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Cognitive Training and Neuroplasticity in Mild Cognitive Impairment (COG-IT): Clinical Rationale and Study Design
A two-site, blinded, randomized, controlled treatment trial.

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ABSTRACT

Introduction: Mild cognitive impairment (MCI) is common in older adults and represents a high-risk group for progression to Alzheimer's disease (AD). Medication trials in MCI have generally failed, but new discoveries with brain plasticity in aging have led to the study of cognitive training as a potential treatment to improve cognitive abilities. Computerized Cognitive Training (CCT) involves computerized cognitive exercises that target specific cognitive abilities and neural networks to potentially improve cognitive functioning through neuroplasticity.

Methods and Analysis: In a two-site study (New York State Psychiatric Institute/Columbia University Medical Center and Duke University Medical Center) we will randomize 100 patients with MCI (WMS-III Logical Memory II score 0-11; MMSE $\geq$ 23) to home-based CCT (suite of exercises: memory, matching, spatial recognition, processing speed) or a home-based active control condition (computerized crossword puzzle training; CPT) with 12 weeks of intensive training followed by regular booster sessions up to 78 weeks. All patients will receive standard neuropsychological and functional assessments in clinic as well as structural/functional brain MRI scans at study entry and endpoint. We will test if CCT, versus CPT, leads to improved cognitive functioning, transfers to functional ability and tasks of everyday life, and impacts hippocampal volume changes and changes in the default mode network (DMN) of the brain measured by resting-state fMRI.

Ethics: The study will be conducted following ethics approval and written informed consent will be obtained from all subjects.

Dissemination/Significance: Study results will be disseminated via publication, clinicaltrials.gov, media and conference presentations. This will be the first controlled long-term trial to evaluate the effects of home-based computerized cognitive training versus computerized crossword puzzle training on not only cognitive abilities, but also functional measures and neural outcomes as determined by MRI indices in patients with MCI. Positive results from this pilot trial may support further development of home-based cognitive training in people at risk for dementia.

Trial Registration: ClinicalTrials.gov Identifier: NCT03205709.

ARTICLE SUMMARY

Strengths and Limitations of this Study

- The study will improve upon limitations of most previous studies by including an "active" control condition, rather than waitlist or control conditions that do not account for engagement and motivation.

- This study will evaluate performance on traditional cognitive and functional assessments (e.g., ADAS-Cog 11, UPSA) in addition to performance on a self-administered, computerized cognitive test, the NeuroCognitive Performance Test (NCPT), which consists of 10 subtests that are online adaptations of widely used neuropsychological tests.

- The trial will utilize a remote internet-based CCT intervention that can be done at home; compared to most existing treatments under investigation, it is easily accessible, relatively inexpensive, non-invasive, and scaled to the skill level of each individual.

- The trial will include evaluation of clinically relevant genetic, brain network, and neuronal loss markers as moderators of outcome; this will be one of the first trials to examine long-term effects on cognition, daily functioning, and neuroplastic changes in DMN with CCT in MCI.

- As our trial will be restricted to English-speaking participants because the online training platform is only available in English, we are unsure how this will generalize to non-English speaking individuals.

- In addition, the inclusion criteria state that the participant must have an at-home desktop or laptop computer, which, in low socioeconomic class homes, is not always available.

INTRODUCTION

Alzheimer's disease (AD) is a major public health concern affecting over 40 million people worldwide and there is an urgent need to develop new treatment modalities to prevent or delay the onset of dementia. Mild cognitive impairment (MCI) is common in older adults and represents a high-risk group for AD, but medication trials in MCI have generally failed. There is no FDA-approved treatment for MCI or to prevent the progression of MCI to AD.

There is growing evidence that a cognitively active lifestyle may reduce rates of dementia. A systematic review of 22 population-based studies found that mental activities may reduce overall incident dementia risk by 46% over a median 7-year period [1]. Computerized Cognitive Training (CCT) provides a novel strategy to improve cognitive performance in MCI by establishing a more cognitively active lifestyle. CCT involves computerized cognitive exercises that target specific abilities to improve cognitive functioning, and this effect is likely to be mediated by neuroplasticity. CCT has been used successfully to improve cognitive functioning in healthy adult populations [2, 3, 4, 5]. In particular, two studies in older healthy controls have garnered much attention. The ACTIVE trial is the first ever large-scale, randomized trial to show evidence of transfer from cognitive training to improved daily function, but only in participants who completed reasoning or speed of processing focused training, and not memory training [6]. In this ten-year follow up study with 2,832 healthy adults (average age = 73.6), participants were randomized to one of three intervention groups (memory, reasoning, or speed of processing) or a no-contact control group. Booster sessions occurred for 39% of participants in all active groups at 11 and 35 months after initial training, but the cognitive effects of the memory training did not persist over the ten-year follow up period [6]. In addition, a large online cognitive training study was originally considered to be negative in terms of cognitive gains. However, in an examination of an older subsample, training was effective in improving cognitive abilities and instrumental activities of daily living [7].

In a recent meta-analysis examining CCT in older adults with MCI or dementia, the overall efficacy of cognitive outcomes in MCI was moderate and statistically significant [8]. This pattern was also found for global cognition, verbal learning and memory, nonverbal learning, working memory, attention, and psychosocial functioning (e.g. depression, quality of life, neuropsychiatric symptoms). However, for the efficacy of cognitive outcomes in patients with dementia, the overall effect was found to be small, though statistically significant.

Early interventions at the stage of MCI, and not dementia, may be more helpful for improving cognition. In fact, Hill et al. [8] concluded that CCT is a feasible intervention for improving cognition in patients with MCI. Transfer effects have also been found in studies evaluating CCT in healthy older adults, supporting the potential for transfer of CCT benefits to daily life [6, 9]. In this study, we will assess for transfer effects by administering the following functional assessments at specific timepoints: Functional Activity Questionnaire (FAQ) and University of California Performance-Based Skills Assessment (UPSA).

Although CCT has received more support in the past few years as a viable treatment option for older adults with MCI, the brain mechanisms underlying the observed cognitive changes remain elusive. Many studies of CCT that include imaging components have only been conducted with healthy older adults [10, 11, 12, 13]. CCT may have neuroplastic effects in the brain, including in the hippocampus, a key region that supports memory [13, 14, 15, 16]. Additional research needs to be done that evaluates both structural and functional data within a rigorously-conducted clinical trial. In this study, patients will undergo a structural MRI and fMRI at both study entry and exit to assess for changes in hippocampal volume and the default mode network.

The default mode network (DMN) of the brain is crucial to evaluate in patients with MCI as dysfunction in the DMN has been implicated in the progression of MCI to AD [17]. The DMN is a resting state neural network of several highly interconnected cortical hubs, including the posteromedial parietal, anteromedial frontal, and inferolateral parietal cortices. We have shown that impaired deactivation and functional connectivity in the DMN may be a significant predictor in MCI of poor memory and transition to dementia over a 2-3 year follow-up period [18]. Neuronal dysfunction precedes structural atrophy in AD, and functional magnetic resonance

imaging (fMRI) offers the potential for identifying specific patterns of disruption in the memory networks affected early in MCI and AD.

Limitations of prior CCT trials include the inconsistent demonstration of transfer to everyday functioning, reliance on waitlist control conditions as opposed to active control conditions, and lack of long-term follow-up. Most studies have not assessed transfer of cognitive improvement to everyday function or quality of life [19, 20, 21, 22, 23]. While CCT may produce transfers to untrained cognitive domains, the few studies that evaluate transfer to everyday functioning have reported mixed findings [24, 25, 26-29]. This is particularly important given the strong association between cognitive decline and functional disability [30]. Many studies use waitlist control conditions or control conditions that do not account for engagement and motivation in the task [22]. Such designs are biased in favor of the treatment condition because waitlisted subjects are not receiving any form of cognitive treatment and, therefore, may be more likely to drop out of such studies due to lack of engagement and motivation. In the current study, patients will be assigned to one of two cognitively stimulating exercises, computerized cognitive training (suite of exercises) or crossword puzzle training (crossword puzzles). Since one of the purposes of CCT in patients with MCI is to reduce the risk of progression to dementia, longer follow-up times are necessary to be able to accurately capture patient progression. However, most studies have only used no follow-up or short-term follow-ups, with the notable exception of the ACTIVE trial [6, 31-33].

Overall, recent findings in the field suggest that computerized cognitive training could benefit patients at risk for dementia. The current study will build on these findings by implementing a study design with an active control group, a longer trial duration, an increased intensity of computerized cognitive training, examination of generalizability to functional abilities beyond cognitive training skills, structural and functional MRI assessment, and rigorously blinded methodology.

METHODS AND ANALYSIS

Study Design Features and Rationale

One-hundred patients clinically diagnosed with mild cognitive impairment (MCI) will be randomized. There will be two sites: New York State Psychiatric Institute/Columbia University Medical Center in New York, NY (NYSPI as lead coordinating site) and Duke University Medical Center in Durham, NC. Patients will be randomized to one of two computerized cognitively stimulating exercises: crossword puzzle training (CPT) or a suite of exercises (CCT; memory tasks, matching tasks, spatial recognition tasks, processing speed tasks). These patients will be randomized by MCI type (early MCI or late MCI), age (70 and below or 71 and above), and site (NYSPI/CUMC or DUMC) as the stratification factors and will be followed for 78-weeks. The randomization sequences will be balanced in blocks of random size (2, 4) to prevent clinicians from guessing what the next patient's treatment might be.

In order to maintain neutrality and mitigate expectancy bias among patients, the informed consent form signed by all patients during the screening visit will not indicate which group is the active group (suite of exercises) or the control group (crosswords). Rather, it will indicate that the patient may be assigned to one of two cognitively stimulating exercises, CCT or CPT.

Role of Sponsor

The study is funded entirely by a National Institute on Aging grant and supervised by a Data Safety Monitoring Board. Using Lumosity, a web-based gaming platform from Lumos Labs, we customized a specific set of CCT and CPT training modules for participants to use in this trial. After a comprehensive review of several CCT modules on the market, we chose these modules from Lumosity due to their large selection of games tailored to specific cognitive domains, their research specific platform, availability of active control condition, availability of an online self-administered neuropsychological test battery (NCPT), and our previous pilot data in the elderly with this platform; see figures 1 and 2 for examples of the Lumosity platform. Aside from providing the research platform and technical support at no cost, Lumos Labs provides no financial support for this study and their staff have no significant role in the final study design, study conduct, data interpretation or publication. Patients will not be required to pay for the platform and will not have a post-study commitment to the platform. None of the study team has any financial conflicts with Lumos Labs.

Recruitment, Eligibility, Consent

Patients will be recruited from the current patient caseload of the investigators, referral by neurology, psychiatry, primary care, public health (inner city) and geriatric medical clinics affiliated with the centers and supplemented by advertisement.

Inclusion/Exclusion Criteria.

Detailed inclusion/exclusion criteria are described in Table 1. Notable inclusion criteria will be age range restriction 55-95 years, subjective cognitive complaints (i.e., memory or other cognitive complaints, e.g., naming/language), Wechsler Memory Scale-III (WMS-III) Logical Memory Story A delayed recall score 0-11, Folstein Mini Mental State Examination (MMSE) score ≥ 23 out of 30, availability of an informant, and access to a home desktop or laptop computer with full access to the internet for the study duration. Patients who have a history of major psychiatric or neurological illness, a dementia diagnosis of any type, contraindication to MRI scan, lack of English-speaking ability, or have been defined as regular online brain training or regular crossword puzzle users (≥ 2 times per week in the past year) will be excluded. Depression will be assessed using the 15-item Geriatric Depression Scale (GDS); a diagnosis of Major Depressive Disorder is exclusionary.

Table 1. Inclusion/Exclusion Criteria

Inclusion Critera
1. Males and females 55 to 95 years of age (inclusive) at the time of informed consent.
2. Subjective cognitive complaints, i.e., memory or other cognitive complaints, e.g., naming/language.
3. Meets criteria for cognitive impairment (CI) defined as scores >1 SD below standardized norms on memory function as identified by the Wechsler Memory Scale (WMS) III Logical Memory delayed recall score.
4. Folstein Mini Mental State (MMSE) score ≥ 23 out of 30.
5. A family member or other individual who is in contact with the patient and consents to serve as informant during the study; this could be a telephone informant in case of patients who do not have a live-in informant or close significant other.
6. Access to a home desktop or laptop computer at acceptable speed for the study duration.
Exclusion Criteria
1. Diagnosis of dementia of any type.
2. Current clinical evidence of schizophrenia, schizoaffective disorder, major depression, psychosis, or bipolar I disorder (DSM-IV TR criteria).
3. Active suicidal ideation or plan.
4. Current or recent (past 6 months) alcohol or substance use disorder (DSM-5 criteria).

5. Clinical stroke with residual neurological deficits. While we will not exclude patients with cerebrovascular disease, we will not include patients who have had a stroke with residual clinical deficits because it is not clear that this type of patient is similar to the MCI patient generally, and clear-cut neurological impairment, e.g., hemiplegia/hemiparesis or speech impairment, may compromise the patient's ability to do the CCT or active control procedures and to complete the neuropsychological tests.
6. Use of medications known to have a negative impact on cognition: benzodiazepines in lorazepam equivalents $\geq$ 1 mg daily, narcotics, anticholinergics. Other patients receive medications that may be associated with cognitive impairment but are rarely considered the likely etiology, e.g., theophylline, nifedipine, beta blockers; they will not be excluded. Patients receiving other psychotropic medications not expected to have a material impact on cognition, e.g., SSRIs and SNRIs will be eligible.
7. Presence of any of the following disorders: a) CNS infection, with CSF evidence of meningitis, encephalitis, or other infectious process; b) dementia of any type; c) Huntington's disease; d) Multiple sclerosis; e) Parkinson's disease; f) Other neurologic disorders with focal signs, e.g., amyotrophic lateral sclerosis; g) Mental retardation.
8. Acute, severe unstable medical illness. For cancer, acutely ill patients (including those with metastases) will be excluded, but past history of successfully treated cancer will not result in exclusion.
9. Contraindication to MRI scan: pacemaker, metal implants following surgery, any other contraindication to MRI. Eligibility for the MRI scan is a requirement for the study.
10. UPSIT exclusions: current smoker $>$ 1 pack daily, current upper respiratory infection (retested as soon as the infection clears). UPSIT scores are reduced in schizophrenia, Parkinson's disease and Parkinson's related conditions; these disorders are exclusion criteria for this study. Patients with UPSIT exclusions will not receive the UPSIT but will continue to participate in all other aspects of the study.
11. Patients lacking English-speaking ability as determined by self-report and clinical evaluation.
12. Regular online brain training or regular crossword puzzle user, defined as doing these procedures at a frequency of twice weekly or greater during the year prior to screening. Eligible participants who join the trial are instructed not to do these procedures on their own during the trial, i.e., independent of the study.
13. Participation in another intervention trial for cognitive impairment.

Mild Cognitive Impairment Criteria

Mild cognitive impairment (MCI) and type of MCI (early MCI or late MCI) will be assessed by the delayed recall score of WMS-III Logical Memory and by the score on the Folstein Mini Mental Status Examination (MMSE). On Logical Memory II Story A, a score from 0-11 will indicate cognitive impairment, per the Alzheimer's Disease Neuroimaging Initiative (ADNI) criteria. MCI type will be determined from this score combined with years of education of the patient. Early MCI (eMCI) will be defined as a delayed recall score of 3-6 with 0-7 years of education, score of 5-9 with 8-15 years of education, and score of 9-11 with 16 or more years of education. Late MCI (lMCI) will be defined as a delayed recall score of $\leq$ 2 with 0-7 years of education, score of $\leq$ 4 with 8-15 years of education, and score of $\leq$ 8 with 16 or more years of education. For both eMCI and lMCI, everyday function must be well preserved for study inclusion. A MMSE score $\geq$ 23 will also be required to indicate mild cognitive impairment, and this is required for study inclusion.

Length of Clinical Trial

Most transitions from MCI to AD typically occur by three years of follow-up after the diagnosis of MCI is made [34]. We chose 18-months as the length of this clinical trial to decrease dropouts that can occur in a very long controlled trial. Thus, we will conduct a follow-up visit one year after the last study visit, which is a total duration of 2.5 years of participation. Since this study is considered low risk, we do not anticipate participants to suffer harm from trial participation.

Treatment Regimen

Enrolled participants will come to the clinic for five scheduled visits (Weeks 0, 12, 32, 52, and 78) and will receive at least three scheduled phone calls with research staff (Weeks 20, 42, and 64). Participants will be enrolled into the study after screening for eligibility and consent is signed. The randomization will be assigned by the statistician and then carried out by the unblinded research coordinator, with individuals stratified by MCI type, age group, and site. The term "control" will not be used in the consent form in order to reduce the participant's expectancy bias.

Randomization.

The blinded research coordinator (at NYSPI or Duke) will complete the Training Group Randomization Form to indicate the following information for the patient: site, age, and MCI type. This form will be verified by the unblinded research coordinator at NYSPI, who will then assign a study ID to that patient, using a pre-populated form from the statistician's randomization assignment. The order of the study ID assignment will determine which study condition the patient will receive: CPT or CCT. The Lumosity account information will be generated after the MRI has been completed and quality checked. Lumosity account credentials will include a research-specific COGIT ID email address and password, which will enable users to log into an account specific to their study condition. The unblinded research coordinator at NYSPI will then send the login credentials to the blinded research coordinator at the appropriate site.

Randomization will be complete when the patient logs into his/her account for the first time at the baseline visit and sees which condition he/she is in. At this visit, patients will be trained by unblinded study staff in their assigned training condition. Eighteen modules were selected to

target various cognitive domains: (A) Memory (Tidal Treasures, Familiar Faces, Memory Matrix) (B) Processing Speed (Speed Match) (C) Response Inhibition (Color Match) (D) Verbal Fluency/Vocabulary Proficiency (Word Bubbles, Word Snatchers, Editor's Choice, Continuum) (E) Planning/Divided Attention (Train of Thought, Brain Shift, Trouble Brewing, Disillusion) (F) Visual Interference (Lost in Migration, Ebb and Flow, Masterpiece) (G) Identification (River Ranger) (H) Visualization (Speed Pack). These cognitive domains were chosen as they are areas that are often impaired in patients with MCI and thus represent areas that can be targeted for improvement [35]. Each CCT session will consist of a random selection of six modules. Each module will require the use of various cognitive abilities and will scale in difficulty with the patient's progress. The Lumosity platform will scale difficulty by using the patient's Lumosity Performance Index (LPI). The LPI will consider the following areas for each patient: Game Performance Index, Cognitive Area Performance Index, and overall Cognitive Performance Index. The Game Performance Index will be determined by reviewing score distributions for each game. The Cognitive Area Performance Index (speed, memory, attention, flexibility and problem solving) will be calculated using a weighted average of the Game Performance Index. Lastly, the overall Cognitive Performance Index will be calculated using a weighted average of the Game Performance Indices from all cognitive areas. A complete list of selected CCT games and the associated cognitive abilities being tested are described in Table 2. There should be no case in which an emergency unblinding will need to take place, as the blinded intervention is a computerized intervention.

