

Research Article

Evaluation of a Multidisciplinary “Brain Fitness Program” for Treatment of Cognitive Impairment in Elderly

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- Comprehensive treatment

Abstract

Objective: Cognitive impairment in elderly is often due to a combination of different etiologies. Thus, multidisciplinary programs that offer a combination of different interventions are more likely to be successful than those that offer a single intervention. The aim of the present study was to evaluate the effectiveness of an intensive multi-factorial treatment plan, named the Brain Fitness Program (BFP), in elderly patients with cognitive impairment.

Methods: We developed a 3-month multidisciplinary BFP for a total of five hours a week. We provided this program as an open clinical trial for 34 patients who presented to the NeurExpand Brain Center with concerns about a decline in their cognitive function. We conducted pre- and post-testing on cognitive function by using a reliable ($\alpha > 0.90$) 10-test battery of neurocognitive tests containing Letter Fluency subtest of Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency Test; Color naming, Word reading, and Inhibition subtests of D-KEFS Color-Word Interference Test; Trail Making Test A and B; Hopkins Verbal Learning Test-Revised; and Brief Visuospatial Memory Test-Revised. The BFP included cognitive training, meditation, fitness training, and neurofeedback therapy which were administered by specialists in each training program.

Results: A repeated measure MANOVA with two factors (the neurocognitive battery with ten tests and the change, measured by a pre- and post-test) showed an overall significant improvement in the whole battery of neuro cognitive function in patients after completing the program.

Conclusion: The results from this open clinical trial indicate that our multifactorial BFP has produced significant improvement in elderly with cognitive impairment.

INTRODUCTION

It is estimated that the number of older people over 65 years old will increase to more than one billion worldwide during the next 40 years [1,2]. Normal aging is often accompanied by decline in cognitive function, particularly in delayed episodic recall, associative memory, and prospective memory [3,4]. Projections by Alzheimer's disease International suggest that 115 million people worldwide will be living with AD/dementia in 2050, with a markedly increasing proportion of this total in less developed countries [1,5]. Given the high prevalence of dementia

and its enormous burden on the society, it is not surprising that a variety of current clinical programs are aimed at helping older patients compensate for memory impairment [6]. Although some treatments, either pharmacologic or non-pharmacologic, can provide symptomatic improvement in patients with dementia and Alzheimer's disease, they do not completely stop the course of the disease [1,7-9]. Therefore, attention has been recently turning toward the detection of preclinical or early-stage disease and the development of treatments to prevent or delay the onset of dementia and age-related cognitive decline [10,11].

Cognitive impairment with aging is often due to a combination of different etiologies [12,13]. As such, multidisciplinary programs that offer a combination of different interventions are more likely to be successful in the improvement of cognitive decline than those that offer a single intervention [14,15]. There are a number of non-pharmacological interventions which can potentially slow cognitive degradation with aging. A strong association exists between mentally stimulating activities and better cognitive performance [7,14-16]. Therefore, one conventional intervention has been cognitive training programs with an emphasis on learning and practicing memory strategies [15]. Accordingly, previous studies demonstrate that memory programs can provide a number of positive outcomes and are consistent with the fact that older adults can still acquire new knowledge and skills related to memory and other domains of cognitive function [17].

Accumulating evidence indicates that lifestyle factors such as social engagement, nutrition, and stress management have a positive impact on memory and other cognitive abilities and can decrease the risk of developing cognitive disorders [18,19]. Among the many forms of interventions is mindfulness meditation, a type of meditation that emphasizes a mental state characterized by full attention to internal and external experiences that are occurring currently, and includes the maintenance of a non-judgmental reflection of our thoughts and behaviors. Numerous studies suggest that mindfulness may improve attention and other cognitive domains [20,21]. In a recent study it was found that marines who practiced mindfulness over eight weeks improved their focus and working memory capacity. Increasing amounts of meditation correlated with improved performance in each area [22]. The improvements in attention and working memory may be in part due to an increase in neural connections. In a separate study, MRI diffusion tensor imaging revealed that subjects who practiced mindfulness for two weeks had greater white matter density than control group given relaxation training. After an additional two weeks, the effects were even more apparent [23]. Further studies have suggested that long-term meditation is correlated with greater cortical thickness which is associated with improved attention and mood [24]. The importance of mindfulness meditation as an effective intervention is also supported by the finding that individuals with more mindfulness training show improvements in response inhibition and executive processing [25].

