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MIND food and speed of processing training in older adults with low education, the MINDSpeed Alzheimer's disease prevention pilot trial

Daniel O. Clark[a,b,c,*], Huiping Xu[a,b,d], Lyndsi Moser[e], Philip Adeoye[a,b], Annie W. Lin[f], Christy C. Tangney[g], Shannon L. Risacher[h], Andrew J. Saykin[h], Robert V. Considine[i], Frederick W. Unverzagt[a,b,e]

[a] Indiana University Center for Aging Research, Indianapolis, IN, United States of America
[b] Regenstrief Institute, Inc., Indianapolis, IN, United States of America
[c] Department of Medicine, Division of General Internal Medicine and Geriatrics, Indiana University School of Medicine, Indianapolis, IN, United States of America
[d] Indiana University Richard M. Fairbanks School of Public Health, Indianapolis, IN, United States of America
[e] Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, United States of America
[f] Department of Preventive Medicine, Northwestern University, Chicago, IL, United States of America
[g] Department of Clinical Nutrition, Rush University Medical Center, Chicago, IL, United States of America
[h] Center for Neuroimaging, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, United States of America
[i] Department of Medicine, Division of Endocrinology, Indiana University School of Medicine, Indianapolis, IN, United States of America

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ABSTRACT

Background: Multiple national organizations and leaders have called for increased attention to dementia prevention in those most vulnerable, for example persons with limited formal education. Prevention recommendations have included calls for multicomponent interventions that have the potential to improve both underlying neurobiological health and the ability to function despite neurobiological pathology, or what has been termed cognitive reserve.

Objectives: Test feasibility, treatment modifier, mechanism, and cognitive function effects of a multicomponent intervention consisting of foods high in polyphenols (i.e., MIND foods) to target neurobiological health, and speed of processing training to enhance cognitive reserve. We refer to this multicomponent intervention as MINDSpeed.

Design: MINDSpeed is being evaluated in a 2 × 2 randomized factorial design with 180 participants residing independently in a large Midwestern city. Qualifying participants are 60 years of age or older with no evidence of dementia, and who have completed 12 years or less of education. All participants receive a study-issued iPad to access the custom study application that enables participants, depending on randomization, to select either control or MIND food, and to play online cognitive games, either speed of processing or control games.

Methods: All participants complete informed consent and baseline assessment, including urine and blood samples. Additionally, up to 90 participants will complete neuroimaging. Assessments are repeated immediately following 12 weeks of active intervention, and at 24 weeks post-randomization. The primary outcome is an executive cognitive composite score. Secondary outcomes include oxidative stress, pro-inflammatory cytokines, and neuroimaging-captured structural and functional metrics of the hippocampus and cortical brain regions.

Summary: MINDSpeed is the first study to evaluate the multicomponent intervention of high polyphenol intake and speed of processing training. It is also one of the first dementia prevention trials to target older adults with low education. The results of the study will guide future dementia prevention efforts and trials in high risk populations.

1. Introduction

Testing dementia prevention interventions in high risk populations has been a recent research recommendation of multiple leading organization, including the National Academy of Medicine (NAM) [1], the National Institutes of Health [2,3], and internationally recognized

* Corresponding author at: 1101 West 10th Street, Indianapolis, IN 46202, United States of America.
E-mail address: daniclar@iu.edu (D.O. Clark).

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leaders [4–6]. In fact, some of the world's leading dementia scientists recommend a policy and research shift toward reducing risk and increasing reserve; neural or cognitive reserve is one's ability to function despite pathology [5].

In Dementia Prevention—a call for contextualized evidence, Drs. Lafortune and Brayne highlight that "very limited evidence is available regarding effective dementia prevention for populations of low socioeconomic status (SES) and for minority or marginalized groups." [6] The NAM Cognitive Aging report recommended evaluation of multicomponent cognitive interventions for vulnerable populations. In the study described here, we seek to test an intervention involving two positive behaviors that may have additive effects on cognition—consumption of high polyphenol foods and speed of processing training. Diet addresses neurobiologic risk factors and indirectly addresses cognitive reserve, while cognitive training directly addresses cognitive reserve.

Low education [7] is the top population-attributable Alzheimer's disease (AD) risk factor worldwide [8]. Low cognitive reserve is a leading hypothesis for low education's effects on early cognitive decline and AD onset [9]. Adult hippocampal neurogenesis (AHN) is fundamental to maintaining cognitive reserve [10] and diet plays a critical role in maintaining an environment conducive to AHN [11]. Unfortunately, low education is often associated with unhealthy dietary habits [12] that are difficult to completely eliminate [13]. However, supplementing unhealthy dietary habits with healthier foods has real potential to impact cognitive health and function [13]. For example, moderate adherence to the "MIND" diet developed by the Rush Memory and Aging group cut AD risk by one-third over 4.5 years [14]. The diet was built from epidemiological [15,16] and randomized controlled trial evidence that consumption of certain foods can improve short-term cognition [17–19]. Specifically, plant-based polyphenol compounds have emerged as key interventions for cognitive health and function [11,20].

