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RESEARCH PAPER

Feasibility of online self-administered cognitive training in moderate–severe brain injury

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ABSTRACT

Purpose: Cognitive environmental enrichment (C-EE) offers promise for offsetting neural decline that is observed in chronic moderate–severe traumatic brain injury (TBI). Brain games are a delivery modality for C-EE that can be self-administered over the Internet without therapist oversight. To date, only one study has examined the feasibility of self-administered brain games in TBI, and the study focused predominantly on mild TBI. Therefore, the primary purpose of the current study was to examine the feasibility of self-administered brain games in moderate–severe TBI. A secondary and related purpose was to examine the feasibility of remote monitoring of any C-EE-induced adverse symptoms with a self-administered evaluation tool.

Method: Ten patients with moderate–severe TBI were asked to complete 12 weeks (60 min/day, five days/week) of online brain games with bi-weekly self-evaluation, intended to measure any adverse consequences of cognitive training (e.g., fatigue, eye strain).

Results: There was modest weekly adherence (42.6% ± 4.4%, averaged across patients and weeks) and 70% patient retention; of the seven retained patients, six completed the self-evaluation questionnaire at least once/week for each week of the study.

Conclusions: Even patients with moderate–severe TBI can complete a demanding, online C-EE intervention and a self-administered symptom evaluation tool with limited therapist oversight, though at daily rate closer to 30 than 60 min per day. Further self-administered C-EE research is underway in our lab, with more extensive environmental support.

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➤ IMPLICATIONS FOR REHABILITATION

- Online brain games (which may serve as a rehabilitation paradigm that can help offset the neurodegeneration observed in chronic TBI) can be feasibly self-administered by moderate-to-severe TBI patients.
- Brain games are a promising therapy modality, as they can be accessed by all moderate-to-severe TBI patients irrespective of geographic location, clinic and/or therapist availability, or impairments that limit mobility and access to rehabilitation services.
- Future efficacy trials that examine the effect of brain games for offsetting neurodegeneration in moderate-to-severe TBI patients are warranted.

Introduction

Cognitive environmental enrichment (C-EE) refers to exposure to intensive cognitive stimulation that is continuously novel, challenging and engaging.[1] The broader term of environmental enrichment (EE) refers to intensified cognitive as well as social and physical stimulation.[2] In the context of traumatic brain injury (TBI), and in particular moderate–severe injuries, EE is an important intervention. Patients with moderate–severe TBI show only limited recovery from their injuries,[3] leaving life-long residual deficits in cognitive functioning. EE shows promise of enhancing brain function and even reversing deficits. Given growing evidence of neural deterioration in the chronic stages of TBI,[4,5] when most patients are receiving no further therapies, and many live remote from treatment centers, there is a critical need for accessible therapies which show promise for preventing or mitigating decline.

The benefits of EE have been well-documented in the animal and human literature. In animals, level of EE is manipulated by changing the complexity of the environment, and this is typically accomplished by varying the toys, exercise equipment and number of animals housed in a cage.[2] Healthy animals, when exposed to enriched as compared to conventional or deprived environments, have shown increased proliferation of hippocampal neurons,[6–8] increased dendritic branching,[9] greater neuronal connectivity and synaptic plasticity,[10] up-regulation of neurotrophic factors, such as nerve growth factor and brain-derived growth factor,[2] as well as associated behavioral improvements (e.g., improved spatial

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navigation).[11,12] Brain-injured animals exposed to EE have shown better indices of recovery, including greater reductions in lesion size,[13–15] increased synaptic and cellular plasticity,[16,17] increased progenitor cells in the dentate gyrus,[18] up-regulated neurotrophins such as brain-derived neurotrophic factor,[2] and improved cognitive performance on measures of spatial learning and memory.[15,19,20]

In humans, the benefits of EE have been extensively studied in neurologically vulnerable populations. In older adults, several large scale, longitudinal, multi-site observational studies (e.g., the Victoria Longitudinal Study [21] and the Bronx Aging Study [22]) have demonstrated that intellectually, physically and socially engaging lifestyles are associated with better cognitive and neural outcomes.[23] While the interpretation of these studies is limited by a "chicken and egg" problem (i.e., that higher functioning people may lead more active lives), several further experimental studies have provided compelling causal evidence for the benefits of C-EE.[24–26] For example, the ACTIVE, multi-site randomized control trial showed that cognitive training (10 sessions of strategy training in multiple cognitive domains) improved the ability to carry out activities of daily living even five years post-treatment.[25] Other prospective experiments in older adults have found cognitive benefits of C-EE for working memory and speed of processing,[27,28] as well as neural benefits such as increased total brain volume, cortical thickness and the BOLD response on functional MRI (for reviews, see [29,30]). In brain-injured adults, a body of literature on "intensification" in acute TBI has demonstrated that increasing the number of hours of therapy for subacute TBI patients results in improved functional recovery, as measured by shorter lengths of stay in rehabilitation centres and increased scores on functional indices (e.g., the widely used "Functional Independence Measure").[31–33]

