BRAIN
CLINICAL TRIAL

A randomized clinical trial of plasticity-based cognitive training in mild traumatic brain injury

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Clinical practice guidelines support cognitive rehabilitation for people with a history of mild traumatic brain injury (mTBI) and cognitive impairment, but no class I randomized clinical trials have evaluated the efficacy of self-administered computerized cognitive training. The goal of this study was to evaluate the efficacy of a self-administered computerized plasticity-based cognitive training programmes in primarily military/veteran participants with a history of mTBI and cognitive impairment.

A multisite randomized double-blind clinical trial of a behavioural intervention with an active control was conducted from September 2013 to February 2017 including assessments at baseline, post-training, and after a 3-month follow-up period. Participants self-administered cognitive training (experimental and active control) programmes at home, remotely supervised by a healthcare coach, with an intended training schedule of 5 days per week, 1 h per day, for 13 weeks. Participants (149 contacted, 83 intent-to-treat) were confirmed to have a history of mTBI (mean of 7.2 years post-injury) through medical history/clinician interview and persistent cognitive impairment through neuropsychological testing and/or quantitative participant reported measure. The experimental intervention was a brain plasticity-based computerized cognitive training programme targeting speed/accuracy of information processing, and the active control was composed of computer games. The primary cognitive function measure was a composite of nine standardized neuropsychological assessments, and the primary directly observed functional measure a timed instrumental activities of daily living assessment. Secondary outcome measures included participant-reported assessments of cognitive and mental health.

The treatment group showed an improvement in the composite cognitive measure significantly larger than that of the active control group at both the post-training [+6.9 points, confidence interval (CI) +1.0 to +12.7, $P = 0.025$, $d = 0.555$] and the follow-up visit (+7.4 points, CI +0.6 to +14.3, $P = 0.039$, $d = 0.591$). Both large and small cognitive function improvements were seen twice as frequently in the treatment group than in the active control group. No significant between-group effects were seen on other measures, including the directly-observed functional and symptom measures. Statistically equivalent improvements in both groups were seen in depressive and cognitive symptoms.

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Abbreviations: ANAM = Automated Neuropsychological Assessment Metrics; ITT = intent-to-treat; mTBI = mild traumatic brain injury; RNBI = Ruff Neurobehavioral Index; TIADL = Timed Instrumental Activities of Daily Living

Introduction

Mild traumatic brain injury (mTBI, concussion) is the most common type of brain injury in the USA.[1] While most individuals recover well after injury, some have persistent physical, mental, and cognitive health complaints, the cause of which is related to a variety of factors.[2–4] These post-concussive symptoms[5] can have a significant impact on daily functioning and quality of life. Recovery is of particular significance to the military, where the military engagements in Afghanistan and Iraq have led to significant numbers of service members suffering mTBIs. Military veterans are at higher risk for poor recovery than civilians suffering single mTBIs,[6–9] likely because of co-occurring psychological trauma and related sequelae.

Current clinical guidelines for post-concussive symptoms in civilian[10] and military[11] populations recommend non-pharmacological treatments for each of the symptom categories (with certain exceptions, e.g. medication for depression). Treatments for mental and cognitive health issues typically focus on cognitive behavioural therapy, psychoeducation, in-person compensatory/strategy training, and assistive memory aids.[12]

Improving cognitive function could lead to significantly better outcomes and reduced costs in this population. Cognitive impairment is associated with issues with return to work in mild/moderate TBI.[13] An estimate from RAND[14] in a study of post-deployment health-related needs in patients with mTBI suggested an annual cost of ~$25 000 per person/year, with ~50% of costs derived from lost productivity, which could potentially be helped with effective cognitive remediation.

However, the strength of evidence for cognitive remediation in mTBI guidelines is typically described as low, due to the small number of trials conducted with strong designs (e.g. adequate statistical power, randomization, and active control groups). These guidelines, as well as a recent meta-analysis[15] and systematic review[16] show only seven randomized controlled trials (RCTs) of cognitive remediation conducted primarily with patients with mTBI; including five trials with in-person compensatory interventions,[17–21] a single trial with a mix of manualized and computerized interventions,[22] and a single trial with a virtual reality intervention.[23] A recent review of computerized cognitive training programmes for adults with TBI found no RCTs meeting the American Academy of Neurology standards for a class I efficacy trial.[24]

Computerized cognitive training programmes could offer benefits to people with a history of mTBI and cognitive impairment. First, appropriately designed programmes can intensively and adaptively engage neural systems involved in sensory and cognitive processing, with the goal of engaging brain plasticity to re-normalize brain and cognitive function. This approach is distinct from compensatory strategy coaching. Second, such programmes offer the opportunity for in-home self-administered training, which could complement in-clinic programmes.[21,22,25] Third, remote clinical oversight for patients located far from clinical centres can provide a means for continued intervention to maintain gains as well as an avenue for clinicians to monitor performance post-discharge.

One specific restorative approach has been derived from brain plasticity experiments in animal and human models showing that it is possible to reorganize neural systems using intensive adaptive training programmes. For example, in an animal model a training programme required rats to detect a tone of a specific frequency in a sequence of tones of various frequencies.[26] As performance improved, the sequence was made faster and the tones made more similar, requiring faster and more accurate information processing on the part of the rat auditory system to detect the target tone among the sequence of distractors. Behavioural task performance improved over the 4-week training period, as did (in a related way) neurophysiological measures of speed and accuracy in primary auditory cortex (e.g. tuning curve bandwidth, pulsed noise training following rate), as well as cellular (e.g. parvalbumin-labelled inhibitory cortical neurons) and molecular (e.g. myelin) markers of brain health.

In parallel, it has been argued that a key contributor to poor cognitive function is an underlying deficit in the speed and accuracy of neural information processing coupled with relatively weakened neuromodulatory control over learning.[27,28] In ageing, this viewpoint is referred to as the information degradation hypothesis,[29] and it has been argued that these same principles apply to cognitive impairment following mTBI.[30]

In combination, the observations that (i) appropriate training programmes improve the speed and accuracy of neural information processing in animal models; and (ii) the speed and accuracy of neural information processing contributes to cognitive impairment in various neurological conditions suggest that training programmes appropriate for humans may improve cognitive function. Such programmes offer the potential to improve cognitive function by improving the quality of information available from neural systems involved in early sensory/perceptual processing for use by neural systems involved in cognitive function.

Based on this view, cognitive training exercises have been developed on these principles (BrainHQ, Posit Science). These exercises have been shown to improve both cognitive function and functional performance in normally ageing populations with mild levels of cognitive impairment similar to post-concussive symptoms,[31,32] and show promise in several clinical populations.[33–35] Studies employing a single exercise of this type (referred to as 'speed training') in a single sensory modality (the visual domain) showed within-domain improvement in visual cognitive and functional measures, but did not show improvement in other cognitive function measures.[36,37] Studies involving multiple exercises of this type, including purely auditory[31] as well as auditory, visual, and multimodal exercises[38] that have shown improvements in multiple measures of cognitive function (including composite measures), suggesting that programmes composed of multiple exercises, which may improve speed and accuracy of information processing across multiple neural systems, may drive larger effects on overall cognitive function and broader functional

benefits than individual exercises alone. Several studies have documented a relationship between neural target engagement by the training (assessed by improvements in a psychophysical measure of processing speed) and change in cognitive function.[39,40] Additional brain imaging studies have shown that the training alters early sensory processing (measured with EEG) in a way correlated with changes in cognitive function[41] and functional connectivity across cortical networks involved in cognitive function (measured with functional MRI).[42]

These results from related conditions, as well as pilot studies in TBI,[43,44] led us to conduct the current BRAVE trial as a multisite, randomized, active-controlled trial of a brain plasticity-based cognitive training programme (BrainHQ, Posit Science) in people with a history of mTBI with cognitive impairment. Based on the putative mechanism of action (improving the speed and accuracy of information processing in the auditory and visual systems with multiple cognitive training exercises in the auditory, visual, and multi-modal domains) and based on results from trials in normal ageing, we hypothesized that the intervention would improve cognitive function across a broad range of measures, including working memory, recall, and executive function; as well as a speed-based directly observed functional measure and participant self-report measures of symptoms.

