Feasibility of an Online Cognitive Environmental Enrichment Intervention for Patients with Moderate-to-Severe Traumatic Brain Injury

by

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A thesis submitted in conformity with the requirements
for the degree of Master's of Science

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University of Toronto

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2014

Abstract

Recent research has documented progressive cognitive and neural decline in the *chronic* stages of moderate-to-severe traumatic brain injury (TBI). Offsetting this putative neurodegeneration offers a new target for cognitive neurorehabilitation. Cognitive environmental enrichment (C-EE; novel, challenging, and engaging cognitive stimulation) delivered early post-TBI has been shown to buffer against neurodegeneration in humans and animals. Some online "brain games" (which can be accessed by patients regardless of location or mobility restrictions) offer intensive cognitive stimulation that meet the criteria for C-EE. Here, the feasibility of administering a home-based, online "brain game" suite to 11 moderate-to-severe TBI patients who participated in 12 weeks of intensive cognitive training was examined. Modest adherence and attrition, high acceptability of the program, and promising findings on limited-efficacy testing involving neuropsychological outcomes were observed. Online cognitive training is a feasible and potentially efficacious intervention for TBI patients. Means of improving adherence are discussed.

Acknowledgments

The past two years have been an incredible learning experience. I am grateful to those who made the experience as rewarding and memorable as it was.

My supervisor, Dr. Robin Green, I thank for the ongoing mentorship and guidance that has prepared and motivated me to continue with research. Robin, I appreciate the time you have taken to discuss my questions about my thesis and career, and for the numerous opportunities you have provided. Your advice has been invaluable and will always be remembered. Dr. Jennifer Tomasczcyk, my supporting supervisor, I thank for always being available to discuss my project, and for the day-to-day council on everything thesis-related. My committee members, Drs. Deirdre Dawson and Gary Turner, I thank for their expertise and perspective, which has shaped – and strengthened – my graduate research. I also thank all members of our lab for their willingness to help me, whether it be sharing a new paper or helping me improve my presentations. I also thank my graduate department for their ongoing support. I am grateful to you all for making my graduate experience as rewarding and memorable as it was.

To my family and friends, I appreciate your support and encouragement. I am grateful for your patience and understanding – especially when it greatly exceeds mine.

Thank you.

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TBI – Traumatic brain injury
EE – Environmental enrichment
C-EE – Cognitive environmental enrichment
GCS – Glasgow Coma Scale
PTA – Post-traumatic amnesia
LOC – Loss of consciousness
WHO – World Health Organization
CDC – Centers for Disease Control and Prevention
ICF – International Classification of Functioning, Disability, and Health
FIM – Functional Independence Measure
DTI – Diffusion tensor imaging
BAPP – Beta-amyloid precursor protein
NMDA – N-methyl-D-asparate
MRI – Magnetic resonance imaging
BDNF – Brain derived neurotrophic factor
NGF – Nerve growth factor
LTP – Long-term potentiation
RCT – Randomized controlled trial
CBT – Cognitive Behavioural Therapy
ANAM-4 – Automated Neuropsychological Assessment Metrics version 4
WTAR – Wechsler Test of Adult Reading
SART – Sustained Attention Response Task
RAVLT – Rey Auditory Verbal Learning Test
CVLT – California Verbal Learning Test
CAMH – Centre for Addiction and Mental Health
GMT – Goal Management Training

Chapter 1
Background Information and Literature Review

1 CHARACTERIZATION OF TBI

Traumatic brain injury (TBI), a type of acquired brain injury, is defined by an alteration in brain function and/or consciousness. It is caused when the brain is subject to external acceleration and/or rotational forces (1). The degree of severity of moderate-to-severe TBI is indexed by both alterations to level of consciousness, as measured by the Glasgow Coma Scale (GCS; (2)), and the duration of these alterations, as measured by the length of post-traumatic amnesia (PTA) and of loss of consciousness (LOC; (3)). Moderate-to-severe TBI, typically associated with a combination of hemorrhage and traumatic axonal injury, most often occurs during motor vehicle collisions, falls, and participation in sports (4, 5). Injuries at this more severe end of the spectrum can result in enduring behavioural, emotional, and functional consequences (6).

With regard to prevalence, the World Health Organization (WHO) predicts that by 2020, TBI will emerge as the third leading cause of mortality and disability (7), and current estimates indicate that there are already more than 12 million people that live with TBI-related disability (8). In Canada, it is predicted that 1.4 million individuals live with the effects of an acquired brain injury, and that there are 46 daily hospital admissions for TBI (9, 10).

Adding to the very considerable healthcare burden is the finding that adolescents and young adults are at particularly high risk of sustaining a TBI (4, 11). Thus, TBI is a leading cause of disability in people under 40, with many survivors of TBI – especially moderate and severe TBI – requiring rehabilitation services for a considerable proportion of their lives. As a result, the economic toll of moderate-to-severe TBI is also exceedingly high. A recent review conducted by the Centers for Disease Control and Prevention (CDC) concluded that the direct (e.g., hospitalization) and indirect (e.g., downstream management and rehabilitation) costs of TBI may

exceed 75 billion US dollars annually, with severe TBIs accounting for the large majority of these costs (12-14).

Framing moderate-to-severe TBI in the context of a model of disablement, such as the WHO's International Classification of Functioning (ICF), permits a deeper understanding of TBI-related disability (15). The ICF measures disability at the individual and population level, providing a framework for understanding the health and environmental factors that contribute to disablement (16). In the context of moderate-to-severe TBI, at an individual level, this injury can be disabling as it may limit activity and social participation due to injury-induced functional impairments. On the other hand, contextual or environmental factors (such as low-accessibility public transit systems) may also limit activity and community participation by imposing socially constructed mobility restrictions on moderate-to-severe TBI patients. Therefore, measuring disablement following moderate-to-severe TBI using the ICF shows that disability is a function of both individual and population level barriers, the removal of which facilitates rehabilitation.

In sum, moderate-to-severe TBI is an injury of considerable public health concern that represents an enormous healthcare burden, and it bears considerable personal costs to patients and their families. This toll is attributable in large part to the extended treatment and management that is often needed for decades, because of the enduring disability caused by these injuries. Improving recovery would diminish this toll, however, treatments to date have had only modest success (17-19). In the next section, we discuss our conventional understanding of recovery, and how new conceptions of recovery offer novel targets for the treatment of moderate-to-severe TBI.

2 RECOVERY FOLLOWING MODERATE-TO-SEVERE TBI: CONVENTIONAL AND NOVEL NOTIONS OF RECOVERY

2.1 Conventional Understanding of Recovery Following Moderate-to-Severe TBI: Limited Yet Stable

A large number of recovery studies demonstrate that patients show a steep early period of spontaneous recovery of cognitive and motor functions, followed thereafter by a plateau in recovery (20-29). The nature of this recovery curve and plateau depend to some extent on how recovery is measured. For example, on functional measures of recovery, such as the Functional Independence Measure (FIM), patients typically reach a plateau by 3- to 6-months post-injury (30, 31). In contrast, neuropsychological tests, which measure recovery across cognitive domains, reveal a longer recovery period. Depending on the particular neuropsychological tests used, studies show that patients often do not reach a plateau until 12 to 24-months post-injury (20, 25, 27, 29, 32-36). Regardless of the outcome measure, however, studies show that moderate-to-severe TBI patients reach an asymptote in their performance that is often well below their pre-morbid level of functioning (20, 25, 29), and with persistence of cognitive impairment thereafter (37).

The earliest recovery is likely driven by the resolution of acute neurological injury, such as the resolution of widespread edema and disruptions in cerebral microvasculature (38-40). The reversal of acute neurophysiological abnormalities also plays a significant role in early, acute neurological recovery. One relevant example is the restoration of metabolic crisis (e.g., elevated lactate:pyruvate ratios) and resolution of reduced extracellular glucose levels (41, 42). Importantly, the remediation of these physiological alterations can help to resolve diaschisis, which is the impairment of an area of the brain not afflicted by the original trauma but inhibited, nonetheless, by damage to an interconnected, neighboring region (43). At a higher level of analysis, and presumably later in the recovery period, functional reorganization of the brain may also occur, which involves the recruitment of new neural resources and networks to compensate for a loss of brain function (44-47). Other studies suggest that following TBI, functional engagement (or unmasking) can also take place. This involves the recruitment of brain networks

that are typically dormant or latent in healthy brains to compensate for trauma-induced functional losses (48). Therefore, in the acute stages of injury, the brain is dynamic and it is physiologically and functionally adapting to the manifestations of trauma. Despite these changes, however, conventional understanding of TBI suggests that there is stability in the later stages of brain injury, as lesions remain stable, static, and non-progressive in chronic moderate-to-severe TBI (6).