Table 2. Complete list of CCT game battery and associated cognitive domains (provided by Lumos Labs)

Game Name	Cognitive Domain
Tidal Treasures	Working Memory i.e., delayed, non-matching to sample; self-ordered pointing
Speed Match	Processing Speed
Color Match	Response Inhibition
Word Bubbles	Verbal Fluency
Train of Thought	Planning Divided Attention Multiple attractions
Familiar Faces	Episodic Memory
Memory Matrix	Episodic Memory; Visuospatial memory
Lost in Migration	Visual Interference

Brain Shift	Task Switching
Trouble Brewing	Multitasking, divided attention, sustained attention, planning, working memory
Ebb and Flow	Task switching, semantic and visual interference
Masterpiece	Mental rotation; visualization; spatial reasoning
River Ranger	Identification
Word Snatchers	Vocabulary proficiency
Speed Pack	Visualization
Disillusion	Task Switching
Editor's Choice	Vocabulary Proficiency
Continuum	Vocabulary Proficiency

Participants in the computerized cognitive training group and the crossword puzzle training group will spend the same amount of time on the platform during the intensive training phase, which will consist of four 30-minute training sessions per week for 12 weeks. For both groups, responses will be entered via mouse and keyboard. For the crossword puzzle training group, questions will not need to be completed in order and there will not be any feedback for the accuracy of the response at the time of entry by the participant. Upon completion of the CCT suite of exercises after 30 minutes, participants will receive a score. Similarly, after 30 minutes the crossword training will automatically end. If a participant were to finish an entire crossword puzzle before the 30-minute cutoff, they would be directed to another puzzle to ensure they complete a total of 30 minutes. Global automated feedback will be given in a similar manner for both groups.

Following the intensive training phase of 12 weeks, participants will be instructed to complete six booster sessions. Each booster session will consist of four computerized cognitive training/crossword puzzle training sessions. Booster sessions will be completed at weeks 20, 32, 42, 52, 64, and 78. At weeks 32, 52, and 78, patients will be instructed to complete three booster sessions at home and to complete the fourth session in-clinic with research staff. At weeks 20, 42, and 64, patients will be instructed to complete all four booster sessions at home. Generally, in previous cognitive training studies, booster sessions have been limited. For instance, the ACTIVE trial had two booster sessions, each consisting of four 75-minute trainings at 11 and 35 months. During the course of the trial, booster sessions included a total of 8 trainings, for a total of 10 hours [6]. In contrast, COGIT will have six booster sessions (24 total training sessions each lasting 30 minutes) over 15 months. Thus, COGIT will include 12 hours total for booster

sessions during the trial. The ACTIVE trial only required compliant participants to complete the booster sessions, whereas all participants will complete booster sessions in the COGIT study [6].

Clinic Based Cognitive, Functional, and Smell Assessments.

At baseline (week 0) The Alzheimer's Disease Assessment Scale-Cognition Subscale 11 (ADAS-Cog 11) will be administered, in addition to the following neuropsychological test battery: WAIS-III Block Design (to assess visuospatial skills), Digit Symbol Substitution Test (to assess attention), Trail Making A & B (to assess attention and executive function), Verbal Fluency and 15-item Boston Naming Test (to assess language), Auditory-Verbal Learning Test (to assess verbal learning and memory), and WMS-III Visual Reproduction Test (to assess nonverbal learning and memory). In addition, the University of California Performance-Based Skills Assessment (UPSA) and University of Pennsylvania Smell Identification Test (UPSIT) will be administered. The Functional Activity Questionnaire will be administered to the patient's informant, either during the study visit or shortly after the visit over the phone.

Self-Administered Cognitive Test Battery.

Another unique aspect of the study is the use of an online self-administered test, the NeuroCognitive Performance Test (NCPT), which will be self-administered via computer. It will test various cognitive domains outlined in the Study Measures section. The NCPT will allow us to examine the efficacy of a self-administered test, in combination with standardized, clinic-based neuropsychological tests.

Timeline of Longitudinal Assessments

At subsequent in-clinic visits (weeks 12, 52, and 78), the same neuropsychological battery of testing will be completed. At the week 12 and week 78 visits, patient will be asked to complete the User Engagement Scale, which will be adapted to capture usage of a computerized platform. This scale will measure aspects of engagement, usability, and satisfaction with the computerized platform on a 5-point Likert scale. Week 20 will be a phone interview between study physician/neuropsychologist and patient to follow-up on how the patient has been doing, and to remind the patient to complete a booster session of computerized training.

Blinded Training Procedure

The blinded research coordinator will administer the full neuropsychological test battery, including the UPSA and FAQ. The blinded clinician will complete the Diagnosis Form and the Contributing Features to MCI form after clinical interview and review of the neuropsychological testing. The unblinded research coordinator will be responsible for administering the initial computerized training and all subsequent booster sessions of training to patients in the clinic. Each week, the unblinded research coordinator will review the compliance of all patients. Over any two week period, a patient must be 50% compliant with the computerized training sessions. If the participant does not demonstrate this level of compliance, the unblinded research coordinator will call the patient to ensure high compliance rates and to provide assistance with technical problems.

Hypotheses

See Figure 3 for a Conceptual Model of specific study aims and outcome measures. The primary aim of the study is to assess change in cognitive and functional status over 18 months in MCI patients comparing the CCT and CPT groups. Hypothesis 1: MCI patients randomized to CCT will show better cognitive outcomes on the ADAS-Cog 11 (primary outcome measure), Neuropsychological Testing Composite score (secondary outcome measure), and NeuroCognitive Performance Test (exploratory outcome measure) compared to active control (CPT). Hypothesis 2: MCI patients randomized to CCT will show better functional outcomes as assessed by the UPSA (primary functional outcome) and the FAQ (secondary functional outcome) by the end of the 18-month trial compared to active control. Hypothesis 3: brain pathology (smaller hippocampal volumes, lower odor identification scores on the UPSIT, ApoE e4 allele present) will moderate the relationship between treatment assignment and cognitive and functional outcomes.

The secondary aim of the study is to examine the effects of CCT on resting-state DMN connectivity as well as other networks modulated by CCT effects. Hypothesis 1: MCI patients randomized to CCT will demonstrate greater change in an index of DMN functional connectivity compared to patients randomized to active control. Hypothesis 2: indicators of brain pathology (smaller hippocampal volumes, lower odor identification scores on the UPSIT, ApoE e4 allele

present) will moderate the relationship between change in the DMN and treatment assignment (see Figure 4 [36]).

The tertiary aim of the study is to examine differences in rates of progression to dementia and AD in the two randomized treatment groups, recognizing that if progression to these outcomes is uncommon there will be insufficient statistical power. Hypothesis 1: the proportion converting to dementia will be lower in the CCT group compared to active control.

Study Measures

Study measures with time-points of administration are listed in Table 3. The MMSE will be administered at screen and each subsequent in-clinic visit using five different versions of the three-word recall item to reduce practice effects [37]. The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) and The Framingham Stroke Risk Scale will be completed by the study physician at screen and week 78 to assess for cardiovascular disease risk factors and other medical conditions.

Table 3. Table of Study Procedures

Measure	Screen	Baseline	12 Weeks	20 Weeks Phone Interview	32 Weeks	42 Weeks	52 Weeks	64 Weeks	78 Weeks
ADAS-Cog11		X	X				X		X
APOE & blood test	X								
CIRS-G	X								X
Cognitive Reserve Index	X								
Cognitive Training or Control training booster session			X	X	X	X	X	X	X
Contributing Features to MCI		X			X				X
Demographics History (Patient Tracking Form)	X								
Diagnosis Form			X		X				X
Digit Symbol Substitution Test		X	X				X		X
Expectancy Scale (Participant & Informant)		X			X				X
Family History	X								
FAQ		X	X	X	X		X		X
Framingham Stroke Risk	X								X
Geriatric Depression Scale	X		X		X		X		X
History of Game Use Questionnaire	X		X						X
Inclusion/ Exclusion Form	X								
Informed Consent	X								

Medications (Chart List & Database List)	X		X	X	X	X
MMSE	X		X	X	X	X
MRI Scan of Brain	X					X
NCPT online cognitive performance test		X	X			X
Neuropsychological Battery: AVLT, Block Design, Verbal Fluency, Visual Reproduction, Boston Naming Test, Trails A & B		X	X		X	X
Physical Activity Assessment	X					
UPSA		X		X		X
UPSIT		X				X
User Engagement Scale			X			X
WMS-III Logical Memory I & II	X					

The Geriatric Depression Scale will be administered at screen and each subsequent in-clinic visit to assess for depression. If GDS is greater than 5 at any visit, the patient will be evaluated by a psychiatrist and an appropriate clinical referral will be made, if needed, for treatment of depression. The Cognitive Reserve Index is a brief questionnaire that will be administered by the research coordinator at screen and will evaluate the cognitive reserve of an individual by means of the compilation of information as it relates to his/her adult life.

At screen, the research coordinator will be responsible for administering the History of Game Use Questionnaire, Physical Activity Assessment, and WMS-III Logical Memory I & II. The History of Game Use Questionnaire will be administered again at weeks 12 and 78 to ensure that patients are not partaking in any other types of cognitive training games while in the study.

At screen and week 78, patients will undergo an MRI scan of the brain. The MRI scan will include the following sequences: Localizer, high-resolution T1-weighted IR prepped 3DSPGR, and T2 FLAIR, and GE-EPI resting-state fMRI scans.

At weeks 0 and 78, the UPSIT will be completed by the patient, which is a 40-item scratch and sniff multiple-choice olfactory identification test.

At each in-clinic visit, apart from week 32, the ADAS-Cog 11 and full neuropsychological test battery will be administered. The NCPT will be administered at weeks 0, 12, and 78. The NCPT

is a brief, unsupervised, online battery of cognitive assessments developed by Lumosity. The cognitive domains measured by the NCPT are memory (visuo-spatial working memory, short-term memory), processing speed (visual search, psychomotor speed), problem solving (logical reasoning, numerical calculation), attention (selective, divided), and flexibility (response inhibition, task-switching). The assessments, 10 total "subtests," are online adaptations of widely used neuropsychological tests whose test properties are not affected by shifting to computerized administration [38].

The neuropsychological test battery includes: WAIS-III Block Design, Digit Symbol Substitution Test, Trail Making A & B, Verbal Fluency and 15-item Boston Naming Test, Auditory-Verbal Learning Test, and WMS-III Visual Reproduction Test. The UPSA will be administered only at weeks 0, 32, and 78 due to the high tendency for practice effects. It is a performance-based measure of functional abilities that includes measures of simulated real-world activities; for example, planning a trip to the beach, remembering documents to bring to a medical appointment, and dialing a phone number.

At screen and weeks 12, 32, 52, and 78 the participant will meet with the study physician or the neuropsychologist to assess for illness progression and adverse events. Adverse events that are spontaneously reported to research coordinators at any clinic visit will be discussed with the study physician or the neuropsychologist in order to determine how to proceed. Adverse events and subsequent steps to deal with the adverse events will be documented in the patient chart and serious adverse events will be reported to the Data Safety and Monitoring Board and study sponsor, National Institute on Aging.

Additionally, the research coordinator will conduct an interview with the informant at, or shortly after, each visit to complete the Functional Activity Questionnaire.

Criteria for Early Discontinuation

We expect early discontinuation to occur because of one or more of the following reasons: (1) the patient's decision not to continue the computerized training (CCT or CPT) due to lack of interest, motivation, or available time; (2) unavoidable circumstances, e.g., moving residence and

unwillingness to return for in-person evaluations; (3) investigator decision to terminate; (4) death or prolonged hospitalization for medical reasons. We will not terminate participation for non-adherence because even if the patient is non-adherent to the protocol, we will document level of adherence (done electronically in this computerized training protocol) and still include the patient's data in the analyses based on the intent-to-treat principle.

Data Management

Data entry will be completed by Program Managers, Clinical Research Coordinators, and Research Assistants on the study protocol. Data entry/cleaning will be done throughout the project. The data collected in this study will be monitored by the Data Coordinating Center at NYSPI. The unit will work closely with the research assistant/coordinator and the Principal Investigator to facilitate independent auditing of primary subject records. The database will provide reports indicating all modifications that have been made in the database together with paper communications (fax, e-mail) confirming and authorizing these modifications. Access to the data system is available only to authorized users, with multiple levels of security including user id/password authentication via MS Active Directory overseen by experienced IT personnel. Other authorized users with direct access to the data system will be Data Coordinating Center (DCC) staff. DCC data-related operations and the SIR/Citrix system have been certified by Columbia University's Information Security Office. The dataset will not be published in a data repository.

Genetic Testing

Apolipoprotein E (ApoE) genetic analysis on a blood sample will be done through the laboratory of the Human Genetics Resources Core (HGRC) at Columbia University Medical Center. We will assess the ApoE ε4 allele as potentially associated with response to CCT; a prior trial found an association between the ε4 allele and cognitive improvement on donepezil [39].

Concomitant Medications

Putative cognitive enhancers, narcotics, all classes of psychotropic medications, and over 20 other classes of commonly prescribed and over the counter (and alternative) medications will be documented in a rating form at screen and subsequent in-clinic visits. An exclusion criterion will

be daily use of medications known to have a negative impact on cognition: high-dose narcotics, anticholinergics, and benzodiazepines in lorazepam equivalents ≥ 1 mg daily. During the first 12 weeks of the study, the intensive cognitive training phase, patients are encouraged not to change any of their medications, unless clinically indicated.

Statistical Analysis and Sample Size

Outcome Measures (Primary and Secondary Hypotheses Testing).

Aim 1 Hypothesis 1 and 2. MCI patients on CCT will show a lower rate of cognitive and functional decline compared to MCI patients on active control by the end of the 18-month trial. We will use generalized linear mixed effects models of cognitive and functional measures collected repeatedly across the 78 weeks according to the schedule (see Table 3). For example, $\text{cognitive measure}_{ik} = \beta_0 + \beta_1 \text{Time}_{ik} + \beta_2 \text{Group}_i + \beta_3 (\text{Group}_i \text{ x Time}_{ik}) + v_{0i} + v_{1i} \text{Time}_{ik} + \varepsilon_{ik}$ where Group_i indicates treatment group for subject i (Group = 1 CCT, 0 for control), k = time (baseline, 12 weeks, 20 weeks, 52 weeks, 78 weeks), and v_{0i} is a subject-specific random intercept. Time will be treated as categorical if linearity is not plausible and group effects at 18 months can be tested by forming contrasts from the fitted model. Potential site differences will be evaluated using descriptive statistics and site will be included in all analyses as a covariate, as will other stratification variables including age group and MCI type at baseline.

Aim 2 Hypothesis 1. MCI patients randomized to CCT will demonstrate either more of an increase or less of a decrease in DMN connectivity (goodness-of-fit [GOF] index scores) compared to patients randomized to active control. To test this hypothesis, we will use a repeated measures Analysis of Covariance (ANCOVA) with time (baseline vs. post treatment) as the repeated measure, DMN connectivity as an outcome, treatment condition (CCT vs CPT) as a predictor, and site, age, and MCI status at baseline as covariates.

Moderating Effects in Aim 1 Hypothesis 3 and Aim 2 Hypothesis 2. As a part of our exploratory analyses, we will examine specific potential moderators: Apolipoprotein E ε4 allele, MRI indices, UPSIT. To show, for example, that baseline hippocampal volume is a moderator, we will test its interactive effect with treatment on outcomes. Moderator and moderator-interaction terms can be easily accommodated in the mixed effects regression models described in Aim 1,

Hypotheses 1 and 2. A similar approach will be used by adding moderator and moderator x Group interactions to the ANCOVA described in Aim 2 Hypothesis 1. The results must be interpreted with the caveat that there may not be enough power to assess these interactions, especially for moderators with low prevalence.

Aim 3 Hypothesis 1. The proportion diagnosed with dementia during follow-up will be lower in the CCT group compared to active control. Logistic regression will be used to test the binary outcome of dementia status at 18 months predicted by treatment group controlling for site, age group, and MCI type at baseline.

Sample Size.

A power analysis was conducted using the RMASS program for longitudinal studies, which determined that a total sample size of 100 participants will provide a sufficient effect size to evaluate our hypotheses.

Patient and Public Involvement

Patients will first be involved in the research after study design is finalized by the study investigators. At this stage, patients will be referred by physicians or self-referred from online and newspaper advertisements for their initial screening visit. The patients will not be involved in study design, study recruitment or conduct, or dissemination of study results. We will assess the burden of the trial intervention on patients using the User Engagement Scale and the Participant/Informant Expectancy Scales. Patients will not be invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients will not be invited to contribute to the writing or editing of this document for readability or accuracy.

ETHICS

This study has been approved by NYSPI IRB, Duke University IRB, and Queens College IRB. All COGIT patients at entry will be required to have the capacity to provide informed consent and sign the IRB-approved informed consent form. Local IRB and state regulations for consent will be followed. Patient confidentiality as it pertains to potential and enrolled participants

before, during, and after the trial will be collected, shared, and maintained strictly according to HIPAA law.

Important protocol modifications will be communicated to the Data Safety and Monitoring Board, NYSPI IRB and Duke University IRB, and updated online for trial registries.

The research data on specific moderators, including UPSIT and apolipoprotein E genotyping, will not be not released to the patient, and this will be specified in the consent form. The cognitive testing results and clinical reading of the MRI scan will be released to the patient (and the patient's primary physician, if requested); the MRI research volumetric ratings and fMRI findings will not be released.

Data Safety and Monitoring Board (DSMB)

Three independent experts with expertise in conducting clinical trials in mild cognitive impairment will form the DSMB. All serious adverse events (SAEs) will be reported to the DSMB. The DSMB will audit the trial conduct, review all SAEs, participate in a teleconference twice a year to determine if the study should continue, and then will provide an actionable report to the Principal Investigator. This process will be independent from the investigators.

DISSEMINATION

The study results will be disseminated through publications and conference presentations as well as on public websites, including clinicaltrials.gov. Researchers will be eligible for authorship after consideration by the principal investigators; no professional writers will be utilized.

SIGNIFICANCE

This will be one of the first controlled long-term trials to evaluate the effects of home-based computerized cognitive training versus computerized crossword puzzle training on cognitive, functional, hippocampal and default mode network connectivity neural outcomes in MCI.

Positive results from this pilot trial may support the further development of home based cognitive training and self-assessments in people at risk for dementia.

