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Nurse Enhanced Memory Intervention in Heart Failure: The MEMOIR Study

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Abstract

Background—Many patients with heart failure (HF) have cognitive deficits, including memory loss.

Objectives—To evaluate the efficacy of a cognitive training intervention on memory (primary outcome), working memory, psychomotor speed, executive function, and performance of cognitive activities and instrumental activities of daily living (IADLs).

Methods—Forty patients with HF were randomly assigned to the computerized plasticity-based cognitive training intervention called Brain Fitness and to the health education active control intervention. Advanced practice nurses made weekly home visits to assess symptoms and monitor intervention adherence. Patients completed demographic and clinical data (baseline), neuropsychological tests (baseline, 8, and 12 weeks), and measures of cognitive and IADLs performance (baseline and 12 weeks) and satisfaction (12 weeks).

Results—Linear mixed models analyses indicated a significant group by time interaction for delayed recall memory ($p = .032$) and a significant time effect for total (list learning) ($p < .001$) and delayed ($p = .015$) recall memory, psychomotor speed ($p = .029$), and performance of IADLs ($p = .006$). Intervention adherence and patient satisfaction were high.

Conclusions—To our knowledge, this was the first test of Brain Fitness in HF. Although it was a preliminary study with limitations, results support the need for a large randomized, controlled trial to determine whether the memory loss of HF is amenable to plasticity-based interventions.

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Keywords

heart failure; cognitive deficits; memory loss; cognitive training

Introduction

More than 5.7 million Americans have heart failure (HF) and 670,000 new cases are reported annually in people age 45 years and older.¹ The 12-month mortality rates for HF remain high, ranging from 15 to 50%, depending upon severity. Heart failure continues to be a leading cause of hospital readmission, contributing substantially to increased health care costs.² In patients with HF, quality of life is diminished by dyspnea, fatigue, cognitive deficits, and depression.³⁻⁵

In past studies, 23% to 50% of patients with HF have cognitive deficits, including the devastating problem of memory loss.^{3,4,6,7} In 166 HF patients, left ventricular ejection fraction (LVEF) and cognitive deficits predicted 12-month all-cause mortality; memory loss was the most significant cognitive deficit that predicted mortality.⁸ Despite the prevalence and importance of memory loss in HF, few interventions have been tested to improve memory and no evidence-based recommendations are currently available for HF patients whose care is complicated by memory loss and other cognitive deficits.⁹ Novel interventions are needed to address this life-threatening problem.

Therefore, the Nurse Enhanced Memory Intervention in HF Study (MEMOIR), a randomized controlled pilot study, was conducted among patients with chronic HF. The aim was to evaluate the efficacy of the cognitive training intervention on the primary outcome of memory (verbal learning) and the secondary outcomes of working memory, psychomotor speed, executive function, performance of cognitive activities, and performance of instrumental activities of daily living (IADLs) compared with patients in the active control group who received the health education intervention. All patients received weekly nurse visits from advanced practice nurses (APNs) to assess physical health and monitor intervention adherence. Adherence to and patient satisfaction with the interventions were evaluated.

Theoretical and Scientific Background

The exact etiology of memory loss in HF patients has not been determined, but it is most likely the result of brain injury due to decreased cerebral blood flow (this may be due to elevated vascular resistance, elevated central venous pressure, decreased arterial pressure, or decreased cardiac output) or microembolism leading to cerebral hypoperfusion, hypoxia, and disrupted cerebral autoregulation.¹⁰⁻¹³ In a recent study examining cognitive deficits in 249 HF patients, memory loss was the most common type of deficit, found in 23% of patients; psychomotor slowing and decreased executive function were found in 19% of the patients.⁴ The HF patients had significantly more cognitive deficits than comparison groups of 63 healthy participants and 102 participants with major medical conditions other than HF. Increased HF severity was associated with more memory deficits; increased HF severity and older age were associated with more deficits in executive function. In unstructured interviews, the HF patients discussed the challenges of living with memory loss, including the inability to perform complex cognitive activities and IADLs (e.g., managing a checkbook).¹⁴

The memory deficits of HF detected on neuropsychological tests are consistent with the injured brain areas in the hippocampus and prefrontal lobes detected in animal models of

cerebral hypoxia,¹⁵ case and autopsy reports,¹⁶ and neuroimaging studies of patients with HF.^{13,17,18} Neuronal loss has been documented in the hippocampus in animals and humans who have experienced cerebral ischemia.^{11,15,16}

In addition to cerebral hypoperfusion and hypoxia, other factors may contribute to memory loss and deficits in other cognitive domains in HF. First, age-related cognitive decline begins as early as the third decade of life,¹⁹ and many HF patients are elderly. The peripheral sensory organs may deteriorate with age and the input from the visual, auditory, tactile, and proprioceptive systems is degraded. The time required to integrate auditory stimuli and detect signals in speech is increased. As a result, the brain may not be able to accurately interpret details of complex auditory signals. This inability is manifested as slowed psychomotor speed, which occurred in 19% or more of HF patients.⁴ The neurotransmitters (acetylcholine, dopamine, serotonin, norepinephrine) that modulate the synaptic plasticity in the cerebral cortex and hippocampus and that regulate learning and plasticity may degrade with age and further contribute to memory loss.²⁰

