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Randomized Controlled Trial of a Cognitive Intervention to Improve Memory in Heart Failure

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Abstract

Background: The objective of this 3-arm randomized controlled trial was to evaluate the efficacy of computerized cognitive training (CCT) in improving primary outcomes of delayed-recall memory and serum brain-derived neurotrophic factor (BDNF) levels; and the secondary outcomes were working memory, instrumental activities of daily living (IADLs) and health-related quality of life (HRQL) in patients with heart failure (HF).

Methods and Results: Patients (n = 256) were randomly assigned to 8 weeks of CCT using BrainHQ, computerized crossword puzzles active control intervention, and usual care. All patients received weekly nurse-enhancement interventions. Data were collected at enrollment and baseline visits and at 10 weeks and 4 and 8 months. In mixed effects models, there were no statistically significant group or group-by-time differences in outcomes. There were statistically significant differences over time in all outcomes in all groups. Patients improved over time on measures of delayed-recall memory, working memory, IADLs, and HRQL and had decreased serum BDNF.

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Conclusions: CCT did not improve outcomes compared with the active control intervention and usual care. Nurse-enhancement interventions may have led to improved outcomes over time. Future studies are needed to test nurse-enhancement interventions in combination with other cognitive interventions to improve memory in persons with HF.

Lay Summary

In 256 patients with heart failure, 8 weeks of computerized cognitive training, computerized crossword puzzles or usual care were studied for effects on (1st) delayed recall memory and serum brain-derived neurotrophic factor (BDNF) and (2nd) working memory, instrumental activities of daily living (IADLs), and health-related quality of life (HRQL). Measurements were at baseline, 10 weeks, and 4 and 8 months. Nurse-enhancement interventions (eg, support, assessment) were provided. Delayed recall memory, working memory, IADLs, and HRQL improved over time. There were no statistically significant differences among treatment groups over time. BDNF unexpectedly decreased. Nurse-enhancement interventions may explain improved outcomes. Future studies are needed.

Keywords

heart failure; cognitive dysfunction; computerized cognitive training; nurse-enhancement intervention

More than 6.2 million adults in the United States have heart failure (HF),[1] and cognitive dysfunction occurs in 23% to 75% of these adults.[2–4] Memory is the cognitive domain most often impaired,[2,3] and memory dysfunction is an independent predictor of mortality in patients with HF.[5] The relationship has been established between HF and both memory dysfunction and structural brain damage.[3,4,6–17] In addition, memory dysfunction is associated with poorer performance of instrumental activities of daily living (IADLs)[18] and worse health-related quality of life (HRQL).[19,20] Improving memory is essential to maintaining independent living, enhancing HRQL, and preventing the trajectory of decline that occurs in patients with HF. Few interventions have been tested that target memory improvement using randomized controlled trial (RCT) designs in adequately sized samples of patients with HF.[21–26]

The evidence is compelling: HF is associated with memory dysfunction as measured using screening tests,[27,28] neuropsychological tests[2,3] and self-report.[19,20] The prevalence of dysfunction varies across studies based on research design, measures and sample characteristics. Increased HF severity and older age are associated with increased memory dysfunction, although associations vary across studies.[2,3,14] By gender, in a study of 249 patients with HF, men had poorer memory scores than women in total and delayed recall.[2] Taken together, the literature supports the fact that patients with HF experience dysfunction in memory and working memory; older patients with more severe HF are at greater risk of memory dysfunction, and men may be at increased risk.

Structural brain damage[4,7–17] in patients with HF occurs in areas of the brain responsible for memory and working memory. Major pathophysiological processes thought to be responsible are low cardiac output leading to cerebral hypoperfusion[4,6–11] and atrial

fibrillation leading to cerebral microemboli.[13,14] In a series of case-controlled studies, the structures damaged with neuronal loss include the hippocampi,[11] fornix fibers,[6] amygdalae,[6] mamillary bodies,[6] medial temporal and frontal lobes,[6–8,10,11,14,15] and cerebellum.[17] Recently, N-terminal prohormone of brain natriuretic peptide was significantly and negatively correlated with reduced density of gray matter in the medial and posterior cingulate cortex, hippocampus and precuneus.[15]

A growing body of science supports the idea that brain plasticity-based computerized cognitive training (CCT) may be an efficacious intervention to improve memory performance by improving sensory processing of information and increasing neuronal growth.[21 26,29] This approach targets the memory dysfunction and brain structural damage of neuronal loss found in HF. Efficacy has been supported of cognitive training to improve memory in meta-analyses among healthy older adults[30] and adults with mild cognitive impairment.[31] In preliminary studies among 40[21] and 27[24] patients with HF, patients randomized to CCT had significantly improved memory,[21] working memory[21,24] and serum brain-derived neurotrophic factor (BDNF)[24] levels over 12 weeks. Serum BDNF is a neurotrophin involved in neurogenesis and neuroplasticity changes related to memory and learning.[32–35] In a pilot study of 69 patients with HF, patients randomized to a combined exercise and CCT intervention had improved verbal memory at 3 months after intervention compared with patients randomized to attention control and exercise only, but not at 6 months.[26] To our knowledge, no other randomized clinical trials have tested the efficacy of CCT in patients with HF.

The purpose of Cognitive Intervention to Improve Memory in Heart Failure Patients (NR016116; NCT #03035565; Pressler MPI) (MEMOIR-HF) was to conduct a full-scale efficacy test of the CCT intervention against a general cognitive stimulation computerized crossword puzzle active-control intervention and a usual-care control group who received no computerized cognitive intervention.[36] The first study aim was to evaluate the efficacy of CCT to improve coprimary outcomes of memory and serum BDNF levels and secondary outcomes of working memory, IADLs and HRQL. It was hypothesized that patients randomized to the CCT using BrainHQ would have improved delayed-recall memory, increased serum BDNF and improved working memory, IADLs and HRQL at 10 weeks and 4 and 8 months after baseline in comparison to the computerized puzzles active control and usual-care control groups. CCT is a feasible, low cost and potentially scalable intervention for improving memory.

Methods

Design and Procedures

MEMOIR-HF was a 3-arm RCT. The protocol was approved by the university's institutional review board. All patients provided written informed consent prior to data collection. At enrollment, patients completed the Montreal Cognitive Assessment (MoCA) test,[37] and venipuncture for biospecimens and baseline visits were scheduled. After baseline data collection, patients were randomized to 1 of the 3 groups for the 8-week intervention phase. After completion of the intervention phase, patients completed follow-up data collection at 10 weeks and 4 and 8 months after baseline. Baseline and follow-up data collection

were completed in patients' homes, clinics or school of nursing research offices, based on their preferences. Follow-up data were collected by trained research assistants masked to randomization group. Data were collected between February 2017 and November 2020.

Patients were randomized to the 3 groups using stratified randomization. The strata were defined by gender and global cognitive function as measured by the MoCA test, with scores of normal (26–30) or low (19–25). Patients were assigned to 1 of the 3 groups with equal probability. A computer-generated randomization list was maintained on a secure website accessed by 1 coinvestigator (MJ) and the project manager to determine group assignments after baseline data collection.