The results will help inform the design of a more powerful RCT in many ways: determine sample size for a multicenter trial, identify subgroups more likely to benefit, identify subdomains and exercises most likely to improve, optimize training dose and duration, learn how subjects engage, identify gender effects, model slopes and long-term benefits, assess value of a self-administered cognitive test, understand brain networks affected, and examine the potential moderating role of apolipoprotein E ε4 status on CCT outcome.

AUTHOR CONTRIBUTIONS

DPD, PMD, JRP, and JRS conceived and designed the study and obtained funding. All other authors assisted with elements of study design, database, and conduct. HA contributed to statistics design and JRP to design of MRI component. DPD is the overall study PI and PMD is the PI at the Duke site. JLD and LSP did the initial draft of the paper and all authors contributed to manuscript edits and revisions.

FUNDING STATEMENT

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COMPETING INTERESTS

JLD, LSP, TEG, SNR, SNT, EP, JRP, CAH, HFA, JRS, NAK have no competing interests. PMD has received research grants and advisory fees from several companies in this field for other studies, and owns shares in several companies whose products are not discussed here. DPD serves as a consultant on the advisory board to Acadia, Avanir, and Eisai.

Table 1. Inclusion/Exclusion Criteria

Inclusion Critera
1. Males and females 55 to 95 years of age (inclusive) at the time of informed consent.
2. Subjective cognitive complaints, i.e., memory or other cognitive complaints, e.g., naming/language.
3. Meets criteria for cognitive impairment (CI) defined as scores >1 SD below standardized norms on memory function as identified by the Wechsler Memory Scale (WMS) III Logical Memory delayed recall score.
4. Folstein Mini Mental State (MMSE) score ≥ 23 out of 30.
5. A family member or other individual who is in contact with the patient and consents to serve as informant during the study; this could be a telephone informant in case of patients who do not have a live-in informant or close significant other.
6. Access to a home desktop or laptop computer at acceptable speed for the study duration.
Exclusion Criteria
1. Diagnosis of dementia of any type.
2. Current clinical evidence of schizophrenia, schizoaffective disorder, major depression, psychosis, or bipolar I disorder (DSM-IV TR criteria).

3. Active suicidal ideation or plan.
4. Current or recent (past 6 months) alcohol or substance use disorder (DSM-5 criteria).
5. Clinical stroke with residual neurological deficits. While we will not exclude patients with cerebrovascular disease, we will not include patients who have had a stroke with residual clinical deficits because it is not clear that this type of patient is similar to the MCI patient generally, and clear-cut neurological impairment, e.g., hemiplegia/hemiparesis or speech impairment, may compromise the patient's ability to do the CCT or active control procedures and to complete the neuropsychological tests.
6. Use of medications known to have a negative impact on cognition: benzodiazepines in lorazepam equivalents $\geq$ 1 mg daily, narcotics, anticholinergics. Other patients receive medications that may be associated with cognitive impairment but are rarely considered the likely etiology, e.g., theophylline, nifedipine, beta blockers; they will not be excluded. Patients receiving other psychotropic medications not expected to have a material impact on cognition, e.g., SSRIs and SNRIs will be eligible.
7. Presence of any of the following disorders: a) CNS infection, with CSF evidence of meningitis, encephalitis, or other infectious process; b) dementia of any type; c) Huntington's disease; d) Multiple sclerosis; e) Parkinson's disease; f) Other neurologic disorders with focal signs, e.g., amyotrophic lateral sclerosis; g) Mental retardation.
8. Acute, severe unstable medical illness. For cancer, acutely ill patients (including those with metastases) will be excluded, but past history of successfully treated cancer will not result in exclusion.
9. Contraindication to MRI scan: pacemaker, metal implants following surgery, any other contraindication to MRI. Eligibility for the MRI scan is a requirement for the study.
10. UPSIT exclusions: current smoker > 1 pack daily, current upper respiratory infection (retested as soon as the infection clears). UPSIT scores are reduced in schizophrenia, Parkinson's disease and Parkinson's related conditions; these disorders are exclusion criteria for this study. Patients with UPSIT exclusions will not receive the UPSIT but will continue to participate in all other aspects of the study.
11. Patients lacking English-speaking ability as determined by self-report and clinical evaluation.
12. Regular online brain training or regular crossword puzzle user, defined as doing these procedures at a frequency of twice weekly or greater during the year prior to screening. Eligible participants who join the trial are instructed not to do these procedures on their own during the trial, i.e., independent of the study.
13. Participation in another intervention trial for cognitive impairment.

Table 2. Complete list of CCT game battery and associated cognitive domains (provided by Lumos Labs)

Game Name	Cognitive Domain
Tidal Treasures	Working Memory i.e., delayed, non-matching to sample; self-ordered pointing
Speed Match	Processing Speed
Color Match	Response Inhibition
Word Bubbles	Verbal Fluency
Train of Thought	Planning Divided Attention Multiple attractions
Familiar Faces	Episodic Memory
Memory Matrix	Episodic Memory; Visuospatial memory

Lost in Migration	Visual Interference
Brain Shift	Task Switching
Trouble Brewing	Multitasking, divided attention, sustained attention, planning, working memory
Ebb and Flow	Task switching, semantic and visual interference
Masterpiece	Mental rotation; visualization; spatial reasoning
River Ranger	Identification
Word Snatchers	Vocabulary proficiency
Speed Pack	Visualization
Disillusion	Task Switching
Editor's Choice	Vocabulary Proficiency
Continuum	Vocabulary Proficiency

Table 3. Table of Study Procedures

Measure	Screen	Baseline	12 Weeks	20 Weeks Phone Interview	32 Weeks	42 Weeks	52 Weeks	64 Weeks	78 Weeks
ADAS-Cog11		X	X				X		X
APOE & blood test	X								
CIRS-G	X								X
Cognitive Reserve Index	X								
Cognitive Training or Control training booster session			X	X	X	X	X	X	X
Contributing Features to MCI		X			X				X
Demographics History (Patient Tracking Form)	X								
Diagnosis Form			X		X				X
Digit Symbol Substitution Test		X	X				X		X

Expectancy Scale (Participant & Informant)		X			X		X
Family History	X						
FAQ		X	X	X	X	X	X
Framingham Stroke Risk	X						
Geriatric Depression Scale	X		X		X	X	X
History of Game Use Questionnaire	X		X				X
Inclusion/ Exclusion Form	X						
Informed Consent	X						
Medications (Chart List & Database List)	X		X		X	X	X
MMSE	X		X		X	X	X
MRI Scan of Brain	X						X
NCPT online cognitive performance test		X	X				X
Neuropsychological Battery: AVLT, Block Design, Verbal Fluency, Visual Reproduction, Boston Naming Test, Trails A & B		X	X			X	X
Physical Activity Assessment	X						
UPSA		X			X		X
UPSIT		X					X
User Engagement Scale			X				X
WMS-III Logical Memory I & II	X						

Table 3 Legend: ADAS-Cog 11 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 11. ApoE = Apolipoprotein E gene. CIRS-G = Cumulative Illness Rating Scale for Geriatrics. MCI = Mild Cognitive Impairment. FAQ = Functional Assessment Questionnaire. MMSE = Mini Mental Status Examination. MRI = Magnetic Resonance Imaging. NCPT = NeuroCognitive Performance Test. AVLT = Auditory Verbal Learning Test. UPSA = UCSD Performance-Based Skills Assessment. UPSIT = University of Pennsylvania Smell Identification Test. WMS-III = Wechsler Memory Scale-III.

Figure 1. Example of Crossword Puzzle Training Condition

This figure is a snapshot of the crossword puzzle training platform. This is an example of the interface a patient in this treatment arm works on to complete training sessions.

Figure 2. Example of Computerized Cognitive Training Condition

This figure is a snapshot from the computerized cognitive training platform. This is an example of the interface a patient in this treatment arm works on to complete training sessions. The picture game is entitled Trouble Brewing.

Figure 3. Conceptual Model

In the intervention phase patients are randomly assigned to either CCT or CPT. To evaluate cognitive status, the primary outcome measure will be the ADAS-Cog 11, the secondary outcome measure will be the Neuropsychological Testing Composite Score, and the exploratory outcome measure will be the NeuroCognitive Performance Test. To evaluate functional status, the primary outcome measure will be the UPSA and the secondary outcome measure will be the FAQ. To evaluate changes in the default mode network, the primary outcome measures will include hippocampal volume (MRI) and DMN connectivity (fMRI).

Figure 4. Model of CCT Impact on Neural Circuits [36].

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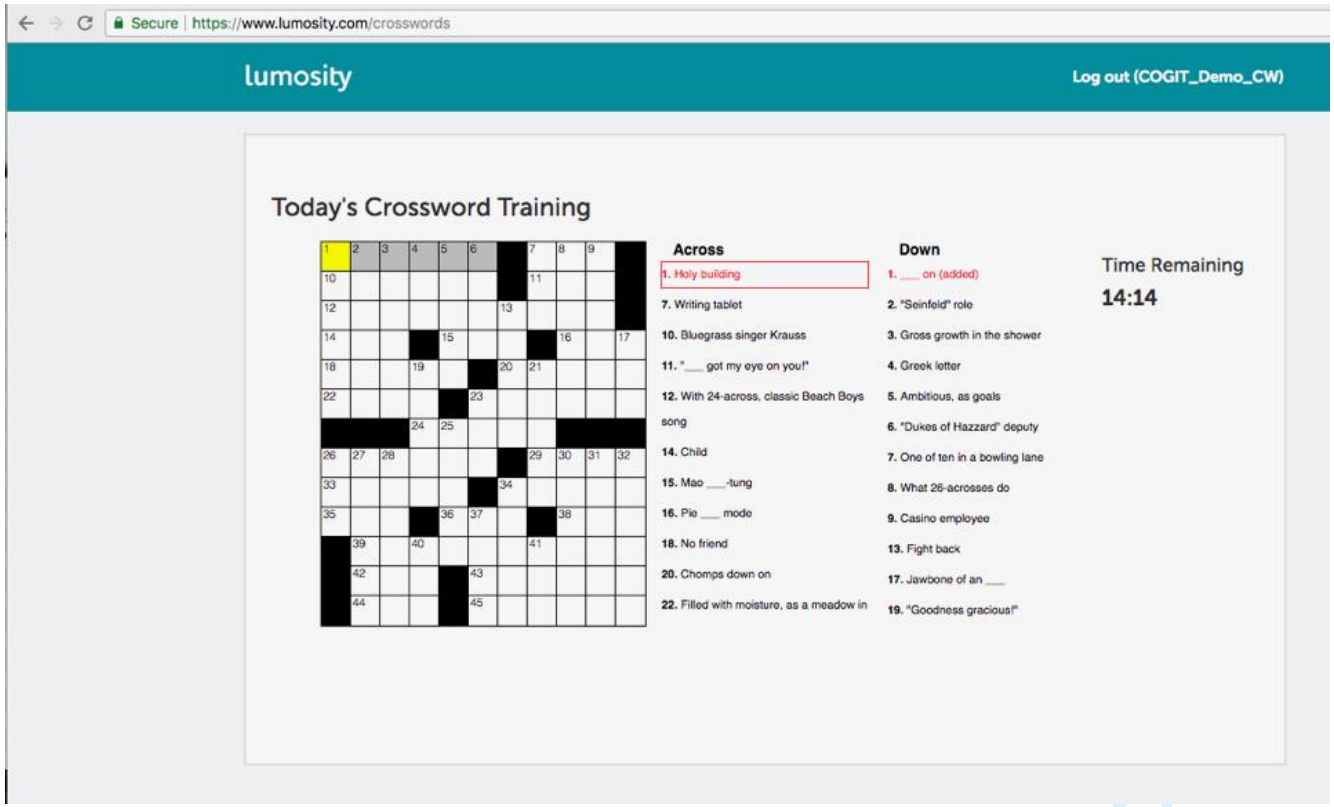
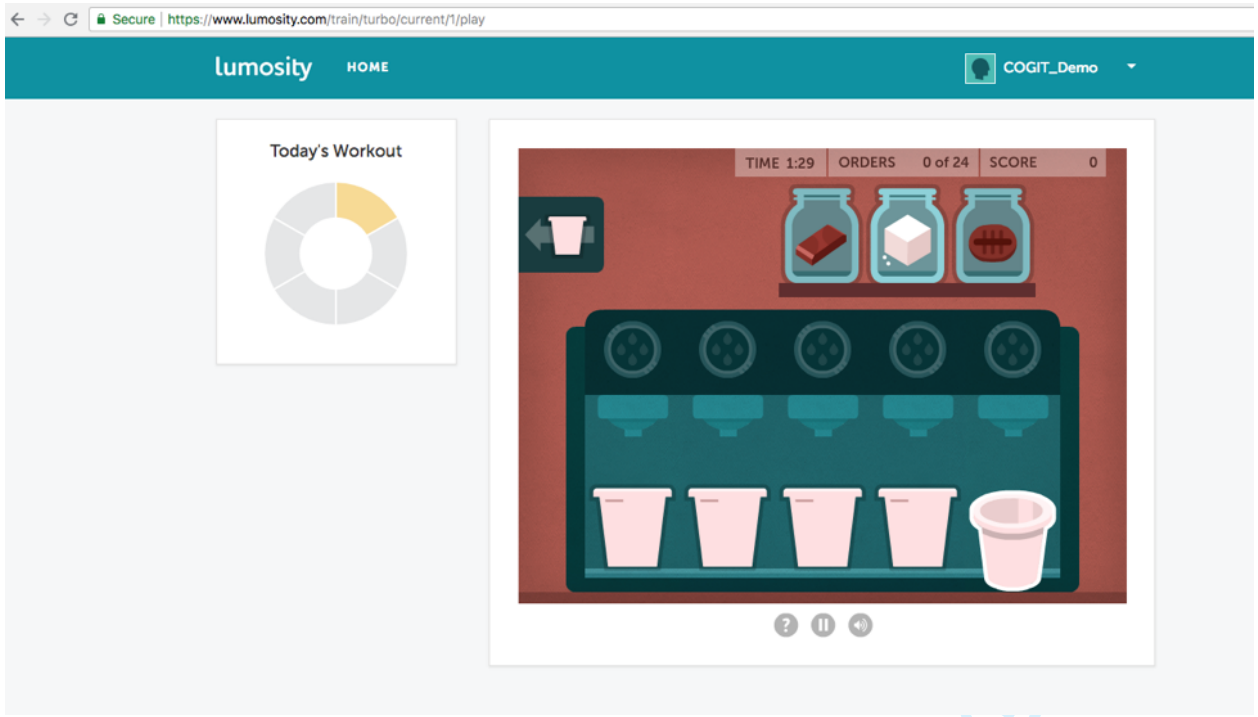
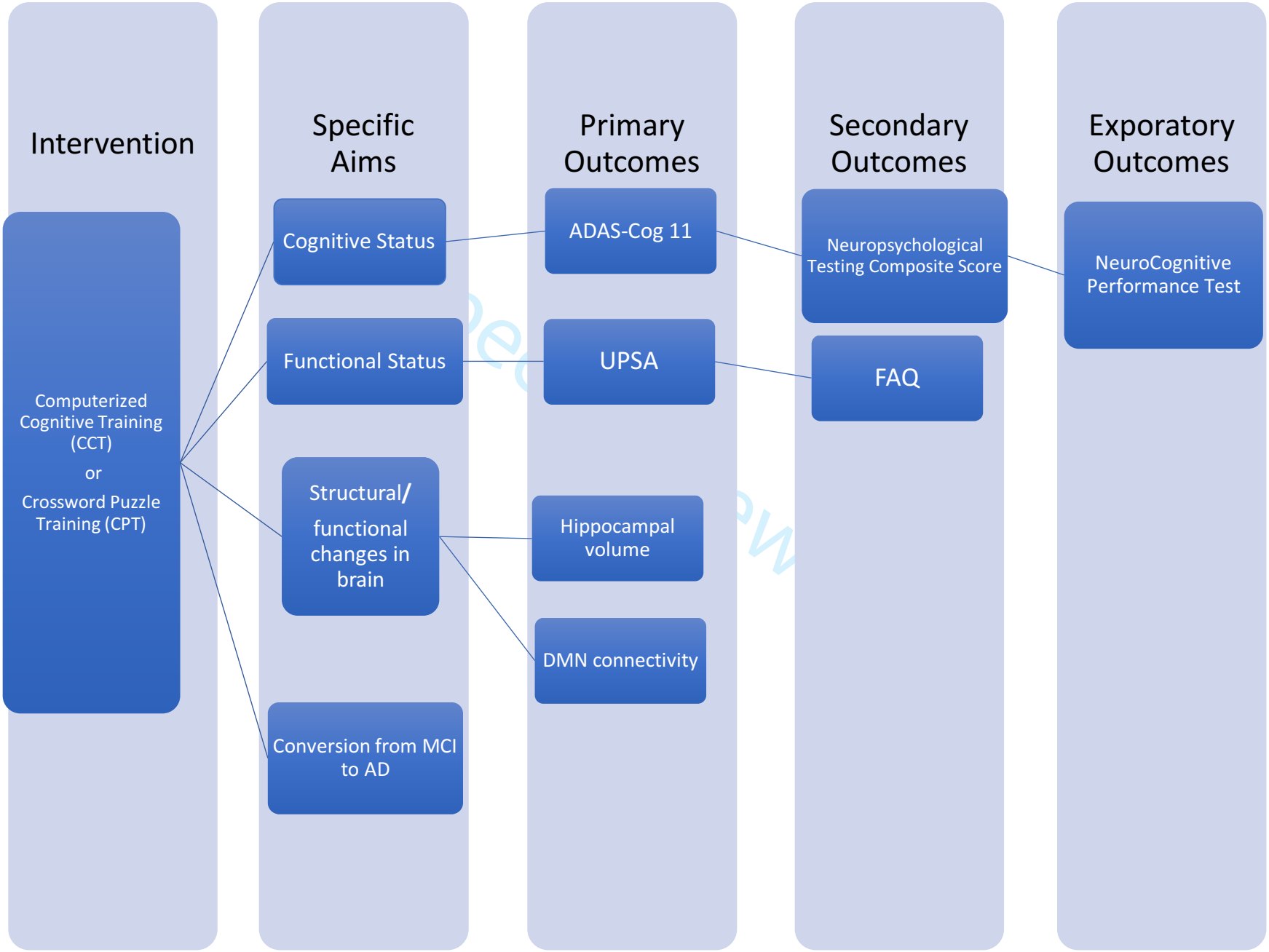
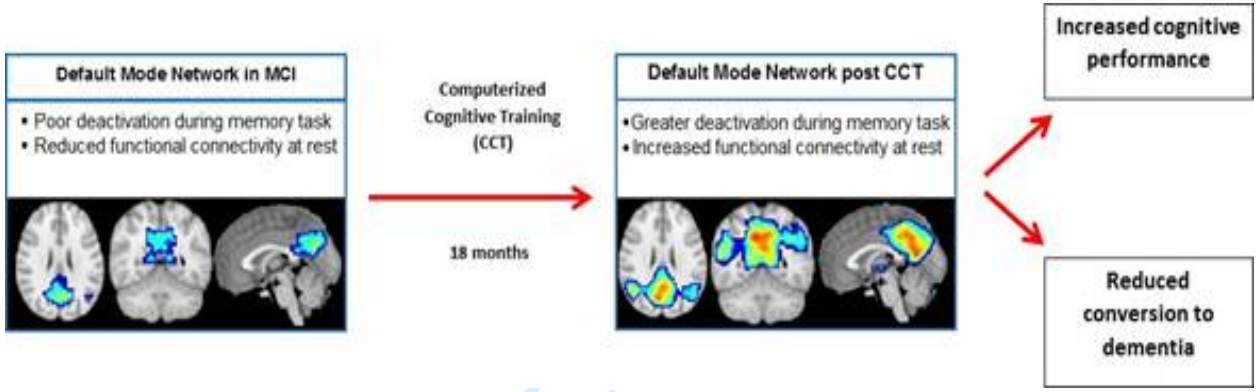





Intervention
Specific Aims
Primary Outcomes
Secondary Outcomes
Exporatory Outcomes
Computerized Cognitive Training (CCT)
or
Crossword Puzzle Training (CPT)
Cognitive Status
Functional Status
Structural/ functional changes in brain
Conversion from MCI to AD
ADAS-Cog 11
UPSA
Hippocampal volume
DMN connectivity
Neuropsychological Testing Composite Score
FAQ
NeuroCognitive Performance Test



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Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	7; 22
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1;22
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	1

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	7;22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18;21
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-6
Objectives	#7	Specific objectives or hypotheses	14-15
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6-19
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-14
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	17-18

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	18-19
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	See note 1
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13; 15-17
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	20
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7; 10-11
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10-12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10-12;14

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-17
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17-18
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	See note 2
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19-20
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19-20
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	21
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	21

Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17; 21
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	21
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	20-21
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7-8; 20
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	18
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20-21
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18; 20
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	10
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	18

Author notes

1. 14-15; 19-20

2. 14-15;19-20

BMJ Open

Cognitive Training and Neuroplasticity in Mild Cognitive Impairment (COG-IT): Protocol for a two-site, blinded, randomized, controlled treatment trial.