2.2 A Novel Notion of Recovery Following Moderate-to-Severe TBI: Progressive and Deteriorating

While our conventional understanding of recovery suggests that chronic moderate-to-severe TBI follows a stable neurological course, a growing number of studies suggest otherwise. Many studies have now demonstrated that cognitive decline as well as brain volume loss, lesion expansion, and reductions in white matter integrity characterize the sub-acute and chronic stages of moderate-to-severe TBI (6, 29, 49-66).

Progressive Neural Decline in Chronic Moderate-to-Severe TBI

A review of the literature reveals no widely accepted definition of "chronic" in the case of moderate-to-severe TBI. As described above, the outcomes used to measure recovery following moderate-to-severe TBI, to some extent, dictate the shape of the recovery curve and timing of recovery plateau. However, I operationally define the chronic stage of moderate-to-severe TBI as the period after which acute neurological events of the brain have resolved (e.g., metabolic crises and edema) and the spontaneous early period of recovery has occurred. This early spontaneous recovery typically occurs within the initial weeks and months of injury (67).

A number of studies have now shown that in the chronic stages of injury, moderate-to-severe TBI patients undergo structural volume losses and reductions in white matter integrity. In a recent review of volumetric brain changes in chronic moderate-to-severe TBI, progressive

brain atrophy was documented consistently across ten longitudinal studies (50). Moreover, this review summarized findings that progressive brain atrophy was significantly, positively correlated to acute indices of brain injury severity, including duration of LOC and PTA, hypoperfusion, brain oxidative metabolism, and cerebral lactate:pyruvate ratio (50).

More specifically, Mackenzie et al. (58) found that the rate of decline in brain parenchyma volume was greater in moderate-to-severe TBI patients (n = 10) relative to healthy controls (n =4). In this study, patients were initially imaged, on average, 125 days post-injury, and again at least 3-months later (with a mean time between assessment of 350 days). Similarly, it was reported that moderate-to-severe TBI patients (n = 37) relative to healthy controls (n = 30) experienced significantly greater declines in percent brain volume change between roughly 3- and 15-months post-injury (59). Sidaros and colleagues (61) demonstrated that the brain volume of moderate-to-severe TBI patients, relative to healthy controls, was reduced by 8.4% at 2-months post-injury, and decreased by a further 4.0% by 12-months post-injury. Furthermore, Aziza et al. (68) reported greater bilateral hippocampal volume reductions in moderate-to-severe TBI patients relative to matched, healthy controls imaged at least 6-months post-injury. It has also been shown that moderate-to-severe TBI patients, relative to healthy controls, demonstrate progression of hippocampal atrophy on structural neuroimaging from 4.5- to 30-months post-injury (55). Moreover, these changes appear to be ubiquitous. Green et al. (51) reported that chronic stages losses in ventricle-to-brain ratio, corpus callosum and/or left or right hippocampi were observed in 54 of 56 patients between 5- and 20-months post-injury (51).

It is important to note that given that resolution of edema is associated with a natural reduction in brain volume, any baseline neuroimaging performed prior to the resolution of acute neurological events (including edema) would inflate the magnitude of chronic volume reductions that occur following moderate-to-severe TBI. The studies discussed above, however, performed baseline imaging in the post-acute stages of injury, and are not confounded by the effects of edema.

Longitudinal studies have also demonstrated white matter integrity reductions following moderate-to-severe TBI on diffusion tensor imaging (DTI). For example, Greenberg et al. (52) found evidence of reduced white matter integrity in 13 moderate-to-severe TBI patients from 4.5- to 30-months post-injury, in the frontal and temporal tracts, right and left frontal areas, and

the left temporal area. Another study has provided converging evidence, showing that from 2-months to 12-months post-injury, white matter integrity deceased in multiple brain regions as measured by changes in fractional anisotropy – or water diffusivity – in brain white matter (64).

Several mechanisms have been proposed to explain chronic stage neural decline in TBI patients. Marcoux et al. (60) found that the lactate:pyruvate ratio remains elevated in the brain following moderate-to-severe TBI, resulting in a metabolic crisis which is predictive of frontal lobe atrophy at 6-monts post-injury. Other groups suggest that neuroinflammation, which has been shown to persist years after moderate-to-severe TBI (69) may contribute to neural degeneration in the chronic stages of injury by increasing microglial activation (6, 70). Chronic stage neural decline may also result from disconnection between neighboring brain regions and networks (6, 43, 71). The mechanisms listed above are not mutually exclusive, but may operate in concert to contribute to neural decline.

Post-traumatic neural changes are also observed at a cellular level. In particular, following moderate-to-severe TBI, a number of proteins accumulate in the brain. These include beta-amyloid precursor protein (BAPP), neurofilament proteins, and tau proteins (72). BAPP are the constituent precursors to beta-amyloid plaques, commonly found in patents with Alzheimer's disease, and may localize in swollen axons and contribute to impaired axonal transport (73). Neurofilament proteins are normally involved in maintaining the structure and integrity of the neuronal cytoskeleton (74). Following brain injury, however, these proteins may be disturbed, resulting in neuronal impairment (75). The function of tau proteins, like neurofilament proteins, has been linked to the maintenance of neuronal architecture (76). Normally, tau proteins are involved in the stabilization of microtubules, however, they may accumulate in axons (77) and cerebrospinal fluid (78) following TBI. Together, these changes may contribute to progressive decline in chronic TBI (79).

These studies collectively suggest that moderate-to-severe TBI is progressive, and that despite our conventional understanding of this injury, patients do not achieve stability in the chronic stages of injury. However, understanding mechanisms of decline increases scope for targeted therapies and, therefore, improved patient outcomes.

Progressive Cognitive Decline in Chronic Moderate-to-Severe TBI

Our traditional understanding of cognitive recovery following moderate-to-severe TBI suggests that early gains are made and maintained over time, even though complete cognitive recovery following moderate-to-severe TBI is rare (37). Indeed, studies from our laboratory and others have reported that patients can decline in cognitive functioning following the initial months and years post-injury (22-29). Longitudinal studies have also found that young adults who suffered a brain injury demonstrated exacerbated cognitive declines 3 decades later (26). The degree of variability in cognitive recovery following brain injury is exemplified by the findings of Ruff et al. (23), who report that 33%, 50%, and 17% of severe TBI patients (n = 59) demonstrated declines, improvements, or no change, respectively, in verbal memory performance from 6- to 12-months post-injury. It is important to note that despite ubiquitous chronic neural atrophy following TBI, cognitive gains (such as those reported above) may still be observed due to functional mechanisms of recovery, including reorganization or unmasking as described above (44-48).

Relationship Between Chronic Neural and Cognitive Decline in Moderate-to-Severe TBI

Studies have also demonstrated negative associations between neural decline and behavioural and functional outcomes. For example, Sidaros et al. (62) report that white matter integrity (as measured by fractional anisotropy values on DTI) was greater primarily in patients with "favourable" functional outcome at one-year post-TBI. In this study, "favourable" functional outcome was defined by a Glasgow Outcome Scale score of 4-5 out of 8, which is indicative of good functional recovery (62, 80). In a later study using volumetric neuroimaging, this group demonstrated that the magnitude of volume loss between 2- and 12-months post-TBI was associated with a lower FIM at follow-up (61). More recently, Farbota et al. (65) have shown that fractional anisotropy values in the corpus callosum and sagittal stratum correlate negatively with neuropsychological performance on finger tapping (at one-year post-injury) and

visuomotor speed tasks (at 2- and 12-months post-injury), respectively. Furthermore, this study reports that changes in performance on visuomotor speed tasks from 2-months to 3-years post-injury positively correlated with changes in fractional anisotropy values in the right sagittal stratum, right orbitofrontal cortex, and left superior longitudinal fasciculus. Bendlin et al. (64) reported that increased regional mean diffusivity (a proxy of reduced white matter integrity) correlated negatively with memory function. Earlier studies on the topic have demonstrated positive correlations between hippocampal volume and memory performance (56, 57), and negative correlations between memory and increased temporal horn volume (33) and degree of fornix atrophy (49). These correlational findings suggest that developing interventions targeted at mitigating neural decline may promote behavioural recovery (or vice-versa), marking a possible avenue for treatment of moderate-to-severe TBI.

The Need for Rehabilitation of Chronic Deficits in Moderate-to-Severe TBI

A growing literature now suggests that there is neural instability and cognitive decline in the chronic stages of TBI. These findings suggest that TBI is more akin to a progressive disease than an event from which patients can recover and achieve stable outcomes (6, 51, 53). While these findings are discouraging, they also open up a new avenue for treatment, which involves targeting this decline. Clinical outcomes in the chronic stage of brain injury may be attributable not only to the limited initial recovery, but also to atrophy and loss of white matter integrity in the chronic stages of moderate-to-severe TBI. Thus, interventions that offset these latter losses may improve outcomes.

