Journal of Alzheimer's Disease 44 (2015) 1181–1191
DOI 10.3233/JAD-142061
IOS Press

Randomized Controlled Trial of a Healthy Brain Ageing Cognitive Training Program: Effects on Memory, Mood, and Sleep

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Handling Associate Editor: Michael Hornberger

Accepted 17 October 2014

Abstract.
Background: With the rise in the ageing population and absence of a cure for dementia, cost-effective prevention strategies for those 'at risk' of dementia including those with depression and/or mild cognitive impairment are urgently required.
Objective: This study evaluated the efficacy of a multifaceted Healthy Brain Ageing Cognitive Training (HBA-CT) program for older adults 'at risk' of dementia.
Methods: Using a single-blinded design, 64 participants (mean age = 66.5 years, SD = 8.6) were randomized to an immediate treatment (HBA-CT) or treatment-as-usual control arm. The HBA-CT intervention was conducted twice-weekly for seven weeks and comprised group-based psychoeducation about cognitive strategies and modifiable lifestyle factors pertaining to healthy brain ageing, and computerized cognitive training.
Results: In comparison to the treatment-as-usual control arm, the HBA-CT program was associated with improvements in verbal memory ($p = 0.03$), self-reported memory ($p = 0.03$), mood ($p = 0.01$), and sleep ($p = 0.01$). While the improvements in memory ($p = 0.03$) and sleep ($p = 0.02$) remained after controlling for improvements in mood, only a trend in verbal memory improvement was apparent after controlling for sleep.
Conclusion: The HBA-CT program improves cognitive, mood, and sleep functions in older adults 'at risk' of dementia, and therefore offers promise as a secondary prevention strategy.

Keywords: Depression, memory, mild cognitive impairment, neuropsychology, sleep disorders

INTRODUCTION

With the projected rise in the aging population and absence of a cure for dementia, cost-effective prevention strategies for those 'at risk' of dementia are urgently required. Cognitive training (CT) is one strategy that holds promise for healthy and 'at risk' aging populations [1–4] including those with depression and/or mild cognitive impairment (MCI). While efficacy for CT has been reported using both strategy-based and computer-based techniques, few studies have combined the two. Moreover, it is argued that programs should provide a multifaceted approach to CT, including education regarding optimization of healthy brain aging. Provision of such information may enable consumers to make informed medical and lifestyle choices, adopt healthier lifestyles, and adhere to treatment regimes.

Previously, in late-life depression and Parkinson's disease, we have reported a multifaceted Healthy Brain Ageing Cognitive Training (HBA-CT) program to be efficacious in improving memory [5, 6] and knowledge of healthy brain aging [6, 7]. Other large scale studies

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ISSN 1387-2877/15/$35.00

[8, 9] investigating multi-domain interventions are also now underway and will no doubt provide invaluable information about the efficacy of non-pharmacological interventions for cognitive decline in older adults.

In this study, we seek to extend our prior work by conducting a randomized controlled trial investigating the efficacy of the HBA-CT program in older adults 'at risk' of dementia.

METHODS

Sample

In accordance with our previous research on cognitive training in older adults [5, 10], we conducted *a priori* power calculations based on 80% power, medium effect sizes, and $\alpha = 0.05$ and revealed that we required 90 participants.

Commencing August 2009, 112 help-seeking older adults 'at risk' of cognitive decline were recruited from the 'Healthy Brain Ageing' Clinic, a specialist early intervention clinic at the Brain & Mind Research Institute, Sydney, Australia. Follow-up assessments for this sample were completed in March 2012. For the purpose of this study, 'at risk' was defined as individuals help-seeking for new onset cognitive impairment and/or major depression. Additional inclusion criteria were: aged $\geq$50 years; adequate English for neuropsychological assessment; stabilization on medication regimes; normal to mild depressive symptoms as determined by a Hamilton Depression Rating Scale score (HDRS) [11] of <20; and willingness to attend seven weeks of twice-weekly therapy. Exclusion criteria were: history of stroke; neurological disorder; head injury with loss of consciousness $\geq$30-min; medical condition known to affect cognition (e.g., cancer); dementia and/or a Mini-Mental State Examination (MMSE) [12] score of <24. This research was approved by the Human Research Ethics Committee of the University of Sydney. Written informed consent was obtained from all participants. This study was registered with the Australian and New Zealand Clinical Trials Register No. ACTRN12611000570987.