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Cognitive Training and Neuroplasticity in Mild Cognitive Impairment (COG-IT): Protocol for a two-site, blinded, randomized, controlled treatment trial.

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ABSTRACT

Introduction: Mild cognitive impairment (MCI) is common in older adults and represents a high-risk group for progression to Alzheimer's disease (AD). Medication trials in MCI have generally failed, but new discoveries with brain plasticity in aging have led to the study of cognitive training as a potential treatment to improve cognitive abilities. Computerized Cognitive Training (CCT) involves computerized cognitive exercises that target specific cognitive abilities and neural networks to potentially improve cognitive functioning through neuroplasticity.

Methods and Analysis: In a two-site study (New York State Psychiatric Institute/Columbia University Medical Center and Duke University Medical Center) we will randomize 100 patients with MCI (WMS-III Logical Memory II score 0-11; MMSE $\geq$ 23) to home-based CCT (suite of exercises: memory, matching, spatial recognition, processing speed) or a home-based active control condition (computerized crossword puzzle training; CPT) with 12 weeks of intensive training followed by regular booster sessions up to 78 weeks. All patients will receive standard neuropsychological and functional assessments in clinic as well as structural/functional brain MRI scans at study entry and endpoint. We will test if CCT, versus CPT, leads to improved cognitive functioning, transfers to functional ability and tasks of everyday life, and impacts hippocampal volume changes and changes in the default mode network (DMN) of the brain measured by resting-state fMRI.

Ethics: The study will be conducted following ethics approval and written informed consent will be obtained from all subjects.

Dissemination/Significance: Study results will be disseminated via publication, clinicaltrials.gov, media and conference presentations. This will be the first controlled long-term trial to evaluate the effects of home-based computerized cognitive training versus computerized crossword puzzle training on not only cognitive abilities, but also functional measures and neural outcomes as determined by MRI indices in patients with MCI. Positive results from trial may support further development of home-based CCT.

Trial Registration: ClinicalTrials.gov Identifier: NCT03205709.

ARTICLE SUMMARY

Strengths and Limitations of this Study

- The study will improve upon limitations of most previous studies by including an "active" control condition, rather than waitlist or control conditions that do not account for engagement and motivation.

- This study will evaluate performance on traditional cognitive and functional assessments (e.g., ADAS-Cog 11, UPSA) in addition to performance on a self-administered, computerized cognitive test, the NeuroCognitive Performance Test (NCPT), which consists of 10 subtests that are online adaptations of widely used neuropsychological tests.

- The trial will utilize a remote internet-based CCT intervention that can be done at home; compared to most existing treatments under investigation, it is easily accessible, relatively inexpensive, non-invasive, and scaled to the skill level of each individual.

- The trial will include evaluation of clinically relevant genetic, brain network, and neuronal loss markers as moderators of outcome; this will be one of the first trials to examine long-term effects on cognition, daily functioning, and neuroplastic changes in DMN with CCT in MCI.

- As our trial will be restricted to English-speaking participants because the online training platform is only available in English, we are unsure how this will generalize to non-English speaking individuals.

- In addition, the inclusion criteria state that the participant must have an at-home desktop or laptop computer, which, in low socioeconomic class homes, is not always available.

INTRODUCTION

Alzheimer's disease (AD) is a major public health concern affecting over 40 million people worldwide and there is an urgent need to develop new treatment modalities to prevent or delay the onset of dementia. Mild cognitive impairment (MCI) is common in older adults and represents a high-risk group for AD, but medication trials in MCI have generally failed. There is no FDA-approved treatment for MCI or to prevent the progression of MCI to AD.

There is growing evidence that a cognitively active lifestyle may reduce rates of dementia. A systematic review of 22 population-based studies found that mental activities may reduce overall incident dementia risk by 46% over a median 7-year period [1]. Computerized Cognitive Training (CCT) provides a novel strategy to improve cognitive performance in MCI by establishing a more cognitively active lifestyle. CCT involves computerized cognitive exercises that target specific abilities to improve cognitive functioning, and this effect is likely to be mediated by neuroplasticity. CCT has been used successfully to improve cognitive functioning in healthy adult populations [2, 3, 4, 5]. In particular, two studies in older healthy controls have garnered much attention. The ACTIVE trial was the first large-scale, randomized trial to show evidence of transfer from cognitive training to improved daily function, but only in participants who completed reasoning or speed of processing focused training, and not memory training [6]. In this ten-year follow up study of 2,832 healthy adults (average age = 73.6), participants were randomized to one of three intervention groups (memory, reasoning, or speed of processing) or a no-contact control group. Booster sessions occurred for 39% of participants in all active groups at 11 and 35 months after initial training, but the cognitive effects of the memory training did not persist over the ten-year follow up period [6]. In a second large, well-publicized online cognitive training study, findings were originally considered to be negative in terms of cognitive gains. However, in an examination of an older subsample, training was effective in improving cognitive abilities and instrumental activities of daily living [7].

In a recent meta-analysis examining CCT in older adults with MCI or dementia, the overall efficacy of cognitive outcomes in MCI was moderate and statistically significant [8]. This pattern was also found for global cognition, verbal learning and memory, nonverbal learning, working

memory, attention, and psychosocial functioning (e.g. depression, quality of life, neuropsychiatric symptoms). However, for the efficacy of cognitive outcomes in patients with dementia, the overall effect was found to be small, though statistically significant.

Early interventions at the stage of MCI, and not dementia, may be more helpful for improving cognition. In fact, Hill et al. [8] concluded that CCT is a feasible intervention for improving cognition in patients with MCI. Transfer effects have also been found in studies evaluating CCT in healthy older adults, supporting the potential for transfer of CCT benefits to daily life [6, 9]. In this study, we will assess for transfer effects by administering the following functional assessments at specific timepoints: Functional Activities Questionnaire (FAQ) and University of California San Diego Performance-Based Skills Assessment (UPSA).

Although CCT has received more support in the past few years as a viable treatment option for older adults with MCI, the brain mechanisms underlying the observed cognitive changes remain elusive. Many studies of CCT that include imaging components have only been conducted with healthy older adults [10, 11, 12, 13]. CCT may promote neuroplasticity in the brain, including in the hippocampus, a key region that supports memory [13, 14, 15, 16]. Additional research needs to be done that evaluates both structural and functional data within a rigorously-conducted clinical trial. In this study, patients will undergo a structural MRI and fMRI at both study entry and exit to assess for changes in hippocampal volume and the default mode network (DMN). The latter is crucial to evaluate in patients with MCI as dysfunction in the DMN has been implicated in the progression of MCI to AD [17]. The DMN is a resting state neural network of several highly interconnected cortical hubs, including the posteromedial parietal, anteromedial frontal, and inferolateral parietal cortices. We have shown that impaired deactivation and functional connectivity in the DMN may be a significant predictor in MCI of poor memory and transition to dementia over a 2-3 year follow-up period [18]. Neuronal dysfunction precedes structural atrophy in AD, and functional magnetic resonance imaging (fMRI) offers the potential for identifying specific patterns of disruption in the memory networks affected early in MCI and AD.

Limitations of prior CCT trials include the inconsistent demonstration of transfer to everyday functioning, reliance on waitlist control conditions as opposed to active control conditions, and lack of long-term follow-up. Most studies have not assessed transfer of cognitive improvement to everyday function or quality of life [19, 20, 21, 22, 23]. While CCT may produce transfers to untrained cognitive domains, the few studies that evaluate transfer to everyday functioning have reported mixed findings [24, 25, 26-29]. This is particularly important given the strong association between cognitive decline and functional disability [30]. Many studies use waitlist control conditions or control conditions that do not account for engagement and motivation in the task [22]. Such designs are biased in favor of the treatment condition because waitlisted subjects are not receiving any form of cognitive treatment and, therefore, may be more likely to drop out of such studies due to lack of engagement and motivation. In the current study, patients will be assigned to one of two cognitively stimulating exercises, computerized cognitive training (suite of exercises) or crossword puzzle training (crossword puzzles). Since one of the purposes of CCT in patients with MCI is to reduce the risk of progression to dementia, longer follow-up times are necessary to be able to accurately capture patient progression. However, most studies have only used no follow-up or short-term follow-ups, with the notable exception of the ACTIVE trial [6, 31-33].

Overall, recent findings in the field suggest that computerized cognitive training could benefit patients at risk for dementia. The current study will build on these findings by implementing a study design with an active control group, a longer trial duration, an increased intensity of computerized cognitive training, examination of generalizability to functional abilities beyond cognitive training skills, structural and functional MRI assessment, and rigorously blinded methodology.

METHODS AND ANALYSIS

Study Design Features and Rationale

One hundred patients clinically diagnosed with mild cognitive impairment (MCI) will be randomized. There will be two sites: New York State Psychiatric Institute/Columbia University Medical Center in New York, NY (NYSPI as lead coordinating site) and Duke University

Medical Center in Durham, NC. Patients will be randomized to one of two computerized cognitively stimulating exercises: crossword puzzle training (CPT) or a suite of exercises (CCT; memory tasks, matching tasks, spatial recognition tasks, processing speed tasks). These patients will be further randomized by MCI type (early MCI or late MCI), age (70 and below or 71 and above), and site (NYSPI/CUMC or DUMC) as the stratification factors and will be followed for 78-weeks. The randomization sequences will be balanced in blocks of random size (2, 4) to prevent clinicians from guessing what the next patient's treatment might be. The term "control" will not be used in the consent form in order to reduce the participant's expectancy bias.

In order to maintain neutrality and mitigate expectancy bias among patients, the informed consent form signed by all patients during the screening visit will not indicate which group is the active group (suite of exercises) or the control group (crosswords). Rather, it will indicate that the patient may be assigned to one of two cognitively stimulating exercises, CCT or CPT.

Role of Sponsor

The study is funded entirely by a National Institute on Aging grant and supervised by a Data Safety Monitoring Board. Using Lumosity, a web-based gaming platform from Lumos Labs, we customized a specific set of CCT and CPT training modules for participants to use in this trial. After a comprehensive review of several CCT modules on the market, we chose these modules from Lumosity due to their large selection of games tailored to specific cognitive domains, their research specific platform, availability of active control condition, availability of the online self-administered NeuroCognitive Performance Test (NCPT), and our previous pilot data in the elderly with this platform. Aside from providing the research platform and technical support at no cost, Lumos Labs provides no financial support for this study and their staff have no significant role in the final study design, study conduct, data interpretation or publication. Patients will not be required to pay for the platform and will not have a post-study commitment to the platform. None of the study team has any financial conflicts with Lumos Labs.

Recruitment, Eligibility, Consent

Patients will be recruited from the current patient caseload of the investigators, referral by neurology, psychiatry, primary care, public health and geriatric medical clinics affiliated with the centers and supplemented by advertisement.

Inclusion/Exclusion Criteria.

Detailed inclusion/exclusion criteria are described in Table 1. Notable inclusion criteria will be age range restriction 55-95 years, subjective cognitive complaints (i.e., memory or other cognitive complaints, e.g., naming/language), Wechsler Memory Scale-III (WMS-III) Logical Memory Story A delayed recall score 0-11, Folstein Mini Mental State Examination (MMSE) score ≥ 23 out of 30, availability of an informant, and access to a home desktop or laptop computer with full access to the internet for the study duration. Patients who have a history of major psychiatric or neurological illness including motor disorders like Parkinson's disease, a dementia diagnosis of any type, contraindication to MRI scan, lack of English-speaking ability, or have been defined as regular online brain training or regular crossword puzzle users (≥ 2 times per week in the past year) will be excluded. Depression will be assessed using the 15-item Geriatric Depression Scale (GDS); a diagnosis of Major Depressive Disorder is exclusionary.

Mild Cognitive Impairment Criteria

Mild cognitive impairment (MCI) and type of MCI (early MCI or late MCI) will be assessed by the delayed recall score of WMS-III Logical Memory and by the score on the MMSE. On Logical Memory II Story A, a score from 0-11 will indicate cognitive impairment, per the Alzheimer's Disease Neuroimaging Initiative (ADNI) criteria. MCI type will be determined from this score combined with years of education of the patient. Early MCI (eMCI) will be defined as a delayed recall score of 3-6 with 0-7 years of education, score of 5-9 with 8-15 years of education, and score of 9-11 with 16 or more years of education. Late MCI (lMCI) will be defined as a delayed recall score of ≤ 2 with 0-7 years of education, score of ≤ 4 with 8-15 years of education, and score of ≤ 8 with 16 or more years of education. For both eMCI and lMCI, everyday function must be well preserved for study inclusion. A MMSE score ≥ 23 will also be required to indicate mild cognitive impairment, and this is required for study inclusion.

Length of Clinical Trial

Most transitions from MCI to AD typically occur within three years of follow-up after the diagnosis of MCI is made [34]. We chose 18-months as the length of this clinical trial to decrease dropouts that can occur in a very long controlled trial. Since this study is considered low risk, we do not anticipate participants to suffer harm from trial participation.

Treatment Regimen

Enrolled participants will come to the clinic for five scheduled visits (Weeks 0, 12, 32, 52, and 78) and will receive at least three scheduled phone calls with research staff (Weeks 20, 42, and 64). Participants will be enrolled into the study after screening for eligibility and consent is signed. The randomization will be assigned by the statistician and then carried out by the unblinded research coordinator, with individuals stratified by MCI type, age group, and site.

Randomization.

The blinded research coordinator (at NYSPI or Duke) will complete the Training Group Randomization Form to indicate the following information for the patient: site, age, and MCI type. This form will be verified by the unblinded research coordinator at NYSPI, who will then assign a study ID to that patient, using a pre-populated form from the statistician's randomization assignment. The order of the study ID assignment will determine which study condition the patient will receive: CPT or CCT. The Lumosity account information will be generated after the MRI has been completed and quality checked. Lumosity account credentials will include a research-specific COGIT ID email address and password, which will enable users to log into an account specific to their study condition.

Randomization will be complete when the patient logs into his/her account for the first time at the baseline visit and sees which condition he/she is in. At this visit, patients will be trained by unblinded study staff in their assigned training condition. Eighteen modules were selected to target various cognitive domains: (A) Memory (Tidal Treasures, Familiar Faces, Memory Matrix) (B) Processing Speed (Speed Match) (C) Response Inhibition (Color Match) (D) Verbal Fluency/Vocabulary Proficiency (Word Bubbles, Word Snatchers, Editor's Choice, Continuum) (E) Planning/Divided Attention (Train of Thought, Brain Shift, Trouble Brewing, Disillusion) (F) Visual Interference (Lost in Migration, Ebb and Flow, Masterpiece) (G) Identification (River

Ranger) (H) Visualization (Speed Pack). These cognitive domains were chosen as they are areas that are often impaired in patients with MCI and thus represent areas that can be targeted for improvement [35]. Verbal Fluency and Vocabulary Proficiency tasks were included to promote verbal learning in the CCT group. Each CCT session will consist of a random selection of six modules. Participants in the CCT condition are not allowed to choose the games, and are not allowed to skip over or change the suite of games. The Lumosity platform will scale difficulty by using the patient's Lumosity Performance Index (LPI). The LPI will consider three areas for each patient. The Game Performance Index will be determined by reviewing score distributions for each game. The Cognitive Area Performance Index (speed, memory, attention, flexibility and problem solving) will be calculated using a weighted average of the Game Performance Index. Thirdly, the overall Cognitive Performance Index will be calculated using a weighted average of the Game Performance Indices from all cognitive areas. A complete list of selected CCT games are described in Table 2. Crosswords engage primarily verbal abilities and perhaps, executive and attentional mechanisms. The Lumosity games target different cognitive domains, such as speed of processing and memory, as well as verbal abilities. The effect that these different trainings have on the so-called far transfer problem will of course be of major interest. There should be no case in which an emergency unblinding will need to take place, as the blinded intervention is a computerized intervention.

Participants in the computerized cognitive training group and the crossword puzzle training group will spend the same amount of time on the platform during the intensive training phase, which will consist of four 30-minute training sessions per week for 12 weeks. Participants are not required to have any particular level of computer skills for study inclusion; however, at the initial baseline training, all participants will be trained on how to successfully access the training platform, and how they could obtain help both from research staff and their informant throughout the study. For both groups, responses will be entered via mouse and keyboard. For the crossword puzzle training group, questions will not need to be completed in order and there will not be any feedback for the accuracy of the response at the time of entry by the participant. Upon completion of the CCT suite of exercises after 30 minutes, participants will receive a score. Similarly, after 30 minutes the crossword training will automatically end. If a participant were to

finish an entire crossword puzzle before the 30-minute cutoff, they would be directed to another crossword puzzle to ensure they complete a total of 30 minutes.

