits across the 14-week study. Also, Chi-Square Tests of Independence will assess differences in the proportion of participants that completed training in our experimental group relative to active controls. Further, successful completion of PT and FU outcome assessments will be defined as obtaining valid outcome data in 90% of assessing randomized participants. Hypothesis 1.b: An intervention attrition rate of <15% of both cognitive and *Tai Chi* exercises will define successful study retention. Dropping out of the intervention will mean notifying project staff of discontinuation, or not responding to participation reminders after falling behind training goals. Exploration of participant satisfaction will additionally be undertaken with the use of modified a 6-item survey assessing questions of challenge/enjoyment for each aspect of the intervention, appropriateness of cognitive difficulty, appropriateness of exercise intensity, helpfulness in improving brain health, and overall program satisfaction; we specified an a priori overall satisfaction level of ≥70%. *One-sample proportion tests* will be used in both hypotheses to determine differences from expectation.

Power: Based on previous literature, we are not anticipating difference in compliance between experimental and active control groups. Using a similar paradigm in MCI participants, previous research observed differences in adherence rates of only 2.7% between experimental and control groups, resulting in a power difference of 0.068 at a significance level of 0.05.

Specific Aim 2: Investigate if a lifestyle intervention improves (2a) cognition and (2b) functioning and mood in participants with EOAD compared to an active control condition.

Analysis: Primary outcome measures will be PT and FU improvements on the CANTAB Connect cognitive measures. Secondary outcomes include CSRQ, ADCS-ADL, and BDI-2 scores. Hypothesis 2.a: Treatment effect will be analyzed using Analysis of Covariance (ANCOVA) comparing CANTAB Connect cognitive values at both the PT and FU visits for the experimental group versus active controls, while controlling for the baseline performance. Hypothesis 2.b: ANCOVA analyses will be used to compare treatment effects at PT and FU for functioning and mood-related outcomes.

Power: We expect to complete the PT and FU visits for 92.5% and 85% of the 60 randomized subjects, respectively (which accounts for attrition). Power estimates were based on a study of an 8-week RCT of cognitive training, physical exercise, and dietary education in patients with MCI (n = 57) and normal cognition (n = 62). The authors calculated a cognitive composite from the ADAS-Cog, Trail-Making Test B, Symbol Digit Modalities Test, and Category Fluency test, with z score differences between experimental and control groups being z = 0.25 at both 3- and 6-months post treatment. Based on this data, with our sample size we will have 90% power with a 2-sided $\alpha = 0.05$ to detect effect size differences of 0.23 at PT and FU visits.

Specific Aim 3: Explore potential moderators (training, clinical) on lifestyle intervention benefit.

Analysis: Although this preliminary study's sample size is limited, the impact of moderators on training benefit will be examined as follows: linear mixed effect regression will be used to model longitudinal data including random effects for participants to examine the impact of training dose, sex, and disease severity on CANTAB performance between groups, with separate interaction models being applied (treatment assignment x training hours/sex/severity).

Power: As indicated previously, the focus of Aim 3 will be on determining effect sizes and the magnitude of sample sizes needed for future work. We will not estimate the sizes of these effects as feasibility trials are underpowered for reliable estimates.

All statistical analysis will be conducted with the Biostatistics Core Leader of LEADS, Ani Eloyan, PhD.

Primary data will be collected via remote data capture from measurement instrument and stored electronically in REDCap. The storage location will be backed up automatically. Other data sources include data from the LEADS study that will be stored in separate electronic files and merged with the primary data as needed. Quality assurance steps will include built in range checks, and testing of database by study team prior to moving to production mode. The following quality control methods will be used: extraction and cleaning of data that will be used for analysis every 12 months.

13.0 Privacy/Confidentiality Issues

Data will be obtained from individually identifiable living human subjects in the form of demographic information, medical and psychiatric history, presence of memory and other cognitive complaints, report of activities of daily living, performance on neuropsychological tests, and responses on a depression assessment measure. Most of this information will be collected during one-on-one remote research visits with the participants. Information will also be collected from interviews with knowledgeable informants. LEADS records will be accessed to confirm diagnosis. Data will be obtained specifically for research purposes and it will not be used for clinical or other purposes. Research data will only be accessible to members of the research team. To maintain privacy/confidentiality, study identification

numbers will be created to match the LEADS identification number for use in research databases, with a name-to-identification number key store in a separate document to reduce the likelihood of loss of confidentiality. Some research team members will have access to greater levels of individually identifiable information. For example, the research assistants who schedule visits, obtain consent, and collect cognitive test data will have access to the most identifiable information. Conversely, the biostatisticians will only have access to data that has already been largely de-identified (e.g., identification numbers instead of names of participants).

14.0 Data Management

Primary data will be collected via direct data capture from measurement instrument and stored electronically in REDCap. The storage location will be backed up automatically. Other data sources include data from LEADS that will be stored in separate electronic files and merged with the primary data as needed. Quality assurance steps will include: 1) built in range checks; and 2) testing of database by study team prior to moving to production mode. The following quality control method will be used: extraction and cleaning of data that will be used for analysis every 1 year.

15.0 Follow-up and Record Retention

For each participant, treatment will last approximately 14 weeks, followed by post-treatment follow-up and 6-month post-treatment visits. This will result in the length of involvement for a particular participant being approximately 11 months. The duration of the entire study will be three years. Records will be retained for seven years following the completion of the study, with paper records being shredded and electronic records being deleted at that time.

16.0 References

1. Zhu XC, Tan L, Wang HF, et al. Rate of early onset Alzheimer's disease: a systematic review and meta-analysis. Ann Transl Med 2015;3:38.
2. Rosness TA, Barca ML, Engedal K. Occurrence of depression and its correlates in early onset dementia patients. Int J Geriatr Psychiatry 2010;25:704-711.
3. Wattmo C, Wallin AK. Early- versus late-onset Alzheimer's disease in clinical practice: cognitive and global outcomes over 3 years. Alzheimers Res Ther 2017;9:70.
4. Mendez MF. Early-Onset Alzheimer Disease. Neurol Clin 2017;35:263-281.
5. Palasi A, Gutierrez-Iglesias B, Alegret M, et al. Differentiated clinical presentation of early and late-onset Alzheimer's disease: is 65 years of age providing a reliable threshold? J Neurol 2015;262:1238-1246.
6. Gerritsen AA, Bakker C, Verhey FR, et al. Prevalence of Comorbidity in Patients With Young-Onset Alzheimer Disease Compared With Late-Onset: A Comparative Cohort Study. J Am Med Dir Assoc 2016;17:318-323.
7. Migliaccio R, Agosta F, Possin KL, et al. Mapping the Progression of Atrophy in Early- and Late-Onset Alzheimer's Disease. J Alzheimers Dis 2015;46:351-364.
8. Chiaravalloti A, Koch G, Toniolo S, et al. Comparison between Early-Onset and Late-Onset Alzheimer's Disease Patients with Amnestic Presentation: CSF and (18)F-FDG PET Study. Dement Geriatr Cogn Dis Extra 2016;6:108-119.
9. Caso F, Agosta F, Mattavelli D, et al. White Matter Degeneration in Atypical Alzheimer Disease. Radiology 2015;277:162-172.