Design

This was a randomized controlled design. Figure 1 illustrates the timeline of the assessment and intervention procedure. Participants were randomly allocated to either: a) immediate intervention (treatment group); or b) treatment-as-usual waitlist (control group) on a 1:1 basis using simple randomization methods. Randomization was carried out by a Clinical Trials Manager who was blinded to patient status throughout the study. The randomization scheme was prepared prior to study commencement using a computerized random number generator (GraphPad Software Inc.). The randomization scheme was stored on a password protected server and concealed from participants and researchers alike. After baseline assessments, all participants received a sealed envelope containing their randomization outcome. Regardless of the participants' allocated condition, all baseline assessments were conducted within a fortnight of the seven-week intervention period commencement (i.e., weeks one and two), and all follow-up assessments were conducted within a fortnight of the intervention period cessation (i.e., weeks ten and eleven). All clinicians conducting baseline and follow-up assessments were blinded to participants' allocated condition. For ethical reasons, after completion of the follow-up assessments (i.e., after week eleven), all control participants were offered the next available place in a subsequent CT group.

Procedure

At baseline, all participants completed a standardized battery of neuropsychological tests and were assessed by an Old Age Psychiatrist (LN, MP). These assessments were repeated following the seven-week intervention period.

Measures

Psychiatric and medical assessment

As described previously [13], an Old Age Psychiatrist recorded depressive symptoms using the 17-item HDRS, medical burden using the Cumulative Illness Rating Scale–Geriatric version [14] and general psychosocial functioning using the Global Assessment of Functioning Scale (GAFS) [15]. The Structured Clinical Interview for DSM-IV [16] Disorders was used to ascertain current and lifetime major depression diagnoses.

Neuropsychological assessment

A Clinical Neuropsychologist administered a battery of standardized neuropsychological tasks. Where possible standard and alternate forms were utilized and counter-balanced across baseline and follow-up assessments. Standardized scores (i.e., *z*-scores or age scaled scores) were calculated for all tests. For descriptive purposes, premorbid intellectual ability