Following the intensive training phase of 12 weeks, participants will be instructed to complete six booster sessions. Each booster session will consist of four CCT/CPT sessions. Booster sessions will be completed at weeks 20, 32, 42, 52, 64, and 78. At weeks 32, 52, and 78, patients will complete three booster sessions at home and complete the fourth session in-clinic with research staff. At weeks 20, 42, and 64, patients will complete all four booster sessions at home. Generally, in previous cognitive training studies, booster sessions have been limited. For instance, the ACTIVE trial had two booster sessions, each consisting of four 75-minute trainings at 11 and 35 months. During the course of the trial, booster sessions included a total of 8 trainings, for a total of 10 hours [6]. In contrast, COGIT will have six booster sessions (24 total training sessions each lasting 30 minutes) over 15 months. Thus, COGIT will include 12 hours total for booster sessions during the trial. The ACTIVE trial only required compliant participants to complete the booster sessions, whereas all participants will complete booster sessions in the COGIT study [6].

Clinic Based Cognitive, Functional, and Smell Assessments.

At baseline (week 0) The Alzheimer's Disease Assessment Scale-Cognition Subscale 11 (ADAS-Cog 11) will be administered, in addition to the following neuropsychological test battery: WAIS-III Block Design (to assess visuospatial skills), Digit Symbol Substitution Test (DSST) (to assess attention), Trail Making A & B (to assess attention and executive function), Verbal Fluency and 15-item Boston Naming Test (to assess language), Auditory-Verbal Learning Test (to assess verbal learning and memory), and WMS-III Visual Reproduction Test (to assess nonverbal learning and memory). In addition, the UPSA and University of Pennsylvania Smell Identification Test (UPSIT) will be administered. Testing fatigue is mitigated by allowing participants to take breaks during the testing. If there is missing data from one time point, the study team will attempt to bring the participant back to the clinic within the allowed window to complete missing measures. The FAQ will be administered to the patient's informant, either during the study visit or shortly after the visit over the phone.

Self-Administered Cognitive Test Battery.

Another unique aspect of the study is the use of the NCPT, an online, computerized, self-administered battery developed by Lumosity. It will test various cognitive domains outlined in the Study Measures section. The NCPT will allow us to examine the efficacy of a self-administered test, in combination with standardized, clinic-based neuropsychological tests.

Timeline of Longitudinal Assessments

At in-clinic visits (baseline and weeks 12, 52, and 78), the same neuropsychological battery of testing will be completed. At the week 12 and week 78 visits, the patient will be asked to complete the User Engagement Scale, which will be adapted to capture usage of a computerized platform. This scale will measure aspects of engagement, usability, and satisfaction with the computerized platform on a 5-point Likert scale. Week 20 will be a phone interview between study physician/neuropsychologist and patient to follow-up on how the patient has been doing, and to remind the patient to complete a booster session.

Blinded Training Procedure

The blinded research coordinator will administer the full neuropsychological test battery, including the UPSA and FAQ. The blinded clinician will complete the Diagnosis Form and the Contributing Features to MCI form after clinical interview and review of the neuropsychological testing. The unblinded research coordinator will administer the initial computerized training and all subsequent booster sessions to patients in the clinic. To track type of games/crossword puzzles and amount of time that the subject spends doing the games/crossword puzzles, only unblinded study coordinators receive reports from Lumosity each week. If the Lumosity reports of computer games/crosswords access do not match the subject's assigned instructions, the unblinded coordinator then contacts the subject to guide and ensure adherence to the protocol.

Hypotheses

See Figure 1 for a Conceptual Model of specific study aims and outcome measures. The primary aim of the study is to assess change in cognitive and functional status over 18 months in MCI patients comparing the CCT and CPT groups. Hypothesis 1: MCI patients randomized to CCT will show better cognitive outcomes on the ADAS-Cog 11 (primary outcome measure),

Neuropsychological Testing Composite score (secondary outcome measure), and NCPT (exploratory outcome measure) compared to active control (CPT). Hypothesis 2: MCI patients randomized to CCT will show better functional outcomes as assessed by the UPSA (primary functional outcome) and FAQ (secondary functional outcome) by the end of the 18-month trial compared to active control. Hypothesis 3: brain pathology (smaller hippocampal volumes, lower odor identification scores on the UPSIT, ApoE e4 allele present) will moderate the relationship between treatment assignment and cognitive and functional outcomes.

The secondary aim of the study is to examine the effects of CCT on resting-state DMN connectivity as well as other networks modulated by CCT effects. Hypothesis 1: MCI patients randomized to CCT will demonstrate greater change in an index of DMN functional connectivity compared to patients randomized to active control. Hypothesis 2: indicators of brain pathology (smaller hippocampal volumes, lower odor identification scores on the UPSIT, ApoE e4 allele present) will moderate the relationship between change in the DMN and treatment assignment.

The tertiary aim of the study is to examine differences in rates of progression to dementia and AD in the two randomized treatment groups, recognizing that if progression to these outcomes is uncommon there will be insufficient statistical power. Hypothesis 1: the proportion converting to dementia will be lower in the CCT group compared to active control.

Study Measures

Study measures with time-points of administration are listed in Table 3. The MMSE will be administered at screen and each subsequent in-clinic visit using five different versions of the three-word recall item to reduce practice effects [36]. The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) and The Framingham Stroke Risk Scale will be completed by the study physician at screen and week 78 to assess for cardiovascular disease risk factors and other medical conditions.

The Geriatric Depression Scale will be administered at screen and each subsequent in-clinic visit to assess for depression. If GDS is greater than 5 at any visit, the patient will be evaluated by a psychiatrist and an appropriate clinical referral will be made, if needed, for treatment of

depression. The Cognitive Reserve Index is a brief questionnaire that will be administered by the research coordinator at screen and will evaluate the cognitive reserve of an individual by means of the compilation of information as it relates to his/her adult life.

At screen, the research coordinator will be responsible for administering the History of Game Use Questionnaire, Physical Activity Assessment, and WMS-III Logical Memory I & II. The History of Game Use Questionnaire will be administered again at weeks 12 and 78 to ensure that patients are not partaking in any other types of cognitive training games while in the study.

At screen and week 78, patients will undergo an MRI scan of the brain. The MRI scan will include the following sequences: Localizer, high-resolution T1-weighted IR prepped 3DSPGR, and T2 FLAIR, and GE-EPI resting-state fMRI scans.

At weeks 0 and 78, the UPSIT will be completed by the patient, which is a 40-item scratch and sniff multiple-choice olfactory identification test.

At each in-clinic visit, apart from week 32, the ADAS-Cog 11 and full neuropsychological test battery will be administered. The NCPT will be administered at weeks 0, 12, and 78. The cognitive domains measured by the NCPT are memory (visuo-spatial working memory, short-term memory), processing speed (visual search, psychomotor speed), problem solving (logical reasoning, numerical calculation), attention (selective, divided), and flexibility (response inhibition, task-switching). The assessments, 10 total "subtests," are online adaptations of widely used neuropsychological tests whose test properties are not affected by shifting to computerized administration [37].

The neuropsychological test battery includes: WAIS-III Block Design, Digital Symbol Substitution (DSST), Trail Making A & B, Verbal Fluency and 15-item Boston Naming Test, Auditory-Verbal Learning Test (AVLT), and WMS-III Visual Reproduction Test. For word learning lists, the neuropsychological testing materials provide different but parallel word lists, so as to avoid practice effects in MMSE and ADAS-Cog, but not for AVLT. With respect to the latter we did not adopt this approach because we were concerned that different forms have not

been established as equivalent in difficulty level. The UPSA will be administered only at weeks 0, 32, and 78 due to the high tendency for practice effects. It is a performance-based measure of functional abilities that includes measures of simulated real-world activities; for example, planning a trip to the beach, remembering documents to bring to a medical appointment, and dialing a phone number. When a participant wears corrective lenses during the testing battery, this is documented in the participant's research chart.

At screen and weeks 12, 32, 52, and 78 the participant will meet with the study physician or the neuropsychologist to assess for illness progression and adverse events. Adverse events that are spontaneously reported to research coordinators at any clinic visit will be discussed with the study physician or the neuropsychologist in order to determine how to proceed. Adverse events and subsequent steps to deal with the adverse events will be documented in the patient chart and serious adverse events will be reported to the Data Safety and Monitoring Board and study sponsor, National Institute on Aging.

Additionally, the research coordinator will conduct an interview with the informant at, or shortly after, each visit to complete the FAQ.

Criteria for Early Discontinuation

We expect early discontinuation to occur because of one or more of the following reasons: (1) the patient's decision not to continue the computerized training (CCT or CPT) due to lack of interest, motivation, or available time; (2) unavoidable circumstances, e.g., moving residence and unwillingness to return for in-person evaluations; (3) investigator decision to terminate; (4) death or prolonged hospitalization for medical reasons. We will not terminate participation for non-adherence because even if the patient is non-adherent to the protocol, we will document level of adherence (done electronically in this computerized training protocol) and still include the patient's data in the analyses based on the intent-to-treat principle.

Data Management

Data entry will be completed by Program Managers, Clinical Research Coordinators, and Research Assistants on the study protocol. Data entry/cleaning will be done throughout the

project. The data collected in this study will be monitored by the Data Coordinating Center at NYSPI. The unit will work closely with the research assistant/coordinator and the Principal Investigator to facilitate independent auditing of primary subject records. The database will provide reports indicating all modifications that have been made in the database together with paper communications (fax, e-mail) confirming and authorizing these modifications. Access to the data system is available only to authorized users, with multiple levels of security including user id/password authentication via MS Active Directory overseen by experienced IT personnel. Other authorized users with direct access to the data system will be Data Coordinating Center (DCC) staff. DCC data-related operations and the SIR/Citrix system have been certified by Columbia University's Information Security Office. The dataset will not be published in a data repository.

Genetic Testing

Apolipoprotein E (ApoE) genetic analysis on a blood sample will be done through the laboratory of the Human Genetics Resources Core (HGRC) at Columbia University Medical Center. We will assess the ApoE ε4 allele as potentially associated with response to CCT; a prior trial found an association between the ε4 allele and cognitive improvement on donepezil [38].

Concomitant Medications

Putative cognitive enhancers, narcotics, all classes of psychotropic medications, and over 20 other classes of commonly prescribed and over the counter (and alternative) medications will be documented in a rating form at screen and subsequent in-clinic visits. An exclusion criterion will be daily use of medications known to have a negative impact on cognition: high-dose narcotics, anticholinergics, and benzodiazepines in lorazepam equivalents ≥ 1 mg daily. During the first 12 weeks of the study, the intensive cognitive training phase, patients are encouraged not to change any of their medications, unless clinically indicated.

Statistical Analysis and Sample Size

We powered our trial to detect an effect size at 18 months of d=.58 (80% power). This effect size is more conservative than published treatment changes associated with CCT (for instance, see [39]). We assume that dropout is distributed uniformly across waves of follow-up assessments

(with 5% attrition between each consecutive pair of the 5 major time-points, i.e. 20% by 18 months).

Outcome Measures (Primary and Secondary Hypotheses Testing).

Aim 1 Hypothesis 1 and 2. MCI patients on CCT will show a lower rate of cognitive and functional decline compared to MCI patients on active control by the end of the 18-month trial. We will use generalized linear mixed effects models of cognitive and functional measures collected repeatedly across the 78 weeks according to the schedule (see Table 3). For example, cognitive measure$_{ik}$ = $\beta_0 + \beta_1$ Time$_{ik}$ + β_2 Group$_i$ +β_3 (Group$_i$ x Time$_{ik}$) + v_{0i} + v_{1i} Time$_{ik}$ + ε_{ik} where Group$_i$ indicates treatment group for subject i (Group = 1 CCT, 0 for control), k = time (baseline, 12 weeks, 20 weeks, 52 weeks, 78 weeks), and v_{0i} is a subject-specific random intercept. Time will be treated as categorical if linearity is not plausible and group effects at 18 months can be tested by forming contrasts from the fitted model. Potential site differences will be evaluated using descriptive statistics and site will be included in all analyses as a covariate, as will other stratification variables including age group and MCI type at baseline.

Aim 2 Hypothesis 1. MCI patients randomized to CCT will demonstrate either more of an increase or less of a decrease in DMN connectivity (goodness-of-fit [GOF] index scores) compared to patients randomized to active control. To test this hypothesis, we will use a repeated measures Analysis of Covariance (ANCOVA) with time (baseline vs. post treatment) as the repeated measure, DMN connectivity as an outcome, treatment condition (CCT vs CPT) as a predictor, and site, age, and MCI status at baseline as covariates.

Moderating Effects in Aim 1 Hypothesis 3 and Aim 2 Hypothesis 2. As a part of our exploratory analyses, we will examine specific potential moderators: Apolipoprotein E ε4 allele, MRI indices, UPSIT. To show, for example, that baseline hippocampal volume is a moderator, we will test its interactive effect with treatment on outcomes. Moderator and moderator-interaction terms can be easily accommodated in the mixed effects regression models described in Aim 1. Hypotheses 1 and 2. A similar approach will be used by adding moderator and moderator x Group interactions to the ANCOVA described in Aim 2 Hypothesis 1. The results must be

interpreted with the caveat that there may not be enough power to assess these interactions, especially for moderators with low prevalence.

Aim 3 Hypothesis 1. The proportion diagnosed with dementia during follow-up will be lower in the CCT group compared to active control. Logistic regression will be used to test the binary outcome of dementia status at 18 months predicted by treatment group controlling for site, age group, and MCI type at baseline.

Missing data is managed statistically through use of mixed model repeated measures analyses.

Sample Size.

A power analysis was conducted using the RMASS program for longitudinal studies, which determined that a total sample size of 100 participants will provide a sufficient effect size to evaluate our hypotheses. We have two primary outcome measures (i.e., multiple outcome measures), namely ADAS-Cog and the UPSA. For multiple outcome measures, statistical significance on any one measure is meaningful and there is no need to correct for multiple comparisons (unlike co-primary outcome measures). All other outcome measures are secondary and exploratory.

Patient and Public Involvement

Patients will first be involved in the research after study design is finalized by the study investigators. At this stage, patients will be referred by physicians or self-referred from online and newspaper advertisements for their initial screening visit. The patients will not be involved in study design, study recruitment or conduct, or dissemination of study results. We will assess the burden of the trial intervention on patients using the User Engagement Scale and the Participant/Informant Expectancy Scales. Patients will not be invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients will not be invited to contribute to the writing or editing of this document for readability or accuracy.

ETHICS

This study has been approved by NYSPI IRB, Duke University IRB, and Queens College IRB. All COGIT patients at entry will be required to have the capacity to provide informed consent and sign the IRB-approved informed consent form. Local IRB and state regulations for consent will be followed. Patient confidentiality as it pertains to potential and enrolled participants before, during, and after the trial will be collected, shared, and maintained strictly according to HIPAA law.

Important protocol modifications will be communicated to the Data Safety and Monitoring Board, NYSPI IRB and Duke University IRB, and updated online for trial registries.

The research data on specific moderators, including UPSIT and apolipoprotein E genotyping, will not be not released to the patient, and this will be specified in the consent form. The cognitive testing results and clinical reading of the MRI scan will be released to the patient (and the patient's primary physician, if requested); the MRI research volumetric ratings and fMRI findings will not be released.

Data Safety and Monitoring Board (DSMB)

Three NIA-approved independent experts with expertise in conducting clinical trials in mild cognitive impairment will form the DSMB. All serious adverse events (SAEs) will be reported to the DSMB. The DSMB will audit the trial conduct, review all SAEs, participate in a teleconference twice a year to determine if the study should continue, and then will provide an actionable report to the Principal Investigator. This process will be independent from the investigators.

DISSEMINATION

The study results will be disseminated through publications and conference presentations as well as on public websites, including clinicaltrials.gov. Researchers will be eligible for authorship after consideration by the principal investigators; no professional writers will be utilized.

SIGNIFICANCE

This will be one of the first investigator-blinded and controlled long-term trials to evaluate the effects of home-based computerized cognitive training versus computerized crossword puzzle training on cognitive, functional, hippocampal and default mode network connectivity neural outcomes in MCI. Positive results from this pilot trial may support the further development of home based cognitive training and self-assessments in people at risk for dementia.

The results will help inform the design of a more powerful RCT in many ways: determine sample size for a multicenter trial, identify subgroups more likely to benefit, identify subdomains and exercises most likely to improve, optimize training dose and duration, learn how subjects engage, identify gender effects, model slopes and long-term benefits, assess value of a self-administered cognitive test, understand brain networks affected, and examine the potential moderating role of apolipoprotein E ε4 status on CCT outcome.

AUTHOR CONTRIBUTIONS

DPD, PMD, JRP, and JRS conceived and designed the study and obtained funding. All other authors assisted with elements of study design, database, and conduct. HA contributed to statistics design and JRP to design of MRI component. DPD is the overall study PI and PMD is the PI at the Duke site. JLD and LSP did the initial draft of the paper and all authors contributed to manuscript edits and revisions.

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COMPETING INTERESTS

JLD, LSP, TEG, SNR, SNT, EP, JRP, CAH, HFA, JRS, NAK have no competing interests. PMD has received research grants and advisory fees from several companies in this field for other studies, and owns shares in several companies whose products are not discussed here. DPD serves as a consultant on advisory boards to Acadia, Avanir, Genentech, Eisai, and Neuronix.