Sample

Patients were recruited from 7 multidisciplinary HF and cardiology clinics. Inclusion criteria were: (1) age 21 years or older; (2) understanding of English; (3) telephone access; (4) hearing of normal conversation; (5) able to read computer screen; (6) chronic HF, stage C; (7) New York Heart Association (NYHA) class I, II or III; and (8) receiving optimized medical therapies. Patients were excluded if they had a comorbid condition known to cause memory loss or terminal illness or a MoCA[37] score less than 19, which suggests possible dementia.[38]

Interventions

The study interventions are described in detail elsewhere.[21,36] Briefly, the CCT intervention BrainHQ developed by PositScience (https://www.brainhq.com/) was designed to improve memory and working memory using scientific principles of neuroplasticity. It is a tailored, adaptive intervention that assesses baseline cognitive performance and increases in difficulty (titrates) as the individual successfully progresses through the program. Patients randomized to CCT were instructed to use the program 5 hours a week for 8 weeks, for a total of 40 hours, as recommended by the developers of BrainHQ.[39–41] The exact time for brain plasticity improvement to occur after training is unknown, but it may take at least 1 month.[42,43] The structural integrity of white matter was shown to be increased after 8 weeks of training (n = 11 healthy adults).[44] The 4-month follow-up time allowed for development of plasticity, and the 8-month follow-up time allowed for evaluation of sustained change.[45,46] The computerized puzzles' active control intervention was designed to match the CCT intervention in delivery mode and time. Patients randomized to puzzles were instructed to use free puzzles from Crossword Fun (Crossword Fun-Chrome Web Store) (google.com) [accessed 05/07/2021] and Bestcrosswords (Free Crossword Puzzles/ BestCross words.com) [accessed 05/07/2021] for 5 hours a week for 8 weeks for a total of 40 hours. Patients randomized to usual care did not receive any specific cognitive interventions from the study team and continued to receive care from multidisciplinary health care professionals, including cardiologists.

The prespecified adherence level was   90% of 40 hours. Adherence was measured for the CCT group using documentation from the BrainHQ program (time spent; number of exercises completed; and notification of completion) and patient self-report (time spent). Adherence was measured for the puzzles group using documentation by patients' self-

reporting of time spent. After each puzzles session, patients were requested to document the time they spent on the calendar provided to them by the study team.

All patients in the 3 groups received nurse-enhancement interventions during the 8-week intervention periods.[21,24,36] Core elements of the nurse-enhancement interventions were providing support and education for the CCT interventions, assessing patients' health status and surveilling changes in clinical condition, and monitoring treatment fidelity. The rationale was 3-fold for the core elements. First, strong empirical evidence exists that nurse-led interventions that provide education and support are associated with improved HRQL and reduced hospitalization among patients with HF.[47–49] Second, changes in the clinical condition of patients with HF need to be surveilled because they may interfere with performance of the interventions.[50] Third, treatment fidelity to cognitive training interventions needs to be monitored to evaluate efficacy.[51] The nurse-enhancement interventions were delivered under the guidance of a coinvestigator (MJ). Over the course of the study, interventions were delivered by 8 registered nurses (6 with bachelor's and 2 with PhD degrees) who had experience in caring for persons with chronic illness; 1 undergraduate social work student; and the project manager (bachelor's degree in business) with 6 years of health-research experience. The nurse-enhancement interventions included a 1-hour home visit to educate patients about performing the CCT and puzzles interventions and weekly telephone calls during the 8 weeks of intervention (CCT and puzzles groups). Patients in the usual-care group did not receive cognitive interventions, and the nurse-enhancement intervention focused on surveillance of patients' clinical conditions. Weekly telephone calls during the 8 weeks were to provide the core elements, guided by the treatment group assignment. If patients needed more assistance in performing interventions, intervenors made additional telephone calls and home visits.

Outcome Measures

The outcome measures were chosen based on past successful study outcomes for this population of patients.[21,24,36] All outcome measures have documented validity and reliability. The coprimary outcome measures were the Hopkins Verbal Learning Test Revised (HVLT-R)[52] delayed-recall memory score and serum BDNF levels. To complete the HVLT-R delayed-recall score, the patient is requested to learn and remember 12 words over 3 trials and recall the words 20 minutes later. Possible scores range from 0 to 12 for the delayed-recall measure, and higher scores indicate better performance. Serum BDNF levels were measured at the enrollment visit and at 10 weeks, 4 months and 8 months after baseline. BDNF was assayed using a commercially available ELISA (R&D Systems, Minneapolis, MN) in batches with duplicates for each patient. The limit of detection was 20 pg/mL. None of the samples were below the detection limit.

The secondary outcomes measured were the CogState One Back Accuracy task[53] to assess working memory, the Everyday Problems Test for Cognitively Challenged Elderly[54] to assess IADLs, and the Minnesota Living with Heart Failure Questionnaire[55] to assess HRQL. The CogState One Back Accuracy task is a computerized neuropsychological test that uses playing cards as the stimulus to assess working memory. Transformed scores of the arcsine of correct responses were used in the analyses. Higher scores indicate better

performance. The Everyday Problems Test for Cognitively Challenged Elderly is a 16-item performance-based test with 2 questions per item. Total possible scores range from 0 to 32, and higher scores indicate better performance. The Minnesota Living with Heart Failure Questionnaire is a 21-item questionnaire on 6-point response scales designed to measure the impact of physical and emotional symptoms on patients' ability to live as they want. Possible total scores range from 0 to 105, and higher scores indicate poorer HRQL. A 5-point change is clinically meaningful.[56] Other variables were collected to characterize the sample and monitor treatment fidelity. Patient satisfaction with the study was completed at 8 months by using the 9-item Patient Satisfaction Questionnaire.[57]

Statistical Analysis

MEMOIR-HF was designed to have 80% power based on a 2-tailed test at a 5% significance level to test the hypotheses that patients in the CCT group would have improved memory and increased serum BDNF levels compared with the puzzles and usual-care groups at 8 months.[36] Details of the sample size were published elsewhere.[36] The planned sample size was 264 patients to ensure 70 patients per group at completion. The sample size was adjusted to 276 during year 4 to account for withdrawals. Patients who completed baseline interviews were randomly assigned as planned in the randomization scheme and analyzed in the group to which they were originally assigned (intention to treat).

Descriptive statistics were computed for all variables, scores were examined for outliers, and density plots were evaluated for variable distributions. Baseline comparisons were evaluated for demographic and clinical variables among the 3 groups using analysis of variance (ANOVA) and the Fisher's exact and χ^2 tests.

Mixed effects models were conducted to test the hypotheses for the 5 outcome measures collected at baseline, 10 weeks, and 4 and 8 months. The main effect for each group was not included in the models in order to enforce the equal group mean assumption at baseline, given the RCT design.[58] Time and group-by-time interactions were included in the mixed models while controlling for the stratifying variables of gender and MoCA with an unstructured covariance matrix. Comparisons were conducted among the 3 group means at each postrandomization time 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 alpha < .05.

A sensitivity analysis was conducted using multiple imputation to evaluate the influence of missing follow-up data on study outcomes, particularly missing data because of the coronavirus disease 2019 (COVID-19). During year 4, month 9, of the study (March 2020), the COVID-19 pandemic began in the state, and face-to-face research visits were prohibited. The patients in the computerized-intervention groups continued to complete them, and the nurse-enhancement interventions continued to be delivered by telephone. The protocol was modified to change follow-up data collection from face-to-face to telephone interviews. The modified protocol received emergency approval from the institutional review board and was initiated on March 16, 2020. The COVID-19 restrictions necessitated a change in 4 outcome measures that required face-to-face administration. This change resulted in missing data for a subset of patients. The numbers of patients who withdrew or were lost to follow-up

are provided in Fig. 1. COVID-19-related missing data accounted for most of the missing outcomes; the highest percentages of missing data were for CogState working memory and Everyday Problems Test IADLs, and serum BDNF (all 24.5%) at the 8-month follow-up. The percentage of missing for the HVLT delayed-recall memory was 18.5% at 8-month follow-up. There were no missing values for the Living with Heart Failure Questionnaire HRQL measure.