Current behavioural TBI interventions have demonstrated limited efficacy in improving long-term outcomes (17-19, 81). Behavioural interventions are defined as interventions designed to modify observable behaviour (e.g., cognition, communication,) through the provision of therapy or clinical supports (82, 83). However, as discussed above, recent findings suggest a need to improve outcomes in the chronic stages of moderate-to-severe TBI through targeted intervention, given the scale of decline in this population. Findings that demonstrate a correlation between neural decline and cognitive outcome also identify potential therapeutic targets for

intervention; by offsetting neurodegeneration through targeted intervention, it may be possible to rehabilitate behavioural outcomes.

3 COGNITIVE NEUROREHABILITATION

Overview

As discussed above, neural and cognitive decline has been widely documented in the chronic stages of moderate-to-severe TBI. Evidence for the efficacy of post-TBI cognitive rehabilitation is growing: recent reviews have concluded that metacognitive strategies demonstrate efficacy in improving attention and executive impairments following TBI, while compensatory memory strategies have been shown to improve memory performance (84-88). However, there is need for novel rehabilitation approaches to further promote outcomes following brain injury, particularly in the chronic stages of injury, as patients continue to experience limited recovery and poor outcomes (19). Rehabilitation approaches that specifically target neurodegeneration – a new target for cognitive neurorehabilitation – show potential and warrant further investigation. This section of the thesis provides context on pertinent cognitive neurorehabilitation theory, and then introduces a rehabilitation paradigm that may improve outcomes in chronic moderate-to-severe TBI by offsetting decline.

3.1 Cognitive Neurorehabilitation and Neuroplasticity

Defining Cognitive Neurorehabilitation

Although definitions of cognitive neurorehabilitation vary, it can be understood as the process of remediating or alleviating cognitive deficits that arise as a result of a traumatic insult, with the ultimate goal of enabling individuals to achieve optimal community integration and

improve everyday functioning (89, 90). Cognitive neurorehabilitation may be holistic, attempting to restore global cognitive functioning (i.e., functioning across a number of cognitive domains), or it may target specific cognitive domains, such as memory, attention, speed of processing, or executive function (89). According to Prigatano (91), cognitive rehabilitation often requires a multi-faceted approach. This is because the symptoms being treated are not only caused by brain pathology, but may also be a feature of pre-morbid cognitive conditions and/or personal characteristics. This notion is supported by the cognitive neurorehabilitation framework proposed by Ben-Yishay (92), and it is further supported by a review by Cicerone et al. (19), which concluded that comprehensive and holistic neuropsychological rehabilitation may best promote outcomes following moderate-to-severe TBI.

Cognitive neurorehabilitation following brain injury often uses a remediative approach that attempts to restore cognitive functions to pre-injury levels through the input of targeted stimulation that promotes the restitution of function in lesioned neuronal networks (46). It should be noted, however, that rehabilitation for those with cognitive impairments can also be accomplished through compensatory approaches that try to offset the consequences of cognitive deficits through: (i) assistive devices, such as smartphones, that remind patients to attend appointments and complete daily tasks; or (ii) the uptake of alternative cognitive strategies (93). The compensatory approach is not aimed at the restitution of function in damaged neural networks. However, this does not preclude changes to brain structure and function. The present thesis does not focus on compensation of cognitive impairment, and is instead exclusively centered on remediation-driven cognitive neurorehabilitation.

Harnessing Neuroplasticity to Promote Recovery Following Moderate-to-Severe TBI

The brain's ability to recover following a traumatic insult is a function of its capacity to adapt to environmental changes (94), otherwise known as experience-dependent neuroplasticity (67, 95). Specifically, neuroplasticity refers to changes in synaptic connectivity and organization of neural networks, driven by behavioural or environmental changes (96). It is important to note that neuroplastic changes can be adaptive (resulting in a net gain in function) or maladaptive

(causing abnormal connections that give rise to lost function or connectivity) (97, 98). A related but distinct concept is that of positive and negative neuroplasticity. Positive neuroplasticity refers to the brain's inherent potential to strengthen neuronal connectivity when exposed to novel and challenging stimuli, while negative neuroplasticity speaks to the potential of the brain to weaken neuronal connections and produce detrimental morphological changes when exposed to a dearth of stimulation (99). The direction of neuroplastic change is, therefore, largely contingent on a patient's behaviours and environment.

Influencing Neuroplasticity Through Environmental Enrichment

A large body of research has explored how environmental enrichment (EE), the stimulation of the brain through cognitive, physical, and/or social interaction with the external environment (100, 101), affects brain and behaviour by inducing neuroplastic change. Animal EE studies manipulate the environment of rodents or other animals extensively to produce multiple experimental conditions, allowing for a detailed examination of enrichment effects. With respect to humans, however, enrichment is dependent not only on the nature of the environment (e.g., continually novel, challenging, complex, and intensive), but also the degree to which one engages in that environment (100, 102, 103). This notion is supported by suggestions that enrichment in humans is a relative concept, as what is enriching for one individual may not be enriching for another (103-106). Nonetheless, in the context of human research, EE has been defined as engagement and participation with a continually novel, challenging, and complex environment, which can be achieved through therapy intensification or the provision of additional rehabilitation services. This ultimately results in the stimulation of the brain, which produces adaptive morphological and behavioural changes (100, 106).

3.2 Cognitive EE In Healthy, Adult Animals

Neural Effects of Cognitive EE On Healthy, Adult Animals

A large body of research demonstrates the beneficial effects of EE on the animal brain. Although cognitive, physical, and social enrichment have shown independent neural influences (101, 107-109), the present thesis is focused exclusively on cognitive EE. Henceforth, the term C-EE will be used to refer specifically to cognitive environmental enrichment. Studies on the effects of C-EE in animals typically involve continuous or temporary exposure of animals to new toys or environmental constructs (such as mazes, stairs, and balance beams). By providing multiple sources of cognitive stimulation, these conditions maximize cognitive enrichment. However, they do not foster an exclusively cognitively enriching environment, as animals may be physically enriched through physical interaction with these objects and other forms of activity.

Early studies on the topic show that relative to animals reared in standard condition housing, C-EE animals showed increased brain weight and dendritic branching (110, 111). Nilsson et al. (112) subsequently demonstrated that C-EE increased survival of newborn dentate gyrus neurons, though not their proliferative rate. These findings are of considerable importance, as the dentate gyrus, a region of the hippocampus, is integral for memory (including verbal and spatial memory) processes (113, 114). Other groups have also reported similar findings. For example, Valero et al. (115) showed that C-EE increased the number of dendritic projections (a proxy of neurogenesis) in the CA3 region of the dentate gyrus, while more recently, Curlik and Shors (116) showed that learning promotes the survival of newborn neurons in the hippocampus. In this study, the authors first administered a pharmacological agent, namely, an N-metyhl-D-asparate (NMDA) receptor antagonist to preclude learning, and observed that C-EE did not increase hippocampal cell survival. Subsequently, the authors administered an agent to enhance NMDA receptor activity, and found that under this second condition, the number of hippocampal cells that survived after C-EE was increased (116).

In addition to the promotion of hippocampal cell survival, other studies have shown that C-EE may promote neurogenesis itself. For example, it was found that exposure to C-EE for 10 months, relative to a standard control condition that provided minimal cognitive stimulation, resulted in a fivefold increase in hippocampal neurogenesis, in addition to increased survival of these newly generated neurons (117). The authors of this study concluded that increased neurogenesis may be a necessary first step towards cell survival (117). Other studies have shown increases in total hippocampal volume (118), cortical capillary volume (119), and axon and myelin sheath volumes in rodents housed in cognitively enriched conditions relative to those housed in standard, non-enriched cages (120).

In addition to structural changes, Little et al. (121) used resting state magnetic resonance imaging (MRI) and found that rats receiving C-EE, relative to those housed in standard conditions, had greater connectivity between the CA1 region of the hippocampus and cortical areas. Similarly, Jung et al. (122) conducted a study wherein young and adult mice received 3 weeks of C-EE, and concluded, using *in vivo* microscopy (wherein a cranial window is surgically placed into an animal, which permits *in vivo* microscopic observation), that C-EE results in greater neuronal connectivity in the somatosensory cortex of both young and adult mice. Leger et al. (123) suggested that C-EE may cause restructuring of neural networks in the hippocampus and infralimbic cortex, and this may underlie some of the behavioural benefits of C-EE.