While dietary components support the creation of new neurons, cognitive training promotes integration of neurons into neural networks [21–23]. Speed of processing training, in particular, results in very large performance gains [24–26] that have been maintained for years [27,28]. "Speed training" targets fluid mental processing speed and reduces the length of time needed to process more and more complex information [29]. In a secondary analysis of data from the largest cognitive training trial ever conducted, we showed speed training had a large effect among participants with fewer than 12 years of education; the effect size was 50% larger in those with fewer than 12 years of education compared to the subsample with 16 or more years and this difference was maintained to 5 year follow-up [30].

At this time, we are not aware of any published randomized trials of speed of processing training, i.e., Speed, combined with high polyphenol foods, i.e., MIND foods. Nor are there published randomized trials of MIND foods or Speed training properly designed and powered to assess effects in older adults with low education. This is the intent of the MINDSpeed trial.

2. Methods

In a 2 × 2 factorial design, we are testing in a randomized controlled trial the effects of high polyphenol "MIND" foods and speed training (MINDSpeed) in older adults with low education (see Fig. 1). Support for the feasibility and efficacy of the MINDSpeed intervention could lead to a follow-on AD prevention trial through existing and scalable programs and applications such as home-delivered meal programs and home Internet.

The primary specific aim of this pilot clinical trial is to determine MINDSpeed effects on an executive cognitive composite score relative to control interventions. The primary hypotheses are that MINDSpeed is more effective than MIND food or Speed training alone and all are more effective than control in improving the objective composite measure at

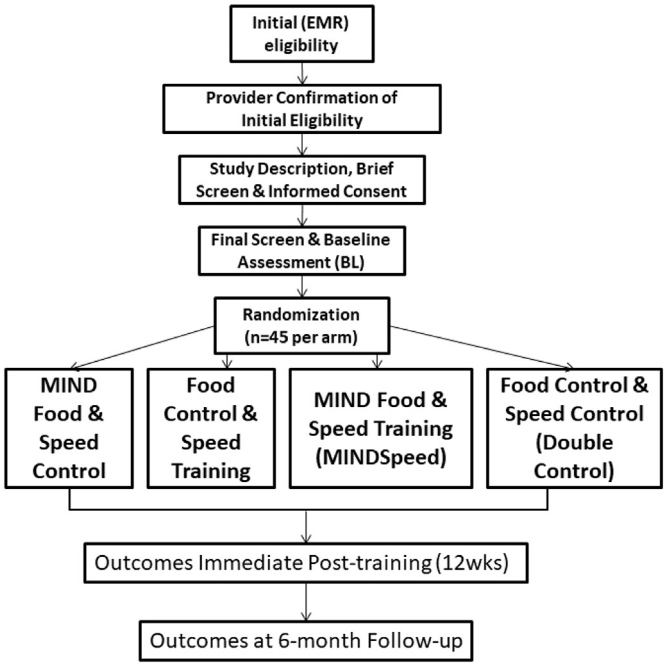

Fig. 1. Study design.

immediate post-training (3 months post-randomization) and then at 3-months post-training (6 months post-randomization).

Secondary aims are to determine: 1) feasibility (i.e., adherence, adverse events, costs), 2) treatment effect modifiers (e.g., education, age, baseline cognitive status, *APOE* ε4 carrier status), and 3) mechanisms including the roles of inflammation, oxidative stress, hippocampal and cortical volume, and functional connectivity.

The MIND Food and Speed of Processing Training in Older Adults with Low Education Alzheimer's Disease Prevention Pilot Trial is funded by the National Institute on Aging (R01 AG052439). The study is approved by the Indiana University Institutional Review Board and registered in clinicaltrials.gov (NCT 1703766063).

3. Recruitment and randomization process

Recruitment is a multi-step process in cooperation with Eskenazi Health. Eskenazi is one of the five largest safety-net health systems in the United States and actively provides care to approximately 20,000 adults aged 60 years or over. First, health system data managers with access to the electronic medical record (EMR) will identify patients who meet study demographic and clinical criteria. Second, providers will be alerted that their patient may be eligible, and given the opportunity to opt-out any patient from contact for potential participation. Third, potentially eligible participants will be approached at an Eskenazi federally qualified health center (FQHC) visit or called by telephone by a research assistant. Those indicating interest will complete a brief screener followed by information about the study interventions and assessments. Fourth, those who remain interested and eligible will schedule an appointment to complete informed consent and baseline assessment. Assessments will be completed at the Eskenazi Center for Brain Care Innovation and the IU Center for Neuroimaging by trained assessors. Finally, participants completing all baseline assessments will be randomized. Randomization will be stratified by age (60–69; 70 and over) and neuroimaging completion. Within each stratum, subjects will be randomized to one of the four training arms with random block sizes of 4 and 8. The randomization list will be generated using computer software and placed in sealed envelopes that are consecutively numbered. Following completion of the baseline assessment, the research coordinator will open the next available envelope in the appropriate

stratum to assign treatment.