A regression imputation approach was used to generate predicted values for those with missing outcomes by using baseline characteristics and observed outcomes with separate group means while adjusting for randomization strata.[59,60] Mixed effects models were conducted using the data generated by multiple imputations, and results were combined to provide parameter estimates and hypothesis tests results. The statistical software SAS 9.4 was used for the analyses. The significance level was alpha < .05.

Two additional sensitivity analyses were completed to further evaluate the effects of adherence to the CCT intervention on outcomes. First, a per protocol analysis was completed using mixed effects models to compare the patients in the CCT group who had 90% and higher adherence with the patients in the puzzles active control and usual-care control groups. Second, a dose/response analysis was completed using mixed effects models in the patients randomized to CCT, adjusting for age, gender, years of education, and left ventricular ejection fraction (LVEF).

Results

A total of 276 patients consented, 256 were randomized, and 233 (91%) completed the study (Fig. 1). Stratification by gender and MoCA score yielded a sample of 139 (54.3%) women and 117 (45.7%) men; the sample included 121 (47.3%) patients with normal MoCA scores and 135 (52.7%) with low MoCA scores (Table 1). The mean age was 66.4 years (SD = 12.3), and the mean education level was 13.9 years (SD = 2.6). The sample included patients with both reduced and preserved ejection fraction; mean LVEF was 49.3% (SD = 14.4). NYHA class was: I, n = 23 (9%); II, n = 96 (37.5%); III, n = 134 (52.3%); and IV, n = 1 (0.4%). Baseline comparisons are presented for the groups in Table 1. No statistically significant differences were found in baseline variables among the groups.

Intervention data are presented in Table 2. In the intervention groups, 42 (49%) of the 85 patients randomized to CCT and 57 (66%) of the 86 randomized to puzzles met the 90% adherence rate. The total time spent by intervenors on nurse-enhancement interventions was 35.2 hours for the CCT group, 34.3 hours for the puzzles group, and 23.1 hours for the usual-care group. There were no statistically significant differences in patient satisfaction with the study among patients randomized to the 3 groups ($P = 0.768$). At the final 8-month data-collection timepoint, patients were asked if they would like to receive a complimentary copy of BrainHQ access for 8 weeks from PositScience. If patients said yes, the study team member sent them a link to request the copy. Of the 233 patients who completed the study, 117 replied yes (31 in BrainHQ; 38 in puzzles; 48 in usual care); 78 replied no (29 in BrainHQ; 29 in puzzles; 20 in usual care); and 38 (12 in BrainHQ; 13 in puzzles; 13 in usual

care) did not send response. We do not know how many patients requested or used the copy because it occurred after the study's completion.

The observed means are presented for the primary and secondary outcomes for the groups in Table 3. There were no statistically significant differences in group by time interactions for the primary and secondary outcomes of HVLT-R delayed-recall scores, serum BDNF levels, CogState One Back Accuracy task, Everyday Problems Test scores, and Living with Heart Failure Questionnaire scores. However, there were statistically significant differences in time effects from baseline for all 5 outcome variables of HVLT-R delayed-recall scores ($P < .0001$), serum BDNF levels ($P = 0.0007$), CogState One Back Accuracy task ($P = 0.0495$), Everyday Problems Test ($P = 0.023$), and Living with Heart Failure scores ($P = 0.025$). The time-dependent changes were evident by 10 weeks and persisted until the end of follow-up (8 months) in the neuropsychological tests and IADL variables, the biological (ie, BDNF) variable, and the psychological HRQL variable. Post hoc analysis results comparing the predicted group means at each follow-up time are presented in Table 4. There were no significant differences among the 3 groups at any follow-up evaluations.

Results from mixed effects models are presented in Table 5, in which multiple imputation was used to compare the outcome measures at 10 weeks and at 4 and 8 months, adjusting for missing data. The primary and secondary outcomes results did not differ substantially from the results in Table 3, using observed data without imputation.

The per protocol analysis was conducted to test for the robustness of the intention-to-treat results. The findings were similar to those of the main mixed effects model analysis. Compared with patients randomized to the puzzles-active control (n = 86) and usual-care control groups (n = 85), patients randomized to CCT who had 90% and higher adherence (n = 43) had no statistically significant differences in group by time interactions for the outcomes of HVLT-R delayed-recall scores ($P = 0.456$), serum BDNF levels ($P = 0.718$), CogState One Back Accuracy task ($P = 0.646$), Everyday Problems Test scores ($P = 0.461$), or Living with Heart Failure Questionnaire scores ($P = 0.527$). Notably, the time-dependent changes remained statistically significant for 4 of the outcome variables: HVLT-R delayed-recall scores ($P < .0001$); serum BDNF levels ($P = 0.006$); Everyday Problems Test ($P = 0.004$); and Living with Heart Failure scores ($P = 0.006$). In contrast to the main results, the CogState One Back Accuracy task was not statistically significantly different over time ($P = 0.120$).

The primary and secondary outcomes did not differ with the dose or duration of the CCT intervention. Results from the dose/response analysis, conducted in patients randomized to CCT, indicated that there were no statistically significant differences in outcomes based on the time-by-dose interactions at 8 months. The P values for the time-by-dose interactions were: HVLT-R delayed-recall scores ($P = 0.355$); serum BDNF levels ($P = 0.4826$); CogState One Back Accuracy task ($P = 0.538$); Everyday Problems Test ($P = 0.316$); and Living with Heart Failure Questionnaire scores ($P = 0.915$).

Discussion

MEMOIR-HF was a well-powered RCT that examined whether a CCT intervention (BrainHQ) could improve delayed-recall memory, serum BDNF levels, working memory, IADLs, and HRQL in patients with HF. To our knowledge, it is the first intention-to-treat RCT conducted to test the efficacy of CCT in these outcomes in patients with HF. Patients in the sample had LVEFs ranging from 15% to 80% (mean, 49.3%) and nearly one-fourth (24.2%) had moderate to severe HF with LVEFs < 40%. Patients were stratified by gender and global cognitive function prior to randomization. Outcome measures were prespecified and validated. We hypothesized that compared with patients randomized to the computerized puzzles active-control and usual-care control groups, patients randomized to 8 weeks of CCT would have improved outcomes over 8 months. The hypotheses were not supported; no statistically significant group-by-time-interaction effects were found for the primary and secondary outcomes. However, consistent and statistically significant time effects were found for all 5 outcome variables beginning 10 weeks after initiation of the intervention and persisting until 8 months. Patients in all groups had statistically significant improvement over time on measures of delayed-recall memory, working memory, IADLs, and HRQL and a statistically significant decrease in serum BDNF levels. The time-dependent results were unexpected for patients with HF, given the declining trajectory of cognitive function unresponsive to known drug therapies.

The changes over time in memory and IADLs are consistent with our preliminary studies in which cognitive training and active-control interventions led to improvement over time, independent of group assignment.[21,24] In MEMOIR-HF, a larger, more diverse sample was studied; the puzzles intervention was matched to the CCT intervention in intensity and delivery mode, and the follow-up time was longer (8 months vs 12 weeks) to enable emergence of differences requiring a sustained intervention. The 5-point improvement in HRQL over time is clinically meaningful for the population with HF. It is intriguing to postulate that the MEMOIR-HF nurse-enhancement interventions drove the improvement in outcomes because it was a common denominator in all 3 groups. Patients with HF have frequent changes in clinical conditions, and nursing interventions that provide support and surveillance improve HRQL and increase the likelihood of survival.[47–49] Future studies are needed to evaluate the core elements of the nurse-enhancement interventions that may have contributed to improvements in memory and the other outcomes. The most efficacious elements of the nurse-enhancement interventions should be included into integrative medicine programs to enhance well-being in persons with HF.