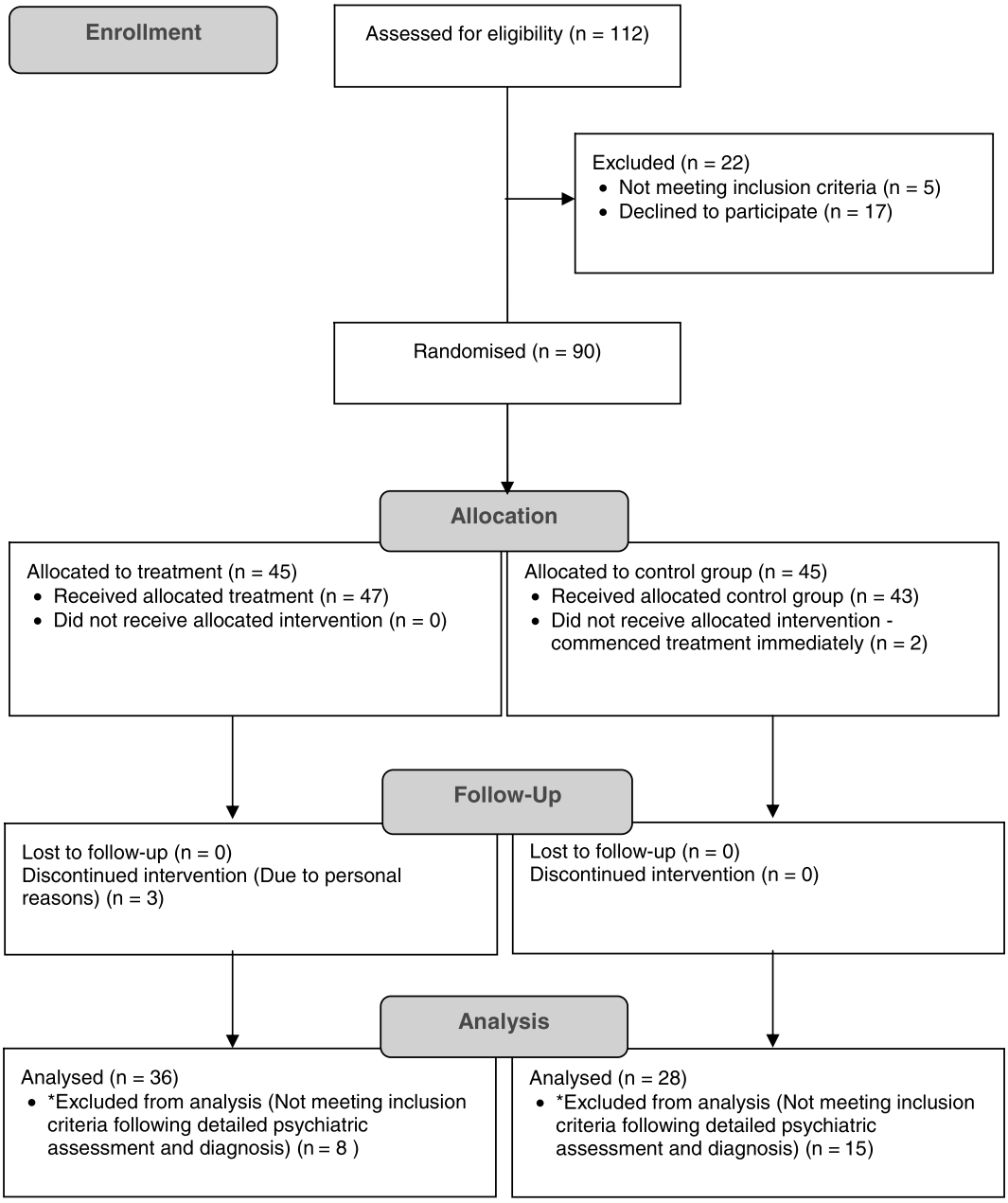

Fig. 1. Flowchart of the study design.
*Note: The decision to exclude participants was made after detailed review of baseline assessments and prior to any data analysis.

was estimated using the Wechsler Test of Adult Reading [17] and global cognition was measured using the MMSE.

Neuropsychological assessment results were used to determine MCI diagnosis using Winblad's criteria [18] and by consensus rating. For descriptive purposes, single and multiple domain MCI were categorized according to the presence of impairment in only one versus multiple cognitive domains, respectively. Individuals were further categorized as demonstrating either amnestic (aMCI) or non-amnestic (naMCI) MCI [13, 19].

Primary outcomes: Verbal learning and memory

Based on our prior work in this area [5, 6, 20], the following tests were used to objectively evaluate memory:

a) The *Rey Auditory Verbal Learning Test* (RAVLT) [21] was administered to measure unstructured verbal learning and recall. Total learning over five trials (RAVLT-15; maximum = 60) was examined. To obtain a measure of memory consolidation, percent retention scores (i.e., [Trial 7/ Trial 5]*100) were also calculated (RAVLT%). Alternate forms were available for this test.
b) The *Logical Memory* subtest of the Wechsler Memory Scale-III [22] was used to assess structured verbal learning and memory. Total learning comprised summed scores for recall of story A and first and second recall of story B (LOGMEM-I). Once again, percent retention scores (LOGMEM delayed recall / [LOGMEM-I story A+ second recall Story B]*100) were calculated (LOGMEM%) as a measure of memory consolidation, regardless of learning.

Secondary outcomes: General cognition

a) The *Rey Osterrieth Complex Figure Test* (RCFT) [23] three-minute recall was used to assess non-verbal memory. The Taylor Figure was used as an alternate form.
b) *Language generativity* was assessed using *phonemic* (F, A, S) and *semantic* (types of animals) verbal fluency, comprising the total number of words generated in three minutes and one minute respectively [23]. Alternate forms (C, F, L) were used for phonemic fluency.
c) The total score from the *Wechsler Adult Intelligence Scale–III Digit Span* [24] subtest was used as a measure of auditory *working memory*.
d) The *Trailmaking Test* Part A (TMT-A, seconds) [25] was used to assess psychomotor speed. Alternate forms were used for this test.
e) The *Trailmaking Test* Part B (TMT-B, seconds) [25] was used to assess set-shifting/cognitive flexibility. Alternate forms were used for this test.

Secondary outcomes: Self-reported functioning

a) *Subjective memory:* The Everyday Memory Questionnaire – revised (EMQ) [26] was used to assess subjective memory functioning. This 13-item questionnaire measures the frequency of subjective memory difficulties in everyday life. Higher total scores are suggestive of poorer subjective memory.
b) *Subjective mood:* Participants completed the 30-item Geriatric Depression Scale (GDS) [27]. Scores between 0–9, 10–19, and 20–30 are suggestive of "normal", "mild", and "severe" depression, respectively.
c) *Sleep:* The Pittsburgh Sleep Quality Index (PSQI) [28] was used to measure sleep disturbance. Higher total scores (range 0–21) indicate poorer sleep quality.

Intervention

The intervention comprised a seven-week: a) treatment-as-usual control condition; or, b) the HBA-CT treatment, detailed as follows:

a) Control – Treatment-as-usual: This included a waitlist period of no contact from the researchers. However, participants received standard clinical care from their usual health-care professionals.
b) Treatment – HBA-CT: The intervention was an extended version of that published previously [5]. In this trial, we extended the number of CT sessions from 10 to 14, and conducted the sessions twice weekly over seven weeks, instead of once a week for 10 weeks. Each group session comprised a maximum of 10 participants and included: i) one-hour of Healthy Brain Ageing psychoeducation; and ii) one-hour of computer-based CT.

i) *Psychoeducation*: This program has been described previously [5, 7] but included four extra sessions for rehearsal of memory strategies, elaboration of diet and exercise material, and inclusion of a practical session on 'using the internet'. All material was delivered by specialists (e.g., Psychiatrists, Neurologists, Neuropsychologists, Clinical Psychologists) via *PowerPoint* and was supplemented with handouts.
ii) *Cognitive training*: As employed previously [5, 6, 20], the CT intervention was delivered by Clinical Neuropsychologists and utilized Medalia's Neuropsychological Educational Approach to Remediation [29]. As reported previously [5, 6, 20], computer-based CT tasks included a variety of widely available educational software and specific 'brain-training' packages.