10. Phillips NL, Mandalis A, Benson S, et al. Computerized Working Memory Training for Children with Moderate to Severe Traumatic Brain Injury: A Double-Blind, Randomized, Placebo-Controlled Trial. J Neurotrauma 2016;33:2097-2104.
11. Smith G, Chandler M, Locke DE, et al. Behavioral Interventions to Prevent or Delay Dementia: Protocol for a Randomized Comparative Effectiveness Study. JMIR Res Protoc 2017;6:e223.
12. Ball K, Berch DB, Helmers KF, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. JAMA 2002;288:2271-2281.
13. Unverzagt FW, Kasten L, Johnson KE, et al. Effect of memory impairment on training outcomes in ACTIVE. J Int Neuropsychol Soc 2007;13:953-960.
14. Wolinsky FD, Unverzagt FW, Smith DM, Jones R, Stoddard A, Tennstedt SL. The ACTIVE cognitive training trial and health-related quality of life: protection that lasts for 5 years. J Gerontol A Biol Sci Med Sci 2006;61:1324-1329.
15. Rebok GW, Ball K, Guey LT, et al. Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults. J Am Geriatr Soc 2014;62:16-24.
16. Lee HK, Kent JD, Wendel C, et al. Home-Based, Adaptive Cognitive Training for Cognitively Normal Older adults: Initial Efficacy Trial. J Gerontol B Psychol Sci Soc Sci 2020;75:1144-1154.
17. Humeidan ML, Reyes JC, Mavarez-Martinez A, et al. Effect of Cognitive Prehabilitation on the Incidence of Postoperative Delirium Among Older Adults Undergoing Major Noncardiac Surgery: The Neurobics Randomized Clinical Trial. JAMA Surg 2021;156:148-156.
18. Loewy R, Fisher M, Ma S, et al. Durable Cognitive Gains and Symptom Improvement Are Observed in Individuals With Recent-Onset Schizophrenia 6 Months After a Randomized Trial of Auditory Training Completed Remotely. Schizophr Bull 2021.
19. McMaster M, Kim S, Clare L, et al. Lifestyle Risk Factors and Cognitive Outcomes from the Multidomain Dementia Risk Reduction Randomized Controlled Trial, Body Brain Life for Cognitive Decline (BBL-CD). J Am Geriatr Soc 2020;68:2629-2637.
20. Phatak VS, Smith GE, Locke D, et al. Computerized Cognitive Training (CCT) versus Yoga Impact on 12 Month Post Intervention Cognitive Outcome in Individuals with Mild Cognitive Impairment. Brain Sci 2021;11.
21. Morimoto SS, Altizer RA, Gunning FM, et al. Targeting Cognitive Control Deficits With Neuroplasticity-Based Computerized Cognitive Remediation in Patients With Geriatric Major Depression: A Randomized, Double-Blind, Controlled Trial. Am J Geriatr Psychiatry 2020;28:971-980.
22. Bamidis PD, Fissler P, Papageorgiou SG, et al. Gains in cognition through combined cognitive and physical training: the role of training dosage and severity of neurocognitive disorder. Front Aging Neurosci 2015;7:152.
23. Rahe J, Liesk J, Rosen JB, et al. Sex differences in cognitive training effects of patients with amnestic mild cognitive impairment. Aging, Neuropsychology, and Cognition 2015;22:620-638.
24. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. Arch Phys Med Rehabil 2004;85:1694-1704.
25. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA 2008;300:1027-1037.
26. Jia RX, Liang JH, Xu Y, Wang YQ. Effects of physical activity and exercise on the cognitive function of patients with Alzheimer disease: a meta-analysis. BMC Geriatr 2019;19:181.
27. Wayne PM, Walsh JN, Taylor-Piliae RE, et al. Effect of tai chi on cognitive performance in older adults: systematic review and meta-analysis. J Am Geriatr Soc 2014;62:25-39.
28. Lim KH, Pysklywec A, Plante M, Demers L. The effectiveness of Tai Chi for short-term cognitive function improvement in the early stages of dementia in the elderly: a systematic literature review. Clin Interv Aging 2019;14:827-839.
29. Karssemeijer EGA, Aaronson JA, Bossers WJ, Smits T, Olde Rikkert MGM, Kessels RPC. Positive effects of combined cognitive and physical exercise training on cognitive function in older adults with mild cognitive impairment or dementia: A meta-analysis. Ageing Res Rev 2017;40:75-83.

