New York State Psychiatric Institute

Institutional Review Board

November 1, 2023

To: Dr. Davangere Devanand

From: Dr. Richard Foltin, Interim Co-Chair

Subject: Approval Notice: Continuation Expedited per 45CFR46.110(b)(1)(f)(8c)

Your protocol # **7395** entitled: **COGNITIVE TRAINING AND NEUROPLASTICITY IN MILD COGNITIVE IMPAIRMENT** Protocol version date 11/01/2023 has been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **November 1, 2023 to October 30, 2024.**

Consent requirements:

√ Not applicable: Data analysis only

☐ 45CFR46.116 (f)(3) waiver of consent

☐ Signature by the person(s) obtaining consent is required to document the consent process

☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: ☐ No ☐ Yes

Field Monitoring Requirements: ☐ Routine ☐ Special: _____

✓ Only copies of consent documents that are currently approved by the IRB may be used to obtain consent for participation in this study.

✓ A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.

✓ Changes to this research may not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.

✓ All serious and/or unanticipated problems or events involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website website at PRISM for Adverse Event Reporting Procedures and additional reporting requirements.

[1] ***Please note, all NYSPI investigators must follow the current institutional directives with regard to interactions with human subjects for research. Research is paused for the NYSPI site and NYSPI investigators regardless of site. If you have questions, please refer to the email announcements that went out to the research community on 06/12/2023 and 6/27/2023 from Dr. Thomas Smith Chief Medical Officer, New York State Office of Mental Health.***

RWF/alw

Signed copy on file at IRB

Protocol Title:
Cognitive Training and Neuroplasticity in Mild Cognitive Impairment

Version Date:
11/01/2023

Protocol Number:
7395

First Approval:
11/07/2016

Research Area:
Brain Aging & Mental Health
Division:
Geriatric Psychiatry

Expiration Date:
10/30/2024

Contact Principal Investigator:
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Co-Investigator(s):
Nancy Kerner, MD
Terry Goldberg

Research Chief:
Davangere Devanand, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

Department & Unaffiliated Personnel

Department

What Department does the PI belong to?
Geriatric Psychiatry
Within the department, what Center or group are you affiliated with, if any?
Memory Disorders Center (MDC)

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.

P. Murali Doraiswamy M.B.B.S. (Duke University) Joel Sneed, Ph.D. (Queens College, C.U.N.Y.)

Application for Continuation of Research

Status

Current Status of Study:
All research interventions were completed. Only data analysis is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
Project goals are to assess change in cognitive and functional status over 18 months in Mild Cognitive Impairment (MCI) patients comparing Computerized Cognitive Training (CCT) versus active control (crossword puzzles). The project was funded as of 7/15/2017. Duke University Medical Center in Durham, NC is executing an identical protocol as a sub-site. At NYSPI/Columbia, the last participant completed study measures as of 9/28/21. One participant was lost to follow-up and one participant exited the protocol early (completed all endpoint measurements). Upon study completion, all participants received an appropriate referral. As of 10/14/2022, NYSPI screened 83 participants and enrolled 57 participants total. As of 10/14/2022, Duke University screened 85 participants and enrolled 52 participants total. In total, 109 out of the originally planned 110 subjects were enrolled across both sites. The study was closed to accrual across sites in March 2020, following IRB mandated "COVID-19/ Pandemic Research Pause" (which prohibited enrollment of new subjects and implementation of in person assessments and procedures on site). The investigational team decided to close accrual with 109 subjects to focus on completing these subjects safely and compliantly. Lastly, there are no new developments in the field that impact the science or the risk/benefit balance of this protocol.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No

Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
Yes
Certificate expiration date (mm/dd/yyyy)
2022-06-30

Overall Progress

Approved sample size
109
Total number of participants enrolled to date
109
Number of participants who have completed the study to date
95
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Select the # of samples applicable
Specify population
Adults with mild cognitive impairment
Total number of participants enrolled from this population to date
57
Gender, Racial and Ethnic Breakdown
Of those enrolled at NYSPI/Columbia (as of 10/14/2022), 36 are female and 21 are male. 35 are White, non-Hispanic, 2 are White, Hispanic, 19 are Black, non-Hispanic, 1 identifies as other, Hispanic, and 0 are Asian.

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
0
Number of participants currently enrolled
0
Did the investigator withdraw participants from the study?
No
Did participants decide to discontinue study involvement?

No

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Internet-based Data Collection or Transmission
✓ MRI
✓ Neuropsychological Evaluation
✓ Psychiatric Assessment
✓ Studies of DNA

Population

Indicate which of the following populations will be included in this research

✓ Adults who may have impaired decision-making ability
✓ Adults over 50

New York State
Psychiatric Institute
Institutional Review Board
PRISM 2022

Protocol Summary Form

Instructions:

The new Protocol Summary Form is now included in this Word template. You will begin a new protocol by completing all sections which pertain to your study. Not all sections are required. If a section is not applicable to your study, delete it.

If you are submitting an Amendment or Continuation, you will need to obtain a copy of the most recent approved PSF. This will be found in the list of forms submitted under the protocol selected. Once you have downloaded the PSF, you can convert the PDF to Word document using this link https://www.adobe.com/acrobat/online/pdf-to-word.html

After converting the PSF, you can copy the information to the new PSF Word template and make any changes to the PSF as necessary for your Amendment or Continuation. From here, follow the instructions provided for creating the appropriate form.

Research Support / Funding

This section is to describe the funding sources for your protocol.
If an internal account is to be used, please describe. N/A; the protocol uses external funding.

The internal account is ☐ RFMH ☐ CU
If the project is using, or planning to use, external funding, provide the details for each external funding source.
Example:

Principal Investigator on grant/contract	**Davangere Devanand, MD**
Status of Grant	is currently funded
Source of Funding	Federal
Institute / Agency	National Institute of Health - National Institute on Aging
Grant Name	Cognitive Training and Neuroplasticity in Mild Cognitive Impairment
Grant Number	1R01AG052440-01A1
Sponsor	N/A
Is this research initiated by the investigator?	Yes
Site description (select one)	Multicenter (NYSPI is the lead site)
Business Office (select one)	CU
If the grant/contract includes a subcontract, please describe. (To / From, Name of institution(s). Be sure to specify To or From)	1. Research Foundation for Mental Hygiene 2. Duke University Medical Center, Department of Psychiatry (Site Principal Investigator: P. Murali Doraiswamy, M.B.B.S.) 3. Queens College, C.U.N.Y. (Site P.I. Joel Sneed, Ph.D.)

Study Location

Indicate if the research is/will be conducted at any of the following:

☒ NYSPI ☐ Washington Heights Community Service ☐ Other Columbia University Medical Center Facilities

This Protocol describes research conducted by the PI at other facilities/locations:

☐ Office Of Mental Health Facilities

☐ Binghamton Psychiatric Center	☐ Bronx Children's Psychiatric Center
☐ Bronx Psychiatric Center	☐ Brooklyn children's Psychiatric Center

☐ Buffalo Psychiatric Center	☐ Capital District Psychiatric Center
☐ Central New York Psychiatric Center	☐ Creedmoor Psychiatric Center
☐ Elmira Psychiatric Center	☐ Greater Binghamton Health Center
☐ Hudson River Psychiatric Center	☐ Hutchings Psychiatric Center
☐ Kingsboro Psychiatric Center	☐ Kirby Forensic Psychiatric Center
☐ Manhattan Psychiatric Center	☐ Middletown Psychiatric Center
☐ Mid-Hudson Psychiatric Center	☐ Mohawk Valley Psychiatric Center
☐ Nathan S. Kline Institute	☐ Pilgrim Psychiatric Center
☐ Queens Children's Psychiatric Center	☐ Rochester Psychiatric Center
☐ Rockland Children's Psyciatric Center	☐ Rockland Psychiatric Center
☐ Sagamore Children's Pyschiatric Center	☐ St. Lawrence Psychiatric Center
☐ South Beach Psychiatric Center	☐ Western NY Children's Psychiatric Center

Click or tap here to enter text.

☒ Hospitals, clinics and other healthcare facilities

- ☐ Bridge Plaza Medical Center
- ☐ Harlem Hospital
- ☐ St. Luke's-Roosevelt Hospital Center
- ☐ Mount Sinai Medical Center
- ☐ Weill Cornell Medical Center

Or type in location(s)..

Duke University Medical Center, Department of Psychiatry (Site Principal Investigator: P. Murali Doraiswamy, M.B.B.S.)

☒ Schools/Educational Institutions

Queens College, C.U.N.Y. (Site Principal Investigator. Joel Sneed, Ph.D.)

☐ Prison System(includes Parole)
☐ International Sites
☐ Other Facilities
☐ Community Sources

Lay Summary of Proposed Research

This section is intended to provide a basic overview of the study including a description of its purpose, study procedures, and subject population. The summary should provide a concise overview of the study for non-scientific and scientific members of the IRB. Please avoid medical or technical terminology. In general, the abstract of a grant does not provide a suitable lay summary.

Mild cognitive impairment (MCI) is common in older adults and represents a high-risk group for Alzheimer's disease (AD). Advances in biomarker assessment have improved the early diagnosis of clinical AD but medication trials in MCI have generally failed. New discoveries about brain plasticity in aging have led to the study of cognitive training as a treatment to improve cognitive abilities.

Computerized Cognitive Training (CCT) provides an exciting opportunity and a new strategy to improve cognitive performance in MCI. CCT involves computerized cognitive exercises that target specific abilities/neural networks to potentially improve cognitive functioning through neuroplasticity. In a two-site study (NYSPI/Columbia and Duke) we will randomize 100 patients with MCI to CCT (suite of exercises) or an active control condition (crossword puzzles).

The initial 12 weeks will involve intensive CCT or active control conditions and this will be followed by regular booster sessions for a total of 18 months. We have extensive pilot data that strongly support this planned approach. We will address three key issues that have not been addressed systematically in a single well-controlled study in MCI: does CCT lead to improved cognitive functioning, do the effects of CCT transfer to functional ability and tasks of everyday life, and does CCT lead to long-term changes in brain networks, e.g., the default mode network (DMN) using resting fMRI? We aim to assess change in cognitive and functional status over 18 months in MCI patients comparing CCT versus active control condition, and hypothesize that MCI patients on active CCT will show better cognitive and functional outcomes by the end of the 18-month trial. We will also explore the sensitivity and validity of an unsupervised web-based neuropsychological battery (Neurocognitive Performance Test, NCPT) for detecting CCT effects and its associations with change in cognitive and functional measures in MCI. We also hypothesize that patients with MCI randomized to CCT will show greater changes in the DMN with resting fMRI compared to the control condition and that these changes will be associated with improvement on specific cognitive tests. We will compare rates of transition to a clinical diagnosis of AD in the two groups, and explore potential moderators of improvement, including hippocampal and entorhinal cortex atrophy, olfactory identification deficits, and apolipoprotein E ε4 allele status.

In this study, cognitive training using the Lumosity platform requires the use of a desktop or laptop home computer. By definition, computerized cognitive training requires a computer, and in our experience the majority of patients do have such access. U.S. statistics in 2014 show that 57% of individuals 65 and older use the internet compared to over 90% of young adults; this statistic is from an online, international database, Statista. Usage in older adults keeps growing steadily and in the future nearly all older adults will be internet users. Therefore, this study will have broad applicability.

Background, Significance, and Rationale

In this section, provide a brief summary of the status quo of the relevant work field and how the proposed study will advance knowledge. Specifically, identify the gaps in knowledge that your project is intended to fill. If no gaps exist that are obviously and directly related to your project, explain how your proposed research will contribute to the overall understanding of your field. Describe potential impacts of your project within your field of study and in a broader context. Provide a critical evaluation of existing knowledge. The literature review does not have to be exhaustive.

