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Effectiveness of a Personalized Brain-Computer Interface System for Cognitive Training in Healthy Elderly: A Randomized Controlled Trial

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Abstract.
Background: Cognitive training has been demonstrated to improve cognitive performance in older adults. To date, no study has explored personalized training that targets the brain activity of each individual.
Objective: This is the first large-scale trial that examines the usefulness of personalized neurofeedback cognitive training.
Methods: We conducted a randomized-controlled trial with participants who were 60–80 years old, with Clinical Dementia Rating (CDR) score of 0–0.5, Mini-Mental State Examination (MMSE) score of 24 and above, and with no neuropsychiatric diagnosis. Participants were randomly assigned to the Intervention or Waitlist-Control group. The training system, BRAINMEM, has attention, working memory, and delayed recall game components. The intervention schedule comprised 24 sessions over eight weeks and three monthly booster sessions. The primary outcome was the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score after the 24-session training.
Results: There were no significant between-subjects differences in overall cognitive performance post-intervention. However, a sex moderation effect ($p = 0.014$) was present. Men in the intervention group performed better than those in the waitlist group (mean difference, +4.03 (95% CI 0.1 to 8.0), $p = 0.046$. Among females, however, both waitlist-control and intervention participants improved from baseline, although the between-group difference in improvement did not reach significance. BRAINMEM also received positive appraisal and intervention adherence from the participants.

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Conclusion: A personalized neurofeedback intervention is potentially feasible for use in cognitive training for older males. The sex moderation effect warrants further investigation and highlights the importance of taking sex into account during cognitive training.

Keywords: Brain-computer interface, cognitive training, older adults, personalized neurofeedback

INTRODUCTION

Cognitive performance deterioration that accompanies aging has far-reaching impacts on aspects of daily functioning like independent living [1], work performance [2], leisure activities [3], and navigation [4]. With the growing urgency for non-pharmacological approaches to preserve cognitive vitality in the aging population, myriad cognitive training (CT) protocols [5] have been explored in the last few decades. These interventions, which target domains such as memory, attention, and executive function, have been demonstrably promising [6–9].

In recent times, there is a trend toward gamification of training paradigms and employing technology as a vehicle for training delivery. This mirrors the rapid technological innovation and the burgeoning market of CT smartphone applications and computer games [10]. Meta-analytical reviews have concluded that computerized CT is less labor-intensive than traditional CT, making it a feasible and cost-effective approach that can be implemented widely in the community setting [11, 12]. At the same time, finer approaches like electroencephalography (EEG) neurofeedback CT, which optimizes cognitive function by targeting specific components of brain activity, have been designed [13, 14]. Nevertheless, person-to-person variability in brain activity exists [15] and tailoring neurofeedback CT to each individual based on his/her brain activity could maximize the precision of the training. Yet, this is an unexplored area.

Capitalizing on the strengths of computerized cognitive training and neurofeedback, our team developed a personalized neurofeedback system for training attention and working memory in healthy elderly. The system employs EEG-based Brain-Computer Interface (BCI) technology. The current project is a larger trial that extends our earlier pilot studies [16, 17]. We examined the efficacy of our training system in a bigger sample. We also extended training to an additional component of delayed recall as impairment in delayed recall of information, which occurs with normal cognitive aging [18], is involved in everyday functional impairment in patients with mild cognitive impairment [19] and is a sensitive predictor of eventual Alzheimer's disease diagnosis [20, 21]. The aim was to observe how training would affect performance in attention, working memory, and delayed recall domains of cognitive assessments and determine if there were any transfer of training effects to other cognitive domains and everyday memory functioning.

Our primary hypothesis was that from pre- to post- intervention, participants randomized to the Intervention group (INT) compared with participants randomized to the Waitlist-Control (WL) group will exhibit greater improvement in total score on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [22]. Our secondary hypothesis was that the INT group will have greater improvement in scores than WL group in the five RBANS domains of Attention, Delayed Memory, Immediate Memory, Language, and Visuospatial Construction and in the total Rivermead Behavioral Memory Test (RBMT-II) [23] scale. Additionally, we predict that BRAINMEM is safe and acceptable, based on the incidence of adverse events (AE), adherence rates, and response to the acceptability questionnaire.

MATERIALS AND METHODS

Trial design and participants

This was a single-center, open-label trial with a waitlist-control group. Eligible participants were English-literate Chinese elderly between 60 and 80 years old, with a Clinical Dementia Rating (CDR) [24] score of 0–0.5, Mini-Mental State Examination (MMSE) [25] score of 24 and above, Geriatric Depression Scale (GDS) [26] of 4 and below, with no diagnoses of neuropsychiatric disorders, no uncorrected hearing, visual, or speech impairments, no color-blindness, and not taking rivastigmine, donepezil, galantamine, or memantine. Advertisements were displayed at hospitals and older adult organizations and published in newspapers to facilitate recruitment. Potential participants were also identified by the study team through word-of-mouth, and by referrals from investigators of the Singapore Longitudinal Aging Study (SLAS). The SLAS does

not have any procedures or assessments similar to the ones used in this study. The study procedures were conducted at the Neuroscience and Behavioral Disorders Department of the Duke-National University of Singapore Medical School in Singapore from July 2015 to June 2017.

