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Protocol

Crossword puzzle training and neuroplasticity in mild cognitive impairment (COGIT-2): 78-week, multi-site, randomized controlled trial with cognitive, functional, imaging and biomarker outcomes

Laura A. Wang[1]*, Terry E. Goldberg[2,3], Philip D. Harvey[4], Angela J. Hanson[5], Jeffrey Motter[3], Howard Andrews[3], Min Qian[6], Renjie Zhang[2], Meaghan Janis[2,3], P. Murali Doraiswamy[1,7], Davangere P. Devanand[2,3]

[1]Department of Psychiatry, Duke University Medical Center, Durham, North Carolina, USA
[2]Area Brain Aging and Mental Health, New York State Psychiatric Institute, New York, USA
[3]Department of Psychiatry, Columbia University Irving Medical Center, New York, USA
[4]Department of Psychiatry, University of Miami Miller School of Medicine, Miami, Florida, USA
[5]Department of Gerontology and Geriatric Medicine, University of Washington, Seattle, WA, USA
[6]Department of Biostatistics, Columbia University Irving medical Center, New York, USA
[7]Duke Center for the Study of Aging and the Duke UNC Alzheimer's Disease Research Center, Durham, NC, USA

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***Correspondence:**
Laura A. Wang,
E-mail: law84@duke.edu

ABSTRACT

Background: Cognitive training represents an important potential therapeutic strategy for mild cognitive impairment (MCI). In our recently completed trial, crossword puzzles were superior to computerized cognitive training on Alzheimer's disease assessment scale–cognitive subscale-11 (ADAS-Cog11) and function, correlating with decreased brain atrophy over 78 weeks.
Methods: COGIT-2 is a 78-week, multicenter, clinical trial comparing home-based, high-dose crosswords (4 puzzles per week) to low-dose crosswords (1 puzzle per week) and a health education control group in 240 MCI subjects. Crossword puzzles, administered by the CogniFit research platform, have been designed to have a moderate level of difficulty.
Results: The primary outcome is change in ADAS-Cog14 and the main secondary outcome is change in informant reported daily functioning. Additional outcomes include changes in magnetic resonance imaging (MRI) hippocampal volume and cortical thickness as well as changes in plasma neurofilament light and plasma pTau217.
Conclusions: If the efficacy of computerized crossword puzzle training is confirmed in COGIT-2, crosswords training could become a low-cost, home-based, scalable, cognitive enhancement tool for people at risk for Alzheimer's disease. The dose comparison will provide useful information on the preferred frequency of crossword puzzle training.
Trial Registration: Trial registration number ClinicalTrials.gov identifier (NCT06601933).

Keywords: Alzheimer's disease, Computerized cognitive training, MCI, MRI, ATN, Blood-based biomarkers

INTRODUCTION

Mild cognitive impairment (MCI) in older adults confers an increased risk of progression to Alzheimer's disease (AD).[1] Non-pharmacologic cognitive training represents an important therapeutic strategy for MCI. Computerized cognitive training shows some evidence of efficacy in healthy adults and patients with neuropsychiatric disorders.[2-5] In MCI, computerized cognitive training has been studied mainly in small samples that showed some efficacy across different cognitive domains in different studies with few showing transfer from cognitive to

functional gains.[6] In older adults, crossword puzzle training has been studied as an active control or comparison but rarely as an active intervention. There is limited clinical trial evidence that crossword puzzle training may have cognitive-enhancing effects in MCI.[7,8]

Crossword puzzle training efficacy in prior studies

In the Bronx aging study, among 528 cognitively intact community-residing individuals assessed every 12-18 months, those who reported doing crossword puzzles had an average 2.54 years delayed onset of memory decline defined by change in selective reminding test scores (episodic verbal memory), compared to the rest of the cohort. This effect remained significant after controlling for education and verbal IQ.[9]

Few prospective controlled studies have examined crosswords as an active intervention, possibly because of a lack of commercial interest as crosswords are widely available at little to no cost. In an 8-week trial in patients with heart failure, crosswords, computerized games, and usual care showed similar effects on cognition, though a nurse-enhanced intervention was a confound.[8] In a randomized trial of 351 older adults in assisted living and independent living, crossword puzzles showed a large effect size advantage compared to visual processing speed training on cognitive and quality of life outcomes in assisted living, but this difference was not seen in independent living.[7] Many assisted living participants would have had MCI while those in independent living are more likely to be cognitively normal; the dose of crossword puzzles was unspecified. This evidence, while limited, supported the need for prospective clinical trials of crosswords in MCI.