Background:

There is growing evidence that a cognitively active lifestyle may delay dementia. A systematic review of 22 population-based studies found mental activities may reduce overall incident dementia risk by 46% over a median 7-year period (34).

In a trial of 42 elderly subjects randomized to 8-week verbal memory training versus control, memory training improved source memory performance and increased regional cortical thickness. Thickness change in the right fusiform and lateral orbitofrontal cortex correlated positively with improvement in memory, suggesting possible functional significance of the structural changes(35). In the eLORETA 8-week trial, 70 MCI subjects were randomized to combined CCT plus physical exercise or control. The CCT/exercise group showed improvements in MMSE and an EEG measure of neuroplasticity in the precuneus/posterior cingulate region(36).

A study published in Nature tested the effect of 4-week training on a car racing video game on cognition in 46 elderly subjects. Trained subjects had higher scores than untrained 20-year-olds, and the skill remained six months later without practice. Certain abilities that were not specifically targeted by the game improved and remained improved, e.g., working memory, sustained attention. Both skills are important for daily tasks, from reading a newspaper to cooking a meal, supporting the potential for transfer of CCT benefits into daily life(37).

Does CCT enhance short-term cognitive functions beyond active control? The IMPACT trial was a multicenter trial of 487 community-dwelling cognitively normal older adults where participants were randomized to CCT or active control. Duration of training was 1 hour per day, 5 days per week, for 8 weeks, for a total of 40 hours. Primary and multiple secondary measures of memory and attention improved significantly in the CCT group (word list total score, word list delayed recall, digits backwards, letter- number sequencing) as did the participant-reported outcome measure(38), and CCT improved cognition more than active control.

Are the benefits of CCT sustained long-term? A randomized trial found that training older adults with 20 hours of CCT improved processing speed, attention and spatial memory as well as two measures of subjective well-being, but without booster sessions such benefits were lost(39). The long-term persistence and transfer of benefits were evaluated in the ACTIVE randomized, controlled single-blind trial evaluating a commercial CCT intervention against a no-contact control group in 2,832 older normal persons. CCT consisted of 10 sessions for memory, reasoning, and speed of processing followed by 4 sessions of booster training 11 and 35 months after initial training. Trained subjects showed less difficulty with instrumental activities of daily living (IADLs) (memory: effect size = 0.48, speed of processing: effect size = 0.36). At 10-year follow up, more of the original CCT participants than controls were at or above their baseline level of self-reported IADL function(40).

There is no FDA-approved treatment for MCI; cholinesterase inhibitors have only short-term cognitive enhancing effects. During this project, new medications are unlikely to be approved to treat MCI. Therefore, novel cognitive enhancement strategies are important to consider in MCI.

Imaging and cognitive neuroscience studies have shown the aging brain to have a rich capacity to reorganize and have reframed our conceptualization of cognitive aging from one of inevitable decline to one that emphasizes its potential for neuroplasticity. The hippocampus is vulnerable to early damage in MCI and AD; preclinical studies in mice show environmental enrichment can stimulate hippocampal neurogenesis. There is growing evidence that a cognitively active lifestyle may delay 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.

CCT consists of computerized cognitive exercises that can be used to target specific neural networks in order to improve cognitive functioning through neuroplasticity. CCT has been used successfully to improve cognitive functioning in healthy adult populations and in several diagnostic conditions. The application of CCT in MCI has received attention only recently.

Results of most CCT trials are limited because of inconsistent demonstration of transfer to everyday functioning and reliance on waitlist control conditions as opposed to active control conditions. Most studies do not assess transfer of cognitive improvement to everyday function and quality of life. While CCT may produce transfers to untrained cognitive domains, the few studies that evaluate transfer to everyday functioning have reported mixed findings. This is particularly important given the strong association between cognitive decline and functional disability. Most studies use waitlist control conditions or control conditions that do not account for engagement and motivation in the task. Such designs are biased in favor of the treatment condition because patients assigned to CCT have tasks that are engaging and motivating (e.g., completing a task or seeing your score go up) whereas those assigned to waitlist control lose interest and motivation.

Significance and Innovation:

Several aspects of our trial and research strategy make it unique and innovative: 1) This is the first randomized controlled trial in MCI patients to examine short-term and long-term benefits of CCT versus active control (crosswords) condition over 18 months; 2) The trial utilizes a remote internet-based CCT intervention that can

be done at home. Compared to existing treatments under investigation, it is easily accessible, relatively inexpensive, non-invasive, and scaled to the skill level of each individual. CCT, therefore, is consistent with the goal of personalized medicine, and it avoids medicinal side effects or drug interactions. Compliance with CCT is easily monitored electronically and protocol adherence documented with the CCT platform; 3) The trial focuses on cognition and function using clinic-based cognitive outcomes (primary: ADAS-Cog; secondary: Neuropsychological Testing Composite Score and home-based unsupervised cognitive (exploratory: NCPT) and functional (primary: UPSA; secondary: FAQ) outcomes. Thus, the study will inform about the utility of clinic-based versus home-based tools. The availability of unsupervised online cognitive tests will allow researchers to recruit participants for specific studies and trials more efficiently and to evaluate cognition in larger samples than previously studied using conventional in-clinic assessments. Several versions of online assessments with the NCPT allow for repeated administrations with minimal learning effects, improving the use of online assessments to monitor individuals over time; 4) Broad inclusion/exclusion criteria for MCI will be used, thereby increasing applicability to clinical settings. Recruitment will be from Psychiatry, Neurology and Internal Medicine in two large medical centers, thus potentially capturing the full range of MCI patients who present clinically and enhancing generalizability; 5) The trial includes evaluation of clinically relevant genetic, brain network and neuronal loss markers as moderators of outcome; 6) This is the first trial to examine long-term neuroplastic changes in DMN with CCT in MCI; 7) The study improves upon limitations of previous studies by including an “active” rather than a waitlist control condition or control conditions that do not account for engagement and motivation.

Rationale:

Implications of the project. Imaging and cognitive neuroscience studies have shown the aging brain to have a rich capacity to reorganize and have reframed our conceptualization of cognitive aging from one of inevitable decline to one that emphasizes its potential for neuroplasticity. The hippocampus is vulnerable to early damage in MCI and AD; preclinical studies of mice show environmental enrichment can stimulate hippocampal neurogenesis. There is growing evidence that a cognitively active lifestyle may delay dementia. A systematic review of 22 population-based studies found mental activities may reduce overall incident dementia risk by 46% over a median 7-year period.

Improving cognition in older adults, especially those at high risk of transitioning to clinical AD, is an important public health goal. If the study goals are achieved it will have major implications for improving quality of life and reducing disability and healthcare costs in this growing demographic. This study is consistent with the NIA AD 2015 summit recommendations and NIA priorities, and the movement toward patient-driven personalized medicine.

Specific Aims and Hypotheses

Concisely state the objectives of the study and the hypothesis or primary research question(s) being examined. There should be one hypothesis for every major study procedure or intervention. For pilot studies, it is important not to overstate the study's objectives. If there are no study hypotheses, describe broad study goals/aims.

Specific Aims and Hypotheses

This pilot trial will enroll 100 MCI patients who present to the departments of Psychiatry, Neurology and Internal Medicine at Columbia University and Duke University medical centers, ensuring broad representation for clinical relevance. In the treatment protocol, all 100 MCI patients will be randomized to CCT (suite of exercises) or active control (crosswords) for 12 weeks followed by regular booster CCT (active or control) sessions. Patients will be followed for a total period of 18 months (78 weeks) in the trial.

Aim 1 (main aim of the study): To assess change in cognitive and functional status over 18 months in MCI patients comparing CCT versus active control (crossword puzzles).

> Hypothesis 1. MCI patients randomized to CCT will show better cognitive outcomes (primary: ADAS-Cog; secondary: Neuropsychological Testing Composite Score, exploratory: Neurocognitive Performance Test (NCPT)), by the end of the 18-month trial compared to patients randomized to active control. We will also compare the changes in the two randomized groups on the Neurocognitive Performance Test (NCPT), an exploratory outcome that is an online cognitive assessment battery.
>
> Hypothesis 2. MCI patients randomized to CCT will show better functional outcomes (primary: UPSA, secondary: FAQ) by the end of the 18-month trial compared to patients randomized 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.

Aim 2: 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. 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.

Aim 3: We will examine differences in rates of progression to dementia, and AD, in the two randomized treatment groups.

> Hypothesis 1. The proportion converting to dementia will be lower in the CCT group compared to control.

Description of Subject Population

In this section, you are to describe each subject population of the study. The demographics of the population should reflect the gender and ethnic distribution of each population being studied. Enter each subject population's sample size, Gender, Racial, and Ethnic breakdown, and finally, describe each subject population.

Sample subject population:

Subject Population	Number of completers required to accomplish study aims	Projected number of subjects who will be enrolled to obtain required number of completers	Age range of subject population
Adults with Mild Cognitive Impairment (MCI)	50 at NYSPI; 50 at Duke University Medical Center	60 at NYSPI, 60 at Duke University Medical Center	55-95

Gender, Racial, and Ethnic Breakdown:

The total recruitment numbers for NYSPI/Columbia and Duke are 100 completers required to accomplish study aims. No minority group is excluded from research participation. Based on our current clinic distributions at NYSPI, 70% are expected to be non-Hispanic white, 15% Hispanic, 12% African American, and 3% Asian American, and this is the expected representation in the proposed study. Based on our experience in our clinics, women will constitute 55% and men 45% of elderly subjects.

Based on Duke's experience, they are likely to have a similar gender distribution to Columbia/NYSPI and an ethnic distribution of 90% Caucasian and 10% African American.
Description of subject population
All 100 patients whom we will include will need to meet criteria for cognitive impairment as specified in the Inclusion Criteria. Adults ages 55-95 of either gender will be included. Since the CCT platform is in English, patients should have sufficient facility with English to participate in the trial; this will be determined in a training session in doubtful cases

Suicide Risk Management Plan

This section will include all information regarding the Suicide Risk Management Plan.

Recruitment Procedures

This section will include all information regarding your study's recruitment process/procedures.

Describe settings where recruitment will occur.

The proposed study will be conducted at the New York State Psychiatric Institute. Patients will be recruited from NYSPI (Memory Disorders Clinic), CUMC (Behavioral Neurology Practice Group, referrals from Internal Medicine), and advertising. Advertising will include electronic media through CUMC's RecruitMe website recruit.cumc.columbia.edu and antidote.me/bridge. We will also advertise in the newspaper and on Facebook. We will also post the IRB-approved advertisement on bulletin boards at NYSPI and print the advertisement to distribute as a flyer to patients and families.

At Duke, we anticipate that subjects will be recruited from the current patient caseload of the investigators, Center for the Study of Aging and from referral by neurology, psychiatric, primary care, public health (inner city) and geriatric medicine clinics affiliated with Duke, as well as the Duke memory disorders clinics. Community referrals will be enhanced via advertisement. The recruitment rate at Duke will be very similar to NYSPI/Columbia and we estimate about 15 patients per year.

How and by whom will subjects be approached and/or recruited?

At NYSPI/Columbia, patients will be approached and recruited by Dr. Devanand through the Columbia University Medical Center and groups described above. We will use a web posting through recruit.cumc.columbia.edu, antidote.me/bridge, and Facebook. We will also advertise in the newspaper. We will also post the IRB-approved advertisement on bulletin boards at NYSPI and print the advertisement to distribute as a flyer to patients and families.

How will the study be advertised/publicized?

The study will be advertised on recruit.cumc.columbia.edu and on antidote.me/bridge, as well as on Facebook and in the newspaper. We will also post the IRB-approved advertisement on bulletin boards at NYSPI and print the advertisement to distribute as a flyer to patients and families.