There is a large body of research that emphasizes the role of fitness in preserving one's cognitive integrity. Several landmark studies attributed increased physical activity to increases in brain volume, specifically the hippocampus, improvements in areas of memory, and increases in levels of brain neurotrophic factors [26-29]. A review of the literature suggests that one of the most effective exercise methods is aerobic fitness which is associated with increased cortical volume and healthy brain aging [30]. Therefore, a physical activity program could be an additional approach for improving cognitive function.

Recently, neuro feedback has become a promising candidate for enhancing memory among the elderly [31]. Accumulating evidence indicates that neurofeedback can improve certain cognitive performance measures such as working memory [32-36], mental rotational ability [37] and attention [33].

Studies which have focused on individual interventions for improving cognitive performance have often failed to demonstrate significant enhancements [38]. Thus, there is a need to investigate the effectiveness of a multidisciplinary approach in treating patients with cognitive decline associated with modifiable factors. Accumulating evidence indicates that a comprehensive approach to improve brain health and performance may strengthen the brain and delay the onset of cognitive deficits [7,15]. The aim of this study was to assess the effectiveness of a three-month multi-factorial Brain Fitness Program (BFP) that emphasizes cognitive training, mindfulness meditation, fitness training, and neuro feedback on improving the cognitive function of elderly individuals with significant.

MATERIALS AND METHODS

Participants

Following local Institutional Review Board (IRB) approval of the study by New England IRB, participants were recruited among patients at the Neur Expand Brain Center. The patients included physician- and self-referred individuals from across the Baltimore-Washington D.C. areas who were seeking treatment for memory loss. Exclusion criteria were a Mini-Mental State Examination (MMSE) score below 21, current Axis II disorder and limited time availability for attending an intensive training program in the clinic three days a week for 3 months. Patients did not receive compensation for their participation in the study. Written informed consent was obtained from all participants.

Interventions

Participants were enrolled in our clinic's Brain Fitness Program (BFP). As detailed in the following sections, the program consisted of five one-hour sessions a week for twelve weeks. Each week during the program, patients attended two neurofeedback sessions, two cognitive skills training sessions, and one brain coaching session. The interventions were performed by certified clinicians or had received additional training at our center.

Neuro feedback: Each patient received a personalized protocol contingent on the findings of the Quantitative Electroencephalogram (QEEG), neuropsychological testing, and self-reported concerns. The sessions utilized the latest versions of Brain Master Hardware and Software programs for training. Patients underwent training, through operant conditioning paradigms to enhance and/or inhibit different waveforms based on their personalized protocol designs. The EEG was recorded and the relevant frequency components were extracted and fed-back using an audio-visual online feedback loop in the form of a video game for the visual feedback and/or earning different sounds as rewards for the auditory feedback. The participants' task was to do better in the video game for the visual feedback and to earn more sounds for the auditory feedback.

Cognitive skills training: We used the computer-based Captain's Log Professional System program to train the patients' cognitive abilities. The program is comprised of numerous cognitive skill tests designed to guide patients through increasingly challenging stages. It provides patients with many different game-like exercises to improve their working and short-

term memory, attention, mental processing speed, listening skills, problem solving, and more.

Brain coaching: Brain coaches are trained health care professionals that educated patients about specific interventions to improve their memory, stress level, and sleep. Brain coaches also proposed various methods to improve physical fitness to supplement the suggestions from the exercise physiologist. The fundamental focus during these sessions was memory training which was taught through exercises that focused on visual memory, name memorization and list recall. Additionally, brain coaches emphasized mindfulness meditation during sessions to reduce stress, and enhance attention and working memory.

Outcomes

Upon entering the program, patients underwent a general neurological evaluation to determine and address potential medical causes of memory loss and cognitive impairment such as sleep apnea, depression, and vitamin B₁₂ deficiency. The medical conditions were treated in parallel to their participation in the program. After this initial consultation, patients received baseline and post-evaluations on neuropsychological testing, cardiopulmonary exercise testing and QEEG.