Materials and methods

Design

This was a multisite, prospective, parallel-arm, randomized, active controlled, double-blinded trial conducted at five military and Veteran Affairs (VA)-based trial sites.

Participants

BRAVE recruited participants from five military and VA sites (Walter Reed National Military Medical Center, Schofield Barracks, VA Boston Healthcare System, Michael E. DeBakey VA Medical Center, and VA Connecticut Healthcare System).

Inclusion and exclusion criteria were chosen to identify participants with (i) a history of mTBI; and (ii) evidence of current cognitive impairment.

A history of mTBI was confirmed by the Ohio State University TBI Identification Method-Short Form (including a requirement that the mTBI caused a loss of consciousness lasting less than 30 min). The most recent mTBI was required to have occurred more than 3 months prior to enrolment.

A central goal of the trial was to recruit a participant population that was representative of people seeking treatment for cognitive impairment with a history of mTBI in military/VA clinics, while meeting standard diagnostic criteria for this disorder. To this end, evidence of current cognitive impairment was verified by meeting either of two criteria, corresponding to the diagnostic criteria for post-concussion disorder from the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV; requiring a neuropsychological measure of cognitive impairment) and the International Classification of Diseases, 10th Edition (ICD-10, requiring a self-report measure of cognitive impairment) definitions.

The Automated Neuropsychological Assessment Metrics (ANAM) TBI Battery score[45] was used as the neuropsychological measure, and employed seven cognitive tests generally focused on processing speed combined into a standardized composite score. Recommended cut-off scores for cognitive impairment vary.[46,47] For this trial, a composite score of 1 standard deviation (SD) below the norm was required for a participant to be included based on the ANAM (neuropsychological) criterion, placing a participant in the 16th percentile or lower (consistent with definitions of mild levels of cognitive impairment). Sensitivity analyses were conducted *post hoc* to determine if this specific cut-off affected results. For clarity, the ANAM was not used to diagnose mTBI, but rather to characterize cognitive impairment given a history of mTBI. It should be noted that an advantage of a neuropsychological measure is that participants meeting the criterion have a clear deficit, which may make them more likely to respond to the cognitive training treatment, and a disadvantage is that the criterion will exclude participants with a higher-than-average pre-morbid function who experience a true cognitive decline that leaves them in the normal range.

The Ruff Neurobehavioral Inventory (RNBI)[48] was used as the self-report measure. The RNBI is a quantitative questionnaire-based measure that asks a participant to compare their function at the current time as compared to their pre-morbid condition. A subset of 21 questions on a four-point scale were used that composed the four cognitive scales of the RNBI (attention and concentration, executive functions, learning and memory, speed and language). A normed T-score of >70 (as recommended by the RNBI manual as documenting significant post-morbid impairment) on any of these four cognitive scales was required for a participant to be included based on the RNBI (self-report) criterion. For clarity, the RNBI was not used to diagnose mTBI, but rather to characterize cognitive change given a history of mTBI. It should be noted that an advantage of a self-report measure is that participants meeting the criterion have a sense of their deficit and it will include participants with high pre-injury functioning who have declined to normal function, and a disadvantage is that the criterion may include participants who are exaggerating the magnitude of their deficit.

In addition, participants were required to be fluent English speakers (to ensure their neuropsychological testing data were valid), and to have the visual, auditory, and motor capacity to use the computerized intervention. Exclusion criteria were a history of penetrating head wounds or a diagnosis of moderate/severe TBI, in-patient status, a diagnosis with cognitive consequences (e.g. schizophrenia, bipolar disorder, cancer, multiple sclerosis; however, common mTBI comorbidities including PTSD, depression, and chronic pain, were not exclusion criteria), or participation in a concurrent clinical trial that could affect the outcome of this one (however, participation in standard treatments e.g. occupational therapy or use of prescribed medications such as antidepressants were not exclusion criteria). Participants with significant visual field deficits were excluded, as were those with active suicidal ideation/behaviour. At first, participants aged 18–40 were included and participants were excluded if they scored <45 on one of the trials of Test of Memory Malingering (TOMM)[49]; after eight participants enrolled this criterion was updated to exclude participants if they scored <41 (Trial 1) or <45 (Trial 2) to reflect updated best practices regarding the TOMM[49] and at this time the age range was also expanded to 18–50. Participants continued in any standard therapies recommended by their treating clinicians (e.g. physical therapy, medication, group counselling). Recruitment procedures focused on military populations, but civilians who encountered recruitment materials and volunteered were not excluded from the trial.

Procedures

Institutional review board approval was obtained at the coordinating centre and at each trial site. All participants provided written informed consent. Participants were reimbursed up to $550 by completing study activities.

Participants were randomized following baseline assessment using minimization. Participants were stratified on two baseline

conditions thought to relate to cognitive impairment[50]: post-traumatic stress symptoms [using the PTSD Checklist C (PCL-C)] and depressive symptoms [using the Beck Depression Index (BDI)-II]. Sites requested randomization allocation through e-mail, and a single coordinating centre staff member fulfilled requests through a concealed randomization allocation sequence.

To maintain the participant blind, consent forms described the study as comparing two distinct types of cognitive training. Clinician/neuropsychological raters were blinded. Participants were reminded not to discuss their training with clinicians/raters. Coaches (trained site staff) who interacted with participants to support cognitive training were unblinded. Coaches were trained to describe both the experimental treatment and active control programmes as potentially beneficial based on prewritten scripts referencing specific features in the experimental treatment and active control programmes.

Cognitive training was delivered in 1-h sessions, 5 days per week, for 13 weeks. Participants self-administered training on study-supplied laptops at home. Coaches reviewed progress data regularly and provided telephone-based coaching on a weekly basis. Coaching content was designed to be similar and balanced across the two groups, differing only where required, such as with exercise or game-specific instructions. Coaching focused on motivating participants (e.g. rewarding progress with praise, aligning participant real-world goals with specific features of the exercises/games they were using, helping participants define and adhere to a training schedule) and providing technical support (e.g. resolving internet issues, reminding participants how to launch their assigned programme, reminding participants how to perform the exercises/games in their assigned programmes).

Assessments were performed at baseline, after training completion, and after a 3-month no-training follow-up period.

Cognitive training programmes

Experimental treatment

The experimental cognitive training programme was a commercially available cognitive training programme (BrainHQ), with a schedule of 23 exercises selected for this trial with the goal of improving cognitive functions affected by mTBI. All exercises targeted the speed and accuracy of neural information processing, required attentional focus to perform correctly, and were accompanied by video game-like rewards when trials were performed correctly. Each exercise adapted on a trial-by-trial basis to an individual's performance at that time with the goal of ensuring users completed ~80% of trials correctly. Exercises were made available to users in a systematic sequence over the 12-week period of use, with participants performing six exercises in each 60-min session. Exercises presented earlier in the period of use targeted speed and accuracy of information process under attentional demand and involved minimal higher-order cognitive demands (for example, a visual speed task shown in Fig. 1A, where participants identify the location of a peripheral target among distractors, with presentation time adapted to control task difficulty). These exercises were intended to improve information flow through earlier sensory stages of cortical information processing. Exercises presented later in the period of use continued to focus on speed and accuracy of information processing with attentional focus, and introduced higher order cognitive requirements (for example, social cognition task shown in Fig. 1B, where participants were shown a face, and then had to identify the face from a different viewing angle among several similar distractors, with presentation time of the initial face adapted to control task difficulty). These exercises were intended to extend the benefits of improved information flow from earlier sensory stages of cortical information processing up through later stages of cortical and subcortical systems (e.g. frontal, associational, hippocampal).