Decreased stimulation of the sensory and cognitive systems may occur because of illness-related secondary problems, such as reduced interactions with others and with the environment. Patients may perform fewer cognitively demanding activities because of such problems as well as age-associated environmental issues (e.g., retirement). Together, these factors may decrease sensory and cognitive stimulation and potentially lead to negative changes in neuronal metabolism, learning, and memory. Performing novel or demanding cognitive activities becomes more difficult.²⁰ In HF, the physical and cognitive demands of illness become progressively complex and patients perform fewer cognitively challenging activities.^{14,21}

In the current study, a plasticity-based cognitive training program called Brain Fitness was selected for testing. Many computerized cognitive training programs are available, but most have not been scientifically tested.²²⁻³⁷ After evaluating and using Brain Fitness and other cognitive training programs, Brain Fitness was selected because it: 1) was developed based on scientific principles of neuroplasticity and incorporates core elements to improve plasticity;^{38,39} 2) had demonstrated efficacy among healthy elders;^{38,40} 3) focused on improving sensory function and processing speed to improve memory and these functions may underlie some memory deficits in HF; and 4) is customized so that the difficulty of the program progresses based on the individual's performance as ability improves.^{40,41} The plasticity-based cognitive training intervention used in this study, Brain Fitness, is designed to enhance sensory stimulation in order to improve memory, psychomotor speed, executive function, performance of cognitive activities, and performance of IADLs. The intervention is derived from knowledge about neurogenesis and neuroplasticity.⁴²⁻⁴⁴ Neurogenesis is the ability to generate new neurons and neuroplasticity is the capacity that neurons have to modify their synaptic structure and form new neural connections. The knowledge that brain neurons are capable of neuroplasticity in the presence of injury can be used as a basis for intervention. Neuroplasticity occurs in brain areas that are associated with learning and memory. Recent evidence indicates that neurogenesis can occur in the hippocampus after injury and in HF, the hippocampus is damaged.^{11,13,44,45} Neurogenesis and neuroplasticity are mechanisms through which the brain may recover from small, silent infarcts and compensate for periods of oxygen deprivation.^{42,44,45} Data from animal and human studies provide promising, preliminary evidence that intensive training to increase sensory stimulation and performance of cognitively challenging activities promotes neuroplasticity and improves cognitive outcomes.^{20,40,43,46-47}

Cognitive training interventions based on scientific principles of neuroplasticity have been tested among healthy elders, including persons at risk of age-related cognitive

decline. Individuals who received plasticity-based interventions had improved memory, psychomotor speed, reasoning, and IADLs.^{38,48-50} Using a non-computerized cognitive training intervention delivered in ten sessions over 5 to 6 weeks among 2,832 healthy elders, participants who received the specific cognitive training interventions had improvement immediately after the intervention in psychomotor speed (87% improved), reasoning (74%), and memory (26%).⁴⁸ For the memory training group, improved memory scores seen immediately after the intervention were sustained over two and five years.⁵⁰ Self-reported performance of IADLs significantly improved two years after the reasoning intervention and performance of IADLs significantly improved five years after the speed of processing intervention with booster training.⁵⁰

In a plasticity-based, computerized cognitive training intervention among 182 healthy elders, those who completed the intervention had significant improvement in memory compared with older adults in the attention control and no-contact groups.⁴⁰ In a multisite randomized controlled double-blind trial, the Improvement in Memory with Plasticity-Based Adaptive Cognitive Training (IMPACT) Study using the Brain Fitness computerized training program in 487 community-dwelling older adults without cognitive impairment, improvement in memory and attention was significantly greater ($p = .02$) in the group who received the plasticity-based cognitive training intervention (3.9 points, 95% confidence interval = 2.7 – 5.1) than in the active control group who received general cognitive stimulation (1.8 points, 95% CI 0.6 – 3.0).³⁸ The investigators concluded that the magnitude of the effect sizes is clinically meaningful.

No studies testing plasticity-based interventions, including Brain Fitness, aimed at improving memory or other cognitive abilities in HF were found in an extensive review of the literature.³ No evidence-based recommendations are available for patients who have cognitive loss in HF. In the current randomized pilot study, it was hypothesized that the patients who received the plasticity-based computerized Brain Fitness intervention would have improved memory (list learning and recall), working memory, psychomotor speed, executive function, performance of cognitive activities, and performance of IADLs compared with the patients who received the health education attention control intervention.

Methods

Design and Procedures

The MEMOIR Study used a two-group randomized experimental design to evaluate the cognitive training intervention in HF patients. The study was approved by the university institutional review board and all patients gave written informed consent prior to participation. The data were collected from April 2008 to July 2010. Data were collected at baseline, 8 weeks (defined as within 1 week of completion of the 8-week interventions), and 12 weeks (defined as within 4 weeks of completion of the 8-week interventions). The length of time to obtain consent and administer the baseline questionnaires and tests was 90 to 120 minutes. After baseline data collection, patients were randomly assigned to the Brain Fitness and health education interventions using a computer-generated list of random numbers and a 1:1 ratio. During the eight weeks of intervention delivery, APNs who were members of the research team made weekly home visits to assess HF-related physical symptoms, discuss problems or concerns about the interventions, and monitor intervention adherence. All patients were requested to maintain a calendar log of the time they spent performing the interventions. The data were collected by research assistants (RAs) who were graduate nursing students and a licensed psychologist with training in neuropsychological testing. The neuropsychologist co-investigator (BG) selected the test battery and assisted with training for administration and scoring of the neuropsychological tests. All neuropsychological testing was completed in patients' homes and environmental distractions were controlled.