Neuropsychological testing: Patients underwent neuropsychological testing before and after the program. Patients were evaluated on the following metrics: Trail-Making Test A and B (TMT-A and TMT-B), Hopkins Verbal Learning Test- Revised (HVLTR), Brief Visuospatial Memory Tests-Revised (BVMT-R), Delis-Kaplan Executive Function System (D-KEFS) tests consisted of (i) Color-Word Interference Tests (Color Naming [COLOR], Word Reading [WORD], Inhibition) and (ii) Verbal Fluency Test (Letter Fluency [LETTER]). The participants' scores on each metric were converted to pre-determined percentiles and z-scores. In our data analysis, we reviewed the average percentile change for each metric, as well as evaluated the significance for each test. Trained psychometricians who performed the cognitive testing were blinded to the information regarding the patients' involvement in this study.

Cardiopulmonary Exercise Test (CPET): Patients completed a pre- and post- cardiopulmonary exercise test (CPET). An ECG was used to monitor the patient while on a cycle ergometer (stationary bike). An individual's fitness level is measured by maximal oxygen consumption (VO₂ Max), which is the amount of oxygen extracted with maximum exertion on a stationary bike. VO₂ Max is defined as the ability to transport and consume oxygen during exhausted work and is related to cardiorespiratory fitness [39]. After determining the patient's baseline VO₂ Max, the exercise physiologist proposed various methods to improve physical fitness based on the participant's level of fitness. For our analysis, we reviewed the change in VO₂ Max before and after the completion of the brain fitness program.

Quantitative Electroencephalogram (QEEG): We reviewed the quantitative analysis of EEGs (QEEG) in all our patients. Previous research suggests that QEEG measures can be used as an indicator for the degree of cognitive impairment [40]. QEEG results, in combination with findings from the neuropsychological testing results, assisted in formulating an individualized neurofeedback protocol for each patient.

Statistical analysis

A repeated measure MANOVA with two factors (the neurocognitive battery with ten tests and the change in standardized z-score, measured by a pre- and post-) was run as the main analysis to assess for an overall effect for the BFP. Also, a series of *a-priori* paired samples t-tests were conducted for each of the individual tests in the battery using the pre- and post-standardized z-scores to ascertain whether or not improvements were seen on a particular neurocognitive test. Finally, a series of *post hoc* paired samples t-tests were conducted on the pre- and post- raw scores for each test on only the participants who saw improvement in order to assess if that improvement was significant. The performance scores on the neurocognitive tests were recorded as raw scores and then converted to standardized z-scores. Statistical significance was set at the 0.05 level.

RESULTS

Among the forty-one patients were initially enrolled in the program, five left due to transportation issues and one left due to medical reasons (hospitalization). One participant failed to return for follow-up testing after completing the program (Figure 1). After excluding these individuals, 34 individuals were included in the analysis; 11 males and 23 (67.6%) females, with a mean age of 69.74 years (S.D: 14.91 years). Demographic data are represented in Table 1.

The effect of the interventions on our primary outcome of cognitive change in the whole battery of cognitive tests is shown in Tables 2 and 3. A repeated measures MANOVA with two factors (the neurocognitive battery with ten tests and the change, measured by a pre- and post-test) showed an overall significant improvement in the whole battery of neurocognitive function in patients after completing the program ($P = 0.026$). The significant overall effect suggests the program's participants made significant improvements when compared to their baseline performances on this neurocognitive battery. To test the latter scenario, a series of *post hoc* t-tests were run on the raw data of the participants that saw improvement in each individual subtest