Intervention

The cognitive training system, BRAINMEM, trains attention, working memory, and delayed recall through a brain-computer interface. The participants wore an adjustable BCI headband with dry EEG electrodes [27] to control the computer game. The intervention consisted of thrice-weekly training sessions for eight weeks followed by once-monthly booster sessions for three months. The duration of the study involvement was five months with a total of 27 training sessions. INT participants were given the intervention first, from Week 1 to 8 and went through their booster sessions on Weeks 12, 16, and 20. On the other hand, WL participants went about their lives as per normal from Week 1 to 8 before going through the intervention from Week 10 to 17 and booster sessions on Weeks 21, 25, and 29.

A color Stroop task calibration [27] was administered before the first training session to obtain a personalized electroencephalograph profile of each participant and was later used as the basis for neurofeedback, in the form of a Brain Score, during subsequent training. The training sessions were conducted on individual computer stations in separate cubicles at the BCI laboratory. A trained research staff was present to monitor the stability of the EEG signal transmission and to assist the participants when they encountered difficulties.

Each session took 40 minutes to complete and constituted a few rounds of the gameplay (Fig. 1). The number of rounds is dependent on how fast and accurate the participant is in memorizing and recalling items. Each round has three segments: Shopping List, Card Matching, and Shopping List Recall. During Shopping List, participants are shown some grocery items which they have to remember. The opacity of the items fluctuates according to their attentional levels which is reflected in the Brain Score (Range 0–100) on screen. They are required to modulate their attention such that it is high enough for the items to appear clearly. Participants learn to do so via feedback from the clarity of the items and their Brain Score. After which, the Card Matching segment is a distractor task that trains working memory and attention. At the beginning of each Card Matching round, cards are revealed for three seconds and participants are to memorize the positions of the matching pairs. Once the cards close, participants proceed to open or close the cards by regulating their Brain Score [16]. They have to maintain a certain level of attention for a certain amount of time, determined by the game parameters, to manipulate the cards successfully. Participants receive feedback via the time taken for them to open or close the cards and their Brain Score. After a stipulated amount of time has elapsed on Card Matching, they are directed to Shopping List Recall, a shopping page where they recall the grocery items in either an item-selection format or a free-response format. They are then shown their recall score on a feedback page. The difficulty of the subsequent round is dependent on their performance in the preceding round. Participants proceed to a more challenging level (i.e., More items to memorize in a shorter span of time, increase in duration of card matching segment before recall page appears) if they can recall all items. If they are unable to do so, they will replay the same level of the game with different grocery items. Participants also complete a transfer task (Face Matching) on alternate sessions. Here, participants memorize names of corresponding real-life human faces within the stipulated time. After which, the faces and names are jumbled up and participants match them. As training progresses, participants practice regulating their attention so that Shopping List items appear clearer and cards open or close faster. They also develop strategies independently to remember and recall grocery items, cards, and faces. They indicated their choice of strategies during their last training session in the acceptability questionnaire.

The study was reviewed and approved by National University of Singapore Institutional Review Board (NUS IRB), Reference Code B-14-099, before the commencement of any study procedures. All participants were given an explanation of the study before they signed an informed consent document and underwent the study protocol. Participants were free to withdraw consent and discontinue participation at any point. They could choose to withdraw from the intervention but continue with the remaining assessments or withdraw from the study completely. This was explicitly inquired upon their withdrawal. Their reasons for discontinuing were also documented if provided. Participants are considered 'lost to follow-up' if they discontinue their study participation completely.

Fig. 1. Screenshots of the BRAINMEM interface (L-R from top: Home page, Shopping List, Card Matching, Shopping List Recall [item-selection], Shopping List Recall [free-recall], Face Matching).

Outcome

The primary efficacy outcome was defined by the change in RBANS total score from the baseline after the INT participants had completed their eight-week intervention. The secondary efficacy outcomes were change-scores in RBMT-II total scale and RBANS domains of Attention, Delayed Memory, Immediate Memory, Language, and Visuospatial Construction in the same time frame. Trained research staff with at least a Bachelor's Degree in Psychology or Laboratory Medicine administered both the RBANS and RBMT-II to the participants during assessment visits. Assessment visits for both INT and WL groups were at Week 0 (baseline) and Week 9 (after the eight-week intervention for INT participants). Subsequently, the INT group was assessed again 12 weeks post-intervention and WL group was assessed after their eight-week intervention and 12 weeks post-intervention. The administration of assessments was standardized and conducted face-to-face. The RBANS and RBMT-II tests consist of four equivalent versions published by test developers for measuring change over time. Each version has the same format and number of questions. However, test questions are different across versions to prevent practice effects. The order of administration of the versions was randomized for each participant using an online list randomizer [28].