Fifty-one percent of the follow-up data collection was completed by data collectors who were blinded to group assignment.

Sample

The patients were recruited from a multidisciplinary HF clinic affiliated with the university medical center in a Midwestern city. Clinic staff approached potentially eligible patients and invited them to participate; the names and contact information of interested patients were provided to research team members. Eligibility criteria were: 1) adults age ≥ 21 years; 2) able to understand English; 3) have access to a working telephone; 4) able to hear normal conversation; 5) able to see and read a computer screen; 6) have a current diagnosis of chronic systolic HF documented by echocardiography, nuclear imaging, or cardiac catheterization within the past two years and LVEF equal to or less than 40%;⁵¹⁷) NYHA class 2, 3, or 4; and 8) optimized medical therapy.⁹ Patients were excluded from participation if they had a condition likely to cause reduced cognitive function (e.g., neurological disorders) or terminal illness.

Interventions

Brain Fitness Intervention—Patients randomly assigned to the intervention group received the Brain Fitness Program developed by PositScience. This program, based on principles of neuroplasticity, was designed to increase sensory integration of information and strengthen neuromodulatory chemicals necessary for encoding information. A person's ability to remember information (i.e., encode, recall, and use information) is closely linked to the ability to hear and interpret auditory information accurately. The computerized program is designed to be completed in 40 1-hour sessions over eight weeks. Computers were placed in patients' homes and usage was demonstrated to patients by the APNs. All computers were a standardized size with a 14 inch monitor screen to provide delivery of high quality visual and auditory components of the intervention. Noise-cancelling headphones that were able to be worn alone or over hearing aids were provided to patients to use while completing the intervention.

The Brain Fitness program incorporates interesting visual and auditory components to deliver exercises, scenes, and stories designed to strengthen the person's ability to learn and recall information. The program provides intensive and progressive training of the auditory system by asking the person to distinguish between similar speech components.⁴¹ Stories are provided that have novel events and the person is asked to answer series of questions about the events. Intensive practice is believed to improve precision and accuracy in understanding speech and thereby improve memory recall. Progressive training is provided in the program - the exercises become increasingly complex as the person progresses through the program. Speech used in the program is processed by an algorithm to increase the rate and complexity over the training sessions in order to facilitate the person's ability to comprehend and encode speech. The computer program monitors the person's performance and ensures that he or she is training at threshold level (i.e., the uppermost level of current skill). This is a unique element of the program because it individualizes the training to the person's performance. Information that is associated with stronger emotions is more novel and more easily recalled,^{15,41} and Brain Fitness incorporates surprising and novel content to strengthen recall. Finally, feedback and rewards are provided by Brain Fitness to strengthen learning.^{40,41} Intervention adherence (time on task) is monitored by the computer program.

Health Education Intervention—The health education intervention was designed to provide an active control intervention. Patients randomly assigned to the health education intervention were required to read information about maintaining cardiovascular health. The reading materials were eight issues of Heart Insight, the quarterly consumer-oriented

magazine published by the American Heart Association (AHA) and Lippincott Williams and Wilkins.⁵² This official AHA publication is focused on preventing and managing cardiovascular disease and was developed for patients and their families. Patients were requested to read one issue each week for at least one hour.

Measures

Demographic and clinical variables were obtained at the baseline interviews (age, gender, race, ethnicity, marital status, education, and blood pressure) and from the medical records (LVEF and NYHA classification, devices, and medications) to describe the sample and evaluate baseline equivalencies of the groups. Perceived physical functional capacity, HF-related physical symptoms, and comorbidities were assessed at baseline to describe the sample and evaluate baseline equivalencies because these variables may influence patients' cognitive function and limit their ability to perform and adhere to interventions.

The Duke Activity Status Index was used to measure perceived physical functional capacity, defined as the maximal capacity that a person believes he/she has to perform particular physical tasks.⁵³ The Index consists of twelve items on 4-point response scales. Possible weighted scores range from 0 to 58.2; higher scores indicate greater perceived functional capacity. Internal consistency of the Duke Activity Status Index is satisfactory; Cronbach's alpha was 0.82 in 249 HF patients and 0.86 in 246 patients with implantable cardioverter defibrillators.^{4,54} Validity was supported by a correlation of 0.80 between the index and peak oxygen uptake by exercise testing.^{53,55} In the current sample, the Cronbach's alpha was 0.87.

The Minnesota Living with Heart Failure (LHFQ) Physical Subscale was used to measure physical symptom impact.⁵⁶ The LHFQ is a HF-specific quality of life questionnaire that was developed to measure the impact of physical and emotional HF-related symptoms on patients' ability to live as they wanted in the past month. The Physical Subscale consists of five 6-point response scales. Possible scores on the Physical Subscale range from 0 to 25; higher scores indicate greater impact of physical symptoms and worse quality of life. Internal consistency of the LHFQ Physical Subscale was 0.94 and 0.91 in 211 HF patients and construct validity was supported by factor analysis.^{57,58} In the current sample, the Cronbach's alpha was 0.85.