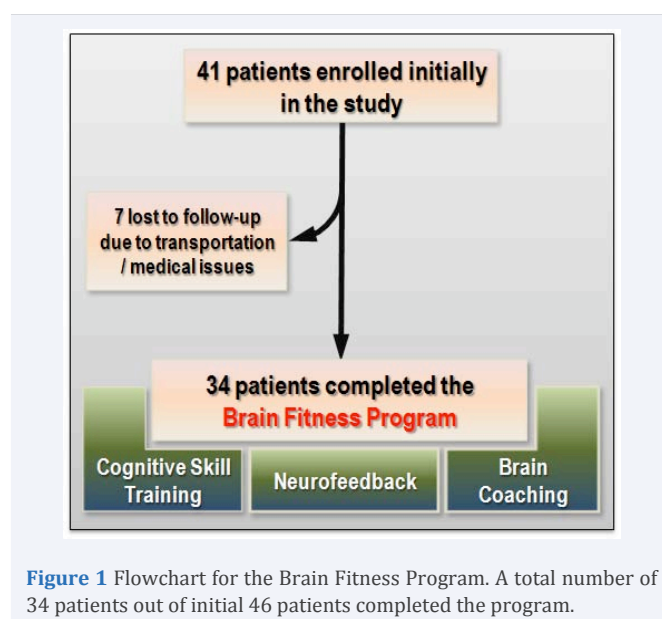


Figure 1 Flowchart for the Brain Fitness Program. A total number of 34 patients out of initial 46 patients completed the program.

Table 1: Demographic characteristics of study participants (total No. = 34).

Characteristic	Number (total No. = 34)
Age (mean ± S.D.), years	69.74 ± 14.961
Female sex, No. (%)	23 (67.6%)
Educational level (mean ± S.D.), years	14.86 ± 2.69
Ethnicity, No. (%)	
Caucasian	26 (76.5%)
African-American	8 (23.5%)
Marital status: Married, No. (%)	21 (67.8%)
MMSE score	26.47±4.433

Table 2: Cognitive function evaluated by a 10-test battery of neurocognitive tests at the baseline and post-intervention (after 3 months brain fitness program) in patients with memory impairment (total No. = 34).

Measurements	Baseline		Post-Intervention		T	P
	Mean	S.D.	Mean	S.D.		
D-KEFS Verbal Fluency Test						
Letter Fluency subtest	30.97	15.06	15.90	2.73	-1.56	0.328
D-KEFS Color-Word Interference Test						
Color Naming	36.59	17.72	34.82	17.11	0.87	0.323
Word Reading	26.56	9.47	28.12	13.27	-1.33	0.220
Word Inhibition	91.76	43.06	99.03	49.02	-1.25	0.392
HTLV-R						
Immediate Recalling	19.65	7.12	19.65	8.22	0.00	0.192
Delayed Recalling	5.94	4.63	5.74	4.69	0.46	1.00
BVMT-R						
Immediate Recalling	12.88	8.10	15.26	9.78	-2.81	0.649
Delayed Recalling	4.56	3.72	5.35	3.90	-2.50	0.008
TMT-A	65.06	47.16	63.03	48.22	0.99	0.018
TMT-B	157.82	92.98	148.29	91.93	1.00	0.128

Table 3: Standardized mean change in cognitive function evaluated by a 10-test battery of neurocognitive tests in patients with memory impairment after completion of brain fitness program (total No. = 34).

Treatment Course	Mean standardized change (95% CI), total No. = 34	P Value
Composite Score	0.19	0.026*
D-KEFS Verbal Fluency Test		
Letter Fluency subtest	0.22	0.183
D-KEFS Color-Word Interference Test		
Color Naming	0.21	0.076
Word Reading	0.00	1.000
Word Inhibition	0.00	1.000
HVLT-R		
Immediate Recalling	0.11	0.979
Delayed Recalling	0.01	0.521
BVMT-R		
Immediate Recalling	0.36	0.028
Delayed Recalling	0.29	0.090
TMT-A	0.16	0.320
TMT-B	0.53	0.004*

of the neurocognitive battery to see if the subtest improvement in those individuals was significant. Twenty patients (59%) had significant improvement on Letter Fluency with an average of 12% improvement. Nineteen (56%), 14 (41%), and 17 (50%) patients had significant improvement in D-KEFS Color Naming, Word Reading, and Inhibition subtests, respectively. HVLT-R immediate and delayed recalling were significantly improved

in 16 (47%) and 11 (32%) patients, respectively. BVMT-R immediate and delayed recalling were improved significantly in 23 (68%) and 15 (44%) patients. TMT-A and TMT-B were also significantly improved in 18 (52%) and 16 (47%) patients. The percentage of improvement in each component in these patients is presented in Figure 2. The t-test results suggest that the patients who have improvements in a component of the

neurocognitive battery do see significant change, suggesting that patients may improve significantly in individually different ways as an explanation for the overall effect without significance for many individual neurocognitive components.

