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Feasibility of a Functional Medicine Approach to Slowing Clinical Cognitive Decline in Patients over Age 55: A Multiple Case Study Report

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Abstract

***Background*:** The current study examined a multifaceted anti-neuroinflammatory intervention that included physical exercise, mental exercise, grain-free/sugar-free diet, anti-inflammatory nutritional supplements, sleep optimization, and stress management within the context of a functional medicine practice for five patients with varying levels of cognitive impairment.

***Methods*:** In a prospective chart review, we examined impact measures including assessment of (1) cognitive skills, (2) brain connectivity, and (3) daily functioning.

***Results*:** Three of the five patients were no longer classified as cognitively impaired, while a fourth patient improved from moderately-to-severely impaired to mildly impaired. Patients

reported improved memory, mental clarity, and outlook on life. fMRI analyses revealed changes in brain connectivity and efficiency.

***Conclusions*:** The current study provides preliminary support for and feasibility of the use of a multi-component approach to slowing cognitive decline.

Keywords

Cognition; exercise; cognitive training; MCI; neuroinflammation; functional medicine

1. Introduction

A mono-therapeutic approach to slowing clinical cognitive decline in patients over age 55 likely fails to target the many sources of neuroinflammation thought to be responsible for the progression of dementia. Instead, a multi-component intervention may prove to be more successful in targeting each inflammatory contributor. The current study examined a multifaceted anti-neuroinflammatory intervention that included physical exercise, mental exercise, grain-free/sugar-free diet, anti-inflammatory nutritional supplements, sleep optimization, and stress management within the context of a functional medicine practice for five patients with varying levels of cognitive impairment. Outcome measures included neuropsychological test results, functional Magnetic Resonance Imaging (fMRI) scans, and personal interviews.

2. Background

Age-related cognitive decline occurs on a continuum from mild to severe deficits in memory, language, reasoning, and even social skills. Mild cognitive impairment (MCI) is a clinical diagnosis of slight decline in cognitive abilities noticeable to the individual—and sometimes others—but does not interfere with independent living. MCI represents the stage between healthy age-related cognitive decline and dementia but does not always progress to dementia. MCI affects 10% to 15% of people over 65, and the prevalence increases with age [1]. The American Academy of Neurology diagnostic and treatment guidelines for MCI include recommendations to (a) assess with validated screening tools, (b) monitor ongoing cognitive condition, (c) encourage physical exercise and cognitive training interventions, and (d) discuss the current absence of evidence for effective drug treatment [2]. However, to date there is no definitive remedy, drug, or cure for dementia or cognitive decline [3]. Pharmaceutical interventions such as memantine or cholinesterase inhibitors have been the first-line treatment of many medical practitioners, regardless of the lack of evidence for effectiveness [1-4]. Yet recent studies abound with recognition of lifestyle changes, such as diet and exercise, for amelioration of cognitive decline [5-7].

Neuro-inflammation is a prominent finding in age-related cognitive impairment and Alzheimer's Disease (AD). It has been presumed that this inflammation was a response to the pathology of AD; however, recent findings reported in the literature suggest neuro-inflammation contributes to AD pathogenesis [8]. MCI is a precursor to AD with up to 50% of individuals with MCI converting to AD within 1 to 3 years. Thus, neuro-inflammation is assumed to be a contributing factor to both MCI and AD. Numerous cellular pathways are associated with

inflammatory responses. Successful treatment of inflammation will likely require targeting these multiple pathways as well as minimizing factors that elicit inflammatory response.

In the first of a series of seminal studies on reversing cognitive decline, Bredesen [9] investigated outcomes for patients with MCI (*n* =9) following adherence to a multi-faceted anti-neuro-inflammatory protocol. The protocol included aerobic exercise, cognitive training, changes in diet to remove factors that can contribute to neuro-inflammation, addition of supplements that target multiple inflammatory pathways, optimized sleep, and stress management. With adherence to this protocol, all patients in the study reported improved memory and quality of life. In a 2016 follow-up study (*n* =19), Bredesen and other researchers [10] designed the metabolic enhancement for neurodegeneration (MEND) protocol, which addressed similar multimodal aspects affecting metabolic processes. Researchers reported clinical and pathological improvements in all 19 patients. And in 2018, Bredesen reported improved clinical outcomes for 100 patients following the MEND protocol [3]. Further, the literature is rife with current research addressing the need for and efficacy of non-pharmaceutical interventions for targeting cognitive decline such as physical activity, ample sleep, and healthy diet [11-15]. Coupled with the new AAN recommendations for treating MCI, medical practitioners are moving away from prescription drug treatment and are now considering cognitive training along with modification of such lifestyle variables [2, 16]. Therefore, the purpose of the current study was to examine changes in cognition and daily functioning following adherence to a multicomponent approach to slowing cognitive decline within the context of a functional medicine practice, furthering Bredesen's research design in three distinct ways. First, we administered comprehensive neuropsychological testing batteries to all the participants to enable group statistical analyses on the pre-treatment and post-treatment scores. Second, we added pre and post intervention functional magnetic resonance imaging (fMRI) using identical scanning protocols across all participants to enable group analyses and identify trends not only in the changes in network connectivity for the group, but also the correlations between connectivity and changes on cognitive test scores. Finally, we implemented a structured cognitive training program delivered by a clinician to examine feasibility of adherence to such a critical element of the intervention protocol.

3. Aim

The purpose of the current study was to conduct a series of case studies on individuals with varying degrees of clinical cognitive decline to document the effects and feasibility of adherence to a clinical anti-neuroinflammatory functional medicine protocol that included a focus on physical and mental exercise coupled with dietary changes, nutritional supplementation, stress management, and sleep optimization. In a prospective chart review, we examined impact measures including assessment of (1) cognitive skills, (2) brain connectivity, and (3) daily functioning.

4. Materials and Methods

The current study was approved by the Institutional Review Board (IRB) at Gibson Institute of Cognitive Research under Approval Number 09162016 on 9/21/2016 which certified the study met the criteria for Subpart A Basic HHS Policy of Protection of Humans Research Subjects of the Code of Federal Regulations, Title 45, Part 46.

4.1 Sample and Recruitment

The sample for the study (*n* = 5) was recruited from existing functional medicine patients of the first author at the beginning stages of treatment for cognitive impairment or subjective cognitive decline. Patients were identified by the physician and given a recruitment flyer. Those interested in participating, and over the age of 55, were screened for eligibility by a member of the research team using a cutoff score of 24 or below on the Montreal Cognitive Assessment (MoCA) [17]. There were no other inclusionary or exclusionary criteria for participation. Eight patients were screened and five met both age and MoCA cut-off requirements. The five eligible patients were given informed consent documents in accordance with 45 CFR Part 46, which were reviewed with patient, patient's spouse, and a member of the research team. All five patients capably provided consent, as determined by the physician and validated by the research team psychologist. Through discussion with each patient and spouse, both clinicians assessed the patient's decisional capacity and ability to understand information presented in the informed consent documents; their appreciation of how study risks and benefits applied to them; their ability to reason through options of participating versus not participating; and their ability to express choice to participate. This clinical judgement is supported by established guidance for working with research patients who have dementia or age-related cognitive decline [18, 19]. After consenting, patients were scheduled for and administered the remaining neuropsychological and neuroimaging assessments. The group ranged in age from 55 to 72, including three women and two men. Detailed descriptions of each patient are provided in the case presentations.

4.2 Outcome Measures and Data Collection

The primary outcome measures included two dementia-specific assessments of cognitive impairment: Dementia Rating Scale (DRS-2) [20] total score and subtest scores (Attention, Initiation, Construction, Conceptualization, Memory) and the Montreal Cognitive Assessment (MoCA), along with two measures of executive functioning: Delis-Kaplan Executive Function System (D-KEFS) [21] Trail Making Test and Tower Test. Dementia-specific assessments were administered three times: before the intervention began, after eight weeks on functional medicine protocols to assess progress, and again at the end of the 9-month study period. Secondary measures included both the "self" report and "spouse" report versions of the Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A) [22] using the Global Executive Composite score (representing all 9 scales including Inhibit, Self-Monitor, Plan/Organize, Shift, Initiate, Task Monitor, Emotional Control, Working Memory, and Organization of Materials). These were administered at the beginning and the end of the 9-month study period. Secondary measures also included the Woodcock Johnson III (WJ III) Tests of Cognitive Abilities [23] overall IQ score and subtest scores (Working Memory, Associative Memory, Visual Processing, Auditory Processing, Processing Speed, Fluid Reasoning, Verbal Comprehension) administered immediately before adding cognitive training and at the end of the 9-month study period.

Compliance to each of the intervention pillars was documented on a daily protocol tracking form and converted to a daily index score on a scale from 0 (Not compliant) to 10 (Fully Compliant) for each pillar and then averaged across the study period. The protocol tracking form, called the "Brain Saving Daily Checklist," required patients to check off compliance with each intervention

pillar daily. Each element was worth one point, leading to a possible score for each element, each week. Each score was divided by the number of possible points to determine the percentage compliance with each pillar. For example, patients were required to take their prescribed nutritional supplements two times daily for a possible 2 points each day times 7 days per week, giving them 14 total possible points for the Nutritional Supplements pillar each week. If a patient earned 12 points one week, the percent compliance would be 85.7% (calculated by dividing 12 by 14). Then, the percentage was converted to an Index Score on a scale from 1 to 10. In this example, the Index Score would be 8.57. The Index Scores for each week were averaged over the study period to create a compliance score for each pillar.

