



The Preventing Alzheimer's with Cognitive Training (PACT) randomized clinical trial

Jody S. Nicholson^{a,*}, Elizabeth M. Hudak^b, Christine B. Phillips^c, Marianne Chanti-Ketterl^d, Jennifer L. O'Brien^e, Lesley A. Ross^c, Jennifer J. Lister^f, James R. Burke^g, Guy Potter^d, Brenda L. Plassman^d, Adam J. Woods^h, Jeffrey Krischerⁱ, Jerri D. Edwards^b

^a Department of Psychology, University of North Florida, 1 UNF Dr, Jacksonville, FL 32224, United States

^b Department of Psychiatry & Behavioral Neurosciences, University of South Florida, 3515 E. Fletcher Ave, Tampa, FL 33613, United States

^c Department of Psychology, Institute for Engaged Aging, Clemson University, 298 Memorial Dr, Seneca, SC 29672, United States

^d Department of Psychiatry and Behavioral Sciences, Duke University, Duke University Medical Center, Box 102505, Durham, NC 27705, United States

^e Department of Psychology, University of South Florida, DAV 100, 140 7th Ave South, St. Petersburg, FL 33701, United States

^f Department of Communication Sciences and Disorders, University of South Florida, 4202 E. Fowler Ave, PCD1017, Tampa, FL 33620-8200, United States

^g Department of Neurology, Duke University, Bryan Research Building, 311 Research Dr, Durham, NC 27710, United States

^h Department of Clinical and Health Psychology, University of Florida, 1225 Center Dr, Gainesville, FL 32610-0165, United States

ⁱ Health Informatics Institute, University of South Florida, 3650 Spectrum Blvd, Tampa, FL 33612, United States

ARTICLE INFO

Keywords:

Alzheimer's disease

Dementia

Aging

Useful field of view training

Blood biomarkers

ABSTRACT

Background: To address the rising prevalence of Alzheimer's disease and related dementias, effective interventions that can be widely disseminated are warranted. The Preventing Alzheimer's with Cognitive Training study (PACT) investigates a commercially available computerized cognitive training program targeting improved Useful Field of View Training (UFOVT) performance. The primary goal is to test the effectiveness of UFOVT to reduce incidence of clinically defined mild cognitive impairment (MCI) or dementia with a secondary objective to examine if effects are moderated by plasma β -amyloid level or apolipoprotein E e4 (APOE e4) allele status. **Methods/design:** This multisite study utilizes a randomized, controlled experimental design with blinded assessors and investigators. Individuals who are 65 years of age and older are recruited from the community. Eligible participants who demonstrate intact cognitive status (Montreal Cognitive Assessment score > 25) are randomized and asked to complete 45 sessions of either a commercially available computerized-cognitive training program (UFOVT) or computerized games across 2.5 years. After three years, participants are screened for cognitive decline. For those demonstrating decline or who are part of a random subsample, a comprehensive neuropsychological assessment is completed. Those who perform below a pre-specified level are asked to complete a clinical evaluation, including an MRI, to ascertain clinical diagnosis of normal cognition, MCI, or dementia. Participants are asked to provide blood samples for analyses of Alzheimer's disease related biomarkers.

Discussion: The PACT study addresses the rapidly increasing prevalence of dementia. Computerized cognitive training may provide a non-pharmaceutical option for reducing incidence of MCI or dementia to improve public health.

Registration: The PACT study is registered at <http://Clinicaltrials.gov> NCT03848312

1. Introduction

Dementia imposes a substantial economic burden with direct (e.g., medical care), indirect (e.g., lost productivity), and intangible (e.g., suffering, grief) costs [1]. Dementia is the main cause of disability in

people over 65, is projected to increase four-fold to affect 8 to 13 million people in the United States by 2050 [2], and may affect 50% of older adults at time of death [3]. Given the costs and societal impact of this disease, prevention is urgently needed [4,5]. Computerized cognitive training programs offer a cost-effective, noninvasive, and easily

* Corresponding author at: Department of Psychology, University of North Florida, 1 UNF Drive, Jacksonville, FL 32224, United States.

E-mail address: jody.nicholson@unf.edu (J.S. Nicholson).

<https://doi.org/10.1016/j.cct.2022.106978>

Received 9 August 2022; Received in revised form 19 October 2022; Accepted 25 October 2022

Available online 28 October 2022

1551-7144/Published by Elsevier Inc.

disseminated option that could buffer the projected increase in dementia prevalence [5–7].

The Advancing Cognitive Training for Independent and Vital Elderly (ACTIVE, <http://ClinicalTrials.gov>: NCT00298558) multisite clinical trial randomized 2832 healthy older adults without dementia to examine the effects of three types of cognitive training on cognition and everyday function [8,9]. Strategy-based cognitive training (i.e., memory and reasoning training) and process-based, computerized speed of processing training (SPT), which targeted improved Useful Field of View (UFOV) performance, were compared to no-contact controls. The SPT group demonstrated the largest cognitive improvements on proximal outcomes (i.e., UFOV performance) with an effect size of 0.72 standard deviations (*SD*) immediately post-training relative to no-contact controls. Further analyses indicated that SPT continued to show the largest cognitive effects on the targeted proximal outcome with improvements still evident at 10 years. ACTIVE participants randomized to any type of cognitive training further experienced less functional decline across time relative to controls [10].

To date, SPT has been investigated in numerous randomized trials with results indicating that SPT not only improves cognition, but also transfers to improve everyday function. A systematic review and meta-analysis of SPT research identified 44 published studies from 17 randomized trials. Twelve of the 17 studies reviewed included community-dwelling older adults and the other studies included middle aged adults, or persons with mild cognitive impairment (MCI), Parkinson's disease, HIV, breast cancer, or stroke [11]. Results showed that SPT was effective when compared to active control conditions (e.g., computer games, $d = 0.77$, $p < .001$) or when compared to no-contact controls ($d = 0.63$, $p < .001$). In addition to improving the primary targeted outcome of UFOV ($d = 0.70$, $p < .001$), SPT enhances performance on other cognitive measures of speed of processing and attention ($d = 0.14$ – 0.22 , $ps < 0.03$) [11]. Additionally, SPT transfers to improved instrumental activities of daily living ($d = 0.27$, $p < .001$) [10,12–16], including driving outcomes [17–21], and enhances well-being as evident by improved sense of control [22], maintained health-related quality-of-life [23,24], decreased estimated health care utilization costs [25], and decreased risk of depression [26]. Thus, SPT indicates potential for functional benefits in addition to cognitive improvements, which is why it is likely to delay the onset of MCI and dementia.

1.1. Cognitive speed of processing training and dementia risk

Of particular interest, SPT was the only intervention in ACTIVE to significantly reduce risk of dementia [7]. Those randomized to SPT were 29% less likely to meet research-based diagnostic criteria for dementia across 10 years (HR = 0.67, 95% CI 0.49–0.91, $p = .012$) [7]. The effects were dose dependent, and those completing >10 hours of SPT were up to 48% less likely to meet dementia criteria than no contact controls (HR = 0.52, 95% CI 0.33–0.82, $p = .005$). While ACTIVE results suggest promise for the efficacy of SPT to reduce dementia risk, the dementia outcome used neuropsychological and functional assessment data as diagnostic criteria; a clinical diagnosis was not obtained. Further, whether such training reduces risk of MCI is not known.