Attach any ads/recruitment materials requiring review at this time in the Uploads section.

Clinical Trials:

Does this study involve a clinical trial? ☐ No ☒ Yes

Please provide the NCT Registration Number for your Clinical Trial. 03205709

YOU MUST REGISTER AT ClinicalTrials.gov IMMEDIATELY UPON RECEIPT OF IRB APPROVAL AND PRIOR TO ENROLLMENT OF THE FIRST SUBJECT. YOU WILL BE PROVIDED WITH A NCT REGISTRATION NUMBER ON REGISTRATION. PLEASE REVISE THIS SECTION OF THE PROTOCOL SUMMARY FORM TO INCLUDE THE NCT NUMBER AND RE-SUBMIT AS AN AMENDMENT TO THE IRB.

Concurrent Research Studies

In this section, please identify if subjects in this study participate in or will be recruited from other studies.

Describe where subjects are recruited from.

We will recruit patients who complete protocol #6655, meet inclusion/exclusion criteria for this protocol, and express interest in study participation.

Describe the recruitment source for (Must provide IRB Number, PI and Title).

Subjects may also participate in protocol 7779 concurrently, which is an observational study with only one study visit. Any neuropsych testing measures that are identical among protocol 7779 and 7395 may be shared among the investigators in order to reduce the possibility of participant fatigue and practice effects. Copies of assessments and labs, including (but not limited to) APOE e4 genetic test results, will be shared from this study to reduce the burden to participants who are enrolled in #7779. The following data will be shared from the COGIT study: APOE genotype (ε2, ε3, and ε4 alleles), demographics, GDS, medications, Cognitive Reserve Index (CRI), Trail Making A+B (new variable-executive function to be added to the OSA/ApoE for data analyses), Cumulative Illness Rating Scale (CIRS-G), Auditory-Verbal Learning test (AVLT), Wechsler Logical Memory, MCI by ADNI criteria, and Clinical Dementia Rating (CDR) <1, MMSE.

Inclusion/Exclusion Criteria

This section details your study sample(s) and addresses the requirement for risk minimization.
You may choose to divide your sample by population (healthy controls vs. patient population) or by procedure (subjects who will have an MRI vs. those who will not) and then define different sets of criteria for each.
For each sample, create or insert a table to describe detailed criteria for study inclusion and exclusion and the method you will use to ascertain each criterion. The method of ascertainment may describe tests, scales and instruments. When relevant, indicate the level of training of the person who will make the assessment (e.g. clinical interview by a psychiatrist).
Inclusion/Exclusion Criteria need to be numbered and listed in outline form (see Table template below).

Sample 1

Inclusion CRITERION	METHOD OF ASCERTAINMENT
1. Males and females 55 to 95 years of age (inclusive) at the time of informed consent.	Patient Report
2. Subjective cognitive complaints, i.e., memory or other cognitive complaints, e.g., naming/language.	Patient Report
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.	Physician Evaluation
4. Folstein Mini Mental State (MMSE) score ≥ 23 out of 30.	Neuropsychological testing
5. A family member or other individual who is in contact with the patient and	Patient Report

consents to serve as informant during the study; this can be a telephone informant in the 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 internet speed for the study duration.	Patient Report

Exclusion CRITERION	METHOD OF ASCERTAINMENT
1. Diagnosis of dementia of any type.	Physician Evaluation
2. Current clinical evidence of schizophrenia, schizoaffective disorder, major depression, psychosis, or bipolar I disorder (DSM-IV TR criteria).	Physician Evaluation
3. Active suicidal ideation or plan.	Physician Evaluation
4. Current or recent (past 6 months) alcohol or substance use disorder (DSM-5 criteria).	Physician Evaluation
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 test battery.	Physician Evaluation
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,	Physician Evaluation

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.	Physician Evaluation
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.	Physician Evaluation
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.	Physician Evaluation
10. UPSIT (odor identification test) 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, e.g., current heavy smoker (less than 3% of older adults in our experience), will not receive the UPSIT but will continue to participate in all other aspects of the study.	Physician Evaluation
11. Patients lacking English-speaking ability as determined by self-report and clinical evaluation.	Physician Evaluation/ Patient Report
12. Regular online brain training or regular crossword puzzle user, defined as doing	Physician Evaluation

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.	Patient Report

Consent Procedures

Explain, in this section, the procedures for obtaining consent from study participants.
If the eligibility screening for this study is conducted under a different IRB protocol, enter the NYSPI IRB# 6655

Waiver of Consent / Authorization

The following sections are to be completed for the appropriate waiver/alteration of consent.

Waiver of Consent for use of Protected Health Information (PHI)

What records do you wish to review?
What information are you seeking access to?
Describe your plan to protect identifiers from improper use and disclosure.
Describe your plan to destroy the identifiers as soon as possible, consistent with the conduct of the research, or provide a health or research justification for retaining the identifiers or explain how retention is required by law.
Explain why the research could not be practicably carried out without the information (for which you are requesting access).
Explain why the research cannot be practicably carried out without the waiver.
Explain how/if subjects will be provided with additional pertinent information after participation.

Justification for Waiver or Alteration of Consent

Waiver of consent is requested for the following.
Explain why your research cannot be practicably carried out without the waiver or alteration.
Describe whether and how subjects will be provided with additional pertinent information after participation.

Waiver of Documentation of Consent

Would the consent form signature be the only link between the subject's identity and the research data?
Is breach of confidentiality the main study risk?

Is consent for this research procedure ordinarily not required outside of the research context? Explain.

Describe the study component(s) for which waiver of documentation is requested.

Waiver of Parental Consent

Explain why parental/guardian consent is not a reasonable requirement to protect the minor participants in this study.
If parental consent is waived, describe a mechanism that will be substituted to provide appropriate protections for the subjects.

Assent Procedures

In this section, please describe the procedures by which subject assent will be assessed and / or recorded.

If the patient appears eligible based on screening, Drs. Devanand, Kerner, and Goldberg will confirm by patient interview that all inclusion/exclusion criteria are met and they will go over the details of the study with the patient and the informant as described in the informed consent form. Subjects will also be informed that they need to have an informant available to be interviewed in order to be in the study. Patients will be given ample time to review the consent form and will be given the opportunity to ask questions. Throughout the study, the study physicians will cross-cover each other for patient assessments and management in the study. All study physicians are board certified psychiatrists and their clinical role is to serve as the study physicians.

Voluntary informed consent will be obtained from all subjects. The consent form describes the nature of the procedures and time requirements, potential risks, the confidentiality of information, the limited direct benefits, and the rights of research subjects, including their right to withdraw from the research at any time without loss of benefits to which they are otherwise entitled. It is made explicit that this protocol involves a double-blind, randomized controlled trial of computerized cognitive training versus a control condition with return visits at specified time points. The consent process also includes documentation of permission to obtain previous medical records, as needed. In addition, because of online cognitive testing and data storage using a study specific Lumosity platform, appropriate language in the informed consent for such research, including privacy and data sharing issues, will be included. Subjects will go to a study-specific platform portal that they access using study IDs only and hence Lumos will not have access to subject PHI.

Capacity to Consent:

Based on IRB requirements at both sites, MCI patients will be recruited by an experienced research coordinator or study physician who signs the consent form in addition to the patient. The inclusion/exclusion criteria are such that essentially all patients at the time of study entry will have the capacity to consent to the protocol. If a patient transitions to a diagnosis of dementia, or the Folstein MMSE declines to below 20/30, a repeat assessment of capacity will be made to ensure that the patient retains the capacity to continue in the protocol. The procedure is described below under Independent Assessment of Capacity.

In our experience, e.g., DOTCODE study at Columbia and Duke involving patients with depression and cognitive impairment (NYSPI IRB protocol #6459), even patients who are initially diagnosed with MCI and are given a diagnosis of dementia during follow-up invariably retain the capacity to consent in a study that lasts a total of 18 months.

All MCI patients are required to have the capacity to provide informed consent, since subjects will not meet criteria for dementia at initial evaluation. In this regard, for NYSPI/Columbia, the regulations of the Office of Mental Hygiene, New York State, as used by the New York State Psychiatric Institute IRB, will be followed. Local regulations will be followed at Duke. Under no circumstance will a patient objecting to participation be included in the study.

Informants:

In our prior studies, 92% of patients had at least one informant available for interview. Most informants provided information by telephone interview. In the proposed study, we will use this approach for informants (primarily for FAQ functional assessment) who cannot accompany the patient for visits. All informants will need to indicate verbal consent to provide this information on an ongoing basis during the study. The informants will solely be interviewed to provide information on the study participants and will not be providing any information about themselves. Therefore, the informants are not considered research participants, and do not require written consent. We will obtain verbal consent from all study informants prior to each interview and note this in the participants' charts with the following language, "I obtained verbal consent from the caller to participate in a confidential telephone interview for _____."

The IRB-approved forms for informed consent and for assessment of capacity are made part of the patient's permanent medical record, with a copy being filed in the research chart.

The individual obtaining consent will explain to subject that some assessments (select neuropsychological testing and informant interviews) may be completed remotely, by a Study Physician, member of the investigational staff or by the research coordinator. MRI and majority of subject neuropsychological testing must be completed in person, on site. The individual obtaining consent will explain the technology requirements necessary for completion of remote assessments, and will stipulate that HIPAA compliant phone calls will be the method used. The subject will be given sufficient time to discuss any concerns they may have, such as access to a private space in which to complete remote assessments, and home access to adequate devices, cell signal or touch tone phone. Documentation of the aforementioned discussion will be retained in subject research chart.

Additionally, COVID-19 risks related to travel for research purposes will be discussed by the individual obtaining consent. The individual obtaining consent will explain that during Stage I reopening, research participants will only come on-site if absolutely necessary for completion of study assessments and procedures.

Any participant coming to NYSPI, Mind Brain Behavior Institute (MBBI) and Citigroup Biomedical Imaging Center (CBIC) at Weill Cornell Medical College for conduct of study assessments and procedures may be at

increased risk of contracting COVID-19 en route. The Principal Investigator and study team will take all precautions necessary to ensure that risk remains minimal, including paying for the transport of participants to site via car service or ride share (utilizing services such as Uber or Lyft).

Research Coordinator will remind participants to wear mask and practice frequent hand hygiene while in transport to study visit, during the 24 hour pre-visit reminder call. The subject will be provided with ample time to discuss this point and have any questions answered.

Documentation of the aforementioned discussion will be retained in subject research chart.

Persons Designated to Discuss and Document Consent

Please list all the names of persons designated to obtain consent / assent. All persons must complete CITI training for NYSPI. The PI affirms that each name listed has completed the appropriate training.

Devanand, Davangere, MD
Goldberg, Terry
Huey, Edward, MD

Kerner, Nancy, MD
Ndouli, Charlie
Phillips, Julia
Pollina, Julianna

Independent Assessment of Capacity

This section is designated for those studies that have been identified where subjects May Lack capacity to consent.

Describe the Methods/procedures for capacity assessment.

Based on IRB requirements at both sites, MCI patients will be recruited by an experienced research coordinator or study physician who signs the consent form in addition to the patient. The inclusion/exclusion criteria are such that essentially all patients at the time of study entry will have the capacity to consent to the protocol. If a patient transitions to a diagnosis of dementia, or the Folstein MMSE declines to below 20/30, a repeat assessment of capacity will be made to ensure that the patient retains the capacity to continue in the protocol. In our experience, e.g., DOTCODE study at Columbia and Duke involving patients with depression and cognitive impairment (NYSPI IRB protocol #6459), even patients who are initially diagnosed with MCI and are given a diagnosis of dementia during follow-up invariably retain the capacity to consent in a study that lasts a total of 18 months.