Finally, no-contrast functional Magnetic Resonance Imaging (fMRI) to assess changes in neural network connectivity and its correlation with cognitive test scores was conducted at the beginning and end of the study period. MRI imaging, as described in detail in Appendix A, was performed on a 3 Tesla Siemens Skyra (Erlangen, Germany) MR system and included both a high-resolution anatomical scan and a BOLD (blood oxygen level dependent) resting-state functional scan. Resting state acquisitions were acquired over 12 minutes, with one image acquired every 3 seconds. Image pre-processing and data analysis were performed using the CONN toolbox as this software package incorporates tools that minimize the effects of motion artifacts and physiological noise and allows for valid interpretation of negative, or anti, correlations [24]. As part of pre-processing subject brains are spatially normalized and segmented into 164 regions of interest (ROI) according to the Montreal Neurological Institute (MNI) template brain. First-level ROI-to-ROI correlation maps were generated by extracting the residual BOLD time series from each ROI and calculating Pearson's correlation coefficients between all ROIs (164x164). Correlation coefficients were transformed into Fisher's *Z* scores for use in second-level analyses.

4.3 Research Design

The study used a single case research design across multiple cases. The multiple, or collective, case study has a long history in medicine as a vehicle for in-depth study of a particular clinical phenomenon or approach to care. This design enabled us to assess feasibility of delivering a complex, multi-component strategy for slowing cognitive decline in a clinical setting and to collect preliminary evidence to support a large controlled study.

After completing pre-intervention baseline testing, patients began five of six pillars of the intervention: physical exercise, diet, nutritional supplements, sleep optimization, and stress management. After eight weeks, patients were given progress-monitoring dementia-specific assessments, additional secondary cognitive skills assessments, an executive function inventory, and then scheduled to begin adding cognitive training (mental exercise) to their protocol. The intentional delay in beginning cognitive training was to ease patients into the demanding schedule and to maximize the benefits of the additional therapeutic mental exercise pillar by targeting neuroinflammation for eight weeks first. Patients completed at least 72 hours of cognitive training for a total study duration of nine months.

4.4 Intervention Pillars

For the current study, patients took part in a Functional Medicine Protocol (FMP) for slowing cognitive decline. The FMP included six components individualized in response to diagnoses, deficiencies, and abnormal laboratory results: physical exercise, mental exercise in the form of cognitive training, grain-free/sugar-free diet, nutritional supplementation, sleep optimization, and stress management. The components are discussed below.

4.4.1 Physical Exercise

Under the supervision of the research team physician, all patients were instructed to engage in at least 30 minutes of aerobic activity 5 days per week. Physical activity as a neuroprotective practice has been well documented in the past decade [25-28], and with recent advances in medical technology we are now able to understand some of the underlying mechanisms of why this is so. Both human and animal trials establish the link between physical exercise and neurobiological improvements, such as brain plasticity, hippocampal stability, gray and white matter volume, neuronal fiber integrity, reduced inflammation, and increased brain-derived neurotropic factor (BDNF) levels [29-35]. However, there is a gap in the literature regarding the relationship between exercise, cognition, and brain network connectivity, which the current study attempts to address. Meta-analysis, cross-sectional studies, and randomized controlled trials confirm aerobic activity improves neurological function and cognitive outcomes for aging populations and is negatively correlated with subjective cognitive impairment (SCI), MCI, and Alzheimer's disease [36-40]. In the current study, patients noted their physical activity on a daily protocol tracking form. A member of the research team met with patients weekly to monitor progress and provide motivational support. Physical exercise was a self-guided component of the program, but spouses were encouraged to monitor and participate in the activities.

4.4.2 Mental Exercise

Under the supervision of the psychologist on the research team, all patients received clinician-delivered cognitive training using the Brain Booster [41] program by LearningRx. Although cognitive training programs vary in the skills targeted and delivery mechanism of training (for example, computer games that target memory and attention [42-44] versus comprehensive clinician-delivered cognitive training of multiple cognitive skills [45-48]), cognitive training is supported by a growing body of research suggesting it can improve brain plasticity, memory, quality of life, and outlook [45, 49-51]. Brain Booster targets multiple cognitive constructs including processing speed, attention, working memory, long-term memory, fluid reasoning, visual processing, and auditory processing. The program consists of more than 400 training tasks utilizing 16 core exercises each with 30 to 40 variations. The curriculum is sequenced in order of difficulty and complexity with each variation progressively harder than the one before it. Patients attended two or three 90-minute training sessions each week at a cognitive training center in Colorado. Four patients received 72 hours of training and the fifth patient received an additional 18 hours of training due to the severity of her cognitive impairment. Training was provided by certified cognitive trainers and monitored by a doctoral level psychologist to ensure treatment fidelity. Progress was tracked using a task flow sheet for each patient. A unique attribute of Brain Booster

is the individualized, human-delivered training process. This method departs from typical digital 'brain games' and programs found pervasively in extant research. An illustration of the training dynamic is shown in Figure 1.

Figure 1 Cognitive trainer delivering a fluid reasoning training task to a patient.

4.4.3 Diet

Under the supervision of a certified nutritionist, patients were encouraged to follow the ReNew Food Plan from the Institute for Functional Medicine [52].The individual elements of the Renew Food Plan are grounded in a large body of research that supports elimination of sugar [53, 54], gluten and other grains [55, 56], and processed foods [57, 58]. The suggested elimination of caffeine and alcohol—despite the potential positive effects of each on cognition—is based on a growing body of research that suggests even moderate alcohol consumption contributes to hippocampal atrophy and cognitive decline in the aging [59] and impacts important REM sleep [60]; and caffeine consumption disrupts circadian rhythms and the sleep cycle [61]. Further, the integration of neuro-protective and inflammation-reducing dietary changes—such as increased leafy greens and other low-glycemic raw vegetables; the addition of healthful fats such as nuts, seeds, olives, and coconut oil, and removal/reduction of neuroinflammatory grains, sugars and other simple carbohydrates—are well corroborated as neurologically healthful interventions for reduction and delay of cognitive decline [62-65] and positively correlated with better cognition, memory, and decreased occurrence of Alzheimer's disease [66-68]. In the current study, patients were given a 51-page weekly planner with recipes, a shopping list, and refrigerator magnet with a list of foods to eat frequently, to eat only on occasion, and to avoid. Patients noted their compliance with the food plan on the daily protocol tracking form and met weekly with a member of the research team to increase compliance and motivation.

4.4.4 Nutritional Supplements

Under the supervision of the physician on the research team, each patient was given a basic nutritional supplement panel. All the supplements selected were supported by prior research on their individual benefits to cognitive function [69-93]. We chose two brain supportive combination supplements for patients to take in addition to the individual supplements. We did so because (a) we were working specifically with MCI, and there is evidence supporting the synergistic effect of combining various supplements that are known to enhance certain neurophysiologic pathways, and (b) we sought to enhance compliance with fewer pills to take. To facilitate the ease of sticking to a supplement regimen, the supplier (Xymogen©) packaged the morning and evening supplements in labeled single-dose packs for each participant. A powdered shake was delivered separately in a large 30-day supply jar. The following is a list of ingredients in the basic supplement panel:

- Multivitamin [69,70]
- Omega 3 Fatty Acids 860 mg [71-73]
- Vitamin K2 45 mcg [74]
- Vitamin D 11,000 units [75]
- Probiotic 15 Billion CFU: Lactobacillus acidophilus, Bifidobacterium longum, Lactobacillus plantarum plus 15 billion CFU Bifidobacterium lactis [76-78]
- Vitamin B12 as methylcobalamine 1100mcg [79-80]
- Methyl-Folate 900mcg [79-80]
- Coenzyme Q10 200mcg [81]
- Phosphatidylserine 215mg [82-84]
- Acetyl-L-Carnitine 1050mg [85,86]
- Alpha-Lipoic Acid 200mcg [87]
- Ginko Extract 60mg [88]
- N-Acetyl-L-Cysteine 400mg [89]
- Vinpocetine 5mg [90]
- Huperzine A 100mcg [91]
- Benfotiamine 50mg [92]
- transResveratrol 1mg [93]

In addition to the basic supplement panel described above, patients were also prescribed supplements that targeted any other individual nutritional deficits as identified by the physician on the team.