1.2. Study objectives

The primary objective of PACT is to test the effectiveness of cognitive training targeting improved UFOV performance (UFOV training or UFOVT) to reduce incidence of MCI or dementia through a multisite study utilizing a randomized, controlled experimental design with blinded assessors and investigators. A secondary objective is to determine if UFOVT effects are moderated by the plasma β -amyloid level or apolipoprotein E e4 (APOE e4) allele status.

2. Methodology

2.1. Participants

PACT includes participants 65 years of age and older with intact cognitive abilities. Table 1 provides inclusion and exclusion criteria for the study. Our goal is for the study sample to include at least 8.5% who identify as Black race and at least 7% who identify as Hispanic ethnicity.

2.2. Recruitment and retention

The trial was registered at <http://clinicaltrials.gov> (NCT03848312) and a study website was designed (<http://PACTstudy.org>). Each site has a designated recruitment and retention coordinator responsible for tracking and reporting recruitment metrics and adjusting strategies as needed to meet enrollment goals. To quantify and track referral source, participants are asked to complete marketing questionnaires [27]. A co-investigator led recruitment and retention team meets monthly to discuss any recruiting challenges and potential solutions. Solutions are guided by past successes across sites and published strategies for recruitment to studies related to Alzheimer's disease and related dementias [28,29]. The team employs a multipronged approach to recruitment and retention, comprised of the following broad strategies:

- 1) Community outreach and educational activities include educational talks, memory screenings, information tables at senior expos and health fairs, as well as developing and nurturing relationships with community clubs, places of worship, organizations, and older adult service providers. Relationships with well-known community leaders

Table 1
Trial inclusion and exclusion criteria.

Inclusion
Be age 65 or older at time of consent
Have the ability to speak and understand English or Spanish
Report adequate sensorimotor capacity to perform the computer exercises
Report adequate visual capacity to read from a computer screen at a typical viewing distance
Show adequate auditory capacity to understand conversational speech
Show adequate motor capacity to touch a computer screen or control a computer mouse
Have no evidence of mild cognitive impairment (MCI) or dementia at baseline, as assessed by education adjusted Montreal Cognitive Assessment score ≥ 26
Have adequate mental health (no self-reported diagnosis or mental illness that would interfere with ability to comply with study procedures or benefit from intervention)
Willing to complete all study activities
Ability to understand study procedures and comply with them for the length of the study
Exclusion
Currently enrolled in another randomized clinical trial, or treatment trial, or another research study that assesses cognition
Previous participation in a cognitive training study
Self-reported vision, hearing, or motor difficulties that would interfere with the ability to complete the study interventions
Self-reported diagnosis of mild cognitive impairment, dementia, stroke, traumatic brain injury, brain tumor, or a neurological disorder that affects cognition or would interfere with the ability to benefit from the study intervention (e.g., Parkinson's disease, multiple sclerosis), or any other unstable medical condition that is predisposing to imminent cognitive or functional decline (e.g., congestive heart failure, chronic obstructive pulmonary disorder dependent on oxygen, or undergoing chemotherapy or radiation)
Self-reported use of medications typically prescribed for dementia such as Namenda, Memantine, Namzaric, Donepezil, Aricept, Rivastigmine, Exelon, Razadyne, Galantamine, Reminyl, Aduhelm or Aducanumab
Completion of 10 or more hours of a computerized cognitive training program in the last 5 years such as Lumosity, Posit Science Brain Fitness, InSight or Brain HQ, Listening and Communication Enhancement (LACE), CogMed, CogniFit, Happy Neuron, Elevate, or Dakim
Severe depressive symptoms (GDS short form score ≥ 5)

and organizations, such as local Alzheimer’s Association groups and senior centers are cultivated. The recruitment and retention coordinators are responsible for establishing rapport with the community and providing information to encourage study endorsement through each organization’s established communication structure (e.g., direct mail, email, monthly newsletter, or in-person announcements).

- 2) Marketing and advertising consist of print, electronic/digital, radio, and TV media. The marketing team designed recruitment materials for various media platforms with images and messaging reflecting our diversity goals. To achieve a strong identity, a study logo was established, and materials and messaging are uniform across sites. Both paid (e.g., newspaper advertorials, Facebook ads) and no-cost (e.g., public service announcements, community bulletin boards) marketing efforts are implemented.
- 3) Research registries, patient databases, and voter registration rolls are used to identify prospective participants. The trial is listed in national registries such as the Alzheimer’s Prevention Registry and the Alzheimer’s Association TrialMatch. Other site-specific registries are used as available. Potential participants are contacted by letter, email, post-card, and/or telephone.

Retention strategies include, but are not limited to, consistent contact (e.g., regular newsletters and greeting cards), meet the team handouts, flexible appointment times and reminders, and tokens of appreciation [30]. When consented, participants are provided with a flow chart of the study visits to communicate the demands and timeline of the study, and a detailed laypersons summary of what to expect as a study participant. Participants are asked to share their preferred contact

method (e.g., email, phone, text) and for the contact information of at least one person who does not reside with the participant. Study identity is maintained by having all correspondence with participants and tokens of appreciation branded with the study logo and site contact information. Study staff administer a questionnaire to understand participants’ motivations for joining the study and draw on these motivations to encourage continued participation. Participants who miss a study visit or do not respond to a contact attempt are contacted regularly so that visits are promptly rescheduled. If enrolled participants are not successfully reached within three weeks, a letter requesting a reply is mailed, and after 30 days, staff reach out to the participant’s secondary contact(s).

2.2.1. *Minority Recruitment and Retention*

Black/African American and Hispanic/Latino/a communities are underrepresented in Alzheimer’s research despite being at greater risk [31,32]. Failure to recruit diverse study participants has been identified as a significant barrier to progress and health disparities are propagated by the under-representation of minorities in clinical research [33]. To achieve our diversity goals, we embed minority recruitment and retention strategies into the general strategies listed above and into the overall study operations [34,35]. In addition to that described above, other minority recruitment and retention strategies include, but are not limited to, involving Black and Hispanic/Latino/a study personnel, having fluent Spanish-speaking site personnel and clinicians, translating the study materials into Spanish, and over-recruiting from predominantly minority communities.

Table 2
Measures and study activities.