Table 1. Inclusion/Exclusion Criteria

Inclusion Critera
1. Males and females 55 to 95 years of age (inclusive) at the time of informed consent.
2. Subjective cognitive complaints, i.e., memory or other cognitive complaints, e.g., naming/language.
3. Meets criteria for cognitive impairment (CI) defined as scores >1 SD below standardized norms on memory function as identified by the Wechsler Memory Scale (WMS) III Logical Memory delayed recall score.
4. Folstein Mini Mental State (MMSE) score ≥ 23 out of 30.
5. A family member or other individual who is in contact with the patient and consents to serve as informant during the study; this could be a telephone informant in case of patients who do not have a live-in informant or close significant other.
6. Access to a home desktop or laptop computer at acceptable speed for the study duration.
Exclusion Criteria
1. Diagnosis of dementia of any type.
2. Current clinical evidence of schizophrenia, schizoaffective disorder, major depression, psychosis, or bipolar I disorder (DSM-IV TR criteria).
3. Active suicidal ideation or plan.
4. Current or recent (past 6 months) alcohol or substance use disorder (DSM-5 criteria).
5. Clinical stroke with residual neurological deficits. While we will not exclude patients with cerebrovascular disease, we will not include patients who have had a stroke with residual clinical deficits because it is not clear that this type of patient is similar to the MCI patient generally, and clear-cut neurological impairment, e.g., hemiplegia/hemiparesis or speech impairment, may compromise the patient's ability to do the CCT or active control procedures and to complete the neuropsychological tests.
6. Use of medications known to have a negative impact on cognition: benzodiazepines in lorazepam equivalents ≥ 1 mg daily, narcotics, anticholinergics. Other patients receive medications that may be associated with cognitive impairment but are rarely considered the likely etiology, e.g., theophylline, nifedipine, beta blockers; they will not be excluded. Patients receiving other psychotropic medications not expected to have a material impact on cognition, e.g., SSRIs and SNRIs will be eligible.
7. Presence of any of the following disorders: a) CNS infection, with CSF evidence of meningitis, encephalitis, or other infectious process; b) dementia of any type; c) Huntington's disease; d) Multiple sclerosis; e) Parkinson's disease; f) Other neurologic disorders with focal signs, e.g., amyotrophic lateral sclerosis; g) Mental retardation.
8. Acute, severe unstable medical illness. For cancer, acutely ill patients (including those with metastases) will be excluded, but past history of successfully treated cancer will not result in exclusion.
9. Contraindication to MRI scan: pacemaker, metal implants following surgery, any other contraindication to MRI. Eligibility for the MRI scan is a requirement for the study.
10. UPSIT exclusions: current smoker > 1 pack daily, current upper respiratory infection (retested as soon as the infection clears). UPSIT scores are reduced in schizophrenia, Parkinson's disease and Parkinson's related conditions; these disorders are exclusion criteria for this study. Patients with UPSIT exclusions will not receive the UPSIT but will continue to participate in all other aspects of the study.
11. Patients lacking English-speaking ability as determined by self-report and clinical evaluation.
12. Regular online brain training or regular crossword puzzle user, defined as doing these procedures at a frequency of twice weekly or greater during the year prior to screening. Eligible participants who join the trial are instructed not to do these procedures on their own during the trial, i.e., independent of the study.
13. Participation in another intervention trial for cognitive impairment.

Table 2. Complete list of CCT game battery and associated cognitive domains (provided by Lumos Labs)

Game Name	Cognitive Domain
Tidal Treasures	Working Memory i.e., delayed, non-matching to sample; self-ordered pointing
Speed Match	Processing Speed
Color Match	Response Inhibition
Word Bubbles	Verbal Fluency
Train of Thought	Planning Divided Attention Multiple attractions
Familiar Faces	Episodic Memory
Memory Matrix	Episodic Memory; Visuospatial memory
Lost in Migration	Visual Interference
Brain Shift	Task Switching
Trouble Brewing	Multitasking, divided attention, sustained attention, planning, working memory
Ebb and Flow	Task switching, semantic and visual interference
Masterpiece	Mental rotation; visualization; spatial reasoning
River Ranger	Identification
Word Snatchers	Vocabulary proficiency
Speed Pack	Visualization
Disillusion	Task Switching
Editor's Choice	Vocabulary Proficiency
Continuum	Vocabulary Proficiency

Table 3. Table of Study Procedures

Measure	Screen	Baseline	12 Weeks	20 Weeks Phone Interview	32 Weeks	42 Weeks	52 Weeks	64 Weeks	78 Weeks
ADAS-Cog11		X	X				X		X
ApoE & blood test	X								
CIRS-G	X								X
Cognitive Reserve Index	X								
Cognitive Training or Control training booster session			X	X	X	X	X	X	X
Contributing Features to MCI		X			X				X
Demographics History (Patient Tracking Form)	X								
Diagnosis Form			X		X				X
Digit Symbol Substitution Test		X	X				X		X
Expectancy Scale (Participant & Informant)		X			X				X
Family History	X								
FAQ		X	X	X	X		X		X
Framingham Stroke Risk	X								
Geriatric Depression Scale	X		X		X		X		X
History of Game Use Questionnaire	X		X						X
Inclusion/ Exclusion Form	X								
Informed Consent	X								
Medications (Chart List & Database List)	X		X		X		X		X
MMSE	X		X		X		X		X
MRI Scan of Brain	X								X
NCPT online cognitive performance test		X	X						X
Neuropsychological Battery: AVLT, Block Design, Verbal Fluency, Visual Reproduction, Boston Naming Test, Trails A & B		X	X				X		X
Physical Activity Assessment	X								
UPSA		X			X				X
UPSIT		X							X
User Engagement Scale			X						X
WMS-III Logical Memory I & II	X								

Table 3 Legend: ADAS-Cog 11 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 11. ApoE = Apolipoprotein E gene. CIRS-G = Cumulative Illness Rating Scale for Geriatrics. MCI = Mild Cognitive Impairment. FAQ = Functional Assessment Questionnaire. MMSE = Mini Mental Status Examination. MRI = Magnetic Resonance Imaging. NCPT = NeuroCognitive Performance Test. AVLT = Auditory Verbal Learning Test. UPSA = UCSD Performance-Based Skills Assessment. UPSIT = University of Pennsylvania Smell Identification Test. WMS-III = Wechsler Memory Scale-III.

Figure 1. Conceptual Model

In the intervention phase patients are randomly assigned to either CCT or CPT. To evaluate cognitive status, the primary outcome measure will be the ADAS-Cog 11, the secondary outcome measure will be the Neuropsychological Testing Composite Score, and the exploratory outcome measure will be the NeuroCognitive Performance Test. To evaluate functional status, the primary outcome measure will be the UPSA and the secondary outcome measure will be the FAQ. To evaluate changes in neural circuitry, the primary outcome measures will include hippocampal volume (MRI) and DMN connectivity (fMRI).

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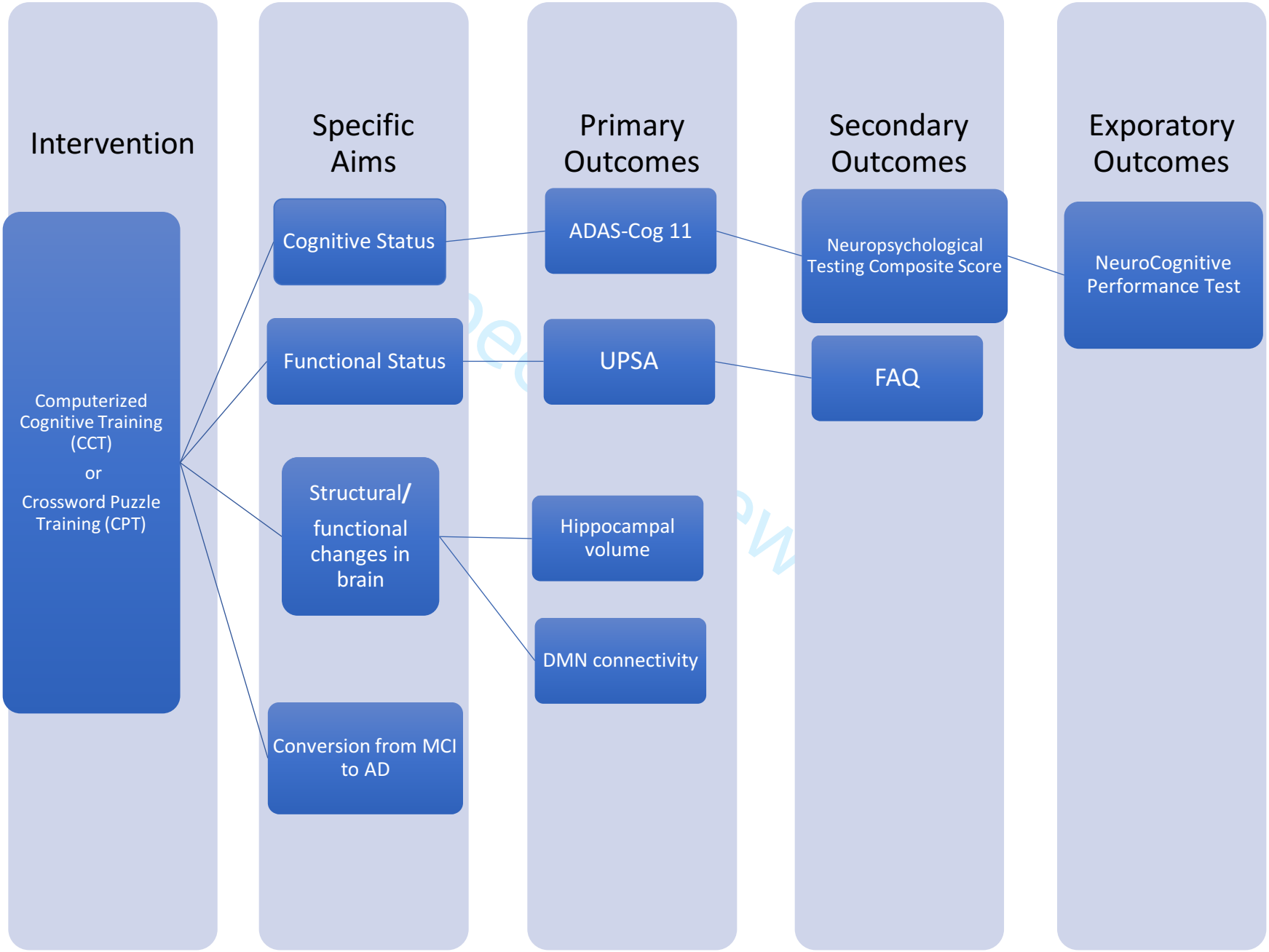
Intervention
Specific Aims
Primary Outcomes
Secondary Outcomes
Exporatory Outcomes
Computerized Cognitive Training (CCT)
or
Crossword Puzzle Training (CPT)
Cognitive Status
Functional Status
Structural/ functional changes in brain
Conversion from MCI to AD
ADAS-Cog 11
UPSA
Hippocampal volume
DMN connectivity
Neuropsychological Testing Composite Score
FAQ
NeuroCognitive Performance Test

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	7; 20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1;20

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	7;20
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18-19
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-6
Objectives	#7	Specific objectives or hypotheses	12-13, 16-17
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6-16
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-14
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	15
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11-12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13, 16-17
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13-15, 23
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16-18
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 16

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9, 12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10, 12
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-17
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11, 13-15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	15

		(eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15, 19
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14-15; 19
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	18-19
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 9
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19-20
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	16

Author notes

BMJ Open

Cognitive Training and Neuroplasticity in Mild Cognitive Impairment (COG-IT): Protocol for a two-site, blinded, randomized, controlled treatment trial.

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Cognitive Training and Neuroplasticity in Mild Cognitive Impairment (COG-IT): Protocol for a two-site, blinded, randomized, controlled treatment trial.

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ABSTRACT

Introduction: Mild cognitive impairment (MCI) is common in older adults and represents a high-risk group for progression to Alzheimer's disease (AD). Medication trials in MCI have generally failed, but new discoveries with brain plasticity in aging have led to the study of cognitive training as a potential treatment to improve cognitive abilities. Computerized Cognitive Training (CCT) involves computerized cognitive exercises that target specific cognitive abilities and neural networks to potentially improve cognitive functioning through neuroplasticity.

Methods and Analysis: In a two-site study (New York State Psychiatric Institute/Columbia University Medical Center and Duke University Medical Center) we will randomize 100 patients with MCI (WMS-III Logical Memory II score 0-11; MMSE $\geq$ 23) to home-based CCT (suite of exercises: memory, matching, spatial recognition, processing speed) or a home-based active control condition (computerized crossword puzzle training; CPT) with 12 weeks of intensive training followed by regular booster sessions up to 78 weeks. All patients will receive standard neuropsychological and functional assessments in clinic as well as structural/functional brain MRI scans at study entry and endpoint. We will test if CCT, versus CPT, leads to improved cognitive functioning, transfers to functional ability and tasks of everyday life, and impacts hippocampal volume changes and changes in the default mode network (DMN) of the brain measured by resting-state fMRI.

Ethics: The study will be conducted following ethics approval and written informed consent will be obtained from all subjects.

Dissemination/Significance: Study results will be disseminated via publication, clinicaltrials.gov, media and conference presentations. This will be the first controlled long-term trial to evaluate the effects of home-based computerized cognitive training versus computerized crossword puzzle training on not only cognitive abilities, but also functional measures and neural outcomes as determined by MRI indices in patients with MCI. Positive results from trial may support further development of home-based CCT.

Trial Registration: ClinicalTrials.gov Identifier: NCT03205709.

ARTICLE SUMMARY

Strengths and Limitations of this Study

- The study will improve upon limitations of most previous studies by including an "active" control condition, rather than waitlist or control conditions that do not account for engagement and motivation.

- This study will evaluate performance on traditional cognitive and functional assessments (e.g., ADAS-Cog 11, UPSA) in addition to performance on a self-administered, computerized cognitive test, the NeuroCognitive Performance Test (NCPT), which consists of 10 subtests that are online adaptations of widely used neuropsychological tests.

- The trial will utilize a remote internet-based CCT intervention that can be done at home; compared to most existing treatments under investigation, it is easily accessible, relatively inexpensive, non-invasive, and scaled to the skill level of each individual.

- The trial will include evaluation of clinically relevant genetic, brain network, and neuronal loss markers as moderators of outcome; this will be one of the first trials to examine long-term effects on cognition, daily functioning, and neuroplastic changes in DMN with CCT in MCI.

- As our trial will be restricted to English-speaking participants because the online training platform is only available in English, we are unsure how this will generalize to non-English speaking individuals.

- In addition, the inclusion criteria state that the participant must have an at-home desktop or laptop computer, which, in low socioeconomic class homes, is not always available.

INTRODUCTION

Alzheimer's disease (AD) is a major public health concern affecting over 40 million people worldwide and there is an urgent need to develop new treatment modalities to prevent or delay the onset of dementia. Mild cognitive impairment (MCI) is common in older adults and represents a high-risk group for AD, but medication trials in MCI have generally failed. There is no FDA-approved treatment for MCI or to prevent the progression of MCI to AD.

There is growing evidence that a cognitively active lifestyle may reduce rates of dementia. A systematic review of 22 population-based studies found that mental activities may reduce overall incident dementia risk by 46% over a median 7-year period [1]. Computerized Cognitive Training (CCT) provides a novel strategy to improve cognitive performance in MCI by establishing a more cognitively active lifestyle. CCT involves computerized cognitive exercises that target specific abilities to improve cognitive functioning, and this effect is likely to be mediated by neuroplasticity. CCT has been used successfully to improve cognitive functioning in healthy adult populations [2, 3, 4, 5]. In particular, two studies in older healthy controls have garnered much attention. The ACTIVE trial was the first large-scale, randomized trial to show evidence of transfer from cognitive training to improved daily function, but only in participants who completed reasoning or speed of processing focused training, and not memory training [6]. In this ten-year follow up study of 2,832 healthy adults (average age = 73.6), participants were randomized to one of three intervention groups (memory, reasoning, or speed of processing) or a no-contact control group. Booster sessions occurred for 39% of participants in all active groups at 11 and 35 months after initial training, but the cognitive effects of the memory training did not persist over the ten-year follow up period [6]. In a second large, well-publicized online cognitive training study, findings were originally considered to be negative in terms of cognitive gains. However, in an examination of an older subsample, training was effective in improving cognitive abilities and instrumental activities of daily living [7].

In a recent meta-analysis examining CCT in older adults with MCI or dementia, the overall efficacy of cognitive outcomes in MCI was moderate and statistically significant [8]. This pattern was also found for global cognition, verbal learning and memory, nonverbal learning, working

memory, attention, and psychosocial functioning (e.g. depression, quality of life, neuropsychiatric symptoms). However, for the efficacy of cognitive outcomes in patients with dementia, the overall effect was found to be small, though statistically significant.

Early interventions at the stage of MCI, and not dementia, may be more helpful for improving cognition. In fact, Hill et al. [8] concluded that CCT is a feasible intervention for improving cognition in patients with MCI. Transfer effects have also been found in studies evaluating CCT in healthy older adults, supporting the potential for transfer of CCT benefits to daily life [6, 9]. In this study, we will assess for transfer effects by administering the following functional assessments at specific timepoints: Functional Activities Questionnaire (FAQ) and University of California San Diego Performance-Based Skills Assessment (UPSA).

Although CCT has received more support in the past few years as a viable treatment option for older adults with MCI, the brain mechanisms underlying the observed cognitive changes remain elusive. Many studies of CCT that include imaging components have only been conducted with healthy older adults [10, 11, 12, 13]. CCT may promote neuroplasticity in the brain, including in the hippocampus, a key region that supports memory [13, 14, 15, 16]. Additional research needs to be done that evaluates both structural and functional data within a rigorously-conducted clinical trial. In this study, patients will undergo a structural MRI and fMRI at both study entry and exit to assess for changes in hippocampal volume and the default mode network (DMN). The latter is crucial to evaluate in patients with MCI as dysfunction in the DMN has been implicated in the progression of MCI to AD [17]. The DMN is a resting state neural network of several highly interconnected cortical hubs, including the posteromedial parietal, anteromedial frontal, and inferolateral parietal cortices. We have shown that impaired deactivation and functional connectivity in the DMN may be a significant predictor in MCI of poor memory and transition to dementia over a 2-3 year follow-up period [18]. Neuronal dysfunction precedes structural atrophy in AD, and functional magnetic resonance imaging (fMRI) offers the potential for identifying specific patterns of disruption in the memory networks affected early in MCI and AD.

Limitations of prior CCT trials include the inconsistent demonstration of transfer to everyday functioning, reliance on waitlist control conditions as opposed to active control conditions, and lack of long-term follow-up. Most studies have not assessed transfer of cognitive improvement to everyday function or quality of life [19, 20, 21, 22, 23]. While CCT may produce transfers to untrained cognitive domains, the few studies that evaluate transfer to everyday functioning have reported mixed findings [24, 25, 26-29]. This is particularly important given the strong association between cognitive decline and functional disability [30]. Many studies use waitlist control conditions or control conditions that do not account for engagement and motivation in the task [22]. Such designs are biased in favor of the treatment condition because waitlisted subjects are not receiving any form of cognitive treatment and, therefore, may be more likely to drop out of such studies due to lack of engagement and motivation. In the current study, patients will be assigned to one of two cognitively stimulating exercises, computerized cognitive training (suite of exercises) or crossword puzzle training (crossword puzzles). Since one of the purposes of CCT in patients with MCI is to reduce the risk of progression to dementia, longer follow-up times are necessary to be able to accurately capture patient progression. However, most studies have only used no follow-up or short-term follow-ups, with the notable exception of the ACTIVE trial [6, 31-33].

Overall, recent findings in the field suggest that computerized cognitive training could benefit patients at risk for dementia. The current study will build on these findings by implementing a study design with an active control group, a longer trial duration, an increased intensity of computerized cognitive training, examination of generalizability to functional abilities beyond cognitive training skills, structural and functional MRI assessment, and rigorously blinded methodology.