Active control

The active control programme was designed to provide an experience that could be matched to the experimental treatment programme in intensity and duration, while plausibly engaging cognitive systems to maintain the patient blind. active control exercises were chosen to minimize demands on speed and accuracy of information processing, and were generally not rapidly adaptive to user performance. Thirteen off-the-shelf computer games were selected (e.g. hangman, Boggle, mah-jong), and delivered with a schedule similar to the experimental treatment programme. Representative screenshots of two active control exercises are shown in Fig. 1C and D.

Outcome measures

Cognitive measures

The primary cognitive function measure was a composite score, derived from a battery of standardized neuropsychological tests, as recommended by current guidance[51] to preserve statistical power and avoid multiple comparisons. At the time of the development of the BRAVE protocol, NIH Toolbox was under development[52] and no standardized neuropsychological battery to assess cognitive function in mTBI was available.[53] For this study a set of nine well-standardized measures were selected. Six measures were traditional pencil and paper neuropsychological tests, and three were computerized measures; in no case was any cognitive training exercise specifically designed to mimic or practice a specific neuropsychological test. The nine tests used were the Rey Auditory Verbal Learning Test (RAVLT) sum of trials 1–5 and delayed recall,[54] the Ruff Light Trails Test (RULIT) sum of trials 2–10 and delayed recall,[55] Digit Span (WAIS,[56] sum of forwards, backwards, sequencing), Symbol Span (WMS[57]) anti-saccades, flanker, and set-shifting (each from the EXAMINER battery[58]). For all assessments, alternate forms were used and counterbalanced to minimize practice effects. The composite score was calculated using standard neuropsychological techniques[59] with a balancing summation of the nine individual scores that was normalized to a mean of 100 and SD 15, creating the composite.

Functional and participant-reported outcome measures

At the time of the development of the BRAVE protocol, there was no strong consensus regarding directly-observed functional outcome measures with mTBI. Timed Instrumental Activities of Daily Living (TIADL), a measure used in healthy ageing studies[60] but which had not been previously used in an mTBI population, was selected as a primary directly-observed functional outcome measure. Secondary outcome measures were focused on participant-reported outcome symptom measures and included the SF-12 mental component score,[61] the Beck Depression Inventory (BDI-II[62]) the Post-Traumatic Stress Disorder Checklist–Civilian version [PCL-C[63](p5)], the Frontal Symptoms Behavioral Scale (FrSBe[64]) the Cognitive Failures Questionnaire (CFQ[65]) the Neurobehavioral Symptoms Inventory (NSI[66]) and the Mayo-Portland Adaptability Index (MPAI[67]).

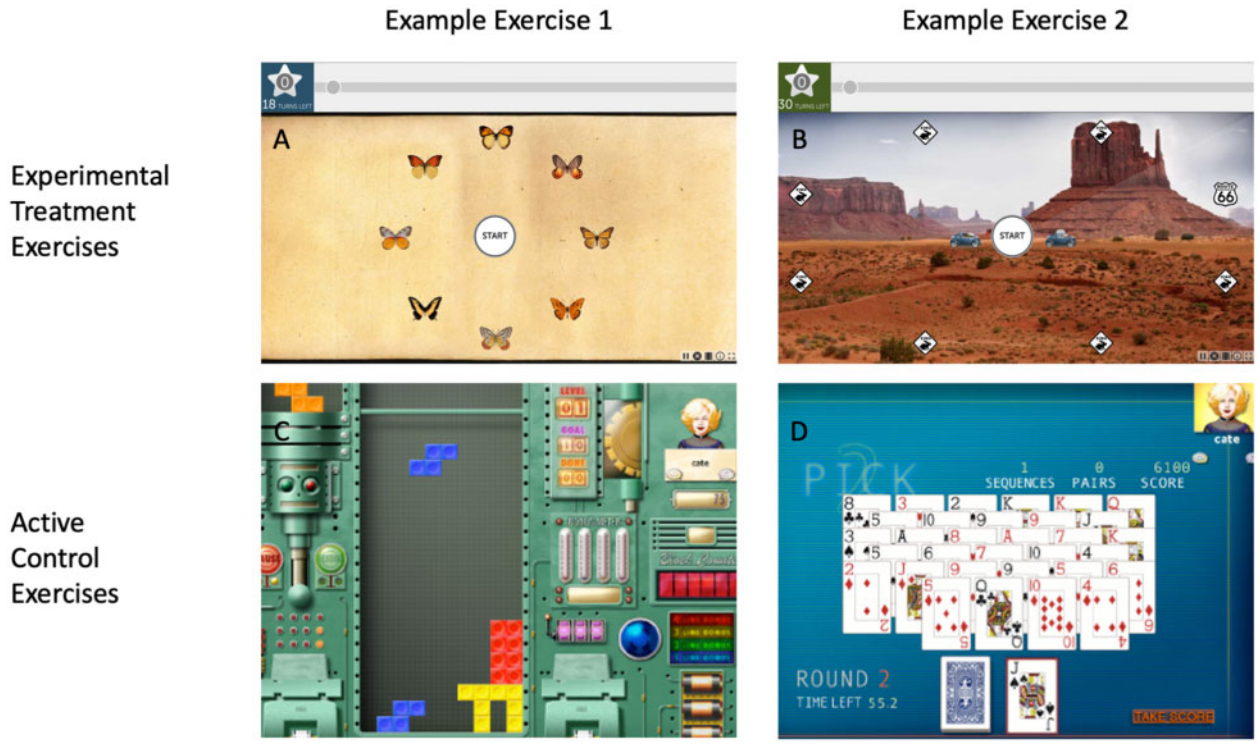

Figure 1 Screenshots of example cognitive training exercises. *Top row*: Screenshots of example exercises from theexperimental treatment cognitive training programme. (**A**) Hawk Eye, designed to train visual speed and accuracy in peripheral vision, requiring users to locate a peripheral target among distractors; and (**B**) Recognition, designed to train visual speed and accuracy in the context of a social cognition task requiring users to match faces presented under speeded viewing conditions. *Bottom row*: Active control cognitive training programme. (**C**) A Tetris-like game, involving visuo-spatial manipulation and reaction time; and (**D**) an advanced solitaire game, involving executive function.

Task-related measures

Two computerized assessments based on cognitive exercises from the experimental treatment programme were used to measure task learning and target engagement, including an auditory time order judgment task where observers must correctly identify and sequence a pair of frequency-modulated auditory sweeps that can either ascend or descend in frequency and are separated by a brief inter-stimulus interval,[68] and a useful field of view task where observers must identify the identity of a central target and the location of a peripheral target after both are briefly simultaneously presented.[69]

Statistical analysis

A predefined analysis plan specified an intent-to-treat (ITT) population (all randomized participants who completed their first training session), and the statistical approach. The trial was powered to detect an effect size of 0.5 (Cohen's *d*′) at the pre-specified statistical significance level of 0.05. All statistical tests were two-tailed, and all confidence limits are reported are the 95% level. The enrolment goal was specified as 132 participants. The co-primary outcome measures were the cognitive composite score and the TIADL total score, evaluated at the post-training assessment (V2) time point.

Baseline data were compared across the experimental treatment and active control groups with *t*-tests or chi-squares. Outcome measures were evaluated using linear mixed effects models, providing a robust approach to estimated statistical parameters even when data is missing, as is common in longitudinal clinical trials. Missing data were accounted for using iterative full-information maximum likelihood estimation. Each model included treatment group and time as fixed factors and site as a random factor. Within group effects for each time point (post-training, follow-up) were calculated using data from each group. Between groups effects for each time point were calculated in the same way, adding an interaction term (Training group × Time) that estimated the effect of cognitive training on outcome measure change. Confirmatory analysis was performed on the fully evaluated populations using *t*-tests of difference scores.

Data availability

Data will be deposited in a publicly available repository 1 year after publication to allow the investigators to complete secondary analyses. The complete cognitive training programme is available upon request to the corresponding author.