As in several protocols involving similar patient samples, participants with MCI will not be required to appoint a surrogate at the beginning of the study. However, as in protocol# 6655 and related protocols, they will all need to provide an informant who needs to be available to complete the required informant interviews.

All MCI patients will have an MMSE score 23 or greater at the beginning of the study and therefore are expected to have the capacity to provide informed consent. Based on our experience, we anticipate that very few participants will deteriorate to the point of needing to appoint a surrogate. If, however, the MMSE declines to below 20 and there is concern about whether capacity to consent is still present, we will obtain an independent evaluation to determine the patient's status in this regard. If the patient no longer has capacity to consent, the patient will need to retain the capacity to designate a surrogate we will use the PCS forms to document the choice of surrogate: PCS Form III(b) Record of Choice of Surrogate, PCS Form III(c) Statement by Witnesses, and PCS Form IV Consent by Surrogate.

For NYSPI/Columbia, New York State regulations regarding capacity to consent, as used by the New York State Psychiatric Institute IRB, will be followed as we do in all IRB protocols for the following group in the study. Under no circumstance will a patient objecting to participation be included in the study.

1. A psychiatrist or licensed clinical psychologist who is independent of the research must confirm that the patient still retains the capacity to designate a surrogate, i.e., identify the surrogate and indicate that the surrogate can consent on the patient's behalf for the research study. Drs. Bret Rutherford, Joel Sneed, Karen Marder, Karen Bell, Joan Prudic, Scott Small, Clara Boyd, Alon Seifan, and Jamie Noble will be the independent evaluators for this study. They will follow the procedures described here using the forms attached as an addendum to the Informed Consent Form.

2. The document designating the research surrogate must be witnessed by two persons who areindependent of the research. The psychiatrist or licensed clinical psychologist who assesses the patient's capacity to choose a surrogate may also be witness to the choice of the surrogate.

3. If the patient chooses a surrogate but is unable to sign the document, another person may sign for the patient and the two witnesses shall, in writing, confirm the patient's choice of a surrogate and witness the signature of the person signing for the patient.

4. The surrogate cannot function as a witness to the choice of the surrogate. A family member or friend of the patient who is not the surrogate may function as a witness.

5. The surrogate cannot be an administrator or employee of the facility at which the research is conducted or the facility conducting the research. This restriction does not apply if the person is related to the patient by blood, marriage, or adoption. The selection of a patient's spouse as a surrogate is revoked upon the legal separation or divorce of the patient and spouse unless the patient specifies otherwise.

6. Notice of the appointment of a surrogate must be provided to the Mental Health Legal Service (MHLS). We will inform MHLS each time a patient who lacks capacity to consent and appoints a surrogate is recruited for this protocol.

If your study involves subjects who DO LACK capacity to consent, please justify.

We anticipate that very few participants will deteriorate to the point of needing to appoint a surrogate. If, however, the MMSE declines to below 20 and there is concern about whether capacity to consent is still present, we will obtain an independent evaluation to determine the patient's status in this regard.

Procedures for surrogate consent.

If the patient no longer has capacity to consent, the patient will need to retain the capacity to designate a surrogate we will use the PCS forms to document the choice of surrogate: PCS Form III(b) Record of Choice of Surrogate, PCS Form III(c) Statement by Witnesses, and PCS Form IV Consent by Surrogate.

Study Procedures

Provide a clear, concise narrative of study procedures with special attention to the subjects' involvement. Detail the overall study timeline and location of study procedures, list all interventions, assessments and interviews, estimate the duration of each procedure, provide dosing schedules, identify study personnel involved in each procedure, and provide credentials for relevant personnel. If treatment is provided, specify the minimum credentials for providing that treatment. For complicated study designs, we strongly encourage attaching tables, flow-charts, and study algorithms.

Describe the Procedures Required for This Study:

I attest to follow the COVID-19 Safety Guidelines for Columbia Psychiatry, NYSPI and CBIC's Re-Entry outlined in the NYSPI Director's June 1st memo, which include but are not limited to:
-Infection Control/PPE – Guidelines
-Research participants will only come on-site if absolutely necessary for study procedures.

-No volunteers/externs on-site during Stage 1.

-Clinical research teams will screen their participants for COVID symptoms (night before and day of onsite visit, documenting this in the chart), and escort them in and out of the building.
-COVID/COVID-like symptoms in participants will be reported to the IRB via PRISM as an SAE.

Roles and Responsibilities:
1. Columbia University Medical Center/ New York State Psychiatric Institute

Dr. Davangere Devanand will be the Principal Investigator. He will recruit approximately half the subjects at Columbia/NYSPI. He will advise and back-up Dr. Kerner for the patients that Dr. Kerner treats and follows during the study. Dr. Devanand is responsible for making diagnostic judgments for all patients at baseline and at subsequent major time points. He is also responsible for the conduct and coordination of all procedures, all study personnel and the supervision of research assistants. He will liaison with Dr. Howard Andrews, who will be responsible for managing the database. He assumes final responsibility for data analysis, presentation of results and writing of publications for this project. He will train and maintain ongoing reliability with Dr. Kerner on rating instruments and supervise the research assistant on the administration of relevant rating scales.

Dr. Terry Goldberg is the Co- Investigator. He will be responsible for patient recruitment with Dr. Devanand and will be the study neuropsychologist at NYSPI/Columbia. He will maintain reliability of the research assistant raters on the administration of relevant rating scales. He will also assist Dr. Devanand in data analysis, presentations and publication of results from this study.

Dr. Joel Sneed (with his team) will be the Analysis Research Rater. He established strong intra- and inter- rater reliability in the conduct of these procedures, including several approaches to assessing the hippocampus and entorhinal cortex. These volumetric assessments will involve identification of the hippocampus and parahippocampal gyrus and entorhinal cortex, demarcation of brain tissue from CSF, and contour tracing in a large number of slices per subject. These procedures are conducted on a Sun workstation, located at New York State Psychiatric Institute, which will be used for this project.

Dr. Howard Andrews will be the PI of the RFMH subcontract and Database Manager. Dr. Andrews will manage the RFMH subcontract. He is a highly experienced database manager and programmer who has functioned in these roles for several research studies. He will be the database manager for the proposed study. With his team, he will help to develop the forms used in the study in collaboration with Dr. Devanand, program the computers for data entry, develop algorithms for range checking and logical checking, and prepare programs to generate reports to the Principal Investigator regarding subject accrual, follow-up scheduling, and error checking. Dr. Andrews will work closely with the research staff to make any necessary corrections to the database and will maintain an audit trail documenting these changes. Dr. Andrews will arrange for backup of all project data and for verification of database integrity. He will do the required programming to create output files in SPSS or SAS format to the investigators.

Dr. Seonjoo Lee will be the statistician. Dr. Lee will be responsible for the statistical analyses for the project. She has worked closely with Dr. Devanand and is also experienced in the overall statistical approaches to data obtained from image analysis. She will work closely with Dr. Devanand, the database management team and the MRI image analysis team that will provide the necessary derived variables from MRI that will be used in the broader analyses of the entire project.

Dr. Hyun Kim will be a study personnel. She will be responsible for reviewing study procedures and questionnaires. She will also assist Dr. Devanand in data analysis, presentations, and publication of results from the study.

Dr. Nancy Kerner is another Co- Investigator. Dr. Kerner will complete rating instruments and supervise the research assistant on the administration of relevant rating scales. She will also assist Dr. Devanand in data analysis, presentations, and publication of results from this study.

2. Duke University Medical Center

Dr. P. Murali Doraiswamy will be the study PI and responsible for managing the project at Duke and coordinating with Columbia, make sure that the deliverables are met with the planned time-frame and budget. He will oversee regulatory, recruitment and all study conduct. He also serves as a study psychiatrist at Duke to oversee the study coordinator, study radiologist and any other physicians in their research activities. He will also see the patients at their visits and oversee their treatment in the study. He will assist with interpreting results, and with publication and dissemination.

Dr. Jeffrey Petrella will be a study investigator. In this study will serve as the study radiologist to do clinical reads on the Duke scans and as the fMRI expert to coordinate the acquisition, QC, and analyses of fMRI data.

Dr. Elena Perea is an experienced geriatric focused psychiatrist who will provide back up to the PI and see patients for usual care over the course of the study.

Clinical Research Coordinator: Caroline Hellegers. She will assist in all aspects of study coordination including recruitment, consent, neuropsychological testing, data entry and regulatory records.

3. Queens College, City University of New York (CUNY)

Dr. Joel Sneed will be the site PI. Because of his expertise in the quantification of cerebrovascular disease, measurement of executive functioning, and knowledge of the computerized cognitive training paradigms, Dr. Sneed's primary role on this study will be supervising the collection and scoring of neuropsychological data, quantifying white matter hyperintensity burden on MRI, quality assurance between sites with regard to online game training and data collection.

Graduate Research Assistant (Sara Rushia) will assist Dr. Sneed in overseeing neuropsychological assessment and scoring of the neuropsychological test battery. Under Dr. Sneed's supervision, this individual will assist in the preparation of structural MRI data for the assessment of cerebrovascular disease (both qualitative and quantitative methods will be used). The GRA will work with Dr. Devanand's and Dr. Doraiswamy's research assistants to coordinate study assessments and procedures (neuropsychological testing and MRI) as well provide quality assurance and technical assistance to patients regarding computerized (online) cognitive training. The GRA in collaboration with Dr. Devanand's and Dr. Doraiswamy's research assistants will also be responsible for data cross-checking and ensuring the integrity of the research charts and forms that are submitted for data entry to the database management group. Sara may administer the neuropsychological test battery to patients during the in-clinic study visits.

Structural image Analysis at NYSPI/Columbia for MRI acquired across both sites

MRI will be conducted in the NYSPI MRI facility, Columbia University's Zuckerman Mind Brain Behavior Institute, or Citigroup Biomedical Imaging Center at Weill Cornell Medical College.

For volumetric image analysis, all data from scans done at Duke will be sent to NYSPI/Columbia using secure ftp. Since the two GE scanners are essentially identical, there should be no issues with hardware/software compatibility in reading all the data sent from Duke to NYSPI. The MRI volumetric analyses will be conducted by Dr. Joel Sneed and his team.

Image Analyses at Duke for fMRI data acquired at both sites

fMRI scan data from NYSPI will be sent to Duke using secure ftp. Dr Petrella, who directs the Alzheimer's Imaging Research Lab, is an expert in fMRI data analyses and directs a core BIAC faculty. He will oversee QC and fMRI analyses for this study using MATLAB, SPM8 and FSL and will coordinate with Drs Doraiswamy, Devanand and the Columbia/NYSPI MRI and statistical teams on the analyses.

Computer and database facilities- Data Coordination

The data collected in this study will be entered and monitored by the Database Management Unit at NYSPI. This unit is headed by Dr. Howard Andrews, whose unit has 2000 square feet of office space, and can easily accommodate the data management activities in this proposal.

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. Additional security is provided by SIR software. Authorized users will include one and at most two research assistants/coordinators at each participating site who will conduct data entry; the only 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.

These guidelines and procedures, specific to COVID-19 risk reduction and infection control, will be followed throughout Stage I re-opening, during all study visits, assessments and procedures:

In Preparation for every Study Visit at NYSPI/MBBI/CBIC:
One additional party (i.e. informant) may accompany subject to research study visit.

Subjects and informants will complete A "COVID-19 Exposure Questionnaire,"over the telephone (with research coordinator) within 24 hours prior to scheduled, in person study visit. Questions cover active COVID-

19 infection and/or exposure. The research coordinator will record responses to all questions as provided by subject and informant and will store completed questionnaires in subject research chart.