Those consented and randomized will receive a study provided iPad tablet running our MINDSpeed application. The app will provide each participant with 12 weeks of access, support, and incentives for the interventions of the 4-arm randomized controlled trial: 1) MIND food + Speed training, 2) MIND food + Speed training control, 3) MIND food control + Speed training, or 4) MIND food control + Speed training control.

4. Inclusion and exclusion criteria

As noted, the target population is adults aged 60 years or over born in the United States who self-report 12 or fewer years of lifetime formal educational attainment. Additional inclusion criteria are English speaking, native-born U.S. resident living in Marion County, Indiana. Exclusion criteria include EMR or self-reported diagnosis of dementia, Alzheimer's disease (AD), multiple sclerosis, epilepsy, schizophrenia, bipolar disorder, Parkinson's disease; cancer with short life expectancy or current cancer treatment; stroke or myocardial infarction within the past 12 months; brain tumor, brain surgery, or brain infection; current alcohol consumption ≥ 8 drinks per week for women or ≥ 15 drinks per week for men; self-reported poor vision (difficulty reading a newspaper) or color blind; low communicative ability (examiner rated) that would interfere with interventions and assessments; prior involvement in similar cognitive training studies; unwilling or unable to provide blood sample at baseline assessment. In addition, participants who complete optional neuroimaging will be withdrawn if baseline MRI shows clinical evidence of tumor, hemorrhage, aneurysm, or hydrocephalus.

5. Interventions

Active (i.e., MIND and Speed) and control interventions will be delivered through an app operating on study-provided iPads. In an effort to maximize uptake, adherence, and scalability, our professional design team worked with older less educated adults and consultants to create the interventions. User-centered design and behavioral principles guided the intervention development. In particular, design preferences were guided by two principles: 1) "easy" substantially increases uptake [31], and 2) small incentives as frequent and close in time to the behavior as possible significantly improve adherence [32,33] [34].

Our UX design team led a user-centered design research effort to integrate the speed of processing and MIND food interventions. First, five older adults evaluated application screens and functions rendered on Sketch (https://www.sketchapp.com/). Second, these same users experienced tablet-operated, interactive prototypes created through an application called Axure (http://www.axure.com/). Third, the design was evaluated by an outside expert team including human factors and software engineers and design researchers. Finally, the MINDSpeed app was evaluated in a different group of five users for 1 week (ages 52–76 years). The pilot study involved a combination of interview sessions, iterative design and usability evaluation of the prototype, food delivery and reporting, and game play (BrainHQ) (see Fig. 2 MINDSpeed – "Good Afternoon"). Some older adults with low education have limited reading skills, low computer familiarity, and limited eyesight. Thus, a major objective of the design work was to make the application easy for the target group to use. This has been achieved. First time users reported "this is self-explanatory" and "I will know how to use after first time, pretty simple." Findings from the pilot indicated that participants shop through the app, received home delivered foods, played speed training games, and tracked incentives with ease and high satisfaction.

5.1. The speed intervention arm

Speed of processing training will be provided by the Internet-based BrainHQ program from Posit Science, Inc. BrainHQ contains five different speed training modules (Hawk Eye, Visual Sweeps, Fine Tuning, Eye for Detail, Sound Sweeps) that tap time-order judgment, visual discrimination, spatial-match, forward-span, instruction-following, and memory [35]. The Posit program systematically reduces stimulus presentation time to maintain an 85% accuracy rate and launches each new session based on the stopping point of the preceding session. Participants will receive performance ratings relative to their prior trial upon completion of each "exercise." Participants will be incentivized to train 100 min (minimum) per week for 12 weeks, which exceeds by 15 min the training in the successful Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study [24,29]. Participants will be encouraged to play 15 min per day, and 5¢ will be added to the incentive account for every minute of play up to $5 per week. The cumulative incentive amount will be displayed at the top of the home screen in the app. Through the Posit Science research platform, we will have real-time, objective records of training time per module, per session, for each participant.

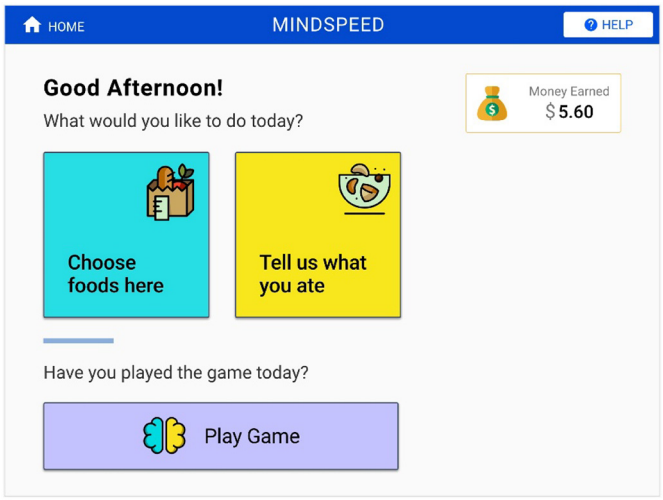

Fig. 2. MINDSpeed home page.