Results

Participants

Of 149 assessed for eligibility, 83 participants were randomized and provided with the appropriate training programme, forming the ITT population (experimental treatment = 41; active control = 42). Thirty-nine of the ITT participants were included based on both the neuropsychological (ANAM) and self-report (RNBI) criteria, 26 with the neuropsychological and not the self-report criterion, and 18 with the self-report and not the neuropsychological criterion. Achieved power to detect an effect size of 0.5 was 0.61 with this sample size. Recruitment began in September 2013; the final participant completed in February 2017. Enrolment ceased at the end of the grant funding period.

Pretraining demographic and baseline measures are shown in Table 1. ANAM scores of –2.21 ± 1.71 indicated significant cognitive impairment, and RNBI domain scores of (at the low end) 59.9 ± 13.2 and (at the high end) 73.8 ± 16.8 indicated meaningful levels of perceived cognitive loss post-injury. These baseline scores, combined with OSU TBI Identification Method data, indicate that the ITT population included participants with cognitive impairment and a history of mTBI. To characterize the population further, the other baseline scores were examined. BDI scores of 18.7 ± 11.9 indicated mild levels of depressive symptoms. PCL-C scores of 44.9 ± 15.7 were consistent with moderate PTSD symptoms. FrSBe scores of 75.9 ± 21.6 were consistent with moderate levels of frontal/dysexecutive symptoms. NSI scores of 31.6 ± 16.0 indicated higher than typical levels neurobehavioural symptoms.[70] MPAI total scores of 36.2 ± 15.3 suggested mild limitations on abilities. SF-12 scores of 45.4 ± 12.1 (physical component score) and 39.5 ± 12.8 (mental component score) indicated mild to moderate contributions of physical and mental health issues to restrictions on everyday activities. Time since the most recent TBI was 7.3 ± 6.5 years, 24% of participants engaged in at least one TBI rehabilitation programme post-injury (e.g. occupational therapy, speech therapy), and 12% were involved in a TBI rehabilitation programme at the time of study enrolment. Review of TBI characteristics indicated that 63% were classified as closed head injuries, 35% as blast-related injuries, and 2% as crash-related injuries; while 43% occurred during military deployment, 20% on streets/highways, 16% during sports/recreation activities, and 8% at work/school/public location (and the remainder in other locations).

Following randomization, there were no significant differences between the experimental treatment and active control groups except for the Double Decision exercise-based measure, where experimental treatment participants were slower than active control participants; and the CFQ, where active control participants had higher levels of self-reported cognitive failures than experimental treatment participants. Given the baseline difference in CFQ scores, all mixed models for outcome data analysis included CFQ as a baseline covariate.

A complete CONSORT flow is shown in Fig. 2. Drop/withdraw rates were not significantly different between groups ($P = 0.554$, chi-square), and there were no significant differences between completers and non-completers (data not shown) nor between the experimental treatment drop/withdraw and active control drop/withdraw groups (data not shown). Reasons for drop/withdraw were typically the time commitment of study participation or change in life circumstances. Number of sessions completed was not significantly different between groups (experimental treatment 38.7 ± 24.4, active control 42.4 ± 23.4, $P = 0.470$).

Table 1 Baseline demographic, inclusion, and outcome measures

	ITT group ($n = 83$)	Experimental treatment group ($n = 41$)	Active control group ($n = 42$)
Demographic			
Age, years	33.8 ± 8.7	35.4 ± 8.8	32.3 ± 8.5
Education, years	14.4 ± 2.0	14.2 ± 1.7	14.6 ± 2.2
Gender, % male	81	78	83
Ethnicity, % caucasian	77	78	76
Military/veteran, %	77	78	76
Time since most recent TBI, years	7.3 ± 6.5	7.4 ± 6.1	7.2 ± 6.9
Ever in TBI rehabilitation, %	24	27	21
Currently in TBI rehabilitation, %	12	12	12
Inclusion			
ANAM	–2.21 ± 1.71	–2.22 ± 1.97 ($n - 2$)	–2.20 ± 1.45
RNBI Attention	67.5 ± 14.0	64.5 ± 14.2	69.5 ± 13.5
RNBI Executive	59.9 ± 13.2	58.2 ± 13.4	61.5 ± 13.0
RNBI Learning and Memory	73.8 ± 16.8	71.6 ± 16.3	75.9 ± 16.1
RNBI Speech and Language	67.0 ± 17.2	64.6 ± 15.8	69.3 ± 18.4
TOMM	97.6 ± 3.1	97.6 ± 3.2	97.6 ± 3.0
Primary measures			
Cognitive composite	101.5 ± 15.3 ($n - 1$)	98.3 ± 14.3 ($n - 1$)	104.5 ± 15.8
TIADL Total	194 ± 80	199 ± 86	190 ± 75
Train-To-Task measures			
Auditory Time Order Judgment	87 ± 50	91 ± 59	83 ± 40
Useful field of view*	397 ± 186	441 ± 195	354 ± 168
Secondary measures			
SF-12 PCS	45.4 ± 12.1	46.4 ± 9.7	44.4 ± 14.0
SF-12 MCS	39.5 ± 12.8	38.9 ± 12.9	40.2 ± 12.9
BDI	18.7 ± 11.9	17.6 ± 11.2	19.9 ± 12.6
PCL-C	44.9 ± 15.7	43.2 ± 13.9	46.5 ± 17.3
FrSBe	75.9 ± 21.6	73.3 ± 20.3	78.4 ± 22.7
CFQ*	56.7 ± 17.7	52.6 ± 17.7	60.6 ± 17.0
NSI	31.6 ± 16.0	28.9 ± 15.2	34.2 ± 16.5
MPAI	36.2 ± 15.3	34.5 ± 15.0	37.8 ± 15.6

BDI = Beck Depression Index; CFQ = Cognitive Failures Questionnaire; FrSBe = Frontal Symptoms Behavioural Scale; MCS = Mental Component Score; MPAI = Mayo-Portland Adaptability Index; NSI = Neurobehavioural Symptom Inventory; PCL-C = Post Traumatic Stress Disorder Checklist Civilian; PCS = Physical Component Score; SF-12 PCS/MCS = Short-Form 12 Physical/Mental Component Score; TOMM = Test Of Memory Malingering.

*$P < 0.05$; mean ± 1 SD or % of variable, missing data-points shown as ($n - x$).