	Screening	Visit 1: Baseline	Visit 2: Training	Initial At-Home Training	Booster Training	Three-Year Follow-Up Visit	Clinical Evaluation	MRI
Screening and enrollment								
Telephone screening interview	x							
Informed consent		x						
Demographics		x						
Montreal Cognitive Assessment (MoCA) [37]	x	x				x		
Geriatric Depression Scale short form (GDS) [73]	x	x				x		
Randomization		x						
Recruitment & retention*								
Cognitive Aging Lab Marketing Questionnaire [27]	x	x						
Vismory marketing survey	x	x						
Participant motivation questionnaire		x						
Training								
Computerized exercises		x	x	x	x			
Progress checks				x	x			
Clinical and biomarker assessments								
Alzheimer’s Disease Cooperative Study-Cognitive Function Instrument (ADCS-CFI)						x		
Blood sample [†]		x				x		
Neuropsychological assessments (see Table 4)						x		
Medical conditions, neurological exam, medications, health history, family history							x	
Clinical diagnosis							x	x
Potential covariates & planned sensitivity analyses								
Expectation Assessment Scale [‡]			x	x		x		
Patient Health Questionnaire-8						x		
Health questionnaire						x		
Near visual acuity						x		
Train-to-task assessments		x		x	x	x		

Note. Timing of study visits is relatively flexible. Marketing questionnaires, MoCA, and GDS are administered either during the screening process or at visit 1, not at both. MoCA scores are education adjusted. [†]Blood samples may be collected at visit 1- and/or at or after the three-year follow-up visit. Participants are not allowed to complete multiple visits on the same day and are asked not to complete multiple training sessions on the same day. The initial training phase can last up to 18 weeks. [‡]A subset of items from the Expectation Assessment Scale is repeated at the end of the initial training phase and during an exit interview. Booster training phases are initiated at about 12- and 30- months after visit 1 completion and may last up to 10 weeks. Regular progress checks are made during initial and booster training phases. The three-year follow up visit is completed at 36 months or later after visit 1. The clinical diagnosis requires information from the neuropsychological assessment, clinical evaluation, and MRI (if obtained) to be completed. *A study exit questionnaire is administered upon withdrawal or study completion.

2.3. Study visits, randomization, and intervention

The PACT trial design is efficient by minimizing initial assessments and staff effort while conducting additional assessments on those who demonstrate cognitive decline at a 3-year follow-up visit. Table 2 presents the timeline of measures.

2.3.1. Telephone Screening and Visit 1

Most individuals complete a telephone screening interview to assess potential eligibility prior to scheduling study visit 1. At the first study visit, staff assess participant eligibility by administering an inclusion/exclusion self-report questionnaire, a short form of the Geriatric Depression Scale (GDS) [36], and the Montreal Cognitive Assessment (MoCA) [37]. Study procedures, study timeline, and required commitment to the study are explained in detail to the participant during the informed consent process. Participants also complete open-ended questions about their motivation for participation as well as marketing questionnaires. Eligible participants are randomized to the intervention or active control condition. Randomization is stratified by university site, using a fixed block size, with couples (i.e., individuals who live together) randomized together, nested within site. Randomized assignment is created using the Statistical Analysis System (SAS). The randomization table is incorporated into a REDCap database that is separate from the data entry database. REDCap checks the allocation table and assigns the randomization value, which cannot be changed after assignment, is associated with a specific arm, and is accessible only by unblinded staff. At or shortly after visit 1, willing participants may provide a blood sample for biomarker analysis, though this is not a requirement for participating in the study.

2.3.2. Intervention and Active Control Conditions

Both randomized conditions are described to participants as “brain games”, are commercially available, and are accessed by participants through a BrainHQ research portal developed specifically for the PACT study. The UFOVT intervention under investigation combines the most recent version of SPT, which includes exercises in the UFOV paradigm [38], with tonic and phasic alertness training, which includes exercises in a continuous performance task paradigm [39]. These training exercises enhance speed of processing, attention, and executive function among older adults [11,39]. The duration, number, and frequency of initial and booster training sessions as detailed below were informed by prior research showing that participants can adhere to and benefit from this schedule of at-home training [7,38,40–42]. Our prior results showed that there was not an asymptote of benefit after 20 hours of training and for each 1-hour session of SPT completed, a 10% reduced risk of dementia was observed [7].

The active control condition is comprised of computer games. Games providing face-valid cognitive stimulation that are rated E (for everyone) by the Entertainment Software Rating Board are used. The randomized conditions are designed to match with the expectation-based influence on cognitive performance, intensity, and overall engagement and have been validated in our pilot testing and prior research (e.g., [43–48]). Additional detail on the study exercises may be obtained by contacting the Principal Investigator but are not shared here to prevent unblinding. Participants are given a user manual that details information about the exercises, indicates how to access the assigned exercises, and includes answers to frequently asked questions. After randomization, participants are introduced to and practice the assigned exercises at visit 1 and are asked to complete at least one training session at home before returning for a second in-person visit at the study site.

2.3.3. Visit 2

At visit 2, participants complete a one-hour training session led by a trainer. Training is conducted individually or in groups of up to 9 participants randomized to the same condition. At the end of visit 2, the Expectation Assessment Scale [49] is administered to assess attitudes

and expectations about the randomly assigned exercises.

2.3.4. At Home Training

Participants complete the remainder of the training sessions at home and are instructed to complete 2–3 sessions per week until 525 levels (about 25, 1-hour sessions) are completed in the initial training phase. However, participants are allowed to complete additional training sessions at the study site, if desired. Participants’ completion of exercises is automatically recorded by BrainHQ. Study staff monitor participant progress through the BrainHQ portal and encourage/reinforce participant training adherence. For the initial training phase, participants are monitored for up to 18 weeks after their first training session through regular progress checks by email or phone. Participants receive a congratulatory email/letter when completing the initial phase of training and are reminded not to enroll in other research studies while participating in PACT and to refrain from participating in other computerized brain training programs outside of the study. Participants are informed they may continue to complete 1 hour of training exercises each week, if desired. Participant expectations for computerized cognitive training are again assessed after completion of initial training.

2.3.5. Booster 1 and 2 Training

After 12 months and again after 30 months from visit 1, participants are contacted and encouraged to complete an additional 10 sessions of training over an 8–10 week period, referred to as booster training. Thus, participants are asked to complete a total of 45 sessions across the study period. During these booster training phases, study staff monitor participants’ progress through the BrainHQ portal and contact participants to encourage adherence. As in initial training, a congratulatory message is sent at the end of the booster phases with relevant study reminders.

2.3.6. 3-Year Follow-up Visit

About three years after visit 1, participants are asked to return to complete a MoCA, GDS, and the Alzheimer’s Disease Cooperative Study Cognitive Function Instrument (ADCS-CFI) [50]. Near visual acuity and depressive symptoms are further assessed with the Patient Health Questionnaire-8 [51], and a health questionnaire is administered. All measures are administered by a tester blinded to randomized assignment. Participants are also asked to provide a blood sample to determine APOE genotype and for quantifying plasma β -amyloid. The specific β -amyloid assay used will be based on expert input at the time of the sample analyses. Based on MoCA and ADCS-CFI scores, the participant may be defined as cognitively normal, or be asked to complete a neuropsychological battery for further assessment. The decision to administer the neuropsychological battery is based on the MoCA change score from visit 1 and the ADCS-CFI score. See Table 3 for criteria. At the end of the study visit, the train-to-task assessments are completed.

