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Design and Rationale of the Cognitive Intervention to Improve Memory in Heart Failure Patients (MEMOIR-HF) Study

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Abstract

Background—Memory loss is an independent predictor of mortality among heart failure (HF) patients. Twenty-three to 50% of HF patients have comorbid memory loss but few interventions are available to treat the memory loss. The aims of this three-arm randomized controlled trial are to: 1) evaluate efficacy of computerized cognitive training intervention using BrainHQ to improve primary outcomes of memory and serum brain-derived neurotrophic factor (BDNF) levels and secondary outcomes of working memory, instrumental activities of daily living, and health-related quality of life among HF patients; 2) evaluate incremental cost-effectiveness of BrainHQ; and 3) examine depressive symptoms and genomic moderators of BrainHQ effect.

Methods—A sample of 264 HF patients within four equal sized blocks (baseline cognitive function normal/low and gender) will be randomly assigned to: 1) BrainHQ; 2) active control computer-based crossword puzzles; and 3) usual care control groups. BrainHQ is an 8 week, 40-hour program individualized to each patient's performance. Data collection will be completed at baseline and at 10 weeks, 4 months and 8 months. Descriptive statistics, mixed model analyses, and cost-utility analysis using intent-to-treat approach will be computed.

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Conclusions—This research will provide new knowledge about efficacy of BrainHQ to improve memory and increase serum BDNF levels in HF. If efficacious, the intervention will provide a new therapeutic approach that is easy to disseminate to treat a serious comorbid condition of HF.

Keywords

computerized cognitive training; cognitive dysfunction; brain-derived neurotrophic factor; *apolipoprotein (APOE)-ε4*

Among the 6.5 million Americans with heart failure (HF),[1] 23 to 50% have comorbid cognitive dysfunction, including memory loss likely resulting from cerebral hypoperfusion and injury to the hippocampus and related structures.[2–7] Pressler and colleagues[2] found that among 249 HF patients 23% had memory dysfunction and 19% had working memory dysfunction. Memory is a foundational cognitive process central to survival and well-being. Memory loss interferes with patients' ability to perform instrumental activities of daily living (IADL) that are essential for independent living,[8] diminishes health-related quality of life (HRQL),[9] and independently predicts mortality[10] and cardiovascular events.[11,12]

Despite high prevalence and severe consequences of memory loss in HF, there are no widely accepted evidence-based therapies to improve memory in HF patients.[13] Prior to the publication of our preliminary work,[14,15] there were few studies in which interventions were tested to improve memory in HF that had potential for widespread dissemination[16–21] and these studies were limited by not targeting memory,[16–21] lack of control groups,[16–18,20] lack of inclusion of variables that may moderate intervention effect (e.g., depressive symptoms, genotype),[16–21] and small, primarily male samples.[16–19,21] In addition, apart from our preliminary study,[15] none of these intervention studies measured depressive symptoms or serum or genomic biomarkers to evaluate intervention response and determine which patients might benefit the most from this intervention.

The purpose of this article is to present the design and rationale of the three-arm randomized controlled trial titled "Cognitive Intervention to Improve Memory in Heart Failure Patients" (MEMOIR-HF). Previously, in two randomized controlled pilot studies (n = 40 and n = 27 HF patients)[14,15,22] preliminary evidence was found of efficacy and incremental cost-effectiveness when using the scientifically based, easily disseminated, computerized cognitive training program Brain Fitness, now part of BrainHQ.[23] In these studies, HF patients who completed training had improved delayed recall memory (effect size [ES] = 0.75),[14] improved working memory (ES = 0.64),[15] and a trend of lower healthcare costs ($3821 vs $7730)[22] 12 weeks after baseline. In addition, patients who completed training in the second preliminary study had increased (improved) serum brain-derived neurotrophic factor (BDNF) levels (ES = 1.21),[15] A full-scale efficacy study will now be conducted among a larger, more diverse sample of HF patients without a diagnosis of dementia.

MEMOIR-HF has three specific aims and six hypotheses. Aim one is to evaluate the efficacy of BrainHQ among HF patients. Aim one hypotheses are:

> Compared with active control and usual care control groups, HF patients who receive BrainHQ will have greater improvement over time (10 weeks, 4 and 8 months) in:

H.1.1. delayed recall memory (primary outcome);

H.1.2. (increased) serum BDNF levels (co-primary outcome);

H.1.3. working memory (secondary outcome);

H.1.4. instrumental activities of daily living (secondary outcome); and

H.1.5. health-related quality of life (secondary outcome).

Aim two is to evaluate the incremental cost-effectiveness of BrainHQ among HF patients. The aim two hypothesis is: H.2.1. Using an 8-month time horizon and from societal and healthcare payer(s) perspectives, BrainHQ will be a cost-effective option in terms of dollars per quality-adjusted life years (QALYs) gained compared with control groups at a willingness to pay of $50,000 per QALY. Aim three is an exploratory aim to examine depressive symptoms, *BDNF* genotype of the *Val66Met* polymorphism, and *apolipoprotein (APOE)-ε4* allele as moderators of BrainHQ effect on primary and secondary outcomes.