5.2. MIND foods intervention arm

Participants randomized to the MIND food intervention arm will shop for and receive high polyphenol foods through the app (see Fig. 3, "Order Food"). The food component of the intervention is intended to replace some usual food items and thus is not intended to add additional calories to one's diet. Participants will select seven food items; one for each day of a week. Servings of each item have been designed to provide a minimum of 1000 mg of polyphenols with up to 500 mg coming from flavonoids, in particular flavanols, as determined from the Phenol-Explorer database [36,37]. These minimum polyphenol levels were determined from existing evidence regarding mechanistic changes related to polyphenol levels [38,39]. The food options within the app are restricted to those selected or created by our study nutrition scientists working with Eskenazi nutritionists. Selected foods will be delivered to the participant's place of residence once per week by Eskenazi Health food and nutrition services. Having ordered the week's food, participants will be prompted each day of the week to report whether the purchased food was consumed. An incentive of $1 for each daily report will be added to the cumulative incentive total.

The Control interventions are designed to mimic the activities of the MIND and Speed interventions. The food control participants will experience all of the features of the MIND food participants with the exception that the foods available to order will be limited to whole foods very low in polyphenols (e.g., corn, rice, potatoes, iceberg lettuce, pears, etc). Speed control participants will experience the same app features as Speed participants but in place of speed training will play

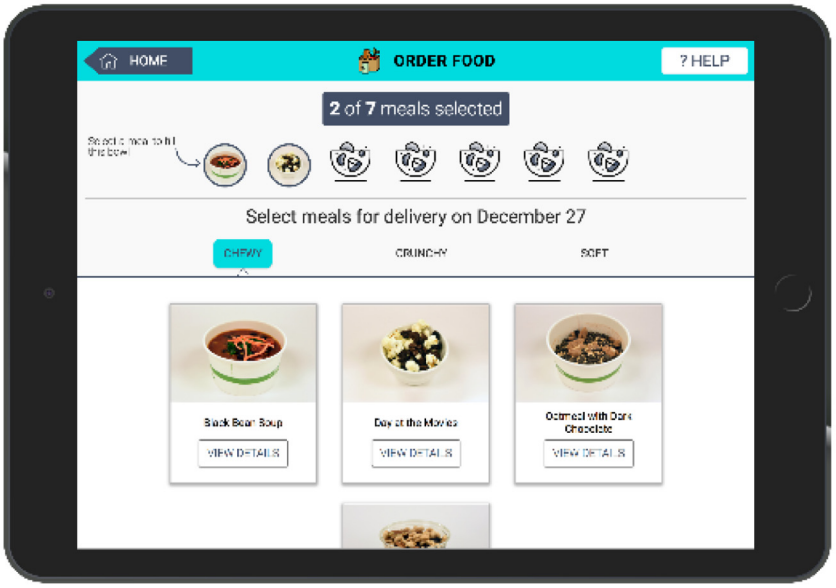

Fig. 3. Food ordering screen.

control games on the iPad judged to be inert (e.g., War Ship, Bricks Squasher). The control games were created by independent game developers, and the games are hosted by BrainHQ for research purposes. All participants regardless of intervention type will be eligible for up to $12 per week of incentives (maximum of $7 for daily food reports and $5 for 100 min of game play).

5.3. Intervention maintenance

After the 12-week post-training assessment, incentives and food allowances will cease but participants will have continued access to games on the project iPad. Those in the MIND or MINDSpeed arm will receive recipes and ingredient lists and be encouraged to maintain MIND food consumption. Maintenance was chosen over total cessation of the intervention because it holds potential to maximize treatment potency, provides information on the rates of self-managed adherence, which speaks to reach and effectiveness of the interventions, and may enhance subject retention to the 6-month follow-up.

5.4. Intervention fidelity

Treatment fidelity and monitoring as defined by the NIH Behavior Change Consortium Strategies [40] and checklist [41] is enhanced by app-delivery and daily food and objective game data. A help button on the MINDSpeed app allows participants to reach staff or request a call back (8 to 5, M-F). All staff have personally played BrainHQ active and control games, and experienced the MIND foods and control foods. Staff have quick access to our UX designer and programmer, as well as Posit Science technical support and our clinical nutritionists. The intervention support staff and blinded assessor complete study training prior to working with enrolled subjects.

6. Measures

All assessments will be completed at the Eskenazi Center for Brain Care Innovation and the IU Health Neuroscience Center by trained, certified, and blinded assessors. Unless otherwise noted, measures are taken at baseline (BL), immediate post-training (PT), and 6 month follow-up (FU). Participants will indicate occurrence of leisure-time cognitive training, physical exercise, and formal educational activities [42]. At each assessment, we will measure body weight and height. Subjects will stand flat footed, shoes removed, in light clothing. Blood pressure will be taken from the left arm using an automatic device after the participant has been resting 5 min in an upright, seated position. For blood pressure, two separate measurements will be taken and averaged.