Random sampling, balanced across treatment arms, will be used to identify a cognitively intact subsample ($n = 100$) who will also be asked to complete the neuropsychological and clinical assessments for the

Table 3
Decision chart for administration of the neuropsychological assessment battery.

If MoCA change is:	Then ADCS-CFSI score to trigger the neuropsychological assessment must be:
1 point	4.0 or greater
2 points	3.5 or greater
3 points	3.0 or greater
4 points or greater	
-or- Year 3 MoCA score 25 or less after education points added	
-or- Self-report of MCI or dementia diagnosis	Administer neuropsychological battery regardless of ADCS-CFSI score
-or- Randomly selected normal subsample	

Note. MoCA = Montreal Cognitive Assessment, ADCS-CFSI = Alzheimer’s Disease Cooperative Study Cognitive Function Instrument.

purposes of estimating false negative rates of MCI/dementia. Selection procedures will be carefully designed to help ensure balanced groups. Participants who do not advance to the stage of the clinical evaluation are considered to have demonstrated sufficiently intact cognitive function to be classified as cognitively normal.

The neuropsychological battery includes measures from the National Alzheimer’s Coordinating Center (NACC) [52,53], the Rey Auditory Verbal Learning Test (RAVLT) [54], and the Symbol Digit Modality Test (SDMT) [55]. See Table 4 for details on the neuropsychological assessments and functional questionnaires. Test performance is interpreted based on published demographically adjusted norms [54–56]. Participants who score $\leq 1.5 SD$ (i.e., at or below the 7th percentile) below the normative mean on 2 or more assessments are further asked to complete a clinical evaluation visit. Participants with fewer than 2 impaired scores are considered cognitively normal.

2.3.7. Clinical Evaluation Visit

Participants invited to complete the clinical evaluation visit are asked to identify an individual willing to serve as a study partner, typically a family member or friend who is familiar with them and their everyday activities. This individual is interviewed by the tester to obtain information about the participant’s memory and ability to perform everyday activities. A self-report and study partner report are collected for the Clinical Dementia Rating [57] and the Alzheimer’s Disease Cooperative Study-Activities of Daily Living Prevention Instrument (ADCS-ADL-PI) [58]. Medical history, neurological evaluation, and prescribed medications taken by the participant are obtained using NACC/Uniform Data Set forms [52,53]. Family medical history is also assessed. The study clinician, who is blinded to the participants randomized arm, reviews the neuropsychological battery results and depressive symptom inventories, in addition to meeting with the study participant for a clinical interview. The study clinician may also review Magnetic Resonance Imaging scans (MRI) to assist in diagnosing the possible cause of cognitive impairment. The MRI is used for the clinical evaluation of ischemic disease, structural deformities, regional atrophy

Table 4
Neuropsychological measures and functional questionnaires.

Test name	Primary domains	Subtests administered
RAVLT [54]	Anterograde verbal episodic memory	Immediate Recall, Delayed Recall, Delayed Recognition
SDMT [55]	Processing speed, Visual working memory	N/A
Trail Making Test [74,75]	Processing speed, executive function (visual search, attention switching)	Trail A, Trail B
ADCS-ADL-PI [58]	Self-reported everyday function Study partner report of everyday function	N/A
National Alzheimer’s Coordinating Center (NACC) Selected Assessments [52,53]		
Craft Story 21 Recall	Attention, concentration, verbal episodic memory	Immediate Recall, Delayed Recall,
Benson Complex Figure Copy	Visuoconstruction, visual memory	Immediate Recall, Delayed Recall, Delayed Recognition
Number Span Test	Working memory	Forward Recall, Backward Recall
Category Fluency	Semantic memory (verbal fluency, language)	Animals, Vegetables
MiNT [76]	Visual object naming	N/A
Letter Fluency [77]	Speeded word retrieval to phonemic cues	Letters F & L
CDR [57,78]	Global dementia rating, sum of boxes	N/A

Abbreviations: RAVLT, Rey Auditory Verbal Learning Test; SDMT, Symbol-Digit Modalities Test; ADCS-ADL-PI, Alzheimer’s Disease Cooperative Study-Activities of Daily Living-Prevention Instrument; MiNT, Multilingual Naming Test; CDR, Clinical Dementia Rating.

and ventricular enlargement.

2.3.8. Study Exit

Participants are asked to complete an exit interview that enquires about their experience and serves as a third assessment of expectations for computerized cognitive training.

2.3.9. Diagnosis Consensus

The consensus diagnosis is based on review of the neuropsychological assessment, clinical evaluation by the site clinician, and MRI. The three possible diagnostic outcomes are: cognitively normal, MCI, or dementia. In addition to the physician who conducted the clinical evaluation, other reviewers are selected from a pool of experts in dementia that may include geriatric psychiatrists, clinical neuropsychologists, and neurologists. All reviewers will be blinded to randomization arm and will independently make their clinical diagnoses from criteria set forth by the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease, which includes separate criteria for diagnosis of MCI [59] and dementia [60]. Each of three reviewers submit their clinical diagnosis (cognitively normal, MCI, dementia) and if consensus is achieved, the participant is assigned the diagnosis. If consensus is not achieved, reviewers will convene by phone or teleconference to attempt to reach a consensus diagnosis. If this does not yield a consensus diagnosis, all information from the prior steps is referred to an additional two experts who will review and come to a final diagnostic decision based on the clinical information and the majority opinion to that point. Although there are only three defined diagnostic endpoints, the clinicians are encouraged to make note of diagnostic subtypes and suspected etiologies of MCI and dementia. If neuropsychological or comprehensive clinical assessments are not done due to refusal or death, a diagnosis is assigned based on all available data, including any medical records.

2.4. Analytic approach

Interim analyses will include monitoring for early futility. Efficacy analysis on the primary endpoint will be conducted when 50% of the target study population has been followed for the planned three years. The level of significance for primary analyses will be set at two-tailed 0.05, adjusted for the interim analysis. We expect the randomized arms to be balanced in their baseline characteristics due to the randomization and relatively large sample. A Chi-Square Test will be performed to compare whether the proportions of MCI or dementia at the end of the trial are statistically different by treatment arm. We will estimate the risk of conversion to MCI or dementia as a function of the intervention using binary logistic regression presented in the form of odds ratios (OR) with point estimates and confidence intervals (CI) reported to show the direction and magnitude of the effects. For any unbalanced factors identified between the randomized groups, logistic regression analysis will be performed with group assignment as the main predictor. We may examine any unbalanced baseline factor(s) as covariates and plan to examine effects after considering other health-related covariates indicative of risk for MCI or dementia measured at the three year visit (e.g., depressive symptoms, diabetes, heart disease, myocardial infarction, hypertension, stroke, Parkinson’s disease, multiple sclerosis, or other reported neurologic conditions, undergoing chemotherapy, radiation, or general anesthesia). Secondary subgroup analyses based upon site, sex, education, and age will be explored. Factors known to moderate the effectiveness of the intervention will also be examined such as visual acuity and depressive symptoms. Sensitivity analyses are planned to examine the intervention effect in the subset of participants who were adherent, completing at least 80% of the initially assigned sessions (i.e., 20 sessions or 420 levels). We may also conduct analyses to compare incidence of MCI and dementia among those who did versus did not experience reliable training improvements as indicated by pre- to post- performance on the proximal train-to-task assessments.