Online PROTECT study

In the online PROTECT study of 19,078 individuals aged 50-93 years, performing word puzzles was associated with better performance on the 14 cognitive measures examined.[10] Improvement in measures of speed and grammatical reasoning showed the greatest advantage in crossword puzzle users. Paired associate learning, digit span, and spatial working memory test performance did not differ among those who did crossword puzzles more than once a day, once a day, and once a week, but verbal reasoning was better in those who did crossword puzzles more than once a week. For several outcomes, doing crosswords once a week or more often was associated with better performance than doing crosswords occasionally or never. These findings, in a large British sample of older adults that included people with MCI (percent not reported), support the prospective study of crossword puzzles at different frequencies in MCI.

Columbia-Duke COG-IT clinical trial

In our two-site (Columbia, Duke), blinded, 78-week COG-IT trial, 107 participants with MCI were randomized to computerized cognitive training or crossword puzzle training for 12 weeks of intensive training followed by booster sessions for a total of 78 weeks. In mixed model analyses, participants randomized to crosswords showed superior efficacy to computerized cognitive training on the ADAS-Cog11 and the functional activities questionnaire. Endpoint reductions in hippocampal volume and cortical thickness were smaller with crosswords than with computerized cognitive training. Participants with late MCI (lMCI) showed an efficacy advantage for crossword training over computerized cognitive training but in early MCI (eMCI) there were no treatment differences. In MCI, increased disease severity may decrease participant engagement in computerized cognitive training, which can be difficult to understand and execute, compared to crosswords. The results suggest efficacy for crosswords compared to computerized cognitive training on cognition and function with decreased brain atrophy over 78 weeks in MCI.[11]

Knowledge gaps

Despite these promising data on crossword puzzle training, there remain some gaps in knowledge. The efficacy and optimal dosage of crosswords use (frequency, difficulty level) are not established in cognitively impaired individuals. Further, few studies have evaluated transfer from cognitive improvements to functional benefits in MCI, and the results are inconsistent in these studies.[12,13] In the ACTIVE trial of computerized cognitive training in a broad sample of older adults, effects were strongest for speed training being associated with improvement in highly learned prior skills, e.g. driving.[14] Transfer, even to prior skills, is important for practical clinical utility and because of the strong association between cognitive decline and functional disability.[15] Our COG-IT study showed that crosswords were superior to computerized cognitive training on cognition and activities of daily living with significant correlations between changes in cognitive and functional outcomes. There is also limited information from clinical trials on whether crossword puzzle training can impact pathological biomarkers of AD such as cortical amyloid and tau, and potentially delay progression from MCI to AD dementia.[16-19]

Neural mechanisms

Crossword puzzles challenge several cognitive abilities: retrieval memory, verbal knowledge, language skills, attention, processing speed, and executive function. Based on the literature, we suggest the following cognitive mechanisms may be important: general language ability (reading, comprehension, vocabulary); orthographic knowledge (spelling); semantic memory (for general knowledge and information); executive function for search strategies, retrieval, and hypothesis testing with rejection or acceptance of a word; verbal working memory for maintaining information about already defined letters in a given word. The neural circuitry, while not well-defined, may include large scale prefrontal networks for executive function and verbal working memory, the temporal lobe, Broca's area, the angular gyrus for reading,

fusiform cortex for object recognition, inferior prefrontal and inferior temporal lobe for orthographic knowledge, and the lateral temporal lobe for semantic information. A relatively preserved hippocampus may support storage and retrieval of important events and names, which can be useful for completing crosswords. Remote memory for factual information, also important for crosswords, may be distributed over wide areas of neocortex and thus sensitive to MRI cortical thickness measurements. Prefrontal areas, included in cortical thickness measurements, may be engaged by developing and modifying search strategies for specific words. These types of processes when tuned by crossword training can increase their access and precision when used in everyday life and thus result in improvements in everyday function. They might also promote resilience if compensatory cognitive approaches are demanded.[20] In COG-IT, we found no associations between treatment group and change in default mode network or other fMRI network measures possibly due to the fact that we did not measure fMRI changes after acute training.[21] The aging brain, however, has some potential for neuroplasticity.[20] The hippocampus shows atrophy in MCI, and in COG-IT, crossword training was associated with less brain atrophy than computerized cognitive training on hippocampal volume and cortical thickness.[22,23]

Blood-based biomarkers

Blood-based biomarkers of neurodegeneration and AD pathology have now emerged, including neurofilament light (Nfl), glial fibrillary acidic protein (GFAP), phosphorylated Tau217 (pTau217) and amyloid beta 42 (Aβ42). A few pilot studies have examined the impact of cognitive training on blood-based biomarkers.[16-18] However, there is a need for additional information on whether different doses of crossword puzzle training can impact blood-based biomarkers of neurodegeneration as well as cortical amyloid and tau pathology in MCI.