4.4.5 Stress Management

Patients were coached in the development of individual plans for managing stress. Research from the past two decades replicates findings of negative cognitive responses to stress, including performance deficits in memory, attention, visual processing, and decision making [94-96]. Stress can produce negative cognitive responses resulting from elevated levels of norepinephrine and cortisol [97, 98]. Additionally, chronic and acute stress contributes to negative changes in the hippocampus and prefrontal cortex due to altered glutamate neurotransmission via the release of catecholamines and glucocorticoids [99, 100]. However, stress reduction strategies, such as

participation in relaxing activities akin to reading, knitting, listening to music, or intentional meditation, prayer, and mindfulness, contribute to the physiological repair of stress-induced damage [101-103]. In the current study, plans were tailored to fit within the patient's own spiritual paradigm as well as his/her own goals and desires. At the beginning of the study period, all five patients were coached in biofeedback that monitored heart rate variability and provided interactive feedback on a computer screen. Patients were given unlimited access to this in-office technology as a primary stress management option. However, because regular office visits were not convenient for all of them, patients were also coached in other options including prayer, meditation, and yoga that could be implemented independently or with the help of their spouse. After coaching was provided, the stress management pillar was self-guided and not a structured element of the intervention. Patients noted stress management methods and compliance on their daily protocol tracking form.

4.4.6 Sleep Optimization

The patients were coached on improving sleep and sleep habits, such as no use of electronics within two hours of bedtime, and on how to develop consistent bedtime routines. Due to the vital importance of consistent and restorative sleep, it is a foundational aspect of the functional medicine healthcare approach [104]. Therefore, a sleep assessment was conducted by the physician on our research team during the initial evaluation and interview. Because all the patients live at high altitude, an overnight sleep study was included in the evaluation. Adequate sleep is vital for maintaining adult neurogenesis, and disrupted or insufficient sleep corrupts healthy cognitive physiology and neural plasticity [105, 106]. For example, sleep deprivation negatively impacts attention, processing speed, response inhibition, and memory function [107-109]. A growing body of scientific literature supports the connection between sleep loss and reduced neural connectivity, procedural errors, neurodegenerative disease, dementia, and Alzheimer's disease [110-113]. Individual sleep needs vary according to age, lifestyle, and medical conditions, but for aging adults the National Sleep Foundation recommends 7-9 hours for adults 26-64 years and 7-8 hours for older adults 65+ years [114]. Patients noted the number of hours they slept on their daily protocol tracking form.

4.5 Data Analysis

4.5.1 Statistical Analyses

Data analysis included group statistics for quantitative assessment scores as well as a cross-case synthesis of qualitative outcomes. To analyze pre-post differences in the study metrics across all five patients, we used non-parametric tests due to the small sample size. All cognitive test analyses were conducted with IBM SPSS Version 24. For those metrics with three time periods, we used Friedman's test, which is analogous to a repeated measures ANOVA. For metrics with two time periods, we used a Wilcoxon test, the non-parametric equivalent to a paired samples t-test. Next, we conducted a qualitative thematic analysis on the interview data to identify trends across cases in self-reported changes in daily functioning. Finally, using the CONN toolbox, we analyzed the fMRI data to assess changes in brain network connectivity and correlations with changes on MoCA and DRS-2 scores. Group pre-post changes in brain connectivity between the 164 sub-

divided brain ROIs were assessed using paired t-tests. Changes in functional connectivity that correlated to changes in testing scores were identified using bivariate regression. For false positive control, false discovery rate (FDR) corrected p-values of $p<0.05$ were utilized and are reported.

4.5.2 Qualitative Thematic Analysis

Qualitative data were collected through semi-structured intake interviews, mid-intervention interviews, and exit interviews. Data were objectively gathered throughout the study with intentional disregard for prior commentary at each stage [115]. Validity and rigor were aided by application of triangulation, grounded methodology, and objectivity in audit [116]. Triangulation was applied via collection of commentary from multiple data sources (participant, spouse, trainer), by multiple investigators (research associate, research director, trainer), and across multiple investigative perspectives (pre, mid, and post intervention). Comments were gathered and recorded with epoché and evaluated without pre-existing bias or preconceived expectations of outcome. Results from the qualitative analyses are presented in the individual case results and in the cross-case synthesis.

4.6 Case Descriptions

4.6.1 Patient 1

Patient 1 is a 72-year-old male who presented with gradual memory loss, difficulty following conversations, trouble with numerical calculation, and executive function deficits, such as selecting items from a menu and navigating traffic signs or driving directions. For example, he stated, “When I’m driving. I can’t read the signs fast enough to know where to go.” Based on his initial neuropsychological assessment results, his level of cognitive impairment at the beginning of the study period was classified as *mild*. He reported he was no longer capable of handling personal or family financial matters and struggled with time management. His wife noted that he increasingly forgot simple instructions or requests for help, had trouble recalling people’s names, and no longer seemed to participate in conversations. She indicated she had recently taken over driving duties. The patient felt overwhelmed when presented with menus or other complex choice options, was embarrassed by forgetting names of friends and acquaintances, and was unable to follow and recall conversations or verbal requests. He explained, “My wife will ask me to do something and as soon as I walk away, I forget. [She] says I don’t enter in with conversations – but I just can’t follow along.” His desire was to have memory function restored so he could remember things, like where he put the keys, and so his wife would not be frustrated by his lack of follow through on verbal requests or instructions.

The patient had a medical history of acute hypothyroidism, Vitamin D deficiency, high blood pressure, colitis, mixed sleep apnea, depression and anxiety, blood clots, and bilateral pulmonary emboli. At his initial exam, he was overweight with a body mass index (BMI) of 28.2 and a stable visceral fat level of 9. His Apolipoprotein E (ApoE) genotype is 3/3 and is positive for one copy of the A1298C variant in the methylenetetrahydrofolate reductase (MTHFR) gene. His pre-intervention level of inflammation as measured by serum C-Reactive Protein (CRP) was normal at .9 mg/L.

4.6.2 Patient 2

Patient 2 is a married 70-year-old female with progressive memory loss, disorientation, and diminished ability to follow conversation. Based on her initial neuropsychological assessment results, her level of cognitive impairment at the beginning of the study period was classified as *severe*. Although not confirmed by imaging, the patient had received a prior clinical diagnosis of Stage 2 AD by an independent neurologist one week before enrolling in the study. The patient was unable to recall the names of family members, suffered extreme anxiety about being left alone, had voluntarily stopped driving, and did not go anywhere without her husband. She laughed frequently and reported being happy, while her husband reported she was often moody, anxious, and tearful, could not remember dates or events, frequently lost personal and household items, and was unable to follow conversations.

At her initial evaluation, the patient was slightly underweight with a BMI of 19.5, low muscle tone, and a healthy visceral fat level of 5. Her ApoE genotype is 4/4, and she has two copies of the A1298C variant of the MTHFR gene. The patient was a non-smoker in otherwise excellent physical health with no major medical history issues except for a recent concussion, abnormal glucose, and hypothyroidism associated with surgery. Her pre-intervention level of inflammation as measured by serum CRP was normal at < .2 mg/L.

4.6.3 Patient 3

Patient 3 is a married 71-year-old female who presented with subjective complaints of difficulty remembering names, dates, and daily activities. Based on her initial neuropsychological assessment results, her level of cognitive impairment at the beginning of the study period was classified as *mild*. She maintained a busy lifestyle volunteering with her church. The patient stated that in social situations she would suddenly "lose words" in the middle of conversation or lose her train of thought and struggle to get back on track. She reported her memory problems had progressively worsened over the prior several months, and it was impacting her quality of life, saying, "I feel so frustrated and insecure about forgetting things now." The patient's spouse confirmed the relatively sudden decline of her memory and her struggles to keep up with daily activities at home and church. Her response to the declining memory had been to withdraw from activities and forego plans for continued education.

The patient was overweight with a BMI of 28.4 and relatively high visceral fat level of 17. She has diagnoses of Crohn's disease, ulcerative colitis, high blood pressure, hair loss, and progressive weight gain. She is a non-smoker with an ApoE genotype of 3/3 and one copy of the C677T variant of the MTHFR gene. Her pre-intervention level of inflammation as measured by serum CRP was high at 6.7 mg/L. Her primary complaints were problems with memory and focus and the resulting decline in quality of life and outlook.

4.6.4 Patient 4

Patient 4 is a married 66-year-old male who presented with complaints of progressive memory loss, worsening over the prior year. Based on his initial neuropsychological assessment results, his level of cognitive impairment at the beginning of the study period was classified as *moderate*. The patient reported trouble remembering names, losing track of what he was saying at work, and

forgetting important appointments. He had recently stopped writing professionally due to cognitive decline and had cancelled other upcoming personal and work plans. His wife concurred that his lifestyle and outlook had declined in the prior six months, and she was concerned about his resulting mood swings, irritability, and depression. The patient reported feeling incompetent in his personal and professional life, saying, "I remember things from a long time ago but forget things that happened last week and stuff that happened yesterday."

Patient 4 had a medical history of hyperlipidemia, diabetes mellitus, obstructive sleep apnea, hypertension, and prior traumatic brain injury. He was clinically classified as obese with a BMI of 31 and elevated visceral fat level of 11. He has an ApoE genotype of 3/4 and one copy of the C677T variant of the MTHFR gene. His pre-intervention level of inflammation as measured by serum CRP was normal at .4 mg/L. He reported he had not previously sought treatment for his cognitive decline.