30. Li F, Harmer P, Fitzgerald K, Winters-Stone K. A cognitively enhanced online Tai Ji Quan training intervention for community-dwelling older adults with mild cognitive impairment: A feasibility trial. BMC Geriatrics 2022;22:76.
31. Fissler P, Kuster O, Schlee W, Kolassa IT. Novelty interventions to enhance broad cognitive abilities and prevent dementia: synergistic approaches for the facilitation of positive plastic change. Prog Brain Res 2013;207:403-434.
32. Trachtenberg JT, Chen BE, Knott GW, et al. Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. Nature 2002;420:788-794.
33. Subramaniam K, Luks TL, Garrett C, et al. Intensive cognitive training in schizophrenia enhances working memory and associated prefrontal cortical efficiency in a manner that drives long-term functional gains. Neuroimage 2014;99:281-292.
34. Herold F, Hamacher D, Schega L, Müller NG. Thinking While Moving or Moving While Thinking - Concepts of Motor-Cognitive Training for Cognitive Performance Enhancement. Frontiers in aging neuroscience 2018;10:228-228.
35. Erickson KI, Leckie RL, Weinstein AM. Physical activity, fitness, and gray matter volume. Neurobiol Aging 2014;35 Suppl 2:S20-S28.
36. Northey JM, Rattray B, Pumpa KL, et al. Objectively measured physical activity is associated with dorsolateral prefrontal cortex volume in older adults. NeuroImage 2020;221:117150.
37. Rouse HJ, Small BJ, Faust ME. Assessment of Cognitive Training & Social Interaction in People with Mild to Moderate Dementia: A Pilot Study. Clin Gerontol 2019;42:421-434.
38. Li F, Harmer P, Voit J, Chou L-S. Implementing an Online Virtual Falls Prevention Intervention During a Public Health Pandemic for Older Adults with Mild Cognitive Impairment: A Feasibility Trial. Clinical interventions in aging 2021;16:973-983.
39. Spina L, Ruff R, Mahncke H. Cognitive Self-Report Questionnaire (CSRQ) Manual. San Francisco, CA: Posit Science Corporation, 2006.
40. O'Brien JL, Lister JJ, Fausto BA, Clifton GK, Edwards JD. Cognitive Training Enhances Auditory Attention Efficiency in Older Adults. Frontiers in Aging Neuroscience 2017;9.
41. Smith GE, Housen P, Yaffe K, et al. A cognitive training program based on principles of brain plasticity: results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study. Journal of the American Geriatrics Society 2009;57:594-603.
42. Galasko D, Bennett D, Sano M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997;11 Suppl 2:S33-39.
43. Beck AT, Steer RA, Brown G. Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation, 1996.
44. Apostolova LG, Aisen P, Eloyan A, et al. The Longitudinal Early-onset Alzheimer's Disease Study (LEADS): Framework and methodology. Alzheimers Dement 2021.
45. McMaster M, Kim S, Clare L, Torres SJ, D'Este C, Anstey KJ. Body, Brain, Life for Cognitive Decline (BBL-CD): protocol for a multidomain dementia risk reduction randomized controlled trial for subjective cognitive decline and mild cognitive impairment. Clin Interv Aging 2018;13:2397-2406.
46. Li F. Transforming traditional Tai Ji Quan techniques into integrative movement therapy-Tai Ji Quan: Moving for Better Balance. J Sport Health Sci 2014;3:9-15.
47. Li F, Harmer P, Fitzgerald K, et al. Effectiveness of a Therapeutic Tai Ji Quan Intervention vs a Multimodal Exercise Intervention to Prevent Falls Among Older Adults at High Risk of Falling: A Randomized Clinical Trial. JAMA Intern Med 2018;178:1301-1310.

17.0 Appendix

The Appendix includes materials that participants will receive regarding BrainHQ, CANTAB, Cognitive Self-Report Questionnaire, ADCS-ADL, BDI-2, PCQ.

BrainHQ Training

The core battery of BrainHQ tasks are taken from the “Focus on Visual Process” schedule. This focus is designed to improve the speed and accuracy of visual processing, attention, and memory. The overall program is composed of five interrelated training exercises that in aggregate span the organization of visual perception and cognition from spatial frequency processing to visuo-spatial memory. The tasks include speed of processing time-order judgments, discrimination between pairs of like items, and sustained tracking of multiple objects that increase their complexity by progressively moving to more and more rapidly presented stimuli and greater memory loads. A detailed description of the course can be found in this white paper.

This Focus presents five exercises (Double Decision, Eye for Detail, Target Tracker, Hawk Eye, Visual Sweeps) that are delivered over 40 sessions. Here is a description of each exercise (click the suite of the exercise you want to learn about then the exercise, e.g., Click “Memory” to find “Memory Grid”). Each exercise has a 1-2 page description of how the exercise works, how it adapts based on user behavior, and what it specifically trains.

The tables below describe more detailed aspects of the exercises (Table 1) as well as which exercises and stages are presented for each of the 40 sessions (Table 2). We provide step-by-step instructions for how to assign this Focus to your participant’s account (see the Focus Header).

Table 1

Commercial name	~ levels per stage	# of stages	~ minutes per stage
Eye for Detail	6	4	18
Double Decision	6	7	18
Target Tracker	9	7	27
Hawk Eye	6	10	18
Visual Sweeps	8	7	24

Table 2

session	exercise name & stage number	~ mins per session
1	Target Tracker 1, Double Decision 1	24
2	Visual Sweeps 1, Eye for Detail 1	30
3	Hawk Eye 1, Visual Sweeps 2	30
4	Target Tracker 2, Eye for Detail 2	45
5	Visual Sweeps 3, Double Decision 3	42
6	Target Tracker 3, Hawk Eye 2	45
7	Visual Sweeps 4, Eye for Detail 3	42
8	Target Tracker 4, Double Decision 4	45
9	Visual Sweeps 5, Hawk Eye 3	42
10	Target Tracker 5, Eye for Detail 4	45
11	Visual Sweeps 6, Double Decision 6	42
12	Target Tracker 6, Hawk Eye 4	45
13	Visual Sweeps 7, Eye for Detail 2	42

14	Target Tracker 7, Double Decision 7	45
15	Visual Sweeps 2, Hawk Eye 5	42
16	Target Tracker 2, Eye for Detail 3	45
17	Visual Sweeps 3, Double Decision 10	42
18	Target Tracker 3, Hawk Eye 6	45
19	Visual Sweeps 4, Eye for Detail 4	42
20	Target Tracker 4, Double Decision 3	45
21	Visual Sweeps 5, Hawk Eye 7	42
22	Target Tracker 5, Eye for Detail 2	45
23	Visual Sweeps 6, Double Decision 4	42
24	Target Tracker 6, Hawk Eye 8	45
25	Visual Sweeps 7, Eye for Detail 3	42
26	Target Tracker 7, Double Decision 6	45
27	Visual Sweeps 2, Hawk Eye 9	42
28	Target Tracker 2, Eye for Detail 4	45
29	Visual Sweeps 3, Double Decision 7	42
30	Target Tracker 3, Hawk Eye 10	45
31	Visual Sweeps 4, Eye for Detail 2	42
32	Target Tracker 4, Double Decision 10	45
33	Visual Sweeps 5, Hawk Eye 2	42
34	Target Tracker 5, Eye for Detail 3	45
35	Visual Sweeps 6, Double Decision 3	42
36	Target Tracker 6, Hawk Eye 3	45
37	Visual Sweeps 7, Eye for Detail 4	42
38	Target Tracker 7, Double Decision 4	45
39	Visual Sweeps 2, Hawk Eye 4	42
40	Target Tracker 2, Eye for Detail 2	45