We acknowledge that using the MoCA as a screening test and obtaining a clinical diagnosis of MCI or dementia for those who exhibit cognitive decline may lead to verification bias. With a random subsample ($n = 100$), we will also estimate the proportion of those who do not meet the primary end point of MCI/dementia diagnosis, arriving at an estimate of false positives.

To address the secondary objective, a logistic regression model will be fitted using clinical diagnosis of cognitive status (normal, MCI, dementia) as the primary dependent variable, randomization arm as the independent variable, and interaction terms between randomized arm and APOE e4 allele status, and between randomized arm and amyloid burden. A statistically significant interaction will indicate moderation effects of APOE e4 allele status or amyloid burden. For significant interactions, ORs and CIs in strata defined by the moderator will be reported separately to characterize effects [61].

2.5. Sample size calculations, and attrition

Power calculations indicate that at a 0.05 level of significance with a 20% attrition rate, the two-group, randomized design will require a total sample size of 7600 participants to ensure at least 82% power to detect a 20% reduction from an estimated 3-year incidence rate of 10.5% for conversion to MCI or dementia [62]. We expect to have a final sample of 6080 participants, of whom about 640 are expected to exhibit MCI or dementia across the 3 years of follow-up (i.e., 3.5% per year conversion rate) [62]. Should we not achieve this enrollment goal, further follow-up beyond three years and additional analyses may be warranted to achieve adequate statistical power to meet our primary objective. To adjust for mortality and attrition for the MCI/dementia endpoint, we may apply the Semi-Markov modeling approach [63].

3. Discussion

The PACT study focuses on the importance of mitigation to counter the projected increase in prevalence of cognitive impairment including Alzheimer's disease and related dementias. Computerized cognitive training is recognized as one of the three most promising ways to prevent cognitive decline and dementia [5]. Computerized cognitive training programs are readily available commercially [64], are noninvasive, are less costly than pharmaceuticals, and have the potential for efficient, scalable, and personalized delivery [6,65]. Moreover, participants do not need advanced technological skill to complete or benefit from cognitive training [6]. PACT is being conducted during the COVID-19 pandemic, providing further indication that this type of low-contact, predominantly home-based intervention is feasible for individuals who are not able to attend in-person programs due to mobility, transportation, or comfort in social situations. Results will advance knowledge, inform theory, and improve clinical practice by facilitating implementation of effective interventions to attenuate cognitive decline and improve public health.

PACT includes study design improvements based on critiques of the ACTIVE study, such as the inclusion of an active control group and consideration of participant expectations across conditions [66]. Additionally, the outcome of a rigorously established diagnosis of MCI or dementia assigned by a panel of experts improves upon prior methodology. The neuropsychological and clinical comprehensive assessments in this study incorporate multiple features consistent with best practices in randomized trials of cognitive aging [67,68]. PACT also utilizes an expert consensus panel to assign a diagnosis. This procedure addresses a limitation of the ACTIVE study, namely the absence of a clinical dementia diagnosis. Thus, the PACT study will answer one of the looming questions – that is, does computerized cognitive training reduce incidence of MCI and dementia.

Blood draws will be requested from participants to address the second aim of PACT, which is to examine how biologically based risk for Alzheimer's disease interacts with the effectiveness of UFOVT. Using

blood-based biomarkers to examine amyloid burden and APOE e4 allele status is less invasive and more cost-efficient than PET scans [69]. Furthermore, the blood will be analyzed, stored, and made available to researchers by the National Centralized Repository for Alzheimer's disease (NCRAD) to further examine various Alzheimer's disease biomarkers in support of the larger mission of NCRAD [70].

Beyond the objectives of the study, we have included key elements in the study design as well as recruitment and retention efforts that are important for translation of the trial. First, the study aims to enroll a diverse population in terms of participants' minority group identification and education to counter the existing underrepresentation of individuals who may be disproportionately impacted by dementias such as Alzheimer's diseases [32,35,71]. Second, PACT uses a marketing questionnaire to quantify recruitment source and exposure to marketing materials which will provide important information for future initiatives about the most effective means for engaging diverse older adults in clinical trials for prevention of cognitive impairment [27]. Finally, participants are asked about their satisfaction with different aspects of their experience in cognitive training [49], which will allow for comparison of participant expectations across study conditions [66]. Increasing diversity, understanding successful recruitment initiatives, and establishing how participant expectations influence retention and adherence satisfy future directions in the literature as outlined by experts in the field of cognitive aging that will support computerized cognitive training and broader prevention trials related to Alzheimer's disease [27,66,71].

4. Conclusion

The significance of the PACT study is considerable as an intervention delaying the onset of dementia by only one year will result in 9.2 million fewer cases over 30 years [72]. Our innovative trial design is highly efficient and minimizes initial effort to apply an optimized version of the intervention while collecting detailed information on those who demonstrate cognitive decline.

Funding

Research reported in this publication was supported by the National Institute on Aging of the National Institutes of Health under award numbers: R56 AG058234 and R01 AG070349. The research was supported 100% with R56 funds of \$2,701,645 and R01 funds of \$44,362,843. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The sponsor did not have any role in data collection, study design, writing, or in the decision to submit the protocol for publication.

Data availability

No data were used for the research described in this article.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Edwards worked between 1996 and 2005 as a consultant conducting related research studies for Visual Awareness, Inc., who owned the intellectual property surrounding the speed of processing training software. Posit Science now markets the newest version of the training program. Over an approximate three-month period in 2008, Dr. Edwards worked as a limited consultant to Posit Science, Inc. to analyze data and prepare a publication. Dr. Edwards worked as a consultant to Wilson, Sonsini, Goodrich & Rosati across an approximate three-month period between May–August of 2015.

Data availability

No data was used for the research described in the article.

Acknowledgements

We would like to express our gratitude to all study participants, as well as PACT site coordinators and study staff and volunteers and the USF Health Informatics team. We acknowledge Dave Morgan, PhD and Ming Ji, PhD who contributed to the study design and protocol development.