6.1. Cognitive status determination

We complete the Mini-mental State examination (MMSE) because it has: 1) been widely used as a global measure of cognitive status [43], which facilitates the characterization of our sample to those of past studies, 2) excellent reliability and validity [44], and 3) modified scoring for low education samples [45]. In scoring, both a traditional and education-modified score will be computed.

6.2. Feasibility outcome measures

We will track the number of potential participants approached, screened, and enrolled to gauge recruitment success using ≥50% of eligible participants enrolled as the criterion. We will also monitor the safety, acceptability, and adherence of the app-delivered interventions and outcome measurements. Safety will be assessed by comparing adverse event rates, both serious (i.e., hospitalizations) and non-serious (i.e., anxiety, allergy symptoms) across treatment groups. The acceptability of the experimental and control interventions will be measured using weekly self-report survey asking of satisfaction (i.e., 1 = very satisfied, 3 = neutral, 5 = very dissatisfied) with scores from 1 to 2 indicating acceptability. Adherence will be documented by dates, episodes, and time spent in completing speed training modules and food reports. Maintenance will be determined from training data and diet assessments (see below) at PT to FU.

6.3. Cognitive outcome measures

Consistent with the conceptual model, the primary outcome is a cognitive function composite. Our executive cognitive composite consists of verbal fluency (Controlled Oral Word Association, 3-letter phonemic fluency; Category Fluency, 3-category semantic fluency) [46], Symbol Search from the WAIS-IV [47], Trail Making Test (Parts A & B, *sec* to complete) [48], and Stroop Interference (number completed in 45 s on the color-word trial) [49] for each participant at each occasion of measurement. Raw scores for each test are standardized using the baseline mean and standard deviation. A composite is then formed as an average of z-scores. In addition, List Learning from the Repeatable

Battery for the Assessment of Neuropsychological Status (RBANS) will also be administered to assess new learning and memory.

6.4. Diet assessment

At each assessment (BL, PT, and FU), participants will be asked to complete the VioScreen Food Frequency Questionnaire (FFQ), a validated web-based FFQ which allows for complex skip patterns, portion size estimation based on images, and real-time error checking [50]. The FFQ will be interviewer-administered and will provide an estimation of usual kilocalories, and macro- and micro-nutrients [50]. In addition, we will use urine samples to obtain "biomarkers of compliance" as was done in the recently completed PREDIMED multisite RCT [51]. We will use the "fast and simple" rapid Folin-Ciocalteu method to determine total polyphenols at BL, PT, and FU [52].

6.5. Self-reported outcomes

The Geriatric Depression Scale will measure depression [53], a modified Cognitive Self-Report Questionnaire will measure cognition and engagement, and one question of the SF-36 [54] to measure self-reported health. Instrumental activities of daily living will be measured by self-report using portions of Minimum Data Set-Home Care [24].

6.6. APOE collection and assay

Genomic DNA will be extracted from blood samples using the DNeasy Blood & Tissue Kit (Qiagen, Inc., Valencia, CA) according to the manufacturer's protocol. Approximately 50 ng of genomic DNA will be used for amplification. *APOE* genotypes will be determined by restriction enzyme digestion of amplified DNA [55].

6.7. Treatment and adherence modifiers

Individual difference factors with potential to modify response to treatment and adherence will be measured at BL including: age, race, gender, years of education, *APOE* ε4 allele status, baseline cognitive status (via the MMSE), height and weight to compute body mass index, blood pressure, Charlson Comorbidity Index [56], depression, self-reported visual acuity, and reading ability (via Wide Range Achievement Test-IV Reading).

6.8. Blood biomarkers

Fasting blood samples will be obtained at BL, PT, and FU in all subjects to explore the mechanisms of action. The conceptual model holds that the cognitive benefit of combined training is achieved through modulation of physiologic processes related to neural proliferation, oxidative balance, and metabolic function. As a result, we will measure circulating levels of the pro-inflammatory cytokines IL-1α, IL-1β, IL-6, and TNF-α; the anti-inflammatory cytokines IL-1ra and IL-10; the acute-phase reactant C-reactive protein; vascular endothelial growth factor and brain derived neurotrophic factor; and also metabolic processes reflected in insulin resistance and blood glucose. Oxidative stress will be determined from thiobarbituric acid reactive substances (TBARS), a byproduct of lipid peroxidation. We will also measure plasma biomarkers for levels of amyloid-β as a predictor for amyloid-β deposition in the brain, which is the earliest pathological sign of Alzheimer's disease. We will obtain 4 ten ml purple top EDTA tubes of blood taken in the fasting state. Blood samples will be centrifuged within 10 min of collection. Plasma aliquots will be stored at −80 °C until the time of assay. Measures will be performed in the Analyte Lab at the Center for Diabetes and Metabolic Diseases at Indiana University (1P30DK097512 Mirmira R [PI]). We will obtain a Paxgene RNA tube at these same 3 intervals and bank for future RNA-sequence analysis since the intervention may alter the transcriptome / mRNA expression levels.

6.9. Cost

We will track all personnel, equipment, technology, and support costs associated with delivering the interventions thus allowing an estimation of intervention costs on a per subject basis.