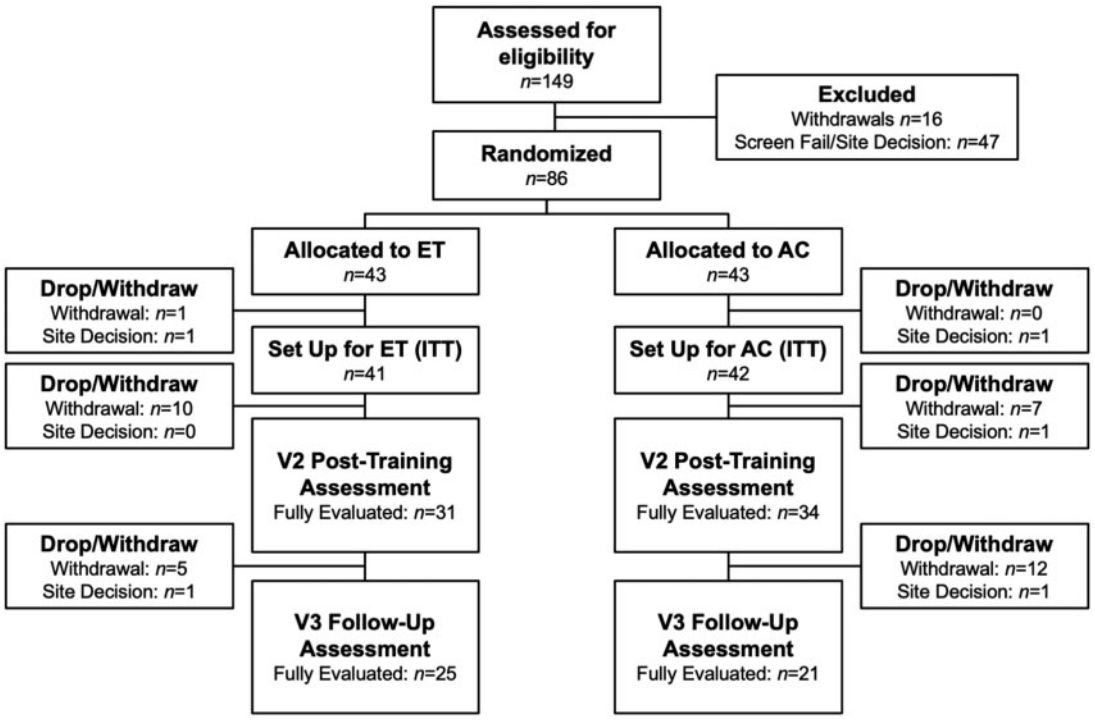

Figure 2 CONSORT diagram. Fully Evaluated = attended assessment visit and completed the majority of assessments (individual assessments still may be missing data).

Training effects on outcome measures

Pre/post training data are reported in Table 2. Change in the experimental treatment group showed a significant advantage over the active control group on the cognitive composite measure (+6.9 points, $P = 0.025$, $d = 0.555$). On a within-group basis, improvement in the experimental treatment group (+9.0 points) was 3.9 times larger than that of the active control group (+2.3 points). There was no significant between-group difference in the directly-observed functional measure (TIADLs); on a within-group basis, both the experimental treatment and active control groups improved numerically from baseline to the post-training visit. There were no significant between group differences on any secondary measure. The BDI, CFQ. FrSBe, and NSI each showed significant within-group changes in both the experimental treatment and active control groups. There were no significant between-group differences on the train-to-the-task auditory measure. The experimental treatment group showed a significant advantage over the active control group on the train-to-the-task visual measure.

Data regarding the follow-up visit are reported in Table 3, and were largely consistent with the post-training data. Change in the experimental treatment group showed a significant advantage over the active control group on the cognitive composite measure *t* (+7.4 points, $P = 0.039$, $d = 0.591$). On a within-group basis, improvement in the experimental treatment group (+9.0 points) was 4.9 times larger at follow-up (experimental treatment: +9.4, active control +1.9). There was no significant between group difference in the directly-observed functional measure (TIADLs); on a within-group basis, both groups continued to improve numerically from baseline to the post-training visit to the follow-up visit. There were no significant between-group differences on any secondary measure, with the exception of the PCL which showed a significant advantage favouring the active control at the follow-up time point. The BDI and CFQ each showed significant within group changes at the follow-up visits. There were no significant between-group differences on the train-to-the-task auditory measure. The experimental treatment group showed a non-significant trend advantage over the active control group on the train-to-the-task visual measure.

Clinically significant change score analysis with two criteria for a significant change (+0.2 SD of the pretraining scores as a minimal effect;[71] and +1.0 SD as a large effect) demonstrated that more than twice the fraction of participants in the experimental treatment group showed changes larger than criterion at both criteria levels than then in the active control group (+0.2: 77% versus 38%, $P = 0.002$; +1.0: 37% versus 18%, $P = 0.085$) at the post-training visit.

Although baseline differences in the primary cognitive composite measure were not significant, and the linear mixed model incorporates baseline function as a covariate, two analyses were conducted to confirm that gains favouring the experimental treatment were not due to regression to the mean. First, regression to the mean in the active control group was directly calculated, showing an expected significant relationship (+0.27 points of cognitive composite score change per 1.0 point of lower baseline cognitive composite score). This indicates that the lower baseline experimental treatment score could have been associated with a 1.7-point between group change difference, which is meaningfully lower than the numerically observed 7.1 point treatment-related difference. Second, through a Winsorization process that pairwise excluded Experimental treatment participants with low baseline scores and active control participants with high baseline scores from the fully-evaluable population, a series of groups were created with increasingly similar baseline scores; at the fourth step the baseline scores were equivalent (experimental treatment 100.9, active control 100.7) with a similar effect size to the ITT group still observable despite loss of power ($n = 46$, +5.8 points, $d = 0.455$, $P = 0.084$).

A dot plot showing each fully-evaluable participant is shown in Fig. 3 for the cognitive composite (Fig. 3A) and TIADL (Fig. 3B) measures with a box plot showing the treatment effect and 95% confidence limits from the ITT linear mixed model analysis.

Table 2 Outcome measure analysis (ITT population) post-training visit

	Experimental training within group differences (V2 – V1)		Active control within group differences (V2 – V1)		Between groups difference (V2 – V1)		
	Baseline Mean ± SD (range)	Change Mean (95% CI)	Baseline Mean ± SD (range)	Change Mean (95% CI)	Change difference (95% CI)	F-value (df)	Effect size, P-value
Primary measures							
Cognitive composite	98.3 ± 14.3 (67–131)	+9.0 (+5.0 to +13.1)	104.5 ± 15.8 (71–146)	+2.3 (–1.9 to +6.5)	+6.9 (+1.0 to +12.7)	$F = 5.27$ (68.4)	$d = +0.555$ $P = 0.025$
TIADL total (s; lower is better)	192 ± 86 (61–422)	–22 (–56 to +12)	180 ± 71 (57–343)	–34 (–62 to –6)	+13 (–31 to +56)	$F = 0.323$ (72.0)	$d = –0.134$ $P = 0.572$
Train-To-Task measures							
Auditory Time Order Judgment (ms; lower is better)	91 ± 59 (26–309)	–24 (–38 to –10)	83 ± 40 (29–182)	–17 (–25 to –8)	–8 (–24 to +8)	$F = 0.934$ (66.3)	$d = +0.237$ $P = 0.337$
Useful Field of View (ms; lower is better)	441 ± 195 (60–1000)	–193 (–292 to –93)	354 ± 168 (72–743)	–89 (–138 to –41)	–96 (–173 to –19)	$F = 6.03$ (69.4)	$d = +0.589$ $P = 0.017$
Secondary measures							
SF-12 PCS	46.4 ± 9.7 (21–66)	–0.4 (–2.8 to +1.9)	44.4 ± 14.0 (14–65)	–1.1 (–3.3 to +1.1)	+0.5 (–2.7 to +3.7)	$F = 0.092$ (66.1)	$d = +0.075$ $P = 0.762$
SF-12 MCS	38.9 ± 12.9 (10–59)	+2.3 (–0.6 to +5.3)	40.2 ± 12.9 (8–68)	+3.8 (+0.5 to +7.2)	–1.5 (–6.0 to +3.0)	$F = 0.415$ (68.8)	$d = –0.155$ $P = 0.521$
BDI-II (lower is better)	17.6 ± 11.2 (1–39)	–3.0 (–5.1 to –0.9)	19.9 ± 12.6 (0–45)	–3.1 (–6.1 to –0.2)	+0.1 (–3.6 to +3.8)	$F = 0.002$ (67.8)	$d = –0.010$ $P = 0.968$
PCL-C (lower is better)	43.2 ± 13.9 (18–70)	–2.8 (–5.8 to +0.2)	46.5 ± 17.3 (18–82)	–4.4 (–7.3 to –1.5)	+1.5 (–2.6 to +5.7)	$F = 0.529$ (67.5)	$d = –0.177$ $P = 0.470$
FRsBe (lower is better)	73.3 ± 20.3 (37–114)	–13.0 (–18.4 to –7.6)	78.4 ± 22.7 (51–171)	–10.8 (–15.4 to –6.1)	–1.6 (–8.7 to +5.5)	$F = 0.194$ (69.5)	$d = +0.106$ $P = 0.661$
CFQ (lower is better)	52.6 ± 17.7 (15–87)	–10.1 (–14.3 to –5.9)	60.6 ± 17.0 (27–94)	–9.4 (–14.3 to –4.5)	–0.7 (–7.3 to +5.8)	$F = 0.050$ (67.9)	$d = +0.054$ $P = 0.823$
NSI (lower is better)	28.9 ± 15.2 (4–59)	–5.2 (–9.6 to –0.7)	34.2 ± 16.5 (3–74)	–5.5 (–8.8 to –2.2)	+0.3 (–5.2 to +5.8)	$F = 0.014$ (70.5)	$d = –0.028$ $P = 0.908$
MPAI (lower is better)	34.5 ± 15.0 (–16 to +54)	–4.5 (–9.4 to +0.4)	37.8 ± 15.6 (–4 to +70)	–3.6 (–6.8 to –0.3)	–1.1 (–6.9 to +4.7)	$F = 0.133$ (71.1)	$d = +0.086$ $P = 0.717$