The effects of C-EE have also been studied at a molecular level. A recent review of the literature concluded that C-EE induces changes in hippocampal physiology, in particular, synaptic transmission and excitability, which ultimately alters neural connectivity (124). An early study showed that following 80 days of C-EE, acetylcholinesterase activity remained significantly decreased in the brain even 47 days following removal from C-EE, indicating that C-EE resulted in sustained neurotransmitter release (125). Other studies have shown that relative to rats housed in standard conditions, rats receiving C-EE had increased serum levels of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), proteins that are involved with the growth and maintenance of neurons (126, 127). Li et al. (128) showed that rats receiving four weeks of C-EE for 8 hours a day increased hippocampal long-term potentiation, a marker of synaptic plasticity. In sum, these studies show the neural benefits of enrichment on the healthy brain.

Behavioural Effects of C-EE On Healthy, Adult Animals

In 1978, Rosenzweig et al. (129) demonstrated the benefits of EE on mice. In their study, the enriched condition was defined as the environment in which mice were housed together to permit social interaction, and received the most exposure to inanimate, but cognitively stimulating objects, such as toys and mazes. This EE paradigm derived from the seminal research of Donald Hebb, which showed that mice that were raised outside of a cage and reared in a human environment (which provided greater opportunity for engagement with novel and complex cognitive, physical, and social stimuli) had better cognitive abilities than mice reared in a typical caged environment (130). Therefore, C-EE not only has an effect on the brain, but also shows notable behavioural benefits.

More specifically, Spiesman et al. (131) found that adult rats housed in cognitively enriched conditions for 10 weeks were able to more rapidly process spatial information on the Morris Water Maze task. This task is a commonly used test of spatial learning and memory that requires rats placed in a pool of water to find a hidden platform (which has been submerged just under the surface of the water) by using spatial cues (132). Cognitively enriched rats, relative to rats housed in standard conditions, have also shown significantly improved performance on the Hebb-Williams maze, a test of spatial memory (133).

Studies have also reported on the intensity and duration of C-EE that is required to improve behavioural outcomes. For example, it has been shown that a short period of C-EE, namely 3 hours per day for 14 days, improved long-term spatial memory as evidenced on an object-recognition task (134). Kobayashi et al. (133) reported that although short-term C-EE (lasting 3 months) resulted in significant improvements on a learning task (as measured on the Hebb-Williams maze), long-term cognitive enrichment resulted in an even greater effect. Furthermore, Amaral et al. (135) conducted an experiment in which adult rats were exposed to cognitively enriched environments for 1, 4 or 8 weeks. It was found that rats demonstrated reduced locomotion on an open-field habituation task only when they were cognitively enriched for at least 4 weeks. The authors concluded, therefore, that the minimum period of cognitive enrichment required to elicit behavioural benefits lies between 1 and 4 weeks (135). However, behavioural benefits persisted 6-months post-injury only in rats cognitively enriched for 8 weeks

(135). In sum, it appears that there is a minimum duration of C-EE that is required to produce a significant behavioural effect, although a longer duration of C-EE is required for enrichment effects to persist at long-term follow-up.

3.3 C-EE in Brain-Injured, Adult Animals

Neural Effects of C-EE On Brain-Injured, Adult Animals

Especially relevant to the current study, C-EE has been studied in the context of brain-injured animals. For example, Will et al. (136), in a review of the C-EE literature, concluded that studies have consistently shown that brain-injured animals housed in cognitively enriched conditions demonstrated increased hippocampal neurogenesis relative to standard condition controls. Interestingly, the review also concluded that cognitive enrichment is more effective therapy than physical activity in improving neural outcomes following TBI (136). Other C-EE studies support the above notion, and have found that that following TBI, C-EE increased dendritic branching and the number of dendritic spines in the contralateral cortex (106), increased synaptic and cellular plasticity (137, 138), and up-regulated neurotrophins such as NGF and BDNF (139) similar to the findings in healthy animals (107, 116, 126-128).

Passineau et al. (140) showed that following severe TBI, rats housed under C-EE conditions for 11 days had a 50% smaller lesion than standard condition controls, indicating that C-EE promoted neural recovery. Similar findings have been reported more recently by Sozda et al. (141) and Monaco et al. (142). At a cellular level, it has been shown that following trauma, C-EE promoted the expression of genes important for healthy signal transduction, membrane homeostasis, and metabolism in the substantia nigra (143). This finding suggests C-EE may alter gene expression and induce neural changes that may promote recovery and mitigate neurodegeneration following TBI. In sum, these findings show that C-EE promotes neural recovery not only in healthy, adult animals, but also animals with TBI. These studies provide further support for the utility of C-EE as an intervention for moderate-to-severe TBI patients.

Behavioural Effects of C-EE On Brain-Injured, Adult Animals

The behavioural effects of C-EE in brain-injured animals have also been investigated. For example, Hamm et al. (144) showed that rats housed in cognitively enriched conditions for 11-15 days following induced TBI performed better on the Morris Water Maze than standard-condition controls. Other studies have shown that both male and female rats benefit from C-EE, as indicated by performance on balance beam and spatial learning tasks (142). It is important to note that many former studies on C-EE in brain-injured animals comprised an exclusively male sample (142). The above findings are of value, as they provide further support for the potential benefits of C-EE in humans as a clinical rehabilitation tool, by demonstrating that the behavioural benefits of C-EE are similar in male and female animals.

Several studies have examined the intensity, duration, and timing of C-EE that are required to improve behavioural outcomes. De Witt et al. (145), similar to the groups listed above, found that cognitively enriched rats performed better than non-enriched rats on the Morris Water Maze. This study, however, also provided important information on intensity of C-EE: rats enriched for 2 hours/day and 4 hours/day benefitted comparably (145). In addition, it was shown that rats receiving 6 hours of daily C-EE did not differ from those rats being continuously cognitively enriched throughout the day, though the 6-hour and continual C-EE cohorts did demonstrate significant improvements over rats that were cognitively enriched for 2 or 4 hours/day (145). Together, these findings suggest that "abbreviated" C-EE can yield cognitive benefits similar to those produced by continuous C-EE. More recently, Cheng et al. (146) found that rats housed in cognitively enriched conditions for 3 weeks, who were then transferred to standard housing, performed as well on the Morris Water Maze at 6-months post-injury as rats that were continually cognitively enriched for a 6-month study period (146). These findings are promising for clinical practice and application, as they suggest that a brief period of C-EE early post-injury has lasting cognitive benefits.

Other studies have investigated timing of C-EE in improving behavioural outcomes using a different set of outcome measures. For example, Hoffman et al. (147) showed that rats cognitively enriched for 1 week post-injury, followed by 2 weeks of standard housing, performed similarly to rats continually cognitively enriched for 3-weeks on a beam-walking task, a measure

of motor functioning. It is important to note that rats initially housed in standard conditions, and then transferred to a C-EE condition, performed significantly worse than rats cognitively enriched in the early stages post-injury and those that were continuously cognitively enriched (147). Furthermore, the rats that were transferred from a C-EE to standard condition performed comparably to rats housed exclusively in standard conditions for the duration of the study (147). Matter et al. (148) report similar findings, as they demonstrated that early and continuous – but not delayed – cognitive enrichment improved performance on a balance beam task and a spatial learning task. Together, these findings suggest that early C-EE is necessary to improve behavioural outcomes. These findings demonstrate the promise of C-EE as a clinical intervention, as they suggest that abbreviated and continuous C-EE yields similar cognitive benefits. This indicates that it may be possible to cognitively enrich patients for short periods of time early post-injury and still observe behavioural gains similar to those that would be achieved through continual enrichment.

3.4 C-EE in Healthy, Adult Humans

It is more difficult to prospectively demonstrate the neural and cognitive benefits of C-EE in humans than in animals. Experimental manipulations permissible with rodent models (such as assignment to "enriched" and "non-enriched" conditions) are not, for obvious ethical reasons, acceptable with human subjects. It is, however, possible to examine how patients receiving intensified therapy compare to those receiving standard care. Many studies have examined this retrospectively, and therefore most C-EE studies involving human subjects are observational and correlational. Although these studies offer insights, they do not demonstrate causality. This makes it difficult to conclude whether cognitively enriched environments improve neural and cognitive outcomes in humans, or if those of a particular neural and cognitive complement seek cognitively enriched environments.

Neural Effects of C-EE on Healthy, Adult Humans

A seminal study by Maguire et al. (149) demonstrated that London taxi drivers, compared to demographically matched bus-drivers, had greater gray matter volume in the mid-posterior hippocampi. In this study, the C-EE condition was based on the criteria of extensive use of spatial navigation skills. Therefore, the taxi drivers comprised the C-EE condition, given that they had to exercise greater cognitive skills to freely navigate a large city. The bus drivers, navigating a more constrained set of routes requiring limited exercise of spatial navigation skills, comprised the control condition (149). Therefore, this study suggests that C-EE may alter neural substrates of healthy humans, although causality could not be established with the correlational findings. However, this study did show that gray matter volume in the right posterior hippocampus correlated with years of driving experience only taxi drivers, with no analogous finding in bus drivers. This suggests that exercising spatial navigation skills with greater frequency may influence the neural substrates underlying this cognitive function.

