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Evaluating Depressive Symptoms, *BDNF Val66Met*, and *APOE-ε4* as Moderators of Response to Computerized Cognitive Training in Heart Failure

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Abstract

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Background: Depressive symptoms, *brain-derived neurotrophic factor (BDNF) Val66Met*, and *apolipoprotein (APOE)-ε4* may moderate response to computerized cognitive training (CCT) interventions among patients with heart failure (HF).

Objectives: The purpose of this study was to examine moderators of intervention response to CCT over 8 months among patients with HF enrolled in a 3-arm randomized controlled trial. Outcomes were memory, serum BDNF, working memory, instrumental activities of daily living (IADLs), and health-related quality of life (HRQL).

Methods: 256 patients with HF were randomized to CCT, computerized crossword puzzles active control, and usual care control groups for 8 weeks. Data were collected at enrollment, baseline, 10 weeks, and 4 and 8 months. Mixed effects models were computed to evaluate moderators.

Results: As previously reported, there were no statistically significant group by time effects in outcomes among the 3 groups over 8 months. Tests of moderation indicated that depressive symptoms and presence of *BDNF Val66Met* and *APOE-ε4* were not statistically significant moderators of intervention response in outcomes of delayed recall memory, serum BDNF, working memory, IADLs, and HRQL. In post hoc analysis evaluating baseline global cognitive function, gender, age, and HF severity as moderators, no significant effects were found. HF severity was imbalanced among groups ($P = .049$) which may have influenced results.

Conclusions: Studies are needed to elucidate biological mechanisms of cognitive dysfunction in HF and test novel interventions to improve memory, serum BDNF, working memory, IADLs and HRQL. Patients may need to be stratified or randomized by HF severity within intervention trials.

Keywords

heart failure; congestive heart failure; computerized cognitive training; memory; brain-derived neurotrophic factor; health-related quality of life

Introduction

Heart failure (HF) is a serious syndrome that affects approximately 6 million people in the United States[1] and 26 million people worldwide.[2] It is associated with high mortality rates that range from 15% at 1 year to 53% at 5 years after diagnosis.[1] Patients with HF have decreased cardiac output that may lead to inadequate cerebral perfusion,[3] cerebral microemboli,[4] damage to brain structures with neuronal loss,[5] and cognitive dysfunction.[6] Cognitive dysfunction occurs in 23% to 80% of patients, depending upon the sample (e.g., HF severity, age) and study characteristics (e.g., control group, screening or neuropsychological test battery).[6,7] Memory and working memory are 2 cognitive domains most often impaired in HF. Importantly, cognitive dysfunction is an independent predictor of 12-month all-cause mortality among patients with HF.[8] It is associated with decreased ability to perform instrumental activities of daily living (IADLs)[9] and worse health-related quality of life (HRQL).[10] Few interventions have been tested that directly target improving cognitive function in HF.

Computerized cognitive training (CCT) interventions are designed to increase neurogenesis and neuroplasticity and thereby improve cognitive function. CCT has been found to be

successful in improving memory, working memory, and IADLs in community-dwelling older adults[11] and older adults with mild cognitive impairment.[12] Preliminarily, CCT interventions were found to have efficacy among patients with HF.[13–17] In pilot studies among 40[15] and 27[16] patients with HF, patients randomized to CCT using BrainHQ© (developed by PositScience) had improved memory,[15] working memory,[16] and serum brain-derived neurotrophic factor (BDNF) levels.[16] These studies supported testing CCT in a larger study over a longer period of time.

The "Cognitive Intervention to Improve Memory in Heart Failure Patients" study (MEMOIR-HF) (NR016116; NCT#03035565) was a 3-arm randomized controlled trial to evaluate efficacy of CCT using BrainHQ among 256 patients with HF.[18,19] The co-primary outcomes were delayed recall memory and serum BDNF level and the secondary outcomes were working memory, IADLs, and HRQL. The 3 arms were the CCT treatment group, the computerized puzzles active control group, and the usual care group with no computerized intervention (See Methods for details).

In the main intention-to-treat analysis of MEMOIR-HF, delayed recall memory, serum BDNF levels, working memory, IADLs, and HRQL were not statistically significantly different by randomization group or group by time.[19] Delayed recall memory, working memory, IADLs, and HRQL significantly improved among patients in all 3 groups over the 8 months. Serum BDNF levels significantly decreased over time. Consistent results were found in the per protocol analyses[19] in which patients randomized to CCT who had ≥ 90% adherence were not significantly different in the group and group by time analyses but were significantly different by time. It is plausible that the lack of significant group or group by time differences was because other variables moderated patients' responsiveness to CCT. In MEMOIR-HF, the pre-specified exploratory aim was to examine 3 potential moderators of CCT's effect on outcomes, including depressive symptoms, *BDNF* genotype of the *Val66Met* polymorphism, and *apolipoprotein* (*APOE*)-*ε4* allele.[18] Moderation analysis was conducted to evaluate the potential boundaries of the CCT intervention, particularly the participants for who the intervention did and did not work.[20–23]

The rationale was twofold for examining depressive symptoms as a moderator. First, depressive symptoms are common in HF and are associated with increased mortality.[24] In a systematic review of 26 studies and 80,627 total patients with HF, the overall rate of depression was 29% and it was significantly associated with increased mortality risk (HR 1.4, 95% CI, 1.22–1.60).[24] Second, there is a body of empirical literature to support CCT as an intervention to reduce depressive symptoms and depression and improve cognition among people with serious chronic conditions.[25–29] In a systematic review and meta-analysis of 9 randomized controlled trials conducted to evaluate the efficacy of CCT among adults with depressive disorders, Motter and colleagues[25] found that CCT had statistically significant small to moderate effects for reducing depressed mood and improving daily functioning and moderate to large effects for improving measures of attention, working memory, and global functioning. In a systematic review and meta-analysis of 36 RCTs among 2551 people with mild cognitive impairment or dementia (mean age > 60), Chan and colleagues[26] evaluated cognitive training effects on depression scores. Participants who received cognitive training interventions had statistically significant decreases in

depression scores compared with control groups (i.e., social, recreational, and psychosocial interventions and usual care).[26] In the 7 randomized controlled trials testing CCT, effect sizes were medium to large in decreasing depression (mean difference 1.16, 95% CI = −2.13 to −0.91).[26]

In a meta-analysis conducted to evaluate effects of cognitive remediation on post-treatment depressive symptoms, cognitive functioning, and daily functioning, Legemaat and colleagues[27] reviewed 21 studies (438 patients with depression who received cognitive remediation with at least a component of a computerized format and 540 patients in control conditions; randomized and non-randomized trials). Results indicated small effects on depressive symptoms (g = 0.28, 95% CI, 0.09–0.46, I^2 40%) and daily functioning (g = 0.22, 95% CI, 0.06–0.39, I^2 3%), medium effects on cognitive functioning (g = 0.60, 95% CI, 0.37–0.83, I^2 44%), and confounding bias that may have led to overestimated effects for depressive symptoms and daily functioning.[27] In a systematic literature review and meta-analysis of 8 controlled studies conducted among 268 adults with depression, Therond and colleagues[28] estimated efficacy of cognitive remediation on improving cognitive outcomes (N = 145 received cognitive remediation and 123 control group). Results indicated that cognitive remediation improved global cognition (g = 0.44, p < .0001), verbal memory (g = 0.60, p < .0001), attention/processing speed (g = 0.41, p = .04), working memory (g = 0.32, p = .02), and executive functioning (g = 0.30, p = .02). The authors concluded that results supported cognitive remediation as an intervention to improve global cognition and selected cognitive domains among adults with major depressive disorder.[28]

Woolf and colleagues[29] conducted a systematic review and meta-analysis of cognitive training among adults with major depressive disorders. The review included 9 studies with sample sizes ranging from 27 to 46 participants. The authors found statistically significantly improved outcomes in cognitive and affective scores with pooled effect sizes that were moderate across studies. They concluded there was strong evidence for cognitive training as a primary therapeutic intervention for treating major depressive disorder.[29] However, given the small sample sizes larger clinical trials are warranted among subgroups of adults.