Statistical analyses

Statistical analyses were performed using SPSS for Windows 20.0.0 (SPSS Inc., Chicago). Baseline group differences for demographic and clinical variables were assessed using one-way analysis of variance (ANOVA). Data were evaluated for deviations from normality. For each outcome measure, a two-way repeated measures ANOVA was constructed. Analyses

tested for a Condition × Time interaction. A complete case analysis was used. Repeated measures analyses were also rerun using mean substitution for participants who were lost to follow-up and the results were largely unchanged. All analyses were two-tailed and used an alpha value of 0.05. Effect sizes were calculated for all significant interactions using Pearson's correlation (r) as recommended by Field [30].

RESULTS

Baseline descriptive sample characteristics

As shown in Fig. 1, of the 112 participants referred into the trial, 90 participants met eligibility criteria and completed baseline assessments. Of this group, 45 were randomized to receive treatment immediately and 45 were randomized to the control group. An administration error occurred in the randomization procedure resulting in two patients incorrectly receiving treatment immediately (i.e., 47 patients received treatment immediately and 43 received treatment-as-usual). Three participants dropped out of the treatment condition due to personal reasons. Prior to analysis, a further eight patients from the treatment group and 15 patients from the control group were excluded because it was determined that they met exclusion criteria following detailed review of their medical/psychiatric assessment and diagnosis. Therefore, the final sample size (i.e., those who completed the study and were deemed eligible for the final analyses) was $n = 36$ treatment participants and $n = 28$ control participants.

On average, participants were 66.5 years old (range: 51–86 years, SD = 8.6) and 67% (i.e., 21/64) of the sample was female. The mean level of education was 14 years (SD = 3.3). Premorbid IQ was in the Average range (mean = 105.2, SD = 8.8) and the average MMSE (mean = 28.4, SD = 1.5) was well above the cut off for dementia (i.e., MMSE = 24).

Clinician-rated mood suggested that patients were generally euthymic (mean HDRS = 5.45, SD = 4.1) and, on average, self-reported levels of depression were in the mild range (mean GDS = 12.9, SD = 7.3). Subjective PSQI ratings were suggestive of compromised sleep quality (mean = 7.03, SD = 4.08). Clinician GAFS ratings suggested that on average, participants were experiencing some difficulty in social or occupational functioning, but were generally functioning well, and had some meaningful interpersonal relationships (mean = 70.9, SD = 11.0, range = 35–95). Eighty one percent (52/64) of participants met criteria for MCI, of which 31% (16/52) demonstrated aMCI and 69% (36/52) demonstrated naMCI. Twenty-nine patients (45.3%) had a lifetime history of depression and of these people, three (4.7%) met DSM-IV criteria for a current Major Depressive Episode at baseline.

Baseline group differences

As shown in Table 1, at baseline, there were no significant differences between the treatment and control groups in terms of demographics, MMSE, psychosocial functioning, mood, sleep quality, subjective memory, MCI diagnosis, depression history, or neuropsychological test performance.

Table 1
Baseline scores for the clinical and demographic characteristics of the control and cognitive training groups

	Treatment ($n = 36$)	Control ($n = 28$)		
Characteristics[a]			F (df)	p-value
Age, years	67.33 (8.7)	65.64 (8.4)	0.61 (1,63)	0.43
Education, years	14.31 (3.4)	13.66 (3.2)	0.56 (1,63)	0.45
Wechsler Test of Adult Reading, FSIQ	106.06 (8.1)	103.75 (9.5)	1.08 (1,63)	0.3
Mini-Mental State Examination (total raw, /30)	28.36 (1.4)	28.50 (1.5)	0.13 (1,63)	0.71
Global Assessment of Functioning Scale (total raw, /100)	72.06 (11.9)	69.21 (9.9)	1.02 (1,63)	0.31
Hamilton Depression Rating Scale (total raw, /64)	5.19 (3.9)	5.79 (4.3)	0.32 (1,63)	0.57
Geriatric Depression Scale (total raw, /30)	13.19 (7.8)	12.61 (6.7)	0.09 (1,63)	0.75
Pittsburgh Sleep Quality Index (total raw, /21)	7.63 (4.0)	6.25 (4.1)	1.84 (1,63)	0.17
Everyday Memory Questionnaire (total raw, /52)	19.72 (10.7)	17.79 (11.2)	0.49 (1,63)	0.48
Characteristics[b]			x^2	p-value
Gender, male (% of total males)	9 (42.9)	12 (57.1)	2.28	0.13
MCI diagnosis (% of total with MCI)	27 (51.9)	25 (48.1)	2.11	0.15
Lifetime history of depression (% of total with lifetime history of depression)	17 (58.6)	12 (41.4)	0.12	0.73
Current DSM-IV depression (% of total with current depression)	2 (66.7)	1 (33.3)	0.14	0.71