In addition to improving cognitive and neural health, C-EE shows evidence of staving off neural deterioration.[24,38] This is of particular importance for patients with moderate–severe TBI who show progressive volume losses to the whole brain and sub-structures, including the hippocampi,[4,34] and losses to white matter integrity long after the resolution of acute neurological injuries.[4,5,35–37] A recent study by our group suggests that such atrophy may be offset through EE.[38] Specifically, in 25 adult patients with moderate–severe TBI, we found that greater self-reported C-EE at five months post-injury was correlated with reduced bilateral hippocampal atrophy from 5 to 24+ months post-injury [38]). In research by Lovden and colleagues, a C-EE spatial navigation intervention was observed to avert aging-related brain volume loss in healthy younger and older adults. Here, new learning on a virtual spatial navigation task over a 16-week period (1 h/every other day) resulted in attenuated hippocampal volume loss over the period of the study that was also maintained 4 months later.[24]

Taken together, the above findings point toward the value of EE for patients with moderate–severe TBI. C-EE shows evidence for promoting brain health and recovery after injury, and for staving off progressive deterioration. Unfortunately, there are numerous barriers to accessing C-EE.[39] These barriers include the dearth of locally available resources that can provide C-EE (e.g., therapy centers, libraries, community centers) as well as lack of transportation and/or accompaniment to such resources even when they are available. Even when resources are available, engagement in an activity may require accompaniment/supervision to ensure that commencement and completion of the activity transpire. Such barriers are particularly problematic given that an active ingredient of C-EE is its intensivity, whereby neural and cognitive benefits are conferred in the context of frequent engagement in cognitive activities.[24,26]

A potential solution to these barriers is the computerized delivery of C-EE in the form of online brain games, which can be self-administered during and after discharge from inpatient rehabilitation. Such games require little-to-no clinician or caregiver oversight and can be delivered to patients in their own homes; moreover, the gaming elements [40] can offset reduced initiation and follow-through deficits that are common consequences of moderate–severe TBI.[41] Some brain games offer many of the active ingredients of C-EE. For example, game-design elements (e.g., point/reward systems and competition) create an immersive and engaging user experience,[40] and many games are designed to continually challenge users through exposure to increasingly difficult conditions. As well, many programs confer continuous novelty, at least for a period of time, through their variety of games; moreover, they are often designed to challenge different cognitive domains, such as attention, executive functions, memory, speed of processing and visuospatial processing.[42] While there is controversy regarding the efficacy of brain games for enhancing cognitive function in healthy adults,[43] a number of studies employing brain games for cognitive functioning in neurologically vulnerable populations have shown efficacy, including studies of healthy older adults,[28,44–51] Alzheimer's disease,[52] mild cognitive impairment [53,54] and multiple sclerosis.[55]

In order to utilize self-administered brain games to enhance outcomes for patients in the chronic stages of moderate–severe TBI, a more immediate aim is to demonstrate the feasibility of use for this population. Given cognitive impairments in this population that include compromised sustained attention, initiation and follow-through,[56,57] uptake of C-EE cannot be assumed. To date, the only previous study examining the feasibility of self-administered brain games, conducted by Lebowitz et al.,[58] employed patients with predominantly mild TBI.

Feasibility studies are considered critical to the success of future, larger efficacy trials, as they generate an understanding of how study protocols and methodologies can be improved to increase, for example, patient retention and compliance.[59–67] Reports indicate that clinical trial dropout rates typically range from 15 to 40%,[68] and this may necessitate study extensions (required to meet recruitment targets) or under-powered analyses. Feasibility studies, however, can help prevent such compromised trials, as they allow for a small-scale assessment of study methodology and obviation of potential pitfalls that may compromise larger efficacy trials.

In the Lebowitz et al.[58] study, the authors assessed the feasibility of a computerized brain game intervention that was accessed offline. These computerized games were installed directly onto a personal computer using a software package. One disadvantage of this offline approach is reduced access: online software permits participation at any internet-ready computer or mobile device. Their study examined 10 TBI patients, half of whom were mildly impaired, four of whom were moderate–severely impaired and a fifth patient with unknown severity of injury. The average time-post-injury was just over nine years, and nine of the 10 participants were female. The study was six weeks in duration, with environmental support comprising daily email reminders plus weekly phone calls. Encouragingly, the authors found high adherence and no attrition. However, given that more than 1.1% of the population is living with enduring effects of TBI,[69] it is of value to know whether self-administered brain games are feasible for patients with greater injury severity and who are earlier post-injury. As well, it is of interest to know whether such patients can adhere to a program for longer than six weeks.

Therefore, the objective of the current study was to evaluate the feasibility of an in-home, self-administered, online brain game

intervention (12 weeks in duration) in a sample of patients predominantly in the moderate–severe range of TBI, who were within the first two years of injury. The study provided weekly reminder calls, but no further environmental support.

A secondary objective of the study was to assess the feasibility of self-administering a self-evaluation questionnaire. The questionnaire was designed to assess adverse effects of intensified therapies, such as headache, eyestrain and fatigue. It was also designed to rate any immediate psychological/cognitive benefits or costs of C-EE, such as increase or decrease in self-confidence, sense of accomplishment and mental sharpness. With the protocol we are examining, any deleterious effects of intensified therapies can only be monitored remotely. Therefore, alternative methods for identifying the presence and ultimately the impact of negative symptoms are needed. As well, ascertaining whether patients perceive psychological benefits or costs of participating might shed light on how to refine an intervention to achieve maximal compliance.