There were 2 rationale for examining *BDNF Val66Met* and *APOE-ε4* as moderators of intervention response in MEMOIR-HF. First, these alleles are associated with increased individuals' risk of mild cognitive impairment and Alzheimer disease.[30,31] Second, this increased risk may influence intervention responsiveness to cognitive outcomes.[30,31] BDNF is a molecule belonging to the neurotrophin family which has an important role in neurological development and degeneration.[30–32] Pleiotropic effects of BDNF in the brain are promotion of neuronal growth and survival and regulation of synaptic neuroplasticity, all of which support learning and memory.[32,33] Circulating blood levels of BDNF have been used to characterize phenotypes of cognitive impairment among persons with different serious chronic conditions (e.g., schizophrenia,[34,35] Alzheimer disease,[36] HF[37,38]).

Circulating BDNF levels have been associated with the severity of Alzheimer disease[39] and may be influenced by the single-nucleotide polymorphisms (SNPs) in the BDNF locus located on chromosome 11.[30] One BDNF SNP (rs6265) produces a valine (Val)-to-methionine (Met) substitution in the pro-BDNF protein at codon 66 (*Val66Met*) and

inhibits the production and release of BDNF.[32] In past studies, presence of this Met allele was associated with learning and memory disorders among adults living in the U.S. and Australia.[33,40–42] Approximately 20% of people of European American descent have at least 1 *BDNF Met* allele (*Val/Met* or *Met/Met* genotype), almost 50% of people of East Asian descent have at least 1 *Met* allele (*Val/Met or Met/Met*), and 5% of people of African American descent have at least 1 *Met* allele.[43] Thus, the prevalence of *BDNF Val66Met* polymorphism varies by population genetic structure, ranging from 0% to 72%.[44] In a small study among 27 patients with HF living in the U.S., 29.6% had *BDNF Val66Met* present.[16]

The *APOE-ε4* allele is associated with memory.[31,45,46] The *APOE* gene locus is on Chromosome 19 which encodes the protein product of APOE, apolipoprotein E.[46] The *APOE* gene has 3 common isoforms of *ε2*, *ε3*, and *ε4*. This classification of alleles is from variations in 2 SNPs, rs7412 and rs429358.[46] *APOE-ε4* is a genetic risk factor for late-onset Alzheimer disease.[3146,47] In a meta-analysis of *APOE* genotype among persons of White race in 11 countries (U.S., Canada, Australia, Belgium, Finland, France, Germany, Italy, Japan, Netherlands, United Kingdom), presence of 1 *APOE-ε4* allele was associated with a 4.3 times greater odds of developing late-onset Alzheimer disease and presence of 2 *APOE-ε4* alleles was associated with a 15.6 times greater odds of developing it.[48] Inheriting 1 or 2 copies of the *APOE-ε4* allele is associated with earlier onset of Alzheimer disease.[31,46] The increased risk of late-onset Alzheimer disease has been validated among people with *APOE-ε4* alleles across countries with some differences by ethnicity and geographical regions.[49–51] For example, in a meta-analysis conducted to compare prevalence of *APOE* genotype among 27,109 persons with Alzheimer disease in 6 regions (Asia; Central, North, and South Mediterranean Europe; North America, South America), the *APOE-ε4* prevalence estimates were higher in Northern Europe and lowest in Asia and Southern Europe.[49,51] In the general U.S. population, prevalence of *APOE-ε4* was 23%.[45]

Prevalence of the *APOE-ε4* allele has been investigated in HF. In 62 patients with HF in the Netherlands, *APOE-ε4* prevalence was 16 (33%) and presence of at least 1 allele was an independent predictor of memory loss.[52] In 29 patients with HF in the U.S., *APOE-ε4* prevalence was 7 (24.1%),[37] similar in prevalence to the U.S. general population.

APOE-ε4 has been examined as a moderator of intervention response in past studies. In a classic study evaluating efficacy of donepezil on mild cognitive impairment among 769 adults with amnestic mild cognitive impairment, *APOE-ε4* was a significant moderator.[53] In a study among 50 older adults (50% with *APOE-ε4* allele present) who completed a multidomain cognitive training intervention with 30 sessions over 12 weeks, the adults without any *APOE-ε4* alleles had significant improvement in sentence comprehension.[54] In a quasi-experimental study to improve cognition among 202 adults with mild cognitive impairment, adults were assigned to 3 computerized intervention groups (combined physical and CCT; CCT control, and physical control) and divided by *APOE-ε4* presence or absence.[55] Interventions were completed over 8 to 12 weeks and follow-up data were collected 1 or 2 weeks after intervention completion. No differences were found in intervention effects among the 3 groups, but *APOE-ε4* presence moderated the effect of the combined physical and CCT intervention on task-switching processing speed and the effect of the physical control intervention on working memory. No moderation was found

for the CCT control group. Although no significant intervention effects were found in this non-randomized study, authors concluded that the combined physical and CCT interventions and the physical control intervention may be more effective for the subgroup of patients with mild cognitive impairment and *APOE-ε4.*[55]

The rationale was provided in prior studies for evaluating gender, global cognitive function, age, and HF severity as moderators of cognitive outcomes.[6,56] Global cognitive function as measured by screening questionnaires such as Montreal Cognitive Assessment (MoCA) test have been significantly associated with performance on domain-based neuropsychological tests.[6,56] Compared with women, men had significantly worse scores on tests of total and delayed recall memory, psychomotor speed, and visuospatial ability than women in a study among 249 patients with HF.[6] HF severity was significantly associated with measures of memory, visuospatial ability, executive function, and psychomotor speed.[6] There was a significant interaction between HF and measures of executive function with older HF patients with more severe HF having poorer executive function.[6]

The purpose of the analysis for this aim was to examine level of depressive symptoms, *BDNF Val66Met*, and *APOE-ε4* as moderators of response to CCT associated with improvement in 5 outcomes over 8 months among patients randomized to the 3 groups. The outcomes were delayed recall memory, serum BDNF, working memory, IADLs, and HRQL. Hypotheses were that patients with moderate to severe depressive symptoms, *BDNF Val66Met* polymorphism present, or *APOE-ε4* allele present would be less responsive to the CCT intervention. In post hoc analyses, gender, global cognitive function, age, and HF severity were examined as moderating variables

Methods

Design and Procedures

MEMOIR-HF was a 3-arm randomized controlled trial. The protocol was approved by the university institutional review board and patients provided written informed consent before participation. After consent, patients completed baseline data collection and were randomized to the CCT intervention, the computerized puzzles active control group, or the usual care group. The randomization assignments were stratified by gender and baseline global cognitive function. Patients randomized to CCT were requested to complete training for a total of 40 hours over 8 weeks (5 hours per week × 8 weeks). Patients randomized to the active control group were requested to complete computerized crossword puzzles for 40 hours over 8 weeks (5 hours per week × 8 weeks). Patients randomized to the usual care control group did not complete any specific computerized intervention. Patients in all 3 groups received nurse enhancement interventions that consisted of weekly telephone calls for 8 weeks to provide support and education about the computerized interventions, surveil changes in patients' clinical condition, and monitor treatment fidelity. Outcomes were measured at baseline and at 10 weeks, 4 months, and 8 months after baseline. These follow-up timepoints were selected based on literature about the time for brain plasticity to emerge. The specific time needed for brain plasticity to develop after CCT is not known, but could take at least 1 month.[57,58] Structural integrity of white matter increased after 8 weeks of training among 11 healthy adults.[59] Additionally, the follow-up times were selected for

evaluation of sustained change in outcomes.[60,61] Data collection was completed at locations preferred by patients from February 2017 to November 2020. Research assistants masked to randomization assignment collected the follow-up data.