[a]Data reported as mean (SD); [b]Data reported as number (%). FSIQ, Full Scale Intelligence Quotient; MCI, mild cognitive impairment.

Table 2
Baseline (BL) and follow-up (FU) neuropsychological and questionnaire data [mean (SD)] for control and treatment groups

	Treatment ($n = 36$)			Control ($n = 28$)			Overall			
	BL	FU	Mean diff	BL	FU	Mean Diff	F^a (*df*)	*p*-value	mean diff	95% CI
RAVLT-15 (z-score)	−0.39 (0.9)	−0.27 (1.0)	0.12 (0.9)	−0.47 (1.2)	−0.68 (1.1)	−0.21 (1.1)	1.83 (1,62)	0.18	0.04	−0.20–0.29
RAVLT% (z-score)	−0.49 (1.3)	−0.18 (1.1)	0.31 (1.0)	−0.40 (1.4)	−0.71 (1.5)	−0.31 (1.2)	5.24 (1,62)	**0.03**	−0.00	−0.27–0.27
LOGMEM-I (ASS)	10.61 (3.1)	10.61 (2.8)	0.00 (2.4)	9.54 (3.9)	9.64 (3.4)	0.11 (1.8)	0.04 (1,62)	0.84	−0.05	−0.60–0.49
LOGMEM% (ASS)	11.69 (2.9)	12.39 (2.9)	0.69 (3.2)	10.68 (3.3)	12.29 (3.6)	1.61 (2.7)	1.46 (1,62)	0.23	−1.15	−1.91–−0.40
RCFT (percentile)	56.44 (34.5)	61.35 (32.8)	4.91 (34.8)	50.11 (39.2)	56.25 (37.3)	6.14 (38.4)	0.02 (1,62)	0.89	−5.53	−14.7–3.64
Phonemic fluency (z-score)	0.03 (1.0)	0.17 (1.1)	0.14 (0.8)	0.02 (1.2)	−0.02 (1.0)	−0.04 (0.8)	0.79 (1,62)	0.38	−0.05	−0.25–0.15
Semantic fluency (z-score)	0.42 (1.2)	0.44 (1.1)	0.02 (1.0)	0.06 (1.3)	0.05 (1.4)	−0.01 (1.3)	0.12 (1,62)	0.91	−0.01	−0.29–0.28
Digit Span (ASS)	10.39 (2.7)	11.64 (2.9)	1.25 (1.8)	10.36 (2.7)	10.75 (3.1)	0.39 (2.3)	2.83 (1,62)	0.1	−0.82	−1.33–−0.31
TMT-A (z-score)	0.23 (0.8)	0.27 (1.0)	0.03 (1.0)	0.23 (1.1)	0.32 (0.7)	0.09 (1.1)	0.06 (1,62)	0.82	−0.06	−0.32–0.20
TMT-B (z-score)	−0.27 (1.1)	−0.13 (0.8)	0.14 (0.9)	−0.08 (0.9)	−0.24 (0.9)	−0.16 (1.1)	1.37 (1,60)	0.25	0.01	−0.25–0.26
GDS (total raw, /30)	13.35 (7.8)	8.47 (5.8)	−4.88 (5.5)	12.22 (6.6)	10.89 (7.3)	−1.33 (4.3)	7.59 (1,59)	**0.01**	0.64	1.82–4.40
EMQ (total raw)	19.62 (11.1)	13.62 (10.5)	−6.0 (8.2)	17.79 (11.2)	16.96 (11.0)	−0.82 (10.4)	4.80 (1,60)	**0.03**	3.41	1.05–5.78
PSQI (total raw)	7.62 (4.1)	6.24 (3.2)	−1.38 (2.6)	6.23 (4.2)	6.84 (4.3)	0.62 (3.44)	6.58 (1,58)	**0.01**	0.38	−0.40–1.16

[a]Interaction; $p < 0.05$, significant values are indicated in bold; RAVLT-15, CI, confidence interval Rey Auditory Verbal Learning Test-total learning over 5 trials; RAVLT%, Rey Auditory Verbal Learning Test-percent retention scores (i.e., (Trial 7 / Trial 5)* 100); LOGMEM-I, total score for stories A and B on Wechsler Memory Scale-III Logical Memory learning trials; LOGMEM%, Wechsler Memory Scale-III Logical Memory percent retention scores (LOGMEM-II delayed recall / [LOGMEM-I story *A*+ second recall Story B]); RCFT, Rey Osterrieth Complex Figure Test; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; GDS, Geriatric Depression Scale (30-item); EMQ, Everyday Memory Questionnaire; PSQI, Pittsburgh Sleep Quality Index; ASS, Age Scaled Score.