If subject and/or informant answers "yes" to any question endorsing active COVID-19 infection, symptoms and/or exposure within the past 14 days, the research study visit will be delayed by at least 14 days with a similar reassessment completed at that time, before the patient is seen. Actual COVID-19 diagnosis/COVID-19 like illness, in all participants, will be logged by study staff and reported to the IRB as a SAE.

If active COVID-19 infection and/or exposure are not identified by phone screening, subject and informant will be brought in for visit.

Building Entry and Screening:

Staff:

Effective June 15, 2020: all staff coming onsite to NYSPI will be asked to complete an online screening questionnaire, before arriving, to attest that they do not have COVID-19 symptoms or recent exposure. This is intended to help staff to self-monitor. The questionnaire will be sent every morning, by NYSPI email, and completion will be audited to ensure adherence.

In instances where any staff member endorses COVID symptoms via daily emailed questionnaire, respective staff member will notify manager and PI and work from home or take Sick Time. Coverage will be assigned.

The only building entry access points for staff will be via the NYSPI Kolb Building at 40 Haven Ave, and the NYSPI parking garage. All employees will be funneled into a single file at respective entry point, to facilitate use of thermal scan temperature reader.

Designated NYSPI staff (from Security and/or Infection Control) will be stationed at aforementioned building entry points and will obtain staff temperature in building lobby.
Questions regarding active COVID symptoms and recent exposure will be posed to staff as well.

In scenarios where staff exhibit a temperature greater than or equal to 100 degrees Fahrenheit (or any active COVID-19 like symptoms or recent exposure) they will be sent home, and back up staff notified, to arrange for work on site. While on site, only one staff member is permitted per each office space.

Staff may remove mask only if sitting in a private office, with door closed and no other occupant(s).

Participants:
Study participants must arrive as scheduled, at the facility, only by private vehicle or Uber/Lyft (reimbursed by grant).

In Preparation for every Study Visit at NYSPI/MBBI/CBIC:
One additional party (i.e. informant) may accompany subject to research study visit.

The 1051 Riverside Drive entrance will be open for participant and informant entry only.
Temperature checks for participants will take place at all facility entrances using contact free thermometers (completed by research coordinator, who will await subject/informant in NYSPI lobby).

Coordinator will log subject and informant temperature on "Subject/Informant Temperature Log").
Temperatures at or above 100 degrees Fahrenheit will result in subject/informant denial of facility entry. The respective in-person visit will be rescheduled.

If temperature screen is passed, the research coordinator will administer the "New York-Presbyterian COVID-19 Clinical Screening Process Form" to both subject and informant. This NYP form will be administered upon subject/informant building entry at NYSPI in order to maintain uniformity in queries posed across facilities. Subject and informant may proceed with in person session if negative for COVID-19 symptoms and exposure.

Subject Temperature Log and completed "New York-Presbyterian COVID-19 Clinical Screening Process Form" will be filed in the subject research study chart, by the Research Coordinator.

All Parties:
Masks will be worn by all parties at all times; if participants do not have a mask, they will be provided with mask(s) by staff, who will always keep extra masks on hand (in addition to mask dispensation at building entrance).

Six feet of distance will be maintained between research staff and participants for all research assessments, except for procedures where this is not possible.

Hand Sanitizing:
Staff and study participants will be required to wash their hands per institutional protocol, upon entering the building; prior to and after each study visit; and when they believe hands may have been soiled. Hand sanitizer (over 60% alcohol) will be available in all hallways and clinic spaces.

Clinic Space and Rooms:
Three people may be in a large clinic room at any given time; the room will require the facility to maintain 6 feet of space between subject/informant and research staff, e.g., 'Black' treatment room in clinic, or a conference room that will be scheduled for use. For smaller clinic interview rooms, a maximum of 2 people will be permitted in the room.

As a general rule, N95 masks will be worn anytime a research staff member cannot maintain 6 feet of distance from subject/informant. Face shield will also be available for staff use.

After each research study visit or procedure is complete, MDC research staff will disinfect areas and equipment used, with SaniCloth or Clorox Wipe. Staff and participants will dispose of disposable PPE in the trash.

When the study visit is complete, subject and informant will be escorted directly out of the building by a research staff member and discharged home: they cannot return to the clinic space or any other area of the building.

SCREENING VISIT
At the time of screening at NYSPI, the patient will be evaluated by a treating physician. In addition, a MMSE and the Logical Memory subtest of the Weschler Memory Scale-III will be administered at the initial evaluation by the research coordinator. If the patient meets protocol inclusion and exclusion criteria, and is willing to participate, the research team will obtain informed consent. Medical records will be obtained from the subject's primary care physician as needed. As part of the screening evaluation, a comprehensive history will be taken to include age, age-at-onset of memory problems, family history of memory problems, handedness, education, and occupation. Medications will also be recorded. The following scales and questionnaires will be administered: Geriatric Depression Scale, Cognitive Reserve Index, Physical Activity Assessment, History of Game Use Questionnaire, Cumulative Illness Rating Scale- Geriatrics, and Framingham Stroke Risk Scale. A blood sample for APOE genetic testing will be collected. The sample of blood drawn will be approximately 8.5 cc, 1.72 tsp. Additional blood samples will be taken: Chemistry (1.2 teaspoons of blood), Complete Blood Count (.8 teaspoons of blood), and Thyroid Function (1.2 teaspoons of blood). Therefore, the total amount of blood taken will be about 5.2 teaspoons.

All eligible patients will also be asked to provide an informant who will be available (in-person or by phone) and willing to provide information or responses to questionnaires and interviews.

For patients who meet the study entry criteria, informed consent will then be obtained by the research team and the patient will be randomized to one of the two treatment groups, CCT arm and active control arm. Individuals will be stratified by MCI type (eMCI or lMCI) and age (70 and below; 71 and above) to ensure comparable representation of MCI type and age across the treatment groups. 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 consent form states that they are being assigned by chance (1:1) to CCT or CPT. The term "control" will not be used to reduce the participant's expectation bias.

Patients will be instructed to complete 48 thirty-minute sessions of CCT over 12 weeks using a study specific research Lumosity platform that is separate from their public platform. Four 30 min sessions will be completed per week and will be accessed by logging into a de-identified online Lumosity account provided for each patient with the code being maintained only by the site. The complete list of the game battery includes Tidal Treasures, Speed Match, Color Match, Word Bubbles, Train of Thought. Familiar Faces, Memory Matrix, Lost in Migration, Brain Shift, Trouble Brewing, Ebb and Flow, Masterpiece, River Ranger, Word Snatchers, Speed Pack, Disillusion, Editor's Choice, and Continuum . Each session will consist of a random selection of 6 modules. Each requires the use of various cognitive abilities and will scale in difficulty with the patient's progress. A complete table of selected Lumosity games has been uploaded.

Participants in the CCT and the crossword conditions will spend the same amount of time training (4 times per week for 12 weeks, 30 minutes per session). Responses are entered via mouse to select the clue and the keyboard to answer. Clues do not need to be completed in order and there is no indication of a correct or incorrect response at time of entry. Upon submission, the participant can see what errors were made. Once time runs out, the participant is prompted to return at the next session for a new puzzle. Participants will not be able to look up the answers in either group. Rather, global automated feedback is given in a similar manner for both groups. Crosswords are not systematically increased in difficulty, since they are intended to mimic the crosswords puzzles an average person does in a daily
newspaper. All programs are completed on the computer.

Throughout study weeks (weeks 12, 32, 52 and 78), remote administration of subject and/or informant measures may be carried out. Measures administered remotely will be conducted by the Study Physician, member of the investigational staff, or research coordinator, using a HIPAA compliant telephone call.

BASELINE/ WEEK 0 VISIT
These guidelines and procedures, as well as the guidelines and procedures stipulated at the top of the

"Study Visit Procedures" section of the PSF(prior to description of screening visit) will be followed throughout stage I re-opening:

Six feet of distance will be maintained between research staff and participants for all research assessments except for procedures where this is not possible, e.g., UPSIT.

While waiting in respective facility waiting area, staff will always maintain a distance of at least 6 feet from participants (subject and informant do not need to maintain a 6 foot distance from each other).

For neuropsychological tests: Research coordinator (tester) will place the materials on the clinic room desk and then guide the subject to complete the test, including verbal and written responses required for specific tests, from a distance greater than six feet whenever possible. If a clinic room with more than 6 feet of distance between tester and subject is not available, a conference room will be used.

Participants will be scheduled so that there is no overlap between participants in the waiting area.

Patients who are enrolled will be asked to come for the baseline visit, typically 1 week after the screening visit, and also following the MRI scan of the brain. Other measures include Contributing Features to MCI Form, ADAS-Cog 11, Online Neuropsychological Cognitive Performance Test, UPSA, Expectancy Scales (Participant and Informant), Stop/Bang Questionnaire, and the neuropsychological testing battery including the AVLT, WAIS-III Block Design subtest, Verbal Fluency, 15-item Boston Naming Task (BNT), Trail Making A and B, Visual Reproduction Test, and the WAIS-III Digit Symbol Substitution Test. The participant will also complete the 40-item UPSIT to assess baseline olfactory performance. The informant will complete the FAQ.

UPSIT specific: subjects will need to remove their masks during this smell test, but mask will be replaced by subject as soon as UPSIT is done. Subject will wear a face shield during testing administration, provided by staff. Study staff will give the subject the test to self-administer, and tester will guide the subject from minimum 6 feet away.

When neuropsych and UPSIT tests are complete, subject will be instructed to place all testing materials in a tray, which study staff will have placed on the desk prior to the visit session. At end of session, research coordinator will perform hand hygiene after interacting with materials handled by subjects. Non paper testing material will be disinfected with SaniCloth or Clorox wipes immediately after session.

MRI will be conducted at Columbia University's Zuckerman Mind Brain Behavior Institute (MBBI) or Citigroup Biomedical Imaging Center (CBIC) at Weill Cornell Medical College. For procedures conducted with collaborators (MBBI, CBIC) we will follow each facility's existing, and in the future updated, regulations.

MBBI:
The research coordinator will administer the "New York-Presbyterian COVID-19 Clinical Screening Process Form" to the subject and the informant after they have passed the temperature check at the appropriate lobby entrance. If responses to questions on the form indicate that the subject and informant do not have evidence of acute infection or exposure, the research coordinator will escort them to MBBI for MRI procedure. If either the subject or informant provide responses that indicate they may have an acute infection or exposure, the visit will be rescheduled.

Informants will not be permitted to attend actual MBBI MRI scan, and will wait in facility waiting room, unless there is an emergency.

Research coordinator will remain at MBBI MRI through completion of scan and will escort

subjects/informants to exit and go home.

CBIC:
All research participants and staff will be required to arrive at CBIC, by private vehicle (i.e. personal car) or by a service such as Uber or Lyft. MDC will pay for car services/ride shares and parking/tolls.

Research staff will meet the subject and informant at CBIC's east 72nd street entrance. Masks will be worn by all parties, at all times.

Scheduling: Staggered appointment times and increased exam duration will be utilized to avoid groups of subjects arriving together.

Pre-registration: All required paperwork will be completed prior to the subject's arrival. Research Coordinators will complete a phone prescreening 24 hours before the appointment, through which they will complete the

CBIC COVID questionnaire (attached in "Uploads"). If the subject reports possible COVID exposure or a fever above 100.0 Fahrenheit, the Research Coordinator will call CBIC to cancel the appointment.

Research Coordinator will also complete the "CBIC MRI Safety Questionnaire" with the subject, and must email the completed, scanned document to CBIC at least 24 hours before the subject's scheduled MRI.

Other forms such as the "Sponsored Research Order Form" will be sent to appropriate CIBIC staff advance of MRI. For subjects who need to sign any paperwork on site, at CBIC, we will provide a sanitized pen and re-sanitize before using the pen for other subjects.