In addition to the efficacy of the BRAINMEM intervention, safety was monitored during all sessions. Research staff recorded AEs, if any, in a structured form detailing the type, severity, its relationship with the BRAINMEM intervention, and outcome. Participants were also advised to contact the study team in case AEs were experienced outside the research laboratory.

Acceptability of the training system was defined by the adherence rates and response to the acceptability questionnaire. Participants had to complete at least 20 training sessions to be considered adherent to the intervention protocol. On the last session of their BRAINMEM intervention, participants responded to an eight-item acceptability questionnaire to rate the BRAINMEM system on a seven-point scale.

Sample size

To detect an effect size of 0.4 with a two-sided 5% significance level and a power of 80%, a sample size of 100 per group was required. Assuming an attrition rate of 20%, a total of 240 participants were recruited for the study.

Randomization

Participants were randomized into the INT or WL group at a 1:1 allocation ratio, based on a computer-generated randomization list prepared by an independent third party (Singapore Clinical Research Institute Private Limited [SCRI]). Balanced treatment assignments were achieved using

block randomization stratified by education level with two levels [education up to secondary level and higher than secondary level]. Random block sizes of 4 and 6 were used. Block sizes were not made known to the research staff. Upon verification of eligibility and obtaining informed consent, authorized research staff randomized participants using a password-protected, web-based program provided by SCRI. The randomization system indicates the treatment group allocation and provides the unique subject number for the participant. In case of internet failure, backup randomization envelopes were available on site.

Masking

Participants and research staff were not blinded to the group allocation due to obvious differences in participation periods for both groups. To reduce bias, all research staff had a detailed manual on standard procedures to carry out during the BRAINMEM and assessment sessions. New staff were also trained and observed by senior research staff before carrying out trial-related activities formally. Research staff also convened weekly to audit and rectify assessment scoring discrepancies.

Statistical methods

A two-sample independent *t*-test was planned for all efficacy endpoints on the modified intention-to-treat (mITT) population. The mITT population includes all participants who were randomized and had completed at least the assessments on Week 0 and 9. However, a pre-specified stratified analysis on the primary endpoint indicated a sex moderation effect which was subsequently investigated via an Analysis of Covariance (ANCOVA) that included "group", "education" (stratification factor), and covariates "age" (years) and "baseline" (score at Week 0), and pre-selected interaction terms in the model. In the four models considered, one full and three reduced, the sex-moderation effect was evaluated by adding "sex" and a "group-by-sex" interaction term and examining the statistical significance of the interaction term at the 5% level. If significant, the sex moderation effect was deemed supported and the efficacy of BRAINMEM was consequently presented for each sex separately. Efficacy was evaluated using the difference in the least squares means between groups with corresponding 95% confidence intervals. This approach was replicated for the secondary efficacy endpoint of RBMT-II. We checked the sustainability of the effect of the BRAINMEM intervention descriptively by confirming non-reversion of their final RBANS and RBMT-II scores to their pre-intervention scores at Week 0 and 9 for INT and WL groups, respectively.

The safety and acceptability of BRAINMEM were assessed on the treated population, consisting of participants who underwent at least one BRAINMEM session. We examined safety by documenting the number of participants who discontinued intervention prematurely and summarizing the frequency and type of AEs for the pooled group of INT and WL participants. To examine acceptability, responses to the questionnaire were tabulated and summarized descriptively per item using means, standard deviations, or proportions, as appropriate. For participants who were not able to complete the questionnaire because of premature discontinuation or loss to follow-up, the missing response was set to the lowest possible rating.

RESULTS

119 participants were randomized to the INT group and 121 to the WL group (Fig. 2). In the INT group, 108 participants completed their study participation according to protocol while 1 participant withdrew from the intervention but attended all assessment sessions. In the WL group, 106 completed their study participation according to protocol while 7 withdrew from the intervention but attended all assessment sessions. A total of 18 participants withdrew from the study and a final 227 (94.6%) participants were considered for the mITT population for efficacy analysis.

The mean age of participants was 66.0 years (SD = 4.70). A majority of them were females (57.3%) and had attained above secondary education levels (63.9%). Overall, both groups were comparable in socio-demographic characteristics (Table 1).

At Week 9, both INT and WL groups improved in the RBANS total score (INT, +3.6 [95% CI 1.5 to 5.7]; WL, +2.9 [95% CI 1.0 to 4.9]), but the mean difference in improvement was not statistically significant (+0.68 [95% CI –2.2 to 3.5], $p = 0.640$). Similar observations were made in the Attention, Delayed Memory, Immediate Memory, and Visuospatial Construction scores, and RBMT-II total scores (Table 2).