Methods

Participants

The Research Ethics Board at the University Health Network approved this study, and all participants provided written informed consent. The study comprised a convenience sample of 10 community-dwelling, moderate–severe TBI participants recruited through a larger, ongoing longitudinal study in our laboratory called the *Toronto TBI Recovery Study*. Recruitment of participants from an ongoing research study may have introduced a selection bias, as our study participants could have a greater predilection for research participation and may be, thereby, more motivated to remain in the study and comply with demands. This would reduce the generalizability of findings. However, it should be noted that the larger study offered free clinical services (i.e., clinical neuropsychological assessment) without any additional experimental demands; thus, the actual experimental burden was minimal. Therefore, we surmise that it is unlikely that patients agreeing to participate in this particular study were motivated than average with regard to research.

Key inclusion criteria for the *Toronto TBI Recovery Study* were as follows: acute care diagnosis of TBI; post traumatic amnesia (PTA) 1 h or more and/or Glasgow Coma Scale (GCS) of 12 or less either at emergency or the scene of accident and/or positive acute care computed tomography (CT) or magnetic resonance imaging (MRI) findings; age between 18 and 80; functional communication in English; and competency to provide informed consent for the study or availability of a substitute decision maker. Exclusion criteria for the *Toronto TBI Recovery Study* included the following: diseases primarily or frequently affecting the central nervous system, (e.g., dementia of Alzheimer's Type, Multiple Sclerosis); history of psychotic disorder; not emerged from PTA by six weeks post-injury; TBI secondary to other brain injury (e.g., a fall due to stroke). Further inclusion criteria for the current study comprised out-patient access to an Internet-ready personal computer and no resumption of full-time employment or school at the time of recruitment. Participants in the present study were recruited over an 11-month period spanning from May 2013 to March 2014. No participants were receiving out-patient day-hospital services over the course of the intervention.

Demographic and injury characteristics of patients were ascertained through medical record review and clinical interview (Table 1). All TBIs were severe enough to warrant in-patient neurorehabilitation. Table 2, presenting injury severity data, reveals that on the basis of PTA, all but one patient sustained a TBI in the "severe" to "very severe" range (from 4 to 60 days [70]). For the patient for whom PTA was unrecorded, the lowest GCS score was 3. GCS scores ranged from mild to severe. The three in the mild range (P1, P2 and P7) had a PTA of 7, 4 and 14 days, respectively.

Table 1. Demographic and injury characteristics of case series.

ID	Age	Sex	YOE	Time post-injury (Months)	Cause of injury
P1	62	M	19	14	Fall (Sport)
P2	40	M	19	2	Fall (Sport)
P3	30	M	21	8	Fall
P4	55	F	13	17	MVC
P5	53	M	19	24	MVC
P6	37	M	17	17	Fall
P7	48	F	17	18	Fall
P8	22	F	15	5	MVC
P9	68	M	21	35	MVC
P10	22	F	14	8	MVC

YOE: years of education; MVC: motor vehicle collision.

Behavioural characterization of patients included baseline neuropsychological assessment undertaken between one and six months post-injury, and functional status at the time of intervention (Table 3). Neuropsychological assessment was carried out by a trained psychometrist. The battery took approximately 5 h to complete and measured multiple domains of cognitive function including: attention, speed of processing, psychomotor speed, language, visual spatial functioning, memory and executive functioning. Neuropsychological assessments revealed moderate or greater impairments in seven patients, and relative impairments (e.g., at least two standard deviations between estimated premorbid verbal IQ and other cognitive measures) in the other three patients. To assess psychological status, the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were used. Findings from a subset of the larger battery are presented in Table 3. With regard to functional status before vs. after injury, eight of 10 participants were employed or in school full-time prior to injury; one participant was employed part-time and in school part-time, and one participant was semi-retired and engaged in private consulting work prior to injury. Nine of the 10 participants were driving prior to the assessment. At the start of the intervention, none of the participants had returned to their pre-injury vocational status, and only one participant had returned to driving (Table 3).

Design

The study was a prospective case-series examining the feasibility of delivering a C-EE intervention in-home to TBI participants via the Internet. The C-EE study of Leibowitz et al.[58] examining a milder population of TBI patients showed good feasibility over a six week period. However, many interventions with demonstrated efficacy employ durations of 12 weeks or longer.[24,26,71] Therefore, we elected to double the previous dose to ascertain whether we would still obtain high retention and compliance.

The primary outcome of the study was feasibility of the intervention protocol, as measured by (1a) attrition, the number of participants that completed all 12-weeks of the study; and (1b) adherence, comprising (i) *Weekly Adherence*, operationalized as the average amount of time trained in a given week, and presented as a percentage of the targeted 300 min (i.e., 60 min/day, five days/week); we also plotted adherence as a proportion of 200 min (which was the training target used in the study by Lebowitz et al.); and, (ii) *Daily Adherence*, operationalized as the total amount of time participants used the cognitive training program per session.