The statistically significant decrease in serum BDNF levels over time in all 3 groups was surprising in directionality but indicative of the biological response to the interventions. BDNF is a complex modulator of neuronal connections and is subject to multiple stimulatory and inhibitory inputs.[34] Theoretically, BDNF stimulates neuroplasticity and might be expected to modulate improvement in cognitive function. In MEMOIR-HF, a consistent and significant decrease in BDNF was observed over a timeframe similar to the observed time-dependent improvements in memory, IADLs, and HRQL. The similar temporal changes in the biological response and neuropsychological and behavioral measures suggest a possible connection. It is intriguing to hypothesize that the improved

cognitive function may have diminished the stimuli to BDNF expression and, thereby, accounted for its directional change. Given the sparsity of serial data in conditions with a high prevalence of vascular cognitive impairment such as HF, the optimal level of serum BDNF is unclear. It is possible that memory dysfunction in HF needs to be assessed through other biomarkers that have a preeminent position over BDNF. For example, serum BDNF levels may be reflective of inflammatory processes manifest in the pathophysiology of HF,[35] and a substantive intervention may indirectly modify BDNF by altering these processes. A systematic evaluation of such factors is warranted in future studies.

One potential limitation of MEMOIR-HF was missing data, arising partially from the severe physical disability present in chronic HF and partially from COVID-19 restrictions. The overall completion rate was high, at 91%, but some outcomes data were lost because of COVID-19 restrictions, and this loss cannot be excluded as a confounder for the nonsignificant group by time differences. It seems unlikely that missing data accounted for the observed neutral primary and secondary outcomes in the interventions because sensitivity testing using multiple imputations did not alter significantly the comparisons by group and time.

A second limitation was that the adherence rates were less than 90% for some patients randomized to BrainHQ and puzzles and significantly lower for the BrainHQ group, which may have contributed to nonsignificant group-by-time results. Post hoc power analysis using sample sizes of the 3 groups in the per protocol analysis yielded 71.9% power, slightly lower than the planned power of 80% for detecting an effect size of 0.48. Sensitivity testing showed little or no change in primary or secondary outcomes based on dosage, duration of or adherence to the CCT. There were no differences in outcomes based on adherence rates in the intention to treat, per protocol or dose/response analyses. The ideal adherence rate required for efficacious cognitive training varied in past studies, but among samples of healthy older adults, 20 to 40 hours were sufficient.[30,31,41,45,61] Despite these results, it remains possible that a higher and more intensive usage of CCT might further improve outcomes in patients with HF. The lower adherence rates for BrainHQ compared with the puzzles intervention may have occurred because BrainHQ is titrated to individual cognitive performance and increases in complexity over time. There were no significant differences in patient satisfaction among the groups at the study's completion. A third limitation was that the measurement of time spent was by self-report for the computerized puzzles intervention, and the number, difficulty and completion of puzzles worked were not documented. In future studies, these factors need to be addressed actively.

Conclusions

In conclusion, CCT using BrainHQ did not improve delayed recall memory, working memory, IADLs, or HRQL when compared with the computerized crossword puzzles active-control intervention and usual care over 8 months in this sample of patients with HF. However, over time, patients in all 3 groups unexpectedly demonstrated statistically significant and, in the case of HRQL, clinically meaningful improved outcomes beginning at 10 weeks and sustained over 8 months; that was unexpected. Nurse-enhancement interventions, available to all 3 groups, may be an important explanation for the time-

dependent effects. Importantly, the findings support the fact that memory and working-memory dysfunction, IADLs, and HRQL do not invariably decline but are amenable to an available intervention. Clinicians caring for patients with HF need to be aware that more than 50% of patients with HF may have memory dysfunction and need assistance in learning and performing IADLs. Patients need to be assessed for memory dysfunction at HF diagnosis and routinely afterwards. Family members should be included in patients' care to facilitate adequate IADLs. Future studies are needed to examine the most efficacious nurse-enhancement interventions and test them in combination with other cognitive interventions. Further characterization of biomarkers associated with memory dysfunction may provide an independent means of assessing cognitive dysfunction and its changes with efficacious therapies.

Acknowledgments

References

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. AHA Statistics Committee & Stroke Statistics Subcommittee. Heart disease and stroke statistics 2020 update: a report from the American Heart Association. Circulation 2020;141: e139–596. [PubMed: 31992061]

2. Pressler SJ, Subramanian U, Kareken D, Perkins SM, Gradus-Pizlo I, Sauve MJ, et al. Cognitive deficits in chronic heart failure. Nurs Res 2010;59:127–39. [PubMed: 20216015]

3. Cannon JA, Moffitt P, Perez-Moreno AC, Walters MR, Broomfield NM, McMurray JJV, et al. Cognitive impairment and heart failure: systematic review and meta-analysis. J Card Fail 2017;23:464–75. [PubMed: 28433667]

4. Ampadu J, Morley JE. Heart failure and cognitive dysfunction. Int J Cardiol 2015;178:12–23. [PubMed: 25464210]

5. Pressler SJ, Kim J, Riley P, Ronis DL. Gradus-Pizlo I. Memory dysfunction, psychomotor slowing, and decreased executive function predict mortality in patients with heart failure and low ejection fraction. J Card Fail 2010;16:750–60. [PubMed: 20797599]

6. Kumar R, Woo MA, Birrer BVX, Macey PM, Fonarow GC, Hamilton MA, et al. Mammillary bodies and fornix fibers are injured in heart failure. Neurobiol Dis 2009;33:236–42. [PubMed: 19022386]

7. Woo MA, Kumar R, Macy PM, Fonarow GC, Harper RM. Brain injury in autonomic, emotional, and cognitive regulatory areas in patients with heart failure. J Card Fail 2009;15:214–23. [PubMed: 19327623]

8. Kumar R, Woo MA, Macey PM, Fonarow GC, Hamilton MA, Harper RM. Brain axonal and myelin evaluation in heart failure. N Neurol Sci 2011;307:106–13.

9. Woo MA, Yadav SK, Macey PM, Fonarow GC, Harper RM, Kumar R. Brain metabolites in autonomic regulatory insular sites in heart failure. J Neurol Sci 2014;346:271–5. [PubMed: 25248953]

10. Kumar R, Yadav SK, Palomares JA, Park B, Joshi SH, Ogren JA, et al. Reduced regional brain cortical thickness in patients with heart failure. PLoS One 2015;10: e0126595. [PubMed: 25962164]

11. Woo MA, Ogren JA, Abouzeid CM, Macey PM, Sairafian KG, Saharan PS, et al. Regional hippocampal damage in heart failure. Eur J Heart Fail 2015;17:494–500. [PubMed: 25704495]

12. Woo MA, Palomares JA, Macey PM, Fonarow GC, Harper RM, Kumar R. Global and regional brain mean diffusivity changes in patients with heart failure. J Neurosci Res 2015;93:678–85. [PubMed: 25502071]

13. Siachos T, Vanbakel A, Feldman D, Uber W, Simpson KN, Pereira NL. Silent strokes in patients with heart failure. J Card Fail 2005;11:485–9. [PubMed: 16198241]

14. Frey A, Sell R, Homola GA, Malsch C, Kraft P, Gunreben I, et al. Cognitive deficits and related brain lesions in patients with chronic heart failure. J Am Coll Cardiol Heart Failure 2018;6:583–92.