When analyses were stratified by sex, divergent outcomes between males and females were observed. INT males performed significantly better than WL

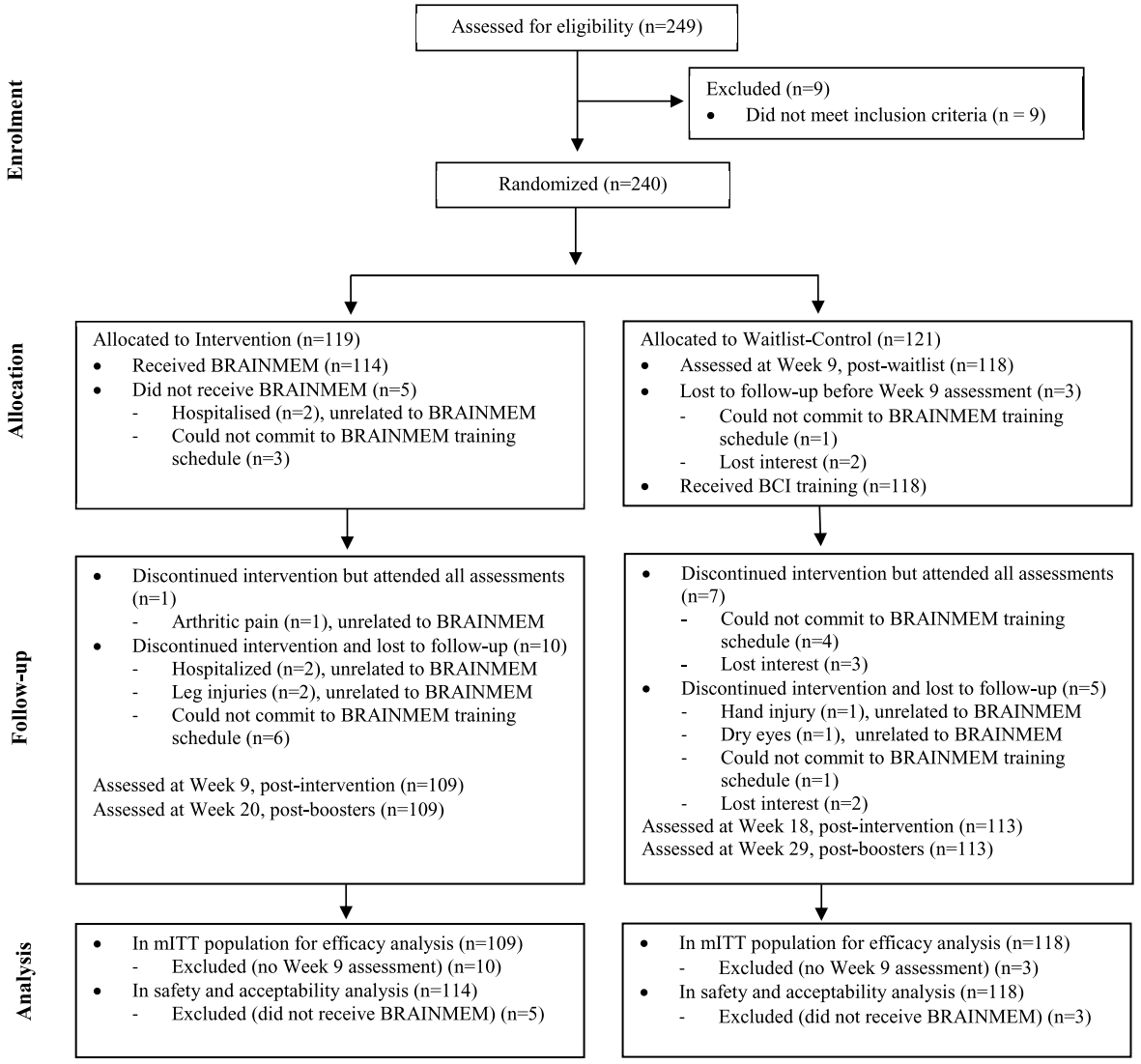

Fig. 2. Trial profile.

males in the RBANS total score at Week 9 (INT, +6.2 [95% CI 2.8 to 9.6]; WL, –0.2 [95% CI –3.3 to 2.9]; mean difference, +6.4 [95% CI: 1.9 to 10.8], $p = 0.006$). In the RBANS subscales of Delayed Memory and Language, INT males also improved significantly more their WL counterparts (Table 2). Among females, INT participants did not improve as much as the WL participants in the RBANS total score (INT, +1.6 [95% CI –1.1 to 4.3]; WL, +5.2 [95% CI 2.9 to 7.5]; mean difference of –3.6 [95% CI –7.1 to –0.12], $p = 0.044$). WL females also improved in the Language score while INT females did worse than their performance at baseline (Table 2).