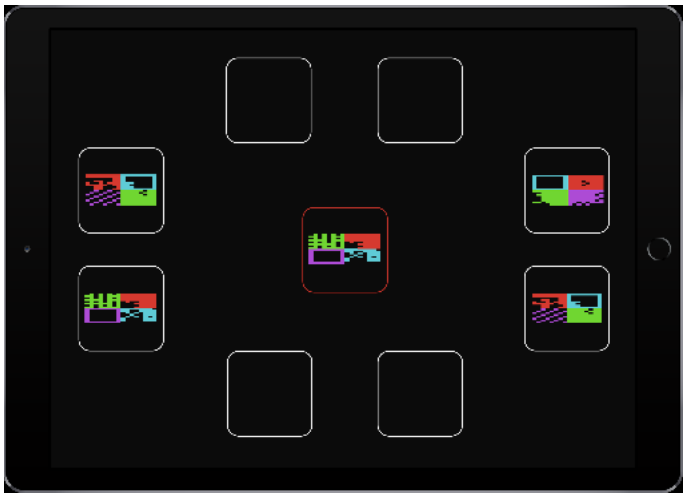
CANTAB Connect Assessment Subtests

Rapid Visual Information Processing (RVP)

RVP is a sensitive tool for assessment of sustained attention. Single digits appear one at a time at a rate of 100 digits per minute. Subjects must detect a series of target sequences (e.g. 3-5-7) and touch a button when they see the last digit of a target sequence. Nine target sequences appear every 100 numbers. Performance on the RVP test has been shown to be associated with activation in a network of brain structures including the frontal and parietal lobes (Coull et al., 1995).

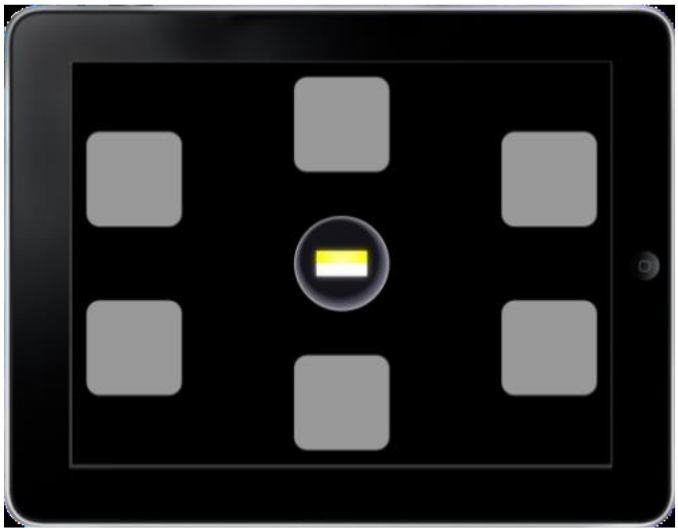
Key outcome measures include RVP A prime, a signal detection measure of target sensitivity and RVP median response latency.

Match to Sample Visual Search (MTS)



MTS assesses attention and visual searching, with a speed-accuracy trade-off. A complex visual pattern is shown in a box in the middle of the screen. After a brief delay, a number of similar patterns are shown in a circle of boxes around the edge of the screen. The subject must touch the one that matches the sample in the middle. The number of patterns to choose from varies across trials, but there is always only one which matches the center pattern.

Paired Associates Learning (PAL)

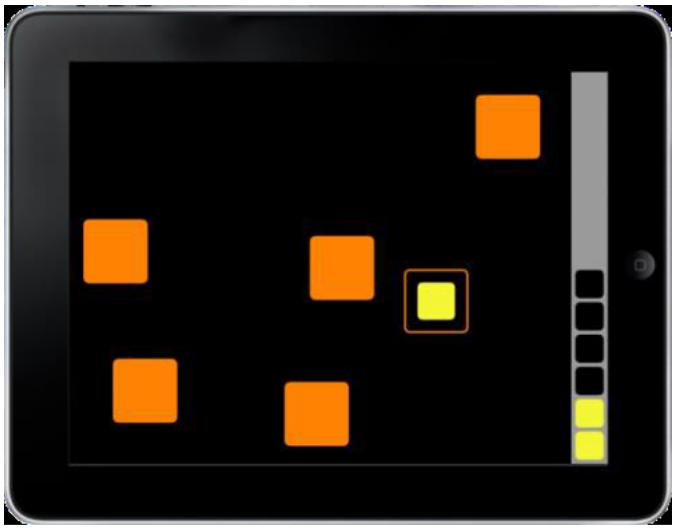


PAL assesses visual memory and new learning, and is a sensitive tool for accurate assessment of episodic memory. Boxes are displayed on the screen and open one by one in a randomized order to reveal patterns hidden inside. The patterns are then displayed in the middle of the screen, one at a time, and the subject must touch the box where the pattern was originally located. If the subject makes an error, the patterns are re-presented to remind the subject of their locations. Practice trials with fewer patterns are available to familiarize subjects with the test.

Pattern Recognition Memory (PRM)

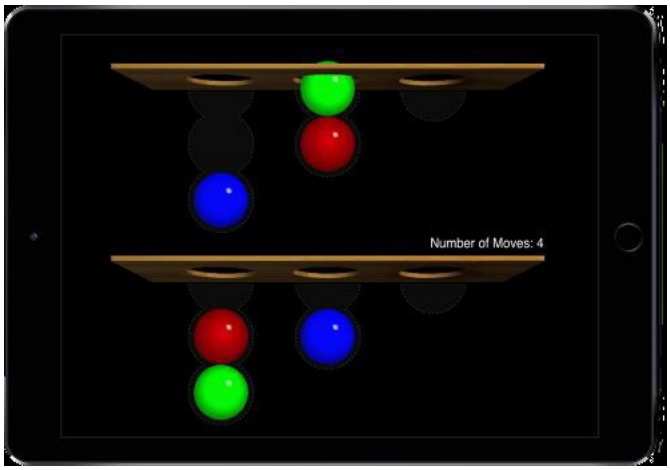
PRM is a measure of visual recognition memory. The subject's watch a series of 12 patterns appear, one at a time, on the screen. These patterns are designed so that they cannot be given verbal labels. In the recognition phase, the subject chooses which two patterns they have alrea

Spatial Working Memory (SWM)



SWM requires retention and manipulation of visuospatial information. This test has notable executive function demands, and measures strategy use as well as errors. The test begins with colored boxes being shown on the screen. The aim of this test is that, by touching the boxes and using a process of elimination, the subject should find one 'token' in each of the boxes and use them to fill up an empty column on the right-hand side of the screen. The key test instruction is that the computer will never hide a token in the same colored box, so once a token is found in a box the subject should not return to that box to look for another token. The color and position of the boxes used are changed from trial to trial to discourage the use of stereotyped search strategies. The key outcome measures for SWM include errors (touching boxes that have been found to be empty and revisiting boxes which have already been found to contain a token) and strategy, a measurement of executive function.