4.6.5 Patient 5

Patient 5 is a married 55-year-old female who presented with complaints of memory loss. Based on her initial neuropsychological assessment and clinical symptom correlation, her level of cognitive impairment at the beginning of the study period was classified as *mild*. She reported 'brain fog' that impacted her daily functioning. For example, she stated, "I'll walk from one room to another and forget what I was doing or going to get." She reported frustration with her inattentiveness to conversation, inability to recall relevant words or names, irritability, lack of patience, and feeling overwhelmed with daily tasks. She also reported low energy, fatigue, negative outlook, and depression attributed to multiple traumatic life events and medical conditions. She stated a desire to regain mental energy and function in order to care for her grandchildren.

Patient 5 suffered a myocardial infarction two years prior and had medical diagnoses of type 2 diabetes mellitus, obesity, hypertension, chronic fatigue, fibromyalgia, and sleep apnea. She reported struggles with sleep, body aches, and digestive discomfort. She is a non-smoker, was clinically classified as obese with a BMI of 38.7 and had a high visceral fat level of 20. Her ApoE genotype is 3/3 and she has one copy of the A1298C variant on the MTHFR gene. Her pre-intervention level of inflammation as measured by serum CRP was high at 14.0 mg/L.

5. Results

5.1 Individual Case Results

5.1.1 Patient 1 Outcomes

During the study, Patient 1 was strongly supported by his spouse in all six of the functional medicine (FM) intervention components. However, he did struggle to eliminate sugar from his diet and received additional coaching for that component. He tended to stay up past midnight in his hobby workshop, regardless of morning commitments and thus had an inconsistent sleep routine. The patient followed a stress-management routine of daily prayer and Bible study and exercised by taking short daily walks in the neighborhood, later added hiking and stair-stepping. Over the course of the intervention period, he increased his physical exercise from 15-30 minutes a day 5

days per week to 45-60 minutes a day 7 days per week. He reported moderate difficulty with developing a habit of taking morning and evening supplements, but he attended all check-in meetings, medical appointments, and cognitive training sessions.

Based on neuropsychological testing with clinical symptom correlation at the beginning of the study period, Patient 1's level of cognitive impairment was classified as mild. At the end of the study period, his level of cognitive impairment based on the same criteria was classified as not impaired. Patient 1's dementia testing scores on the MoCA (Time 1 = 24, Time 2 = 24, Time 3 = 28) and the DRS-2 (Time 1 = 138, Time 2 = 141, Time 3 = 142) indicate improvement across testing intervals, and IQ testing revealed a 15-point increase in overall IQ score from 120 to 135. Executive function symptom ratings reported by the patient's spouse on the BRIEF-A decreased from 79 at the beginning of the study to 72 at the end of the study, indicating improvement; and his own symptom ratings decreased from 70 to 64, also indicating improvement.

After completing the research protocol, Patient 1 reported more energy and endurance, increased confidence, and improved problem solving. He recounted the following experience: "I've been making these coasters and wanted to polish them. I thought to myself, 'how am I gonna do this? I don't have the tools.' Then all the sudden an idea popped into my head…and it worked! I've not been able to come up with ideas like that [since MCI diagnosis] but it just came to me!" The patient's wife concurred, "He definitely has more energy, he's more positive, more self-motivated, and I see him remembering things much better. He's lost lots of weight; is in the same size pants as when I first met him and is exercising now, consistently taking walks. He still has trouble keeping track of things [laugh], but now he is aware of having laid it down somewhere!" He claimed that he was more aware of street signs now and could even drive without a GPS. In addition to the cognitive improvements, the patient lost 23 pounds and attained a healthy BMI of 25 and visceral fat level of 5. Although slightly increased since pre-intervention measurement, his level of inflammation as measured by serum CRP was still low at 2.0 mg/L.

5.1.2 Patient 2 Outcomes

During the study, Patient 2 reported she slept well, intentionally managed stress with reading, ate a healthful diet, and exercised regularly. However, in contradiction to patient report, her husband reported she had trouble sleeping through the night, rarely read anymore, and only wanted to eat sandwiches. The patient displayed perseverative behavior, particularly regarding her past career and isolated work environment, i.e., "Remembering people's names? Well I blame it on all those years of working alone. I didn't have to [remember]." The patient and spouse jointly reported on compliance to dietary changes, supplements, and sleep duration (albeit interrupted sleep), but minimal adherence to the exercise or stress management components of the intervention. She reported consistent physical exercise with an increase over the study period from 3-4 days per week to 6-7 days per week, yet her spouse reported truculence with moving fast enough to elevate her heart rate. The patient attended all check-in meetings, medical appointments, and cognitive training sessions. However, she did not comply with any aspects of the study elements during a three-week vacation in the middle of the study period other than taking nutritional supplements.

Based on neuropsychological testing with clinical symptom correlation at the beginning of the study period, Patient 2's level of cognitive impairment was classified as severe. At the end of the

study period, her level of cognitive impairment based on the same criteria was still classified as severe. Patient 2's dementia testing scores on the MoCA (Time 1 = 13, Time 2 = 13, Time 3 = 15) indicate a small improvement across testing intervals, while scores on the DRS-2 (Time 1 = 102, Time 2 = 119, Time 3 = 99) improved initially but ended with a slight decline. This decline was primarily due to lower scores on the subtest measures of conceptualization and memory. However, IQ testing revealed an 8-point increase in overall IQ score from 83 to 91. Executive function symptom ratings reported by the patient's spouse on the BRIEF-A increased from 59 at the beginning of the study to 70 at the end of the study, indicating worsening of symptoms, but her own symptom ratings decreased from 56 to 48, indicating improvement.

At the end of the study period, Patient 2 had maintained her body weight, BMI of 19.7, and healthy visceral fat level of 6. Although slightly increased since pre-intervention measurement, her level of inflammation as measured by serum CRP was still low at .3 mg/L. The patient's spouse indicated she had enjoyed her cognitive training sessions and her demeanor was better afterwards, but he was not seeing changes at home. Patient 2 asserted her enjoyment of the program and said, "I think I'm doing better." Her spouse concurred, "She was more relaxed after training sessions; I know she enjoyed the training." However, he complained of her worsening anxiety and paranoia, despite improvements with everyday memory and orientation, as he explained, "I don't see any practical improvements, but maybe she's the same."

5.1.3 Patient 3 Outcomes

During the study, Patient 3 was highly motivated but expressed concern about the diet and exercise features due to her struggles with Crohn's disease. However, she followed an adequate sleep schedule and continued a pre-existing stress-management strategy of reading and meditative prayer. She began a walking program for physical exercise and stated her compliance with supplements and diet was motivated by weight loss and an overall feeling of wellness. She attended all weekly check-in meetings, all but one medical appointment, and all cognitive training sessions.

Based on neuropsychological testing with clinical symptom correlation at the beginning of the study period, Patient 3's level of cognitive impairment was classified as mild to moderate. At the end of the study period, her level of cognitive impairment based on the same criteria was classified as not impaired. Patient 3's dementia testing scores on the MoCA (Time 1 = 22, Time 2 = 25, Time 3 = 26) and the DRS-2 (Time 1 = 134, Time 2 = 138, Time 3 = 142) revealed incremental improvements across testing intervals, and IQ testing revealed stability in overall IQ score at 111. Executive function symptom ratings reported by the patient's spouse on the BRIEF-A remained stable from 51 at the beginning of the study to 52 at the end of the study, and her own symptom ratings decreased from 61 to 55, indicating perceived improvement. At the end of the study period, Patient 3 lost 18 pounds, cut her BMI to within average range at 25.1, and reduced her visceral fat level to 12. Although still elevated, her level of inflammation as measured by serum CRP decreased to 3.2 mg/L.

She reported a boost in confidence, outlook, memory, and verbal and visual processing. She described multiple improvements: "The program was so complete, and now I'm better in everything, ways I didn't even know were so wrong [before]. I'm walking and exercising more and more now, better eating, I can pick things up now just from hearing, now I don't worry [because] I

can remember!" Patient 3 also discussed the remittance of symptoms relating to her ulcerative colitis, new focus during medical appointments, and enhanced mental clarity for her church, social, and home activities. She reported life-altering changes such as, "I used to be much more insecure, now I'm so excited about going back to school – to finish my doctorate!"

5.1.4 Patient 4 Outcomes

During the study period, Patient 4 reported he followed a healthy and active lifestyle and was continuing his pre-existing daily stress-management strategies of prayer and Bible study. Although he reported a limited need for sleep, his spouse contended he often napped or fell asleep in the evenings before bedtime. Patient 4 recorded 100% compliance with the supplement and stress-management components during his check-in appointments but reported early in the study he needed no additional exercise because, "I do a lot of exercise in my work." He received additional counseling regarding the exercise component and research-recommended sleep duration. Patient 4 reported minimal increase in physical activity, steady improvements with sleep duration, and compliance with stress-management, diet, and supplements throughout the study period.