Methods

Study Design

The MEMOIR-HF study (R01 NR016116; Clinical Trials.gov identifier NCT 03035565) is a three-arm randomized controlled trial designed to compare computerized cognitive training using BrainHQ (commercially available from Posit Science) with computerized general cognitive stimulation with crossword puzzles (active control) and usual care with no computerized cognitive stimulation (usual care) among 264 patients with HF (Figure 1). The study was approved by the university institutional review board. All patients will provide written informed consent prior to any data collection.

Study Population

The sample will be 264 men and women with HF recruited from multidisciplinary HF and cardiology outpatient clinics at a large health system and a small health system in the Midwest. Inclusion and exclusion criteria are presented in Table 1. The criteria were developed to ensure that enrolled patients have HF, are receiving guideline-derived medical therapy based on national clinical practice guidelines, can complete the computerized interventions, and do not have a diagnosis of dementia or other known major causes of memory loss. The rationale was established for the exclusion criterion cutoff score of MoCA < 19 based on empirical data[24] and preliminary studies.[14,15] Trzepacz and colleagues[24] evaluated sensitivity and specificity of MoCA cutoff scores to detect mild cognitive impairment. The sample was 618 cases from the Alzheimer Disease Neuroimaging Initiative (ADNI-GO and ADNI-2) databases and included 219 cognitively healthy control participants, 299 participants with mild cognitive impairment, and 100 participants with Alzheimer Disease. A MoCA score of < 19 was identified by Trzepacz and colleagues as appropriate to use as a screening cutoff because it would allow for inclusion of as many people as possible with mild cognitive impairment but not dementia. A MoCA score of < 19 had sensitivity of 87.3 and specificity of 77.0 for detecting mild cognitive impairment.[24] In addition, in preliminary studies[14,15] patients with a MoCA score < 19 were unable to complete the computerized cognitive training intervention. Patients will be excluded from

MEMOIR-HF if they are unable to complete the MoCA because of deficits in visual or motor skills. To ensure that patients with likely or diagnosed dementia will be excluded, medical records will be reviewed for any diagnosis of dementia, patients' physicians will verify eligibility, and if needed, data will be discussed by members of the research team including the neuropsychologist (BG).

Sample Size Justification and Power Analysis

Power analyses were conducted based on data from preliminary studies[14,15,22] to determine the required sample size to test all hypotheses. The measure of effect size (ES) was Cohen's d. Cohen defined a small ES as d=0.2, a medium ES as d=0.5, and a large ES as d=0.8.[25] MEMOIR-HF was designed to have at least 90% power to detect effects of the size observed in the preliminary studies for memory[14] and serum BDNF[15] and 70 to 96% power for secondary outcomes.[14,15,22] Assuming 20% attrition, enrollment of 264 patients will result in 70 patients per group (total 210) at study completion. The minimum detectable effect size with 80% power in a sample size of 70 per group is 0.48 (smaller than those reported in preliminary studies).

Randomization and Stratification

Enrolled patients will be randomized within four patient blocks to assign patients to the three intervention groups (computerized cognitive training, puzzles, or usual care).[26] The four blocks will be constructed based on baseline cognitive function (Montreal Cognitive Assessment test [MoCA] score normal ≥ 26 and low 19–25)[11.27,28] and gender. This method will result in four blocks: women with normal cognitive function MoCA 26 to 30, men with normal cognitive function MoCA 26 to 30, women with low cognitive function less than MoCA 26, and men with low cognitive function less than MoCA 26. Patients in each block will be assigned to one of three groups with equal probability. A computer-generated randomization list will be maintained on a secure website and accessed by the project and data managers to determine group assignments after baseline assessment.

Evidence is lacking about which HF patients derive the most benefit from BrainHQ. It is unknown if patients with different levels of baseline cognition have similar improvement with BrainHQ. Therefore, rationale was established for stratification of MoCA ≥ 26 (normal cognitive function) and 19–25 (low cognitive function) based on empirical data from two previous studies.[11,29] Hawkins and colleagues[29] evaluated validity of the MoCA by comparing it with a valid neuropsychological test battery among 106 HF patients (49.1% men; mean age 68.13 years; NYHA class 1, 2, 3, and 4). In Hawkins' cross-sectional study, the sample mean and standard deviation for the MoCA was 23.18 and 3.9, respectively. Hawkins found that a MoCA score of < 25 had optimal sensitivity (0.64) and specificity (0.66). Using the MoCA score, patients were classified correctly 65% of the time. Gelow and colleagues[11] evaluated cognitive dysfunction as measured by the MoCA as a predictor of cardiovascular risk events at 180 days. In Gelow's prospective study, the sample was 246 HF patients (62.2% men; mean age 56.5 years; NYHA class 2, 3, and 4; EF < 40% in 80.3% of sample). The sample mean and standard deviation for the MoCA was 25.9 and 2.6, respectively. Ninety-one (37%) of the patients had a MoCA score < 26. A MoCA score < 26 independently predicted cardiovascular event risk at 180 days after adjusting for HF severity

measured by the Seattle HF Model Score and comorbidity measured by the Charlson Comorbidity Index. The MoCA score of < 26 was selected because of the prospective design and larger sample in the study by Gelow and colleagues.