These findings argue for a randomized clinical trial comparing high-dose crosswords to low-dose crosswords to a carefully chosen control group. If low and high dose crosswords are associated with similar benefits in MCI, then low dose crosswords may be recommended for older adults with MCI. Conversely, if high-dose is superior to low-dose crosswords, the high-dose may be recommended in lifestyle intervention implementation.

METHODS

240 participants with MCI will be recruited at 4 U.S. sites: Columbia University, Duke University, University of Miami, and University of Washington. Participants will be randomized to high-dose crossword training (4 crossword puzzles per week), low-dose crossword training (1 crossword puzzle per week), or health education (1 book chapter per week). There will be an initial intensive 12-week phase followed by booster sessions, each for one week, that occur at weeks 20, 32, 42, 52, 64, and 78. In-clinic assessments will occur at 0, 12, 32, 52, 78 weeks. Both lMCI and eMCI participants will be recruited. Figures 1 and 2 depict the study design.

Unique features of the design include: evaluation of home-based crossword puzzles as the primary intervention; comparison of two crossword dose conditions to a health education comparison group; stratification of random assignment by site, age, and eMCI/lMCI; evaluation of MRI hippocampal atrophy indices and plasma biomarkers of neurodegeneration (Nfl) and amyloid pathology (pTau217). Additionally, blood will be banked for assays of future biomarkers. Approximately 25% of the sample will come from underrepresented minorities.

Inclusion and exclusion criteria

MCI will be defined based on Alzheimer's disease neuroimaging initiative (ADNI) criteria to be consistent with COG-IT and other published studies.[24]

Inclusion criteria

Inclusion criteria included: access to a home desktop or laptop computer or tablet at acceptable internet speed; 55 to 89 years of age (inclusive) at the time of informed consent; females need to be post-menopausal; subjective cognitive complaints, i.e., memory or other cognitive complaints, e.g., naming/language; meets criteria for either eMCI or lMCI, defined as scoring below the education adjusted cutoff on the Wechsler memory scale–III logical memory II subscale (story A, delayed paragraph recall), eMCI is defined by a delayed recall score of 3-6 with 0-7 years of education, score of 5-9 with 8-15 years of education, and score of 9-11 with 16 or more years of education, lMCI is defined by a score ≤ 2 with 0-7 years of education, score ≤4 with 8-15 years of education, and score ≤8 with ≥16 years of education; Montreal Cognitive Assessment (MoCA) score ≥20/30; an informant (relative, friend, other caregiver) who contacts the participant at least weekly is required to provide information about the participant's functioning; and must be English-speaking: at least 6th grade reading level with WRAT 3 score of ≥37.

Exclusion criteria

Exclusion criteria included: diagnosis of dementia of any type; current clinical diagnosis of schizophrenia, schizoaffective disorder, psychosis, or bipolar I disorder (DSM 5 TR criteria); current unstable or untreated major depression or active suicidality based on the GDS and C-SSRS; alcohol or substance use disorder (DSM-5 TR criteria) over the past 6 months; clinical stroke with residual neurological deficits; use of medications known to have a negative impact on cognition: benzodiazepines in lorazepam equivalents >1 mg daily, narcotics, anticholinergics, or large number of sedating medications in combination, medications with anticholinergic/ antihistaminergic properties will be reviewed, e.g. low-dose quetiapine (≤25 mg daily) will be permitted, but daily

use of diphenhydramine or equivalent will be reviewed, current use of lecanemab or donanemab will be exclusionary; presence of any of the following disorders: CNS infection, with CSF evidence of meningitis, encephalitis, or other infectious process, dementia of any type, Huntington's disease, multiple sclerosis, Parkinson's disease, and other neurologic disorders with focal signs; acute, severe, or unstable medical illness in the judgment of the clinician, for cancer, acutely ill participants (including those with metastases) are excluded, but history of successfully treated cancer does not result in exclusion; MRI incompatible pacemakers and metal implants, or any other contraindication to MRI; regular use of crosswords or formal computerized cognitive training platforms averaging once per week or more than once per week in the past year; participation concurrently in another therapeutic clinical trial for cognitive impairment; and Geriatric Depression Scale (short form) score of ≥6.