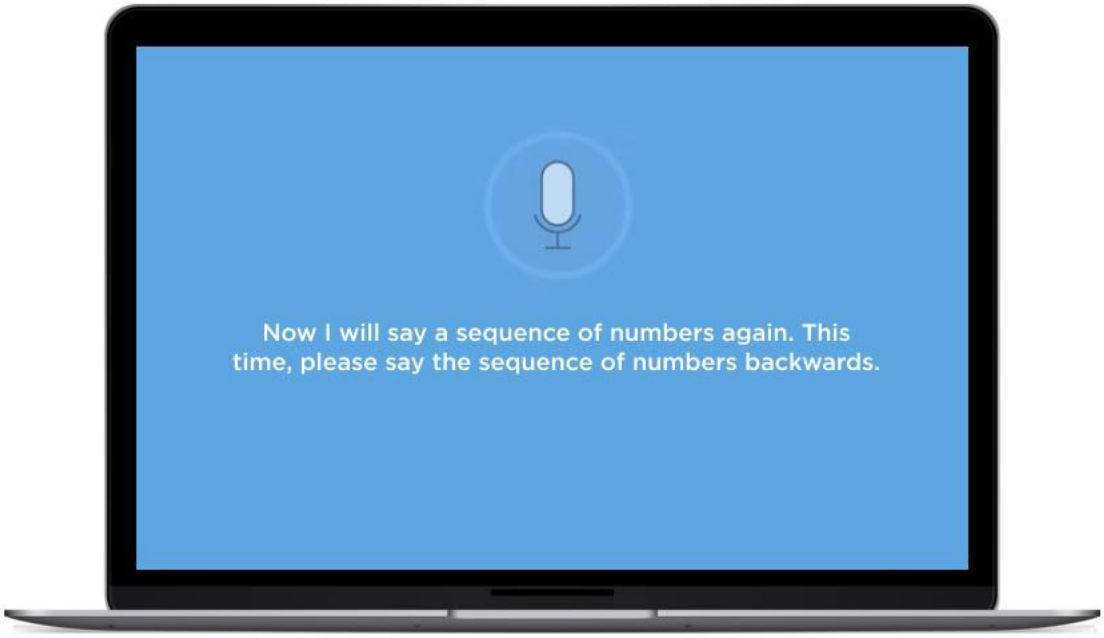
Stockings of Cambridge (SOC)



SOC assesses spatial planning and requires individuals to use problem-solving strategies to match two sets of stimuli. The subject is shown two displays. In each of these displays, three stockings - containing three colored balls - are suspended from a beam. The two displays appear at the top and bottom of the screen. The balls are arranged in different patterns in each display. The subject must move the balls in the bottom display to copy the pattern shown in the top display. The balls are moved one at a time by selecting the required ball, then selecting the position to which it should be moved. The subject is instructed to make as few moves as possible to match the two patterns. In a distinct phase of

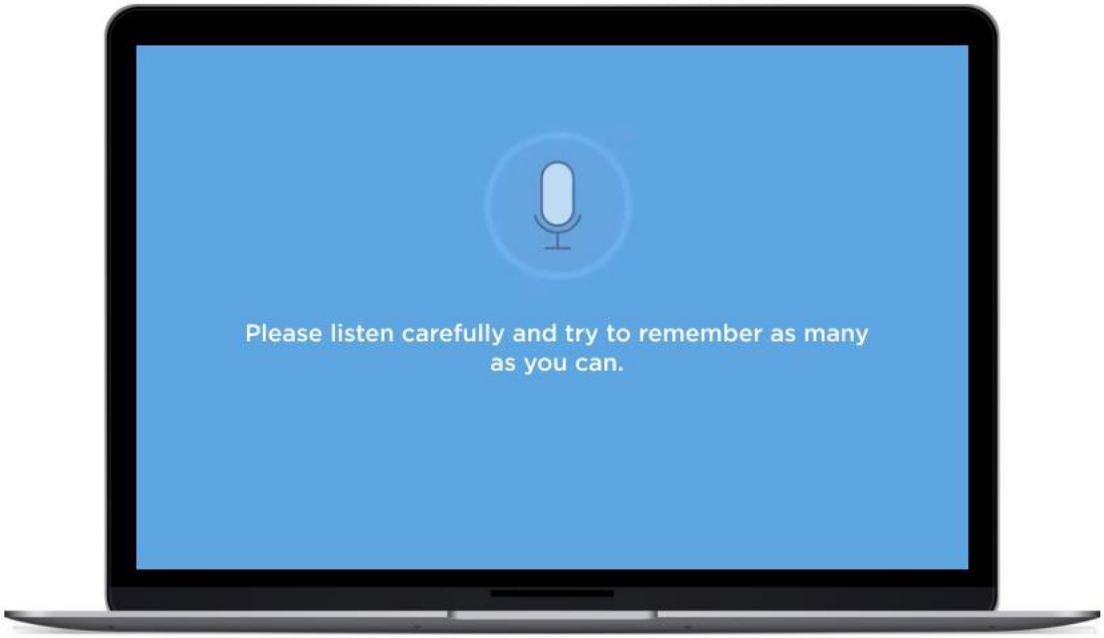
the test, subjects are instructed to copy the moves the computer makes. These moves mimic the moves the subject made, and allow movement time to be discounted from thinking time measures.

Digit Span (DGS)



Digit Span (DGS) is a measure of verbal short term and working memory that can be used in two formats, Forward Digit Span and Reverse Digit Span. This is a verbal task, with stimuli presented auditorily, and responses spoken by the participant and scored automatically by the software. Participants are presented with a random series of digits, and are asked to repeat them in either the order presented (forward span) or in reverse order (backwards span). While superficially very similar tasks, forward and backwards span rely on somewhat separable cognitive capacities: the simpler forward span task requires verbal working memory and attention, while the backwards span task additionally tests cognitive control and executive function.