In one of the few prospective studies of C-EE in human adults, Draganski and colleagues (150) demonstrated the neural benefits of C-EE. This group showed that following a period of intensive studying, there were significant bilateral grey matter increases in the posterior and lateral parietal cortex (151). In another study by this group, 38 medical students (with an age, on average, of 24 years) were serially imaged after being taught to juggle, a cognitively taxing exercise (150). The final scan, completed at the 3-month follow-up, showed that there was an increase in gray matter in the posterior hippocampus relative to baseline (150). It is important to note that learning how to juggle is not exclusively a cognitive task given the motor component involved in juggling. Therefore, it is possible that this study demonstrated, to some degree, the combined benefits of cognitive and physical enrichment on hippocampal volume. Less directly, studies have shown that increased years of education associates with greater dendritic branching (152). This suggests that C-EE (which, in this case, involved being in an intensive learning environment) is associated with neural benefits in healthy humans. In sum, these studies imply that C-EE produces neural benefits in healthy adult humans.

Behavioural Effects of C-EE on Healthy, Adult Humans

In an early study by Gribbin et al. (153), it was shown that healthy adults engaging in more routine, complex cognitive activities (as measured by a questionnaire developed to examine daily cognitive activity) performed better on standardized cognitive tasks. This study, however, did not investigate whether improved performance on these cognitive tasks translated into improvements on more generalized measures of cognitive performance. As a result, the study was not able to demonstrate generalizability, or far-transfer, of its findings (153). A review by Schooler (154) concluded that environmental complexity (with a complex environment being one in which diverse stimuli are present) leads to "effective" cognitive functioning (or, the ability to function optimally under cognitive demand) across the lifespan. More recently, it was shown that increased frequency of cognitive activity, as measured by a 25-item scale, is positively associated with perceptual speed, visuospatial ability, semantic memory, but not episodic or working memory (155). Again, this study did not investigate generalizability to outcomes not included in the investigation (155).

Many studies have shown that C-EE is positively associated with cognitive outcomes in healthy older adults. Given the parallels drawn between cognitive aging and cognitive decline following TBI under the negative neuroplasticity framework (156), aging literature that demonstrates an association between C-EE and cognitive outcomes has relevance to TBI. In particular, under this framework, older adults and TBI patients share the similarity of being cognitively and neurologically vulnerable, potentially because age- or injury-related impairments reduce opportunities for social engagement, and therefore limit exposure to cognitively enriching environments

Christensen et al. (157) showed that in older adults, higher levels of mental activity is associated with higher levels of cognitive performance on both fluid and crystallized intelligence tasks. Similar findings are reported by Hultsch et al. (158) who found that in a sample of 250 older adults, increased level of cognitive activity buffered against cognitive decline. Comparably, Paillard-Borg et al. (159) demonstrated that an active lifestyle (involving participation in routine mental activity) delayed the onset of dementia in older adults. Together, these findings are

consistent with a number of studies that suggest an active cognitive lifestyle is associated with an improved cognitive state later in life (160-163).

Studies have also demonstrated that cognitive training interventions can improve cognitive outcomes in older adults. Mahncke et al. (164) in a randomized controlled trial (n = 182) demonstrated that patients participating in cognitive training, relative to active controls and no activity controls, showed memory improvements that were sustained at follow-up. Furthermore, Ball et al. (165) showed that targeted cognitive training improved speed of processing, reasoning skills, and memory in 87%, 74%, and 26% of patients, respectively. These gains were observed immediately after 10 domain-specific training sessions, although they were only observed in the trained domains (i.e., there was no far-transfer). In sum, these studies show that healthy adults (and older adults) experience behavioural benefits of C-EE, further supporting the ability of C-EE to promote recovery following moderate-to-severe TBI.

3.5 C-EE in Brain-Injured, Adult Humans

Neural Effects of C-EE on Brain-Injured, Adult Humans

A recent correlational study with a sample of 25 moderate-to-severe TBI patients, demonstrated that frequency of cognitive activity at 5-months post-injury (as measured by a self-report questionnaire) negatively correlated with bilateral hippocampal atrophy from 5- to 28-months post-injury (54). The findings of this seminal study suggest that C-EE in the sub-acute or early chronic stages of injury may protect against later neurodegeneration. This research is promising as it suggests that C-EE may protect the hippocampi following trauma by offsetting chronic neural decline. Further research is needed to establish the causality of C-EE in offsetting neurodegeneration, and to support these findings with additional data on the optimal intensity, duration, and timing of C-EE in TBI patients. This is especially important given the recent research indicating that neurodegeneration following TBI is ubiquitous (51). With Miller et al. (54) documenting the ability of early C-EE to mitigate neurodegeneration, additional investigations are now required to establish the efficacy of C-EE as a clinical therapy.

Behavioural Effects of C-EE on Brain-Injured, Adult Humans

Some of the earliest studies examining the effect of treatment intensification (a form of C-EE) on patient outcomes did so in the context of stroke, a type of acquired brain injury. In these studies, intensification was typically achieved by increasing the hours – and not changing the overall content – of therapy. Therefore, in the studies discussed below, the proportion of therapy that was cognitively oriented was similar in both the intensified and non-intensified conditions unless otherwise specified. However, patients in the intensified condition received more cognitive therapy by virtue of receiving a greater amount of total therapy.

One randomized control trial (RCT) involving 133 sub-acute stroke patients allocated to a high intensity group (i.e., four full days of rehabilitation per week, 8 hours per day), moderate intensity group (i.e., three half-days of rehabilitation per week) or a no treatment control group, receiving no routine rehabilitation (166). It was found that intensified therapy was associated with improvements in performance of activities of daily living (namely, self-care activities performed within an individual's residence, such as bathing, dressing, and eating) from 3- to 12-months post-injury. The researchers also reported that those in the moderate and no treatment groups had a significantly higher proportion of patients with functional deterioration (166). Examining the acute phase of stroke, Sivenius et al. (167) also showed that intensified therapy was significantly associated with greater functional gains within the first 3 months post-injury.

Studies have demonstrated the benefits of treatment intensification following TBI in adults. Blackerby et al. (168) showed that increasing the number of hours of inpatient rehabilitation from 5 to 8 hours per day significantly reduced length of stay, indicating that intensified treatment ameliorates functional deficits more quickly. Other groups have reported similar findings (169, 170). In our laboratory, Till et al. (24) also reported that hours of therapy at 4.5 months post-injury was associated with less cognitive decline, as measured on neuropsychological tests from one to two years post-injury. More recent studies have demonstrated that increasing the hours of rehabilitation – without changing the content of therapy – can accelerate functional recovery (171). This study also reported that there was no evidence of diminishing returns for functional gains as therapy intensity was increased (171). These findings are consistent with an RCT that showed that moderate-to-severe TBI patients

receiving intensive rehabilitation, and not those receiving standard care, achieved the maximum FIM score at 3-months post-injury, and the maximum GOS score at 2- and 3-months post-injury (31). However, these group differences were not maintained over time, with patients receiving standard care achieving similar gains as patients receiving intensified treatment by 6-months post-injury (31). These findings suggest that early C-EE may improve behavioural outcomes in TBI patients, although C-EE does not result in improvements that are unachievable by patients receiving standard care at a later time point.

A multi-site prospective cohort study demonstrated that in a sample of 491 adult TBI patients, with a median GCS score in the moderate range, increasing rehabilitation intensity improved FIM motor, but not FIM cognitive, outcomes from admission to in-patient therapy to discharge (172). This finding may be explained by the fact that the therapy provided to patients included a considerable amount of physical therapy, which may have targeted the motor deficits. Leon-Carrion et al. (173) recently showed that intensive rehabilitation for severe TBI patients (i.e., 4 hours per day, 4 days a week, for 6 months) was required to reach an outcome that nears "clinical normalcy" across a number of cognitive domains. Importantly, Cicerone et al. (174) showed that increasing rehabilitation intensity (a form of C-EE) was associated with improvements on the community integration questionnaire (CIQ) in 56 TBI patients, the majority of which were in the moderate-to-severe range, on average 19 months post-injury. The findings of Cicerone et al. (174) show that C-EE improves not only behavioural, functional, and motor outcomes, but it also promote community integration.