Based on neuropsychological testing with clinical symptom correlation at the beginning of the study period, Patient 4's level of cognitive impairment was classified as moderate to severe. At the end of the study period, his level of cognitive impairment based on the same criteria was classified as mild. Patient 4's dementia testing scores on the MoCA (Time 1 = 20, Time 2 = 21, Time 3 = 24) and the DRS-2 (Time 1 = 127, Time 2 = 131, Time 3 = 130) revealed slight improvement across testing intervals, and IQ testing revealed stability in IQ score from 83 to 84. Executive function symptom ratings reported by the patient's spouse on the BRIEF-A decreased from 61 at the beginning of the study to 54 at the end of the study, indicating improvement, and his own symptom ratings decreased from 59 to 56, also indicating improvement. At the end of the study, Patient 4 reported more energy, as well as better and more consistent sleep. The patient also reported improvements in memory, confidence, energy, interpersonal relationships, and outlook. He resumed professional writing duties, reported increased "inspiration and illumination to speak without notes," and said, "I have not had any problems remembering scripture [now]!" His spouse described him as "much more confident than he had been," and asserted, "I think I see more improvements than he does! He's much less frustrated! Now in his [work communication] he doesn't repeat himself or forget; [he] has so much more energy now!" His wife also expressed gratitude for relational improvements: "He's more fun, more talkative. Now [he] is much more attentive – will bring me coffee, will call me just to say 'I love you.'" He also lost 31 pounds, achieved a healthy visceral fat level of 4, and reduced his BMI to 26.5. Although slightly increased since pre-intervention measurement, his level of inflammation as measured by serum CRP was still low at 1.8 mg/L.

5.1.5 Patient 5 Outcomes

During the study, Patient 5 initially expressed concern regarding the diet and exercise components of the FM protocol, due to chronic fatigue and extreme food preferences or intolerances. However, by Week 3, she reported successfully reducing sugar and carbohydrate intake. Due to her pre-existing sleep apnea and Chronic Fatigue Syndrome (CFS), Patient 5 reported a history of sleeping at least 11-12 hours per night and was not motivated to optimize

her sleep routine. She received additional coaching and agreed to try. She was consistent with her supplement regimen and attended all motivation check-in meetings, medical appointments, and cognitive training sessions. She was least compliant with the exercise component of the protocol, reporting only occasional walks with her pet.

Based on neuropsychological testing with clinical symptom correlation at the beginning of the study period, Patient 5's level of cognitive impairment was classified as mild. At the end of the study period, her level of cognitive impairment based on the same criteria was classified as not impaired. Patient 5's dementia testing scores on the MoCA (Time 1 = 23, Time 2 = 24, Time 3 = 29) and the DRS-2 (Time 1 = 127, Time 2 = 139, Time 3 = 139) indicated substantial improvement, and IQ testing revealed 13-point change in IQ score from 116 to 129. Executive function symptom ratings reported by the patient's spouse on the BRIEF-A decreased from 71 at the beginning of the study to 68 at the end of the study, indicating improvement, and her own symptom ratings decreased from 71 to 68, also indicating improvement. By the end of the study period, Patient 5 lost 2.4 pounds and reduced her BMI to 38.5. Although still elevated, her level of inflammation as measured by serum CRP decreased markedly to 3.7 mg/L.

The patient reported improvements with motivation, energy, and mental focus, saying, "It's easier to get up and exercise." She reported having a more efficient morning routine, increased independence, and enhanced ability to complete tasks of daily living, saying, "[Before] I wasn't able to do basic day-to-day things; not able to cook, not able to do the dishes. [Now] I'm just much more able to deal with my life." She stated, "The stresses are still there, but I feel like I can handle things better. It is easier to talk through difficult situations; feels like my brain wiring is better, like this part of my brain is talking to that part of my brain so I can confront and deal with things."

5.2 Cross-Case Synthesis

Table 1 illustrates the synthesis of findings across cases, including initial and final cognitive impairment classification, pre-intervention symptoms reported by each patient, post-intervention outcomes reported by each patient, and pre-intervention and post-intervention scores on the MoCA, DRS-2, and WJ III IQ test.

Pre-intervention complaints were similar across patients, especially related to memory for names and daily events. Compliance with the individual pillars was most consistent for mental exercise at 100% across patients followed by nutritional supplements and sleep optimization. Four of the five patients were moderately compliant with diet and stress management strategies. At the end of the study, improved memory, attention, and mental clarity were the most reported outcomes, followed by increased energy, better mood, and improved outlook on life. Three of the five patients were no longer classified as cognitively impaired based on their MoCA and DRS-2 scores, while a fourth patient improved from moderate-to-severely impaired to mildly impaired.

Table 1 Cross-case synthesis of cognitive outcomes.

	Patient One	**Patient Two**	**Patient Three**	**Patient Four**	**Patient Five**
Pre-Intervention Level of Impairment	Mild MoCA score: 24 IQ Score: 120 DRS-2: 138	Severe MoCA score: 13 IQ Score: 83 DRS-2: 102	Mild-Moderate MoCA score:22 IQ Score: 111 DRS-2: 134	Moderate-Severe MoCA score: 20 IQ Score: 83 DRS-2: 127	Mild MoCA score: 23 IQ Score: 116 DRS-2: 127
Subjective Pre-Intervention Complaints	memory, losing things, trouble following conversations, driving, menus, following instructions	memory, fear of being alone, losing things, disorientation, forgetting names and daily events, anxious/sad	memory, insecurity, forgetting names and daily events	memory, withdrawal from work, driving, forgetting names and daily events	memory, brain fog, losing things, attention for shopping and daily activities
Intervention Compliance by Component	Diet: 7.9 Supps: 9.1 Exercise: 9.2 Stress: 9.0 Sleep: 8.2 Mental Ex: 10.0	Diet: 9.2 Supps: 8.9 Exercise: 7.7 Stress: 7.5 Sleep: 9.4 Mental Ex: 10.0	Diet: 9.3 Supps: 9.7 Exercise: 4.2 Stress: 8.3 Sleep: 9.3 Mental Ex: 10.0	Diet: 9.3 Supps: 9.9 Exercise: 6.1 Stress: 8.5 Sleep: 10 Mental Ex: 10.0	Diet: 4.6 Supps: 9.5 Exercise: 4.1 Stress: 3.9 Sleep: 10 Mental Ex: 10.0
Subjective Post-Intervention Outcomes	better memory, increased energy, mental clarity/focus, driving again, positive outlook	maintained quality of life, improved mood	better memory, confidence, increased energy, mental clarity/focus, new educational pursuit	better memory, confidence, improved relationships, increased energy, driving, work improvements	increased energy, mental clarity/focus, improved outlook
Post-Intervention Level of Impairment	Not Impaired MoCA score:28 IQ Score: 135 DRS-2: 142	Severe MoCA score: 15 IQ Score: 91 DRS-2: 99	Not Impaired MoCA score:26 IQ Score: 111 DRS-2: 142	Mild MoCA score:24 IQ Score: 84 DRS-2: 142	Not Impaired MoCA score:29 IQ Score: 129 DRS-2: 139

5.2 Group Results

5.2.1 Compliance with intervention pillars

Table 2 presents the minimum, maximum, means, medians, and standard deviations for group compliance with the intervention pillars: physical exercise, mental exercise, diet, supplements, sleep, and stress management. As a group, the pillar with the lowest compliance was physical exercise, and there was 100% compliance for the mental exercise component of the intervention.

Table 2 Descriptive statistics for compliance with intervention pillars.

	Min	**Max**	**Mean**	**Median**	***SD***
Physical Exercise	4.1	9.2	6.26	6.10	2.2
Mental Exercise	10.0	10.0	10.0	10.0	0.0
Diet	4.6	9.3	8.06	9.20	2.02
Supplements	8.9	9.9	9.42	9.50	.41
Sleep	8.2	10.0	9.00	9.00	.70
Stress Management	3.9	9.0	7.44	8.30	2.05

5.2.2 Primary Group Outcomes

Table 3 presents descriptive statistics for the primary test metrics. Using means to examine pre-post differences, results indicate patients, on average, saw small differences across the study's time periods. From Time 1 to Time 2 (or pre to post for metrics with only two time periods), metrics almost always increased, with decreases reported in BRIEF self-report and BRIEF spouse report. (Note that decreases on BRIEF indicate improvement in symptoms.) Changes from Time 2 to Time 3 were a mixture of increases and decreases. When subjected to statistical testing, only two metrics saw significant differences—MOCA (χ^2 = 9.33, p = .009) and BRIEF self-report (Z = -2.04, p = .04). Further analyses of the MOCA metric with pairwise comparisons using Wilcoxon tests indicate the Time 1 to Time 3 (Z = -2.06, p = .04) and Time 2 to Time 3 (Z = -2.02, p = .04) differences were significant, but not Time 1 to Time 2.

Table 3 Descriptive statistics for primary test metrics.