Sample

The sample was recruited from HF and cardiology clinics in a Midwestern city. Inclusion criteria were: (1) age 21 years and older; (2) English speaking; (3) access to working telephone; (4) able to hear normal conversation; (5) able to see and read computer monitor; (6) Stage C HF validated by echocardiography; (7) New York Heart Association (NYHA) class I, II, and III; and (8) receiving guideline-derived medical therapies. Exclusion criteria were: (1) neurodegenerative condition known to cause memory loss (e.g., Alzheimer disease; Parkinson's disease); (2) terminal illness; and (3) MoCA test score lower than 19.[62]

Interventions

The interventions are described in detail in separate publications.[15,18,19] The CCT intervention using BrainHQ by Posit Science (https://www.brainhq.com/) was developed to improve brain plasticity, memory, and working memory. This program was designed based on scientific principles of brain plasticity. It is a tailored program that gradually increases in difficulty as the individually progresses through it. Six BrainHQ exercises were used in MEMOIR-HF: (1) Sound Sweeps; (2) Fine Tuning; (3) Memory Grid; (4) Syllable Stacks; (5) To-Do List Training, and (6) In the Know. Patients were provided a laptop computer and if necessary, a mobile internet access card, to complete the intervention at home. Patients were asked to complete the program 5 hours a week for 8 weeks, for a total of 40 hours as recommended by the developers of BrainHQ.[63,64]

The computerized puzzles active control intervention was designed by the research team members to match the CCT intervention mode by laptop computer and time of 5 hours per week for 8 weeks for a total of 40 hours. Patients randomized to puzzles were provided free puzzles available in the public domain from Crossword Fun (Crossword Fun-Chrome Web Store) at google.com (most recently accessed 12/09/2022) and Bestcrosswords (Free Crossword Puzzles/BestCrosswords.com (most recently accessed 12/09/2022). This intervention was not tailored to individual performance but did allow patients to select the puzzles they wanted to work. Patients were provided a laptop computer and mobile internet access if needed to complete the intervention at home.

The usual care control group did not receive any computerized cognitive interventions from the research team. They continued to receive health care from their multidisciplinary teams.

Patients in all 3 groups received weekly telephone calls to deliver nurse-enhancement interventions over the 8 weeks of the intervention phase.[18,19] The rationale for the development of these interventions was threefold. First, there is strong empirical evidence that nurse-led education and support interventions improve HRQL and reduce hospital readmissions among patients with HF.[65–67] Second, patients with HF experience frequent changes in clinical conditions that may interfere with intervention uptake.[68] Third, treatment fidelity is necessary to ensure intervention performance and evaluate efficacy.[69]

Therefore, the nurse-enhancement intervention had 4 core elements: (1) provision of support and education for the CCT intervention and puzzles groups; (2) assessment of patients' health status; (3) surveillance of changes in clinical condition; and (4) monitoring treatment fidelity. The nurse enhancement intervention was developed by nurse researchers with graduate nursing degrees and tested in the preliminary MEMOIR studies[15,16] Intervenors received training from study investigators that included education and practice of intervention delivery prior to beginning in the intervenor role. In MEMOIR-HF, a co-investigator (MJ) supervised delivery of the nurse enhancement interventions for the entire length of the study. Intervenors were not masked to group assignment. The weekly intervenors remained the same for individual patients as much as possible except when scheduling in personnel required a change. Standardized scripts were used to guide the weekly telephone calls to maintain treatment fidelity. During the weekly telephone calls, patients randomized to the CCT and puzzles groups were asked about intervention performance time, health status, changes in clinical condition, and other study issues over the past week. Patients randomized to the usual care group were asked about health status and changes in clinical condition. The intervenors made additional telephone calls and home visits to patients who needed more assistance performing interventions.

Intervention adherence was measured in the CCT group by the BrainHQ program time tracker and patient written self-report on calendar time sheets. Intervention adherence was measured in the puzzles group by patient written self-report on calendar time sheets.

Measures

Delayed recall memory was measured by the Hopkins Verbal Learning Test Revised (HVLT-R).[70] This test was selected because it measures one of the cognitive domains most often impaired among people with vascular cognitive disorders (delayed recall memory) and is commonly used in neuropsychological examinations for people with these disorders. The HVLT-R is a test of delayed recall in which the patient is requested to remember 12 words repeated over 3 trials, after 20 minutes. Possible scores range from 0 to 12 and higher scores indicate better delayed recall memory. Validity and reliability have been supported[70] and the test was sensitive to CCT training in a preliminary study.[15]

Serum BDNF levels were measured using commercially available ELISA (R&D Systems, Minneapolis, MN). Levels were obtained at the enrollment visit and at 10 weeks, 4 months, and 8 months. Batches with duplicates were obtained for each patient. The limit of detection for the serum BDNF was 20 pg/mL and no samples were below this limit.[71]

Working memory was measured by the CogState One Back Accuracy task.[72] This test was selected because it measures a cognitive domain often impaired among people with vascular cognitive disorders (working memory) and is used in neuropsychological examinations for people with this type of disorder. This task is a computerized neuropsychological test on which the patient is asked to use playing cards as the stimulus for response. As recommended by developers of the task, scores used were the arcsine of the patient's correct responses. Higher scores indicate better working memory performance. Validity and reliability have been supported and the test was sensitive to CCT in a preliminary study.[16]

IADLs were measured using the Everyday Problems Test for Cognitively Challenged Elderly.[73] It is a 16-item performance-based test with 2 questions for each item. Possible scores range from 0 to 32. Higher scores indicate better IADLs performance. Validity and reliability have been supported in past studies.[73]

HRQL was measured using the Minnesota Living with Heart Failure Questionnaire, a 21-item questionnaire with 6-point response scales.[74] The Questionnaire was designed to evaluate the impact of physical and emotional symptoms on the patient's ability to live as wanted. Possible total scores range from 0 to 105, with higher scores indicating poorer HRQL. Validity and reliability have been supported.[75]

Depressive symptoms were measured using the Patient Health Questionnaire-8 (PHQ-8),[76] an 8-item questionnaire with 4-point response scales (0 = "Not at all" to 3 = "Nearly every day"). Item scores are summed to obtain the total score that may range from 0 to 24. Higher scores indicate current more or more severe depressive symptoms. Cutoff scores have been validated for level of depression severity as follows: 0 – 4, minimal; 5 – 9, mild; 10 – 14, moderate; 15 – 19 moderately severe; 20 – 27, severe.[76] In the planned analysis, the PHQ-8 scores were categorized into 2 groups: 0 – 9, minimal to mild; 10 – 24, moderate to severe. The PHQ-8 has documented validity and reliability among patients with HF.[77]