Experimental treatment $n = 41$ (except cognitive composite, $n = 40$); active control $n = 42$; effect size signs oriented so positive numbers represent a greater change for the experimental treatment group. BDI-II = Beck Depression Index II; CFQ = Cognitive Failures Questionnaire; FrSBe = Frontal Symptoms Behavioural Scale; MPAI = Mayo-Portland Adaptability Index; NSI = Neurobehavioural Symptoms Inventory; PCL-C = Post Traumatic Stress Disorder Checklist Civilian; SF-12 PCS/MCS = Short-Form 12 Physical/Mental Component Score.

Table 3 Outcome measure analysis (ITT population) follow-up visit

	Experimental training within group differences (V3 – V1)		Active control within group differences (V3 – V1)		Between groups difference (V3 – V1)		
	Baseline Mean ± SD (range)	Change Mean (95% CI)	Baseline Mean ± SD (range)	Change Mean (95% CI)	Change Difference (95% CI)	F-value, (df)	Effect size, P-value
Primary measures							
Cognitive composite	98.3 ± 14.3 (67 to 131)	+9.4 (+4.5 to +14.3)	104.5 ± 15.8 (71 to 146)	+1.9 (–2.9 to +6.7)	+7.4 (+0.6 to +14.3)	$F = 4.5$ (51.5)	$d = +0.591$ $P = 0.039$
TIADL total (s; lower is better)	192 ± 86 (61–422)	–72 (–105 to –40)	180 ± 71 (57–343)	–49 (–84 to –14)	–23 (–71 to +25)	$F = 0.858$ (61.2)	$d = +0.237$ $P = 0.358$
Train-To-Task measures							
Auditory Time Order Judgment (ms; lower is better)	91 ± 59 (26–309)	+11 (–35 to +57)	83 ± 40 (29–182)	–23 (–35 to –11)	+33 (–17 to +83)	$F = 1.65$ (69.5)	$d = -0.308$ $P = 0.203$
Useful Field of View (ms; lower is better)	441 ± 195 (60–1000)	–202 (–270 to –134)	354 ± 168 (72–743)	–99 (–177 to –20)	–105 (–209 to –1)	$F = 3.93$ (63.8)	$d = +0.496$ $P = 0.052$
Secondary measures							
SF-12 PCS	46.4 ± 9.7 (21–66)	–1.5 (–3.8 to +0.9)	44.4 ± 14.0 (14–65)	+1.1 (–1.7 to +4.0)	–2.6 (–6.2 to +1.1)	$F = 1.89$ (47.3)	$d = -0.400$ $P = 0.176$
SF-12 MCS	38.9 ± 12.9 (10–59)	+3.3 (+0.6 to +6.6)	40.2 ± 12.9 (8–68)	+1.5 (–3.3 to +6.3)	+1.3 (–4.1 to +6.7)	$F = 0.229$ (52.4)	$d = +0.132$ $P = 0.634$
BDI-II (lower is better)	17.6 ± 11.2 (1–39)	–2.8 (–5.6 to –0.0)	19.9 ± 12.6 (0–45)	–4.3 (–7.0 to –1.5)	+1.4 (–2.5 to +5.4)	$F = 0.503$ (50.1)	$d = -0.200$ $P = 0.481$
PCL-C (lower is better)	43.2 ± 13.9 (18–70)	–0.2 (–3.4 to +3.0)	46.5 ± 17.3 (18–82)	–6.9 (–11.7 to –2.2)	+6.5 (+0.9 to +12.1)	$F = 5.14$ (52.6)	$d = -0.625$ $P = 0.028$
FrSBe (lower is better)	73.3 ± 20.3 (37–114)	–7.1 (–14.9 to +0.8)	78.4 ± 22.7 (51–171)	–8.9 (–14.3 to –3.4)	–4.2 (–11.8 to +3.5)	$F = 1.14$ (53.0)	$d = +0.293$ $P = 0.291$
CFQ (lower is better)	52.6 ± 17.7 (15–87)	–9.8 (–13.6 to –6.1)	60.6 ± 17.0 (27–94)	–12.0 (–17.4 to –6.6)	+2.6 (–3.8 to +9.1)	$F = 0.651$ (49.4)	$d = -0.230$ $P = 0.424$
NSI (lower is better)	28.9 ± 15.2 (4–59)	–2.8 (–6.7 to +1.0)	34.2 ± 16.5 (3–74)	–4.4 (–10.1 to +1.3)	+1.2 (-5.6 to +8.0)	$F = 0.119$ (54.3)	$d = -0.093$ $P = 0.732$
MPAI (lower is better)	34.5 ± 15.0 (–16 to +54)	–6.0 (–10.3 to –1.8)	37.8 ± 15.6 (–4 to +70)	–4.1 (–8.7 to +0.5)	–2.0 (–8.2 to +4.3)	$F = 0.378$ (54.8)	$d = +0.116$ $P = 0.541$

Experimental treatment $n = 41$ (except cognitive composite, $n = 40$); active control $n = 42$; effect size signs oriented so positive numbers represent a greater change for the experimental treatment group. BDI-II = Beck Depression Index II; CFQ = Cognitive Failures Questionnaire; FrSBe = Frontal Symptoms Behavioural Scale; MPAI = Mayo-Portland Adaptability Index; NSI = Neurobehavioural Symptoms Inventory; PCL-C = Post Traumatic Stress Disorder Checklist Civilian; SF-12 PCS/MCS = Short-Form 12 Physical/Mental Component Score.

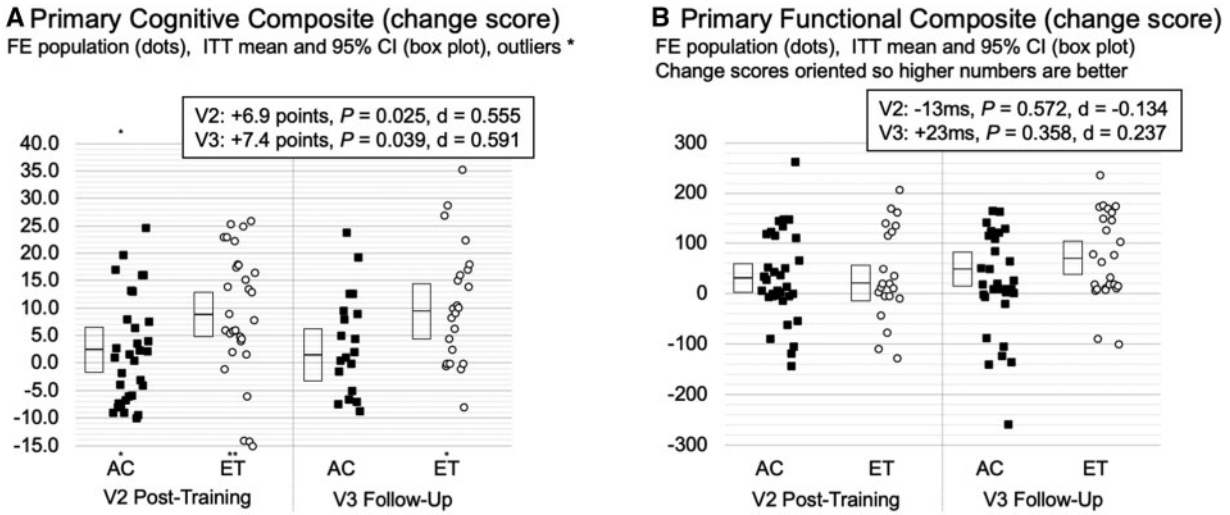

Figure 3 Composite cognitive function and TIADL (change scores). Each icon represents the change score (from baseline) for a single fully-evaluated participant; asterisk indicates outliers, boxes = the change score derived from the linear mixed model of the ITT population with the centre representing the model estimate of the change score and the upper/lower boundaries showing the 95% confidence limits of the change score