The rationale for stratification by gender was based on previous HF studies. Although women have similar risk for developing HF, women have been under-represented in HF studies. In a review of 264 studies published in 2013 in 11 peer-reviewed journals, the mean percentage of women in the samples was 32% across 129 studies with original data and 34% across 135 studies with data obtained from existing datasets.[30] The median percentage of women was 29% across the 264 studies. In regards to cognitive dysfunction in HF, men may have more cognitive dysfunction than women. In a past study among 249 HF patients, men had poorer memory scores than women.[2] It is unknown if women and men have similar improvements with BrainHQ. Therefore, patients will be stratified by gender.

Computerized Cognitive Training Intervention

In MEMOIR-HF, the intervention will be the six BrainHQ exercises used in the preliminary studies: 1) Sound Sweeps, 2) Fine Tuning, 3) Memory Grid, 4) Syllable Stacks, 5) To-Do List Training, and 6) In the Know. Patients will be given a laptop computer and if needed, internet access with a mobile internet card to perform BrainHQ. They will be taught to perform the intervention 1 hour per day, 5 days per week for 8 weeks for a total of 40 hours.

The computerized cognitive training intervention using BrainHQ was selected for MEMOIR-HF based on scientific rationale and empirical literature. BrainHQ is guided by knowledge of neurogenesis and neuroplasticity.[23,31–34] Neurogenesis occurs in the hippocampus after injury and the hippocampus may be damaged in HF.[31–34] Woo, Kumar, and colleagues[7,35,36] documented neuronal loss and loss of axonal integrity in multiple areas of the brain of HF patients when compared with control participants, including the mammillary bodies, fornix, and hippocampus which are part of the memory structures of the brain. Neurogenesis and neuroplasticity are mechanisms through which the brain may recover from events (e.g., small or silent infarcts) and compensate for oxygen deprivation.[31,32] There is promising evidence that intensive training designed to increase sensory stimulation and perform cognitively challenging activities promotes neuroplasticity and improves memory.[37–39]

BrainHQ provides core elements which are necessary for inducing neuroplasticity (Table 2). The six core elements are: 1) intensive and progressive training of the auditory system, 2) processed speech, 3) behavioral tracking, 4) working memory training, 5) attentive listening, and 6) response feedback and rewards. Intensive training (defined as 1 hour per day, 5 days per week for 8 weeks, for a total of 40 hours) provides repetitive practice that is necessary to improve precision and accuracy in understanding speech which may improve recall. Progressive training provides exercises that are increasingly complex as the person progresses through the program. Speech used in the program is processed by an algorithm that increases the rate and complexity of speech over the training sessions to enhance the person’s ability to understand and encode speech. Behavioral tracking is used to monitor individual performance and ensure that the person is training at a threshold level that is at the uppermost level of his/her skill. This threshold training is a unique element because it

tailors training to the person's performance. Working memory training is incorporated because it is central to memory formation. For example, attentive listening is incorporated by requiring the person to press the start button to begin each exercise, which assists in focusing. Finally, feedback and rewards provided in the program may strengthen learning.[37,39]

The ability to encode, recall, and use information obtained through speech is closely linked to the ability to hear and interpret speech accurately. BrainHQ was developed to improve a person's ability to hear speech and thereby improve ability to encode, recall, and use information. Refining listening skills to more clearly distinguish individual sounds that are part of speech improves recall. Recall of information is quicker and more accurate. The emotional context of auditory information that is received influences a person's ability to recall the information. Events associated with surprise and stronger emotions are more novel and easier to recall.[40] BrainHQ incorporates surprising and novel content to strengthen recall.

Previously, in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) Trial, Ball and colleagues found that a non-computerized cognitive training intervention improved memory, processing speed, reasoning, IADL, and HRQL performance among 2,832 healthy elders.[41–42] In the ACTIVE trial, Wolinsky found that risk of HRQL decline was reduced by 38% at 2 years ($p = .004$)[42] and the annual predicted healthcare expenditures declined by $223 ($p = .024$) at 1 year post-intervention for the group trained in reasoning.[44]

The ACTIVE Trial served as the basis for a computerized cognitive training intervention tested by Mahncke and colleagues among 182 healthy older adults.[37] Adults who completed the program had significant improvements in memory compared with adults in attention control and no-contact groups.[37] In a multisite double-blind randomized controlled trial of this intervention among 487 older adults, Smith and colleagues found that memory and working memory improvement was significantly greater in adults who received Brain Fitness (now BrainHQ) than in adults who received general cognitive stimulation.[38] Brain Fitness was efficacious in studies among 79 older adults,[45] 47[46] and 12[47] persons with mild cognitive impairment, 32 persons with schizophrenia,[48] and 17 HF patients,[21] but studies were limited by small samples.