The formal investigation of the sex moderation effect supported the initial findings. A significant sex-by-group interaction was found in the total RBANS score ($p = 0.014$) and in the Delayed Memory ($p = 0.043$) and Language ($p = 0.026$) scores. The results were consistent across three other ANCOVA models considered (Supplementary Table 1). When ANCOVA analysis was conducted adjusting for age, education level and baseline score, INT males improved more than WL males in the RBANS total score (INT, +4.06 [95% CI 1.2 to 6.9]; WL, +0.03 [95% CI –2.7 to 2.8]; mean difference, +4.03 [95% CI 0.1 to 8.0], $p = 0.046$). INT males also improved significantly more than WL males in the Delayed Memory and Language scores (Table 3).

Conversely, in females, both INT and WL participants improved in the RBANS total score although

Table 1
Baseline socio-demographic characteristics

	Intervention (N = 109)	Waitlist (N = 118)	Total (N = 227)
Age (y)			
Mean (SD)	66.2 (4.74)	65.8 (4.65)	66.0 (4.70)
Median (IQR)	65.0 (7.00)	65.0 (5.00)	65.0 (7.00)
Min, Max	60.0, 80.0	60.0, 79.0	60.0, 80.0
Sex			
Male	47 (43.1%)	50 (42.4%)	97 (42.7%)
Female	62 (56.9%)	68 (57.6%)	130 (57.3%)
Education level			
Up to Secondary education	39 (35.8%)	43 (36.4%)	82 (36.1%)
Above secondary education	70 (64.2%)	75 (63.6%)	145 (63.9%)
Employment Status			
Unemployed	1 (0.9%)	1 (0.8%)	2 (0.9%)
Self-employed	9 (8.3%)	14 (11.9%)	23 (10.1%)
Employed full-time	6 (5.5%)	10 (8.5%)	16 (7.0%)
Employed part-time	16 (14.7%)	12 (10.2%)	28 (12.3%)
Housemaker	6 (5.5%)	11 (9.3%)	17 (7.5%)
Retired	71 (65.1%)	70 (59.3%)	141 (62.1%)
MMSE			
Mean (SD)	28.6 (1.41)	28.6 (1.42)	28.6 (1.41)
Median (IQR)	29.0 (2.00)	29.0 (2.00)	29.0 (2.00)
Min, Max	24,30	24,30	24,30
CDR			
0	89 (81.7%)	99 (83.9%)	188 (82.8%)
0.5	20 (18.3%)	19 (16.1%)	39 (17.2%)
Baseline RBANS total score			
Mean (SD)	100.5 (11.17)	100.0 (12.05)	100.2 (11.61)
Median (IQR)	100.0 (18.00)	101.5 (16.00)	101.0 (16.00)
Min, Max	77,127	65,137	65,137
Male Baseline RBANS total score			
Mean (SD)	97.2 (11.07)	99.9 (12.01)	98.6 (11.59)
Median (IQR)	97.0 (16.00)	101.5 (15.25)	98.0 (16.00)
Min, Max	77,119	76,137	76,137
Female Baseline RBANS total score			
Mean (SD)	103.0 (10.66)	100.0 (12.17)	101.4 (11.53)
Median (IQR)	104.0 (16.25)	101.5 (15.00)	102.0 (16.25)
Min, Max	80,127	65,125	65,127

MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

the mean difference in improvement did not reach significance (INT, +2.36 [95% CI –0.1 to 4.8]; WL, +4.80 [95% CI 2.5 to 7.1]; mean difference, –2.44 [95% CI –5.8 to 0.9], $p = 0.154$). This trend was also observed in the Attention, Delayed Memory, Immediate Memory, and Visuospatial Construction scores (Table 3). In males and females, there were no significant mean between-group differences in improvement of their scores on the RBMT-II (Table 3). The pattern of results observed in the three ANCOVA reduced models was consistent with that of the full ANCOVA model (Supplementary Table 2).

In the exploration of the sustainability of training effect across INT and WL groups, the change at 12 weeks post-intervention from pre-intervention was positive (Supplementary Table 3). Specifically, the RBANS total scores for the INT males 12 weeks post-intervention was higher than their baseline score (+5.13 [95% CI 1.97 to 8.29], $p = 0.002$). A similar observation was made for their Delayed Memory scores (+7.11 [95% CI 4.30 to 9.92], $p < 0.0001$) and Language scores (+0.17 [95% CI –4.98 to 5.32], $p = 0.947$).

Harms and acceptability

5.2% of the participants experienced an AE during the intervention and a total of 16 AE episodes were reported (Table 4). The types of AEs that were evaluated to be "Possibly related to BRAINMEM training" were headache ($n = 6$), eye strain ($n = 3$), dizziness ($n = 2$), and fatigue ($n = 1$). All AEs were rated to be of mild severity and were resolved without sequelae by the end of the study.