The *BDNF and APOE* candidate gene analyses were completed at laboratories at Indiana University and University of Maryland. The DNA was extracted from samples of whole blood obtained at the enrollment or baseline visit using an AutoGen DNA isolation kit (Qiagen, Venlo, Netherlands). The *BDNF* and *APOE* +/− 10 KB on either side were sequenced on the Twist Bioscience at Indiana University generating 150 bp paired-end reads. Quality of raw sequences was assessed by FastQC[78] software. The reads were then aligned to the reference human genome (GRCh38) using Burrows-Wheeler Aligner software (version 0.7.12).[79] Variants including single nucleotide polymorphisms (SNPs) and indels were identified using the algorithm HaplotypeCaller implemented in Genome Analysis Toolkit (GATK) (version 4.1.9).[80] Integrative Genomic Viewer software (IGV) was used for variants visualization. The variant cell format file from GATK was annotated using SnpEff (version 5.0).[81] The quality of the variants identified by GATK is expressed using Phred scale, whose value can range from 0 to infinity. The higher the value, the higher the accuracy and the lower is the error. Variants whose Phred was lower than 30, which corresponds to 99.9% accuracy versus a 0.1% chance of error. The 3 variants analyzed in this study (rs6265 Phred: 7878.64; rs429358 Phred: 4887.64; and rs7412 Phred: 9697.64) have a Phred value ranging from ~ 5,000 to ~ 10,000 corresponding to a very poor chance of error.

The *BDNF* variant of interest was the *Val66Met* polymorphism rs6265 which is a substitution of methionine at Codon 66.[82] Patients were categorized into 2 groups: *Met* polymorphism absent (*Val/Val*) or present (*Val/Met or Met/Met*). Two SNPs, rs429358 and rs7412, were used to characterize the alleles of *APOE.*[83] Patients were categorized into 2 groups: *APOE-ε4* absent or present in at least 1 allele.

Demographic and clinical variables were obtained from patients' interviews and medical records. Gender and age were obtained by patient self-report. Global cognitive function was

measured by MoCA test at enrollment.[62] HF severity was assessed using patients' NYHA class documented by cardiologists at the clinic visits immediately prior to or on the day of study enrollment.

Statistical Analysis

Descriptive statistics were computed to compare baseline equivalencies of demographic, clinical, and moderator variables among the 3 groups of patients. Mixed effects models[84] were fit to test the moderation hypotheses (separately for each moderator) for the 5 outcome measures collected at baseline, 10 weeks, and 4 and 8 months. The main effects for group and the two-way interactions between group and the moderators were not included in the models to enforce the equal group mean assumption at baseline, given the RCT design.[84] Stratifying variables (gender and MoCA) were controlled prior to testing the effects. Time, group-by-time interactions, moderator-by-time interactions, and the 3-way group-by-time-by-moderator interactions were included in the mixed models with an unstructured covariance matrix. The overall F-tests were computed for the 3-way interactions using F-tests for contrasts within the mixed effects models. In addition, comparisons were conducted among the 3 group means at each post-randomization time at each level of the moderators using F-tests for contrasts within the mixed effects models. Analyses were completed using SAS 9.4 (SAS Institute, Cary, NC). The significance level was set at alpha < .05 for the overall F-tests. A Bonferroni-adjusted alpha of 0.05/6 = 0.008 was used when comparing groups within each post-randomization time and level of moderator (3 × 2 = 6 tests).

Post hoc analyses were conducted to examine 4 additional potential moderators and be hypothesis generating for future research. The 2 stratification variables of gender and global cognitive function at enrollment (MoCA scores normal 26–30 and low 19–25)[62] were evaluated as moderators in separate analyses. Age was evaluated as a moderator using the baseline median age of 67.5 years as the cutpoint. HF severity was evaluated as a moderator using NYHA classes 1 and 2 compared with NYHA class 3.

The COVID-19 pandemic began in March 2020 (year 4, month 9 of MEMOIR-HF) while data collection was ongoing. All face-to-face research interviews were modified to telephone interviews to adhere to university requirements and prevent COVID-19 transmission. At the 8-month interviews, 24.5% of the data were missing for working memory CogState One Back Accuracy, IADLs Everyday Problems Test, and serum BDNF because of COVID-19 restrictions on face-to-face interviews; 18% were missing for delayed recall memory HVLT-R, and none were missing for the HRQL Living with Heart Failure Questionnaire.[19] Multiple imputation models were not completed for this moderation analyses because the missing data did not affect the results in overall tests of the interventions.[19]

Results

A total of 276 patients consented to participate in the study, 256 patients were screened as eligible and randomized, and 233 finished the 8-month study. The 256 patients included 139 (54.3%) women and 117 (45.7%) men. The mean MoCA score was 25.3 (SD = 2.5) for the 256 patients. The mean age was 66.4 (SD = 12.3) years and the mean education was 13.9 (SD = 2.6) years. Self-reported race was: Asian, 1 (0.4%); Native Hawaiian/Pacific

Islander, 1 (0.4%); Black/African American, 37 (14.5%); White, 216 (84.4%), and more than 1 race, 1 (0.4%). Ethnicity was: Hispanic or Latino, 4 (1.6%), Non-Hispanic or Latino, 251 (98.1%); unknown, 1 (0.4%). The mean LVEF of the 256 patients was 49.3% (SD = 14.4%) and NYHA class frequencies were 23 (9%) class I, 96 (37.5%) class II, 134 (52.3%) class III, 1 (0.4%) class IV, and 2 (0.8%) missing. Of the 256 patients, 243 had blood available for genotyping. Of the 243 patients, 71.6% were *BDNF Met* negative and 28.4% were *BDNF Met* positive and 67.9% were *APOE-ε4* negative and 32.1% were *APOE-ε4* positive.

Eighty-five patients were randomized to CCT using BrainHQ and 72 remained for final analysis. Six of the 85 patients did not receive the allocated CCT for the following reasons: too sick, n = 2; lack of interest, n = 2; too busy, n = 1; and died before intervention started, n = 1. Seven of the 85 patients were lost to followup for the following reasons: too busy, n = 3; too sick, n = 2; lack of interest, n = 1; moved out of state, n = 1. Eighty-six patients were randomized to the active control computerized puzzles intervention and 80 remained for final analysis. One of the 86 patients did not receive the allocated puzzles intervention because of entering hospice. Five of the 85 patients were lost to followup for the following reasons: too sick, n = 2; unable to contact, n = 2; died, n = 1.

Eighty-five patients were randomized to usual care and 81 remained for final analysis. Four of the 85 patients were lost to followup because they reported being too sick.

The descriptive statistics are presented for the demographic and clinical variables of the 3 groups in Table 1. There were no statistically significant differences in the pre-specified moderators of level of depressive symptoms, *BDNF Val66Met*, and *APOE-ε4* or the post hoc moderators of gender, global cognitive function (MoCA) and age among the 3 groups (Table 1). Notably, there were significant differences in HF severity because more patients with increased HF severity (NYHA class 3) were randomized to CCT (57.7%) and computerized puzzles (59.3%) than to usual care (41.2%) ($p = .049$).

In the CCT group, 42 (49%) of 85 patients met the 90% adherence rate (≥ 36 minutes) and mean total time spent on telephone calls was 35.2 (SD = 19.9) minutes by intervenors delivering the weekly nurse enhancement interventions. In the puzzles group, 57 (66%) of 86 patients met the 90% adherence rate and mean total time spent was 34.3 (SD = 20.3) minutes by intervenors delivering the weekly nurse enhancement interventions. In the usual care group, mean total time spent was 23.1 (SD = 9.6) minutes by intervenors delivering the weekly nurse enhancement interventions. Adherence was significantly higher among the patients in the puzzles group than the CCT group ($p = .026$). The time spent delivering the weekly telephone calls was significantly different among the groups ($p < .0001$).