15. Mueller K, Thiel F, Beutner F, Teren A, Frisch S, Ballarini T, et al. Brain damage with heart failure. Circ Res 2020;126:750–64. [PubMed: 31969053]

16. Alosco ML, Hayes SM. Structural brain alterations in heart failure: a review of the literature and implications for risk of Alzheimer's disease. Heart Fail Rev 2015;20:561–71. [PubMed: 25896528]

17. Roy B, Woo MA, Wang DJJ, Fonarow GC, Harper RM, Kumar R. Reduced regional cerebral blood flow in patients with heart failure. Eur J Heart Fail 2017;19:1294–302. [PubMed: 28560737]

18. Alosco ML, Spitznagel MB, Coohen R, Sweet LH, Colbert LH, Josephson R, et al. Cognitive impairment is independently associated with reduced instrumental activities of daily living in persons with heart failure. J Cardiovasc Nurs 2012;27:44–50. [PubMed: 21558863]

19. Bennett SJ, Cordes DK, Westmoreland G, Castro R, Donnelly E. Self-care strategies for symptom management in patients with chronic heart failure. Nurs Res 2000;49:139–45. [PubMed: 10882318]

20. Sloan RS, Pressler SJ. Cognitive deficits and chronic heart failure: re-cognition of vulnerability as a strange new world. J Cardiovasc Nurs 2009;24:241–8. [PubMed: 19390342]

21. Pressler SJ, Therrien B, Riley PL, Chou CC, Ronis DL, Koelling TM, et al. Nurse-enhanced memory intervention in heart failure: tthe MEMOIR Study. J Card Fail 2011;17:832–43. [PubMed: 21962422]

22. Ellis MI, Edwards JD, Peterson L, Roker R, Athilingam P. Effects of cognitive speed of processing training among older adults with heart failure. J Aging Health 2014;26:600–15. [PubMed: 24681975]

23. Athilingam P, Edwards JD, Vakles EG, Ji M, Guglin M. Computerized auditory cognitive training to improve cognition and functional outcomes in patients with heart failure: results of a pilot study. Heart Lung 2015;44:120–8. [PubMed: 25592205]

24. Pressler SJ, Titler M, Koelling TM, Riley PL, Jung M, Hoyland-Domenico L, et al. Nurse-enhanced computerized cognitive training increases serum brain-derived neurotropic factor levels and improves working memory in heart failure. J Card Fail 2015;21: 630–41. [PubMed: 25982826]

25. Kua ZJ, Valenzuela M, Dong Y. Can computerized cognitive training improve cognition in patients with heart failure? A review. J Cardiovasc Nurs 2019;34:E19–27. [PubMed: 30585868]

26. Gary RA, Paul S, Corwin E, Butts B, Miller AH, Hepburn K, et al. Exercise and cognitive training as a strategy to improve neurocognitive outcomes in heart failure: a pilot study. Am J Geriatr Psychiatr 2019;27:809–19.

27. Cameron JD, Gallagher R, Pressler SJ, McLennan SN, Ski CF, Tofler G, et al. Sensitivity and specificity of a five-minute cognitive screen in heart failure patients. J Card Fail 2016;22:99–107. [PubMed: 26386450]

28. Patel A, Parikh R, Howell EH, Hsich E, Landers SH, Gorodeski EZ. Mini-Cog performance: novel marker of post discharge risk among patients hospitalized for heart failure. Circ Heart Fail 2015;8:8–16. [PubMed: 25477431]

29. Merzenich MM, Van Vleet TM, Nahum M. Brain plasticity-based therapeutics. Front Hum Neurosci 2014;8:1–16. [PubMed: 24474914]

30. Lampit A, Hallock H, Valenzuela M. Computerized cognitive training in cognitively healthy older adults: a systematic review and meta-analysis of effect modifiers. PLoS Med 2014;11:e1001756. [PubMed: 25405755]

31. Hill NTM, Mowszowski L, Naismith SL, Chadwick VL, Valenzuela M, Lampit A. Computerized cognitive training in older adults with mild cognitive impairment or dementia: a systematic review and meta-analysis. Am J Psychiatry 2017;174:329–40. [PubMed: 27838936]

32. Ernfors P, Lee KF, Jaenisch R. Mice lacking brain-derived neurotrophic factor develop sensory deficits. Nature 1994;368:147–50. [PubMed: 8139657]

33. Erickson KI, Prakash RS, Voss MW, Chaddock L, Heo S, McLaren M, et al. Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. J Neurosci 2010;30:5368–75. [PubMed: 20392958]

34. Miranda M, Morici JF, Zanoni MB, Bekinschtein P. Brain-derived neurotrophic factor: a key molecule for memory in the healthy and the pathological brain. Front Cell Neurosci 2019;13:363. [PubMed: 31440144]

35. Halloway S, Jung M, Yeh A, Liu J, McAdams E, Barley M, et al. An integrative review of BDNF and serious cardiovascular conditions. Nurs Res 2020;69:376–90. [PubMed: 32555009]

36. Pressler SJ, Giordani B, Titler M, Gradus-Pizlo I, Smith D, Dorsey SG, et al. Design and rationale of the Cognitive Intervention to Improve Memory in Heart Failure Patients Study. J Cardiovasc Nurs 2018;33:344–55. [PubMed: 29601367]

37. Nasreddine Z, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695–9. [PubMed: 15817019]

38. Johns EK, Phillips NA, Chertkow H, Bergman L, Solomon S, Desormeau J, et al. The Montreal Cognitive Assessment: normative data in the community. J Int Neuropsychol Soc 2008;41(Suppl 1):58.

39. Mahncke HW, Bronstone A, Merzenich MM. Brain plasticity and functional losses in the aged: scientific bases for a novel intervention. Prog Brain Res 2006;157:81–109. [PubMed: 17046669]

40. Mahncke HW, Connor BB, Appelman J, Ahsanuddin ON, Hardy JL, Wood RA, et al. Memory enhancement in healthy older adults using a brain plasticity-based training program: a randomized, controlled study. Prog Natl Acad Sci USA 2006;103:12523–8.

41. Smith GE, Housen P, Yaffe K, Ruff R, Kennison RF, Mahncke HW, et al. A cognitive training program based on principles of brain plasticity: results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) Study. JAGS 2009;57:594–603.

42. Gage FH. Brain, repair yourself. Sci Am 2009;283:46–63.

43. Valenzuela M, Sachdev P. Can cognitive exercise prevent the onset of dementia? Systematic review of randomized clinical trials with longitudinal follow-up. Am J Geriatr Psychiatry 2009;17:179–87. [PubMed: 19225276]

44. Takeuchi H, Sekiguchi A, Taki Y, Yokoyama S, Yomogida Y, Komuro N, et al. Training of working memory impacts structural connectivity. J Neurosci 2010;30:3297–303. [PubMed: 20203189]

45. Wolinsky FD, Vander Weg MW, Howren MB, Jones MP, Dotson MM. A randomized controlled trial of cognitive training using a visual speed of processing intervention in middle-aged and older adults. PLoS One 2013;8:e61624. [PubMed: 23650501]

46. Wolinsky FD, Vander Weg MW, Howren MB, Jones MP, Martin R, Luger TM, et al. Interim analyses from a randomized controlled trial to improve visual processing speed in older adults: the Iowa Healthy and Active Minds Study. BMJ Open 2011;1:e000225.