Collectively, the clinical studies summarized above demonstrate that C-EE can mitigate neural decline in the chronic stages of moderate-to-severe TBI, and improve behavioural outcomes. These studies are further supported by animal research that shows the more specific neural benefits of C-EE, including increased hippocampal cell survival (107) and up-regulation of neurotrophins (101). Therefore, C-EE has the potential to mitigate the widely observed neural decline observed in TBI patients (51), and thereby promote recovery. In sum, a review of the current literature shows that C-EE has demonstrated promise as a clinical intervention.

Using C-EE to Promote Recovery Following Moderate-to-Severe TBI

Given that animal and human research summarized above demonstrates that C-EE has promise in improving neural and behavioural outcomes following TBI, C-EE has potential as an intervention for patients in the chronic stages of injury. Administering C-EE in the post-acute stages of TBI may promote outcomes, as this increased cognitive activity may buffer against chronic stage neurodegeneration (54) and cognitive decline (24).

Following discharge, almost all TBI patients will experience a drop in the number of hours of therapy received. This is often due to rural residence or accessibility issues that limit access to rehabilitation programs, and/or limited healthcare resources that preclude the provision of ongoing, intensive rehabilitation. Given that intensity is critical to C-EE, and because it is not feasible to bring patients to clinical settings on a daily basis for additional therapy, alternate means of delivering C-EE over the traditional face-to-face format of delivery may be clinically valuable and warrant further research.

3.6 Formats of Delivering Cognitive Therapy

A Tele-Rehabilitation Approach To Delivering Cognitive Therapy

Traditionally, cognitive rehabilitation has been delivered directly by a clinician to a patient, though in recent years, technology-assisted approaches to cognitive rehabilitation have become increasingly common (175). Specifically, rehabilitation that is delivered "at a distance" over, for example, telecommunication networks (i.e., landline and/or cellular phone networks or the Internet) or through use of telecommunication devices is referred to as tele-rehabilitation (176). Accordingly, telephones, smartphones, pagers, computers and Internet-based platforms have become more popular means of delivering therapy.

With technologies such as personal computers and the Internet becoming increasingly widely available, the infrastructure required to administer tele-rehabilitation is currently in place.

Tele-rehabilitation, therefore, has potential to grow in the present healthcare landscape, as it can provide therapy to patients in rural areas and to those patients who cannot access urban rehabilitation centers due to accessibility issues (177). Tele-rehabilitation can also minimize resource strain in a healthcare environment with already limited resources by providing rehabilitation in a cost-effective way to multiple patients under minimal clinician supervision (177).

Delivering Cognitive Therapy Through Brain-Plasticity Based Training Programs

In recent years, "plasticity-based brain training programs" (namely, programs that are designed to improve cognitive performance by harnessing the brain's inherent ability to change through C-EE) have emerged as widely used tools to deliver therapies, including cognitive neurorehabilitation such as C-EE. In general, brain-training programs are designed to provide stimulation and engage users across a number of cognitive domains (such as memory, attention, executive function) to improve day-to-day functioning in these domains. Therefore, these training programs are purported to provide C-EE to users. Many reviews and commentaries have suggested that brain-training programs benefit cognition in these domains and others in healthy populations (178-181), older adults (164, 165, 178, 182-187), and neurological populations, including patients with Alzheimer's disease (188), mild cognitive impairment (189, 190), and multiple sclerosis (191).

Some of the most widely commercially available brain training programs are Brain HQ™ from Posit Science (192), Lumosity™ (193), and MindSparke™ (194). There are other plasticity-based brain training programs such as CogMed™ (195) that are similar in design, though they are designed to be administered by clinicians, and not be directly accessed publically.

Brain HQ™ has the strongest empirical track record of feasibility and efficacy. Upwards of 70 peer-reviewed studies have been published demonstrating the benefits of this C-EE program in improving neuropsychological and functional outcomes in various healthy and

neurological populations, indicating that this training platform has been intensively and widely researched. In comparison, the benefits of Lumosity™ have been documented in 7 studies; there are currently no peer-reviewed publications demonstrating the feasibility or efficacy of MindSparke™ . The peer-reviewed studies investigating the effects of Lumosity™ had modest sample sizes and involved various populations, including cancer survivors, children with Turner Syndrome, individuals with mild cognitive impairment, and healthy older adults. In particular, the Lumosity™ study involving healthy older adults, a population that shares many similarities with the TBI population, such as cognitive and neural vulnerability (156), had a sample of 23 patients (196). This is is considerably smaller than some of the larger, multi-site trails involving the same population and Brain HQ™ (164, 165). Moreover, the Brain HQ™ trials involving healthy older adults demonstrated significant improvements on untrained measures of memory and speed of processing (97, 164, 165, 187). It has also been demonstrated that Brain HQ™ can improve memory and hippocampal activity during verbal memory tasks in patients with mild cognitive impairment (189, 190). Therefore, Brain HQ™ has a strong, empirical track-record of efficacy, and may be of utility as an online C-EE intervention for moderate-to-severe TBI patients.

Efficacy of Current Tele-Rehabilitation Programs for Moderate-to-Severe TBI

There is a growing body of research that has demonstrated the effects of C-EE tele-rehabilitation programs on clinical outcomes following TBI. For example, some studies have investigated the effect of cognitive interventions in improving emotional distress following TBI (197-200). Arundine et al. (197) showed that cognitive behavioural therapy (CBT) delivered over the phone resulted in significant mood and community integration improvements that were observed at follow-up. In a separate study, this group also showed that CBT improved emotional distress in patients that were administered therapy over the phone or in an in-person group format (199). Other studies have also shown that CBT delivered using tele-rehabilitation improves psychosocial outcomes, such as depression, in TBI patients in the chronic stages of injury (198, 200). Although CBT may be cognitively challenging, it is important to note that it is

dissimilar from C-EE as it is a behavioural therapy that is not specifically designed to mitigate neurodegeneration.

Following TBI, tele-rehabilitation programs designed to improve problem solving abilities have also been shown to have a positive effect on the ability to solve problems in a social context, ultimately improving family interactions (201-203). Specifically, in a sample of 40 moderate-to-severe TBI patients, it was demonstrated that problem solving therapy administered online significantly improved problem solving skills and reduced depression at follow-up (202). This group showed in a later study that an online problem solving training program, accessed by teenagers with TBI, significantly reduced conflict with parents and improved problem solving skills (203). Schoenberg et al. (204) also demonstrated that speech-language pathology tele-rehabilitation programs improve functional outcomes similarly to conventional face-to-face therapy in healthy adults. The above studies also demonstrated far transfer, or training benefits extending to tasks beyond those that were trained, and therefore represent a set of effective rehabilitation strategies.

The cognitive benefits of tele-rehabilitation in the context of chronic TBI have also been shown in a limited number of studies. Recently, Ng et al. (205) demonstrated that an online program designed to improve problem solving and executive dysfunction (i.e., the Cognitive Orientation to daily Occupational Performance approach), delivered over videoconference, resulted in self-reported improvements on patient-identified goals in a sample of 3 severe TBI patients who were at least 10-years post-injury. Some of the self-identified goals included becoming more mobile, independent, and organized, while others focused on finding employment or education opportunities (205). Following the intervention, there was reduced reporting of symptoms of executive dysfunction (205). Moreover, the intervention also resulted in far transfer, as post-intervention increases in community integration were reported.

Bergquist et al. (206) showed, with a sample of 14 severe TBI patients injured at least 1-year prior to enrolment, that Internet-based cognitive rehabilitation designed to improve memory by training patients how to use a computerized calendar significantly improved use of compensatory memory strategies. This intervention resulted in far-transfer, as patients learned how to use a compensatory strategy that was applicable in many conditions that demand memory. Furthermore, family members of patients in the aforementioned study reported that

therapy users improved with respect to memory and mood after completing 60 sessions of online rehabilitation (206). Wilson et al. (207) found that a paging system, designed to remind patients (n = 143) of daily tasks such as attending appointments, improved everyday memory performance following TBI. Borgeois et al. (207, 208) demonstrated that delivering spaced retrieval exercises over the phone resulted in improved everyday memory functioning in a sample of 38 TBI patients. It has also been shown that patients receiving online problem-solving training in the chronic stages of TBI improved on self-reported problem solving ability as measured on the Category Test of the Halstead-Reitan Test Battery and self-completed checklists (209).

Extending Current Research on Tele-Rehabilitation Following Moderate-to-Severe TBI

As discussed in the previous section, a few studies have demonstrated the effects of tele-rehabilitation interventions for TBI. However, many of these studies were not explicitly designed to offset neurodegeneration. This is because these studies did not involve C-EE interventions, and therefore explored the effects of interventions that were not necessarily grounded in a paradigm that has been documented to mitigate post-TBI neurodegeneration (54, 100). Recent research showing that the prevalence of chronic neural decline in TBI exceeds 95% (51) and that this decline may be associated with poorer behavioural and functional outcomes (56, 57, 61, 62, 65, 71) offers a new target for neurorehabilitation (i.e., neurodegeneration) that warrants investigation. Moreover, former tele-rehabilitation studies were not designed to provide ongoing therapy to patients. Instead, they were designed to provide therapy to patients for a prescribed period of time (e.g., for a certain number of weeks or therapy sessions) and not on a continual basis. Therefore, further research is required into tele-rehabilitation therapies that can be delivered to patients on a long-term basis for potential ongoing benefit.