Ethical approval

The study has received IRB approval from the Columbia University IRB (coordinating center) and WCG, which is the IRB of record. All participants will provide written informed consent prior to any study procedures. The trial is overseen by an independent Data Safety Monitoring Board (DSMB) comprised of experts in MCI and clinical trials.

Blinded/unblinded procedures

A blinded research coordinator at each site will conduct all cognitive and functional assessments at clinic visits. An unblinded research coordinator will familiarize participants with the CogniFit crossword platform, review compliance metrics, oversee booster sessions at clinic visits, and remind participants (via regular phone calls) to complete booster sessions at home.

Reducing participant expectation bias

Participants will know their treatment condition; however, the term "control" is not used in the consent form to reduce expectation bias. The consent form states that two-thirds of the study participants will receive crossword puzzles training that may improve cognitive performance and overall functioning, and the other third of the sample will receive health education that may be beneficial as well.

Difficulty level and dosing of crossword puzzles

The crosswords puzzles will have a medium difficulty level (similar to the New York Times Tuesday crosswords) and consist of a combination of words of varying lengths and frequencies (measured in number of appearances per million words). The difficulty level will remain at this level and will not be titrated during the study based on individual performance. The words will be selected to match the lexical knowledge of persons of the same age and gender as participants according to existing normative databases of word prevalence. Each crossword puzzle will include the same number of words and clues to allow for between-sessions comparisons.

Creating an optimal puzzle

CogniFit (CogniFit Inc., San Francisco, CA, US) utilized a three-step process to create an optimal puzzle for an elderly population.

Frequency

The largest portion of the words used in the puzzles correspond to medium- and high-frequency words according to standardized counts that are commonly used in experimental psychology and psycholinguistics.

Validation tests

CogniFit independently conducted two different tests with English-speaking middle-aged and senior individuals to evaluate the appropriateness of the crossword puzzles and the levels of difficulty for the aged individuals.

AI-based individual analysis

For each of the crosswords, CogniFit conducted an analysis of the adequacy of the definition to the words, adequacy of the words to the definition, and adequacy of the words and definitions to a figure of a hypothetical senior with average educational level and socioeconomic status. This is a process in which each entry of each puzzle is evaluated with a numerical score, quantifying the optimal level of the crossword puzzles.

Despite these efforts, it is possible that individual differences may play a role in an MCI participant's performance level, making some puzzles more optimal than others for certain participants. In posthoc analyses we plan to define the optimal level of engagement (based on learning curves of number of completed words and time taken to complete each puzzle) to test if the participants that improve across sessions are those who later show improved cognitive, functional, or structural outcomes.

Crossword puzzle and health education training schedule

Figure 1 indicates a schematic of the study design. At baseline, participants in the crossword conditions will be trained on the CogniFit platform using a sample crossword. In the intensive 12-week phase, participants assigned to four 30-minute crosswords/week will complete a total of 48 crossword sessions, those assigned to one 30-minute crossword/week will complete a total of 12 crossword sessions, and the control group will have an introductory review followed by reading 11 health education chapters. If a puzzle is completed within 30 minutes, the participant will be given a new crossword puzzle for the remaining time in the 30-minute slot.

Booster sessions will take place at 20, 32, 42, 52, 64, and 78 weeks with the high-dose group completing 4 crosswords, low-dose group completing 1 crossword, and the health education group reading one chapter during each of these 5 weeks followed by a final review session. In-person crossword puzzle training, chapter review, and cognitive assessments will occur at baseline and weeks 12, 32, 52 and 78. Booster sessions at 20, 42, and 64 weeks will be done entirely at home. At all clinic visits after baseline, the unblinded coordinator will observe the participant complete one crossword puzzle in the clinic (the 4/week group will complete 3 additional crosswords at home and the 1/week group will complete 0 additional crosswords at home). The in-person sessions ensure correct login and technical procedures. For participants in the health education group, the unblinded coordinator will review content from assigned chapter readings with the participant at all clinic visits after baseline. Across the study the high-dose group will finish a total of 72 crossword sessions, the low-dose group will finish a total of 18 sessions, and the health education group will read 16 chapters with two additional review sessions.