METHODS AND ANALYSIS

Study Design Features and Rationale

One hundred patients clinically diagnosed with mild cognitive impairment (MCI) will be randomized. There will be two sites: New York State Psychiatric Institute/Columbia University Medical Center in New York, NY (NYSPI as lead coordinating site) and Duke University

Medical Center in Durham, NC. Patients will be randomized to one of two computerized cognitively stimulating exercises: crossword puzzle training (CPT) or a suite of exercises (CCT; memory tasks, matching tasks, spatial recognition tasks, processing speed tasks). These patients will be further randomized by MCI type (early MCI or late MCI), age (70 and below or 71 and above), and site (NYSPI/CUMC or DUMC) as the stratification factors and will be followed for 78-weeks. The randomization sequences will be balanced in blocks of random size (2, 4) to prevent clinicians from guessing what the next patient's treatment might be. The term "control" will not be used in the consent form in order to reduce the participant's expectancy bias.

In order to maintain neutrality and mitigate expectancy bias among patients, the informed consent form signed by all patients during the screening visit will not indicate which group is the active group (suite of exercises) or the control group (crosswords). Rather, it will indicate that the patient may be assigned to one of two cognitively stimulating exercises, CCT or CPT.

Role of Sponsor

The study is funded entirely by a National Institute on Aging grant and supervised by a Data Safety Monitoring Board. Using Lumosity, a web-based gaming platform from Lumos Labs, we customized a specific set of CCT and CPT training modules for participants to use in this trial. After a comprehensive review of several CCT modules on the market, we chose these modules from Lumosity due to their large selection of games tailored to specific cognitive domains, their research specific platform, availability of active control condition, availability of the online self-administered NeuroCognitive Performance Test (NCPT), and our previous pilot data in the elderly with this platform. Aside from providing the research platform and technical support at no cost, Lumos Labs provides no financial support for this study and their staff have no significant role in the final study design, study conduct, data interpretation or publication. Patients will not be required to pay for the platform and will not have a post-study commitment to the platform. None of the study team has any financial conflicts with Lumos Labs.

Recruitment, Eligibility, Consent

Patients will be recruited from the current patient caseload of the investigators, referral by neurology, psychiatry, primary care, public health and geriatric medical clinics affiliated with the centers and supplemented by advertisement.

Inclusion/Exclusion Criteria.

Detailed inclusion/exclusion criteria are described in Table 1. Notable inclusion criteria will be age range restriction 55-95 years, subjective cognitive complaints (i.e., memory or other cognitive complaints, e.g., naming/language), Wechsler Memory Scale-III (WMS-III) Logical Memory Story A delayed recall score 0-11, Folstein Mini Mental State Examination (MMSE) score ≥ 23 out of 30, availability of an informant, and access to a home desktop or laptop computer with full access to the internet for the study duration. Patients who have a history of major psychiatric or neurological illness including motor disorders like Parkinson's disease, a dementia diagnosis of any type, contraindication to MRI scan, lack of English-speaking ability, or have been defined as regular online brain training or regular crossword puzzle users (≥ 2 times per week in the past year) will be excluded. Depression will be assessed using the 15-item Geriatric Depression Scale (GDS); a diagnosis of Major Depressive Disorder is exclusionary.

Mild Cognitive Impairment Criteria

Mild cognitive impairment (MCI) and type of MCI (early MCI or late MCI) will be assessed by the delayed recall score of WMS-III Logical Memory and by the score on the MMSE. On Logical Memory II Story A, a score from 0-11 will indicate cognitive impairment, per the Alzheimer's Disease Neuroimaging Initiative (ADNI) criteria. MCI type will be determined from this score combined with years of education of the patient. Early MCI (eMCI) will be defined as a delayed recall score of 3-6 with 0-7 years of education, score of 5-9 with 8-15 years of education, and score of 9-11 with 16 or more years of education. Late MCI (lMCI) will be defined as a delayed recall score of ≤ 2 with 0-7 years of education, score of ≤ 4 with 8-15 years of education, and score of ≤ 8 with 16 or more years of education. For both eMCI and lMCI, everyday function must be well preserved for study inclusion. A MMSE score ≥ 23 will also be required to indicate mild cognitive impairment, and this is required for study inclusion.

Length of Clinical Trial

Most transitions from MCI to AD typically occur within three years of follow-up after the diagnosis of MCI is made [34]. We chose 18-months as the length of this clinical trial to decrease dropouts that can occur in a very long controlled trial. Since this study is considered low risk, we do not anticipate participants to suffer harm from trial participation.

Treatment Regimen

Enrolled participants will come to the clinic for five scheduled visits (Weeks 0, 12, 32, 52, and 78) and will receive at least three scheduled phone calls with research staff (Weeks 20, 42, and 64). Participants will be enrolled into the study after screening for eligibility and consent is signed. The randomization will be assigned by the statistician and then carried out by the unblinded research coordinator, with individuals stratified by MCI type, age group, and site.

Randomization.

The blinded research coordinator (at NYSPI or Duke) will complete the Training Group Randomization Form to indicate the following information for the patient: site, age, and MCI type. This form will be verified by the unblinded research coordinator at NYSPI, who will then assign a study ID to that patient, using a pre-populated form from the statistician's randomization assignment. The order of the study ID assignment will determine which study condition the patient will receive: CPT or CCT. The Lumosity account information will be generated after the MRI has been completed and quality checked. Lumosity account credentials will include a research-specific COGIT ID email address and password, which will enable users to log into an account specific to their study condition.

Randomization will be complete when the patient logs into his/her account for the first time at the baseline visit and sees which condition he/she is in. At this visit, patients will be trained by unblinded study staff in their assigned training condition. Eighteen modules were selected to target various cognitive domains: (A) Memory (Tidal Treasures, Familiar Faces, Memory Matrix) (B) Processing Speed (Speed Match) (C) Response Inhibition (Color Match) (D) Verbal Fluency/Vocabulary Proficiency (Word Bubbles, Word Snatchers, Editor's Choice, Continuum) (E) Planning/Divided Attention (Train of Thought, Brain Shift, Trouble Brewing, Disillusion) (F) Visual Interference (Lost in Migration, Ebb and Flow, Masterpiece) (G) Identification (River

Ranger) (H) Visualization (Speed Pack). These cognitive domains were chosen as they are areas that are often impaired in patients with MCI and thus represent areas that can be targeted for improvement [35]. Verbal Fluency and Vocabulary Proficiency tasks were included to promote verbal fluency in the CCT group. Further, the episodic memory task, Familiar Faces, targets verbal memory and learning. With this, it is acknowledged that episodic memory training may be somewhat limited in the selected battery of modules provided by Lumosity. Each CCT session will consist of a random selection of six modules. Participants in the CCT condition are not allowed to choose the games, and are not allowed to skip over or change the suite of games. The Lumosity platform will scale difficulty by using the patient's Lumosity Performance Index (LPI). The LPI will consider three areas for each patient. The Game Performance Index will be determined by reviewing score distributions for each game. The Cognitive Area Performance Index (speed, memory, attention, flexibility and problem solving) will be calculated using a weighted average of the Game Performance Index. Thirdly, the overall Cognitive Performance Index will be calculated using a weighted average of the Game Performance Indices from all cognitive areas. A complete list of selected CCT games are described in Table 2. Crosswords engage primarily verbal abilities and perhaps, executive and attentional mechanisms. The Lumosity games target different cognitive domains, such as speed of processing and memory, as well as verbal abilities. The effect that these different trainings have on the so-called far transfer problem will of course be of major interest. There should be no case in which an emergency unblinding will need to take place, as the blinded intervention is a computerized intervention.

Participants in the computerized cognitive training group and the crossword puzzle training group will spend the same amount of time on the platform during the intensive training phase, which will consist of four 30-minute training sessions per week for 12 weeks. Participants are not required to have any particular level of computer skills for study inclusion; however, at the initial baseline training, all participants will be trained on how to successfully access the training platform, and how they could obtain help both from research staff and their informant throughout the study. For both groups, responses will be entered via mouse and keyboard. For the crossword puzzle training group, questions will not need to be completed in order and there will not be any feedback for the accuracy of the response at the time of entry by the participant. Upon completion of the CCT suite of exercises after 30 minutes, participants will receive a score.

Similarly, after 30 minutes the crossword training will automatically end. If a participant were to finish an entire crossword puzzle before the 30-minute cutoff, they would be directed to another crossword puzzle to ensure they complete a total of 30 minutes.

Following the intensive training phase of 12 weeks, participants will be instructed to complete six booster sessions. Each booster session will consist of four CCT/CPT sessions. Booster sessions will be completed at weeks 20, 32, 42, 52, 64, and 78. At weeks 32, 52, and 78, patients will complete three booster sessions at home and complete the fourth session in-clinic with research staff. At weeks 20, 42, and 64, patients will complete all four booster sessions at home. Generally, in previous cognitive training studies, booster sessions have been limited. For instance, the ACTIVE trial had two booster sessions, each consisting of four 75-minute trainings at 11 and 35 months. During the course of the trial, booster sessions included a total of 8 trainings, for a total of 10 hours [6]. In contrast, COGIT will have six booster sessions (24 total training sessions each lasting 30 minutes) over 15 months. Thus, COGIT will include 12 hours total for booster sessions during the trial. The ACTIVE trial only required compliant participants to complete the booster sessions, whereas all participants will complete booster sessions in the COGIT study [6].

Clinic Based Cognitive, Functional, and Smell Assessments.

At baseline (week 0) The Alzheimer's Disease Assessment Scale-Cognition Subscale 11 (ADAS-Cog 11) will be administered, in addition to the following neuropsychological test battery: WAIS-III Block Design (to assess visuospatial skills), Digit Symbol Substitution Test (DSST) (to assess attention), Trail Making A & B (to assess attention and executive function), Verbal Fluency and 15-item Boston Naming Test (to assess language), Auditory-Verbal Learning Test (to assess verbal learning and memory), and WMS-III Visual Reproduction Test (to assess nonverbal learning and memory). In addition, the UPSA and University of Pennsylvania Smell Identification Test (UPSIT) will be administered. Testing fatigue is mitigated by allowing participants to take breaks during the testing. If there is missing data from one time point, the study team will attempt to bring the participant back to the clinic within the allowed window to complete missing measures. The FAQ will be administered to the patient's informant, either during the study visit or shortly after the visit over the phone.

Self-Administered Cognitive Test Battery.

Another unique aspect of the study is the use of the NCPT, an online, computerized, self-administered battery developed by Lumosity. It will test various cognitive domains outlined in the Study Measures section. The NCPT will allow us to examine the efficacy of a self-administered test, in combination with standardized, clinic-based neuropsychological tests.

Timeline of Longitudinal Assessments

At in-clinic visits (baseline and weeks 12, 52, and 78), the same neuropsychological battery of testing will be completed. At the week 12 and week 78 visits, the patient will be asked to complete the User Engagement Scale, which will be adapted to capture usage of a computerized platform. This scale will measure aspects of engagement, usability, and satisfaction with the computerized platform on a 5-point Likert scale. Week 20 will be a phone interview between study physician/neuropsychologist and patient to follow-up on how the patient has been doing, and to remind the patient to complete a booster session.

Blinded Training Procedure

The blinded research coordinator will administer the full neuropsychological test battery, including the UPSA and FAQ. The blinded clinician will complete the Diagnosis Form and the Contributing Features to MCI form after clinical interview and review of the neuropsychological testing. The unblinded research coordinator will administer the initial computerized training and all subsequent booster sessions to patients in the clinic. To track type of games/crossword puzzles and amount of time that the subject spends doing the games/crossword puzzles, only unblinded study coordinators receive reports from Lumosity each week. If the Lumosity reports of computer games/crosswords access do not match the subject's assigned instructions, the unblinded coordinator then contacts the subject to guide and ensure adherence to the protocol.

Hypotheses

See Figure 1 for a Conceptual Model of specific study aims and outcome measures. The primary aim of the study is to assess change in cognitive and functional status over 18 months in MCI patients comparing the CCT and CPT groups. Hypothesis 1: MCI patients randomized to CCT

will show better cognitive outcomes on the ADAS-Cog 11 (primary outcome measure), Neuropsychological Testing Composite score (secondary outcome measure), and NCPT (exploratory outcome measure) compared to active control (CPT). Hypothesis 2: MCI patients randomized to CCT will show better functional outcomes as assessed by the UPSA (primary functional outcome) and FAQ (secondary functional outcome) by the end of the 18-month trial compared to active control. Hypothesis 3: brain pathology (smaller hippocampal volumes, lower odor identification scores on the UPSIT, ApoE e4 allele present) will moderate the relationship between treatment assignment and cognitive and functional outcomes.

The secondary aim of the study is to examine the effects of CCT on resting-state DMN connectivity as well as other networks modulated by CCT effects. Hypothesis 1: MCI patients randomized to CCT will demonstrate greater change in an index of DMN functional connectivity compared to patients randomized to active control. Hypothesis 2: indicators of brain pathology (smaller hippocampal volumes, lower odor identification scores on the UPSIT, ApoE e4 allele present) will moderate the relationship between change in the DMN and treatment assignment.

The tertiary aim of the study is to examine differences in rates of progression to dementia and AD in the two randomized treatment groups, recognizing that if progression to these outcomes is uncommon there will be insufficient statistical power. Hypothesis 1: the proportion converting to dementia will be lower in the CCT group compared to active control.

Study Measures

Study measures with time-points of administration are listed in Table 3. The MMSE will be administered at screen and each subsequent in-clinic visit using five different versions of the three-word recall item to reduce practice effects [36]. The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) and The Framingham Stroke Risk Scale will be completed by the study physician at screen and week 78 to assess for cardiovascular disease risk factors and other medical conditions.

The Geriatric Depression Scale will be administered at screen and each subsequent in-clinic visit to assess for depression. If GDS is greater than 5 at any visit, the patient will be evaluated by a

psychiatrist and an appropriate clinical referral will be made, if needed, for treatment of depression. The Cognitive Reserve Index is a brief questionnaire that will be administered by the research coordinator at screen and will evaluate the cognitive reserve of an individual by means of the compilation of information as it relates to his/her adult life.

At screen, the research coordinator will be responsible for administering the History of Game Use Questionnaire, Physical Activity Assessment, and WMS-III Logical Memory I & II. The History of Game Use Questionnaire will be administered again at weeks 12 and 78 to ensure that patients are not partaking in any other types of cognitive training games while in the study.

At screen and week 78, patients will undergo an MRI scan of the brain. The MRI scan will include the following sequences: Localizer, high-resolution T1-weighted IR prepped 3DSPGR, and T2 FLAIR, and GE-EPI resting-state fMRI scans.

At weeks 0 and 78, the UPSIT will be completed by the patient, which is a 40-item scratch and sniff multiple-choice olfactory identification test.

At each in-clinic visit, apart from week 32, the ADAS-Cog 11 and full neuropsychological test battery will be administered. The NCPT will be administered at weeks 0, 12, and 78. The cognitive domains measured by the NCPT are memory (visuo-spatial working memory, short-term memory), processing speed (visual search, psychomotor speed), problem solving (logical reasoning, numerical calculation), attention (selective, divided), and flexibility (response inhibition, task-switching). The assessments, 10 total "subtests," are online adaptations of widely used neuropsychological tests whose test properties are not affected by shifting to computerized administration [37].

The neuropsychological test battery includes: WAIS-III Block Design, Digital Symbol Substitution (DSST), Trail Making A & B, Verbal Fluency and 15-item Boston Naming Test, Auditory-Verbal Learning Test (AVLT), and WMS-III Visual Reproduction Test. For word learning lists, the neuropsychological testing materials provide different but parallel word lists, so as to avoid practice effects in MMSE and ADAS-Cog, but not for AVLT. With respect to the

latter we did not adopt this approach because we were concerned that different forms have not been established as equivalent in difficulty level. The UPSA will be administered only at weeks 0, 32, and 78 due to the high tendency for practice effects. It is a performance-based measure of functional abilities that includes measures of simulated real-world activities; for example, planning a trip to the beach, remembering documents to bring to a medical appointment, and dialing a phone number. When a participant wears corrective lenses during the testing battery, this is documented in the participant's research chart.

At screen and weeks 12, 32, 52, and 78 the participant will meet with the study physician or the neuropsychologist to assess for illness progression and adverse events. Adverse events that are spontaneously reported to research coordinators at any clinic visit will be discussed with the study physician or the neuropsychologist in order to determine how to proceed. Adverse events and subsequent steps to deal with the adverse events will be documented in the patient chart and serious adverse events will be reported to the Data Safety and Monitoring Board and study sponsor, National Institute on Aging.

Additionally, the research coordinator will conduct an interview with the informant at, or shortly after, each visit to complete the FAQ.

Criteria for Early Discontinuation

We expect early discontinuation to occur because of one or more of the following reasons: (1) the patient's decision not to continue the computerized training (CCT or CPT) due to lack of interest, motivation, or available time; (2) unavoidable circumstances, e.g., moving residence and unwillingness to return for in-person evaluations; (3) investigator decision to terminate; (4) death or prolonged hospitalization for medical reasons. We will not terminate participation for non-adherence because even if the patient is non-adherent to the protocol, we will document level of adherence (done electronically in this computerized training protocol) and still include the patient's data in the analyses based on the intent-to-treat principle.

Data Management

Data entry will be completed by Program Managers, Clinical Research Coordinators, and Research Assistants on the study protocol. Data entry/cleaning will be done throughout the project. The data collected in this study will be monitored by the Data Coordinating Center at NYSPI. The unit will work closely with the research assistant/coordinator and the Principal Investigator to facilitate independent auditing of primary subject records. The database will provide reports indicating all modifications that have been made in the database together with paper communications (fax, e-mail) confirming and authorizing these modifications. Access to the data system is available only to authorized users, with multiple levels of security including user id/password authentication via MS Active Directory overseen by experienced IT personnel. Other authorized users with direct access to the data system will be Data Coordinating Center (DCC) staff. DCC data-related operations and the SIR/Citrix system have been certified by Columbia University's Information Security Office. The dataset will not be published in a data repository.

Genetic Testing

Apolipoprotein E (ApoE) genetic analysis on a blood sample will be done through the laboratory of the Human Genetics Resources Core (HGRC) at Columbia University Medical Center. We will assess the ApoE ε4 allele as potentially associated with response to CCT; a prior trial found an association between the ε4 allele and cognitive improvement on donepezil [38].

Concomitant Medications

Putative cognitive enhancers, narcotics, all classes of psychotropic medications, and over 20 other classes of commonly prescribed and over the counter (and alternative) medications will be documented in a rating form at screen and subsequent in-clinic visits. An exclusion criterion will be daily use of medications known to have a negative impact on cognition: high-dose narcotics, anticholinergics, and benzodiazepines in lorazepam equivalents ≥ 1 mg daily. During the first 12 weeks of the study, the intensive cognitive training phase, patients are encouraged not to change any of their medications, unless clinically indicated.