The mechanism by which computerized cognitive training using BrainHQ improves memory is undetermined. One potential mechanism is that training increases serum levels of the pleiotropic neurotrophin BDNF. BDNF, a growth factor widely distributed throughout the brain, exerts multiple effects in the brain during and after development. It is involved in regulation of synaptic plasticity and promotion of survival of neurons that influence learning and memory by modulating hippocampal plasticity in the adult mammalian nervous system.[49] In a randomized controlled study among 56 persons with schizophrenia, compared with 26 persons who received an active control intervention of computer games, 30 persons who completed 50 hours of computerized cognitive training using BrainHQ had significantly increased serum BDNF levels at 2 weeks ($p = .03$) and 10 weeks ($p = .02$) after training.[50] Moreover, among the 30 persons in the BrainHQ group, serum BDNF levels normalized

after 10 weeks and increased serum BDNF was associated with improved quality of life (p = .01). The investigators concluded that serum BDNF may be a peripheral biomarker that is responsive to the effects of cognitive training and potentially other cognitive enhancement interventions in persons with schizophrenia. In our preliminary study,[15] compared with 9 HF patients who did not complete cognitive training, 11 HF patients who completed 40 hours of cognitive training using BrainHF over 8 weeks had significantly increased serum BDNF levels (p = .011). Taken together, these studies support the need for further investigation and suggest that increased BDNF may contribute to or underlie the improvements observed in memory performance after computerized cognitive training using BrainHQ.

Rationale for Control Groups

Active Control Group—Patients who are randomly assigned to the active control group will receive a computer-based intervention using crossword puzzles. This intervention consists of a series of crossword puzzles that are available from Internet sites that are free to users. They are visually appealing, have features for solving the puzzles, and come from multiple sources. A menu of puzzles will be provided for patients or they may select their own. Patients will be given a laptop computer and if needed, internet access using a mobile internet card to perform the puzzles intervention. They will be instructed to perform the intervention by working on the puzzles 1 hour per day, 5 days per week for 8 weeks for a total of 40 hours to match BrainHQ time.

The rationale for this intervention is the belief that increased general cognitive activity maintains or improves cognitive function. Performing general cognitively stimulating activities may promote plasticity, but it may not be powerful enough to overcome the existing brain pathology that accompanies HF. There is limited evidence that completion of general interventions such as crossword puzzles generalizes to specific cognitive abilities such as memory. This intervention was designed to be consistent with the common recommendation from providers to stay cognitively active and to match time spent on BrainHQ and computer use.

Usual Care Group—Patients who are randomly assigned to the usual care group will continue to receive usual care based on national HF guidelines[13] but will not receive any specific computerized cognitive interventions from the research team. This group is necessary because: 1) it controls for internal validity threats that may occur if only using BrainHQ and active control interventions; 2) it is hypothesized that BrainHQ is better than usual care; and 3) there are no guideline recommendations for cognitive training for HF.[51] Patients in this group will be offered BrainHQ after study completion at equivalent subscription cost.

Measures

All measures have documented validity and reliability among older adults. Data will be collected by trained interviewers. Neuropsychological tests will be administered by a tester trained by research team members, including a neuropsychologist. Neuropsychological tests will be completed in isolated rooms without external distractions at the patients' homes or at the school of nursing neuropsychological testing room.

Primary Efficacy Outcome Variables

The primary efficacy outcome variables will be delayed recall memory and serum BDNF (Table 3). Delayed recall memory will be measured using the Hopkins Verbal Learning Test – Revised Version[52,53] during face-to-face interviews conducted at patients' homes at baseline, 10 weeks, and 4 and 8 months after baseline. Serum BDNF will be measured within two weeks of the face-to-face interviews at baseline, 10 weeks, and 4 and 8 months after baseline.

Secondary Efficacy Outcomes Variables

The secondary outcomes will be working memory, IADL, HRQL, and cost-effectiveness (Table 3). Changes in working memory will be measured using the CogState Health One Back Accuracy Task[54,55] at baseline, 10 weeks, and 4 and 8 months after baseline. Changes in IADL will be measured using the Everyday Problems Test[56] at baseline, 10 weeks, and 4 and 8 months after baseline. Changes in HRQL will be measured using the Minnesota Living with Heart Failure Questionnaire[57] at baseline, 10 weeks, and 4 and 8 months after baseline. The cost-effectiveness of the computerized cognitive training intervention will be evaluated using data on: 1) time spent by research assistants training and delivering the interventions; 2) time spent by patients learning and completing interventions; 3) healthcare resource use retrieved from the electronic health record; and 4) Health Utilities Index Mark 3[58] completed at baseline, 10 weeks, and 4 and 8 months after baseline.

Potential Moderating Variables

Three potential moderating variables of the effect of computerized cognitive training using BrainHQ will be examined: depressive symptoms, *BDNF* gene *Val66Met* polymorphism, and *APOE-ε4*. Depressive symptoms may occur in HF patients and influence patients' responses to cognitive training. Therefore, depressive symptoms will be evaluated as a moderating variable to deepen understanding of whether patients with high depressive symptoms have different responses to BrainHQ than patients with few or no depressive symptoms. The Patient Health Questionnaire-8 (PHQ-8)[59] will be used to measure depressive symptoms.