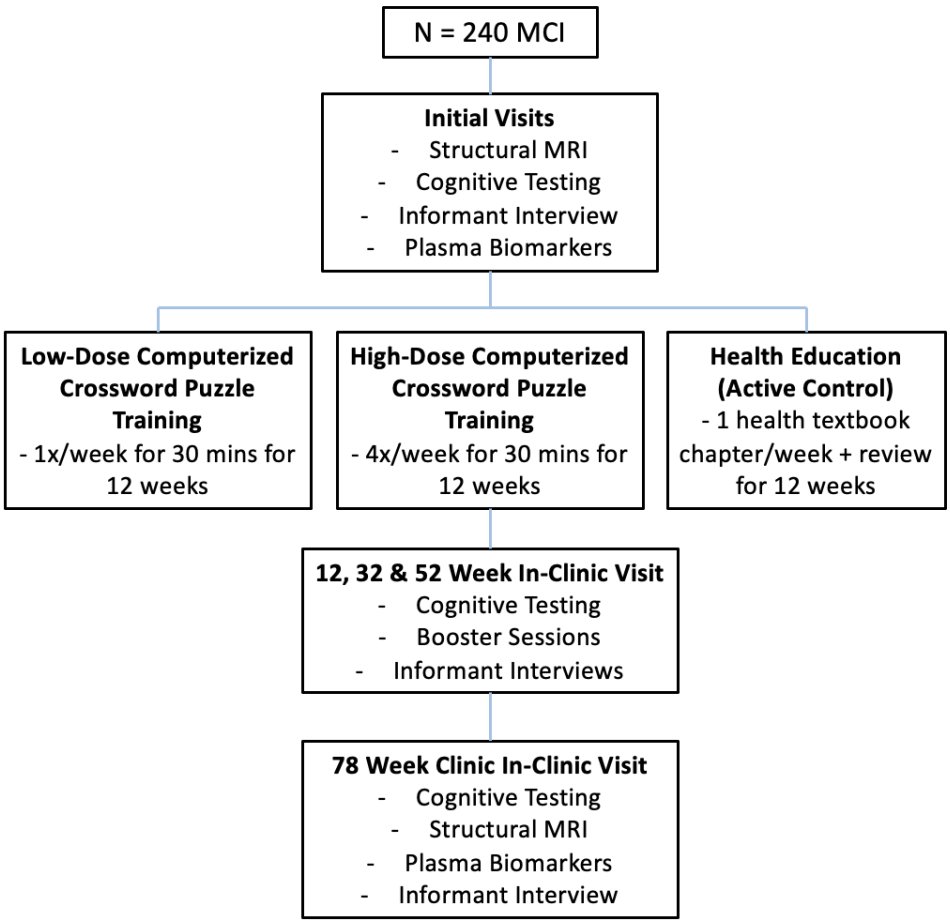

Figure 1: Study design of COGIT-2 RCT in MCI.

Compliance and completion metrics

CogniFit platform generates compliance and accuracy metrics for each participant on a weekly basis. Adherence metrics will be reviewed by the unblinded study staff and participants with poor adherence will receive phone calls to improve adherence. A compliance tracker will be used by unblinded staff across sites to monitor treatment adherence. The clues of each puzzle will not need to be completed in order and accuracy as an outcome will not be presented to participants. For health education, unblinded study personnel will review the assigned readings during scheduled phone calls and in-person visits at the time-points listed in our study design figure.

Adherence definition

Non-adherence is defined as <75% of assigned crosswords attempted or health education chapters read. A weekly report from CogniFit will be used to assess adherence. Non-adherent participants will receive more frequent phone calls to encourage completion. If a participant falls below 75%, they will be contacted to complete make-up sessions to enter the adherent range. Participants who are

non-adherent will still be evaluated at the required time-points based on an intent-to-treat approach.

Aims and hypotheses

Figure 2 depicts a model of the study aims and outcome measures.

Aim 1

Aim 1 was to compare the efficacy of high dose crosswords, low dose crosswords, and a health education control group on cognition (primary outcome: change in ADASCog14 from baseline to 78 weeks) in a 78-week trial with blinded assessments. Hypothesis 1 (primary) was the high dose crosswords will show superior efficacy to the control group on cognition. Hypothesis 2 (secondary) was there will be an increasing trend in treatment effects on cognition across the three ordered groups (control < low dose crosswords < high dose crosswords).

Aim 2

Aim 2 was to compare the efficacy of high dose crosswords, low dose crosswords, and a health education control group on functional outcome (change in informant-reported functional activities questionnaire from baseline to 78 weeks: secondary outcome). Hypothesis 1 (primary) was the high dose crosswords will show superior efficacy to the control group on function. Hypothesis 2 (secondary) was there will be an increasing trend in treatment effects on function across the three ordered groups (control < low dose crosswords < high dose crosswords).