The Charlson Comorbidity Index (chart form) was used to measure comorbidity. This Index evaluates patients' history of having medical problems in 12 areas.⁵⁹ It provides a score based on the severity of the existing health problems; higher scores indicate more or more severe comorbid conditions. The Charlson Comorbidity Index has predictive validity among patients with chronic medical conditions.⁶⁰

The Mini-Mental State Examination (MMSE) was used to measure global cognitive function at baseline and aid in interpretation of the neuropsychological test data.⁶¹ The test has 11 items that produce a total possible score ranging from 0 to 30 points; higher scores indicate better mental status. Twenty-four hour test-retest reliability was $r = 0.83$ with different testers and $r = 0.89$ with the same tester.^{61,62} Construct validity of the MMSE has been supported in elders and it is sensitive to dementia across different age levels.⁶³ The MMSE is a screening questionnaire to identify patients in need of further evaluation; in past studies it was less sensitive than other measures in detecting possible cognitive impairment.^{64,65}

Outcome variables

The Hopkins Verbal Learning Test - Revised total and delayed recall scores were used to measure the primary outcome of memory (specifically, list learning and recall).^{66,67} The Hopkins is a well-established neuropsychological test developed to measure recall and

retention of information. In this test, the person is asked to learn and remember a list of 12 words over three trials and again after a 20-minute delay. The test yields a total list learning score (the sum of the three trials) and a delayed recall score. The possible total list learning score ranges from 0 to 36 and the possible delayed recall score ranges from 0 to 12; higher scores indicate better performance. Nine-week test-retest was $r = 0.66$ (nonsignificant).⁶⁶The Hopkins discriminated between patients with mild cognitive impairment and cognitively healthy persons with a sensitivity of 0.79 and a specificity of 0.95 among 21 patients with mild cognitive impairment and 98 cognitively healthy control participants⁶⁴ and a sensitivity of 0.96 and specificity 0.80 among 541 healthy participants.⁶⁸In this study, equivalent forms were counterbalanced and randomized at the three administrations to minimize the likelihood of practice effects. Raw scores were used in the analyses.

The Digit Symbol Subtest of the Wechsler Adult Intelligence Scale-3 was used to measure psychomotor speed (WAIS).⁶⁹The Digit Symbol is a widely used neuropsychological test in which the person is asked to match a series of numbers with characters over 120 seconds. The number matched is summed and a scaled score is obtained from the standardization sample (Mean = 10, SD = 3). Higher scores indicate better performance. Test-retest and validity have been supported.⁶⁹In the current study, *comparable parallel* forms were counterbalanced and randomized at the three administrations to minimize the likelihood of practice effects. The different forms have not been formally equated, but they are considered comparable based on common practice. Scaled scores were used in the analyses.

The Controlled Oral Word Association Test was used to measure executive function (verbal fluency).⁷⁰This is a widely used neuropsychological test in which the person is presented with a letter and asked to name as many words as possible that begin with the letter over 60 seconds. This is done three times with three different letters. The sum of the words generated is adjusted by age and education and a percentile score is obtained as the final measure; higher scores indicate better performance. Test-retest reliability and validity have been supported.⁶²In this study, equivalent forms were counterbalanced and randomized at the three administrations to minimize the likelihood of practice effects. Scores adjusted by age and education were used in the analyses.

Four tests from the CogState Health neuropsychological test battery were administered to evaluate working memory, memory, and psychomotor speed.⁷¹In addition, the CogState tests were used to compare them with the traditional neuropsychological tests in HF patients for use in future studies. The CogState Health neuropsychological test battery is based on traditional neuropsychological tests but has the advantage of computerized delivery that can be standardized and scored as it is completed. The battery uses playing cards on the computer as the stimulus set. The four tests used in this study were the Detection Task to measure psychomotor speed, the Identification Task to measure working memory, the One Back Task Speed and Accuracy to measure working memory, and the International Shopping List total (list learning) and delayed recall to measure memory. Reliability and construct validity of the CogState Health battery have been supported. One week test-retest reliability among 60 young volunteers had an intraclass correlation coefficient of 0.69 to 0.90.⁷¹The CogState tests were significantly different among samples of 113 healthy young adults, 10 patients with mild head injury, 15 patients with mild cognitive impairment, 15 patients with schizophrenia, and 15 patients with AIDS dementia complex.^{64,72-74}The transformed scores for the Detection, Identification, and One Back tasks were used in the analysis. The numbers of items learned and remembered after three trials and recalled after a 20-minute delay on the International Shopping List were used in the analysis.

The Florida Cognitive Activities Scale was used to measure self-reported cognitive activity performance.⁷⁵ This scale was developed to assess the frequency with which people engage in cognitive activities, including challenging cognitive activities (e.g., preparing new recipes, driving to unfamiliar places). The total Scale has twenty-five items on 5-point response scales. Possible scores range from 0 to 100; higher scores indicate more frequent performance of cognitive activities, including complex activities. Internal consistency reliability of the Scale was Cronbach's alpha from 0.65 to 0.79 in healthy elders and 0.68 among 223 African-American older adults.^{75,76} Construct validity was supported by factor analysis and discriminant validity was supported by comparing scores of healthy elders and persons with neurological impairments.^{75,76} In the current study, the Cronbach's alpha reliability was 0.77 at baseline and 0.76 at 12 weeks.