The results are presented in Tables 2, 3, and 4 for the pre-specified mixed effects models with moderation analyses. Level of depressive symptoms, *BDNF Val66Met*, and *APOE-ε4* were not statistically significant moderators. There were no cases in which group differences were significant for the moderators at specific time points with the Bonferroni corrections, and therefore, the hypotheses were not supported. In the post hoc mixed effects models

with moderation analyses, gender, global cognitive function (MoCA), age, and HF severity (NYHA class) were not statistically significant moderators.

Discussion

The important results of this study were that depressive symptoms, *BDNF Val66Met*, and *APOE-ε4* were not statistically significant moderators of intervention response to outcomes. These results suggest that the cognitive and HRQL improvements among patients in all 3 groups over 8 months[19] were not significantly associated with these moderators.

The hypothesis was not supported that level of depressive symptoms moderated intervention response to outcomes. The percentage of patients with moderate to severe depressive symptoms was highest in the CCT group (22.4%) but lower than the percentage of patients with HF and depressive symptoms (29%) in past meta-analyses.[24] The lower percentage of patients with moderate to severe depressive symptoms may reflect the medical management that the patients received to treat depression. In MEMOIR-HF, 85 (33.2%) of the 256 patients had been prescribed antidepressant medications prior to enrollment.[19] The unequal numbers of patients with minimal to mild and moderate to severe depressive symptoms scores may have limited the ability to detect a moderating effect. A remaining question is whether CCT reduced or alleviated depressive symptoms among patients enrolled in MEMOIR-HF. In a 2-arm randomized controlled trial of CCT using a visual speed of processing intervention among older adults aged 55 to 102 years, CCT decreased depressive symptoms among adults living independently in the community but increased depressive symptoms among adults living in assisted living communities.[85] Future studies may be considered to evaluate biological pathways of depression and CCT efficacy in HF.[86]

The hypothesis was not supported that *BDNF Val66Met* moderated intervention response. The prevalence was similar for this polymorphism in the sample compared with the U.S. population prevalence of 30%,[44] although it did vary among the groups from 19.8% (puzzles group) to 33.0% (usual care group) which may have confounded the results. Multiomics approaches that examine biomarkers associated with this specific polymorphism (e.g., tropomyosin receptor kinase-B) may provide new insights into neuronal function and plasticity in response to CCT and other cognitive interventions.[87]

The hypothesis was not supported that *APOE-ε4* moderated intervention response. In the U.S. the prevalence of people with at least one *APOE-ε4* allele is 30%. In MEMOIR-HF, the prevalence was 28.2% to 33.7% across the groups. Other *APOE* alleles (e.g., *APOE-ε2*) may have neuroprotective effects and need to be evaluated in larger samples of patients.[88]

In post hoc analyses, no statistically significant moderation was found by gender, global cognitive function, age, and HF severity. There are at least 3 plausible explanations for these results. First, there may be no actual moderating effect of these variables. Past studies mainly evaluated associations rather than moderating effects.[6,52,56] Second, variables that were not measured may have confounded the data and contributed to lack of significant results (e.g., pain, sleep-disordered breathing). Third, unidentified etiological pathways may be responsible for moderating effects. Studies of CCT may need to stratify or randomize

patients by measures of HF severity, but it is not clear which measure would be most relevant (e.g., specific echocardiographic indicators; biomarkers like N-terminal prohormone of brain natriuretic peptide).[89]

A possible limitation of this study is missing data resulting from the COVID-19 pandemic. Multiple imputation models were computed to evaluate effects of missing data for the main hypotheses and no statistically significant differences were found.[19] Therefore, it seems unlikely that the missing data accounted for the lack of statistically significant results in this moderation analysis. Another possible limitation is the low intervention adherence rates for some patients. However, the per protocol analyses did not support differences based on adherence rates of the CCT group in the main results.[19]

Conclusion

In conclusion, depressive symptoms, *BDNF Val66Met*, and *APOE-ε4* were not significant moderators of intervention response to outcomes among the 256 patients randomized in the MEMOIR-HF study. Gender, global cognitive function, age, and HF severity were not significant moderators in post hoc analyses. Continued analyses are desirable for MEMOIR-HF data to evaluate variables that may have been associated with the improvement over time found among patients randomized to all 3 groups. These variables, measured in MEMOIR-HF, include the nurse enhancement intervention, change in clinical condition during the intervention phase, physical function, and excessive daytime sleepiness.[19] Clinicians caring for patients with HF ought to continue to assess patients for cognitive dysfunction and how it may reduce their memory, performance of IADLs, and HRQL.[6,10,90] Family caregivers need to be involved in care of patients with HF and cognitive dysfunction to ensure the best care is delivered and continued in home settings.[90] Patients with HF are waiting for novel interventions to be developed and tested to prevent cognitive dysfunction and decline.

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Highlights

- Depressive symptoms, *BDNF Val66Met,* and *APOE-ε4* were not significant moderators.
- Global cognition, gender, age, and HF severity were not significant moderators.
- Studies are needed to elucidate biological mechanisms of cognitive dysfunction in HF and test novel interventions to improve memory in patients.

Table 1.

Baseline demographic and clinical characteristics by group (n = 256)

Characteristic	BrainHQ (n = 85)	Puzzles (n = 86)	Usual Care (n = 85)	*P* Value
Age, y, mean ± SD	67.1 ± 12.9	66.8 ± 12.2	65.2 ± 11.9	.544[a]
Age category, n (%)				.119[b]
< 67.5 y	37 (43.5)	41 (47.7)	50 (58.8)	
>= 67.5 y	48 (56.5)	45 (52.3)	35 (41.2)	
Gender, n (%)				.972[b]
Men	39 (45.9)	40 (46.5)	38 (44.7)	
Women	46 (54.1)	46 (53.5)	47 (55.3)	
Race, n (%)				.560[c]
Asian	0 (0)	1 (1.2)	0 (0)	
Native Hawaiian/Pacific	0 (0)	0 (0)	1 (1.2)	
Black/African American	11 (12.9)	11 (12.8)	15 (17.7)	
White	74 (87.1)	74 (86.1)	68 (80.0)	
More than one race	0 (0)	0 (0)	1 (1.2)	
Ethnicity, n (%)				.649[c]
Hispanic or Latino	2 (2.4)	1 (1.2)	1 (1.2)	
Non-Hispanic or Latino	82 (96.5)	85 (98.8)	84 (98.8)	
Unknown	1 (1.2)	0 (0)	0 (0)	
Marital status, n (%)				.825[b]
Married	42 (49.4)	45 (52.3)	46 (54.1)	
Not married	43 (50.6)	41 (47.7)	39 (45.9)	
Education, y, mean ± SD	13.8 ± 2.9	13.9 ± 2.5	14.0 ± 2.4	.928[a]
LVEF, %, mean ± SD	48.9 ± 14.5	49.3 ± 14.1	49.5 ± 14.6	.965[a]
NYHA Class, n (%)				.049[c†]
I/II	35 (41.2)	35 (40.7)	49 (57.7)	
III	49 (57.7)	51 (59.3)	35 (41.2)	
Missing	1 (1.2)	0 (0)	1 (1.2)	
History comorbid condition, n (%)				
Atrial fibrillation	33 (38.8)	41 (47.7)	36 (42.4)	.500[b]
Hypertension	71 (83.5)	70 (81.4)	69 (81.2)	.907[b]
Coronary artery disease	36 (42.4)	39 (45.4)	37 (43.5)	.924[b]
Coronary artery bypass	17 (20.0)	21 (24.4)	13 (15.3)	.328[b]
Depression	19 (22.4)	13 (15.1)	18 (21.2)	.440[b]
Diabetes	42 (49.4)	39 (45.4)	36 (42.4)	.651[b]
Myocardial infarction	14 (16.5)	19 (22.1)	17 (20.0)	.645[b]