References

- [1] D. Cantarero-Prieto, P.L. Leon, C. Blazquez-Fernandez, P.S. Juan, C.S. Cobo, The economic cost of dementia: a systematic review, *Dementia*. 19 (8) (2020 Nov) 2637–2657.
- [2] P.D. Sloane, S. Zimmerman, C. Suchindran, P. Reed, L. Wang, M. Boustani, et al., The public health impact of Alzheimer's disease, 2000-2050: potential implication of treatment advances, *Annu. Rev. Public Health* 23 (2002) 213–231.
- [3] M.A. Davis, C.-H. Chang, S. Simonton, J.P.W. Bynum, Trends in US medicare decedents' diagnosis of dementia from 2004 to 2017, *JAMA Health Forum*. 3 (4) (2022 Apr 1), e220346.
- [4] G. Livingston, J. Huntley, A. Sommerlad, D. Ames, C. Ballard, S. Banerjee, et al., Dementia prevention, intervention, and care: 2020 report of the lancet commission, *Lancet*. 396 (10248) (2020 Aug 8) 413–446.
- [5] National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, in: A. Downey, C. Stroud, S. Landis, A.I. Leshner (Eds.), Board on Health Sciences Policy, Committee on Preventing Dementia and Cognitive Impairment. Preventing Cognitive Decline and Dementia: A Way Forward, National Academies Press (US), Washington (DC), 2017.
- [6] A.M. Kueider, J.M. Parisi, A.L. Gross, G.W. Rebok, Computerized cognitive training with older adults: a systematic review, *PLoS One* 7 (7) (2012 Jul 11), e40588.
- [7] J.D. Edwards, H. Xu, D.O. Clark, L.T. Guey, L.A. Ross, F.W. Unverzagt, Speed of processing training results in lower risk of dementia, *Alzheimers Dement (N Y)*. 3 (4) (2017 Nov 7) 603–611.
- [8] K. Ball, D.B. Berch, K.F. Helmers, J.B. Jobe, M.D. Leveck, M. Marsiske, et al., Effects of cognitive training interventions with older adults: a randomized controlled trial, *JAMA*. 288 (18) (2002 Nov 13) 2271–2281.
- [9] J.B. Jobe, D.M. Smith, K. Ball, S.L. Tennstedt, M. Marsiske, S.L. Willis, et al., ACTIVE: a cognitive intervention trial to promote independence in older adults, *Control. Clin. Trials* 22 (4) (2001 Aug) 453–479.
- [10] G.W. Rebok, K. Ball, L.T. Guey, R.N. Jones, H.-Y. Kim, J.W. King, 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.* 62 (1) (2014 Jan 13) 16–24.
- [11] J.D. Edwards, B.A. Fausto, A.M. Tetlow, R.T. Corona, E.G. Valdés, Systematic review and meta-analyses of useful field of view cognitive training, *Neurosci. Biobehav. Rev.* 84 (2018 Jan) 72–91.
- [12] F.D. Wolinsky, M.W. Vander Weg, M.B. Howren, M.P. Jones, M.M. Dotson, The effect of cognitive speed of processing training on the development of additional IADL difficulties and the reduction of depressive symptoms: results from the IHAMS randomized controlled trial, *J Aging Health*. 27 (2) (2015 Mar) 334–354.
- [13] J.D. Edwards, V.G. Wadley, R.S. Myers, D.L. Roenker, G.M. Cissell, K.K. Ball, Transfer of a speed of processing intervention to near and far cognitive functions, *Gerontology*. 48 (5) (2002 Oct) 329–340.
- [14] J.D. Edwards, V.G. Wadley, D.E. Vance, K. Wood, D.L. Roenker, K.K. Ball, The impact of speed of processing training on cognitive and everyday performance, *Aging Ment. Health* 9 (3) (2005 May) 262–271.
- [15] F. Lin, K.L. Heffner, P. Ren, M.E. Tivarus, J. Brasch, D.-G. Chen, et al., Cognitive and neural effects of vision-based speed-of-processing training in older adults with amnesic mild cognitive impairment: a pilot study, *J. Am. Geriatr. Soc.* 64 (6) (2016 Jun) 1293–1298.
- [16] D.E. Vance, P.L. Fazeli, L.A. Ross, V.G. Wadley, K.K. Ball, Speed of processing training with middle-age and older adults with HIV: a pilot study, *J Assoc Nurses AIDS Care*. 23 (6) (2012 Dec) 500–510.
- [17] D.L. Roenker, G.M. Cissell, K.K. Ball, V.G. Wadley, J.D. Edwards, Speed-of-processing and driving simulator training result in improved driving performance, *Hum. Factors* 45 (2) (2003) 218–233.
- [18] J.D. Edwards, C. Myers, L.A. Ross, D.L. Roenker, G.M. Cissell, A.M. McLaughlin, et al., The longitudinal impact of cognitive speed of processing training on driving mobility, *Gerontologist*. 49 (4) (2009 Aug) 485–494.
- [19] L.A. Ross, J.D. Edwards, M.L. O'Connor, K.K. Ball, V.G. Wadley, D.E. Vance, The transfer of cognitive speed of processing training to older adults' driving mobility across 5 years, *J Gerontol B, Psychol Sci Soc Sci*. 71 (1) (2016 Jan) 87–97.
- [20] K. Ball, J.D. Edwards, L.A. Ross, G. McGwin, Cognitive training decreases motor vehicle collision involvement of older drivers, *J. Am. Geriatr. Soc.* 58 (11) (2010 Nov) 2107–2113.
- [21] J.D. Edwards, P.B. Delahunt, H.W. Mahncke, Cognitive speed of processing training delays driving cessation, *J. Gerontol. A Biol. Sci. Med. Sci.* 64 (12) (2009 Dec) 1262–1267.
- [22] F.D. Wolinsky, M.W. Vander Weg, R. Martin, F.W. Unverzagt, S.L. Willis, M. Marsiske, et al., Does cognitive training improve internal locus of control among older adults? *J Gerontol B, Psychol Sci Soc Sci*. 65 (5) (2010 Sep) 591–598.
- [23] F.D. Wolinsky, F.W. Unverzagt, D.M. Smith, R. Jones, A. Stoddard, S.L. Tennstedt, The ACTIVE cognitive training trial and health-related quality of life: protection that lasts for 5 years, *J. Gerontol. A Biol. Sci. Med. Sci.* 61 (12) (2006 Dec) 1324–1329.
- [24] F.D. Wolinsky, F.W. Unverzagt, D.M. Smith, R. Jones, E. Wright, S.L. Tennstedt, The effects of the ACTIVE cognitive training trial on clinically relevant declines in health-related quality of life, *J Gerontol B, Psychol Sci Soc Sci*. 61 (5) (2006 Sep) S281–S287.