6.10. MRI acquisition protocol

The following scans will be performed on a research-dedicated new generation Siemens Prisma 3T scanner with a 64CH receiver-only head coil: 1) Sagittal survey 3-plane localizer; 2) T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) 3D anatomical volume; 3) High resolution T2-weighted hippocampal sequence; 4) Axial T2-weighted Fluid-Attenuated Inversion Recovery (FLAIR) sequence; 5) Diffusion field map; (6) Diffusion tensor imaging (DTI); 7) EPI-Field map #1 (anterior to posterior (AP)), 8) EPI-Field map #2 (posterior to anterior (PA)), and 9) Blood Oxygenation Level Dependent (BOLD) functional task-based MRI. The structural MP-RAGE and high-resolution hippocampal sequences will be collected following the Alzheimer's Disease Neuroimaging Initiative protocols (http://adni.loni.usc.edu/methods/documents/mri-protocols/). The FLAIR parameters are as follows: Sagittal T2-weighted 3D acquisition, 144 slices, voxel-size = 0.5 mm × 0.5 mm × 1 mm, TR = 5000 ms, TE = 390 ms, TI = 1800 ms, iPAT factor = 2, scan time = 4:22. The DTI scan parameters are as follows: Axial SS-SE-EPI acquisition; b-value = 1000s/mm^2, 60 directions, 3 b0 images, 69 slices, voxel-size = 2 mm × 2 mm × 2 mm, TR = 2290 ms, TE = 64.8 ms, flip angle = 90, multi-band factor = 3, iPAT factor = 2, scan time = 2:56. The functional MRI task is Scene Encoding and Recognition, modified from Detre and colleagues [57–59], which elicits reliable bilateral medial temporal lobe activation. BOLD fMRI parameters are as follows: Axial GE-EPI acquisition, 54 slices, voxel-size = 2.5 mm × 2.5 mm × 2.5 mm, TR = 1200 ms, TE = 29 ms, flip angle = 65, multi-band factor = 3, scan time = 5:16.

Safety. We have standard regulatory reporting procedures in the Data and Safety Monitoring Plan (DSMP) and the operation of our Data Safety and Monitoring Board (DSMB). Adverse events are documented by study staff and reviewed by the local safety officer and DSMB chair. Cognitive training is relatively safe but anxiety and burden can occur and will be monitored. Magnetic resonance imaging (MRI) is a safe procedure for people who do not have metal implants or other contraindications. Study personnel will screen participants for these risk factors prior to enrollment. Before entering the MRI environment, participants will be re-screened for MRI contraindications. Physical confinement or noise in MRI can be uncomfortable, and all efforts will be made to assure participant's comfort. Blood draws and urine collections will be conducted by trained and certified Eskenazi clinical staff. Finally, a small number of participants may develop depression, dementia, or physical dysfunction during the study. Should this occur, we will direct the subject to appropriate clinical care (i.e., primary care provider or specialty clinic as needed).

7. Sample size and power

The primary analysis of the study focuses on the evaluation of the effectiveness of the interventions on the cognitive outcome, executive cognitive composite. We therefore determined the sample size to ensure adequate power for this analysis. In these prior studies, speed of processing training was found to have an effect size (ES) of 1.4 standard deviation (SD) at immediate post-training (PT) and 1.2 SD at 1 year PT on processing speed outcomes [24]. MIND diet is a brain health optimized hybrid of the Mediterranean-DASH diets, and the latter were found to have an effect size of 0.44 to 0.56 SD on executive function and speed of processing [60]. There are no published trials of speed of

processing training combined with MIND diet but we expect a large effect size of the combined intervention. With an overall alpha level of 0.05 for six Bonferroni-adjusted two-sided comparisons, a conservative estimate of the correlation of 0.7 between baseline and follow-up outcomes, and 15% estimated 6 month attrition rate taken from our prior geriatric intervention trial [61], the sample size of 45 subjects per treatment arm will yield 80% power to detect an effect size of 0.6 SD based on the constrained longitudinal data analysis (cLDA) [62]. The cLDA [63] has been shown to produce greater efficiency and handle missing data more flexibly with valid inference when data are missing at random [62,64]. Cognitive aging studies support an effect size of over one-half standard deviation as clinically meaningful [65–67].

7.1. Secondary aims and power

Secondary outcomes include inflammation, metabolic function, oxidative stress, and hippocampal and cortical structure and function (via MRI). For non-imaging outcomes, we will have a full sample and adequate power to detect effect sizes of 0.6. Imaging creates anxiety and discomfort for some, however. Thus, in addition to using information and communication strategies shown to reduce imaging anxiety [68] we will complete imaging on the minimum necessary. From the literature, we anticipate large effect sizes on the brain outcomes of structure and function. Cognitive training has resulted in changes in brain structure with approximate effect size of 0.56 in left hippocampus volume following spatial navigation training among healthy younger and older men [69] and an approximate effect size of 0.47 in gray matter density (GMD) after the completion of a multi-domain computerized cognitive training among healthy older adults [22]. In addition, our preliminary results showed an effect size of 0.5 in annual percent change in hippocampal volume and 0.8 in annual percent change in hippocampal GMD among older adults without MCI who are frequently engaged in reading and puzzle-solving compared to those who are not. Food interventions alone have had an effect size of 0.7 on hippocampal volume [11,38]. Other studies support effect sizes of 0.64 to above 1.00 on functional connectivity [70,71]. A one-half subsample of each arm ($n = 22$ per arm) with an alpha level of 0.05 and a correlation of 0.7 between baseline and post-training with 15% attrition provides 80% power to detect an effect size of 0.83 or larger for the brain imaging outcome.