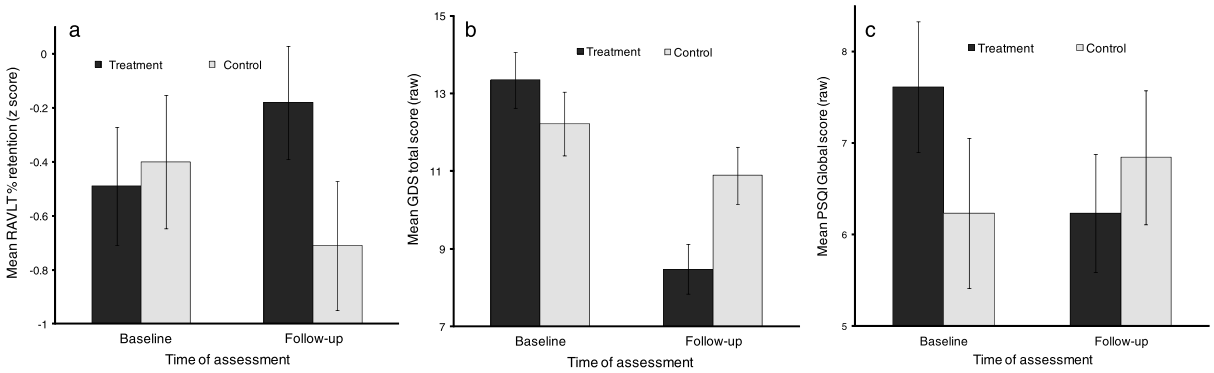

Fig. 2 . a) Improvements in memory retention on the Rey Auditory Verbal Learning Test (RAVLT) from baseline to follow-up for cognitive training treatment versus control group. Note: higher scores indicate better memory recall. b) Improvements in self-reported mood on the Geriatric Depression Rating Scale (GDS) from baseline to follow-up for cognitive training treatment versus control group. Note: higher scores indicate more severe levels of depression. c) Improvements in self-reported sleep quality on the Pittsburgh Sleep Quality Index (PSQI) from baseline to follow-up for cognitive training treatment versus control groups. Note: higher scores indicate poorer sleep quality.

Effects of treatment

Table 2 illustrates baseline and follow-up data for the treatment and control groups. For the primary outcomes, repeated measures ANOVA demonstrated a significant interaction effect, whereby treatment was associated with significant medium effect size ($r = 0.3$) improvements in memory consolidation for unstructured (i.e., RAVLT%) (see Fig. 2a), but not on a structured (i.e., LOGMEM%) verbal material. The data suggest that the control group declined on the RAVLT from baseline to follow-up while the treatment group improved. Based on this finding, *post-hoc* power analyses were conducted using G*Power Version 3.1.7 [31] with alpha set at 0.05, and revealed that with 64 participants, this study had power of 0.92 to detect an effect of this size. The absolute risk reduction attributable to the HBA-CT treatment group was 21% (95% CI: 3%–38%) and the number needed to treat was 4.85 (95% CI: 2.62–31.55), i.e., five people would need to complete this program in order for one participant to experience an improvement.

For secondary outcomes, a significant interaction demonstrated that treatment was associated with medium effect size ($r = 0.3$) improvements in GDS scores (see Fig. 2b). Therefore, since improvements in mood can be responsible for improvements in cognition, we repeated these analyses after controlling for change in mood. We computed a proportion change score for the GDS and entered this as a covariate into the repeated measures analysis for RAVLT%. The interaction remained significant ($F(1,58) = 5.04$, $p = 0.029$, 95% CI: −0.30–0.24) with a medium effect size ($r = 0.3$). This confirms that the treatment-related improvement in verbal memory occurred independently of improvements in mood. However, when a similar *post-hoc* analysis was conducted to investigate the possible contribution of improved sleep quality on memory functioning, the interaction was no longer significant, although it did still approach significance ($F(1,57) = 3.34$, $p = 0.07$, 95% CI: −0.33–1.96). This suggests that the improvement in memory may be partly mediated by concurrent improvements in sleep.