- [25] F.D. Wolinsky, H.W. Mahncke, M. Kosinski, F.W. Unverzagt, D.M. Smith, R. N. Jones, et al., The ACTIVE cognitive training trial and predicted medical expenditures, *BMC Health Serv. Res.* 29 (9) (2009 Jun) 109.
- [26] F.D. Wolinsky, M.W. Vander Weg, R. Martin, F.W. Unverzagt, K.K. Ball, R.N. Jones, et al., The effect of speed-of-processing training on depressive symptoms in ACTIVE, *J. Gerontol. A Biol. Sci. Med. Sci.* 64 (4) (2009 Apr) 468–472.
- [27] D. Julbe-Delgado, J.L. O'Brien, R. Abdulkarim, E.M. Hudak, H. Maeda, J. D. Edwards, Quantifying recruitment source and participant communication preferences for Alzheimer's disease prevention research, *J Prev Alzheimers Dis*. 8 (3) (2021) 299–305.
- [28] National Institute on Aging, Together we make the difference: National strategy for recruitment and participation in Alzheimer's and related dementias [Internet] [cited 2021 Jul 13]. Available from, <https://www.nia.nih.gov/research/recruitment-strategy>, 2018.
- [29] National Institute on Aging, Alzheimer's disease and related Dementias: Clinical studies recruitment planning guide [Internet] [cited 2022 Jul 10]. Available from, <https://www.nia.nih.gov/sites/default/files/2019-05/ADEAR-recruitment-guide-e-508.pdf>, 2019.
- [30] K.A. Robinson, V.D. Dinglas, V. Sukrithan, R. Yalamanchilli, P.A. Mendez-Tellez, C. Dennison-Himmelfarb, et al., Updated systematic review identifies substantial number of retention strategies: using more strategies retains more study participants, *J. Clin. Epidemiol.* 68 (12) (2015 Dec) 1481–1487.
- [31] A.R. Shaw, J. Perales-Puchalt, E. Johnson, P. Espinoza-Kissell, M. Acosta-Rullan, S. Frederick, et al., Representation of racial and ethnic minority populations in dementia prevention trials: a systematic review, *J Prev Alzheimers Dis*. 9 (1) (2022) 113–118.
- [32] G. Green-Harris, S.L. Coley, R.L. Kosciak, N.C. Norris, S.L. Houston, M.A. Sager, et al., Addressing disparities in Alzheimer's disease and African-American participation in research: an asset-based community development approach, *Front. Aging Neurosci.* 31 (11) (2019 May) 125.
- [33] K.N. Fargo, M.C. Carrillo, M.W. Weiner, W.Z. Potter, Z. Khachaturian, The crisis in recruitment for clinical trials in Alzheimer's and dementia: an action plan for solutions, *Alzheimers Dement*. 12 (11) (2016 Nov) 1113–1115.
- [34] A.L. Gilmore-Bykovskiy, Y. Jin, C. Gleason, S. Flowers-Benton, L.M. Block, P. Dilworth-Anderson, et al., Recruitment and retention of underrepresented populations in Alzheimer's disease research: a systematic review, *Alzheimers Dement (N Y)*. 19 (5) (2019 Nov) 751–770.
- [35] A.L. Jefferson, S. Lambe, R.R. Romano, D. Liu, F. Islam, N. Kowall, An intervention to enhance Alzheimer's disease clinical research participation among older African Americans, *J. Alzheimers Dis*. 36 (3) (2013) 597–606.
- [36] J.A. Yesavage, Geriatric depression scale, *Psychopharmacol. Bull.* 24 (4) (1988) 709–711.
- [37] Z.S. Nasreddine, N.A. Phillips, V. Bédirian, S. Charbonneau, V. Whitehead, I. Collin, et al., The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment, *J. Am. Geriatr. Soc.* 53 (4) (2005 Apr) 695–699.
- [38] J.D. Edwards, E.G. Valdés, C. Peronto, M. Castora-Binkley, J. Alwerdt, R. Andel, et al., The efficacy of InSight cognitive training to improve useful field of view performance: a brief report, *J Gerontol B, Psychol Sci Soc Sci*. 70 (3) (2015 May) 417–422.
- [39] T.M. Van Vleet, J.M. DeGutis, M.M. Merzenich, G.V. Simpson, A. Zomet, S. Dabit, Targeting alertness to improve cognition in older adults: a preliminary report of benefits in executive function and skill acquisition, *Cortex*. 82 (2016 Sep) 100–118.
- [40] F.D. Wolinsky, M.W. Vander Weg, M.B. Howren, M.P. Jones, M.M. Dotson, A randomized controlled trial of cognitive training using a visual speed of processing intervention in middle aged and older adults, *PLoS One* 8 (5) (2013 May 1), e61624.
- [41] G.E. Smith, P. Housen, K. Yaffe, R. Ruff, R.F. Kennison, H.W. Mahncke, 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, *J. Am. Geriatr. Soc.* 57 (4) (2009 Apr) 594–603.
- [42] D. Vance, J. Dawson, V. Wadley, J. Edwards, D. Roenker, M. Rizzo, et al., The accelerate study: the longitudinal effect of speed of processing training on cognitive performance of older adults, *Rehabil Psychol*. 52 (1) (2007) 89–96.
- [43] M. Nahum, H. Lee, M. Fisher, M.F. Green, C.I. Hooker, J. Ventura, et al., Online social cognition training in schizophrenia: a double-blind, randomized, controlled multi-site clinical trial, *Schizophr. Bull.* 47 (1) (2021 Jan 23) 108–117.
- [44] H.K. Lee, J.D. Kent, C. Wendel, F.D. Wolinsky, E.D. Foster, M.M. Merzenich, et al., Home-based, adaptive cognitive training for cognitively normal older adults: initial efficacy trial, *J Gerontol B, Psychol Sci Soc Sci*. 75 (6) (2020 Jun 2) 1144–1154.
- [45] F.V. Lin, Y. Tao, Q. Chen, M. Anthony, Z. Zhang, D. Tadin, et al., Processing speed and attention training modifies autonomic flexibility: a mechanistic intervention study, *NeuroImage*. 213 (2020 Jun), 116730.
- [46] F. Lin, K.L. Heffner, P. Ren, D. Tadin, A role of the parasympathetic nervous system in cognitive training, *Curr. Alzheimer Res.* 14 (7) (2017) 784–789.