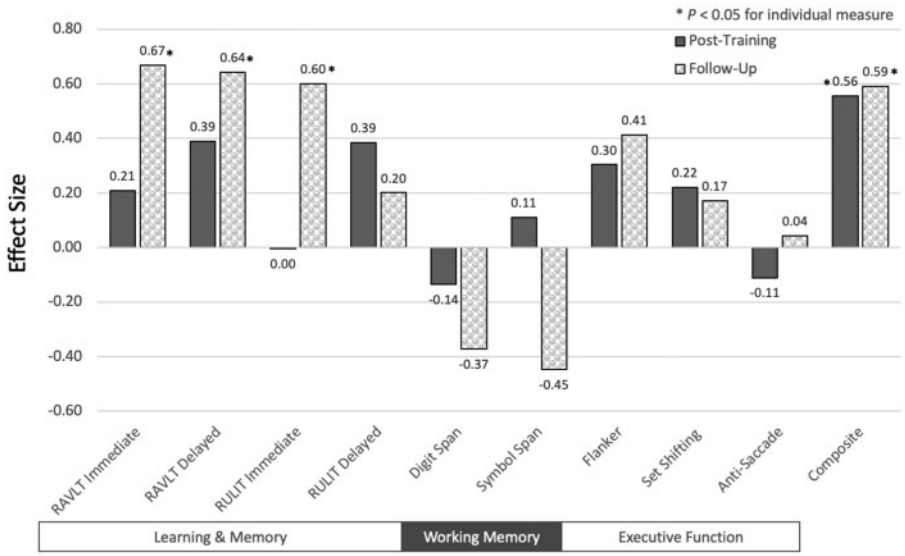

Figure 4 Effects on specific cognitive domains. Effect sizes (Cohen's *d*) at the post-training and follow-up visits, oriented such that positive numbers represent changes favouring the experimental treatment group. Individual neuropsychological tests are grouped into cognitive domains based on properties described in their respective test administration manuals.

Effect sizes for the individual neurocognitive tests comprising the cognitive composite are shown in Fig. 4. Positive effects are generally seen at both the post-training and follow-up visits in the learning and long-term memory measures and the executive function measures (except for the anti-saccade test) and not generally seen in the working memory measures.

Pre-planned secondary analyses evaluated effect sizes in participants included based on the neuropsychological criterion (ANAM cognitive impairment) and the participant-reported criterion (RNBI cognitive impairment). Participants included on the basis of the neuropsychological criterion showed numerically larger effect sizes on the cognitive composite measure (those meeting ANAM and not meeting RNBI, $n = 26$, $d = 0.761$; meeting RNBI and not meeting ANAM, $n = 18$, $d = 0.012$).

In a related *post hoc* analysis, the effects of different cut-off points for cognitive impairment as assessed with the ANAM at baseline were explored. A 1.28 SD cut-off and a 1.5 SD cut-off (each considering only the ANAM-included participants) each showed similar overall effects on the cognitive composite score (<1.28 SD inclusion, $n = 60$, $d = 0.797$, $P = 0.007$; <1.5 SD inclusion, $n = 52$, $d = 0.823$, $P = 0.011$).

In exploratory analyses, the relationship between measures of training (sessions completed, change in train-to-task auditory and visual measures) and various outcome measures were examined. There was no significant relationship between hours of training completed and any outcome measure in either group. In the experimental treatment group, there was a trend towards a significant relationship between the improvement in the train-to-the-task auditory speed measure and the improvement in the cognitive composite measure change ($P = 0.079$), with no significant relationship in the active control group, and no relationship seen in the train-to-the-task visual speed measure.

After each assessment visit, the assessor was recorded if the participant had made comments that broke the assessor blind. No such cases were reported.

Eight study-related adverse events were recorded (experimental treatment: $n = 2$, active control: $n = 6$), generally related to anxiety, headache, and mental fatigue.

Discussion

The BRAVE study is the first randomized controlled trial of a broadly-available cognitive training programme in patients with cognitive impairment and a history of mTBI to address American Academy of Neurology class I standards for an RCT, and the first to show cognitive function improvement in this population with a computerized cognitive training programme. Improvements in cognitive function favouring the experimental treatment group were statistically significant compared to the active control group with a clinically meaningful effect size with improvements 3.9–4.9 times larger in magnitude than seen in the active control group. More than twice the fraction of people in the experimental treatment group showed small and large cognitive improvements than in the active control group.

Improvements in cognitive performance in the treatment group cannot be explained by test-retest effects or expectation/placebo effects because no such changes were seen in the active control arm, nor by differences in adherence because both groups trained an equivalent amount of time and adhered to the schedules equivalently, nor by test rehearsal because the cognitive training tasks did not specifically mimic or practice the neuropsychological assessments. Non-significant baseline differences in cognitive function between the two groups were shown not to be a meaningful contributor to the between-groups difference over the treatment and follow-up periods.

No significant between group differences were seen in the directly-observed functional measure (TIADLs) or on a number of participant-reported outcomes/symptoms scales. In general, the lack of a between group difference was caused by positive response in the active control group equal in magnitude to the positive response in the intervention group, rather than a lack of response in both groups. Potential causes include true benefits from the active control activity (ordinary computer games) that are equal in magnitude to the cognitive training programme, or expectation/placebo/practice effect in both groups, however these alternatives cannot be distinguished with the available data.

Three recent trials of cognitive training with participant populations and outcome measures similar to the current study provide context and comparison for the current findings. First, the SCORE study[22] evaluated a similar participant population ($n = 126$) and compared four distinct treatments, including psychoeducation (structured as a treatment-as-usual control group), therapist-directed manualized cognitive rehabilitation, therapist-directed cognitive rehabilitation combined with cognitive-behavioural psychotherapy, and a non-therapist directed version of the computerized intervention used in the current study. In SCORE, within-group improvements in cognitive performance were seen in all four groups with no significant between group effects. A difference between BRAVE and SCORE that may explain this is the use in BRAVE of a composite cognitive function measure with perhaps better test-retest stability than the single cognitive function measure used in SCORE (PASAT, subject to substantial practice effects[72]), allowing the detection of a between groups difference in cognitive performance in BRAVE. Furthermore, in SCORE improvements in psychological symptoms and cognitive/behavioural difficulties were seen in all four groups. No between groups effects were seen with the exception that the two therapist-directed groups had larger effects on the cognitive/behavioural difficulties measure than the control arm, while the computerized cognitive training group had an intermediate effect size statistically indistinguishable from either the therapist directed groups or the control group. The pattern of results across BRAVE and SCORE suggests that all groups receiving active coaching (the two therapist directed groups in SCORE, and both the intervention and active control group in BRAVE) experience within-group improvements in psychological symptoms.