Table 2. Injury severity of case series. Imaging findings are paraphrased to key findings.

	Lowest GCS Score	PTA in days	Imaging findings (pos/neg)	Key findings from MRI report
P1	13	7	Positive	Encephalomalacia left frontal lobe and right inferior temporal gyrus; diffuse hemosiderin: left frontal lobe, right centrum semiovale, parietal gyri bilaterally. Subarachnoid hemorrhage.
P2	14	4	Positive	Gliosis right temporal and frontal lobes extending into right centrum semiovale. (Craniectomy with shunt performed.)
P3	3	n/a	Positive	(From CT report) Right frontal subdural hemorrhage with midline shift; left temporal lobe uncal herniation; diffuse sub-arachnoid hemorrhage.
P4	3	7	Positive	Probable gliosis anterior left temporal lobe; hemosiderin deposition right frontal white matter and genu; diffuse T2 hyperintensities.
P5	8	7	Positive	Multiple T2 hyperintensities periventricular white matter; 1–2 cm hypointensity (probable hemosiderin) left cerebral peduncle; hypointensities right frontal and temporal lobes; flow alterations circle of Willis.
P6	3	21	Positive	Left frontal encephalomalacia and hemosiderin. Hemosiderin also: gray-white junction right frontal lobe, temporal lobe, parasagittal frontal lobe bilaterally, corpus callosum, septum pellucidum and tectal midbrain.
P7	13	14	Positive	Focal lesion left cerebellum with hemosiderin rim and cystic appearance (uncertain association with current trauma); three punctate hypointensities left parasagittal rolandic region.
P8	6	60	Positive	Multiple intra-axial brain hemorrhages bilaterally, largest in the right putamen.
P9	8	30	Positive	Left frontal and right temporal subdural hemorrhages; left parietal hematoma; hemosiderin parietal and temporal lobes, right cerebellum, pons. Necrosis occipital lobes and left parietal; posterior circulation infarcts; multiple parenchymal and intracranial hemorrhages. (Craniotomy performed.)
P10	6	9	Positive	Scattered foci of hypointensity in right temporal lobe, corona radiata, splenium and subcortical frontal lobes (bilaterally). Wallerian degeneration in cortico-spinal tract.

GCS: Glasgow Coma Scale; PTA: Post-Traumatic Amnesia; n/a: not available.

The secondary outcome of the study was feasibility of self-administration of the self-evaluation questionnaire. This was measured by two indices of compliance: (2a) *Completion Rate*, operationalized as (i) the number of participants who completed the self-administration questionnaire at least one time/week over the 12 weeks of the study, and (ii) the overall number of scales completed out of the possible 24 for the duration of the intervention; and, (2b) *Consistency of reporting*, operationalized as the number of missed items on the questionnaires.

Materials

Cognitive training intervention protocol

The cognitive training program was Brain HQ™ by Posit Science.[72] Brain HQ was selected because it has the strongest efficacy data for neurological populations of all brain games in the public domain, and it was most similar to the program used by Lebowitz and colleagues.[28,44–55,58] The protocol was designed to deliver challenging tasks across six cognitive domains, namely attention, speed of processing (“brain speed”), memory, executive function (“intelligence”), social cognition (“people skills”) and spatial navigation skills. Tasks require processing of visual and/or auditory stimuli. Each training domain contains a suite of 4–5 brain games that users can self-select. All games require users to follow on-screen instruction and cues to successfully complete each game objective.

All games are self-calibrating, with game difficulty adjusting to a level commensurate with a user’s performance capability. As a result, when users perform well in a game (indicated to the user by a high-score or greater in-game reward), the difficulty of the game will increase when subsequently accessed. A similar adjustment is made in the opposite direction after a low-score or lesser in-game rewards. These adjustments are made to ensure that users continuously experienced an appropriate level of challenge.

Self-evaluation questionnaire For the purpose of the current study, we developed a brief self-report questionnaire to measure any adverse effects of the protocol and to measure any perceived psychological benefits or costs of the cognitive training sessions. The items of the questionnaire were developed in two expert consensus meetings involving a panel of clinicians and researchers with expertise and experience in TBI or rehabilitation. The 13 items of the questionnaire are as follows: Headachy, Tired, Dizzy/Lightheaded, Foggy, Eyestrain, Irritability, Happiness/Contentment, Boredom, Sense of Accomplishment, Confidence in Abilities, Mental Sharpness, Ability to Think Clearly, Ability to Think Fast. Item endorsement is measured on a three-point scale, and instructions given to participants were to complete the scale twice weekly immediately following training sessions. Participants were asked to complete each item, indicating whether they experienced “less”, “the same”, or “more” of the symptom or feeling, as compared to immediately before the session. Validation of the questionnaire is pending in an ongoing study.