	Time 1			**Time 2**			**Time 3**		
Test	**Mean**	**Median**	***SD***	**Mean**	**Median**	***SD***	**Mean**	**Median**	***SD***
MoCA Total Score	20.40	22.00	4.39	21.40	24.00	4.93	24.40	26.00	5.59
DRS-2 Total Score	125.60	127.00	14.01	133.60	138.00	8.99	130.40	139.00	18.23
DRS-2 Attention	34.20	36.00	4.09	35.60	36.00	1.52	36.60	37.00	0.55
DRS-2 Initiation	32.80	37.00	8.84	35.40	37.00	3.58	33.00	37.00	7.38
DRS-2 Construction	6.00	6.00	0.00	6.00	6.00	0.00	5.80	6.00	0.45
DRS-2 Conceptualization	35.00	35.00	1.22	37.60	37.00	1.34	36.20	38.00	4.21
DRS-2 Memory	17.60	20.00	5.77	19.00	23.00	5.52	18.80	23.00	6.57

DKEFS Tower Test	10.80	12.00	2.77	12.00	12.00	4.06	11.60	12.00	1.67
DKEFS Trail Making	7.60	9.00	3.78	8.60	11.00	5.03	9.00	10.00	4.74
	Pre-Intervention						**Post-Intervention**		
BRIEF-A Global Executive Composite - Self	63.40	61.00	6.73				58.20	56.00	7.89
BRIEF-A Global Executive Composite - Spouse	64.20	61.00	10.92				63.20	68.00	9.44

5.2.3 Secondary Group Outcomes

Although it was not a primary analysis, we also examined Woodcock Johnson sub-tests from pre to post cognitive training. These included Visual Processing (VP), Auditory Processing (AP), Fluid Reasoning (FR), Processing Speed (PS), Working Memory (WM), Associative Memory (AM), Verbal Comprehension (VC), and overall IQ score. As Table 4 indicates, patients saw, on average, mean increases on all tests, although differences were small. Indeed, Wilcoxon test results showed no significant pre to post differences for any of the tests, which indicates stability of the constructs over time.

Table 4 Descriptive statistics for secondary test metrics.

Woodcock Johnson III	Before Cognitive Training			After Cognitive Training		
Test	Mean	Median	SD	Mean	Median	SD
IQ score	102.60	111.00	18.17	110.00	111.00	22.49
Visual Processing	113.60	113.00	14.03	117.80	118.00	9.12
Auditory Processing	122.80	120.00	11.82	127.60	138.00	18.37
Fluid Reasoning	96.80	101.00	16.63	103.20	109.00	13.41
Processing Speed	98.40	91.00	21.11	104.40	110.00	19.48
Working Memory	106.60	107.00	14.05	107.60	95.00	21.63
Associative Memory	83.80	97.00	36.87	95.40	121.00	57.50
Verbal Comprehension	97.20	91.00	11.43	102.00	97.00	10.00

Altogether, results for primary and secondary metrics indicate stability across almost all the domains tested with some slight increases indicating lack of decline and some improvement. The BRIEF self-report saw a significant decrease in symptomology from pretest to post-test, indicating improvement.

5.2.4 Functional MRI Results

Group analyses were conducted on the pre-treatment and post-treatment resting-state functional MRI data to assess significant changes in functional connectivity across the group. There were four significant changes in connectivity, illustrated in Table 5. However, after thresholding the baseline correlations at .25, two of the four statistically significant changes following treatment met the criteria for practical significance, or size of importance: the connection between the left inferior frontal gyrus and the right frontal pole; and the connection between the right planum polare and the left insular cortex. Figure 2 illustrates the two remaining significant changes in connectivity after thresholding. Although resting state functional MRI is primarily still used for research rather than clinical applications, we hypothesize that changes in brain connectivity underlie changes in function of the brain post-treatment.

Table 5 Single subject correlations in connectivity between regions of interest.

	Case 1	Case 2	Case 3	Case 4	Case 5	Mean	SD	t	p
IFGl:FPr									
Pre	0.04	0.44	0.20	0.53	0.58	0.36	0.23		
Post	-0.28	0.15	0.00	0.24	0.34	0.09	0.24		
Change	-0.31	-0.28	-0.20	-0.29	-0.24	-0.26	0.05	12.8	0.027*
PPr:ICl									
Pre	0.52	0.69	0.67	0.93	0.61	0.69	0.15		
Post	0.14	0.24	0.34	0.57	0.30	0.32	0.16		
Change	-0.38	-0.46	-0.33	-0.36	-0.31	-0.37	0.06	14.3	0.015*
PUTr:ACCr									
Pre	0.06	-0.02	0.12	0.05	0.45	0.13	0.18		
Post	0.28	-0.09	0.30	-0.07	-0.18	0.05	0.22		
Change	0.22	-0.08	0.17	-0.12	-0.63	-0.09	0.34	26.7	0.008
LGr:CBM3r									
Pre	0.15	-0.18	-0.16	0.05	-0.03	-0.03	0.14		
Post	0.38	0.03	0.10	0.31	0.20	0.20	0.14		
Change	0.23	0.21	0.26	0.25	0.23	0.24	0.02	17.5	0.001

* Significant after thresholding baseline correlations at .25.

Abbreviations: IFGl = left inferior frontal gyrus; FPr = right frontal pole; PPr = right planum polare; ICl = left insular cortex; PUTr = right putamen; ACCr = right accumbens; LGr = right lingual gyrus; CBM3r = crus 3 of the right cerebellum.

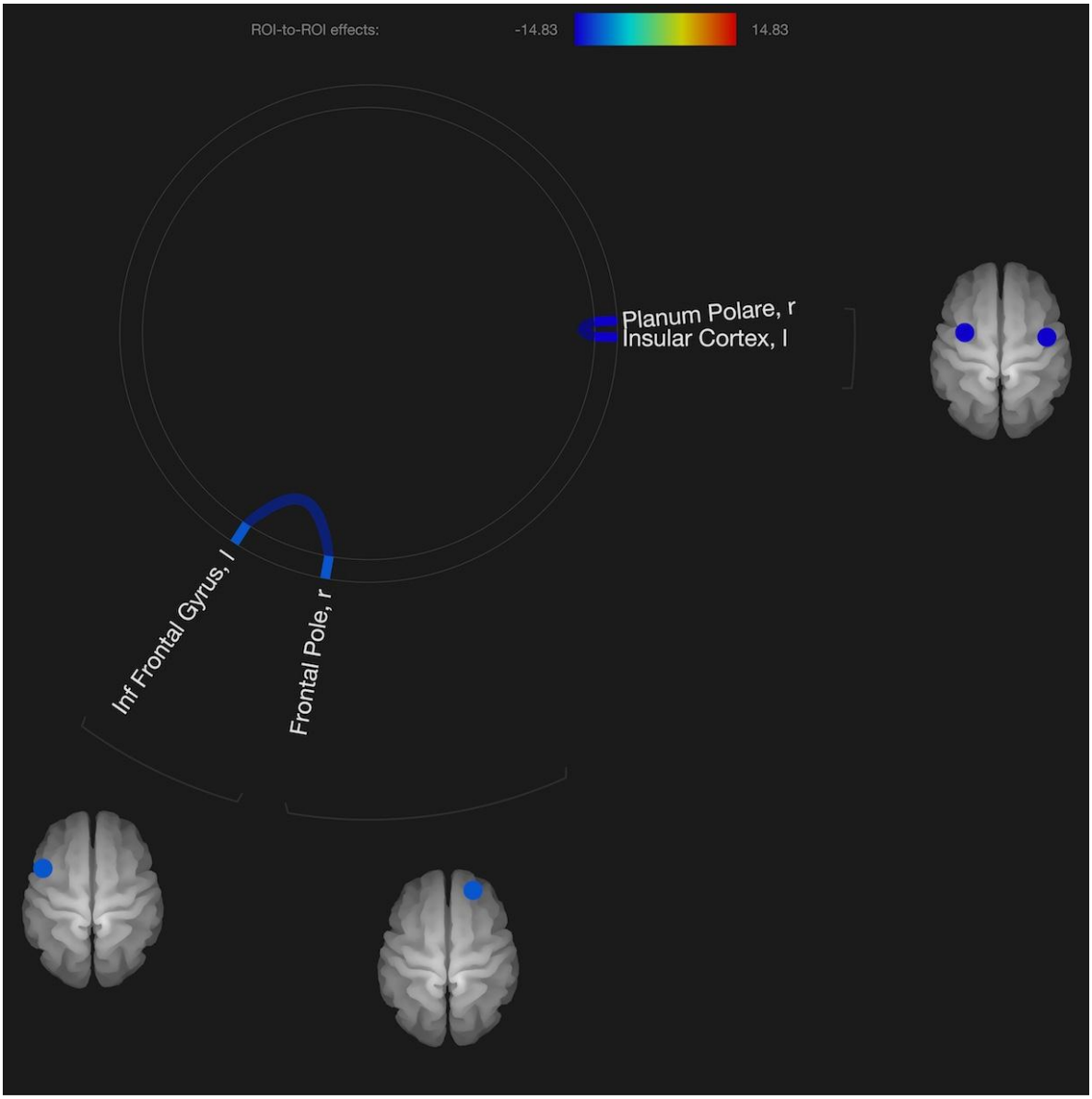

Figure 2 Changes in overall connectivity after thresholding.

In addition to significant changes in connectivity, analyses of the resting state functional data also revealed significant correlations between connectivity and changes on the MoCA and DRS-2 test scores for the group (see Figure 3).