Aim 3

Aim 3 was to evaluate change in brain atrophy measures (MRI hippocampal volume and cortical thickness) in the participants for high dose crosswords and control groups. Hypothesis 1 was decrease in brain atrophy measures from baseline to 78 weeks will be smaller in the high dose crosswords group than the control group.

Exploratory hypotheses

By end-trial, the high dose crossword condition will show efficacy compared to the health education control group on the Preclinical Alzheimer's Cognitive Composite-5 (PACC5, secondary cognitive outcome) and Alzheimer's Disease Cooperative Study Activities of Daily Living Prevention Instrument (ADCS-ADL-PI).

The high dose crossword condition will have greater reduction from baseline to end-trial in plasma neurofilament light (Nfl: marker of neurodegeneration) and pTau217 (marker of AD) than the control group.

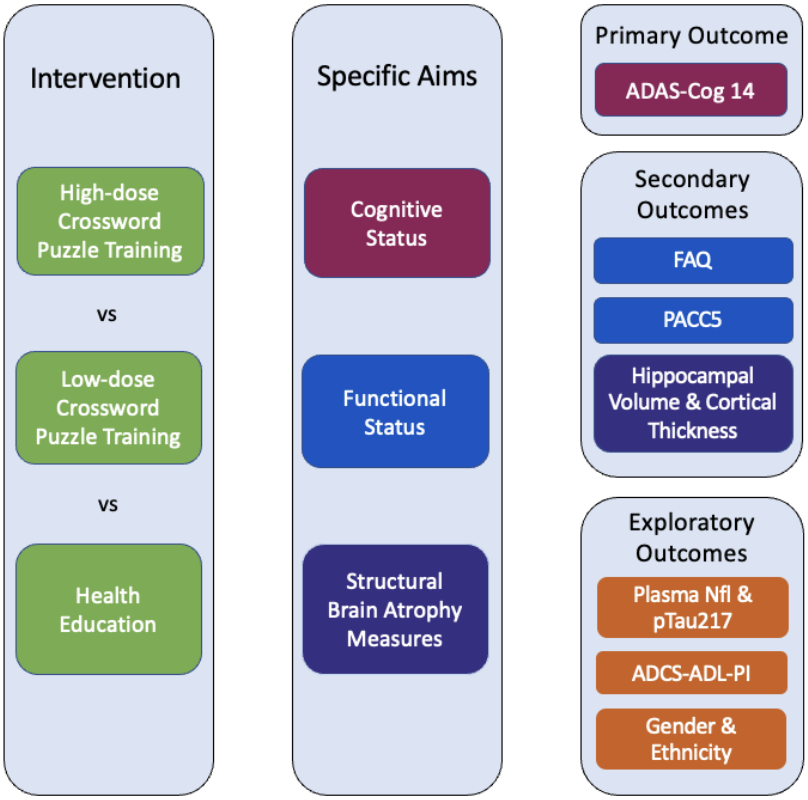

Figure 2: Key study aims and outcome measures.

ADAS-Cog14: Alzheimer's disease assessment scale cognitive subscale 14; FAQ: functional assessment questionnaire; PACC5: preclinical Alzheimer's cognitive composite-5; ADCS-ADL-PI: Alzheimer's disease cooperative study activities of daily living prevention instrument; Nfl: neurofilament light; pTau217: phospho-tau 217.

We will evaluate change in brain atrophy measures and AD plasma biomarkers as mediators between cognitive and functional outcomes in the treatment groups.

We will explore which cognitive domains are more likely to benefit and if there are specific gender and race/ethnicity differences in these changes.

Study measures

Table 1 lists the study measures and their time-points of administration. The MoCA is a widely used global cognitive assessment and will be completed at screen for eMCI/lMCI categorization. At screen, the Framingham stroke risk scale will be administered to assess cerebrovascular risk. This will be a potential moderator in ancillary analyses because vascular and AD pathology often co-exist along a clinical/pathological continuum in MCI.[25] The geriatric depression scale (short form) will be administered at screen and each in-clinic visit to assess depression severity.

At all in-clinic visits (baseline, weeks 12, 32, 52, and 78), the ADAS-Cog14 and PACC5 will be administered. ADAS-Cog14 is widely used in clinical trials and tests several cognitive abilities. ADAS-Cog11 showed an advantage for crosswords compared to computerized cognitive training in COG-IT and is contained in the ADAS-Cog14 that is replacing the ADAS-Cog11 in clinical trials in MCI and AD.[26] The PACC composite is comprised of the mini mental state exam (MMSE), free and cued selective reminding test (FCSRT), logical memory II, and digit symbol coding. We will use the preclinical Alzheimer's cognitive composite-5 (PACC5) which also includes category fluency that is associated with early decline in preclinical AD.[27]

Table 1: Schedule of study procedures.