47. Naylor MD, Brooten DA, Campbell RL, Maislin G, McCauley KM, Schwartz JS. Transitional care of older adults hospitalized with heart failure: a randomized, controlled trial. J Am Geriatr Soc 2004;52:675–84. [PubMed: 15086645]

48. Sochalski J, Jaarsma T, Krumholz HM, Laramee A, McMurray JJV, Naylor MD, et al. What works in chronic care management: the case of heart failure. Health Aff 2009;28:179–89.

49. Koelling TM, Johnson ML, Cody RJ, Aaronson KD. Discharge education improves clinical outcomes in patients with chronic heart failure. Circulation 2005;111:179–85. [PubMed: 15642765]

50. Bennett SJ, Litzelman DK, Wright A, Perkins SM, Wu J, Meyer L, et al. The PUMP UP tailored computerized program for heart failure care. Nurs Outlook 2006;54:39–45. [PubMed: 16487779]

51. Borrelli B, Sepinwall D, Ernst D, Bellg AJ, Czajkowski S, Breger R, et al. A new tool to assess treatment fidelity and evaluation of treatment fidelity across 10 years of health behavior research. J Consult Clin Psychol 2005;73:852–60. [PubMed: 16287385]

52. Benedict RH, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test-Revised. Clin Neuropsychol 1998;12:43–55.

53. Maruff P Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. Arch Clin Neuropsychol 2009;24:165–78. [PubMed: 19395350]

54. Willis SL, Marsiske M. Manual for Everyday Problems Test. University Park, PA: Pennsylvania State University; 1993.

55. Rector TS, Kubo SH, Cohn JN. Patients' self-assessment of their congestive heart failure, part 2: content, reliability and validity of a new measure, the Minnesota Living with Heart Failure Questionnaire. Heart Fail 1987;3:198–209.

56. Rector TS, Tschumperlin LK, Spencer K, Bank AJ, Francis GS, McDonald KM, et al. Use of the Living with Heart Failure Questionnaire to ascertain patients' perspectives on improvement in quality of life versus risk of drug-induced death. J Card Fail 1995;1:201–6. [PubMed: 9420652]

57. Northouse LL, Walker J, Schafenacker A, Mood D, Mellon S, Galvin E, et al. A family-based program of care for women with recurrent breast cancer and their family members. Oncol Nurs Forum 2002;29:1411–9. [PubMed: 12432412]

58. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. 2nd ed Hoboken, NJ: J. Wiley; 2011.

59. Tang L, Song J, Belin TR, Unutzer J. A comparison of imputation methods in a longitudinal randomized clinical trial. Stat Med 2005;24:2111–28. [PubMed: 15889392]

60. Little RJA, Rubin DB. Statistical Analysis with Missing Data. 2nd ed Hoboken, NJ: J. Wiley; 2002.

61. Lee HK, Kent JD, Wendel C, Wolinsky FD, Foster ED, Merzenich MM, et al. Home-based, adaptive cognitive training for cognitively normal older adults: initial efficacy trial. J Gerontol B Psychol Sci Soc Sci 2020;75:1144–54. [PubMed: 31140569]
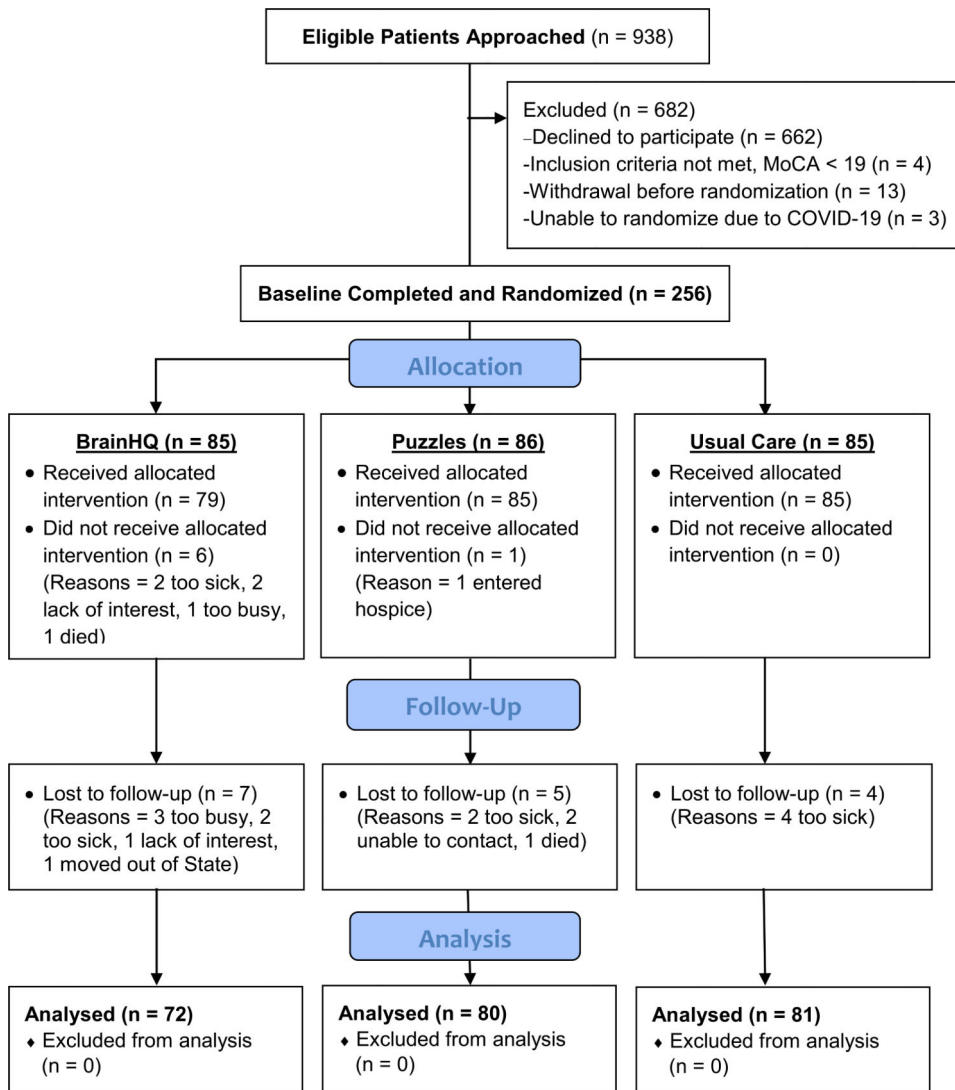
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Fig. 1.
Diagram of the Cognitive Intervention to Improve Memory in Heart Failure Patients (MEMOIR-HF CONSORT) study.

Table 1.