Characteristic	BrainHQ (n = 85)	Puzzles (n = 86)	Usual Care (n = 85)	*P* Value
Sudden cardiac arrest	2 (2.4)	2 (2.3)	2 (2.4)	1.000[c]
Stroke	6 (7.1)	9 (10.5)	9 (10.6)	.669[b]
Transient ischemic attack	5 (5.9)	4 (4.7)	2 (2.4)	.555[c]
Ventricular arrhythmias	13 (15.3)	13 (15.1)	14 (16.5)	.966[b]
MoCA at enrollment, mean ± SD	25.4 ± 2.6	25.1 ± 2.6	25.4 ± 2.5	.683[a]
Normal, mean ± SD	27.5 ± 1.3	27.4 ± 1.3	27.5 ± 1.1	.809[a]
Low, mean ± SD	23.4 ± 1.6	23.1 ±1.6	23.5 ± 1.6	.518[a]
MoCA category, n (%)				.974[b]
Normal, ≥ 26	41 (48.2)	40 (46.5)	40 (47.1)	
Low, 19 – 25	44 (51.8)	46 (53.5)	45 (52.9)	
PHQ-8, mean ± SD	5.9 ± 4.7	6.0 ± 5.8	5.7 ± 4.5	.913[a]
PHQ-8 category, n (%)				.774[b]
Minimal to mild	66 (77.6)	69 (80.2)	70 (82.4)	
Moderate to severe	19 (22.4)	17 (19.8)	15 (17.6)	
BDNF *Val66Met*, n (%)				.284[c]
Met Absent	55 (64.7)	65 (75.6)	54 (63.5)	
Met Present	24 (28.2)	17 (19.8)	28 (33.0)	
Missing	6 (7.1)	4 (4.6)	3 (3.5)	
APOE-ε4, n (%)				.775[c]
Absent	54 (63.5)	53 (61.6)	58 (68.2)	
Present	25 (29.4)	29 (33.7)	24 (28.2)	
Missing	6 (7.1)	4 (4.7)	3 (3.6)	

[†] P <.05

[a] Analysis of variance

[b] Chi-square test

[c] Fisher's exact test

Abbreviations: y, years; SD, standard deviation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; MoCA, Montreal Cognitive Assessment; PHQ-8, Patient Health Questionnaire-8; BDNF, brain-derived neurotrophic factor; *APOE-ε4, apolipoprotein E ε4 allele*.

Table 2.

Moderation results for level of depressive symptoms

		Predicted Means and 95% Confidence Intervals			
Visit	**Depressive Level**	**BrainHQ (n = 85)**	**Puzzles (n = 86)**	**Usual Care (n = 85)**	***P* Value[1]**
Hopkins Verbal Learning Test – Revised, Delayed Recall[2]					.298
10 Weeks	Minimal to mild	9.1 (8.4 to 9.7)	8.9 (8.3 to 9.5)	9.1 (8.6 to 9.7)	.834
	Moderate to severe	8.1 (6.9 to 9.4)	8.8 (7.5 to 10.1)	8.8 (7.5 to 10.1)	.674
4 Months	Minimal to mild	9.3 (8.8 to 9.9)	9.5 (8.9 to 10.0)	9.9 (9.4 to 10.5)	.249
	Moderate to severe	9.8 (8.7 to 11.0)	9.1 (7.9 to 10.3)	8.7 (7.5 to 9.9)	.366
8 Months	Minimal to mild	9.3 (8.8 to 9.8)	9.6 (9.1 to 10.1)	10.0 (9.5 to 10.5)	.161
	Moderate to severe	9.2 (8.1 to 10.3)	9.1 (8.0 to 10.2)	9.2 (8.1 to 10.2)	.995
Serum BDNF, ng/ml[3]					.709
10 Weeks	Minimal to mild	16.4 (14.4 to 18.3)	16.9 (15.0 to 18.8)	16.6 (14.8 to 18.4)	.901
	Moderate to severe	17.2 (13.4 to 21.0)	17.3 (13.3 to 21.4)	15.6 (11.9 to 19.3)	.720
4 Months	Minimal to mild	16.1 (14.1 to 18.2)	17.9 (16.1 to 19.8)	16.6 (14.7 to 18.4)	.297
	Moderate to severe	19.6 (15.6 to 23.6)	17.8 (13.9 to 21.7)	15.9 (11.7 to 20.1)	.385
8 Months	Minimal to mild	15.8 (13.7 to 17.9)	16.0 (14.1 to 17.9)	16.9 (15.0 to 18.9)	.654
	Moderate to severe	19.6 (15.5 to 23.8)	15.9 (11.3 to 20.4)	17.3 (13.1 to 21.5)	.429
CogState One Back Accuracy[4]					.777
10 Weeks	Minimal to mild	1.30 (1.24 to 1.35)	1.33 (1.27 to 1.38)	1.33 (1.28 to 1.37)	.670
	Moderate to severe	1.26 (1.15 to 1.36)	1.33 (1.21 to 1.44)	1.23 (1.12 to 1.34)	.446
4 Months	Minimal to mild	1.32 (1.27 to 1.37)	1.34 (1.30 to 1.39)	1.33 (1.28 to 1.38)	.825
	Moderate to severe	1.27 (1.17 to 1.37)	1.32 (1.22 to 1.43)	1.35 (1.25 to 1.45)	.548
8 Months	Minimal to mild	1.30 (1.24 to 1.35)	1.35 (1.29 to 1.40)	1.31 (1.26 to 1.36)	.380
	Moderate to severe	1.29 (1.17 to 1.40)	1.31 (1.19 to 1.43)	1.33 (1.22 to 1.44)	.833
Everyday Problems Test[5]					.827
10 Weeks	Minimal to mild	26.8 (25.8 to 27.7)	27.4 (26.4 to 28.3)	27.9 (27.0 to 28.8)	.132
	Moderate to severe	26.5 (24.6 to 28.4)	27.7 (25.6 to 29.7)	27.5 (25.5 to 29.4)	.607
4 Months	Minimal to mild	27.0 (26.0 to 28.1)	26.9 (25.9 to 27.9)	27.8 (26.8 to 28.8)	.359
	Moderate to severe	26.5 (24.3 to 28.7)	27.0 (24.8 to 29.2)	25.9 (23.8 to 28.0)	.744
8 Months	Minimal to mild	26.1 (25.0 to 27.2)	27.1 (26.1 to 28.1)	27.9 (26.9 to 28.9)	.044[†]
	Moderate to severe	27.5 (25.2 to 29.7)	28.1 (25.7 to 30.4)	27.2 (25.0 to 29.3)	.893
Living with Heart Failure Questionnaire[6]					.633
10 Weeks	Minimal to mild	23.7 (19.6 to 27.7)	24.3 (20.3 to 28.2)	23.4 (19.6 to 27.2)	.937
	Moderate to severe	51.2 (43.2 to 59.3)	50.3 (41.9 to 58.8)	48.8 (40.7 to 56.9)	.893
4 Months	Minimal to mild	25.2 (20.4 to 30.0)	23.5 (18.9 to 28.0)	25.9 (21.4 to 30.5)	.702
	Moderate to severe	54.1 (44.9 to 63.3)	41.9 (32.4 to 51.4)	48.1 (38.4 to 57.8)	.148

		Predicted Means and 95% Confidence Intervals			
Visit	**Depressive Level**	**BrainHQ (n = 85)**	**Puzzles (n = 86)**	**Usual Care (n = 85)**	***P* Value[1]**
8 Months	Minimal to mild	27.0 (21.8 to 32.3)	24.5 (19.6 to 29.4)	26.2 (21.4 to 31.1)	.752
	Moderate to severe	51.6 (41.6 to 61.6)	47.1 (36.5 to 57.8)	52.8 (42.3 to 63.3)	.712

[†]P <.05

[1]The first p-value for an outcome is the p-value for the overall test of 3-way interaction (compare to alpha = 0.05). The remaining six p-values test for group differences within each time and moderation value combination (compare to alpha=0.008).