The Everyday Problems Test for Cognitively Challenged Elderly was used to measure IADLs.⁷⁷ This test was developed to assess older adults' ability to perform a set of complex tasks that are part of everyday living. The tasks involve global cognitive functions and higher-order executive functions on seven common domains (managing finances, taking medications, transportation, shopping, doing light household chores, preparing meals, and using the telephone).^{77,78} The test has 16 situations with two questions each for a total of 32 items. The difficulty level of the tasks is within the range of performance of patients in the early stage of dementia and elderly persons who have low education level but not dementia.⁷⁸ Possible scores range from 0 to 32; higher scores indicate better performance on the tasks that represent IADLs. Six-month test-retest reliability was 0.81 among 65 patients with Alzheimer Disease.⁷⁸ Construct validity was supported among the 65 patients with Alzheimer Disease because the Everyday Problem Test for Cognitively Challenged Elders was significantly correlated with other neuropsychological tests and with direct observation of tasks performed.⁷⁸ Change in the Everyday Performance Test for Cognitively Challenged Elders was a significant predictor of mortality.⁷⁹

The Patient Satisfaction Questionnaire was used to measure patient satisfaction with the Brain Fitness intervention. This Questionnaire, adapted from Northouse and colleagues,⁸⁰ asked patients to complete five structured items on 5-point response scales (possible score range 5 to 25 with higher scores indicating more satisfaction) and 4 open-ended items. Patients completed the Questionnaire at the 12-week data collection visit. In this sample, the Cronbach's alpha was 0.80.

Intervention adherence was assessed by the Brain Fitness computer program for patients assigned to the intervention group. Completion of the entire program took 2310 minutes. Adherence with the health education intervention was assessed by patients' weekly report of time they spent reading health information, including the Heart Insight magazines. Completion of the control intervention took 480 minutes, although some patients read health information for more than an hour per week. Patients were categorized as adherent if they met or exceeded 90% of the required minutes for the interventions and categorized as non-adherent if they completed less than 90% of the required minutes.

statistically analysis

Baseline descriptive statistics were computed for the demographic, clinical, and study variables and compared between the patients assigned to the Brain Fitness and health education groups using independent t-tests for continuous variables and Chi-square for categorical variables. Cronbach's alpha was computed to estimate internal consistency reliability for multi-item scales. Linear mixed models analyses were conducted for the dependent variables to compare the group, the time, and the group-by-time interaction effects. The dependent variables were the measures for memory (Hopkins Verbal Learning Test), psychomotor speed (Digit Symbol), executive function (Controlled Oral Word

Association), performance of cognitive activities (Florida Cognitive Activities Scale), performance of IADLs (Everyday Problem Test) and the CogState Health tests for psychomotor speed (Detection), working memory (Identification and One Back Task Speed and Accuracy), and memory (International Shopping List). The patterns of change were assessed using planned contrasts between baseline and 8 weeks, baseline and 12 weeks, and 8 and 12 weeks. The mixed models analyses were completed using the intent-to-treat approach with all available data, including baseline data from the patients who did not complete the study. Statistical analyses were completed using SPSS. Intervention adherence and patient satisfaction with the Brain Fitness intervention were evaluated using descriptive statistics. The significance level was set at $\alpha < .05$ for the analyses.

Results

The numbers of patients invited to participate, enrolled, and who completed the study are presented in Figure 1. Forty patients were enrolled and randomly assigned to the Brain Fitness ($n = 21$) and health education ($n = 19$) intervention groups. Sample characteristics of the 40 patients who were randomly assigned in the study are presented in Table 1. No significant differences were found between the groups on demographic and clinical characteristics, but patients assigned to the health education group were on average older, more likely to be men, had lower LVEF, were less likely to be receiving ACE-inhibitors, had fewer devices, and had more comorbidities. Compared with patients assigned to Brain Fitness, patients assigned to the health education intervention reported more physical symptoms on the Living with Heart Failure Questionnaire Physical Subscale at baseline ($p = .044$).

Thirty-four (85%) patients completed the 12-week study (17 patients completed the Brain Fitness intervention and 17 patients completed the health education intervention). Six patients withdrew or were withdrawn by the investigators (four from the Brain Fitness intervention and two from the health education intervention). Reasons for withdrawal were: too ill and too many doctors' appointments ($n = 2$); unable to use the computer ($n = 1$); family obligations ($n = 1$); too busy with work ($n = 1$); and inadequate incentive fees ($n = 1$). No significant differences were found between the patients who did and did not complete the study in demographics (age, gender, race, ethnicity, marital status, years of education), clinical variables (LVEF, NYHA, systolic or diastolic blood pressure, dual chamber pacemakers, cardiac resynchronization therapy, or cardiac medications), perceived functional capacity (Duke Activity Status Index), physical symptoms (Living with Heart Failure Questionnaire Physical Subscale), and the MMSE. Patients who completed the intervention were significantly more likely to have an implantable cardioverter-defibrillator (Chi square = 4.2, $p = .041$) and tended to have fewer comorbidities (Charlson Comorbidity Index mean score, completed, 2.1 ± 1.0 ; did not complete, $3.0 \pm .9$, $t = 2.0$, $p = .058$). At baseline, all of the mean neuropsychological test scores were lower for the patients who did not complete the study compared with the mean scores of the patients who completed the study. The scores of the patients who did not complete the study were significantly lower than the patients who completed the study on tests of memory (Hopkins Verbal Learning Test total list learning, $t = 2.3$, $p = .025$; CogState International Shopping List learning, $t = 2.5$, $p = .018$) and working memory (CogState One Back Task Speed, $t = 2.4$, $p = .021$) and approached significance on other tests of memory (Hopkins Verbal Learning Test delayed recall, $t = 1.9$, $p = .070$; CogState International Shopping List delayed recall, $t = 1.9$, $p = .064$), working memory (CogState Identification Task, $t = 1.9$, $p = .064$), psychomotor speed (Digit Symbol scaled score, $t = 1.9$, $p = .063$), and executive function (Controlled Oral Word Association, $t = 1.8$, $p = .075$). No baseline differences were found between the patients who did and did not complete the study on self-reported performance of cognitive activities (Florida Cognitive Activities Scale, $t = 0.4$, $p = .926$) but patients who did not

complete the study had a significantly lower mean score on the measure of performance of IADLs (Everyday Problems Test, $t = 2.4$, $p = .019$).