BDNF gene *Val66Met* polymorphism influences hippocampal neuronal integrity, learning, and memory. The abnormality in *BDNF* gene termed *Val66Met* polymorphism was linked to learning and memory disorders in past studies[60–62] and will be evaluated as a potential moderating variable that may influence patients' response to cognitive training. Cherran and colleagues[63] reported that 35% of White persons have *BDNF Val66Met* polymorphism. Lang and colleagues[64] reported that 30.7% of 114 healthy adults in Germany had *BDNF Val66Met* polymorphism. Feher and colleagues[65] reported that 41.2% of 160 persons with Alzheimer's disease had *BDNF Val66Met* polymorphism. In the preliminary MEMOIR-2 study,[15] eight (32%) of 25 HF patients had *BDNF Val66Met* polymorphism.

APOE-ε4 allele is a risk factor for late-onset Alzheimer's disease that is associated with decreased learning and memory.[66–69] Presence of *APOE-ε4* allele will be evaluated as a potential moderating variable that may influence responses to cognitive training. Farrer and colleagues conducted a meta-analysis and found that the frequency of the *APOE-ε4* allele

was 36.7% among White persons with Alzheimer Disease, 32.2% among African American persons with Alzheimer Disease, 13.7% among White persons without Alzheimer Disease or other major neurological diseases, and 19.0% among African American persons without Alzheimer Disease.[69] Bertram and colleagues[70] found that the presence of one *APOE-ε4* allele was associated with 4.3 times greater odds of developing late-onset Alzheimer's disease and the presence of two *APOE-ε4* alleles was associated with 15.6 times greater odds of developing late-onset Alzheimer's disease. Cordes and colleagues[71] reported earlier onset of Alzheimer's disease when compared with persons without *APOE-ε4* allele. Finally, Vogels and colleagues[71] reported that 33% of 62 HF patients in the Netherlands had at least one copy of the *APOE-ε4* allele. In the preliminary MEMOIR-2 study, 7 (24.1%) of 29 HF patients had *APOE-ε4* allele,[73] potentially increasing their risk for memory disorders and altering their responses to cognitive training interventions.

Sample Description Variables and Covariates

Demographics, HF-related clinical variables, medical comorbidities, daytime sleepiness, and balance and history of falls will be measured to provide a description of the sample and identify potential covariates (Table 3). Measures of premorbid intellect, visual recognition memory, attention, psychomotor function, and executive function will be measured to provide a more complete description of cognitive function, assist in interpretation of outcome measures of delayed recall memory and working memory, and as possible covariates.

Intervention Treatment Fidelity

Recommended best practices strategies will be implemented to ensure treatment fidelity.[74] To ensure fidelity for study design, the BrainHQ and active control interventions will be delivered for the same length of time (5 hours/week × 8 weeks = 40 hours) and by computer platform. To ensure fidelity for provider training, intervention RAs will be trained carefully and their performance monitored every 6 months over the study duration. To ensure fidelity of intervention delivery, standard size laptop computers will be used for all intervention delivery. Interventions delivered by computers offer advantages that strengthen intervention delivery and reduce variation in delivery. Stimuli are delivered with precision to all participants. Patient responses are measured immediately. The computer quickly adjusts exercises to match individual abilities. Training is tailored for each person daily, progress tracked, and feedback provided. Interventions are self-directed. Prior computer experience is not required.

To ensure fidelity of intervention receipt, intervention research assistants will explain and demonstrate interventions to patients, ask patients to give return demonstrations of accessing and performing interventions, answer questions, and provide written instructions. They will call patients weekly to monitor intervention receipt and time spent using a checklist that will be a covariate.

Mental effort used during the intervention performance will be assessed using a structured form. BrainHQ and active control group patients will be taught to complete a 4-item checklist documenting the mental effort used at the end of each intervention session.

Checklists will be used to assess intervention receipt and as a covariate.[75] Time spent will be monitored using the BrainHQ program and RescueTime software for the active control puzzles group and by patient self-report time logs.

Change in clinical condition (dyspnea, fatigue, emotions, and overall health) will be monitored weekly during the 8-week intervention phase to ensure that patients' clinical condition is stable and they are able to complete the interventions.[76] When the intervention research assistants contact patients by telephone weekly, they will assess change in condition using a structured questionnaire that will be a covariate. Upon completion of the study, patients will complete a satisfaction questionnaire about the program.

Statistical Analysis

Randomization results will be compared to the pre-planned randomization schedule to ensure randomization integrity. Descriptive statistics will be completed for all measures. Scores will be examined for outliers and appropriate strategies used if needed. Distributions based on density plots will be examined. If data are not normally distributed, non-parametric methods will be used for analysis. Demographic, clinical, and study variables will be evaluated for baseline equivalencies prior to hypothesis testing. Variables (e.g., age, gender, smoking status, body mass index, medications) that may influence BDNF interpretation[77] will be evaluated prior to hypothesis testing, although the randomized controlled trial design will likely balance these factors. The significance level will be set at $< .05$ for all analyses.