Procedures

An online account for the software (Brain HQ™ [72]) was set up for each participant. All participants had instruction on the initial log-in and tutorial (i.e., demonstration of how to use the program and access its various components) either during an in-home visit from the experimenter ($n = 1$) or over the telephone ($n = 9$). Participants were instructed to commit an equal amount of time training in each cognitive domain, although this was not enforced by the study administrators, as the purpose of our study was to examine feasibility, and not efficacy as a function of time spent training each cognitive domain. At the end of the study, the amount of time participants committed to each cognitive domain was computed. Throughout the 12-week intervention, the experimenters remained accessible to participants via email or telephone to address any technical difficulties experienced.

Patients were asked to use the cognitive training program for 1 h/day, five days/week for 12 weeks (total of 300 min/week). Breaks were permitted during the expected hour of cognitive training. Note that the duration of training was only measured for active engagement in the training. The self-evaluation questionnaire was introduced to participants during the initial log-in tutorial. Subjects were asked to complete the questionnaire immediately post-training, two times per week. As the questionnaire was not part of Brain HQ™, participants were not prompted by the training program to complete the questionnaire following a training session. However, patients were reminded during weekly calls to complete the questionnaire. We were interested in the extent to which patients would comply under conditions of low environmental support.

Table 3. Injury severity of case series. All scores for neuropsychological tests, including estimated pre-morbid IQ, are presented as *Z*-scores, with scores in the mild-to-severe range emboldened.

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Functional status										
Pre-injury vocational status	Employed FT	Employed FT	Employed FT	Employed FT	Employed FT	Employed FT	Employed PT Student FT	Student FT	Semi-retired/did private consulting work	Student FT; employed part-time
Vocational status at intervention	Employed PT	Unemployed	Unemployed	Unemployed	Unemployed	Unemployed	Employed PT	Had not returned to school	Retired/did not return to private consulting work	Had not returned to work or school
Pre-injury driving status	Driving	Driving	Driving	Driving	Driving	Did not drive	Driving	Driving	Driving	Driving
Driving status at intervention	Not driving	Not driving	Not driving	Not driving	Not driving	N/A	Driving	Not driving	Not driving	Not driving
Estimated Pre-Morbid IQ										
WTAR	1.35	1.35	1.41	1.08	0.47	1.48	0.88	0.33	1.13	0.68
Memory										
RAVLT trials 1–5 total	1.94	1.02	−0.64	**−1.38**	**−3.72**	**−0.55**	−1.00	−0.80	−0.68	**−3.98**
RAVLT delayed recall	1.82	0.56	**−1.91**	**−2.30**	**−3.08**	**−1.04**	**−1.78**	0.00	**−1.87**	**−4.00**
RVDLT trials 1–5 total	0.38	0.13	**−2.86**	−0.77	n/a	−0.39	**−1.32**	0.17	**−2.62**	**−4.10**
Attention/speed of processing/psychomotor speed										
SDMT oral	0.51	0.45	**≤ −3.00**	0.31	**−2.57**	**−1.06**	−0.04	−0.77	**−1.25**	**−2.52**
Trails A	−0.92	−0.61	**≤ −3.00**	−0.81	**−1.76**	0.20	0.31	0.31	−0.61	**−2.50**
Grooved pegboard (dominant hand)	−0.10	−0.68	**≤ −3.00**	**−2.17**	n/a	−0.92	0.00	−0.10	**−1.48**	n/a
Grooved pegboard (non-dominant hand)	−0.68	**−1.28**	n/a	0.68	−0.61	**−1.08**	**−1.75**	**−2.00**	−0.50	**≤ −3.00**
Language										
BNT	−0.46	−0.69	−0.23	0.83	1.06	0.48	1.61	1.44	**−4.46**	**−1.35**
Verbal fluency (phonemic)	0.34	**−1.31**	**−3.23**	**−1.34**	**−3.10**	1.44	0.62	0.37	**−1.16**	**−1.52**
Visuo-spatial functioning										
WAIS block design	1.35	1.00	**−2.00**	0.00	1.00	1.00	0.68	0.68	2.00	**−1.00**
Executive functioning										
Trails B	0.31	0.61	**≤ −3.00**	0.81	−0.50	−0.20	2.70	**−1.08**	**−1.65**	**−1.00**
WCST percent perseverative errors	−0.20	−0.41	**−1.28**	−0.50	**−1.08**	0.00	0.00	2.16	0.50	1.41
Psychological status										
BDI Classification (Score)	Normal range (0)	Normal range (0)	Mild (13)	Moderate–severe (23)	n/a	Normal range (6)	Normal range (8)	n/a	Normal range (2)	Normal range (7)
BAI Classification (Score)	Minimal (0)	Minimal (0)	Minimal (3)	Mild (11)	Minimal (0)	Minimal (3)	Minimal (7)	Minimal (1)	Minimal (3)	Minimal (5)

Bold numbers represent frank impairments.

SDMT: Symbol Digit Modalities Test; BNT: Boston Naming Test; WTAR: Wechsler Test of Adult Reading; WAIS: Wechsler Adult Intelligence Scale; RAVLT: Rey Auditory Verbal Learning Test; RVDLT: Rey Visual Design Learning Test; WCST: Wisconsin Card Sorting Test; CIQ: Community Integration Questionnaire; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; FT: full-time; PT: part-time; n/a: not available data.