The mean scores for patients in both groups are presented in Table 2. Small improvement was found across the groups in memory, working memory, psychomotor speed, executive function, and IADLs. Results for the linear mixed models analyses are presented in Table 2. Memory as measured by the Hopkins Verbal Learning Test total list learning score had a strong and significant time effect ($F [2,65] = 9.04$, $p < .001$) and nonsignificant group ($F [1,37] = 0.03$, $p = .866$) and group by time interaction ($F [2,65] = 0.64$, $p = .530$) effects, indicating that patients in both groups improved over time on total number of words learned and recalled over the test trials. The Hopkins delayed recall demonstrated significant time ($F [2,64] = 4.48$, $p = .015$) and group by time interaction ($F [2,64] = 3.65$, $p = .032$) effects (Table 2) and a nonsignificant group effect ($F [1,37] = 0.49$, $p = .488$), indicating that patients who received the Brain Fitness intervention improved more in delayed recall memory over time than patients who received the health education intervention. The primary hypothesis of the study was supported.

On the secondary outcomes, significant results were found in working memory and performance of IADLs (Table 2). Working memory as measured by the CogState One Back Speed Task indicated a significant time effect ($F [2,65] = 3.75$; $p = .029$) and nonsignificant group and group by time interaction effects. The performance of IADLs as measured by the Everyday Problems Test indicated a strong significant time effect ($F [1,30] = 8.62$, $p = .006$) and nonsignificant group and group by time interaction effects.

The 17 patients who completed the Brain Fitness intervention had a mean adherence time of 1996 (SD = 677) minutes and 13 (77%) patients had 90% and higher adherence rates. The 17 patients who completed the health education intervention had a mean adherence time of 749 (SD = 643) minutes and 14 (82%) patients had 90% and higher adherence rates.

Scores on the patient satisfaction questionnaire for the Brain Fitness intervention were high (mean = 24.3; standard deviation = 1.3). Patients reported that the most helpful aspect of the program was the practice with memory and that the information contained in Brain Fitness did not overlap with any information they had received from their health care providers. Several patients reported that the program became tedious at times because of the repetitive training. Patients had positive comments about the APNs who completed the weekly visits.

Discussion

MEMOIR is an important study because, to our knowledge, it is the first test of the Brain Fitness intervention in HF. Although this was a preliminary study with limitations, the results support the urgent need for further testing to determine whether the memory loss of HF may be amenable to plasticity-based interventions. Linear mixed models analyses using an intent-to-treat design indicated that compared with patients who received the health education intervention, patients who received the Brain Fitness intervention had significantly improved performance over time on the test of delayed recall memory. These results are consistent with the IMPACT study in which investigators found that healthy elders improved on the word list delayed recall as measured by the Rey Auditory Verbal Learning test.³⁸

Patients in both groups demonstrated improvement over time in memory (list learning and delayed recall), working memory, psychomotor speed, executive function, and IADLs. There are three plausible explanations for the improvement noted in both groups. First, the health education intervention provided patients with a high quality magazine, *Heart Insight*, that publishes articles related to cardiovascular health. Second, patients in both groups

received the nurse enhanced component of the intervention that included weekly home visits by APNs and this may have contributed, in part, to the improvement. Home visits and care coordination by APNs reduce hospitalizations and improve quality of life, although no studies were found that evaluated the effects of APNs on specific cognitive abilities in HF and the APNs in this study did not provide care coordination.^{81,82} In this first study, it was important to include the nurse enhanced component to validate that patients could complete the intervention. Results are consistent with past studies that reported cognitive training interventions improved memory and psychomotor speed among healthy elders.^{38,48} A larger randomized controlled trial is urgently needed to evaluate the efficacy of the Brain Fitness intervention in HF independent of APN visits. Third, practice effects may have occurred with repeated administrations of the neuropsychological tests. The finding of a significant group by time interaction for delayed recall memory in the Brain Fitness group compared with the health education active control group suggests that practice effects may not have occurred. Furthermore, alternative test forms were used to minimize the likelihood of practice effects, but future studies are needed to fully evaluate these effects.

The use of an active control intervention that allowed the patients in both groups to receive interventions that might improve cognitive function was an important aspect of the study. To fully evaluate the efficacy of the Brain Fitness intervention, a no-contact control group of HF patients who continue to receive optimized medical therapy but receive no specific intervention that would increase their performance of cognitively-challenging activities is needed. The use of an active control group of patients who perform increased cognitively challenging activities independently on the computer is also necessary to provide a comparison that controls for computer usage.

Another important result of this study was the identification of a subset of patients who were unable or unwilling to complete the interventions. Although the patients reported other reasons for not completing the study, they had lower scores on all neuropsychological tests and on the measure of IADLs. These results support the use of enrollment criteria that pre-specifies a cutoff level for eligibility. Patients who are unable to complete the interventions may be in need of further neuropsychological evaluation and alternative interventions. Although exclusion criteria in the current study included the existence of documented cognitive disorders, it is plausible that the patients who were unable to complete the interventions had early or undiagnosed cognitive disorders.