The primary analyses comparing the three groups will be conducted using the intent-to-treat approach in which patients are considered to be in groups to which they have been randomly assigned, not on treatment or amount of treatment they actually receive. This approach is taken because it is the best method for evaluating potential effects of a treatment policy, which is our focus. Another implication of this approach is that patients who are lost to follow-up are included, ensuring that observed differences between conditions are not due to differential drop out. Use of a mixed model analysis helps achieve this goal.

Analyses for hypotheses testing efficacy of BrainHQ to improve delayed recall memory (primary outcome) and serum BDNF levels (co-primary outcome) at 10 weeks, 4 months, and 8 months after baseline will use the primary and co-primary dependent measures of Hopkins Verbal Learning Test-Revised delayed recall (raw score) and the serum BDNF levels. Both dependent variables are quantitative and likely to be normally distributed either in raw form or after preliminary transformations. Analysis will be conducted using a mixed model analysis[78] of repeated measures data including randomization group, time, and interactions between group and time while adjusting for the four patient blocks defined by baseline cognition and gender using the mixed procedure in SAS. Significant interaction between group and time will indicate differences in the changes of delayed recall and BDNF levels among the three groups. Following significant interactions of time with treatment group, specific contrasts will be tested comparing mean outcome measures in the BrainHQ group with each of the other groups at each specific time point after baseline. Analyses for testing hypotheses for secondary outcomes are similar to analyses for testing hypotheses for primary outcomes and will involve contrasting patients who receive BrainHQ active and

usual care groups on improvements in working memory, IADL, and HRQL. Analyses will use mixed models as described above.

Analyses related to aim one (all primary and secondary outcomes) will determine whether effect of BrainHQ differs by level of baseline cognitive scores (MoCA score normal ≥ 26 or low 19–25) or gender. Interactions between baseline cognitive function and time and between gender and time will be added to the mixed model analyses. Key tests are the product terms that will indicate whether effects of treatment differ by level of baseline cognitive function or gender. Means of outcome measures by treatment group and by time will be examined.

Some secondary analyses related to aim one will step outside of the intent-to-treat approach by determining whether patients received the recommended dosage of the computer interventions. Time spent in training will be analyzed using continuous time data. Because HF severity, comorbidities and change in condition may prevent some patients from adhering to interventions, New York Heart Association class, Charlson Comorbidity Index and change in condition will be tested as potential predictors of number of hours completed and as covariates in the analyses of outcomes. With reasonable variability, the analyses will be critical in showing whether these variables predict amount of time spent completing the intervention and influence outcomes.

Aim two is to evaluate cost-effectiveness of the BrainHQ training intervention. All costs will be reported in a standard currency, such as 2016 U.S. dollars. To test the hypothesis, incremental cost-effectiveness ratios (ICERs) will be computed using the formula: $(C_1 - C_2)/(E_1 - E_2)$. C_1 equals cost associated with the training intervention, C_2 equals cost associated with the control group (either active control puzzles or usual care), E_1 equals the QALYs associated with the training intervention, and E_2 equals the QALYs associated with the control group. To account for the inherent uncertainty associated with both measures of utility and costs, probabilistic cost-effectiveness acceptability curves will be calculated by bootstrapping of ICERs, as has become commonplace in analyses of HF treatments.[79]

Recommendations of the Panel on Cost-Effectiveness in Health and Medicine will be followed where possible.[80,81] Time horizon of the analyses is 8 months (study duration) and thus, discounting is not applicable and long-term net costs will not be estimated. Univariate and multivariate sensitivity analyses will be conducted on all estimations of costs and QALY estimates. Mixed model analysis will be conducted on all three quantitative measures: estimated costs, QALY, and cost/QALY. Taking the societal perspective, the hypothesis is that the training intervention using BrainHQ will be a cost effective option compared with the control groups. In fact, based upon the pilot study,[22] a net cost savings is hypothesized. Taking the third-party perspective, the ICER will be calculated using medical services costs as the measure of effectiveness.

Aim three is exploratory to examine depressive symptoms (measured by PHQ-8), *BDNF* gene *Val66Met* polymorphism, and *APOE-ε4* as moderators of BrainHQ efficacy. For *BDNF* gene analysis, patients will be grouped as Met negative (*ValVal*) or Met positive (*ValMet* and *MetMet*). For *APOE* analysis, patients will be grouped into ε4 carriers and

non-carriers. The effect of BrainHQ training on all measures in aim one are assessed by the interactions of group with time. Analyses for aim three will add PHQ-8, *BDNF Val66Met* polymorphism, and *APOE* carrier status (separately) and interactions of between treatment group and these variables with others in the mixed model. The key tests will be of the interactions. Power for determining these interactions may be lower than what was estimated for aims one and two, but estimated treatment responses within each subgroup will provide preliminary hypothesis-generating data for future studies.