However, the feasibility and preliminary efficacy of a computerized brain-training program has recently been investigated in a sample of TBI patients (210). This study, using a C-EE based intervention, targeted neurodegeneration as a means to promote recovery following brain injury. It is important to note that although other cognitive neurorehabilitation interventions

may ultimately have an influence on the neural substrates of cognition, C-EE is provided on a more continual basis, and may therefore have greater scope to mitigate neurodegeneration through ongoing therapy. Other cognitive therapies can be cognitively enriching, but it is the combination of content and intensive dosage that makes C-EE continually enriching, and therefore distinct.

Lebowitz et al. (210) tested the feasibility and preliminary efficacy of a product called Cortex with InSight (a C-EE program), which was developed by the same parent company as Brain HQ™ . Patients (n = 10) were given a software package that contained the C-EE program, which was subsequently installed onto their personal computers. Their sample included individuals with mild (n = 5), moderate (n = 2), and severe (n = 2) brain injuries. (Note: Injury severity was not specified for one individual.) On average, participants were 9 years and 3 months post-injury (range: 6-months post-injury to 22 years post-injury), and had a mean of 19.0 years of education. The majority of this sample (9/10, 90.0%) was also comprised of females.

All patients were instructed to use this program for 40 minutes a day, 5 days a week, for a total of 6 weeks. Most patients (8/10, 80.0%) used the C-EE program for the required amount of time per day and week. Patients completed baseline and follow-up neuropsychological testing. Specifically, patients completed the self-report Automated Neuropsychological Assessment Metrics Version 4 (ANAM-4) at both time-points. The largest positive pre- to post-intervention effect sizes were observed on the ANAM-4's measure of encoding and memory (cohen's d = 0.47). In contrast, a negative effect size was observed on the simple reaction time sub-test of the ANAM-4 (cohen's d = -0.42). This study also demonstrated far-transfer, as positive effect sizes (with cohen's d values ranging from 0.33-1.45) were observed on the Cognitive Failures Questionnaire, a 25-item measure of self-reported problems with memory, perception, and motor function. Moreover, positive pre- to post-intervention effects were also observed on the Frontal Systems Behavioural Scale, a measure that assesses behaviour related to frontal systems damage (211).

Lebowitz and colleagues (210) made important contributions towards understanding the feasibility and efficacy of C-EE interventions for TBI patients. The current thesis extends the work by Lebowitz et al. (210), and addresses some limitations of their research while further

establishing the feasibility of computerized cognitive training as an intervention for, specifically, moderate-to-severe TBI patients.

The sample in the study of Lebowitz et al. (210) was unrepresentative of the TBI population at large, as it was comprised of 90% females. This is atypical from the general TBI population, which largely consists of males (11). Furthermore, Lebowitz et al. (210) studied patients who were highly educated, with a mean of 19.0 years of education (S.D. 3.6 years). This contrasts to the general TBI population, where patients typically have fewer years of education. Moreover, Lebowitz et al. (210) had a sample of patients who were, on average, 9 years and 3 months (range: 6-months – 22 years) post-injury. Additionally, half of the sample studied by Lebowitz et al. (210) were mTBI patients. As patients were typically mildly injured, highly educated, and used the intervention long-after injury, the study by Lebowitz et al. (210) evaluated the feasibility and preliminary efficacy of the intervention in a sample of patients that were likely to have limited impairments, given their clinical profile. This may result in an ultimate inflation of their feasibility and efficacy results.

The present thesis builds on the research by Lebowitz et al. (210) using a more representative sample, and with exclusively moderate-to-severe TBI patients. This allowed us to investigate the feasibility of computerized cognitive training programs in more severely injured patients earlier post-injury, with more typical TBI profiles. Interventions for patients with chronic moderate-to-severe TBI are needed, as these more severely injured patients are the population most often linked to neural and cognitive decline, poor behavioural and psychosocial health outcomes, considerable economic burden, and long-term disability (6, 53). The current study also extended the Lebowitz et al. (210) study by investigating the feasibility obstacles that may be associated with *online* cognitive training program use. This is of value as online cognitive training offers the opportunity for routine, remote delivery of therapy to patients, irrespective of mobility and travel restrictions.

4 INTERVENTION FEASIBILITY

4.1 Overview and Importance of Feasibility Studies

Intervention feasibility is an important first step when designing a clinical trial (212). Tickle-Degnen (213) suggests that feasibility studies build the foundation for subsequent, larger trials of an intervention. Without establishing the feasibility of an intervention, it is not possible to know whether the intervention can be widely implemented in a clinical setting, where patient adherence, resource or personnel strains may be limiting factors. Therefore, considerations of efficacy are closely tied to those concerning feasibility. The findings of feasibility studies should, in theory, be used to determine whether an intervention is suitable for further efficacy testing (214).

It is important to note that the terms "feasibility" and "pilot" are often conflated (215-218). In a recent review of feasibility and pilot studies, Araim et al. (215) report that feasibility studies should be completed before the main study, examining adherence rates and other aspects of study design that may need to be resolved prior to committing to larger trials. Pilot studies, in contrast, are "a version of the main study that is run in miniature" (215), and therefore will closely resemble the main study and are not primarily focused on addressing weaknesses in study design. Whitehead et al. (216) also endorse this distinction and further suggest that pilot studies should be used in preparation for definitive treatment investigation.

Feasibility studies also help evaluate safety, recruitment, randomization, retention, and assessment procedures, in addition to other aspects of study design (219). In drug trials, these studies typically assess safety issues, while in non-drug trials, methodological issues are more frequently addressed (220). Therefore, feasibility studies should be used to critically assess (and amend, if necessary) a study protocol prior to conducting a larger trial to determine the effect size associated with an intervention (221, 222). Furthermore, determining the effect size of an intervention prior to conducting a feasibility study (and, therefore, finalizing a study protocol) would only reflect the power of an intervention with a provisional protocol that is likely to be amended prior to initiation of the subsequent, full study (223). It is important to note that a formal sample size calculation for a feasibility study *itself* may not be appropriate in many cases

(224). This is because a main finding of a feasibility study may show that there is, for example, a higher than anticipated attrition, thereby making it difficult to accurately conduct an *a priori* sample size estimate.

Furthermore, conducting a feasibility study prior to a pilot efficacy investigation can enhance the likelihood that the efficacy investigation will succeed, as errors in the study protocol that may cause the main study to fail will be corrected during the feasibility phase (218). As a result, by conducting a feasibility assessment, researchers will be able to avoid spending resources on studies with a low likelihood of success (218). This will allow researchers to allocate resources to studies with a proven study protocol, thereby allowing funding to be used for studies with the greatest chance of success (225).

In the context of TBI, it is important to assess the feasibility of interventions designed to improve chronic stage outcomes for many reasons. First, the TBI population is very heterogeneous with respect to injury severity, etiology, and spectrum of cognitive and behavioural complications. It is therefore necessary to determine whether a diverse range of TBI patients can complete the intervention before committing to expensive and lengthy clinical trials (218). Secondly, assessing feasibility of a cognitive intervention provides an opportunity to ensure that intervention procedures do not result in adverse cognitive events on patients. Third, feasibility assessments are important for determining whether there are any barriers to intervention adherence, and how these barriers may be removed. The presence of any barriers may reduce adherence, minimize intervention use, and thereby and limit the scope of intervention benefit. Fourth, it is important to test the feasibility of online interventions as TBI patients may have difficulties operating a computer due to cognitive or upper-extremity motor impairments. Without establishing the acceptability of an intervention, its uptake may be limited. Therefore, it is important to determine whether an intervention produces adverse effects that reduce its acceptability, and also assess how these effects can be mitigated.

Elements of a Feasibility Study

A comprehensive review of the literature indicates that there are no standard guidelines on how to design a feasibility study. However, a recent article outlines important elements of a feasibility study (214), discussed below. Feasibility studies should be designed to assess acceptability, or whether patients will react positively to an intervention. Furthermore, establishing the demand of an intervention (i.e., the degree to which an intervention is used) is an important objective of a feasibility study (214). This objective is most often measured by intervention use or adherence. Bowen et al. (214) suggest that an objective of a feasibility study can include limited-efficacy testing to determine whether an intervention is producing benefits in the predicted direction. However, it is important to note that this suggestion is in contrast to those reported by other groups, suggesting that power calculations that derive from pilot studies may only be reflective of the effect of a provisional protocol (218, 225). However, Bowen et al. (214) suggest that preliminary efficacy testing (which does not necessarily involve power calculations) is an important element of a feasibility study. This is because it allows researchers to determine whether an intervention yields benefits in the anticipated direction and if it should be advanced for full-efficacy testing, or whether the study protocol requires amendment.