Baseline Demographic and Clinical Characteristics by Group (n = 256)

Characteristic	Overall (n = 256)	BrainHQ (n = 85)	Puzzles (n = 86)	Usual Care (n = 85)	P Value
Age, y, mean ± SD	66.4 ± 12.3	67.1 ± 12.9	66.8 ± 12.2	65.2 ± 11.9	.544[a]
Sex, n (%)					.972[b]
Men	117 (45.7)	39 (45.9)	40 (46.5)	38 (44.7)	
Women	139 (54.3)	46 (54.1)	46 (53.5)	47 (55.3)	
Race, n (%)					.560[c]
Asian	1 (0.4)	0 (0)	1 (1.2)	0 (0)	
Native Hawaiian/Pacific Islander	1 (0.4)	0 (0)	0 (0)	1 (1.2)	
Black/African American	37 (14.5)	11 (12.9)	11 (12.8)	15 (17.7)	
White	216 (84.4)	74 (87.1)	74 (86.1)	68 (80.0)	
More than 1 race	1 (0.4)	0 (0)	0 (0)	1 (1.2)	
Ethnicity, n (%)					.649[c]
Hispanic or Latino	4 (1.6)	2 (2.4)	1 (1.2)	1 (1.2)	
Non-Hispanic or Latino	251 (98.1)	82 (96.5)	85 (98.8)	84 (98.8)	
Unknown	1 (0.4)	1 (1.2)	0 (0)	0 (0)	
Marital status, n (%)					.825[b]
Married	133 (52.0)	42 (49.4)	45 (52.3)	46 (54.1)	
Not married	123 (48.1)	43 (50.6)	41 (47.7)	39 (45.9)	
Education, y, mean ± SD	13.9 ± 2.6	13.8 ± 2.9	13.9 ± 2.5	14.0 ± 2.4	.928[a]
LVEF, %, mean ± SD	49.3 ± 14.4	48.9 ± 14.5	49.3 ± 14.1	49.5 ± 14.6	.965[a]
LVEF, n (%)					.872[c]
Normal 50%	139 (54.3)	48 (56.5)	47 (54.7)	44 (51.8)	
Moderately reduced 40–49%	53 (20.7)	14 (16.5)	19 (22.1)	20 (23.5)	
Reduced < 40%	62 (24.2)	22 (25.9)	19 (22.1)	21 (24.7)	
Missing	2 (0.8)	1 (1.2)	1 (1.2)	0 (0.0)	
NYHA class, n (%)					.124[c]

Characteristic	Overall (n = 256)	BrainHQ (n = 85)	Puzzles (n = 86)	Usual Care (n = 85)	P Value
I	23 (9.0)	9 (10.6)	6 (7.0)	8 (9.4)	
II	96 (37.5)	26 (30.6)	29 (33.7)	41 (48.2)	
III	134 (52.3)	48 (56.5)	51 (59.3)	35 (41.2)	
IV	1 (0.4)	1 (1.2)	0 (0)	0 (0)	
Missing	2 (0.8)	1 (1.2)	0 (0)	1 (1.2)	
Medications, n (%)					
ACE inhibitor	85 (33.2)	24 (28.2)	29 (33.7)	32 (37.7)	.425[b]
ARB	63 (24.6)	27 (31.8)	16 (18.6)	20 (23.5)	.131[b]
ARNI	17 (6.6)	5 (5.9)	5 (5.8)	7 (8.2)	.770[b]
Beta-adrenergic blocker	213 (83.2)	74 (87.1)	71 (82.6)	68 (80.0)	.460[b]
Diuretic	199 (77.7)	68 (80.0)	66 (76.7)	65 (76.5)	.827[b]
Aldosterone antagonist	69 (27.0)	26 (30.6)	23 (26.7)	20 (23.5)	.583[b]
SGLT-2 inhibitor	6 (2.3)	2 (2.4)	2 (2.3)	2 (2.4)	1.000[b]
Anticoagulant-warfarin	51 (19.9)	12 (14.1)	21 (24.4)	18 (21.2)	.227[b]
Antiplatelet	57 (22.3)	20 (23.5)	20 (23.3)	17 (20.0)	.827[b]
Factor Xa inhibitor	61 (23.8)	18 (21.2)	22 (25.6)	21 (24.7)	.775[b]
Thrombin inhibitor	4 (1.6)	2 (2.4)	0 (0)	2 (2.4)	.401[c]
Antidepressant	85 (33.2)	24 (28.2)	33 (38.4)	28 (32.9)	.371[b]
Anxiolytic/sedative/hypnotic	26 (10.2)	11 (12.9)	10 (11.6)	5 (5.9)	.269[b]
History comorbid condition, n (%)					
Atrial fibrillation	110 (43.0)	33 (38.8)	41 (47.7)	36 (42.4)	.500[b]
Hypertension	210 (82.0)	71 (83.5)	70 (81.4)	69 (81.2)	.907[b]
Coronary artery disease	112 (43.8)	36 (42.4)	39 (45.4)	37 (43.5)	.924[b]
Coronary artery bypass graft	51 (19.9)	17 (20.0)	21 (24.4)	13 (15.3)	.328[b]
Depression	50 (19.5)	19 (22.4)	13 (15.1)	18 (21.2)	.440[b]

Characteristic	Overall (n = 256)	BrainHQ (n = 85)	Puzzles (n = 86)	Usual Care (n = 85)	P Value
Diabetes	117 (45.7)	42 (49.4)	39 (45.4)	36 (42.4)	.651[b]
Myocardial infarction	50 (19.5)	14 (16.5)	19 (22.1)	17 (20.0)	.645[b]
Sudden cardiac arrest	6 (2.3)	2 (2.4)	2 (2.3)	2 (2.4)	1.000[c]
Stroke	24 (9.4)	6 (7.1)	9 (10.5)	9 (10.6)	.669[b]
Transient ischemic attack	11 (4.3)	5 (5.9)	4 (4.7)	2 (2.4)	.555[c]
Ventricular arrhythmias	40 (15.6)	13 (15.3)	13 (15.1)	14 (16.5)	.966[b]
MoCA at enrollment, mean ± SD	25.3 ± 2.5	25.4 ± 2.6	25.1 ± 2.6	25.4 ± 2.5	.683[a]
Normal, mean ± SD	27.5 ± 1.2	27.5 ± 1.3	27.4 ± 1.3	27.5 ± 1.1	.809[a]
Low, mean ± SD	23.3 ± 1.6	23.4 ± 1.6	23.1 ±1.6	23.5 ± 1.6	.518[a]
PHQ-8, mean ± SD	5.9 ± 5.0	5.9 ± 4.7	6.0 ± 5.8	5.7 ± 4.5	.913[a]

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocking agent; ARNI, angiotensin receptor-neprilysin inhibitor; LVEF, left ventricular ejection fraction; MoCA, Montreal Cognitive Assessment; NYHA, New York Heart Association; PHQ-8, Patient Health Questionnaire-8; SGLT-2, sodium-glucose co-transporter-2.

[a] Analysis of variance

[b] χ^2 test.

[c] Fisher's exact test.

Table 2.

Intervention Variables

Variables	BrainHQ (n = 85)	Puzzles (n = 86)	Usual Care (n = 85)	P value
Computerized interventions				
Adherence in hours, mean ± SD	24.9 ± 14.6	38.7 ± 17.0	N/A	< .0001[a]
Adherence 90%, n (%)	42 (49%)	57 (66%)	N/A	.026[b]
Nurse-enhancement interventions				
Total time spent on telephone calls in minutes, mean ± SD	35.2 ± 19.9[d]	34.3 ± 20.3	23.1 ± 9.6	< .0001[c]

SD, standard deviation.

[a] *t* test

[b] χ^2 test

[c] Analysis of variance

[d] n = 83

Table 3.