Safety Considerations

The study will follow the Policy of the National Institute of Nursing Research for Data and Safety Monitoring of Extramural Clinical Trials. Essential elements of the data and safety monitoring plan are procedures for: a) monitoring overall study by Investigators and Safety Monitoring Committee; b) monitoring study safety, minimizing research-associated risk, and protecting confidentiality of participant data; c) identifying, reviewing, and reporting adverse events and unanticipated problems; d) assessing new information and published data that may impact safety of participants; and e) interim analyses.

Conclusions

To our knowledge, MEMOIR-HF will be the first adequately powered randomized trial of computerized cognitive training among HF patients to date. Findings will provide important new knowledge about the efficacy, cost-effectiveness, and potential moderators of a scientifically-based, easily disseminated computerized cognitive training program for memory loss in HF patients. Importantly, findings will help build the empirical evidence that is needed in clinical practice to address the debilitating problem of memory loss that negatively affects patients' survival and quality of life. If efficacious and cost-effective, the intervention will provide a new therapeutic approach for HF patients and findings can be used to inform health systems to adopt it as an intervention and health insurers to provide coverage for this intervention.

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What is New?

- MEMOIR-HF is a three-arm randomized controlled trial to 1) evaluate the efficacy of BrainHQ among HF patients, 2) evaluate the incremental cost-effectiveness of BrainHQ among HF patients, and 3) examine depressive symptoms, *BDNF* genotype of the *Val66Met* polymorphism, and *apolipoprotein (APOE)-ε4* allele as moderators of BrainHQ effect on primary and secondary outcomes.
- If efficacious and cost-effective, the intervention will provide a new therapeutic approach for HF patients which can be used to inform health systems to adopt it as an intervention and health insurers to provide coverage for this intervention.

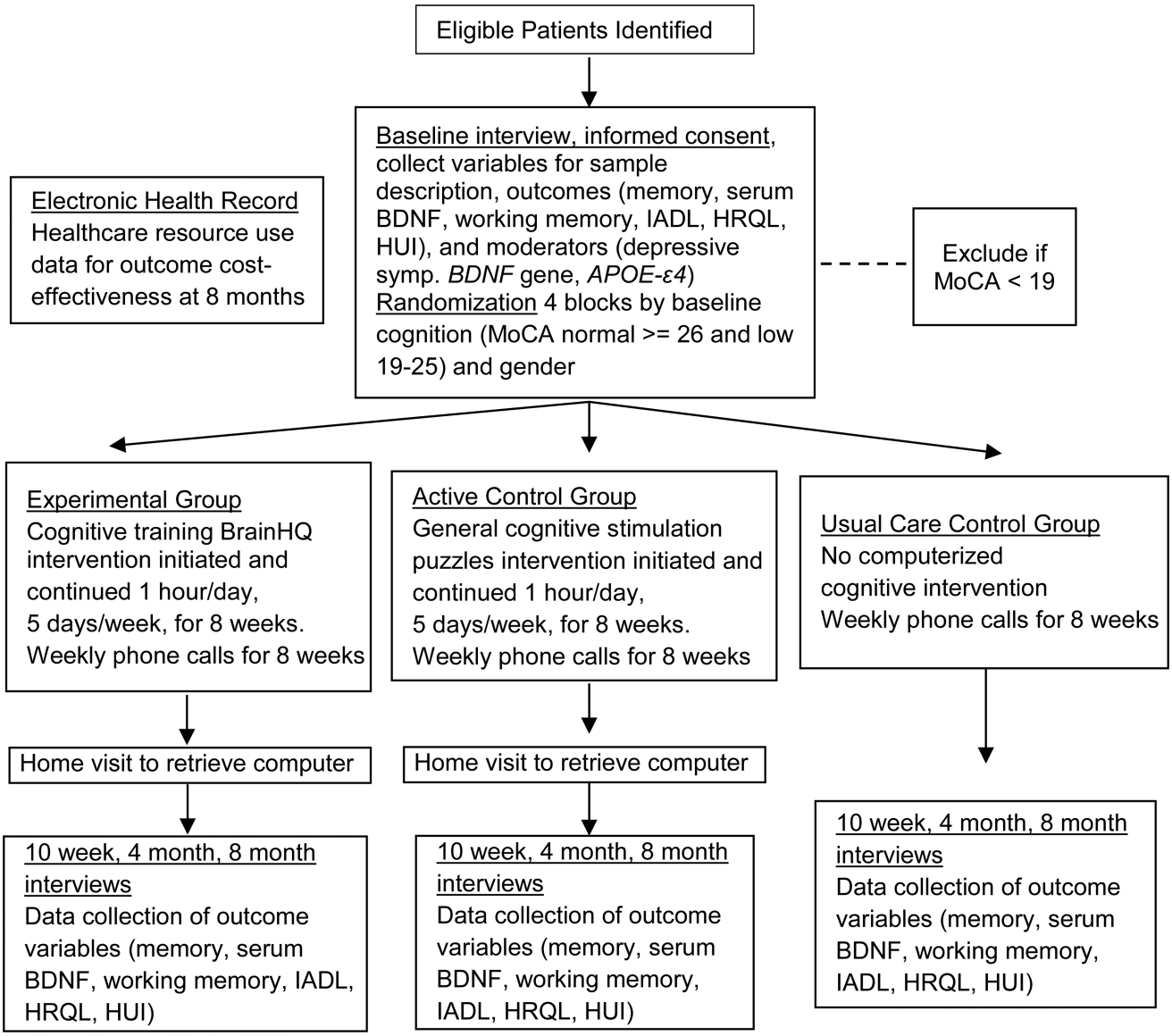

Figure 1.