In Figure 3, we illustrate the following seven significant connections that correlate with gains in scores on the MoCA test: right pars triangularis of the inferior frontal gyrus with the right posterior parietal cortex (β=1.00, p=0.025); Crus 9 of the left cerebellum with the left supracalcarine cortex (β=-0.44, p=0.017); Crus 4 and 5 of the left cerebellum with the right salience network RPFC (β=-1.01, p=0.016); right salience network RPFC with the left salience network anterior insula (β=-0.65, p=0.010); left posterior division of the middle temporal gyrus with the left occipital pole (β=-0.14, p=0.017); right cuneal cortex with the left amygdala (β=0.86, p=0.033); and, left supplementary motor cortex with the left inferior division of the lateral occipital cortex (β=-0.96, p=0.036).

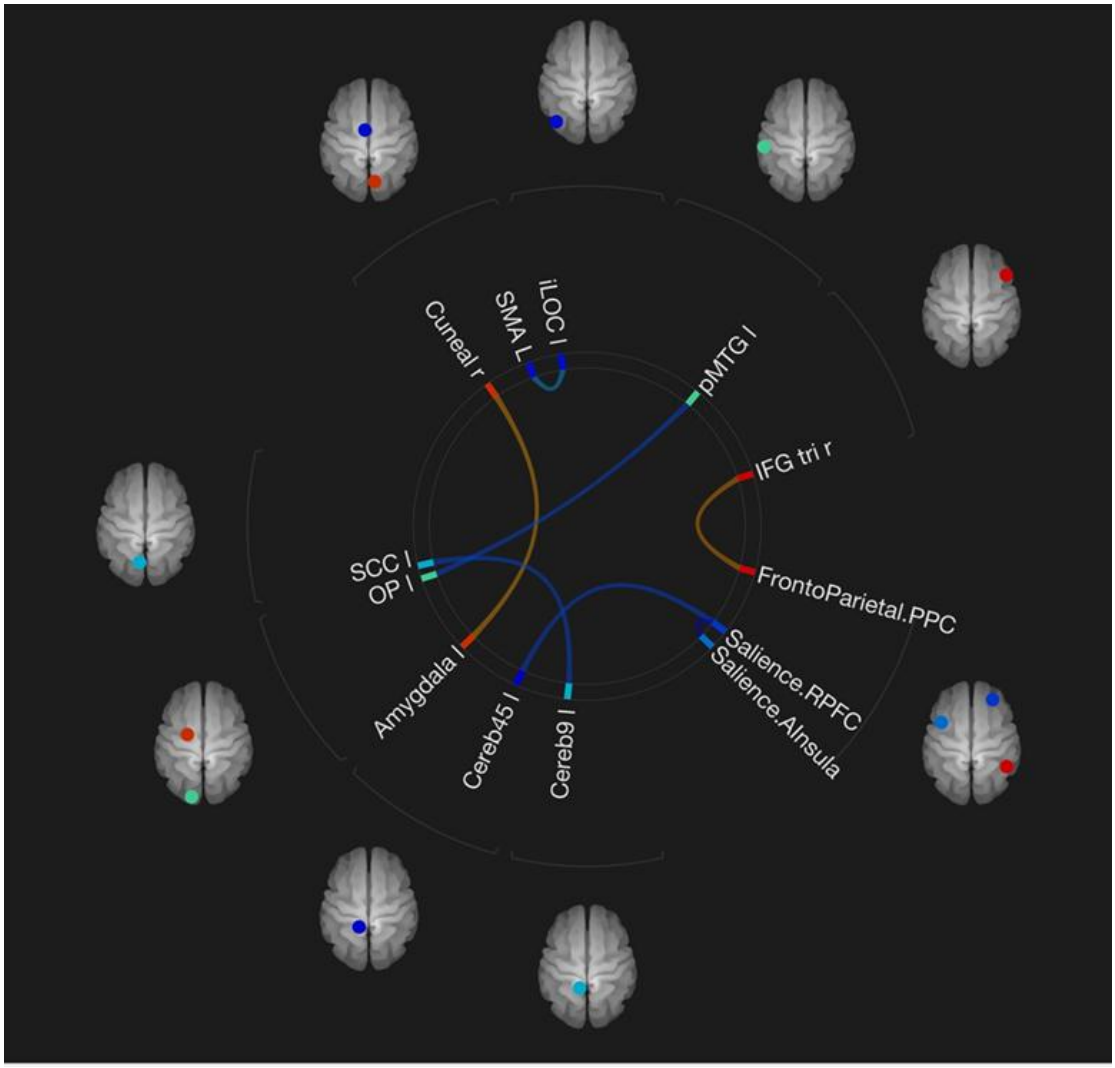

Figure 3 Correlation between functional connectivity and changes in MoCA test scores.

In Figure 4, we illustrate the four significant connections that correlate with gains in scores on the DRS-2 test: left lingual gyrus with the anterior cingulate cortex of the salience network (β=-0.41, p=0.005), right lingual gyrus with the left pars opercularis of the inferior frontal gyrus (β=-0.29, p=-0.012), right intracalcarine cortex with the right amygdala (β=0.27, p=0.032), and right post central gyrus with the left anterior insula of the salience network (β=0.33, p=0.010).

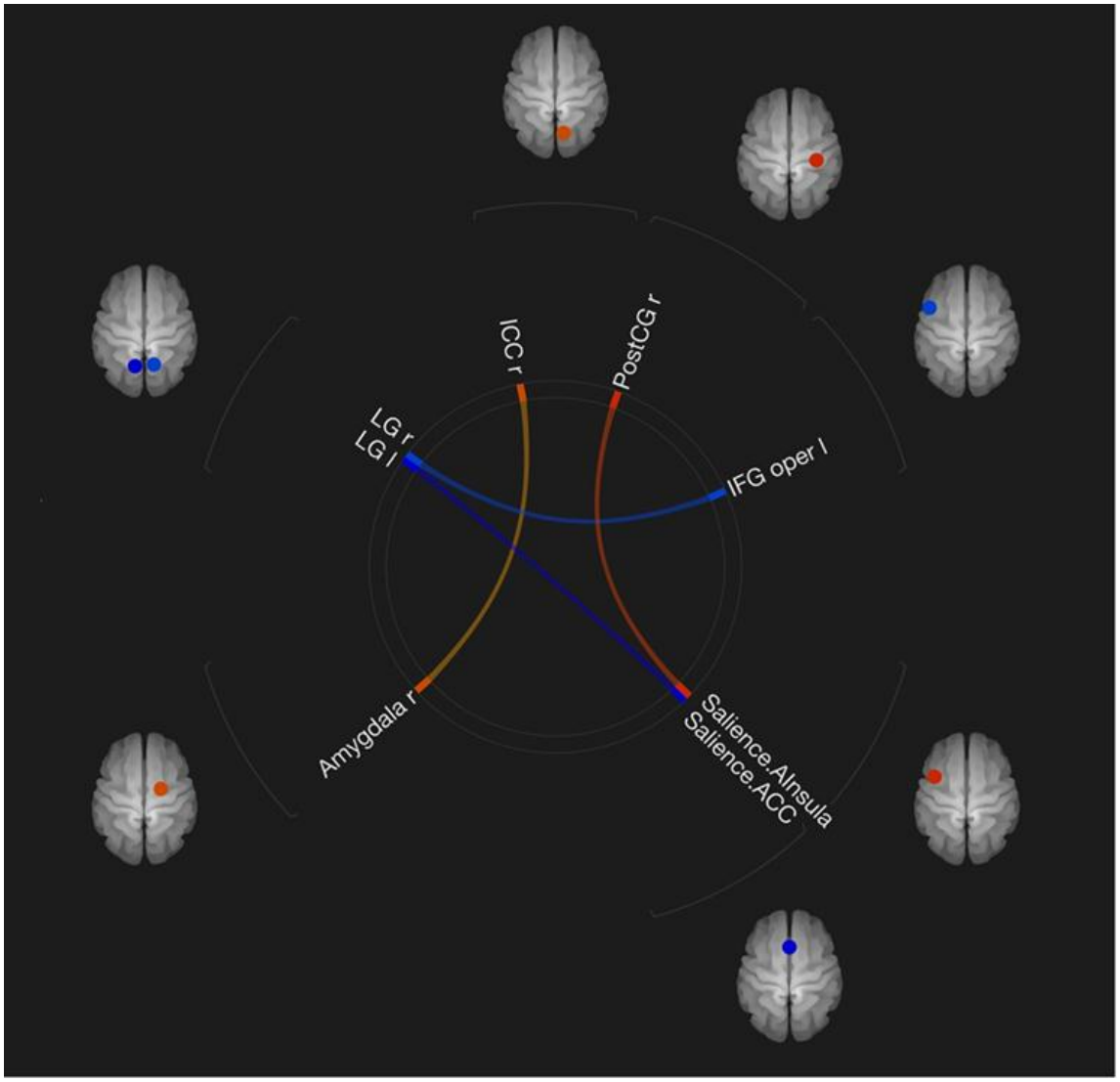

Figure 4 Correlation between functional connectivity and changes in DRS-2 test scores.