In addition to significant improvements in objective measures of verbal memory and mood, significant interaction effects showed that HBA-CT treatment was associated with improvements in subjective memory (i.e., EMQ total) and sleep quality (i.e., PSQI total) (see Fig. 2c), both with medium effect sizes ($r = 0.3$). As was seen on the RAVLT, the data suggest that the control group declined on the PSQI from baseline to follow-up whilst the treatment group improved. After controlling for changes in self-reported mood, only the interaction effect for PSQI total ($F(1,56) = 5.59$, $p = 0.022$, 95% CI: −0.44–1.16) (see Fig. 2b) but not EMQ total ($F(1,58) = 2.92$, $p = 0.093$, 95% CI: 1.07–5.77) remained significant, once again with a medium effect size ($r = 0.3$).

The HBA-CT treatment was not associated with significant changes in other secondary outcomes including measures of verbal fluency, working memory, psychomotor speed, visual memory, or set-shifting aspects of executive functioning.

There were no adverse events to report in this trial.

DISCUSSION

Consistent with our prior work [5, 6, 20], and in accordance with other previous CT work in older 'at risk' adults [see review by 32], this novel randomized controlled trial demonstrates that the HBA-CT program is associated with improvements in objectively measured memory. The circumscribed effect in memory is consistent with the CT research in older 'at risk' adults [32] and in other neuropsychiatric groups [33] demonstrating that improvements in memory with CT are most pronounced. Notably, however, in this study we found improvements on an unstructured (i.e., the RAVLT, a word list task), but not on a structured (i.e., prose passages) verbal memory task. This suggests that the CT effects on memory are not pervasive. While the reasons for this are unclear, it is possible that this finding reflects the nature of the CT program we employed, which focused on the provision and utilization of strategies (e.g., visual imagery, organizational and associative learning). Since the RAVLT relies more heavily on organization and structure for successful encoding and consolidation (mediated by higher-order executive functions subserved by the frontal systems), we posit that this type of memory may preferentially benefit from our focus on strategy use.

Importantly, in addition to improvement in memory, the results of this study also demonstrate that this novel, multifaceted CT program is associated with improvements in perceived mood and sleep quality. Of significance, the effects of the HBA-CT program on objective memory performance and sleep quality occurred independently of improvements in mood. Although mood did not appear to mediate the improvements in objective memory performance or self-reported sleep quality, it did play a role in mediating perceived memory improvements, a finding which is consistent with the literature linking mood and subjective memory complaints [34]. This is particularly interesting, as improvements in perceived memory have important implications for self-esteem and self-efficacy [35] and can therefore be seen as an additional, clinically relevant indirect effect of CT.

Interestingly, further analyses showed that the effect of CT on verbal memory remained only a trend once the effect of improved sleep quality was considered. While we cannot ascertain from this study design and small sample size whether improved sleep actually mediates memory improvements, it is certainly possible that improved sleep is a contributing factor. This would be aligned with our own and other's [36, 37] work in this area, which demonstrates the critical role that sleep plays in both memory consolidation and overall cognitive functioning. Additionally, one other recent study found that sleep improved in association with CT [38]. However, many factors contribute to one's perception of sleep quality, particularly mood state [39]. Thus, further larger studies specifically delineating the role of sleep, mood, and other factors in CT-associated memory improvements are warranted.

The findings of this study extend our prior work investigating CT in patients with depression [5, 20], young people with mental health problems [40], and Parkinson's disease [6], all of whom also demonstrated CT-related improvements in memory. This finding is also aligned with meta-analyses of CT in older healthy [4] and 'at risk' [38, 41, 42] samples. However, this is the first known study to demonstrate concurrent improvements in cognition, mood, and sleep quality, by utilizing a multifaceted intervention simultaneously combining psychoeducation (that promoted modification of vascular and lifestyle risk factors) with targeted computerized CT. It can be argued that while the current HBA-CT program directly provides cognitive remediation via the computer-based CT component as well as direct psychosocial engagement via the group format, it also indirectly encourages participants to modify medical and lifestyle factors that affect healthy brain aging (including vascular risk reduction strategies, promotion of healthy diet, exercise, sleep hygiene, and methods to manage depression and anxiety). Therefore, this multifaceted program may be more enriched than other programs that focus on CT only. At this stage, we cannot determine whether the psychoeducational component measurably translates into altered health behaviors, adherence to prescribed treatments and/or utilization of practical memory strategies; however these issues are certainly worth exploring in further studies as well as follow-up of this cohort.

At present, the mechanisms by which CT may improve cognition, mood, and sleep remain unclear. However, animal and human research is now being directed at examining whether CT programs restore lost functioning and/or encourage anatomical reorganization via neuroplastic mechanisms at molecular, cellular, and cortical levels [43–46], whether the efficacy of these programs lie in teaching individuals to use residual skills more efficiently, or whether CT programs encourage a combination of both compensatory and restorative mechanisms [47]. Further efforts (e.g., more detailed neuroimaging studies) to distinguish these mechanisms may inform more targeted approaches to CT, which may in turn maximize treatment outcomes.