Verbal Paired Associates (VPA)



Verbal Paired Associates (VPA) is an assessment of associative and episodic memory in which the task is to learn a set of word-pairs. This is a verbal task, with stimuli presented auditorily, and responses spoken by the participant and scored automatically by the software. The difficulty of the task (i.e., the memorability of the word-pair items) has been carefully calibrated so that parallel forms of the test can be used in repeated testing.

Cognitive Self-Report Questionnaire

INSTRUCTIONS:

"Below is a list of statements about how you see your everyday thinking skills and feelings. For each statement, please think about whether there has been any change because of the training program you completed as part of this study. If there is no change, or you noticed a change but you think it is because of something other than the training program, then circle "Same as before"

SINCE PARTICIPATING IN THIS STUDY….

1. I lose my train of thought….	Less often 3	Same as before 2	More often 1	Does not apply 0	AT1
2. My ability to pay attention to more than one thing at a time is…	Better 3	Same as before 2	Worse 1	Does not apply 0	EX1
3. My ability to remember phone numbers is…	Better 3	Same as before 2	Worse 1	Does not apply 0	ME1
4. I have trouble finding the right word …	Less often 3	Same as before 2	More often 1	Does not apply 0	LG1
5. My peripheral vision is…	Better 3	Same as before 2	Worse 1	Does not apply 0	VS1
6. My ability to hear what people say when they speak softly or mumble is…	Better 3	Same as before 2	Worse 1	Does not apply 0	HR1
7. I engage in activities with other people…	More often 3	Same as before 2	Less often 1	Does not apply 0	EN1
8. I am happy…	More 3	Same as before 2	Less 1	Does not apply 0	SA1
9. My ability to think quickly is…	Better 3	Same as before 2	Worse 1	Does not apply 0	AT2
10. My mind is sharp…	More 3	Same as before 2	Less 1	Does not apply 0	EX2
11. I can remember where I left things…	More often 3	Same as before 2	Less often 1	Does not apply 0	ME2
12. My ability to express my thoughts in writing is…	Better 3	Same as before 2	Worse 1	Does not apply 0	LG2
13. My ability to see things clearly is…	Better 3	Same as before 2	Worse 1	Does not apply 0	VS2
14. I notice & hear everyday sounds around me…	More 3	Same as before 2	Less 1	Does not apply 0	HR2
15. My level of energy to do daily tasks is…	Better 3	Same as before 2	Worse 1	Does not apply 0	EN2
16. I feel self-confident…	More 3	Same as before 2	Less 1	Does not apply 0	SA2
17. My ability to keep my mind on an activity without my mind wandering is…	Better 3	Same as before 2	Worse 1	Does not apply 0	AT3

18. My ability to organize activities is...	Better 3	Same as before 2	Worse 1	Does not apply 0	EX3
19. My ability to remember the names of people I know (e.g. a neighbor) is…	Better 3	Same as before 2	Worse 1	Does not apply 0	ME3
20. My ability to follow the meaning of a story or article I read is…	Better 3	Same as before 2	Worse 1	Does not apply 0	LG3
21. My ability to judge when it is safe to merge with traffic on the freeway is...	Better 3	Same as before 2	Worse 1	Does not apply 0	VS3
22. My ability to hear things clearly is…	Better 3	Same as before 2	Worse 1	Does not apply 0	HR3
23. I feel tired during the day…	Less 3	Same as before 2	More 1	Does not apply 0	EN3
24. I feel good about myself…	More 3	Same as before 2	Less 1	Does not apply 0	SA3
25. My ability to concentrate on something for a long period of time is…	Better 3	Same as before 2	Worse 1	Does not apply 0	AT4
26. My ability to take-in/process information quickly is…	Better 3	Same as before 2	Worse 1	Does not apply 0	EX4
27. My ability to remember things that people tell me is…	Better 3	Same as before 2	Worse 1	Does not apply 0	ME4
28. My ability to read quickly is…	Better 3	Same as before 2	Worse 1	Does not apply 0	LG4
29. My ability to tell when it is safe to cross the street is…	Better 3	Same as before 2	Worse 1	Does not apply 0	VS4
30. My ability to hear conversations in noisy places (e.g. restaurant or crowded room) is…	Better 3	Same as before 2	Worse 1	Does not apply 0	HR4
31. I get a good night's sleep…	More often 3	Same as before 2	Less often 1	Does not apply 0	EN4
32. I feel pessimistic…	Less 3	Same as before 2	More 1	Does not apply 0	SA4
33. I get distracted….	Less 3	Same as before 2	More 1	Does not apply 0	AT5
34. My ability to switch from one task to another is…	Better 3	Same as before 2	Worse 1	Does not apply 0	EX5
35. I walk into a room and then forget why I needed to go there…	Less often 3	Same as before 2	More often 1	Does not apply 0	ME5
36. My ability to understand what I read (without having to go back and re-read) is…	Better 3	Same as before 2	Worse 1	Does not apply 0	LG5
37. When I meet someone new, my ability to recognize them later is…	Better 3	Same as before 2	Worse 1	Does not apply 0	VS5

38. My ability to hear conversations on the telephone is…	Better 3	Same as before 2	Worse 1	Does not apply 0	HR5
39. I am interested in trying new things...	More 3	Same as before 2	Less 1	Does not apply 0	EN5
40. I feel independent…	More 3	Same as before 2	Less 1	Does not apply 0	SA5
41. My ability to focus on a task is…	Better 3	Same as before 2	Worse 1	Does not apply 0	AT6
42. My ability to organize is...	Better 3	Same as before 2	Worse 1	Does not apply 0	EX6
43. My ability to remember grocery shopping items without looking at the shopping list is…	Better 3	Same as before 2	Worse 1	Does not apply 0	ME6
44. My ability to keep up with a conversation is…	Better 3	Same as before 2	Worse 1	Does not apply 0	LG6
45. When I meet someone new, my ability to remember their name later is…	Better 3	Same as before 2	Worse 1	Does not apply 0	VS6
46. My ability to hear what people say when they speak quickly is…	Better 3	Same as before 2	Worse 1	Does not apply 0	HR6
47. I give up on things I feel are hard to do...	Less Often 3	Same as before 2	More Often 1	Does not apply 0	EN6
48. I feel engaged in life…	More 3	Same as before 2	Less 1	Does not apply 0	SA6
49. My ability to concentrate is...	Better 3	Same as before 2	Worse 1	Does not apply 0	AT7
50. I say or do things without considering the consequences …	Less often 3	Same as before 2	More often 1	Does not apply 0	EX7
51. My memory is…	Better 3	Same as before 2	Worse 1	Does not apply 0	ME7
52. My ability to remember things I read is…	Better 3	Same as before 2	Worse 1	Does not apply 0	LG7
53. My ability to learn my way around a place that I have never been to before is…	Better 3	Same as before 2	Worse 1	Does not apply 0	VS7
54. My ability to tell similar sounds apart is…	Better 3	Same as before 2	Worse 1	Does not apply 0	HR7
55. I feel fatigued...	Less 3	Same as before 2	More 1	Does not apply 0	EN7
56. I feel unproductive…	Less often 3	Same as before 2	More often 1	Does not apply 0	SA7
57. My ability to think clearly is...	Better 3	Same as before 2	Worse 1	Does not apply 0	AT8