Finally, ten patients underwent pre- and post-CPET training to determine their exercise capacity. VO_2 Max measurements were recorded and we used a repeated measures t-test to determine significance. Statistical significance was set at the 0.05 level. Although there was a general improvement in fitness capacity as indicated by an average percentile increase of 12.3%, the results were not significant ($P = 0.092$).

DISCUSSION

In the present study, we evaluated the effectiveness of a three-month multi-factorial approach in improving memory in 34 patients enrolled in the Brain Fitness Program at our clinic. We conducted pre- and post-testing on cognitive functions using a reliable 10-test battery of neurocognitive tests and fitness capacity. Essentially, after reviewing pre- and post-measures of cognitive function, there was an overall significant improvement in the whole battery of neurocognitive function in patients after completing the program. Further analysis also demonstrated that among the cognitive tests, TMT-B was significantly improved in patients. There was also a modest improvement in D-KEFS Color Naming and BVMTR-Immediate recalling. Furthermore, we noted a trend suggesting improvement within our measure of fitness capacity.

The limited data available concerning the effectiveness of a comprehensive approach to improve cognitive deficits demonstrates the need for multidisciplinary studies such as ours. Few studies have evaluated a multi-factorial approach, yet those that have analyzed its value have reported some success

[7]. Our results are in line with a recent holistic program that reviewed the effectiveness of an intervention that emphasized memory training, diet consultation, stress reduction, exercise, and counseling which reported significant improvements on list learning, story learning and story recall [14]. These results suggest that multi-disciplinary and comprehensive cognitive training is impactful for improvement of cognitive dysfunction in older adults. Another recent computer-based intervention (24 weeks) did not show significant differences between baseline and post testing on measures of memory, language or visuo-spatial abilities [41]. However, the intervention group demonstrated improvements in language, memory, attention, and fluency domains [41]. The effectiveness of a physical and cognitive-based approach to improve cognitive abilities has been also examined in another study. When compared to groups that emphasized cognitive and physical approaches independently, the combined group that emphasized both approaches displayed more significant improvements in cognitive speeds immediately and three months after the intervention [42].

Previous studies have shown that memory and cognitive programs can lead to a number of positive outcomes. Considering the fact that older adults can effectively learn new skills and knowledge [17], many programs have considered a variety of memory and cognitive functions to enhance different aspects of metamemory [43,44]. These programs have shown that memory interventions produce various changes in objective memory ability [15,43-45]. For instance, within only six months, older adults who participated in a computerized brain stimulation program showed a significant improvement in delayed memory and moderate improvements in immediate memory and language [46]. Individuals enrolled in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study underwent three