Mixed Effects Models Results for Outcome Variables Adjusted for Stratified Variables of Gender and MoCA (n = 256)

Visit	Observed Means and Standard Deviations			Mixed Models *P* Value	
	BrainHQ (n = 85)	Puzzles (n = 86)	Usual Care (n = 85)	Time	Group × Time
Hopkins Verbal Learning Test–Revised, Delayed Recall				<.0001	.753
Baseline	8.8 ± 2.7	8.4 ± 2.7	8.7 ± 2.5		
10 weeks	9.2 ± 3.0	9.0 ± 2.5	9.1 ± 2.7		
4 months	9.9 ± 2.3	9.4 ± 2.4	9.9 ± 2.0		
8 months	9.5 ± 2.3	9.7 ± 2.4	9.9 ± 1.9		
Serum BDNF, ng/mL				.0007	.709
Baseline	19.2 ± 7.4	17.5 ± 7.8	18.3 ± 7.8		
10 weeks	16.8 ± 8.1	15.9 ± 8.8	16.3 ± 9.0		
4 months	16.8 ± 8.4	16.9 ± 8.8	15.9 ± 8.4		
8 months	16.2 ± 7.7	14.5 ± 8.8	16.2 ± 7.4		
CogState One Back Accuracy				.049	.839
Baseline	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.2		
10 weeks	1.3 ± 0.2	1.3 ± 0.3	1.3 ± 0.2		
4 months	1.3 ± 0.2	1.3 ± 0.3	1.3 ± 0.2		
8 months	1.3 ± 0.3	1.3 ± 0.2	1.3 ± 0.2		
Everyday Problems Test				.023	.263
Baseline	27.1 ± 4.4	26.1 ± 4.8	26.4 ± 4.9		
10 weeks	27.4 ± 4.8	27.5 ± 4.6	27.6 ± 4.6		
4 months	27.8 ± 3.9	26.7 ± 5.2	27.5 ± 4.7		
8 months	27.4 ± 3.8	27.5 ± 5.2	28.5 ± 3.2		
LHFQ				.025	.648
Baseline	30.2 ± 23.0	34.0 ± 24.2	32.6 ± 21.6		
10 weeks	28.8 ± 22.5	29.5 ± 23.1	29.0 ± 21.6		
4 months	30.7 ± 25.8	28.8 ± 23.7	31.1 ± 22.6		
8 months	31.6 ± 26.5	29.6 ± 23.4	32.2 ± 25.4		

BDNF, brain-derived neurotrophic factor; LHFQ, Living with Heart Failure Questionnaire; MoCA, Montreal Cognitive Assessment; ng/ml, nanogram per milliliter

Table 4.

Post hoc Comparisons of Mixed Effects Models Results for Outcome Variables at 10 Weeks and 4 and 8 Months (n = 256)

Visit	Predicted Means and 95% Confidence Intervals			P Value
	BrainHQ (n = 85)	Puzzles (n = 86)	Usual Care (n = 85)	
Hopkins Verbal Learning Test–Revised, Delayed Recall				
10 weeks	8.9 (8.3 to 9.4)	8.9 (8.3 to 9.4)	8.9 (8.6 to 9.3)	.819
4 months	9.4 (8.9 to 9.9)	9.4 (8.9 to 9.9)	9.5 (9.2 to 9.8)	.578
8 months	9.3 (8.8 to 9.7)	9.5 (9.1 to 10.0)	9.5 (9.2 to 9.8)	.222
Serum BDNF, ng/mL				
10 weeks	16.5 (14.8 to 18.2)	17.0 (15.3 to 18.7)	16.7 (15.5 to 17.8)	.851
4 months	16.8 (15.0 to 18.6)	17.9 (16.3 to 19.6)	17.1 (15.9 to 18.3)	.367
8 months	16.6 (14.7 to 18.5)	16.0 (14.3 to 17.8)	16.5 (15.4 to 17.7)	.694
CogState One Back Accuracy				
10 weeks	1.3 (1.2 to 1.3)	1.3 (1.3 to 1.4)	1.3 (1.3 to 1.3)	.543
4 months	1.3 (1.3 to 1.4)	1.3 (1.3 to 1.4)	1.3 (1.3 to 1.4)	.647
8 months	1.3 (1.2 to 1.3)	1.3 (1.3 to 1.4)	1.3 (1.3 to 1.3)	.407
Everyday Problems Test				
10 weeks	26.7 (25.8 to 27.6)	27.4 (26.6 to 28.3)	27.3 (26.7 to 27.9)	.099
4 months	26.9 (26.0 to 27.9)	26.9 (26.0 to 27.8)	27.1 (26.5 to 27.7)	.615
8 months	26.4 (25.4 to 27.4)	27.2 (26.3 to 28.2)	27.1 (26.5 to 27.7)	.092
LHFQ				
10 weeks	29.3 (25.4 to 33.2)	29.2 (25.4 to 33.1)	28.9 (26.2 to 31.7)	.882
4 months	31.2 (26.7 to 35.6)	27.0 (22.8 to 31.3)	29.5 (26.5 to 32.4)	.293
8 months	32.1 (27.3 to 36.9)	28.7 (24.2 to 33.3)	30.7 (27.6 to 33.8)	.529

BDNF, brain-derived neurotrophic factor; LHFQ, Living with Heart Failure Questionnaire; ng/mL, nanogram per milliliter.

Table 5.

Post hoc Comparisons of Mixed Effects Models Multiple Imputation Results for Outcome Variables at 10 Weeks and 4 and 8 Months (n = 256)

Visit	Predicted Means and 95% Confidence Intervals			P Value
	BrainHQ (n = 85)	Puzzles (n = 86)	Usual Care (n = 85)	
Hopkins Verbal Learning Test–Revised, Delayed Recall				
10 weeks	9.0 (8.5 to 9.6)	9.0 (8.5 to 9.5)	9.0 (8.7 to 9.4)	.912
4 months	9.5 (9.0 to 10.0)	9.3 (8.8 to 9.8)	9.5 (9.2 to 9.8)	.452
8 months	9.2 (8.7 to 9.6)	9.5 (9.0 to 9.9)	9.4 (9.1 to 9.7)	.299
Serum BDNF, ng/mL				
10 weeks	16.4 (14.6 to 18.3)	16.6 (14.8 to 18.4)	16.5 (15.3 to 17.6)	.796
4 months	16.6 (14.5 to 18.6)	17.3 (15.5 to 19.1)	16.6 (15.5 to 17.8)	.491
8 months	16.1 (14.1 to 18.0)	15.3 (13.4 to 17.2)	15.9 (14.8 to 17.1)	.475
CogState One Back Accuracy				
10 weeks	1.3 (1.3 to 1.3)	1.3 (1.3 to 1.4)	1.3 (1.3 to 1.3)	.750
4 months	1.3 (1.3 to 1.4)	1.3 (1.3 to 1.4)	1.3 (1.3 to 1.3)	.703
8 months	1.3 (1.2 to 1.3)	1.3 (1.3 to 1.4)	1.3 (1.3 to 1.3)	.627
Everyday Problems Test				
10 weeks	26.8 (25.9 to 27.7)	27.4 (26.5 to 28.3)	27.3 (26.7 to 27.9)	.219
4 months	27.1 (26.0 to 28.1)	26.9 (25.9 to 27.8)	27.1 (26.5 to 27.7)	.583
8 months	26.7 (25.7 to 27.7)	27.1 (26.2 to 28.1)	27.3 (26.7 to 27.8)	.147
LHFQ				
10 weeks	30.9 (26.7 to 35.1)	28.9 (24.7 to 33.1)	29.4 (26.6 to 32.2)	.506
4 months	31.8 (27.3 to 36.3)	27.1 (22.7 to 31.4)	29.9 (26.9 to 32.8)	.208
8 months	33.1 (28.4 to 37.9)	28.2 (23.6 to 32.8)	31.0 (28.0 to 34.0)	.258

BDNF, brain-derived neurotrophic factor; LHFQ, Living with Heart Failure Questionnaire; ng/mL, nanogram per milliliter.