Table 2
Efficacy of BRAINMEM: overall and sex-stratified analyses based on the two-sample *t*-test

	Within-group change scores				Between-group Differences		
	INT ($n = 109$)		WL ($n = 118$)				
	Δ_1 at Week 9	95% CI	Δ_2 at Week 9	95% CI	Mean Difference ($MD = \Delta_1 - \Delta_2$)	95% CI	*p*
ALL ($n = 227$)							
Total RBANS	+3.61	1.48, 5.74	+2.93	0.99, 4.87	+0.68	–2.17, 3.53	0.6399
Attention	+0.98	–1.40, 3.36	+3.55	1.35, 5.75	–2.57	–5.77, 0.63	0.1164
Delayed Memory	+4.53	2.72, 6.84	+2.94	0.88, 5.00	+1.59	–1.12, 4.30	0.2541
Immediate memory	+3.69	1.13, 6.26	+3.49	0.86, 6.12	+0.20	–3.44, 3.84	0.9145
Language	+0.82	–2.38, 4.02	–0.52	–3.50, 2.46	+1.34	–2.98, 5.66	0.5457
Visuospatial Construction	+2.32	–0.42, 5.06	+0.42	–2.02, 2.86	+1.90	1.71, 5.53	0.3041
Total RBMT-II	+1.18	0.45, 1.91	+0.27	–2.13, 2.67	+0.91	–1.57, 3.39	0.4877
MALES ($n = 97$)	$n = 47$		$n = 50$				
Total RBANS	**+6.20**	**2.80, 9.6**	**–0.20**	**–3.30, 2.90**	**+6.40**	**1.92, 10.80**	**0.0061**
Attention	+2.10	–1.30, 5.50	+3.50	0.70, 6.30	–1.40	–5.69, 2.89	0.5220
Delayed Memory	**+6.30**	**3.40, 9.20**	**+0.90**	**–2.00, 3.80**	**+5.40**	**1.40, 9.40**	**0.0095**
Immediate memory	+7.90	4.20, 11.60	+8.80	4.40, 13.20	–0.90	–6.50, 4.70	0.7551
Language	**+5.10**	**0.60, 9.60**	**–2.80**	**–7.60, 2.00**	**+7.90**	**1.49, 14.31**	**0.0180**
Visuospatial Construction	+0.40	–3.40, 4.20	–0.70	–4.70, 3.30	+1.10	–4.28, 6.48	0.6900
Total RBMT-II	+1.10	–0.00, 2.20	+0.8	–0.30, 1.90	+0.30	–1.22, 1.82	0.6994
FEMALES ($n = 130$)	$n = 62$		$n = 68$				
Total RBANS	**+1.60**	**–1.10, 4.30**	**+5.20**	**2.90, 7.50**	**–3.60**	**–7.08, –0.12**	**0.0435**
Attention	+3.00	–0.30, 6.30	+3.70	0.70, 6.70	–0.70	–5.07, 3.67	0.7538
Delayed Memory	+6.40	3.90, 8.90	+7.70	5.00, 10.40	–1.30	–4.91, 2.31	0.4841
Immediate memory	+6.50	3.14, 9.94	+10.00	6.70, 13.30	–3.50	–8.15, 1.15	0.1474
Language	**–2.30**	**–6.20, 1.60**	**+3.50**	**–0.30, 7.30**	**–5.80**	**–11.14, –0.46**	**0.0354**
Visuospatial Construction	+4.00	0.00, 8.00	+4.20	0.20, 8.20	–0.20	–5.75, 5.35	0.9439
Total RBMT-II	+1.80	–1.00, 2.60	+2.00	1.10, 2.90	–0.20	–1.38, 0.98	0.7425

RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RBMT-II, Rivermead Behavioral Memory Test (RBMT-II).

Table 3
Efficacy of BRAINMEM: overall and sex-stratified analyses based on ANCOVA full model