Measure	Screen	Baseline	12 weeks	32 weeks	52 weeks	78 weeks
Phone screen	X					
In-person screen, informed consent signed	X					
MoCA	X					
WMS-III logical memory I and II	X					
Demographics form	X					
Framingham stroke risk scale	X					
C-SSRS scale short form	X					
Cognitive training activities history	X					
Medications list	X	X	X	X	X	X
Geriatric depression scale (short form)	X	X	X	X	X	X
Wide range achievement Test 3 (WRAT3)	X					
MRI scan of brain (between screen and baseline)		X				X
Inclusion/exclusion criteria form (start at screen, complete at baseline after MRI) *	X	X				
Medical history**		X				
Clinical evaluation progress note		X				
Vital signs		X	X	X	X	X
Randomization form		X				
Disgnosis form						X
Physical activities scale		X				
ADAS-Cog14		X	X	X	X	X
PACC5		X	X	X	X	X
FAQ and ADCS-ADL-PI: informant interview***		X	X	X	X	X
Blood: apolipoprotein E genotype		X				
Plasma biomarkers: NfL ptau217 (store plasma)		X	X			X
Calendars		X	X	X	X	
Appointment card		X	X	X	X	
Compliance tracker			X	X	X	X

WMS-III: Wechsler memory scale-III; ADAS-Cog 14: Alzheimer's disease assessment scale – cognitive subscale 14; FAQ: functional activities questionnaire; ADCS-ADL-PI: Alzheimer's disease cooperative study-activities of daily living-prevention instrument; C-SSRS: Columbia-suicide severity rating scale; MoCA: Montreal Cognitive Assessment; PACC5: preclinical Alzheimer cognitive composite, 5 tests; MRI: magnetic resonance imaging. *Form initiate at screen visit, to be completed by baseline visit, **form can be completed at screen or baseline, ***form to be completed with the Informant (either in-person or remotely)

In addition, informants will be interviewed at, or shortly after, each in-clinic visit to complete the FAQ and ADCS-ADL-PI. All informant procedures can be completed remotely. The FAQ assesses instrumental activities of daily living; it showed an advantage for crosswords over computerized cognitive training in COG-IT. ADCS-ADL-PI (informant report) was developed for prevention trials to assess subtle functional deficits in cognitively intact individuals and eMCI and has items for classical amnestic MCI.[28,29]

At baseline and week 78, patients will undergo a 3T structural MRI scan of the brain to analyze hippocampal volume, cortical thickness, and intracranial volume. We will collect blood plasma at baseline, 12 weeks, and 78 weeks for analyses of Nfl (a biomarker of neurodegeneration correlating with decline on cognitive tests) and pTau217 (a marker of cortical amyloid deposition).[19,30,31]

Sample size and randomization

The sample (n=240) will be randomized to high-dose crosswords, low-dose crosswords, and control at 1:1:1 ratio. Individuals will be stratified by site, age (<70 and ≥70 years), and MCI status (eMCI and lMCI) to ensure comparable representation in treatment groups. Randomization sequences will be balanced in blocks of random size (3, 6) to prevent blinded researchers from predicting the next participant's assignment.

Power analysis

Power and effect size calculations are based on 80% power at a 5% significance level, with a total sample size of 240 (80 per group) and a 15% attrition rate, resulting in 68 participants per treatment group at 78 weeks. For aim 1 hypothesis 1 (ADAS-Cog14 change), aim 2 (FAQ change), and aim 3 (brain atrophy change), the minimum detectable effect size is Cohen's d=0.48 for high-dose crosswords versus control. For aim 1 hypothesis 2 (treatment effect trends), based on linear regression for ADAS-Cog14 with treatment groups (1 for control, 2 for low-dose, and 3 or high-dose crosswords) as an ordinal predictor, the minimum detectable Cohen's d=0.24 for high versus low-dose crosswords and low-dose vs. control, and 0.48 for high-dose versus control.

Adverse events

While cognitive training with crosswords and health education are not likely to cause any adverse events, adverse events that occur in this older sample will be recorded. Serious adverse events will be reported to the IRB, a three-member Data Safety Monitoring Board, and the National Institute on Aging.