Adherence with both interventions was high, supporting the feasibility of using these interventions in future studies among HF patients. The high adherence level is particularly important because these patients had advanced HF as evidenced by the low mean LVEF and perceived functional capacity. They were willing and able to complete the interventions when delivered in the home and supported by APNs. Patients had a high level of satisfaction with the program and with the nurse enhanced care. They were interested in maintaining and improving their cognitive health and the content in the Brain Fitness intervention did not duplicate information they had received from their health care providers.

This study had limitations that may have influenced the results. First, the sample size was small; results need to be replicated in a larger randomized controlled trial. With the sample size of 40 patients, the current study had 34% power to detect medium-sized effects and 69% power to detect large effects.⁸³ The significant group by time interaction for the primary outcome variable of delayed memory recall suggests a large effect size. Second, patients randomly assigned to the health education group were on average older, more often men, had lower LVEF, received fewer ACE-inhibitor therapies, had fewer devices, had slightly more comorbidities, and reported poorer physical symptoms at baseline than the Brain Fitness group. Although only differences in physical symptoms were statistically significant,

the health education group may have been sicker compared with the Brain Fitness group. Third, the possibility of selection bias cannot be excluded because patients were recruited from one academic medical center and received care from a multidisciplinary team of providers. However, the baseline mean scores on the neuropsychological tests in this sample were consistent with the scores reported in a larger sample of 249 HF patients enrolled at seven sites in a different state.⁴ The enrollment of patients receiving optimal medical care at a multidisciplinary specialty clinic eliminated some variables that could be responsible for impaired cognition (e.g., lack of medications recommended by guidelines). Academic medical centers often provide care to those patients with the most advanced HF and the finding that memory can be improved in these patients is promising for application to patients with less severe HF treated in other settings. The mean age of the sample was relatively young and this may be different than a community-based sample. Whether this type of intervention would work in groups of older HF patients is unknown. Fourth, the greater time spent by patients who completed the Brain Fitness intervention compared to the time spent by patients in the active control intervention may have contributed to the improvement found in the Brain Fitness group. Additionally, two patients in the health education group reported increasing their cognitive activities as a result of the baseline testing which may have contributed to improved performance. Fifth, the funding of the pilot study limited the ability to have all follow-up data collected by data collectors who were blinded to group assignment. Sixth, depressive symptoms and sleep-disordered breathing, both of which are common in HF, may be alternative explanations for the results and need to be evaluated in a larger study. Finally, plasticity was not directly measured in this study. If the intervention is efficacious in a larger study, investigations into the neural mechanisms responsible for improvement need to be determined.

In conclusion, patients who received the computerized, plasticity-based Brain Fitness cognitivet training intervention had improved performance in delayed memory at 12 weeks. Although significant improvement was not found in working memory and psychomotor speed, the improvement in overall delayed recall was consistent with the IMPACT study.³⁸ Patients had high levels of adherence and satisfaction with the intervention. These preliminary results require testing in a larger randomized controlled trial.

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Figure 1.
Numbers of Patients Invited, Enrolled, and Who Completed the Study

Table 1

Sample Characteristics of Total Group and Patients Who Were Randomly Assigned to the Brain Fitness and Health Education Groups (n = 40)

Characteristic	Total (n = 40)	Brain Fitness (n = 21)	Health Education (n = 19)	p-value
Age, mean $\pm$ SD	57.8 $\pm$ 13.1	54.7 $\pm$ 13.9	61.1 $\pm$ 11.5	.124
Gender, n (%)				
Men	28 (70)	13 (62)	15 (79)	.240
Women	12 (30)	8 (38)	4 (21)	
Race, n (%)				
African-American	7 (17.5)	5 (24)	2 (11)	.543
Asian	2 (5)	1 (5)	1 (5)	
White	31 (77.5)	15 (71)	16 (84)	
Ethnicity, n (%)				
Hispanic	3 (7.5)	2 (10)	1 (5)	.609
Non-hispanic	37 (92.5)	19 (90)	18 (95)	
Marital status, n (%)				
Married	26 (65)	13 (62)	13 (68)	.666
Not married	14 (35)	8 (38)	6 (32)	
Education, years, mean $\pm$ SD	14.0 $\pm$ 2.5	13.9 $\pm$ 2.4	14.2 $\pm$ 2.6	.657
LVEF, ^a mean $\pm$ SD	26.7 $\pm$ 10.3	28.5 $\pm$ 9.6	24.7 $\pm$ 10.8	.252
NYHA ^b class, n (%)				
I	11 (27.5)	6 (29)	5 (26)	
II	20 (50)	11 (52)	9 (47)	.860
III	9 (22.5)	4 (19)	5 (26)	
IV	0 (0)	0 (0)	0 (0)	
Systolic blood pressure, mean $\pm$ SD	113.3 $\pm$ 20.4	116.2 $\pm$ 20.0	110.0 $\pm$ 20.9	.341
Diastolic blood pressure, mean $\pm$ SD	68.0 $\pm$ 13.4	69.4 $\pm$ 13.8	66.4 $\pm$ 13.1	.492
Implantable Cardioverter Defibrillator, n (%)	22 (55)	13 (62)	9 (47)	.356
Cardiac Resynchronization Therapy, n (%)	11 (28)	5 (24)	6 (32)	.583
Dual-Chamber Pacemaker, n (%)	3 (8)	1 (5)	2 (11)	.489
Left Ventricular Assist Device, n (%)	1 (3)	1 (5)		
Medications, n (%)				