Only caregivers or Research Coordinator will be allowed to accompany subjects into the Center. Lobby: All waiting room chairs will be separated by a distance of at least 6 feet.
Elevator: There is 1 elevator at the Center, no more than 2 people may be in the elevator at a time.

Temperature Screening: Completed by RN as soon as subject arrives at CBIC. Any subject/visitor with a temperature reading at or above 100.0 Fahrenheit will not be permitted building entry.

Use of PPE: CBIC is operating under the assumption that any subject arriving at the Center may be infected with COVID-19. All subjects and all staff will wear a surgical mask at all times. If subjects don't have a mask, they will be provided one by CBIC. Face shields, goggles and gowns will be utilized for exams requiring extended face to face contact.

Cleaning of Modalities/Exams rooms: Research Coordinator will have use of the exam room for pre- scan procedures. Exam rooms will be wiped and sanitized between patients by CBIC staff. The MRI scanner will be cleaned after every scan by CBIC Technologists. Restrooms are cleaned by building staff on a daily basis and will taken out of use if a COVID-19 positive or PUI (Patient Under Investigation) patient uses until cleaned.

Only the subject will attend the actual MRI scan. When scan is over, research coordinator, subject and informant will leave the facility taking the same path they entered the facility through.
Subject and informant will be escorted out and instructed to go straight home. 12-WEEK VISIT
All infection control guidelines and procedures stipulated at the top of the "Study Visit Procedures" section of the PSF (prior to description of screening visit) will be followed, as well as those infection control guidelines specific to neuropsychological testing, indicated in the Baseline/Week 0 visit description.

The GDS, FAQ, MMSE, ADAS-COG 11, User Engagement Scale, the neuropsychological testing battery, History of Game Use Questionnaire, and Digit Symbol Substitution Test will be completed. The participant will also complete the NCPT online cognitive test and cognitive training or control training booster session. The study physician or neuropsychologist will complete the Diagnosis Form. Research staff will also complete the Concomitant Medication Form.

20 -WEEK VISIT
This visit will be a follow up evaluation done over the phone. The FAQ will be completed by the informant. The participant will also complete cognitive training or control training booster session.

32-WEEK VISIT
All infection control guidelines and procedures stipulated at the top of the "Study Visit Procedures" section of the PSF (prior to description of screening visit) will be followed, as well as those infection control guidelines specific to neuropsychological testing, indicated in the Baseline/Week 0 visit description.

The GDS, MMSE, FAQ, Expectancy Scale (Participant and Informant), and UPSA will be completed. The study physician or neuropsychologist will complete the Diagnosis Form and Contributing Features to MCI Form. The participant will also complete cognitive training or control training booster session. Research staff will also complete the Concomitant Medication Form.

42-AT-HOME BOOSTER SESSION

During week 42, participants will complete a booster session (4 sessions) of at-home computerized cognitive training.

52 -WEEK VISIT
All infection control guidelines and procedures stipulated at the top of the "Study Visit Procedures" section of the PSF (prior to description of screening visit) will be followed, as well as those infection control guidelines specific to neuropsychological testing, indicated in the Baseline/Week 0 visit description.

The GDS, FAQ, ADAS-COG11, neuropsychological test battery, Digit Symbol Substitution Test, and MMSE will be completed. The participant will also complete cognitive training or control training booster session. Research staff will also complete the Concomitant Medication Form.

64-AT-HOME BOOSTER SESSION

During week 64, participants will complete a booster session (4 sessions) of at-home computerized cognitive training.

78 -WEEK VISIT
All infection control guidelines and procedures stipulated at the top of the "Study Visit Procedures (prior to description of screening visit) and Baseline/Week 0 sections of the PSF will be followed.

A MRI scan, GDS, CIRS-G, FAQ, MMSE, ADAS-Cog11, neuropsychological testing battery, Digit Symbol Substitution Test, Expectancy Scale (Participant & Informant), UPSA, UPSIT, History of Game Use Questionnaire**,** and User Engagement Scale, **Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS)** will be completed. will be completed. The study physician or neuropsychologist will complete the

Diagnosis Form and Contributing Features to MCI Form. The participant will also complete the NCPT online cognitive test and cognitive training or control training booster session.

Time Line. The sample (n=100) will be recruited over 3.5 years (includes 2 months start-up time to set up CCT platform and review MRI phantom scans). Treatment duration is 1.5 years. Total project duration is 5 years. Data entry/cleaning will be done throughout the project. Analyses and publications from baseline data will begin during the study and analyses of trial results will be done at the end of the trial.

Study duration: Total study duration may exceed 78 weeks for those participants encountering delays to in person assessments and/or procedures related to COVID-19 specific pauses to research protocol implementation. Any pause to research activity, specific to COVID-19, has, or may, be put into place as part of institutional risk reduction initiative(s). From a research perspective, this delay will be addressed by evaluating time in study as a covariate in statistical analyses of outcome measures, as appropriate.

Blindness of raters. The raters completing the outcome measures will be blind to which type of cognitive training (active or comparison) the patient is performing. Participants will be instructed not to discuss their online training with any tester or rater in order to maintain blindness.

Diagnosis. We expect a minority of patients to be diagnosed with dementia during the 18-month study. At each site, the new NIA clinical criteria (not the biomarker criteria) will be used to diagnose dementia, and possible and probable AD. “Possible” refers to the presence of comorbid conditions, not necessarily a decreased likelihood of the diagnosis of AD as compared to probable AD. We use standard criteria for Lewy body disease, and vascular and mixed dementia (NINDS-AIREN criteria, recognizing possible overlap). Frontotemporal dementia, including Pick’s disease, is diagnosed by the Lund-Manchester criteria.

Gender and minority. Gender effects will be evaluated in the main analyses. If there are enough subjects in a minority group, their data will be analyzed and compared to the rest of the sample.

Autopsy. Few deaths are expected during the study. Nonetheless, autopsy procedures are available and are organized and highly effective at the Columbia University and Duke University ADRCs.

Clinical Evaluation. History includes chief complaint, referral source, age, age-at-onset of cognitive decline, handedness, education, occupation, medical history, medications used. Alcohol/substance use disorder, head injury, stroke, hypertension, cardiac disease, thyroid disease, other medical conditions, surgery, and recent hospitalization will be assessed at each visit. Family History of dementia, AD, Down’s syndrome, stroke, cardiac disease will be documented. Cognitive Reserve Index a brief questionnaire of cognitive reserve will be collected.

Physician Evaluation. At the initial visit, the attending physician or designee will use standardized forms to collect an extensive history. We will obtain medical records from the participant’s primary care physician as needed.

Cerebrovascular Disease Risk Factors. We will give the Framingham stroke risk scale at baseline only (5 minutes).

During the study, interruption of treatment with a visit delay for up to 1 month will be permitted. Treatment and data collection will resume after the interruption and the patient will continue in the protocol. Any unanticipated or serious adverse events will be reported per IRB guidelines and assessed by our DSMB.

Intent to Treat/ Dropouts and missing data: The primary analyses will be on the Intent-to-treat (ITT) sample, i.e., all randomized subjects according to the treatment that they were assigned. Missing data on outcome variables will be dealt with by using (longitudinal) generalized linear mixed effects models that do not require complete measurements under the "missing at random" assumption. For MRI scan outcomes with just one pre and post measure, inverse probability weighting of cases with complete data will be used where weights are calculated based on the probability of a subject being a completer versus being a dropout. Sensitivity analysis will be performed to provide a range of plausible effect estimates that could arise due to non-ignorable missing data.

A few patients (some will convert to dementia) may receive donepezil or memantine during the trial. This will be documented for analyses and will not affect continued study participation until end-trial.

Criteria for Early Discontinuation

Define criteria that will be used to exit or drop subjects from the study and operationalize. Indicate the time points when such criteria will be applied, and describe the rating instruments, parameters, and thresholds that will lead to a decision to terminate a subject's participation and the role of the person who will make these determinations. Studies which include a medication taper and discontinuation may be asked to include an independent medical monitor (an MD not on the study team) who will aid the study team in determining whether study discontinuation is needed. In addition, explain procedures for managing subjects who are withdrawn from the protocol.
For treatment studies: To minimize risks to subjects, operationalized drop-out criteria should be defined so that subjects who worsen, or in some cases, fail to improve, are removed from the study and offered standard care. The threshold for drop-out should consider the level of risk associated with non-improvement for the specific disorder, the availability of alternatives, and the typical required duration of treatment. For example, emergence of suicidal intent, or psychosis, should prompt immediate clinical evaluation and withdrawal from the study.
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 crossword puzzles) 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. Reason for early termination will be documented in a Protocol Exit Form that will be part of the database and will be utilized in statistical analyses.

Blood and other Biological Samples

Describe how the sample will be used and indicate, when relevant, the amount of the sample. The IRB wants to know that the sample is sufficient for the purposes of the study, but that sampling is limited to what is minimally necessary.
If you've indicated that you intend to store a sample for future use, indicate where the sample will be stored, how long the sample will be stored, and to what purposes the sample will eventually be put. Check the IRB website at https://irb.nyspi.org/investigators/guidance/genetic-research for specific guidance and additional information about future use of DNA samples.

Apolipoprotein E (apoE). In comparing AD to controls, the odds ratio for apoE 4 heterozygotes is around 4 in clinical samples and 2 in community samples, with much higher odds ratios for the rare homozygotes. There are less robust effects for apoE4 predicting MCI conversion to AD. In our clinical MCI sample of 148 patients, apoE4 was a significant predictor of conversion to AD in patients > 70 years old. We will assess the apoE4 allele as potentially associated with response to CCT; there was an association between the apoE4 allele and cognitive improvement on donepezil in a prior trial. Apolipoprotein E genotype will be determined through the Human Genetics Resources Core (HGRC) lab at Columbia University. A portion of the blood will be sent out to Prevention Genetics for identification of APOE genotype. Using a standard protocol, DNA is amplified by the polymerase chase reaction (PCR). The genotypes are determined blind to subject status (patient or control) by the sizes of DNA fragments present.

Assessment Instruments

List all assessment instruments, indicate who will administer them and their credentials/qualifications. Provide an estimate the duration of each measure. The IRB wants to know that assessments instruments are appropriate measures for the purposes of the study and are no more burdensome than necessary. The IRB will consider the burden of assessment instruments (in terms of time, sensitivity of material, etc.) in the risk/benefit analysis. Please attach copies or otherwise provide all non-standard instruments.

Computerized Cognitive Training (CCT). CCT consists of computerized cognitive exercises that can be used to target specific neural networks in order to improve cognitive functioning through neuroplasticity. CCT has been used successfully to improve cognitive functioning in healthy adult populations and in several diagnostic conditions. The application of CCT in MCI has received attention only recently.

Lumosity has agreed to provide and maintain the CCT platform as described in their supporting letter with the grant application. We recently had a teleconference with Lumosity staff (August 12, 2016) and they remain entirely on board with their support of this project. Lumosity will provide, and maintain the platform but will not be involved in data analysis which will be conducted by study investigators only.

CCT program and platform. Patients will complete 48 thirty-minute sessions of CCT over 12 weeks using a study-specific research Lumosity platform that is separated from their public platform. Four 30 min sessions will be completed per week and will be accessed by logging into a de-identified online Lumosity account provided for each patient with the code being maintained only by the site. Each session will consist of a random

selection of 6 modules presented in random order. Each requires the use of various cognitive abilities and will scale in difficulty with the patient's progress.

Informing Subjects of their CCT Scores: Subjects are not blinded to their CCT and active control task scores since they serve to encourage them to continue and perform better.

Compliance: Compliance is monitored automatically through the website with reminder emails as needed.