DISCUSSION

To our knowledge, this will be the first randomized, rater-blinded, 78-week trial to evaluate the effects of two different doses of home-based crossword puzzle training compared to an active control on cognitive, functional, and biomarker outcomes in MCI.

The study was designed specifically to address gaps in knowledge raised by our prior study.[11] Our prior study lacked a non-cognitive training control group and hence we have included health education as a third arm in the present study. Our prior study found crossword training was superior to games but did not examine the optimal dosage of crossword puzzles for efficacy in MCI.[11] The present study will examine the efficacy of low dose (once weekly) versus high dose (four times a week) of crosswords use (versus health education) for enhancing cognition and functioning in cognitively impaired individuals. Our prior study did not examine the effects of crossword puzzles on amyloid, tau, axonal or glial biomarkers. The present study will explore the effects of crossword puzzles on blood-based biomarkers of axonal neurodegeneration (plasma NFL), microglial activation (GFAP) and cortical amyloid and tau deposition (Ab42, pTau217).[17,19,30,31] Our prior study found potential beneficial effects of crossword training on hippocampal volumes but did not establish an optimal dose effect.[11] In the present study we will test the effect of low dose versus high dose crossword training on hippocampal volume as a measure of neuroprotection. Lastly, the present study also has a much larger sample size (N=240) to provide greater power to test for dosage effects as well as gather pilot data on the effects on progression from MCI to dementia.

Determining the optimal dose of crossword puzzle training is a key unanswered question in relation to dementia prevention.[11] We have chosen in this trial to vary frequency rather than difficulty level for the two dose conditions because participants with advanced MCI are likely to become disengaged and lose motivation if crosswords are too difficult to complete. Difficulty will be at medium level during the trial, using a combination of moderately difficult crosswords with simple crossword components to make it feasible for a broad, diverse sample. The high-dose crossword training is the same as in our prior trial COG-IT, allowing for replication. If crosswords are done more often, fatigue and increased dropout are likely. The choice of one crossword/week was guided by the need for a minimum frequency for a meaningful intervention. An acute intensive phase, followed by less frequent booster sessions, was used in our COG-IT trial and will be replicated in COGIT-2. The length of this trial is the same as our 78-week COG-IT trial. Sustained therapeutic effects cannot be examined in a short-duration trial, while a much longer trial is likely to increase dropout. Our trial design balanced these considerations.

We chose the crossword puzzle training platform developed by CogniFit because of its two-decade experience in developing brain training software, adherence to the EU's high data privacy standards, and use in numerous prior academic studies of cognitive training. The 3-step process used to optimize crossword puzzles for an elderly sample as well as a study specific research

platform which autogenerates a weekly adherence report that allows for rigorous monitoring of compliance and performance over time are strengths. This will allow us to maximize participant engagement.

In addition to the above strengths, there are some potential limitations of the study. The sample size of 240, while adequate to measure the cognitive impact of crossword puzzle training, may not allow for a conclusive assessment of its impact on delaying conversion from MCI to AD. Limited budget and trial duration precluded a larger sample size and longer follow-up. We chose not to select MCI participants using PET or CSF markers to make the study more generalizable, but we will obtain pTau217 (an emerging marker of cortical amyloid and tau deposition) to subclassify participants in post-hoc analyses.[31] In addition, while the trial aims to enroll 25% minority participants, there may still be insufficient power to examine the benefits of crossword puzzle training in specific racial/ethnic subgroups or in those with low educational level. In this regard it is of interest that our prior COG-IT study found that crossword puzzle training was at least as effective in blacks as in whites.[11] Lastly, our study excludes concurrent use of amyloid-targeted therapies (e.g. antibody medications including lecanemab and donanemab) to avoid the possible confounding effects of adverse events (such as amyloid-related imaging abnormalities or ARIA) and associated treatment discontinuation. Other studies are needed to evaluate crossword puzzle training as part of a combined medication and lifestyle intervention program to determine the optimal combinations that will provide maximal participant benefit.[6,10,16,20]

CONCLUSION

By assessing the effects of training dosage and duration on cognition, function, and brain atrophy, identifying outcome differences within subgroups, modeling long-term effects, and understanding the neural processes and plasma biomarkers involved, positive findings from this trial will help inform lifestyle interventions and the design of future randomized controlled trials on crossword puzzle training. If efficacy is shown in COGIT-2 for crosswords versus controls, home-based crossword puzzle training with evidence-supported dose parameters could become a low-cost, scalable therapeutic intervention for individuals with MCI.

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