Characteristic	Total (n = 40)	Brain Fitness (n = 21)	Health Education (n = 19)	p-value
ACE-inhibitor ^c	21 (53)	12 (57)	9 (47)	.536
ARB ^d	11 (28)	5 (24)	6 (32)	.583
Beta-adrenergic blocking agent	36 (90)	19 (90)	17 (89)	.916
Diuretic	29 (73)	15 (71)	14 (74)	.873
Aldosterone antagonist	19 (48)	11 (52)	8 (42)	.516
Duke Activity Status Index, mean $\pm$ SD	22.9 $\pm$ 17.1	24.0 $\pm$ 15.5	21.6 $\pm$ 19.1	.662
LHFQ ^e Physical Subscale	8.6 $\pm$ 7.0	6.4 $\pm$ 5.1	11.0 $\pm$ 8.2	.044
Charlson Comorbidity Index, mean $\pm$ SD	2.3 $\pm$ 1.1	2.1 $\pm$ 1.0	2.4 $\pm$ 1.1	.336
MMSE ^f , mean $\pm$ SD	28.2 $\pm$ 1.7	28.1 $\pm$ 1.8	28.2 $\pm$ 1.6	.978

^a Left ventricular ejection fraction

^b New York Heart Association

^c Angiotensin-converting enzyme inhibitor

^d Angiotensin receptor blocking agent

^e Living with Heart Failure Questionnaire

^f Mini-mental State Examination

Table 2

Means, Standard Deviations, and Linear Mixed Models Analysis for Outcome Variables

Variable	Baseline			8 Weeks			12 Weeks			Mixed Models Analysis		
	Brain Fitness (n = 21) Mean ± SD	Health Education (n = 19) Mean ± SD	Brain Fitness (n = 17) Mean ± SD	Health Education (n = 17) Mean ± SD	Brain Fitness (n = 17) Mean ± SD	Health Education (n = 17) Mean ± SD	Brain Fitness (n = 17) Mean ± SD	Health Education (n = 17) Mean ± SD	Group p-value	Time p-value	Group x Time p-value	
Hopkins Verbal Learning Test												
List learning	20.5 ± 4.9	21.7 ± 5.4	23.7 ± 5.0	23.1 ± 5.8	25.2 ± 5.4	24.1 ± 5.4			.866	< .001		.530
Delayed recall	6.0 ± 3.2	7.8 ± 3.0	7.7 ± 3.0	7.8 ± 2.9	8.5 ± 2.7	8.1 ± 3.1 ^a			.488	.015		.032
Digit Symbol Scaled	8.7 ± 1.7	9.8 ± 2.6	8.8 ± 2.1	10.7 ± 2.4 ^a	9.3 ± 2.0	10.5 ± 2.7 ^a			.067	.479		.532
Controlled Oral Word Association (Percentile)	52.5 ± 30.8	45.6 ± 30.6	57.9 ± 28.3	48.5 ± 34.5	65.3 ± 26.0	51.7 ± 32.2			.680	.100		.561
CogState												
Detection	2.5 ± 1.0	2.5 ± 0.1	2.5 ± 0.2	2.5 ± 0.1	2.5 ± 0.1	2.6 ± 0.1			.313	.315		.525
Identification	2.7 ± 0.1	2.7 ± 0.1	2.7 ± 0.1	2.7 ± 0.1	2.7 ± 0.1	2.7 ± 0.1			.112	.159		.704
One Back Speed	2.9 ± 0.1	3.0 ± 0.1	2.9 ± 0.1 ^a	2.9 ± 0.1	2.9 ± 0.1	2.9 ± 0.1			.372	.029		.108
One Back Accuracy	1.3 ± 0.2	1.3 ± 0.3	1.3 ± 0.2 ^a	1.3 ± 0.3	1.3 ± 0.2	1.2 ± 0.2			.718	.423		.193
International Shopping List												
List learning	23.6 ± 8.6	24.8 ± 6.7	27.0 ± 6.9 ^a	24.2 ± 9.2	25.0 ± 9.1	24.7 ± 7.7			.846	.914		.557
Delayed recall	8.3 ± 3.6	9.1 ± 3.2	8.5 ± 4.2 ^a	8.5 ± 3.7	8.5 ± 3.5	8.9 ± 3.6			.587	.575		.926
Florida Cognitive Activities Scale	45.1 ± 9.8	45.6 ± 12.1	–	–	47.2 ± 9.7	44.7 ± 12.7			.759	.779		.276
Everyday												

Variable	Baseline			8 Weeks			12 Weeks			Mixed Models Analysis		
	Brain Fitness (n = 21)	Health Education (n = 19)	Brain Fitness (n = 17)	Health Education (n = 17)	Brain Fitness (n = 17)	Health Education (n = 17)	Brain Fitness (n = 17)	Health Education (n = 17)	Brain Fitness (n = 17)	Group p-value	Time p-value	Group x Time p-value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD			
Problems	27.0 ± 2.8	27.8 ± 2.7	–	–	29.3 ± 2.5	28.2 ± 4.6				.793	.006	.144
T _{test}												

^a n = 16 (data missing or patient unable to complete test at the time of data collection)