All subjects will complete the short User Engagement Scale (version adapted for computer games) at week 12 and study exit. This measures multiple aspects of engagement, usability and satisfaction on a 5-point Likert scale and comprises both negative ("I felt annoyed when on this site", "the game was confusing") and positive ("I really had fun", "It was really worthwhile") items.

Troubleshooting / helping participants with logging into the at-home remotesession:
There have been a few instances where participants are not able to complete the remote at-home sessions using the Lumosity platform. Troubleshooting over the phone or in person if needed:
Confirm active Internet - did they successfully open Yahoo or Google?
Compatible browsers – listed in the Patient Instructions Manual.

Confirm login information. Each person's unique credentials can be found in the study set-up documents.It is allowed to invite a family member or neighbor to help with logging into the on-line battery; assistance will only extend to the actual logging in of the system and not with the actual tasks of the CCT. If these efforts fail, the participant will be brought back into the clinic for retraining and to assess the issue. If they are brought back into the clinic to troubleshoot, they can use the computer in the clinic and complete the remote session. In this situation, the participant will be asked to then repeat the same remote session at home on their own.

Depression Assessment. The Geriatric Depression Scale (GDS) will be used to assess for depression at the screening visit and all subsequent visits in the clinic: weeks 12, 32, 52, and 78. If GDS is greater than 5 at any visit, the patient will evaluated by a psychiatrist and an appropriate clinical referral will be made for treatment of depression. One week after referral, patient will be contacted by the research team to confirm that patient proceeded with follow-up.

Neuropsychological Testing Battery. The test battery was designed to tap into deficits in MCI, to assess key domains, and to be feasible. The Wechsler Memory Scale-III Logical Memory immediate and delayed paragraph recall, will be given at screening to determine inclusion criteria. The test battery will then be given at baseline, 12, 52, 78 weeks (32-week visit skipped to reduce practice effects). ADAS-Cog11 will be administered per ADNI procedures. The ADAS-Cog11 has maximum sensitivity for moderate AD, but is commonly used in MCI trials and has shown sensitivity to change with CCT. Memory. Verbal list learning and memory will be assessed by the AVLT. Total number of words learned over five trials and delayed recall (after a 15-min delay) will be obtained. Non-verbal learning/memory: WMS-III visual reproduction subtest. Visuospatial skills: WAIS-III Block Design subtest. Language tests: verbal fluency (letter and Animal Naming, 60-second trials), and a 15-item version of the Boston Naming Test (total spontaneous responses). Attention:

Trail Making A, and the WAIS-III Digit Symbol Substitution Test (DSST) that also taps into executive function and is a primary outcome measure. Executive function (switching component): Trail Making Test – Part B (Trails B).

Sleep Assessments. The Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) will be used to assess sleep and level of sleepiness at the endpoint visit (Week 78).

Other Measures: The Contributing Features to MCI Form is a form to be completed at weeks 0, 32, and 78 by the study physician or neuropsychologist. This form will indicate the contributing features to the patient's cognitive impairment. This measure will be used as a covariate; it is not a primary outcome measure. The History of Game Use Questionnaire is a questionnaire which assesses the past/present game use of the patient. This will be administered at screen, week 12, and week 78. This measure will be used as a covariate; it is not a primary outcome measure.

Medications: Medications will be listed and the Concomitant Medication Form (drug class list) will be completed at screen, 12, 32, 52, and 78. At weeks 12, 32, and 52 only medications changes to benzodiazepines, narcotics, and anticholinergics will be recorded. This measure will be used as a covariate; it is not a primary outcome measure.

Neurocognitive Performance Test. The Neurocognitive Performance Test (NCPT; developed by Lumos Labs, Inc.) is a brief, unsupervised, online battery of cognitive assessments used to measure functioning in five cognitive domains. The cognitive domains 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 ("subtests"), of which there are 10 total, are online adaptations of widely used neuropsychological tests whose shifting to computerized administration does not affect the test property. NCPT has minimal floor and ceiling effects, has shown good test-retest reliability in pilot analyses of tens of thousands of volunteers, and discriminated MCI from normal elderly in a registry study done at UCSF (unpublished data). It takes about 30 minutes, can be done at home, and new content is generated via algorithms to enable multiple repeated testing. In this study, users will be trained by sites to successfully complete a practice session before they do at-home testing. In NCPT scoring, subtest scores are percentile rank normalized within specific age bins, so that raw scores are transformed to a normal distribution with a mean of 100 and standard deviation of 15. The scaled subtest scores are then summed and the transformation is repeated to generate the aggregate overall score. NCPT change is an exploratory outcome.

Functional Impairment. Functional impairment characterizes AD. We published the first report showing that informant-reported functional deficits (Pfeffer FAQ), but not self-reported deficits, strongly predicted the transition from MCI to AD during follow-up. The Pfeffer Functional Activity Questionnaire (also used in ADNI and NACC) will be given to the informant. We will also be administering the University of California Performance-Based Skills Assessment, UPSA. 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. It is objectively scored and does not

rely on informants who may have positive or negative biases. Here, we will use the validated, brief version of the task that includes the communication and comprehension/planning domains. The dependent measure will be the number of correct items. It takes about ten minutes to administer.

UPSIT
Olfactory identification deficits. Neurofibrillary tangles in the olfactory bulb are one of the earliest pathologic signs of Alzheimer disease (AD), and odor identification deficits during life are associated with tangles in the olfactory bulb and central olfactory projection areas at autopsy. Our Columbia team published the first large-scale clinical study showing that odor identification deficits (lower University of Pennsylvania Smell Identification Test, i.e., UPSIT, scores) strongly predicted progression from MCI to AD and that they contributed unique variance to this prediction in a model that also included SRT total recall, FAQ informant report, hippocampal and entorhinal cortex atrophy. Recently, we found similar results in a large epidemiological study with the additional finding that odor identification deficits, but not SRT total or delayed recall measures, were associated with cognitive decline in cognitively intact older adults. At baseline we will administer the UPSIT, which is a 40-item scratch and sniff multiple-choice test. The UPSIT has been used for over three decades and is extensively validated and highly reliable. We will explore odor identification test performance (total UPSIT score, range 0-40) as a potential moderator of response to CCT in this study.

MRI protocol. Image acquisition, pre-processing. At baseline and end-study, subjects at both sites will receive high-resolution T1-weighted IR prepped 3D-SPGR, T2 FLAIR, and GE-EPI resting-state fMRI scans (adapted from ADNI-2, adni.loni.usc.edu). The total scan time is estimated at about 45 minutes. Subjects will receive a clinical read following the MRI scan. While the Table below lists the parameters we plan to obtain, because of software upgrades some of the parameters may change slightly.

WMH assessment. We will rate the severity of WMH on axial T2 FLAIR images using a semi-automated version of the Fazekas modified Coffey Rating Scale which we have used extensively in our studies of cerebrovascular disease. Using our published methods, we derive both total lesion volume as well as volume by ROI that parallels the Fazekas scale. All volume ratings are normalized to adjust for head size using intracranial cross-section area. Our group has shown strong inter-rater reliability (r >.9). Both WMH measures will be ancillary and may be included as covariates in analyses because they can influence cognitive ability.

Resting-state fMRI. Acquisition. Resting state: participants will be instructed to remain still with their eyes open and fixated on a white cross-hair displayed on a black background. Following shimming and calibration scans, a single 10-minute resting-state scan will be obtained at baseline and endpoint using the same imaging procedures. Pre-processing. Standard image pre-processing methods will be used with SPM8. Functional images will be assessed for poor quality, though in the proposed study significant loss of data due to this is likely to be small. The data will then be distortion and motion corrected. Non-blood-oxygen- dependent signal variation will be regressed out using time-courses from a region-of interest (ROI) placed in the CSF and in white matter. The resting-state data will then be co-registered with the high-resolution T1- weighted anatomic scan, normalized into the Montreal Neurological Institute (MNI) standard template space and smoothed . We will assess pre- and post-treatment differences in DMN connectivity with a single index for each subject scan (goodness-of-fit GOF index). GOF index is a quantitative measure describing DMN expression in an individual

rs-fMRI scan described in our published work and outlined here. Our primary approach will be to analyze the resting-state data time series using group independent components analysis (ICA) as implemented in the Group ICA of fMRI Toolbox. A GOF index that reflects the degree to which DMN maps of subjects with MCI match those of normal controls will be calculated for each subject's scan. We will image all individuals at the last available time-point, including point of dropout. We will control for duration between the two fMRI scans in analyses. We will also use graph theory metrics to compute network parameters in separate analyses.

We will run an exploratory analysis using resting state Spectral Dynamic Causal Modeling (DCM) to determine changes in effective connectivity in specific brain networks as well as more broadly across the whole brain. This Spectral DCM approach will be used to estimate effective connectivity within key networks, on the baseline and post-treatment resting state fMRI scans (N=110, each subject with 2 scans) using SPM12 software. We will first apply DCM to the rsfMRI in the spectral domain (spectral DCM) to estimate a directed network representing effective brain connectivity within the default mode network (DMN). The DMN is a primary apriori network of interest for our study based on our prior data from MCI and AD subjects. We will also apply it to the cognitive control network (CCN) and more broadly in an exploratory manner to other networks.

fMRI:
Default Mode Network. Neuronal dysfunction precedes structural atrophy in AD, and functional magnetic resonance imaging (fMRI) offers potential for identifying specific patterns of disruption in the memory networks affected early in AD. The mapping of brain regions showing a significant change in signal magnitude (relative to noise) by fMRI in response to a specific task is known as functional segregation. A newer approach is functional integration, which allows us to examine the complex interplay of various brain regions comprising a network, i.e., to examine functional connectivity (fc) or how activity in a brain region correlates with activity in other parts. Memory is subserved by many regions integrated by networks and it is likely that even in early AD, there is widespread loss of connectivity between regions. Both EEG and fMRI data show that successful memory retrieval is dependent on the concurrent activity of both the medial temporal lobe and postero-medial cortex, and that a functional disconnection between specific memory network nodes may occur in early AD. We will focus on connectivity analyses that relate to the default mode network (DMN), a resting state neural network of several highly interconnected cortical hubs, including the posteromedial parietal, anteromedial frontal and inferolateral parietal cortices. High levels of hub-related activity in this network in early life may set up a milieu that leads in later life to beta-amyloid deposition and a downstream cascade of events leading either directly or indirectly to anatomic and/or functional network disruption, neuronal damage and structural atrophy. 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 2-3 year follow up. Our CCT intervention is designed to target this system. We published on the effects of intervention with donepezil in MCI using fMRI as an outcome measure, but there are no long-term studies, to date, examining the effects of CCT on DMN connectivity and cognitive outcomes in MCI.

Combination of fMRI data across Columbia and Duke sites. To ensure uniformity of data collection across both sites, we will be using a single MR scanner at each site, identical vendor, field strength and software platform (GE Signa 3T Discovery MR750, Continuum Pack 24) and standardized acquisition parameters (adni.loni.usc.edu/methods/documents/mri-protocols). Each site performs on-going quality control scans and

QC analysis (as outlined in adni.loni.usc.edu/methods/documents). To correct for unforeseen scanner site bias, a nuisance variable for site will be included in statistical models.