Abbreviations: BDNF, brain-derived neurotrophic factor; ng/ml, nanograms per milliliter.

[2]Sample sizes per group (Baseline, 10 weeks, 4 months, 8 months): BrainHQ (85, 69, 62, 57); Puzzles (86, 67, 71, 66); Usual Care (85, 81, 70, 66)

[3]Sample sizes per group (Baseline, 10 weeks, 4 months, 8 months): BrainHQ (79, 64, 56, 49); Puzzles (82, 64, 70, 58); Usual Care (80, 75, 64, 58)

[4]Sample sizes per group (Baseline, 10 weeks, 4 months, 8 months): BrainHQ (80, 68, 62, 54); Puzzles (85, 66, 70, 59); Usual Care (83, 81, 71, 61)

[5]Sample sizes per group (Baseline, 10 weeks, 4 months, 8 months): BrainHQ (85, 69, 62, 54); Puzzles (85, 68, 71, 60); Usual Care (85, 81, 71, 62)

[6]Sample sizes per group (Baseline, 10 weeks, 4 months, 8 months): BrainHQ (85, 74, 72, 72); Puzzles (86, 75, 80, 80); Usual Care (85, 85, 78, 81)

Table 3.

Moderation results for BDNF *Val66Met*

		Predicted Means and 95% Confidence Intervals			
Visit	**BDNF *Met***	**BrainHQ (n = 79)**	**Puzzles (n = 82)**	**Usual Care (n = 82)**	***P* Value[1]**
Hopkins Verbal Learning Test – Revised, Delayed Recall[2]					.253
10 Weeks	Absent	9.4 (8.7 to 10.1)	8.8 (8.2 to 9.5)	9.4 (8.8 to 10.1)	.308
	Present	7.6 (6.5 to 8.6)	9.3 (8.1 to 10.5)	8.6 (7.7 to 9.5)	.079
4 Months	Absent	9.7 (9.1 to 10.3)	9.7 (9.2 to 10.3)	10.1 (9.5 to 10.7)	.497
	Present	8.4 (7.5 to 9.4)	8.6 (7.5 to 9.7)	9.1 (8.2 to 9.9)	.530
8 Months	Absent	9.4 (8.8 to 10.1)	9.6 (9.1 to 10.1)	10.0 (9.4 to 10.5)	.363
	Present	8.7 (7.9 to 9.6)	9.4 (8.4 to 10.4)	9.4 (8.6 to 10.3)	.397
Serum BDNF, ng/ml[3]					.765
10 Weeks	Absent	16.9 (14.8 to 18.9)	17.8 (15.9 to 19.8)	16.9 (14.9 to 18.9)	.672
	Present	15.6 (12.4 to 18.8)	14.2 (10.7 to 17.8)	15.2 (12.5 to 18.0)	.811
4 Months	Absent	17.4 (15.2 to 19.5)	18.1 (16.2 to 20.0)	17.2 (15.1 to 19.3)	.737
	Present	15.4 (12.3 to 18.6)	17.5 (13.9 to 21.1)	14.8 (11.9 to 17.7)	.423
8 Months	Absent	17.6 (15.3 to 20.0)	16.3 (14.4 to 18.3)	17.4 (15.3 to 19.5)	.613
	Present	14.4 (11.2 to 17.6)	15.2 (11.3 to 19.1)	16.0 (12.9 to 19.2)	.720
CogState One Back Accuracy[4]					.480
10 Weeks	Absent	1.29 (1.23 to 1.35)	1.33 (1.27 to 1.38)	1.33 (1.27 to 1.39)	.501
	Present	1.29 (1.20 to 1.38)	1.31 (1.20 to 1.42)	1.28 (1.20 to 1.36)	.884
4 Months	Absent	1.31 (1.25 to 1.36)	1.35 (1.30 to 1.40)	1.33 (1.27 to 1.38)	.517
	Present	1.31 (1.23 to 1.40)	1.32 (1.22 to 1.41)	1.34 (1.27 to 1.42)	.832
8 Months	Absent	1.32 (1.26 to 1.38)	1.34 (1.28 to 1.39)	1.29 (1.24 to 1.35)	.515
	Present	1.25 (1.16 to 1.33)	1.35 (1.24 to 1.45)	1.35 (1.27 to 1.44)	.156
Everyday Problems Test[5]					.445
10 Weeks	Absent	26.6 (25.6 to 27.7)	27.4 (26.4 to 28.4)	28.1 (27.1 to 29.1)	.080
	Present	27.2 (25.5 to 28.9)	27.7 (25.8 to 29.5)	27.3 (25.9 to 28.8)	.907
4 Months	Absent	27.5 (26.4 to 28.7)	27.0 (26.0 to 28.1)	27.9 (26.8 to 29.0)	.480
	Present	25.8 (24.1 to 27.6)	27.3 (25.3 to 29.2)	27.2 (25.6 to 28.7)	.379
8 Months	Absent	26.9 (25.6 to 28.1)	27.3 (26.2 to 28.3)	27.8 (26.7 to 29.0)	.472
	Present	25.6 (23.8 to 27.3)	27.5 (25.4 to 29.6)	27.8 (26.2 to 29.5)	.111
Living with Heart Failure Questionnaire[6]					.958
10 Weeks	Absent	30.5 (25.6 to 35.3)	29.4 (24.8 to 33.9)	29.9 (25.2 to 34.5)	.926
	Present	27.0 (19.5 to 34.5)	29.2 (21.0 to 37.4)	25.7 (18.9 to 32.5)	.742
4 Months	Absent	31.2 (25.6 to 36.9)	27.0 (22.0 to 32.1)	29.9 (24.5 to 35.3)	.451
	Present	29.4 (21.2 to 37.7)	26.4 (17.0 to 35.7)	31.3 (23.7 to 38.9)	.675
8 Months	Absent	32.2 (26.0 to 38.3)	28.3 (22.9 to 33.7)	30.9 (25.2 to 36.7)	.569

		Predicted Means and 95% Confidence Intervals			
Visit	**BDNF *Met***	**BrainHQ (n = 79)**	**Puzzles (n = 82)**	**Usual Care (n = 82)**	***P* Value[1]**
	Present	31.0 (22.1 to 39.9)	29.6 (19.5 to 39.8)	31.4 (23.1 to 39.6)	.958

[1]The first p-value for an outcome is the p-value for the overall test of 3-way interaction (compare to alpha = 0.05). The remaining six p-values test for group differences within each time and moderation value combination (compare to alpha = 0.008).

Abbreviations: BDNF, brain-derived neurotrophic factor; *Met*, methionine substitution for valine at codon 66; ng/ml, nanograms per milliliter.