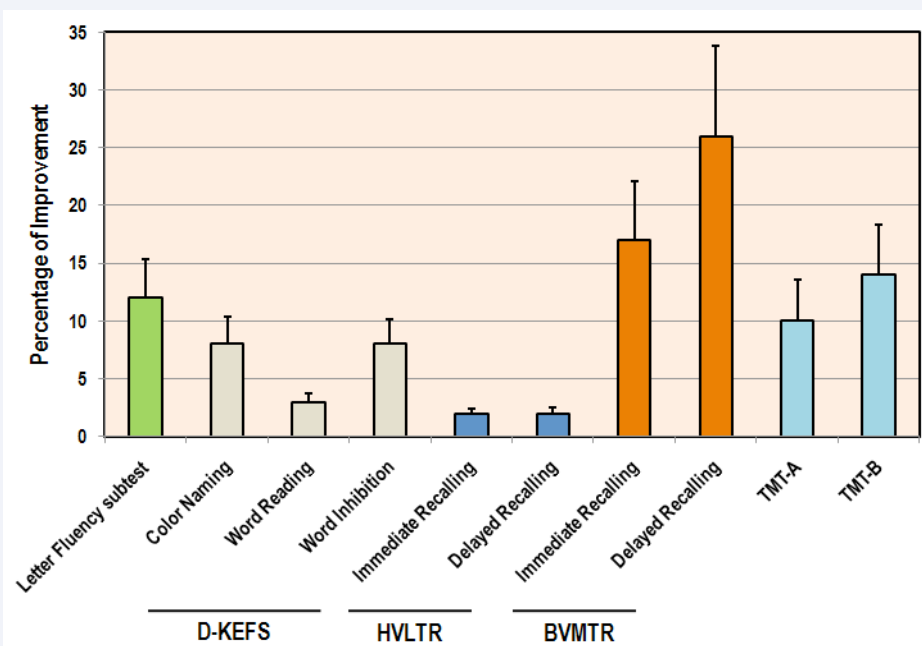


Figure 2 Percentage of improvement in those patients with significant improvement ($P < 0.05$) in cognitive tests. A total number of 34 patients out of initial 46 patients completed the program.

types of cognitive training: verbal episodic memory, executive function, and processing speed. The participants improved on each cognitive domain and these effects persisted five years after the intervention [47,48]. Additionally, targeted memory training interventions have improved verbal and visual memory as well [49]. It is noteworthy that not all memory interventions primarily focus on objective memory, since it does not necessarily predict changes in day-to-day memory functioning [15,50]. In our study, we used a reliable battery of neurocognitive tests to evaluate the efficacy of our Brain Fitness Program. Although there was an overall improvement in the neurocognitive battery, patients had more significant improvements in TMT-B, D-KEFS Color Naming and BVMT-R immediate recall. TMT is a neuropsychological test of visual attention and task switching [51], and it can provide information about speed of processing and executive functioning (e.g., mental flexibility) [51,52]. Poor performance in TMT is associated with many types of brain impairment; in particular frontal lobe lesion [51,53]. The D-KEFS also offers a comprehensive portrayal of individual's verbal and nonverbal executive functions skills, and the complexity of these tasks make them sensitive to the detection of even mild brain damage, specifically in the frontal lobes [54]. The BVMT-R is a commercially available measure of nonverbal memory with demonstrated validity and reliability [55]. Norms on this test are based on studies of 588 individuals (between 18 and 85 years old). The test is sensitive in detecting memory impairment in a number of clinical groups including subjects with amnesia, dementia, and traumatic brain injury [55-57]. Given the low number of subjects recruited in the present pilot study, more investigation using a large number of samples is necessary to validate the present results.

Neuro feedback therapy is a natural, non-invasive therapy and learning procedure that enables individuals to normalize behavior, stabilize mood and improve their cognitive performance. In neuro feedback systems, the EEG is the most used recording technique due to its inexpensive price, portable design, and low-set up cost. Neuro feedback is currently used for clinical treatment of a wide range of neuro-psychiatric diseases including attention-deficit hyperactivity disorder [58], epilepsy [59], anxiety disorders [60], major depression [61] and traumatic brain injury [62]. Several lines of evidence have demonstrated that clinical improvements following neuro feedback coincide with a "normalization" of the EEG frequency spectrum [63,64]. Research on normal healthy subjects has even showed that following a series of neuro feedback sessions, not only are such individuals able to exert some control over their EEG but also that such changes are associated with improved attentional processing in terms of behavioral and electrocortical measures [32,65]. These findings have led to the conceptualization of neuro feedback as a mechanism that may be used to stimulate and/or regulate cerebral activity, and thereby influence several aspects of cognitive processing. It means that training individuals to enhance a particular frequency and reduce another can specifically influence cognitive performance. Angelakis et al. demonstrated that peak alpha frequency training improved verbal memory performance among elderly individuals, ages 70 to 78 [66]. A later study found similar findings after noting that neurofeedback training was correlated to improved attention,