Altogether, the result of the fMRI analyses suggest that intensive interventions aimed at improving cognitive symptoms associated with aging may act by altering the interactions of brain regions. Since the findings are associated with a gain in function, it is presumed the measured changes in connectivity increase the efficiency of the overall brain network structure.

6. Discussion

The purpose of the current study was to conduct a series of case studies on individuals with varying degrees of clinical cognitive decline to document the effects and feasibility of adherence to a clinical anti-neuroinflammatory functional medicine protocol that included a focus on physical and mental exercise coupled with dietary changes, nutritional supplementation, stress management, and sleep optimization. In a prospective chart review, we examined outcome measures including (1) cognitive skills, (2) brain network connectivity, and (3) daily functioning.

Overall, patients showed stability and some improvement in cognitive functioning at the end of the study. When working against the clock in clinical cognitive decline such as MCI and AD, the goal of any intervention is to at least slow the rate of decline. Indeed, reversing decline and

achieving improvement in cognition and functioning would be the optimal outcome of an intervention. In the current study, we documented both. In light of current failures of drug trials to achieve reversal of clinical cognitive impairment, it is important to continue exploring alternative methods for accomplishing the same goal. We recognized a mono-therapeutic approach to targeting cognitive decline has been ineffective and, thus, adapted the work of Bredesen to investigate the multi-component intervention used in the current study. Similar to the 4.9-point mean gain Bredesen noted on dementia screening tools in his 2018 study, all five of the patients in our study showed improvement on the MoCA, with a mean increase of 4 points. Like Bredesen, we also evaluated inflammation and noted the two patients with elevated CRP at the beginning of the intervention period showed marked reduction in their levels. However, the current study departed from Bredesen's work in three primary ways worth noting. First, we administered comprehensive neuropsychological testing batteries to all five patients. This enabled us to conduct both individual and group analyses on the pretest and post-test scores, making our assessment of cognitive change more robust than what was reported in the Bredesen studies. Second, we administered pre and post intervention functional MRI using identical scanning protocols across all patients rather than collecting existing clinical scans as reported by Bredesen. This practice enabled us to conduct group analyses and identify trends in the changes in network connectivity for the group, and the correlations between connectivity and changes on cognitive test scores. Finally, we implemented a structured cognitive training program delivered by a clinician on a consistent schedule. Because all five patients completed the required number of training hours, we were able to conduct group statistical analyses on their training outcomes. This pillar was delivered consistently across patients with zero deviation or attrition.

Based on MoCA and WJ III IQ score testing, we conclude the intervention appears promising regardless of the level of cognitive impairment. The scores of all five participants improved. When compared to the expected decline over a similar time period (9 months) following a diagnosis of MCI or AD, a positive trajectory of change is noteworthy to document. As a group, the largest gains in subtest scores on the WJ III were in associative memory (11.6 points), fluid reasoning (6.4 points), and processing speed (6 points). While not significant improvements, we noted that scores on the Dementia Rating Scale-2 (DRS-2) and the DKEFS tests remained largely the same when compared as a group. When we view the results of individual patients, however, the story is more encouraging. Four of the five patients improved on the DRS-2 across time, and four of the five patients improved on the DKEFS tests across time. Typically, we look for statistically significant differences in test scores when evaluating an intervention. Instead, in the current study, we consider stability in cognitive function a positive outcome.

Compliance to the individual pillars of the intervention was not consistent across patients, particularly the physical exercise, stress management, and diet components. Compliance with the physical exercise component had the lowest mean rating of all the pillars (6.3 out of 10), while compliance with the mental exercise pillar was 100% across patients (10 out of 10). Arguably, the mental exercise component was the easiest to comply with because the training was delivered by a clinician in structured appointments on a consistent schedule throughout the study period. Conversely, the physical exercise component was independently implemented. Patients and their spouses were coached on exercise importance and options, and the study team discussed physical exercise at every check-in meeting. The least compliant with exercise—Patient 5—cited chronic fatigue as the biggest barrier to success with that pillar. Patient 2, the most severely impaired,

failed to make the connection between physical exercise and brain health. Her spouse struggled to participate in physical activity and, thus, was not as supportive as she needed to comply with that element of the intervention. Overall, we suspect the lack of structure, scheduling, and accountability to a trainer or coach contributed to the lower compliance with the physical activity pillar. Although 63% compliance with physical activity is a start, it will be important in future research to explore how to increase participation in the physical activity element of the intervention. Perhaps scheduling workouts as a group or with a personal trainer would be a solution.

Also important for future research will be to explore ways to participate in mental exercise with some independence, since meeting with a cognitive trainer three days per week for life is likely not sustainable. A combination of trainer-delivered mental and physical exercise sessions with spouse-supported independent sessions may be most feasible. Prior research on the cognitive training program used in the current study suggests spouses can effectively deliver part of the training at home and achieve similar results to clinician-only delivery [45].

The next lowest compliance rating as a group was for the pillar of stress management. However, four of the five patients actively implemented strategies for managing stress including prayer, reading, and meditation. Patient 5's rating was an outlier (3.9 out of 10), which skewed the mean rating across patients. Therefore, we conclude stress management was a successfully-implemented pillar of the intervention overall.

Regarding compliance with the diet pillar of the intervention, three of the five patients found the dietary changes to be difficult. Granted, eliminating grains and sugar is certainly restrictive. Because the spouses were primarily responsible for meal preparation, it was important for them to buy-in to the necessity of the dietary changes. Therefore, compliance to the diet pillar largely hinged on spousal support, which was low for two of the five patients. Alternatively, compliance with the sleep pillar of the intervention was high. We surmise the close monitoring and coaching of sleep hygiene by their physician contributed to the ease with which the patients were able to adjust and optimize sleep patterns and behaviors.

Even more meaningful than test scores to patients and families battling clinical cognitive decline are the real-life outcomes of intervention. All five patients indicated improvements in daily functioning, and four of the five spouses noted the same. It is interesting that the self and spouse-reported improvements at the end of the study directly related to reported symptoms at the beginning of the study. Prior to intervention, the prevailing symptoms reported by patients and spouses were poor memory and attention, negative outlook on life, and low mental and physical energy. Four of the five patients reported improvements in those same areas at the end of study. The spouse of Patient 2—the most severely impaired—indicated that although he had not seen improvements at home, she remained the same. It is indeed an encouraging outcome when a patient with a clinical diagnosis of Alzheimer's Disease remains unchanged in daily functioning after almost a year.

A noteworthy aspect of the current study is the use of functional MRI to examine changes in connectivity in the brain following the intervention. Not only did we note significant changes in network connections following the intervention, we also found changes in connectivity correlated with changes in cognitive test scores. These findings are consistent with prior research on network connectivity following the use of the cognitive training program used in the current study [117].

These findings also strengthen results of the study by providing an additional source of evidence when triangulating data to form conclusions about the intervention.

The current study provides preliminary support for and feasibility of the use of a multi-component approach to slowing pathological cognitive decline. However, there are several limitations to the study that should be mentioned. First, the study utilized a multiple case study design with a small sample. Although the design enabled us to collect detailed data on individual patients and to look for trends across cases, we are not able to draw causal connections between intervention and outcomes. It will be important in future research to conduct a controlled study in order to rule out other explanations for the outcomes we observed. Next, there is certainly a risk for selection bias when using a physician's patient sample. A randomized controlled study in the future will mitigate that risk. Finally, without a placebo control group, a placebo effect cannot be completely discounted.

There are strengths of the study worth mentioning. First, we utilized multiple outcome measures from multiple sources: neuropsychological test scores from five different instruments, self-reports, spouse reports, and functional MRI scans. The use of such a diverse set of data types and sources lends a convergence of evidence that strengthens the conclusions we can make about the intervention. Second, long intervention studies such as this are frequently at risk for high attrition. There was no attrition in the current study. Finally, the cases were of varying degrees of cognitive impairment, enabling us to assess the feasibility of delivering this intervention to patients on the entire continuum of clinical cognitive decline.

Our hope is this research sparks interest in continuing the search for effective complementary approaches to slowing cognitive decline and recognizing the need to apply a multi-therapeutic approach to targeting deficits associated with MCI and AD. We also hope our findings provide a springboard to examine *under which* conditions this combination of intervention pillars is most effective and *from which* to test the intervention in a controlled study design.

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Author Contributions

Randolph James acted in the capacity of primary investigator, oversaw the medical care provided to the patients, and edited the manuscript. Amy Lawson Moore supervised the neuropsychological assessments and cognitive training portions of the intervention and drafted the manuscript. Dick Carpenter conducted the quantitative data analyses and edited the manuscript. Terissa Miller conducted the qualitative data collection and analysis, coordinated patient schedules, and drafted the literature review portion of the manuscript. Christina Ledbetter

acted as co-PI, oversaw the fMRI acquisitions, conducted the fMRI data analyses, and edited the manuscript.

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Competing Interests

The first and fourth authors are employed by the nonprofit research institute associated with the cognitive training program used in the current study but have no financial interest in the outcomes.

Additional Materials

The following additional material is available.

1. Appendix A: MRI Imaging Protocol.

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