[2]Sample sizes per group (Baseline, 10 weeks, 4 months, 8 months): BrainHQ (79, 65, 58, 54); Puzzles (82, 66, 70, 64); Usual Care (82, 79, 69, 64)

[3]Sample sizes per group (Baseline, 10 weeks, 4 months, 8 months): BrainHQ (78, 64, 56, 49); Puzzles (82, 64, 70, 58); Usual Care (80, 75, 64, 58)

[4]Sample sizes per group (Baseline, 10 weeks, 4 months, 8 months): BrainHQ (75, 64, 58, 52); Puzzles (81, 65, 69, 59); Usual Care (80, 79, 70, 60)

[5]Sample sizes per group (Baseline, 10 weeks, 4 months, 8 months): BrainHQ (79, 65, 58, 52); Puzzles (81, 67, 70, 60); Usual Care (82, 79, 70, 61)

[6]Sample sizes per group (Baseline, 10 weeks, 4 months, 8 months): BrainHQ (79, 68, 66, 66); Puzzles (82, 71, 76, 76); Usual Care (82, 82, 76, 78)

Table 4.

Moderation results for *APOE-ε4*

		Predicted Means and 95% Confidence Intervals			
Visit	***APOE-ε4***	**BrainHQ (n = 79)**	**Puzzles (n = 82)**	**Usual Care (n = 82)**	***P* Value**[1]
Hopkins Verbal Learning Test – Revised, Delayed Recall[2]					.409
10 Weeks	Absent	9.2 (8.5 to 9.9)	9.2 (8.5 to 9.8)	9.3 (8.6 to 9.9)	.964
	Present	8.1 (7.1 to 9.1)	8.4 (7.4 to 9.3)	9.0 (8.0 to 9.9)	.413
4 Months	Absent	9.4 (8.8 to 10.1)	9.6 (9.0 to 10.3)	10.0 (9.5 to 10.6)	.311
	Present	9.0 (8.1 to 10.0)	9.1 (8.3 to 9.9)	9.1 (8.2 to 10.1)	.984
8 Months	Absent	9.3 (8.8 to 9.9)	9.6 (9.0 to 10.1)	10.1 (9.6 to 10.7)	.111
	Present	9.0 (8.1 to 9.9)	9.5 (8.7 to 10.3)	8.9 (8.0 to 9.8)	.541
Serum BDNF, ng/ml[3]					.122
10 Weeks	Absent	16.2 (14.2 to 18.2)	16.6 (14.5 to 18.6)	16.6 (14.7 to 18.6)	.932
	Present	17.1 (14.0 to 20.2)	17.7 (14.7 to 20.7)	15.8 (12.9 to 18.7)	.589
4 Months	Absent	17.3 (15.1 to 19.4)	16.5 (14.5 to 18.6)	16.7 (14.7 to 18.7)	.863
	Present	15.8 (12.6 to 18.9)	20.4 (17.6 to 23.2)	15.6 (12.5 to 18.7)	.012†
8 Months	Absent	16.7 (14.5 to 19.0)	14.8 (12.7 to 16.9)	17.0 (15.0 to 19.1)	.205
	Present	16.0 (12.7 to 19.4)	18.6 (15.4 to 21.7)	16.6 (13.1 to 20.0)	.463
CogState One Back Accuracy[4]					.056
10 Weeks	Absent	1.32 (1.26 to 1.38)	1.29 (1.23 to 1.35)	1.32 (1.26 to 1.37)	.761
	Present	1.21 (1.12 to 1.30)	1.39 (1.30 to 1.48)	1.30 (1.22 to 1.39)	.014†
4 Months	Absent	1.31 (1.25 to 1.37)	1.32 (1.27 to 1.38)	1.35 (1.30 to 1.40)	.484
	Present	1.30 (1.22 to 1.39)	1.38 (1.30 to 1.45)	1.28 (1.20 to 1.36)	.167
8 Months	Absent	1.29 (1.23 to 1.35)	1.32 (1.26 to 1.38)	1.30 (1.24 to 1.35)	.778
	Present	1.28 (1.19 to 1.37)	1.38 (1.29 to 1.46)	1.36 (1.27 to 1.46)	.290
Everyday Problems Test[5]					.714
10 Weeks	Absent	27.1 (26.0 to 28.2)	27.9 (26.8 to 28.9)	28.2 (27.2 to 29.2)	.247
	Present	26.0 (24.4 to 27.6)	26.5 (24.9 to 28.0)	27.2 (25.7 to 28.7)	.452
4 Months	Absent	27.7 (26.5 to 28.8)	27.1 (26.0 to 28.2)	27.8 (26.7 to 28.8)	.586
	Present	25.5 (23.7 to 27.2)	26.9 (25.4 to 28.4)	27.4 (25.7 to 29.0)	.215
8 Months	Absent	27.0 (25.8 to 28.3)	27.6 (26.4 to 28.7)	28.1 (27.0 to 29.2)	.404
	Present	25.1 (23.3 to 26.9)	26.7 (25.0 to 28.4)	27.2 (25.4 to 29.1)	.200
Living with Heart Failure Questionnaire[6]					.582
10 Weeks	Absent	29.1 (24.2 to 34.0)	30.8 (25.9 to 35.6)	30.1 (25.5 to 34.7)	.855
	Present	30.2 (22.8 to 37.5)	27.0 (19.9 to 34.1)	24.2 (17.2 to 31.2)	.395
4 Months	Absent	30.1 (24.6 to 35.6)	29.6 (24.3 to 35.0)	33.2 (28.1 to 38.4)	.506
	Present	32.0 (23.4 to 40.5)	21.9 (14.4 to 29.5)	23.2 (15.1 to 31.2)	.126

		Predicted Means and 95% Confidence Intervals			
Visit	***APOE-ε4***	**BrainHQ (n = 79)**	**Puzzles (n = 82)**	**Usual Care (n = 82)**	***P* Value**[1]
8 Months	Absent	32.8 (26.8 to 38.8)	31.0 (25.2 to 36.8)	34.4 (28.8 to 39.9)	.658
	Present	29.2 (20.0 to 38.5)	24.3 (16.2 to 32.4)	22.7 (14.1 to 31.4)	.522

[†] P <.05

[1] The first p-value for an outcome is the p-value for the overall test of 3-way interaction (compare to alpha = 0.05). The remaining six p-values test for group differences within each time and moderation value combination (compare to alpha = 0.008).

Abbreviations: APOE-ε4, apolipoprotein E, ε4 allele; BDNF, brain-derived neurotrophic factor; ng/ml, nanograms per milliliter.

[2] Sample sizes per group (Baseline, 10 weeks, 4 months, 8 months): BrainHQ (79, 65, 58, 54); Puzzles (82, 66, 70, 64); Usual Care (82, 79, 69, 64)

[3] Sample sizes per group (Baseline, 10 weeks, 4 months, 8 months): BrainHQ (78, 64, 56, 49); Puzzles (82, 64, 70, 58); Usual Care (80, 75, 64, 58)

[4] Sample sizes per group (Baseline, 10 weeks, 4 months, 8 months): BrainHQ (75, 64, 58, 52); Puzzles (81, 65, 69, 59); Usual Care (80, 79, 70, 60)

[5] Sample sizes per group (Baseline, 10 weeks, 4 months, 8 months): BrainHQ (79, 65, 58, 52); Puzzles (81, 67, 70, 60); Usual Care (82, 79, 70, 61)

[6] Sample sizes per group (Baseline, 10 weeks, 4 months, 8 months): BrainHQ (79, 68, 66, 66); Puzzles (82, 71, 76, 76); Usual Care (82, 82, 76, 78)