Research Design

BDNF, brain-derived neurotrophic factor; HRQL, health-related quality of life; HUI, Health Utilities Index; IADL, Instrumental Activities of Daily Living; MoCA, Montreal Cognitive Assessment test

Table 1

Inclusion and Exclusion Criteria of the MEMOIR-HF Study

Inclusion criteria

- Age ≥ 21 years
- Understands English
- Has access to a telephone
- Hears normal conversation
- For patients with hearing aids, able to wear and hear through headsets
- Diagnosis of chronic HF, Stage C, New York Heart Association class I, II, or III
- HF diagnosis validated by echocardiography or other method in the past 3 years
- Receiving guideline derived medical therapy
- Written informed consent

Exclusion criteria

- History of drug or alcohol abuse or major psychiatric diagnosis (Axis 1) present before the HF diagnosis
- Alzheimer or other dementia diagnosis or central nervous system degenerative disorder
- Terminal cancer
- Baseline Montreal Cognitive Assessment (MoCA) score of < 19 (adjusted by adding 1 point for patients with highest education ≤ 12 years) because this score indicates possible dementia

Table 2

Core Elements of Interventions and Usual Care

Element	Computerized Cognitive Training using BrainHQ	Active Control Crossword Puzzles	Usual Care
Auditory stimuli	Intensive, repetitive training of sounds of speech	None	None
Complexity of stimuli	Progressively increased over time; synthesized speech	Complexity does not progressively increase	None
Cognitive demand	Tailored; Training adjusted by computer to 85% of individual's threshold	Not tailored; consistent; not adjusted to individual's threshold	No additional demand provided
Working memory (e.g., attention)	Training in working memory and directed attention with each exercise	No directed attention from computerized intervention	No additional stimuli provided
Novelty	Provided by feedback and rewards; visual stimuli and content of program; individualized	Some novelty of words may occur; feedback and rewards not provided	None

Table 3

Variables, measures, and sources of data

Variables	Measures	Sources
Primary efficacy outcomes		
Delayed recall memory	Hopkins Verbal Learning Test-Revised[52,53] delayed recall (parallel versions)	Patient
Serum BDNF	Serum	Patient
Secondary efficacy outcomes		
Working memory	CogState Health One Back Accuracy Task[54,55]	Patient
Instrumental activities of daily living	Everyday Problems Test – Cognitively Challenged Version[56]	Patient
Health-related quality of life	Minnesota Living with Heart Failure Questionnaire[2,57]	Patient
Cost-effectiveness - resource use	Cardiology and other outpatient clinic visits, emergency department visits, ambulance services, hospitalizations, procedures, laboratory tests, medications, outpatient treatments, home care	Electronic health record
Cost-effectiveness – quality adjusted life years	Health Utilities Index Mark-3[58,82]	Patient
Potential moderating variables		
Depressive symptoms	Patient Health Questionnaire-8[2,59]	Patient
BDNF gene *Val66Met* polymorphism	N/A	Patient
APOE-ε4 allele	N/A	Patient
Blocking variables		
Global cognitive function	Montreal Cognitive Assessment test[27]	Patient
Gender	N/A	Patient
Sample description variables/Covariates		
Demographics	Demographics form	Patient
HF etiology, duration, BNP, devices, medications	N/A	Electronic health record
Medical comorbidities	Charlson Comorbidity Index[83]	Electronic health record
Daytime sleepiness	Epworth Sleepiness Scale[84]	Patient
Balance	Timed-Up-and-Go test[85]	Patient
Fall history	Falls assessment questionnaire	Patient
Premorbid intellect	Wide Range Achievement Test, 4th ed. Reading[86]	Patient
Memory-Visual recognition	CogState Health One Card Learning Task[54,55]	Patient
Attention and psychomotor function	CogState Health Identification and Detection tasks;[54,55] Digit Symbol Subtest[87]	Patient
Executive function	Category fluency (animal, vegetable)[88] Stroop test[89]	Patient
Intervention fidelity variables		
Time spent each session	Computer program and calendar	Computer, Patient
Mental effort after each session	Mental effort questionnaire	Patient
Change in clinical condition	Clinical change rating scale[76]	Patient
Patient satisfaction with program	Patient Satisfaction Questionnaire[90]	Patient

APOE, apolipoprotein; BDNF, brain-derived neurotrophic factor; BNP, brain-natriuretic peptide; HF, heart failure