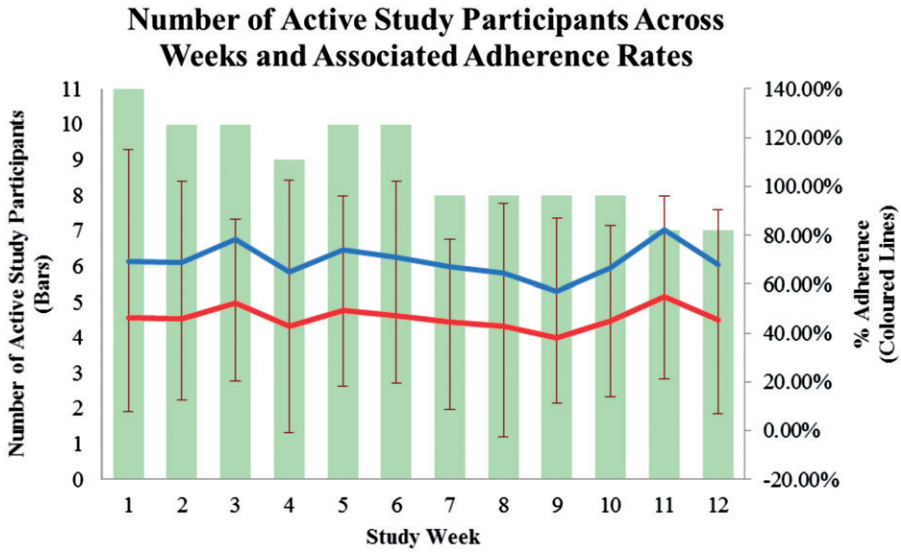

Figure 1. Mean weekly adherence and number of active study participants. (a) The weekly adherence (collapsed across patients) as a percentage of 300 min (the target weekly adherence rate for this study) is illustrated by the red curve and adherence as a percentage of 200 min (the target weekly adherence rate for the Lebowitz et al. study) is illustrated by the blue curve. (b) The number of active study participants across weeks is also plotted, and illustrated by the green bars. Error bars about the red curve represent the range in individual weekly adherence in a given week. N.b. error bars that exceed 100% indicate weeks in which time committed to cognitive training exceeded, on average, 300 min/week.

Each week during the 12-week study, regardless of whether or not participants contacted the experimenters about technical issues, an experimenter called participants to remind them to participate in cognitive training, to complete the self-evaluation questionnaire twice weekly, and to ensure that technical difficulties were not experienced. This was the only environmental support provided to participants through the study; family support was not solicited by the experimenters but was not actively discouraged.

Results

Objective 1: feasibility of the intervention protocol

Attrition

Our attrition rate was 30.0%, with three of the 10 participants lost to the study prior to completion of the 12-week intervention. Participant P6 left the study after week 1 citing insufficient time due to return to school. Participant P2 was lost to the study after week 10, and cited insufficient time due to return to part-time employment. Participant 5 reported lack of interest and lack of time and was lost after week 10.

Adherence

(i) Weekly adherence. Figure 1 illustrates weekly adherence of the group across the 12-weeks of intervention (colored lines), and the number of active study participants in a given study week (columns). The average weekly adherence rate as a percentage of our target adherence was 42.6%, SD = 4.4% (solid red curve). The average weekly adherence rate, when plotted as a percentage of the target adherence of the Lebowitz et al. study,[58] was 63.9%. Further, the adherence rate of the seven participants who were not lost to attrition was 47.1%.

Adherence to protocol varied week-to-week. The number of patients participating in the training intervention each week ranged from 7 to 10. Variability in participant activity was due to attrition and also to vacations that resulted in temporary training intermissions ($n = 2$).

Figure 1 also illustrates variability in *weekly adherence* across participants regarding the amount of training time in a given week. Overall, weekly adherence rates for individual participants ranged from 7.7 to 90.1% (with most cases clustering around 50.0%) demonstrating considerable variability in weekly adherence between participants.

(ii) *Daily adherence.* Average daily adherence for each participant in each study week is illustrated in Figure 2 using a "heat map", with more minutes trained per day denoted by a darker colour. Training participation (i.e., the number of days/week trained) per participant is also illustrated. Four of 10 participants (P1, P3, P8 and P10) trained six days a week at least once (indicating extra training days), and one participant (P8) trained seven days a week five times.

Objective 2: feasibility of self-administering a self-evaluation questionnaire

Completion rate

i. *Number of completers.* Of the seven participants retained for the full study, six participants completed the scale at least once/week for each week of the study. The remaining patients did not complete any scales.
ii. *Number of scales completed.* For each of the six participants completing the scale at least once/week, the range of scales completed was 14–23.

Consistency of responding

Of all scales completed, there were no missed items.

Discussion

This study adds to the literature by studying whether moderate–severe TBI patients are capable of engaging in a high-demand, online, self-administered C-EE intervention designed with minimal environmental support. It also adds to the literature by assessing whether such individuals could regularly self-administer a self-evaluation questionnaire designed to assess burden of the study. We were interested in the feasibility of online brain games as they represent a cost-effective modality of delivery of C-EE for TBI patients, one that can help to obviate access barriers.