	Within-group change scores				Between-group Differences		
	INT ($n = 109$)		WL ($n = 118$)				
	Δ_1 at Week 9	95% CI	Δ_2 at Week 9	95% CI	Mean Difference ($MD = \Delta_1 - \Delta_2$)	95% CI	*p*
ALL ($n = 227$)							
Total RBANS	+3.21	1.32, 5.10	+2.42	0.60, 4.23	+0.79	–1.83, 3.42	0.5517
Attention	+1.03	–1.27, 3.33	+3.65	1.44, 5.86	–2.62	–5.81, 0.57	0.1067
Delayed Memory	+4.47	2.65, 6.29	+2.36	0.61, 4.12	+2.11	–0.42, 4.63	0.1021
Immediate memory	+2.99	0.69, 5.29	+2.90	0.69, 5.12	+0.09	–3.11, 3.28	0.9569
Language	+0.74	–1.79, 3.27	–1.22	–3.65, 1.21	+1.96	–1.55, 5.47	0.2720
Visuospatial Construction	+2.27	0.12, 4.66	–0.25	–2.53, 2.04	+2.52	–0.79, 5.82	0.1357
Total RBMT	+1.01	0.40, 1.61	+0.33	–0.25, 0.91	+0.68	–0.16, 1.51	0.1129
MALES ($n = 97$)	$n = 47$		$n = 50$				
Total RBANS	**+4.06**	**1.19, 6.93**	**+0.03**	**–2.72, 2.78**	**+4.03**	**0.07, 7.99**	**0.0460**
Attention	+0.76	–2.72, 4.24	+2.68	–0.66, 6.03	–1.92	–6.73, 2.89	0.4316
Delayed Memory	**+4.90**	**2.18, 7.63**	**+0.25**	**–2.41, 2.92**	**+4.65**	**0.85, 8.45**	**0.0166**
Immediate memory	+2.70	–0.76, 6.16	+0.15	–3.21, 3.53	+2.55	–2.26, 7.36	0.2973
Language	**+2.69**	**–1.08, 6.46**	**–3.12**	**–6.80, 0.56**	**+5.81**	**0.57, 11.04**	**0.0300**
Visuospatial Construction	+3.33	–0.22, 6.88	–0.93	–4.43, 2.57	+4.26	–0.70, 9.22	0.0916
Total RBMT	+0.55	–0.34, 1.44	+0.05	–0.83, 0.92	+0.50	–0.74, 1.75	0.4246
FEMALES ($n = 130$)	$n = 62$		$n = 68$				
Total RBANS	+2.36	–0.09, 4.81	+4.80	2.50, 7.10	–2.44	–5.80, 0.92	0.1536
Attention	+1.30	–1.66, 4.26	+4.62	1.82, 7.42	–3.32	–7.40, 0.75	0.1097
Delayed Memory	+4.04	1.66, 6.41	+4.48	2.26, 6.70	–0.44	–3.69, 2.81	0.7899
Immediate memory	+3.28	0.31, 6.24	+5.65	2.85, 8.45	–2.37	–6.45, 1.70	0.2523
Language	–1.20	–4.48, 2.07	+0.68	–2.40, 3.76	–1.88	–6.38, 2.61	0.4095
Visuospatial Construction	+1.21	–1.85, 4.26	+0.44	–0.44, 3.37	+0.77	–3.46, 5.00	0.7207
Total RBMT	+1.46	0.69, 2.24	+0.62	–0.12, 1.35	+0.84	–0.22, 1.91	0.1195

RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RBMT-II, Rivermead Behavioral Memory Test (RBMT-II).

Table 4
Safety of BRAINMEM training system

	Intervention ($n = 114$)		Waitlist ($n = 118$)		Total ($n = 232$)	
	n (%)	nAE	*n* (%)	nAE	*n* (%)	nAE
Participants who experienced AE	10 (8.8)	14	2 (1.7)	2	12 (5.2)	16
Eye Strain	1 (0.9)	2	1 (0.8)	1	2 (0.9)	3
Fatigue	2 (1.8)	2	0	0	2 (0.9)	2
Headache	7 (6.1)	8	1 (0.8)	1	8 (3.4)	9
Syncope/Dizziness	2 (1.8)	2	0	0	2 (0.9)	2
Relationship with BRAINMEM training						
None	1 (0.9)	1	0	0	1 (0.4)	1
Unlikely	3 (2.6)	3	0	0	3 (1.3)	3
Possible	7 (6.1)	10	2 (1.7)	2	9 (3.9)	12
Outcome						
Recovered/Resolved	10 (8.8)	14	2 (1.7)	2	12 (5.2)	16
None	10 (8.8)	14	1 (0.8)	1	11 (4.7)	15
Discontinued	0	0	1 (0.8)	1	1 (0.4)	1

AE, adverse events.

Adherence to the BRAINMEM intervention was high with 214 (92.2%) participants completing at least 20 sessions. Additionally, participants who completed the acceptability questionnaire indicated acceptance of the BRAINMEM system. When lowest possible ratings were imputed for 16 participants who received the intervention but did not complete the questionnaire, the results still supported an overall acceptable rating (Table 5).

DISCUSSION

The BRAINMEM intervention did not result in overall cognitive performance gains or improvements in individual cognitive domains like attention or delayed memory. There was also no discernible improvement in everyday memory functioning. However, cognitive performance gains were seen in males, particularly in the domains of delayed memory and language. On the contrary, there were no performance improvements in females who had received the intervention first when compared to females who had not received the intervention. This discrepancy in performance between sexes possibly drove the overall non-significant results.

Sex differences in treatment response have been reported in randomized controlled trials of other cognitive intervention modalities. In older adults with mild cognitive impairment, women responded better than men to pharmacological and physical interventions [29–32]. However, there is no known CT study that has reported sex differences. Moreover, the literature on sex differences in older adult cognitive performance is still unclear. Some studies have indicated that women tend to perform better at baseline and experience less rapid decline in cognitive abilities over time when compared with men [33]. Others have reported that among healthy elderly, while there are sex differences in performances in some cognitive domains, rates of declines between sexes are similar till at least the age of 80 [34]. Among older adults with Alzheimer's disease, however, men perform better than women across cognitive domains [35]. It is plausible that the performance disparities between sexes may be due to the interaction of historical sociodemographic differences [34, 36] with the effects of sex hormones [37] and sex differences in brain structure [33]. Ultimately, there could be many explanations as to why men may have a greater propensity than women to benefit from the BRAINMEM intervention but replicating this result is key.