58. I feel alert…	More 3	Same as before 2	Less 1	Does not apply 0	EX8
59. I forget things that happened the day before…	Less often 3	Same as before 2	More often 1	Does not apply 0	ME8
60. My ability to articulate my thoughts (i.e. get the meaning across easily) is…	Better 3	Same as before 2	Worse 1	Does not apply 0	LG8
61. My eyes can keep track of things that move quickly (e.g. a fly in the room)…	Better 3	Same as before 2	Worse 1	Does not apply 0	VS8
62. My ability to hear what people say on TV is…	Better 3	Same as before 2	Worse 1	Does not apply 0	HR8
63. I feel energetic…	More 3	Same as before 2	Less 1	Does not apply 0	EN8
64. I am in a bad mood…	Less often 3	Same as before 2	More often 1	Does not apply 0	SA8

Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory

This informant-based rating scale assesses the participant's ability to perform a variety of activities of daily living over the past four weeks, and has been shown to discriminate between healthy elderly controls and those with mild AD.

1. Regarding eating: Which best describes subjects usual performance during the past 4 weeks?

- ☐ Ate without physical help
- ☐ Used a fork or spoon, but not a knife to eat
- ☐ Used fingers to eat
- ☐ Usually or always was fed by someone else

2. Regarding walking (or getting around in a wheelchair), in the past 4 weeks, which best describes his/her optimal performance:

- ☐ Mobile outside of home without physical help
- ☐ Mobile across a room without physical help
- ☐ Transferred from bed to chair without help
- ☐ Required physical help to walk or transfer

3. Regarding bowel and bladder function at the toilet, which best describes his/her usual performance in the past 4 weeks:

- ☐ Did everything necessary without supervision or help
- ☐ Needed supervision, but no physical help, and was usually continent
- ☐ Needed physical help, and was usually continent
- ☐ Needed physical help, and was usually incontinent

4. Regarding bathing, in the past 4 weeks, which best describes his/her usual performance:

- ☐ Bathed without reminding or physical help
- ☐ No physical help, but needed supervision/reminders to bathe completely
- ☐ Needed minor physical help (e.g., with washing hair) to bathe completely
- ☐ Needed to be bathed completely

5. Regarding grooming, in the past 4 weeks, which best describes his/her optimal performance:

- ☐ Cleaned and cut fingernails, without physical help
- ☐ Brushed or combed hair without physical help
- ☐ Kept face and hands clean without physical help

☐ Needed help for grooming of hair, face, hands, and fingernails

6a. Regarding dressing, in the past 4 weeks:
Did subject select his/her first set of clothes for the day?
Yes / No / don't know
☐ ☐ ☐

If Yes, which best describes his/her usual performance:
☐ Without supervision or help
☐ With supervision
☐ With physical help

6b. Regarding physically getting dressed,
which best describes his/her usual performance in the past 4 weeks: (check one)
☐ Dressed completely without supervision or physical help
☐ Dressed completely with supervision, but without help
☐ Needed physical help only for buttons, clasps, or shoelaces
☐ Dressed without help if clothes needed no fastening or buttoning
☐ Always needed help, regardless of type of clothing
☐ Don't know

7. In the past 4 weeks, did subject use a telephone
Yes / No / don't know
☐ ☐ ☐

If Yes, which best describes his/her highest level of performance:
☐ Made calls after looking up numbers in white or yellow pages, or by dialing directory assistance
☐ Made calls only to well-known numbers without referring to a directory, list, or preprogrammed numbers
☐ Made calls only to well-known numbers by using a directory or list
☐ Answered the phone; did not make calls
☐ Did not answer the phone, but spoke when put on the line

8. In the past 4 weeks, did subject watch television?
Yes / No / don't know
☐ ☐ ☐

If Yes, ask each of the following:
Yes / No
☐ ☐ a. Did subject usually select or ask for different programs or his/her

favorite show?

☐ ☐ b. Did subject usually talk about the content of a program while watching it?

☐ ☐ c. Did subject talk about the content of a program within a day (24 hours) after watching it?

9. In the past 4 weeks, did subject ever appear to pay attention to consversation or small talk for at least 5 minutes?
(note subject did not need to initiate the conversation)
Yes / No / don't know
☐ ☐ ☐

If Yes, which best describes his/her usual degree of participation:
- ☐ Usually said things what were related to the topic
- ☐ Usually said things that were not related to the topic
- ☐ Rarely or never spoke

10. Did subject clear the dishes from the table after a meal or snack?
Yes / No / don't know
☐ ☐ ☐

If Yes, which best describes how he/she usually performed:
- ☐ Without supervision or help
- ☐ With supervision
- ☐ With physical help

11. In the past 4 weeks, did subject usually manage to find his/her personal belongings at home?
Yes / No / don't know
☐ ☐ ☐

If Yes, which best describes how he/she usually performed:
- ☐ Without supervision or help
- ☐ With supervision
- ☐ With physical help

12. In the past 4 weeks, did subject obtain a hot or cold beverage for him/herself?
Yes / No / don't know
☐ ☐ ☐

If Yes, which best describes his/her highest level of performance:
- ☐ Made a hot beverage, usually without physical help
- ☐ Made a hot beverage, usually if someone else heated the water
- ☐ Obtained a cold beverage, usually without physical help

13. In the past 4 weeks, did subject make him/herself a meal or snack at home?
Yes / No / don't know

☐ ☐ ☐

If Yes, which best describes his/her highest level of performance:

☐ Cooked or microwaved food, with little or no help
☐ Cooked or microwaved food, with extensive help
☐ Mixed or combined food items for a meal or snack, without cooking or microwaving (e.g., made a sandwich)

14. In the past 4 weeks, did subject dispose of garbage or litter in an appropriate place or container at home?
Yes / No / don't know

☐ ☐ ☐

If Yes, which best describes how he/she usually performed:

☐ Without supervision or help
☐ With supervision
☐ With physical help

15. In the past 4 weeks, did subject get around (or travel) outside of his/her home?
Yes / No / don't know

☐ ☐ ☐

If Yes, which best describes his/her optimal performance:

☐ Alone, went at least 1 mile away from home
☐ Alone, but remained within 1 mile of home
☐ Only when accompanied and supervised, regardless of the trip
☐ Only with physical help, regardless or the trip

16. In the past 4 weeks, did subject ever go shopping?
Yes / No / don't know

☐ ☐ ☐

If yes, ask A and B

A) Which one best describes how subject usually selects items?