With regard to the intervention protocol, we found adequate retention to the study with 7/10 participants in the study at week

Patient	Week											
	1	2	3	4	5	6	7	8	9	10	11	12
P1	3	5	4	6	5	4	6	6	4	6	3	5
P2	5	5	3	4	5	1	3	2	2	1		
P3	5	3	3	6	6	4	5	5	4	5	5	5
P4	5	5	5	5	4	5	5	4	3	2	4	5
P5	2	2	2	2	2	1	3	1		1		
P6	5											
P7	4	4	3	4	2	1					3	2
P8	7	6	6	7	7	5	6	7	7	6	6	6
P9	2	4	2		4	3	3	4	2	1	1	1
P10	5	5	5	5	5	5	5	6	5	5	5	5

Figure 2. Mean daily adherence and intensity of training. (a) Adherence to training: the number of days trained/week is represented by coloured numbers. Weeks without a number indicate weeks in which a patient did not participate in cognitive training. (b) Intensity of training is represented by the colour of the number: beige (the lightest shade) represents an average training intensity of 6–19 min/day; orange represents an average training intensity of 20–39 min/day; red (the darkest shade) represents an average training intensity of 40 + min/day.

12. There was modest daily adherence and weekly adherence, with participants reaching just under half of the (high) target demands of 60 min/day over five days. Of those completing the study, six participants completed the self-evaluation questionnaire at least once weekly (half of the target expectation), with a range of 14–23 per patient of a possible 24 completions. All questionnaires were completed without any missed items.

Overall, these preliminary results are encouraging, suggesting that self-administered, on-line brain games could be a feasible, low-resource C-EE intervention even for patients with significant brain injuries, but that modifications to improve adherence are needed. These findings are highly important given that there is a critical need for continued delivery of therapies to the high number of moderate–severe TBI patients (estimated at over 1.1% of the population in the United States; [73]) in the context of low post-discharge clinical resources found in most countries. The need for C-EE is particularly important given the growing evidence of neural and cognitive declines in the chronic stages of injury [4,36,74] and the early evidence that C-EE is associated with diminished neural decline.[24,38]

The results also indicate that TBI patients are capable of self-administering a self-evaluation questionnaire, and again, modifications should be made to improve completion rate. If therapies, particularly intensive ones, are to be delivered to patients in their homes without direct supervision, it is important for those overseeing the intervention to be able to monitor impact and intervene as needed.

Taken together, the current preliminary feasibility findings support the use of this intervention in a larger-scale feasibility study. We do note, however, that the high verbal IQ of our convenience sample (Table 3) may limit the generalizability of our findings to other TBI patients to some extent.

Relationship to past findings and considerations for future research

As compared to the only previous study examining self-administration of computerized C-EE in chronic TBI patients, our findings were weaker in terms of retention and adherence. Apart from severity of injury, differences in outcomes may be attributable to several key methodological differences in the demands of the respective studies. As compared to our study, the Lebowitz et al. study had a shorter training duration (six instead of 12 weeks), lower intensity in min/day (40 instead of 60 min), and greater environmental support.[48] If our findings are computed as a function of 40 min/day (as indicated by the blue line in Figure 1), our average adherence is 63.9%, and therefore closer to the adherence rate reported by Lebowitz et al., who reported that 80% of participants adhered to training for at least 40 min a day, five days per week.[48] Another difference between the studies was sex ratio (90% female in the Lebowitz et al. study,[58] vs. 40% in ours). Although, to our knowledge, there is no literature documenting sex and/or gender differences in adherence to online training programs, a number of studies have shown sex and/or gender differences in adherence to rehabilitative or therapeutic programs, health guidelines, and medication use.[75–79] Therefore, future studies should also consider sex and/or gender and its influence on adherence.

Finally, our study was designed to extend the findings of this prior study in order to ascertain whether more severely injured patients who were also much earlier post-injury (1.25 years on average in our study vs. 9.25 in the Lebowitz et al. study [48]) could complete the demands of an even more challenging protocol. Putatively greater attentional, memory and executive dysfunction may have contributed to lower completion and adherence in our study. Table 1, provided for characterization purposes, indeed shows that at the two extremes, the least and most adherent patients (who were not lost to attrition; P7 and P8), had the overall weakest and strongest neuropsychological performances, respectively.

With respect to time-post-injury, it is possible that being at an earlier stage of injury poses some challenges that are absent later. For example, it may be more difficult to incorporate an intensive new activity into a schedule that is in flux due both to ongoing therapies that may change from week-to-week, and to active efforts to return to vocational activities. Patients at nearly 10 years post-injury are likely to have greater stability in their schedules, which may allow participants to more easily integrate the additional demands of a daily intervention.

A question the current findings raise is whether vocational activities are incompatible with daily C-EE. Two of the three cases lost to attrition cited return to school and resumption of employment as the reason for stopping their participation. In two other ongoing EE studies in our own laboratory, we noted anecdotally that employment was associated with reduced adherence to the same on-line C-EE program as employed in the current study. In sum, these above points taken together suggest the need to take a person's ongoing activities and foreseeable changes in activities into consideration in future studies.