Anatomical MRI. For volumetric analyses, the coronal sequence provides excellent white matter, gray matter and CSF contrast, and permits flexibility of planar reformatting with negligible degradation. Dr. Joel Sneed's team will rate the scans from both sites (transmitted electronically from Duke by ftp). Intracranial volume: every 5th slice from coronal slices (whole brain coverage) will be traced to derive intracranial volume (each hemisphere separate). The boundaries for hippocampus and entorhinal cortex tracings are based on procedures that we have used extensively

Hippocampal and entorhinal cortex atrophy. Medial temporal lobe atrophy occurs early in AD. Longitudinal studies show moderately strong accuracy for hippocampal and entorhinal atrophy in predicting conversion to AD. In our large, single-site MCI study, hippocampal and entorhinal cortex volumes were each highly significant predictors of conversion to AD even after controlling for age, sex, education, and MMSE. Hippocampal and entorhinal cortex atrophy occur in AD. Donepezil may decrease progressive hippocampal and entorhinal cortex atrophy in AD, and smaller hippocampal volumes have been related to donepezil response in 974 patients with vascular dementia. We will focus on hippocampal and entorhinal cortex atrophy; the MRI sequences and acquisition will also permit evaluation of cerebrovascular disease (lacunes, infarcts, and white matter hyperintensities) and allow for the use of voxel-based morphometry in image analysis. This will also permit us to collect pilot data on how CCT alters brain structure in relation to cognition.

Sections to be completed for studies using IND/IDE Drugs and Devices.

Prior to the submission of any study involving a faculty held IND or IDE being approved by the IRB, the IND/IDE holder is required to submit a form signed by the IND/IDE holder and PI.

Which are applicable to your study: ☐ Drug ☐ Device ☐ Radiolabeled drug/compound

Off Label and Investigational Use of Drugs

Enter the information for all drugs to be used in this study:

Name of the drug	N/A
Manufacturer and other Information	N/A
Approval Status (select one)	No IND is required – N/A
IND #	N/A
Who holds the IND (i.e., IND Sponsor). If other than PI/CU Investigator, type name of holder.	N/A
Which applies:	FDA has determined the IND is not required (provide correspondence) FDA conditions are met (see "Rules") – Explain https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-procedures-investigators-responsibilities N/A

Off Label and Investigational Use of Devices

Enter the information for all devices to be used in this study:

Name of the device	
Manufacturer and other Information	
Approval Status (select one)	IDE application is pending IDE is approved No IDE is required
IDE #	
Who holds the IDE (i.e., IDE Sponsor). If other than PI/CU Investigator, type name of holder.	
Is the device marketed?	
Which applies:	FDA has determined that IDE is not required FDA conditions are met (see "Rules") – Explain https://www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-application Device is "Non-significant risk" – Explain

Off Label and Investigational Use of Radiolabeled Drugs / Compounds

Enter the information for all radiolabeled drug/compounds to be used in this study:

Name of the radiolabeled drug/compound	
Manufacturer and other Information	
Approval Status (select one)	IND application is pending IND is approved RDRC approval is pending RDRC is approved No FDA/RDRC approval is required - Explain
IND #	
Who holds the IND (i.e., IND Sponsor). If other than PI/CU Investigator, type name of holder.	

Research Related Delay to Treatment

Research involving participants who are in need of treatment invariably involves delay to care, and this delay is associated with risk. Scheduling of procedures must be carefully organized to minimize delay. Other delay

must involve only that minimally necessary to accomplish the aims of the research while respecting subject well- being and safety. Describe the delay, by virtue of research participation in this study, before a participant can receive treatment of known efficacy or standard care routinely offered in the community.

Most transitions from MCI to AD will occur by 3 years of follow-up. We chose 18 months to decrease dropout that can occur in a very long controlled trial. There will be no treatment provided at the end of the study. Once a subject completes the final study visit, inclusive of the endpoint MRI, the subject will be finished with protocol procedures and given an appropriate clinical referral.

Clinical Treatment Alternatives

Describe what other treatment or assessment options are available to subjects who do not participate in research.

The patient does not have to join this study to receive treatment for memory loss. If the patient decides not to participate, the patient may review treatment options with their doctor.

Risks/Discomforts/Inconveniences

"Risk" is a broad term used to convey the potential for harm, burden, and inconvenience related to research participation. Use this section to provide a comprehensive description of foreseeable physical, psychological, social, interpersonal, and economic risks introduced by the research. Include the source of the information. Consider both the probability and magnitude of harm and its impact. Describe the foreseeable harms associated with the research (untoward effects of a medication) and those related to delay to individualized treatment. Include data from the literature, and local data, if available, on risk rates and subject experiences with research procedures. Describe procedures in place to minimize risk. In general, please create a numbered list of risks/categories of risk, and in general put the list in the order of significance or level of risk, the most significant risks should be listed first.

Risks that could be encountered during the study period:

MRI Scan:

The MRI, conducted at baseline and week 78, does not pose undue risk.
MRI involves lying on a bed which slides into a large cylindrical magnet. Radiowaves are used to obtain images from the internal parts of the subject's body. Before beginning the imaging procedure, we will ascertain that the subject does not have a pacemaker or any metallic implants (other than tooth fillings), and the subject will be asked to remove any metal or magnetized objects (such as keys, chains, hairpins, or credit cards). The subject will be asked to lie flat on their back in the MRI scanner for approximately 45 minutes. The subject will be asked to remain as still as possible. The subject will not feel anything, but will hear a banging noise. If claustrophobia unexpectedly develops during the procedure, we will stop the MRI scan and consider repeating it at a later date.

Neuropsychological Assessment:
During neuropsychological testing, some subjects may find some questions upsetting. The tester willdiscuss the situation with the patient and will allow for an expanded break between tests when feasible. If the patient still chooses not to proceed with testing, the patient's choice will be respected.

Remote Assessments:
Select subject neuropsychological testing and informant interviews may be administered remotely throughout stage I re-opening, as described in previous section of PSF. MRI and majority of subject neuropsychological testing must be completed in person, on site.

With completion of remote assessments also comes the risk for loss of confidentiality. Remote assessments will be administered exclusively through the HIPAA compliant phone calls at a time agreed upon by both the subject and/or informant, and member of the study team. The individual completing the remote assessments will do so by completing tests and/or interviews verbally, and recording replies on paper CRF, for later storage in the subject chart.

Travel for Research Purposes:
During Stage I re-opening: research participants will only come on-site if absolutely necessary for completion of study assessments and procedures. Any participant coming to NYSPI or Cornell facilities for conduct of study assessments and procedures will be at increased risk of contracting COVID-19 en route, but the Principal Investigator and study team will take all precautions necessary to ensure that risk remains minimal, including paying for the transport of participants to site via car service or ride share (utilizing services such as Uber or Lyft). Research Coordinator will remind participants to wear mask and practice frequent hand hygiene while in transport to study visit, during the 24 hour pre-visit reminder call.

In Person Visits and Procedures:
While on site during stage I re-opening, all guidelines and procedures specific to COVID-19 risk reduction (described in "Study Procedures" section, and uploaded as stand alone documents in the "Uploads" section of PRISM) will be implemented by study team and adhered to by participants, in order to reduce the spread of COVID-19 to staff and participants at NYSPI/CUMC facilities. Any staff or participant unwilling to abide by these guidelines will not be permitted to participate in, or complete work at the study visit.

Apolipoprotein E genotyping. In the informed consent form, we will state (1) the presence of specific subtypes of apolipoprotein may be associated with an increased risk of memory disorders, (2) the results will be kept strictly confidential and not released to the subject or to other parties. This approach, required by our IRB for all apolipoprotein genotyping studies, follows from the current ambiguities for clinical application of apolipoprotein E genotyping. Further, given that this involves genotyping, as per our NYSPI IRB requirements, a Certificate of Confidentiality will be obtained from NIA, as we have done in other studies

Procedures for Minimizing Risks:

There are three areas in which safeguards to protect subjects from undue risk require discussion. These include the procedures used to obtain informed consent, the procedures used to ensure confidentiality of subjects' responses and findings on tests, and the procedures used to minimize possible risks associated with the research procedures.

Informed Consent. Informed consent is obtained and documented with a signed consent statement giving full information about the study. In the consent form and in discussion with an investigator, subjects are advised fully of the procedures to be used, the amount of time required of them, the fact that this is a longitudinal treatment study with repeated assessment at specified time points, the possible risks and benefits of the procedures and the treatment conditions, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the Principal Investigator.

Capacity to Consent. Based on IRB requirements, patients will be recruited by a study physician who signs the consent form in addition to the patient. As described earlier, for patients who lack the capacity to consent but retain the capacity to appoint a surrogate, we will follow the procedures required by the NYSPI IRB (based on New York State OMH regulations) regarding assessment of capacity to consent.

Research Procedures. We have described above the potential risks of the research procedures and the safeguards that will be used to minimize risks. These include termination of subjects from research participation if it is believed that such participation endangers their welfare. Monitoring procedures are used to evaluate potential side effects of research procedures. The protocol stipulates an extensive medical, neurological, and psychiatric evaluation of all subjects as a condition for research participation.

Methods to Protect Confidentiality

Describe the data management plan and the methods you will employ to protect subject privacy and the confidentiality of research data. The section should detail how information will be collected, recorded, coded, stored, transmitted, and as applicable, shared with other investigators so as to minimize risks related to breach of confidentiality. Confirm that identifiers are removed, to the extent possible, from research data, and explain if there are links between subject identity and research data, or if the data are anonymous. Also, indicate where the data are stored, who is responsible for data safekeeping, and who has access to subject identity and codes, if any, which cross-link research data and subject identity. Confirm that identifiable data are not collected, stored, or transmitted by mail, fax, on removable drives, laptops, or via the internet without proper protections, e.g. encryption.

In the informed consent form, subjects are told that the information they provide and all findings will be kept strictly confidential, with access limited to the research staff with the possible exception of State or Federal regulatory personnel for audits. All records are kept in locked files. Each subject is given a code number for database purposes, and the patient's name does not reside in the database. Computer files will be stored in a database that is password protected and behind an institute and department firewall. No one but the project staff has access to the master list linking subjects' names to code numbers, and all information obtained is coded.

The master list is kept under strict lock and key. The research data on specific measures are released to the patients, and this is specified in the consent form.

Will the study be conducted under a certificate of confidentiality?

☒ Yes, we will apply for the Certificate of Confidentiality

☐ Yes, we have already received a Certificate of Confidentiality

☐ No

Direct Benefits to Subjects

Describe only benefits to individual subjects that are likely to accrue during the study itself. Do not include subject compensation or treatment to be provided at the end of the study, as these do not figure into the IRB's risk/benefit considerations. Do not describe diagnostic and evaluation components unless subjects receive clinical feedback. Do not describe the anticipated scientific benefits of the research. Some studies offer no direct benefit to subjects.

Participants may or may not benefit from study participation.

Compensation and/or Reimbursement

If compensation or reimbursement for expenses will be offered to subjects, please describe and indicate total amount and schedule of payment(s). If transportation is reimbursed, state if receipts are necessary for reimbursement. Include justification for compensation amounts and indicate if there are bonus payments.

Subjects will receive $50 per MRI scan (baseline and 78 weeks) and $25 at each of the major time points: baseline, 12 weeks, 20 weeks, 32 weeks, 52 weeks, 78 weeks. Participants will be compensated $1 per completed at-home online training session for both training groups. This will be an extra $72 dollars maximum per participant, if he/she completes all required sessions. Therefore, subjects will receive a total of $322 for their participation in the study over the course of 18 months.

Data Management Plan

All federally funded, more than minimal risk studies are required to include a Data Management Plan. The required elements of the Data Management Plan include: identification of the database platform (e.g., REDCap) and inclusion of an attestation that it is Part 11 compliant, identification of a qualified staff member who designs and maintains the database, design and implementation of data system training for all Principal Investigators & research coordinators & all protocol staff, and significant changes to the data management plan will be submitted as protocol amendments in PRISM. More information can be found on the IRB website at https://irb.nyspi.org/forms regarding this plan and should be reviewed prior to submission.

The data collected in this study will be entered and monitored by the Database Management Unit at NYSPI. This unit is headed by Dr. Howard Andrews, whose unit has 2000 square feet of office space, and can easily accommodate the data management activities in this proposal.

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Please limit references, preferably no more than twenty.

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