- [47] B. Biagianni, B.J. Roach, M. Fisher, R. Loewy, J.M. Ford, S. Vinogradov, et al., Trait aspects of auditory mismatch negativity predict response to auditory training in individuals with early illness schizophrenia, *Neuropsychiatr Electrophysiol.* (2017 Jun 9) 3.
- [48] E.M. Hudak, K.L. Bell, C. Hall, L.D. Grismore, J. LaVere, J.D. Edwards, Dynamic useful field of view training to enhance older adults' cognitive and motor function: a pilot study, *J Cogn Enhanc.* 5 (4) (2021 Jul 7) 411–419.
- [49] S. Rabipour, P.S.R. Davidson, Do you believe in brain training? A questionnaire about expectations of computerised cognitive training, *Behav. Brain Res.* (295) (2015 Dec 15) 64–70.
- [50] S.P. Walsh, R. Raman, K.B. Jones, P.S. Aisen, Alzheimer's disease cooperative study group. ADCS prevention instrument project: the mail-in cognitive function screening instrument (MCFSD), *Alzheimer Dis. Assoc. Disord.* 20 (4 Suppl 3) (2006 Dec) S170–S178.
- [51] K. Kroenke, T.W. Strine, R.L. Spitzer, J.B.W. Williams, J.T. Berry, A.H. Mokdad, The PHQ-8 as a measure of current depression in the general population, *J. Affect. Disord.* 114 (1–3) (2009 Apr) 163–173.
- [52] S. Weintraub, L. Besser, H.H. Dodge, M. Teylan, S. Ferris, F.C. Goldstein, et al., Version 3 of the Alzheimer disease Centers' neuropsychological test battery in the uniform data set (UDS), *Alzheimer Dis. Assoc. Disord.* 32 (1) (2018 Mar) 10–17.
- [53] L. Besser, W. Kukull, D.S. Knopman, H. Chui, D. Galasko, S. Weintraub, et al., Version 3 of the National Alzheimer's coordinating Center's uniform data set, *Alzheimer Dis. Assoc. Disord.* 32 (4) (2018 Dec) 351–358.
- [54] N.H. Stricker, T.J. Christianson, E.S. Lundt, E.C. Alden, M.M. Machulda, J.A. Fields, et al., Mayo normative studies: regression-based normative data for the auditory verbal learning test for ages 30–91 years and the importance of adjusting for sex, *J. Int. Neuropsychol. Soc.* 27 (3) (2021 Mar) 211–226.
- [55] J. Ryan, R.L. Woods, C.J. Britt, A.M. Murray, R.C. Shah, C.M. Reid, et al., Normative data for the symbol digit modalities test in older white Australians and Americans, African-Americans, and Hispanic/Latinos, *J Alzheimers Dis Rep.* 4 (1) (2020 Aug 4) 313–323.
- [56] B.C. Sachs, K. Steenland, L. Zhao, T.M. Hughes, S. Weintraub, H.H. Dodge, et al., Expanded demographic norms for version 3 of the Alzheimer disease Centers' neuropsychological test battery in the uniform data set, *Alzheimer Dis. Assoc. Disord.* 34 (3) (2020 Sep) 191–197.
- [57] J.C. Morris, The clinical dementia rating (CDR): current version and scoring rules, *Neurology.* 43 (11) (1993 Nov) 2412–2414.
- [58] D. Galasko, D.A. Bennett, M. Sano, D. Marson, J. Kaye, S.D. Edland, et al., ADCS prevention instrument project: assessment of instrumental activities of daily living for community-dwelling elderly individuals in dementia prevention clinical trials, *Alzheimer Dis. Assoc. Disord.* 20 (4 Suppl 3) (2006 Dec) S152–S169.
- [59] M.S. Albert, S.T. DeKosky, D. Dickson, B. Dubois, H.H. Feldman, N.C. Fox, et al., The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, *Alzheimers Dement.* 7 (3) (2011 May) 270–279.
- [60] G.M. McKhann, D.S. Knopman, H. Chertkow, B.T. Hyman, C.R. Jack, C.H. Kawas, et al., The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, *Alzheimers Dement.* 7 (3) (2011 May) 263–269.
- [61] S. Bullich, J. Seibyl, A.M. Catafau, A. Jovalekic, N. Koglin, H. Barthel, et al., Optimized classification of 18F-Florbetaben PET scans as positive and negative using an SUVR quantitative approach and comparison to visual assessment, *Neuroimage Clin.* (15) (2017 May 13) 325–332.
- [62] R.O. Roberts, Y.E. Geda, D.S. Knopman, R.H. Cha, V.S. Pankratz, B.F. Boeve, et al., The incidence of MCI differs by subtype and is higher in men: the Mayo Clinic study of aging, *Neurology.* 78 (5) (2012 Jan 31) 342–351.
- [63] R.J. Kryscio, E.L. Abner, Y. Lin, G.E. Cooper, D.W. Fardo, G.A. Jicha, et al., Adjusting for mortality when identifying risk factors for transitions to mild cognitive impairment and dementia, *J. Alzheimers Dis.* 35 (4) (2013) 823–832.
- [64] A. Tetlow, J. Edwards, Evaluation of commercially-available computerized cognitive training programs among older adults. *Innov. Aging.* 2 (suppl_1) (2018 Nov 1) 671.
- [65] A.J. Jak, A.M. Seelye, S.M. Jurick, Crosswords to computers: a critical review of popular approaches to cognitive enhancement, *Neuropsychol. Rev.* 23 (1) (2013 Mar) 13–26.
- [66] D.J. Simons, W.R. Boot, N. Charness, S.E. Gathercole, C.F. Chabris, D.Z. Hambrick, et al., Do "brain-training" programs work? *Psychol. Sci. Public Interest* 17 (3) (2016 Oct) 103–186.
- [67] D.K. Burns, C. Chiang, K.A. Welsh-Bohmer, S.K. Brannan, M. Culp, J. O'Neil, et al., The TOMMORROW study: Design of an Alzheimer's disease delay-of-onset clinical trial, *Alzheimers Dement (N Y).* 28 (5) (2019 Oct) 661–670.
- [68] E.M. Reiman, R.D. Brinton, R. Katz, R.C. Petersen, S. Negash, D. Mungas, et al., Considerations in the design of clinical trials for cognitive aging, *J. Gerontol. A Biol. Sci. Med. Sci.* 67 (7) (2012 Jun) 766–772.
- [69] Y. Li, S.E. Schindler, J.G. Bollinger, V. Ovod, K.G. Mawuenyega, M.W. Weiner, et al., Validation of plasma amyloid- β 42/40 for detecting Alzheimer disease amyloid plaques, *Neurology.* 98 (7) (2022 Feb 15) e688–e699.
- [70] National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) [Internet]. https://ncrad.iu.edu/history_and_mission.html, 2022. (Accessed July 2022).
- [71] Y. Zhou, D. Elashoff, S. Kremen, E. Teng, J. Karlawish, J.D. Grill, African Americans are less likely to enroll in preclinical Alzheimer's disease clinical trials, *Alzheimers Dement (N Y).* 3 (1) (2017 Jan) 57–64.
- [72] R. Brookmeyer, E. Johnson, K. Ziegler-Graham, H.M. Arrighi, Forecasting the global burden of Alzheimer's disease, *Alzheimers Dement.* 3 (3) (2007 Jul) 186–191.
- [73] B. Friedman, M.J. Heisel, R.L. Delavan, Psychometric properties of the 15-item geriatric depression scale in functionally impaired, cognitively intact, community-dwelling elderly primary care patients, *J. Am. Geriatr. Soc.* 53 (9) (2005 Sep) 1570–1576.
- [74] E.A. Gaudino, M.W. Geisler, N.K. Squires, Construct validity in the trail making test: what makes part B harder? *J. Clin. Exp. Neuropsychol.* 17 (4) (1995 Aug) 529–535.
- [75] R.M. Reitan, Validity of the trail making test as an indicator of organic brain damage, *Percept. Mot. Skills* 8 (7) (1958) 271.
- [76] I. Ivanova, D.P. Salmon, T.H. Gollan, The multilingual naming test in Alzheimer's disease: clues to the origin of naming impairments, *J. Int. Neuropsychol. Soc.* 19 (3) (2013 Mar) 272–283.
- [77] S.J.D. Canning, L. Leach, D. Stuss, L. Ngo, S.E. Black, Diagnostic utility of abbreviated fluency measures in Alzheimer disease and vascular dementia, *Neurology.* 62 (4) (2004 Feb 24) 556–562.
- [78] C.P. Hughes, L. Berg, W.L. Danziger, L.A. Coben, R.L. Martin, A new clinical scale for the staging of dementia, *Br. J. Psychiatry* 140 (1982 Jun) 566–572.