Statistical Analysis and Sample Size

We powered our trial to detect an effect size at 18 months of d=.58 (80% power). This effect size is more conservative than published treatment changes associated with CCT (for instance, see [39]). We assume that dropout is distributed uniformly across waves of follow-up assessments (with 5% attrition between each consecutive pair of the 5 major time-points, i.e. 20% by 18 months).

Outcome Measures (Primary and Secondary Hypotheses Testing).

Aim 1 Hypothesis 1 and 2. MCI patients on CCT will show a lower rate of cognitive and functional decline compared to MCI patients on active control by the end of the 18-month trial. We will use generalized linear mixed effects models of cognitive and functional measures collected repeatedly across the 78 weeks according to the schedule (see Table 3). For example, $\text{cognitive measure}_{ik} = \beta_0 + \beta_1 \text{Time}_{ik} + \beta_2 \text{Group}_i + \beta_3 (\text{Group}_i \text{ x Time}_{ik}) + v_{0i} + v_{1i} \text{Time}_{ik} + \varepsilon_{ik}$ where Group_i indicates treatment group for subject i (Group = 1 CCT, 0 for control), k = time (baseline, 12 weeks, 20 weeks, 52 weeks, 78 weeks), and v_{0i} is a subject-specific random intercept. Time will be treated as categorical if linearity is not plausible and group effects at 18 months can be tested by forming contrasts from the fitted model. Potential site differences will be evaluated using descriptive statistics and site will be included in all analyses as a covariate, as will other stratification variables including age group and MCI type at baseline.

Aim 2 Hypothesis 1. MCI patients randomized to CCT will demonstrate either more of an increase or less of a decrease in DMN connectivity (goodness-of-fit [GOF] index scores) compared to patients randomized to active control. To test this hypothesis, we will use a repeated measures Analysis of Covariance (ANCOVA) with time (baseline vs. post treatment) as the repeated measure, DMN connectivity as an outcome, treatment condition (CCT vs CPT) as a predictor, and site, age, and MCI status at baseline as covariates.

Moderating Effects in Aim 1 Hypothesis 3 and Aim 2 Hypothesis 2. As a part of our exploratory analyses, we will examine specific potential moderators: Apolipoprotein E ε4 allele, MRI indices, UPSIT. To show, for example, that baseline hippocampal volume is a moderator, we will test its interactive effect with treatment on outcomes. Moderator and moderator-interaction terms can be easily accommodated in the mixed effects regression models described in Aim 1.

Hypotheses 1 and 2. A similar approach will be used by adding moderator and moderator x Group interactions to the ANCOVA described in Aim 2 Hypothesis 1. The results must be interpreted with the caveat that there may not be enough power to assess these interactions, especially for moderators with low prevalence.

Aim 3 Hypothesis 1. The proportion diagnosed with dementia during follow-up will be lower in the CCT group compared to active control. Logistic regression will be used to test the binary outcome of dementia status at 18 months predicted by treatment group controlling for site, age group, and MCI type at baseline.

Missing data is managed statistically through use of mixed model repeated measures analyses.

Sample Size.

A power analysis was conducted using the RMASS program for longitudinal studies, which determined that a total sample size of 100 participants will provide a sufficient effect size to evaluate our hypotheses. We have two primary outcome measures (i.e., multiple outcome measures), namely ADAS-Cog and the UPSA. For multiple outcome measures, statistical significance on any one measure is meaningful and there is no need to correct for multiple comparisons (unlike co-primary outcome measures). All other outcome measures are secondary and exploratory.

Patient and Public Involvement

Patients will first be involved in the research after study design is finalized by the study investigators. At this stage, patients will be referred by physicians or self-referred from online and newspaper advertisements for their initial screening visit. The patients will not be involved in study design, study recruitment or conduct, or dissemination of study results. We will assess the burden of the trial intervention on patients using the User Engagement Scale and the Participant/Informant Expectancy Scales. Patients will not be invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients will not be invited to contribute to the writing or editing of this document for readability or accuracy.

ETHICS

This study has been approved by NYSPI IRB, Duke University IRB, and Queens College IRB. All COGIT patients at entry will be required to have the capacity to provide informed consent and sign the IRB-approved informed consent form. Local IRB and state regulations for consent will be followed. Patient confidentiality as it pertains to potential and enrolled participants before, during, and after the trial will be collected, shared, and maintained strictly according to HIPAA law.

Important protocol modifications will be communicated to the Data Safety and Monitoring Board, NYSPI IRB and Duke University IRB, and updated online for trial registries.

The research data on specific moderators, including UPSIT and apolipoprotein E genotyping, will not be not released to the patient, and this will be specified in the consent form. The cognitive testing results and clinical reading of the MRI scan will be released to the patient (and the patient's primary physician, if requested); the MRI research volumetric ratings and fMRI findings will not be released.

Data Safety and Monitoring Board (DSMB)

Three NIA-approved independent experts with expertise in conducting clinical trials in mild cognitive impairment will form the DSMB. All serious adverse events (SAEs) will be reported to the DSMB. The DSMB will audit the trial conduct, review all SAEs, participate in a teleconference twice a year to determine if the study should continue, and then will provide an actionable report to the Principal Investigator. This process will be independent from the investigators.

DISSEMINATION

The study results will be disseminated through publications and conference presentations as well as on public websites, including clinicaltrials.gov. Researchers will be eligible for authorship after consideration by the principal investigators; no professional writers will be utilized.

SIGNIFICANCE

This will be one of the first investigator-blinded and controlled long-term trials to evaluate the effects of home-based computerized cognitive training versus computerized crossword puzzle training on cognitive, functional, hippocampal and default mode network connectivity neural outcomes in MCI. Positive results from this pilot trial may support the further development of home based cognitive training and self-assessments in people at risk for dementia.

The results will help inform the design of a more powerful RCT in many ways: determine sample size for a multicenter trial, identify subgroups more likely to benefit, identify subdomains and exercises most likely to improve, optimize training dose and duration, learn how subjects engage, identify gender effects, model slopes and long-term benefits, assess value of a self-administered cognitive test, understand brain networks affected, and examine the potential moderating role of apolipoprotein E ε4 status on CCT outcome.

AUTHOR CONTRIBUTIONS

DPD, PMD, JRP, and JRS conceptualized and designed the study and obtained funding. JLD and LSP drafted the initial manuscript. HFA contributed to statistics design and JRP to design of MRI component. TEG, SNR, NAK, CAH, SNT, EP assisted with elements of study design, database, and conduct. DPD is the overall study PI and PMD is the PI at the Duke site. All authors (JLD, LSP, TEG, JRS, SNR, NAK, HFA, CAH, SNT, EP, JRP, PMD, DPD) contributed to manuscript edits and revisions and approved the final manuscript as submitted. All authors agree to be accountable for all aspects of the work.

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COMPETING INTERESTS

JLD, LSP, TEG, JRS, SNR, NAK, HFA, CAH, SNT, EP, JRP have no competing interests. PMD has received research grants and advisory fees from several companies in this field for other studies, and owns shares in several companies whose products are not discussed here. DPD serves as a consultant on advisory boards to Acadia, Avanir, Genentech, Eisai, and Neuronix.

Table 1. Inclusion/Exclusion Criteria

Inclusion Critera
1. Males and females 55 to 95 years of age (inclusive) at the time of informed consent.
2. Subjective cognitive complaints, i.e., memory or other cognitive complaints, e.g., naming/language.
3. Meets criteria for cognitive impairment (CI) defined as scores >1 SD below standardized norms on memory function as identified by the Wechsler Memory Scale (WMS) III Logical Memory delayed recall score.
4. Folstein Mini Mental State (MMSE) score ≥ 23 out of 30.
5. A family member or other individual who is in contact with the patient and consents to serve as informant during the study; this could be a telephone informant in case of patients who do not have a live-in informant or close significant other.
6. Access to a home desktop or laptop computer at acceptable speed for the study duration.
Exclusion Criteria
1. Diagnosis of dementia of any type.
2. Current clinical evidence of schizophrenia, schizoaffective disorder, major depression, psychosis, or bipolar I disorder (DSM-IV TR criteria).
3. Active suicidal ideation or plan.
4. Current or recent (past 6 months) alcohol or substance use disorder (DSM-5 criteria).
5. Clinical stroke with residual neurological deficits. While we will not exclude patients with cerebrovascular disease, we will not include patients who have had a stroke with residual clinical deficits because it is not clear that this type of patient is similar to the MCI patient generally, and clear-cut neurological impairment, e.g., hemiplegia/hemiparesis or speech impairment, may compromise the patient's ability to do the CCT or active control procedures and to complete the neuropsychological tests.
6. Use of medications known to have a negative impact on cognition: benzodiazepines in lorazepam equivalents ≥ 1 mg daily, narcotics, anticholinergics. Other patients receive medications that may be associated with cognitive impairment but are rarely considered the likely etiology, e.g., theophylline, nifedipine, beta blockers; they will not be excluded. Patients receiving other psychotropic medications not expected to have a material impact on cognition, e.g., SSRIs and SNRIs will be eligible.
7. Presence of any of the following disorders: a) CNS infection, with CSF evidence of meningitis, encephalitis, or other infectious process; b) dementia of any type; c) Huntington's disease; d) Multiple sclerosis; e) Parkinson's disease; f) Other neurologic disorders with focal signs, e.g., amyotrophic lateral sclerosis; g) Mental retardation.
8. Acute, severe unstable medical illness. For cancer, acutely ill patients (including those with metastases) will be excluded, but past history of successfully treated cancer will not result in exclusion.
9. Contraindication to MRI scan: pacemaker, metal implants following surgery, any other contraindication to MRI. Eligibility for the MRI scan is a requirement for the study.
10. UPSIT exclusions: current smoker > 1 pack daily, current upper respiratory infection (retested as soon as the infection clears). UPSIT scores are reduced in schizophrenia, Parkinson's disease and Parkinson's related conditions; these disorders are exclusion criteria for this study. Patients with UPSIT exclusions will not receive the UPSIT but will continue to participate in all other aspects of the study.
11. Patients lacking English-speaking ability as determined by self-report and clinical evaluation.
12. Regular online brain training or regular crossword puzzle user, defined as doing these procedures at a frequency of twice weekly or greater during the year prior to screening. Eligible participants who join the trial are instructed not to do these procedures on their own during the trial, i.e., independent of the study.
13. Participation in another intervention trial for cognitive impairment.

Table 2. Complete list of CCT game battery and associated cognitive domains (provided by Lumos Labs)

Game Name	Cognitive Domain
Tidal Treasures	Working Memory i.e., delayed, non-matching to sample; self-ordered pointing
Speed Match	Processing Speed
Color Match	Response Inhibition
Word Bubbles	Verbal Fluency
Train of Thought	Planning Divided Attention Multiple attractions
Familiar Faces	Episodic Memory; verbal memory and learning
Memory Matrix	Episodic Memory; Visuospatial memory
Lost in Migration	Visual Interference
Brain Shift	Task Switching
Trouble Brewing	Multitasking, divided attention, sustained attention, planning, working memory
Ebb and Flow	Task switching, semantic and visual interference
Masterpiece	Mental rotation; visualization; spatial reasoning
River Ranger	Identification
Word Snatchers	Vocabulary proficiency
Speed Pack	Visualization
Disillusion	Task Switching
Editor's Choice	Vocabulary Proficiency
Continuum	Vocabulary Proficiency

Table 3. Table of Study Procedures

Measure	Screen	Baseline	12 Weeks	20 Weeks Phone Interview	32 Weeks	42 Weeks	52 Weeks	64 Weeks	78 Weeks
ADAS-Cog11		X	X				X		X
ApoE & blood test	X								
CIRS-G	X								X
Cognitive Reserve Index	X								
Cognitive Training or Control training booster session			X	X	X	X	X	X	X
Contributing Features to MCI		X			X				X
Demographics History (Patient Tracking Form)	X								
Diagnosis Form			X		X				X
Digit Symbol Substitution Test		X	X				X		X
Expectancy Scale (Participant & Informant)		X			X				X
Family History	X								
FAQ		X	X	X	X		X		X
Framingham Stroke Risk	X								
Geriatric Depression Scale	X		X		X		X		X
History of Game Use Questionnaire	X		X						X
Inclusion/ Exclusion Form	X								
Informed Consent	X								
Medications (Chart List & Database List)	X		X		X		X		X
MMSE	X		X		X		X		X
MRI Scan of Brain	X								X
NCPT online cognitive performance test		X	X						X
Neuropsychological Battery: AVLT, Block Design, Verbal Fluency, Visual Reproduction, Boston Naming Test, Trails A & B		X	X				X		X
Physical Activity Assessment	X								
UPSA		X			X				X
UPSIT		X							X
User Engagement Scale			X						X
WMS-III Logical Memory I & II	X								

Table 3 Legend: ADAS-Cog 11 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 11. ApoE = Apolipoprotein E gene. CIRS-G = Cumulative Illness Rating Scale for Geriatrics. MCI = Mild Cognitive Impairment. FAQ = Functional Assessment Questionnaire. MMSE = Mini Mental Status Examination. MRI = Magnetic Resonance Imaging. NCPT = NeuroCognitive Performance Test. AVLT = Auditory Verbal Learning Test. UPSA = UCSD Performance-Based Skills Assessment. UPSIT = University of Pennsylvania Smell Identification Test. WMS-III = Wechsler Memory Scale-III.

Figure 1. Conceptual Model

In the intervention phase patients are randomly assigned to either CCT or CPT. To evaluate cognitive status, the primary outcome measure will be the ADAS-Cog 11, the secondary outcome measure will be the Neuropsychological Testing Composite Score, and the exploratory outcome measure will be the NeuroCognitive Performance Test. To evaluate functional status, the primary outcome measure will be the UPSA and the secondary outcome measure will be the FAQ. To evaluate changes in neural circuitry, the primary outcome measures will include hippocampal volume (MRI) and DMN connectivity (fMRI).

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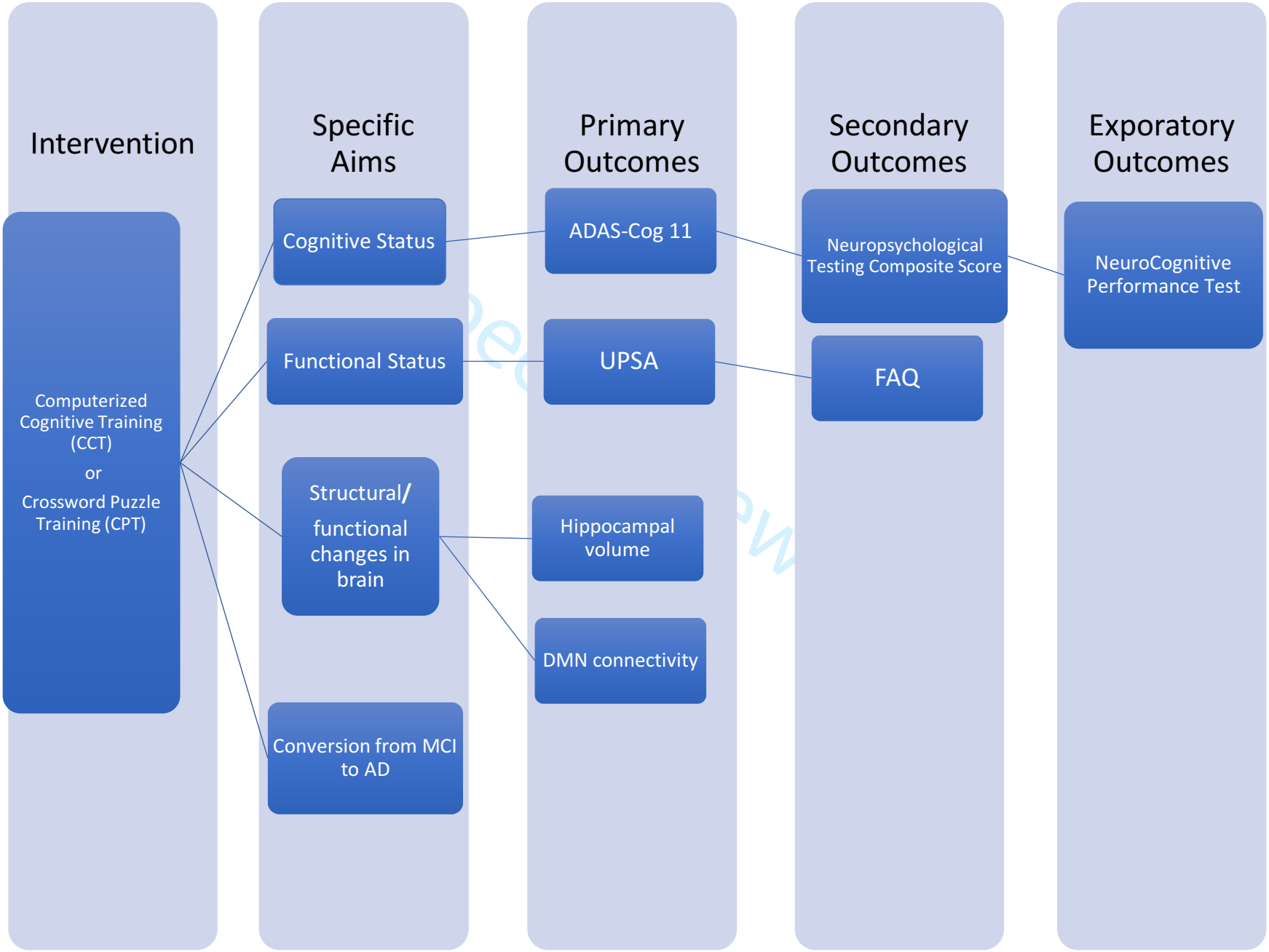
Intervention
Specific Aims
Primary Outcomes
Secondary Outcomes
Exporatory Outcomes
Computerized Cognitive Training (CCT)
or
Crossword Puzzle Training (CPT)
Cognitive Status
Functional Status
Structural/ functional changes in brain
Conversion from MCI to AD
ADAS-Cog 11
UPSA
Hippocampal volume
DMN connectivity
Neuropsychological Testing Composite Score
FAQ
NeuroCognitive Performance Test

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	7; 20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1;20

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	7;20
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18-19
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-6
Objectives	#7	Specific objectives or hypotheses	12-13, 16-17
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6-16
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-14
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	15
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11-12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13, 16-17
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13-15, 23
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16-18
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 16

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9, 12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10, 12
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-17
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11, 13-15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	15

		(eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15, 19
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14-15; 19
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	18-19
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 9
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19-20
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	16

Author notes