☐ Without supervision or physical help
☐ With some supervision or physical help
☐ Not at all, or selected mainly random or inappropriate items

B) Did subject usually pay for items without supervision or physical help?

☐ Yes
☐ No

17. In the past 4 weeks, did subject keep appointments, meetings with other people, such as relatives, a doctor, the hairdresser, etc.?

☐ Usually remembered, may have needed written reminders, e.g., notes, a diary, or calendar

☐ Only remembered the appointment after verbal reminders on the day

☐ Usually did not remember, in spite of verbal reminders on the day

18. In the past 4 weeks, was subject ever left on his/her own?

Yes / No / don't know

☐ ☐ ☐

If yes, ask all questions:

Was subject left:

Yes / No

☐ ☐ a) away from home for 15 minutes or longer, during the day?

☐ ☐ b) at home for an hour or longer, during the day

☐ ☐ c) at home, for less than 1 hour during the day

19. In the past 4 weeks, did subject talk about current events? (This means events or incidents that occurred during the past month.)

Yes / No / don't know

☐ ☐ ☐

If yes, ask all questions:

Did subject talk about events that…:

Yes / No

☐ ☐ a) he/she heard or read about or saw on TV but did not take part in?

☐ ☐ b) he/she took part in outside home involving family, friends, or neighbors?

☐ ☐ c) events that occurred at home that he/she took part in or watched

20. In the past 4 weeks, did subject read a magazine, newspaper or book for more than 5 minutes at a time?

Yes / No / don't know

☐ ☐ ☐

If yes, ask all questions:

Did subject usually:

Yes / No

☐ ☐ a) talk about details of what he/she read while or shortly (less than 1 hour) after reading?

☐ ☐ b) talk about what he/she read 1 hour or longer after reading?

21. In the past 4 weeks, did subject ever write things down?
Yes / No / don't know
☐ ☐ ☐

Note: if subject wrote things only after encouragement or with help, the response should still be 'Yes'.
If yes, which best describes the most complicated things that he/she wrote:

- ☐ Letters or long notes that other people understood
- ☐ Short notes or messages that other people understood
- ☐ His/her signature or name

22. In the past 4 weeks, did subject perform a pastime, hobby, or game?
Yes / No / don't know
☐ ☐ ☐

If yes, how did subject usually perform his/her most common pastimes:

- ☐ Without supervision or help
- ☐ With supervision
- ☐ With help
- ☐ If subject performs hobbies/pastimes only at day care, check here

23. In the past 4 weeks, did subject use a household appliance to do chores? Examples include washer, dryer, vacuum, dishwasher, toaster, toaster over, range, microwave, food processor
Yes / No / don't know
☐ ☐ ☐

If yes, for the most commonly used appliances, which best describes how subject usually used them:

- ☐ Without help, operating more than on-off controls if needed
- ☐ Without help, but operated only on-off controls
- ☐ With supervision, but no physical help
- ☐ With physical help

TOTAL ADCS-ADL: ☐
(ADCS-ADL maximum score = 30)
24 - 30 normal, depending on age, education, complaints
20 - 23 mild
10 - 19 moderate
1 - 9 severe
0 profound

Beck's Depression Inventory- 2

1.
0 I do not feel sad.
1 I feel sad
2 I am sad all the time and I can't snap out of it.
3 I am so sad and unhappy that I can't stand it.

2.
0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel the future is hopeless and that things cannot improve.

3.
0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4.
0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5.
0 I don't feel particularly guilty
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6.
0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7.
0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8.
0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9.

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10.
0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even **though I want to.**

11.
0 I am no more irritated by things than I ever was.
1 I am slightly more irritated now than usual.
2 I am quite annoyed or irritated a good deal of the time.
3 I feel irritated all the time.

12.
0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13.
0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions more than I used to.
3 I can't make decisions at all anymore.

14.
0 I don't feel that I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly.

15.
0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16.
0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.
0 I don't get more tired than usual.
1 I get tired more easily than I used to.

2 I get tired from doing almost anything.
3 I am too tired to do anything.

18.
0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19.
0 I haven't lost much weight, if any, lately.
1 I have lost more than five pounds.
2 I have lost more than ten pounds.
3 I have lost more than fifteen pounds.

20.
0 I am no more worried about my health than usual.
1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21.
0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I have almost no interest in sex.
3 I have lost interest in sex completely.

Perceptions of Change Questionnaire (PCQ)

Please circle the response that best matches how you feel about the following statements:

1. The training program helped improve my memory.

Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree

2. The training program helped improve my overall thinking abilities.

Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree

3. I enjoyed the training program overall.

Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree

4. Since finishing the cognitive training program, how many hours **per week** do you engage in cognitively stimulating activities (e.g., card or board games, puzzles,Sudoku, meaningful conversation, crafts, etc.)?

_____ hours per week

5. Do you think you were assigned to the experimental or control group?(Circle one)

Experimental	Don't Know	Control

6. At any time during your participation in this study, did you participate in anyother research?

- ☐ Yes
- ☐ No

What was the project?

_____

_____

_____

If yes, when did you participate in the project?

_____

7. At any time during your participation in this study, did you engage in cognitivetraining other than training program you did for this study?

- ☐ Yes
- ☐ No

What was this training program?

_____

_____

_____

If yes, when did you do this training?

_____

_ How often did you do this training? _____

_____

We have been sending you copies of our Brain Bulletin, a newsletter with updateson this study. Now that you are finished participating in the study, would you liketo continue to receive these newsletters until the conclusion of the study?

- ☐ Yes
- ☐ No