A number of limitations exist. This study incorporates a heterogeneous sample of older adults who have been identified as being 'at risk' for cognitive decline due to known risk factors for dementia (i.e., MCI and/or depression) [48]. However, we note that these conditions often co-exist and therefore we see this sample as reflective of real-life clinical practice. Within this sample of 'at risk' older adults, a diverse range of underlying pathological mechanisms may underpin cognitive and brain change. Indeed, we did not restrict our sample to those with only amnestic forms of MCI, and did not utilize other biomarker evidence of MCI. Given that we observed a CT treatment effect regardless of diagnosis suggests that CT may be successful despite underlying neurodegenerative pathology. Conversely, if we had included a more homogenous sample, it is possible that the effect size of treatment may have differed.

While the current study did not employ an "active" control, this study did employ a waitlist treatment-as-usual control. We chose this form of control as this intervention was delivered in a clinical setting where the integrity of research versus ethical considerations needs to be balanced. We acknowledge, however that this form of control group is not as rigorous as an active or sham control. Additionally, it is possible that the improvements in memory, mood, and perceived sleep may have been attributed to nonspecific effects from factors such as other interventions that may have formed part of a patient's routine management or cognitive training undertaken by participants of their own accord.

Furthermore, the design of this trial does not allow for evaluation of the extent to which the psychoeducation component contributes to improvements over and above that provided by the computer-based cognitive training. However, the literature suggests that this component alone is unlikely to be responsible for cognitive improvements [49]. Whilst not feasible in this trial, future studies should also include more extensive evaluation of everyday functional outcomes in order to investigate the generalizability of CT effects. This study did not include longitudinal follow-up, and therefore we were not able to evaluate the sustainability of the effects of CT. Future studies would benefit from including this in their design. An additional methodological limitation was that final eligibility was confirmed after completion of baseline assessments, and therefore after randomization had occurred. This highlights the difficulty in implementing clinical trial methodology within a clinical service setting (i.e., where patients were referred for diagnosis and treatment as part of their clinical management). In order to facilitate the process of enrolment, preliminary eligibility screening was completed via telephone prior to assessments; however it was impossible to confirm eligibility without more detailed face-to-face clinical and neuropsychological assessments. Therefore, several participants who were enrolled in the study and were therefore included in the randomization were later deemed ineligible for the trial on the basis of more detailed information obtained during baseline assessments. For ethical purposes, these patients were permitted to engage in the HBA-CT groups, but were appropriately excluded prior to analyses. Finally, given the rate of attrition, we acknowledge that we did not expect to have a medium effect size for our primary outcome measure. Nevertheless, *post-hoc* power calculations performed on our primary outcome measure (i.e., RAVLT) demonstrated that even with this reduced sample size, we still had sufficient power to detect a medium effect size.

Overall, our data shows that this non-pharmacological intervention provides a clinically relevant therapeutic option for older adults 'at risk' of cognitive decline and dementia. Importantly, this intervention can be easily implemented across a variety of settings, and may even enable patients to continue engaging in inexpensive self-directed CT indefinitely. While there are several accepted evidence-based interventions for mental health, sleep, and cognition in this group (such as Cognitive Behavioral Therapy or strategy training), none of these existing interventions simultaneously target such a wide range of risk factors for cognitive decline [50]. Conversely, this HBA-CT program demonstrates that multifactorial interventions may be ideal as holistic, preventative and cost-effective secondary prevention techniques.

ACKNOWLEDGMENTS

We are grateful to the patients who participated in this study. We also thank Dr. Samantha Fearns, Dr. Zoe Terpening, Prof. Naomi Rogers, and Dr. Shantel Duffy for their assistance with conducting assessments and delivering psychoeducation material during the intervention. Dr. Hermens has received honoraria from Janssen-Cilag and Eli Lilly. A/Prof. Lewis is supported by an NHMRC Practitioner Fellowship No. 1003007. Prof. Hickie is the executive director of the Brain and Mind Research Institute which operates two early-intervention youth services under contract to

headspace. He has led a range of community-based and pharmaceutical industry-supported depression awareness and education and training programs. Current investigator-initiated studies are supported by Servier and Pfizer. He has received honoraria for his contributions to professional educational seminars supported by the pharmaceutical industry (including Servier, Pfizer, AstraZeneca, and Eli Lilly). A/Prof. Naismith is the Head of the Healthy Brain Ageing Program at the Brain and Mind Research Institute and is supported by an NHMRC Career Development Award No. 1008117.

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=2605).

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