With regard to modifications to improve adherence, reducing the target length of training sessions might offer greater potential for increasing adherence. In the absence of environmental support, we found that the length of a given session of cognitive training lasted, on average, just under 30 min. Reducing the target duration of each training session to 30 min may improve adherence. However, the internal calculation that patients may make when determining compliance is worthy of exploration. For example, if patients' compliance is related to completing a certain percentage of that asked (e.g., 75% of expected min/day), this would need to be taken into consideration when setting targets.

More nuanced questions about tradeoffs between number of days/week of training vs. amount of time/day should also be examined in future research. For example, it would be of value to examine adherence (and ultimately efficacy) differences of, for

example, a 200-min intervention delivered as 50 min/day × 4 days/week vs. 40 min/day × 5 days/week.

Further, the influence of baseline cognitive functioning on adherence should be investigated in larger trials. It is probable that more severely injured patients would demonstrate lower adherence due to greater impairments in relevant aspects of executive functioning, such as initiation and follow-through.[41,80] Understanding the role of self-awareness and adherence should also be an objective of future trials, as patients who are less aware of their cognitive impairments may not identify the need to participate in C-EE training. If limited awareness restricts adherence, therapies to improve awareness in TBI patients (such as directed feedback, psychotherapy and cognitive therapy [81]) would logically increase adherence.

An important consideration is whether reductions to demands would have any impact at all on adherence. Anecdotal evidence from endorsements of the questionnaire suggests an overall positive experience from the intervention. For example, patients frequently reported that completing cognitive training was associated with an increased sense of accomplishment and confidence, and a decreased sense of boredom. Another approach to improving adherence concerns rewards. Greater "rewards" from the experimenter (e.g., emails with content related to number of minutes completed) might boost adherence. Given that Brain HQ provides automated summaries of participant activities, some minor programming could permit an automated, customized "reward" message from the experimenter. This might keep therapist resources minimal while improving adherence. Yet another approach might be small, token financial rewards. Financial rewards have been shown to increase adherence to exercise programs for up to six months;[82] thus, future studies could assess whether similar incentives benefit adherence to C-EE interventions.

Lastly, increased adherence to the protocol without increased clinical resources might be attained through automated reminding approaches. A number of studies have demonstrated the efficacy of low-resource environmental supports (e.g., smartphones, paging systems, text messaging) for improving everyday memory and planning functions.[83] Moreover, participating in cognitive training on mobile platforms (e.g., cell phones or tablets) may increase adherence, not only because of the increased accessibility these modalities would confer, but also because the modalities are conducive to automated training reminders and alerts that would enhance adherence. Future trials should determine how these supports among others (e.g., family or peer support) influence adherence rates.

Self-evaluation questionnaire and future directions

In order to monitor potentially adverse effects of intervention and to assess perception of immediate psychological and cognitive benefits, we developed a self-evaluation questionnaire. Patients appeared to have no difficulty with the scale, as evidenced by zero missed items on the scales, and an absence of queries about the meaning of items. Completion rate was high for those participants completing the intervention (i.e., 6/7), but scales were completed at only 50% of requested frequency, despite a weekly reminder. Again, a reward system for completion might enhance completion rate.[84] Integrating the self-evaluation questionnaire into the training program may improve adherence to the questionnaire, given that it would be immediately and electronically accessible following cognitive training. In the current study, it constituted a separate and added responsibility. Further, incorporating the self-evaluation questionnaire into the automated training program would provide an opportunity to provide patients with more rapid, tailored feedback. It would also allow for provision of immediate "alerts" to the overseeing therapist in the event of endorsements of items at a threshold reflective of distress of any type.

Our case series study is limited by its small and heterogeneous sample. However, our study was nonetheless able to identify methodological concerns that should be taken into account when designing larger, efficacy trials of brain games in moderate-to-severe TBI.

Conclusions

Our study adds to the literature by demonstrating that a demanding, online self-administered C-EE protocol is feasible even for patients with moderate–severe levels of TBI who are within the first two years of recovery, and that self-evaluation of post-training symptoms is also tenable.

Our results and related literature offer a number of suggestions for enhancing adherence without increasing therapeutic resources. These include automated and customized environmental supports providing rewards and reminders. Future related directions include automated alerts based on the self-assessment endorsements; responses of a given threshold or pattern signifying patient distress could trigger an automated alert to the therapist to then intervene.

These findings have promising clinical implications in a climate of limited interventions for patients in the chronic stages of brain injury. In particular, the findings support the potential for high intensity C-EE interventions that can be administered remotely to participants regardless of geographical location, and with minimal therapeutic resources. Further feasibility studies are needed to determine procedural modifications to enhance retention and adherence. Nonetheless, the online computerized "brain game", a form of C-EE, offers an important rehabilitation approach for the provision of large-scale and long-duration C-EE to moderate–severe TBI patients living in the community. Such an approach is needed given the vast number of patients suffering the life-long effects of TBI, the growing evidence of neural and cognitive decline in the chronic stages of TBI,[4,74] and with preliminary evidence that C-EE holds the potential to offset such decline.[24,38]

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Disclosure statement

The authors report no declaration of interest.

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