Second, the CogSMART compensatory cognitive training programme was evaluated in a trial ($n = 119$) in comparison to a treatment-as-usual control group.[25] Significant between-group effects were seen on three of six cognitive measures, with effect sizes similar to the current study. In addition, significant between-group benefits were noted on two of six self-report measures of cognitive symptoms, with improvements in the treatment group and no change in the treatment-as-usual control group. No significant between-group benefits were seen in the directly observed functional measure. This pattern of results across CogSMART and BRAVE suggests again that all groups receiving active coaching (the intervention group in CogSMART, and both the intervention and active control group in BRAVE) experience within-group improvements in symptom measures.

Third, the SMART executive function training programme was evaluated in a trial ($n = 60$) in comparison to a time-matched active control (health education).[21] Significant between group effects were seen on cognitive performance measures, with effect sizes similar to the current study. In addition, within-group benefits were noted on symptom measures in both groups (significantly larger in the intervention group) that were considerably larger than changes seen in either group in the current study.

These three previous studies considered with BRAVE suggest a coherent framework for the observed pattern of participant-reported outcomes/symptom scales: active interventions with coaching (training programmes, active controls) show within-group improvements, whereas treatment-as-usual groups without coaching do not show such improvements. Consequently, trials comparing an active intervention to a treatment-as-usual control (e.g. SCORE, CogSMART) generally show significant between-groups results on participant-reported outcomes/symptoms scales, whereas trials comparing an active intervention to an active control (BRAVE) show within-group benefits in each group but no between-groups difference (with SMART as an outlier trial, with two active treatments showing large gains in both groups, with a larger gain in the treatment group).

The lack of a significant between groups difference in the directly observed functional measure came as a surprise. Significant benefits of cognitive training with the exercises used in the current study on the TIADL functional measure have been seen in five distinct trials in older adults, with a typical within-group effect size of ~0.3 in the training group (comparable to the current study). No control group in the previous studies showed a within-group improvement. Thus, the main distinction between the current trial in mTBI and the previous trials in normal ageing appears to be the magnitude of the change within the control group. A first potential explanation for this discrepancy is that in mTBI but not normal ageing, the cognitive training improves an underlying cognitive construct as measured by the neuropsychological assessment battery but does not improve the underlying cognitive construct relevant to the TIADL functional measure (leaving both groups with placebo/expectation benefit). A second potential explanation is that the measure may be sensitive to underlying cognitive change in older adults but insensitive in younger adults due to the specific tasks used in the measure, which are familiar to older adults (e.g. using a telephone book) but novel and subjective to practice effects

in younger adults (masking, but not additive, to any benefits of the training programme). Anecdotally, test administrators noted that the relatively young study participants in the current study were not familiar with several tasks used in the assessment at baseline, suggesting that the measure was not appropriate for use in this population and that task familiarity contributed to improvement seen in both groups. It is not possible to distinguish between these alternatives with the current dataset. Further development of directly observed functional performance assessments for mTBI would be useful in future clinical trials.

These results suggest that in a clinical setting, this computerized cognitive training programme should be used only with clinician-directed support and coaching, with the goal of improving cognitive function as assessed with standardized neuropsychological measures, and as part of a part of a broader rehabilitation programme with additional components directed at other issues associated with mTBI (e.g. sleep, headache, functional skills).

An implication from this trial is that different computerized cognitive training programmes work differently. The plasticity-based cognitive training improved cognitive function, while the computer game training programme (which also engaged cognitive abilities) did not. As the field of computerized cognitive training continues to develop in an evidence-based way, it is important to move beyond the question of whether computerized cognitive training works or not, to the question of which specific programmes are effective for which specific populations in which specific ways.

Strengths of the current study include a well-defined participant population matching current VA/Department of Defense (DoD) Clinical Practice Guidelines for a symptom-based approach to treatment, multisite execution, good match between the expectation of benefit between the two groups, use of blinded assessors, use of a follow-up assessment, and use of an *a priori* ITT statistical plan.

Three weaknesses of the current study are noted. First, it did not achieve the enrolment goal, lowering the statistical power from 0.80 to 0.61 to detect an effect size of 0.50. While not optimal, at the observed sample size and power, the study has higher statistical power than ~70% of published studies in neurology.[73] Of the seven RCTs of cognitive remediation in TBI cited in recent guidelines[10,11] and meta-analyses, the current trial would be the second largest. To our knowledge, only two trials in mTBI of cognitive training programmes are larger,[22,25] as was a single trial of web-based psychoeducation with negative results.[74] A second issue of potential concern is the maintenance of the blind for the active control group. While every effort was taken to ensure that participants assigned to the active control group believed in the potential efficacy of their assigned video game treatment (including language in the consent form describing the study as comparing two interventions, coaching materials used with each group, lack of opportunity for participants to interact to discuss their differing treatments, and instructions to study staff), it is possible that some participants concluded that the video game intervention was a control activity and adjusted their expectations and efforts on outcome measures accordingly. Of course, this issue is not unique to cognitive training trials, and can occur with a double-blinded RCT of any type of intervention.[75] A third concern is the participant drop-out rate, particularly at the time of the follow-up assessment. This issue was mitigated by using a linear mixed model for the statistical analysis (which accounts for missing data) and confirming that the drop/withdraw rate was not significantly different between the groups, and that the drop/withdraw population was not statistically different from the completer population on baseline variables. Nonetheless, it is possible that drop-outs have affected the analysis, and the results should be interpreted in that light.

Post hoc subgroup analysis suggests that the treatment benefit may be stronger for people with baseline impairments of processing speed (ANAM criterion) than for people with normal processing speed who self-report cognitive impairment following their mTBI (RNBI criterion). The subpopulations are small, and the data are not fully consistent across the post-training and follow-up assessments. The relationship between participant-reported cognitive symptoms and neuropsychological test performance is complex,[76] and an appropriately powered follow-up study could provide a more definitive answer to this question.

The experimental treatment programme has been shown to drive brain plasticity in animal[26,77,78] and human models.[41,79,80] However, the current study was not designed to determine the mechanism of action linking the putative neural action of the cognitive training programme with the observed pattern of outcomes. Given that the cause of cognitive impairment following mTBI are multi-factorial, it would be of interest to investigate the specific mechanism of action of the current intervention in future studies, incorporating additional assessments and brain imaging techniques capable of detecting the subtle brain injury characteristic of mTBI (e.g. diffusion tensor imaging, resting state functional connectivity).

Treatment of post-concussive syndrome is complex, and patients typically manifest distinctive sets of physical, mental, and cognitive symptoms that require individualized courses of treatment. This trial provides strong evidence that this specific form of coach-supervised, self-administered, plasticity-based cognitive training can be incorporated as part of an evidence-based treatment plan to improve neuropsychological measures of cognitive function in people with a history of mTBI.

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Competing interests

Posit Science was the sponsor of this trial, and is the developer of the BrainHQ cognitive training programmes used in this study. Posit Science holds patents for and a proprietary interest in this software. H.W.M. is an employee of and holds equity in Posit Science, and contributed to the design, conduct, analysis, interpretation, and publication of this study. M.M.M. is an employee of and holds equity in Posit Science and contributed to the interpretation of this study. C.S. and S.J.K. are also employees of and hold equity in Posit Science, and contributed to the conduct of the study. A.R. was an employee of Posit Science and now serves as a consultant to Posit Science, holds equity in Posit Science, and contributed to the analysis of this study. No other author is an employee of or paid consultant to Posit Science, and no other author holds equity or other financial conflict of interest in Posit Science. All sponsor payments related to the BRAVE trial were made through sponsored research agreements with the various academic trial sites; none were made through personal consulting

relationships to individuals. Ultimate responsibility for the design, conduct, analysis, and publication of the trial resided with H.W.M. and J.D.G. J.D.G. has full access to the dataset of the study. The identification of specific products or scientific instrumentation is considered an integral part of the scientific endeavour and does not constitute endorsement or implied endorsement on the part of the authors, Department of Defense, or any component agency. The views expressed in this article are those of the authors and do not reflect the official policy of the Departments of the Army/Navy/Air Force, Department of Defense, or U.S. Government.

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