executive function and memory [67]. Accordingly, several lines of studies have demonstrated that alteration in activity of θ brain waves could affect working memory [32,68] and alteration in Sensorimotor Rhythm (SMR) activity at 12-15 Hz is associated with changes in attention [65,69]. θ Activity has also been shown to influence the cellular mechanisms of memory through its role in facilitating long-term potentiation [70], and there is a link between recognition memory processes and θ activity recorded from the scalp [71,72]. In general, it is believed that θ activity is related to encoding and retrieval during working memory, that upper α activity (\approx 12-15 Hz) is associated with sensory processes in long-term semantic memory, and that lower α activity (\approx 8-10 Hz) is related to attention [32]. In our study, patients underwent neurofeedback training to enhance α and simultaneously inhibit θ activity, while holding β in a steady state. In fact, α rhythm, which is the dominant frequency in the human brain, correlates to several factors such as age, memory performance, brain volume and task demands [73]. More recent studies have also shown that improvement of upper α band is associated with an enhancement of cognitive performance [36,64]. Selective retrieval of a specific target memory often leads to the forgetting of related but irrelevant memories. Such retrieval-induced forgetting is hypothesized to arise due to inhibition of competing memory traces. It has been shown that retrieval-induced forgetting is observed in a condition in which the competitor memory interfered with target retrieval. To the best of our knowledge, this is the first study that used the combined neurofeedback and cognitive training and brain coaching to improve cognitive function in older patients with memory impairment. Our results indicate that in combination with brain coaching and cognitive training, the neurofeedback sessions could robustly improve memory impairment in this group of patients.

It is well established that lifestyle factors such as cognitive and social engagement, nutrition, and also stress reduction can markedly improve memory and other cognitive function and reduce the risk of developing cognitive disorders [18,19]. There is also a large body of research that emphasizes the role of fitness in preserving one's cognitive integrity. It has been demonstrated that physical activity can cause a significant increase in brain volume, specifically the hippocampus, improvement in areas of memory, and increase in levels of brain neurotrophic factors [26-29,74]. Increased cardiovascular fitness can serve to reduce both the neurobiological and cognitive consequences of age-related declines [75]. One of the most effective exercise methods is aerobic fitness, which is associated with increased cortical volume and healthy brain aging [30]. Therefore, in our Brain Fitness Program patients were educated about specific interventions to improve their memory, stress level, sleep and also physical fitness. Our results also showed that after completion of our multi-disciplinary program, in addition to improvement in cognitive function, patients showed a general improvement in fitness capacity as indicated by an average percentile increase of 12.3%. This data is consistent with a recent study that demonstrated that aerobic exercise for 12 weeks significantly improved cognitive function, increased cerebral blood flow in particular in the anterior cingulate region and hippocampus, and improved fitness level as measured by VO_2 max in 37 sedentary adults between 57 - 75 years old [76]. In another recent study

on 126 inactive, community-residing older adults, it was also demonstrated that 12 weeks of physical plus mental activity was associated with significant improvement in global cognitive function [7]. Taken together, it seems that both mental activity and exercise can have beneficial effects on cognitive function in older adults.

This study has several limitations. The participants analyzed in this study represent a convenience sample and do not necessarily serve as a good indicator of the general population. The personalized nature of the protocols each patient received reduces the possibility of determining which strategies proved most effective in treatment. In addition, even though patients underwent a very large set of cognitive tests before and after our program, the possibility of practice effect cannot be excluded. Finally, given the limited number of patients in this pilot study, it is difficult to determine which of our interventions was most effective in improving cognitive performance in our patients. It is also possible that there was a synergistic effect of combining BFP interventions with treatment of medical conditions. We hope to address these limitations in future studies using a larger number of patients.

In conclusion, the present study demonstrated that a comprehensive approach to treatment is a valuable area of research in addressing the cognitive impairment of the rapidly expanding aging population. Our results show that neuro feedback in combination with cognitive training and brain coaching is effective in improving cognitive performance among the elderly. Further studies are needed to evaluate the effectiveness of a variation of Brain Fitness Program treatment protocols with different lengths, intensities, and frequencies of treatment sessions.

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Conflict of interests

Majid Fotuhi is chief medical officer at NeurExpand Brain Center. Brooke Lubinski, Tracy Riloff, Mark Trullinger, and Mehdi Ghasemi are employees of NeurExpand Brain Center. The authors have nothing to disclose regarding conflict of interests.

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