In order to test the mediating effect of blood biomarkers, brain structure, and brain function variables we need to establish the association between the mediating variable and primary outcome, after controlling for the intervention effect. Such an association is evaluated using a partial correlation. With our sample size, we have > 80% power at the 0.05 alpha level to test a partial correlation of 0.3 between mediating variables and the primary memory composite outcome. Evaluation of moderating effects is an exploratory aim and detection of such effects requires large sample sizes. Our study is therefore only able to explore treatment moderators. In addition, our sample size of 45 subjects per arm provides accuracy with no > 8% margin of error at the 95% confidence level for feasibility outcomes.

8. Analyses

8.1. Preliminary analyses

These analyses will include comparing baseline characteristics of participants across treatment arms. We will also compare the baseline scores on outcome measures across treatment arms. For continuous variables, means and standard deviations will be reported. Frequency tables will be reported for categorical variables. Normality of continuous outcomes will be examined using a normal probability plot. For highly skewed measurements, appropriate transformations will be applied to achieve approximate normality. Repeated measurements over time will be graphed as spaghetti plots and examined for outliers. All data will be examined for completeness. The baseline characteristics will be compared across treatment arms and between participants who do and do not complete the study. If any significant differences exist, we will control for differences in the subsequent analyses. Analyses will be performed under the intention-to-treat paradigm.

8.2. Primary analysis

The primary analysis of the intervention effect on executive cognitive composite will be performed using the constrained longitudinal data analysis (cLDA) proposed by Liang and Zeger [63]. Repeatedly measured executive cognitive composite outcomes at BL, PT, and FU will be modeled as dependent variables with the baseline mean responses constrained to be the same across intervention arms due to randomization. This model is flexible in handling missing data and has been shown to provide greater power than other models when testing intervention effects and yields valid results when data are missing at random. The clustering effect of repeated measures within a subject will be accommodated using a random subject effect. Time of measurement (BL, PT, FU) and its interaction with intervention arm will be included in the model. The time of measurement is considered as a categorical variable to allow non-linear time effect. Intervention effects are captured by the significant interaction effect. Comparison of outcome measures across intervention arms at PT and FU will be estimated based on the model using appropriate contrasts. In order to assess whether the intervention effect is affected by physical activity change, weight change, or other factor, we will examine change patterns across intervention arms. If the change pattern differs across intervention arms, that factor will be controlled by including its main effect and interaction with the intervention arm in the primary analysis for intervention effect on executive cognitive composite.

8.3. Analysis of MRI scans

Scans will be processed using standard techniques and normalized to standard space for analysis (i.e. Montreal Neurologic Institute, MNI). Structural MRI scans will be processed using voxel-based morphometry (VBM) in Structural Parametric Mapping (SPM12) and FreeSurfer (v6) as previously described [72–75]. High-resolution hippocampal scans will be processed to generate volumetric estimates of hippocampal subfields as described in previous work [76]. DTI scans will be preprocessed as in [77] and [78], with eddy current and other corrections using FMRIB Software Library (FSL) [79] producing a single corrected image. DTI scalar measures, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) will be computed by using FSL. Using Camino, DWI voxel-wise data will be modeled by using zero (isotropic diffusion), one (one major gradient diffusion), or two tensors (crossing fibers) using cutting-edge techniques as in [80] and [81–83]. Both streamline and probability tractography will be performed to generate specific white matter tracts and structural connectivity. A number of statistics (represented by structural connectivity (SC) matrices) will then be generated from the tractography data, including number of fibers, fiber density (as in [84]), average length of the streamlines (in mm), and average fractional FA and minimum FA within and among the streamlines. Task-related fMRI scans will be processed using methods described our prior work [85,86]. Briefly, contrast images of task-related activation (scene presentation) relative to control conditions (scrambled scenes) will be generated using standard pre-processing techniques (i.e., slice time correction, normalization, etc.) implemented in SPM12 [85,86]. These contrast images (scene > control, control > scene) will be used for further analysis.

Images will be compared between those receiving the combined intervention, a single intervention, and control cross-sectionally and longitudinally on voxel-wise and ROI levels. Cross-sectional voxel-wise analyses will compare the scans between groups at BL and PT.