Another possible reason for the lack of overall efficacy could be due to participant characteristics. Most of the participants responded to our recruitment advertisements on their own initiative and expressed concern about their memory as a major factor for their interest in participation. It is highly probable that the self-selected participants are motivated older adults who are already leading active lifestyles and participating in cognitively stimulating activities. On top of that, 63.7% of the participants had also received education above the secondary level (high school equivalent). Improvements made by participants who were not performing well at baseline could have been masked by the small or lack of improvement in the majority of the participants. It is likely due to this that we were also unable to establish transfer effects of our intervention on everyday memory tasks as assessed by the RBMT-II.

Table 5
Acceptability questionnaire responses (rated on a seven-point scale)

#	Acceptability item	*n*	Mean	SD	Median	IQR	Range	Worst mean ($n = 232$)	Worst SD ($n = 232$)
1	I am satisfied with the whole experience of playing the games with the BCI device	216	6.0	1.2	6.0	1.5	1, 7	5.7	1.7
2	It was difficult to use this device	216	1.9	1.4	1.0	1.0	1, 7	2.3	1.9
3	I enjoyed playing the games	216	6.0	1.4	6.0	2.0	1, 7	5.7	2.0
4	I felt uncomfortable using this device	216	1.8	1.5	1.0	1.0	1, 7	2.2	2.0
5	My memory has become better after using this device	216	5.0	1.4	5.0	2.0	1, 7	4.8	1.7
6	The device is not useful in training my memory and attention	216	2.6	1.5	2.0	3.0	1, 7	3.0	1.9
7	I would recommend this device to my friends and family	216	5.6	1.5	6.0	2.0	1, 7	5.3	1.9
8	Overall, I am not satisfied with the whole system	216	2.0	1.4	1.5	1.0	1, 7	2.4	1.9

The high participant adherence to the intervention and low incidence of mild AEs indicates that BRAINMEM is probably safe and acceptable. AEs like fatigue, eye strain, and headache tend to occur when the BCI headbands are worn too tightly, or when participants are not accustomed to staring at the computer screen for extended periods of time. This can be avoided with proper fitting of the BCI headband and taking intermittent vision breaks when necessary. To the best of the authors' knowledge, no other study on computerized cognitive training has reported on the safety and adverse events. Hence it is not possible to ascertain if the reported AEs are expected with any cognitive training intervention employing a computerized platform. Further, the majority of the participants expressed support for the system and were confident that their memory had improved from participating in the intervention. Although this could be a placebo effect, attitudes and self-efficacy perception are among the most powerful predictors of technology use [38] and such positive response indicates that older adults are open to engaging in CT activities via technological platforms.

Pertinent limitations of this trial require discussion. Firstly, the lack of a sham control restricted our understanding of the specific effects of our intervention. Owing to the nature of our training interface, a sham feedback would subject WL participants to random feedback of their attentional level. This may engender frustration when the game does not proceed despite participants being fully focused, or lead participants to lose motivation when they realize that the feedback is false. Further, a sham feedback might influence participants to modulate their brain activity in a detrimental manner. Consequently, the team chose the waitlist design.

Secondly, it would also have been ideal to deliver BRAINMEM to the WL participants after the INT participants had completed their entire study participation at Week 29 to allow unbiased testing of effect sustainability of the training. However, with the present study design where the WL participants waited for 8 weeks before commencing their training, it was observed that they lost interest in the intervention or took up other commitments during this waiting period and became unable to commit to the training schedule. This contributed to a differential drop-out rate between the INT and WL group. Hence, a longer waiting period would have risked a greater attrition of WL participants. With this design limitation, any statistical testing of the sustainability of effect was confounded with time, permitting only a pre-post comparison without a true control group. Future studies on personalized neurofeedback training may look into statistically testing for effect sustainability so as to empirically validate the current findings.

Finally, the lack of generalizability is problematic. We attempted to recruit participants from a wide range of education backgrounds by advertising the study in various settings and stratifying our participants according to their education levels. Despite so, we did not achieve a diverse enough sample. Therefore, it would not be prudent to generalize these results to other older adults who may not be in the same demographic. Subsequent research should explore the effects of personalized neurofeedback

training on older adults of other ethnicity, education attainment, and socio-economic standing.

Conclusions

All things considered, a personalized neurofeedback system using BCI technology for memory and attention training has potential to be used for cognitive training for healthy older men. Future studies will have to be conducted to establish if BRAINMEM is more efficacious than existing CT paradigms. The novelty of the BRAINMEM system can decrease the barrier to engagement among older adults and sustain motivation for participating in CT for the long haul. Above all, the significant interaction effects between sex and the treatment group highlight the importance of considering sex differences when investigating and remediating cognitive issues in older adults.

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SUPPLEMENTARY MATERIAL

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