Longitudinal voxel-wise analysis will model time-by-group interactions using a two-way Analysis of Covariance (ANCOVA) model. All voxel-wise analyses will be performed in SPM12. For regional analysis, we will extract a mean value for ROIs from the final stage preprocessed scans. Specifically, cross-sectional and longitudinal change in regional brain atrophy (i.e., MTL, frontal lobe, hippocampal subfields), white matter (WM) integrity (i.e., FA, MD from MTL tracts) and structural connectivity, and task-related fMRI activation will be compared between intervention groups over time.

8.4. Secondary analyses

Feasibility outcomes including intervention adherence, acceptability and rates of adverse events will be estimated using the 95% confidence intervals Self-reported outcomes including depression, cognition and engagement, quality of life, and IADL will be examined using the cLDA methods described immediately above.

8.5. Mechanism analyses

Mechanistic hypotheses are that, relative to control at PT, intervention arm participants will have greater hippocampal and cortical volume, better metabolic function, higher levels of neurotrophic growth factors, and lower levels of inflammation and oxidative stress. Hypotheses will be analyzed using cLDA. With regard to MRI, scan analysis described immediately above will be performed on targeted pre-specified ROIs and followed by spatially unbiased whole brain voxel-based analyses. Supplemental analyses will compare across scan modalities to address the relative incremental contribution of each modality (e.g. hippocampal volume, cortical volume, WM integrity, etc.) to capturing the overall neuroimaging outcome.

8.6. Moderator and mediator analyses

Analyses will be performed to determine the role of adherence, years of education, age, baseline cognitive scores, comorbidity, and *APOE* ε4 carrier status (an indicator of elevated ADRD risk) in moderating intervention outcomes using cLDA. We hypothesize in particular that participants with greater adherence, less education, and lower comorbidity will experience larger executive cognitive composite score gains. A three-way interaction between potential moderators, intervention arm, and time of measurement will be included in the model and a significant three-way interaction indicates the moderating effect. To evaluate hypothesized mediators of the speed training and MIND foods (e.g., inflammation, growth factors, oxidative stress, hippocampal and cortical volume), we will use the approach proposed by Krull and Mackinnon (2011) [87] that allows the testing of mediating effects in clustered data. Using the change in executive cognitive composite outcome from baseline as the dependent variable, a series of three mixed effects models will be fit and regression coefficients from these models will be used to estimate the direct and indirect treatment effects.

The cLDA provides valid inference when data are missing due to random dropouts. Sensitivity analyses will be performed to examine to what extent the results are affected when dropouts are not missing at random. Analyses based on complete cases, mean imputation, and worst case imputation will be performed. In addition, missing data patterns will be examined and a pattern mixture model will be used to allow different intervention effects for subjects with different missing data patterns. Results based on these models will be compared to results from cLDA.

9. Discussion

The MINDSpeed trial is among the first to test either high polyphenol foods or speed of processing training among older adults with low education, and as far as we know the first to test these interventions in combination in any group. As such, the feasibility aims of this pilot trial are important. The primary aim, to test the effect of these interventions on our objective executive cognitive composite score, is obviously key but the aims to test mechanisms and moderators of effects of these interventions in this high risk population are also of high significance. Our conceptual model hypothesizing mechanisms through which these interventions could enhance cognitive reserve and sustain or improve cognition is well supported by recent theoretical and empirical literature but much investigation is yet needed. Principally, whether making room in one's usual diet for foods that achieve high polyphenol intake (e.g., > 1000 mg per day) is sufficient to meaningfully reduce inflammation, oxidative stress, insulin resistance, and neurodegeneration. Similarly, whether speed of processing training increases growth factors, neurogenesis, and brain structure and function. Our investigation of moderators is more exploratory in nature, but includes factors, such as age, education, or *APOE* ε4 carrier status, that may be critical to future tailoring or intervention targeting.

Combinatorial interventions for preventing or delaying ADRD have been a recommendation of multiple national organizations and scientific leaders. With few such interventions to date, we believe it is critical to evaluate the feasibility of combinatorial interventions in populations at high risk for ADRD such as older adults with low educational attainment in this trial. With this disadvantaged target group, a key feasibility challenge will be treatment and assessment adherence. If adherence via the MINDSpeed app drops below 80%, we will institute, first, increased incentives and, second, telephone reminder and support calls. Study retention is also a feasibility challenge. With fair subject payments in past work, we have completed one-half day assessments that include imaging at the Indiana University Center for Neuroimaging. We have a “step-down” assessment battery if a participant is not able to tolerate the full outcome assessments.

Accomplishment of the feasibility and efficacy aims of our proposed MINDSpeed pilot trial will support the development of a later stage ADRD prevention trial. Such a trial would be scalable through the study applications described here, and likely would require multiple study sites. These, we imagine, would come through the nation's network of safety-net health systems referred to as America's Essential Hospitals. The Essential Hospitals Institute is the research arm of the network and includes a mission to better understand upstream effects in efforts to improve population health in the communities served by members of America's Essential Hospitals. There are dozens of network sites around the nation, including sites that are also members of the Food as Medicine network, from which to draw upon and engage for an ADRD prevention trial, should our aims show promise.

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