Other groups have also reported on the importance of investigating these feasibility elements. Specifically, Thabane et al. (218) report that the purpose of feasibility studies is to investigate adherence rates (or, demand, as operationalized by Bowen and colleagues (214)), in addition to logistic issues such as the appropriateness of the inclusion/exclusion criteria and measurement tools. Furthermore, consistent with the suggestions of Bowen et al. (214), Van Teijlingen et al. (218) suggest that feasibility studies should be used to determine whether the study being preliminarily tested is worthy of further testing.

Indeed, feasibility studies (or efficacy studies with a feasibility component) involving cognitive training programs commonly investigate acceptability, demand, and preliminary efficacy. For example, in a study evaluating the feasibility of administering cognitive training in patients with early Alzheimer's disease, adherence rates and preliminary efficacy were investigated (226). A similar feasibility investigation involving healthy older adults using an online cognitive training program also reported on the same feasibility outcomes (i.e., adherence

and preliminary efficacy) (227). These same feasibility outcome measures are reported in studies evaluating the feasibility of online cognitive interventions for stroke (228) and pediatric oncological (229) populations. Therefore, adherence, acceptability, and limited efficacy are outcomes common to many feasibility studies.

4.2 Feasibility Studies Involving Tele-Rehabilitation for TBI

A few studies have explored the feasibility of tele-rehabilitation TBI interventions. Importantly, Bergquist et al. (230) demonstrated that patients with severe traumatic and non-traumatic brain injury (n = 14) were able to learn an online instant messaging system for the purposes of cognitive rehabilitation. It was shown that patients were willing to use, and satisfied with, the online rehabilitation platform, demonstrating that it is feasible for severe ABI patients to use online rehabilitation platforms. Recently, Ng et al. (205) showed that TBI patients (n = 3) adhered to an online training program designed to remediate executive function deficits, demonstrating feasibility of the program. In this study, feasibility was measured by patient adherence and receptiveness to the delivery format (i.e., videoconference). Furthermore, one group developed their own web-based rehabilitation tool that provides intensive in-home cognitive training to sample (n = 80) of patients with acquired memory impairments, some of which were TBI patients (n = 20) (231). It was reported that 60% of all patients attended training sessions, and these patients provided positive feedback on the training experience, with only a minority being uninterested in the program. Nearly 40% of the participants required coaching on how to use the program (often provided by a relative), though many of the patients requiring coaching were first time computer users. The authors concluded that the training program was widely accepted by patients and it was feasible to use, though they did not evaluate important elements of feasibility, such as practicality and implementation. Most relevant to this thesis, Lebowitz et al. (208) investigated the feasibility of a computerized C-EE program for TBI patients, as discussed above.

4.3 Gaps in Literature

Currently, the feasibility and preliminary efficacy of Internet-based C-EE interventions exclusively for moderate-to-severe TBI outpatients has not been investigated, despite the identification of neurodegeneration as a target for cognitive neurorehabilitation and C-EE as a therapy that can mitigate neural decline (54). Lebowitz et al. (210) evaluated the feasibility of administering a software-based C-EE intervention (i.e., a computer program that was installed directly onto a patient's computer that did not require access to online content) in a unrepresentative sample of largely mild TBI patients. It is important to determine the feasibility of Internet-based interventions, as these interventions may pose unique problems, such as access issues. Furthermore, online interventions have greater clinical scope, as they can be administered to patients irrespective rural residence and/or mobility restrictions, and they can be continually accessed by patients for ongoing cognitive enrichment and associated benefit. It is therefore important to determine the feasibility of online C-EE interventions, as they are a promising means of delivering intensive therapy to patients on an ongoing basis for continual cognitive neurorehabilitation. This gap in literature is addressed by the present thesis.

5 OBJECTIVES

The objectives of this study were to investigate the feasibility of implementing an online C-EE-based intervention in a sample of moderate-to-severe TBI patients, using the following outcomes: adherence rates, acceptability of the program, and limited-efficacy testing intended to demonstrate behavioural trends on neuropsychological tests in the predicted direction (214).

Chapter 2
Current Study: Feasibility of Online, C-EE Following Moderate-to-Severe TBI

ABSTRACT

Recent research has documented progressive cognitive and neural decline in the *chronic* stages of moderate-to-severe traumatic brain injury (TBI). Offsetting this putative neurodegeneration offers a new target for cognitive neurorehabilitation. Cognitive environmental enrichment (C-EE; novel, challenging, and engaging cognitive stimulation) delivered early post-TBI has been shown to buffer against neurodegeneration in humans and animals. Some online "brain games" (which can be accessed by patients regardless of location or mobility restrictions) offer intensive cognitive stimulation that meet the criteria for C-EE. Here, the feasibility of administering a home-based, online "brain game" suite to 11 moderate-to-severe TBI patients who participated in 12 weeks of intensive cognitive training was examined. Modest adherence and attrition, high acceptability of the program, and promising findings on limited-efficacy testing involving neuropsychological outcomes were observed. Online cognitive training is a feasible and potentially efficacious intervention for TBI patients. Means of improving adherence are discussed.

INTRODUCTION

Many studies have shown that cognitive recovery following moderate-to-severe TBI is asymptotic, with a period of fairly rapid, early recovery that gradually plateaus, for most functions, by 6-12 months post-injury (20, 31, 37). A prevailing assumption was that this recovery was retained throughout the chronic stages of injury (6, 53). This notion, however, is being challenged by studies that have demonstrated cognitive declines in the chronic stages of injury (22-24, 28). Growing evidence of neural decline in the sub-acute and chronic stages of injury suggests an underlying neural explanation for these poorer-than-expected cognitive outcomes (52, 55, 59, 232), especially as a number of studies have also demonstrated behavioural and functional consequences of neural decline. Specifically, these consequences include poorer: functional outcome (62), performance on visuomotor speed tasks (64), memory performance (29, 33, 56, 57, 64) and executive cognitive function (64). Of particular concern is the prevalence of neural decline; a recent study involving 56 complex mild-to-severe TBI patients reported substantive atrophy in 96% of their sample from 5- to 20-months post-injury (51). These findings reveal the vulnerability of the brain during the chronic stages of TBI.

Importantly, however, these findings offer new targets for neurorehabilitation. Interventions targeted at mitigating neural decline may promote behavioural recovery (or *vice-versa*). One candidate therapy for improving outcomes in chronic TBI is cognitive environmental enrichment (C-EE), which refers to the stimulation of the brain through intensive exposure to continuously novel, challenging, and engaging cognitive stimulation (101). There are other forms of enrichment (namely, physical and social; (100, 101)), however, the present study focused exclusively on C-EE.

In a seminal study, Miller et al. (54) reported that in a sample of 25 moderate-to-severe TBI patients, self-reported frequency of cognitive activity at 5-months post-injury (a proxy of C-EE) negatively correlated with bilateral hippocampal atrophy from 5- to 28-months post-injury. These findings suggest that early C-EE may mitigate post-injury neural decline. Moreover, benefits of C-EE have been extensively shown in the animal literature. For example, brain-injured animals exposed to C-EE, relative to those housed in standard environments, have demonstrated greater reductions in lesion sizes (140-142), increased survival of hippocampal

neurons (107), greater dendritic branching (106), increased synaptic and cellular plasticity (137, 138), and up-regulated neurotrophins (i.e., factors that promote neural growth and repair) such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (139). Collectively, these studies suggest that C-EE can mitigate neural decline by increasing brain plasticity and/or up-regulating factors associated with neural repair to potentially promote recovery following moderate-to-severe TBI.

However, fostering an engaging environment that provides patients with continuous novelty and challenge raises feasibility concerns. Conventional forms of cognitive stimulation, such as reading and completing crosswords, offer only a narrow range of stimulation (and therefore limited novelty), may not be progressively challenging, and do not guarantee ongoing engagement. However, computerized delivery of C-EE through online gaming facilitates user engagement through principles of gamification, or the application of game-design elements (e.g., point/reward systems, competition, rule frameworks) to create a more immersive and engaging user experience than, for example, reading or completing crossword puzzles (233). Moreover, these games are designed to continually challenge users through exposure to increasingly difficult paradigms, making them cognitively enriching. A number of commercially available computerized cognitive training programs – or "brain games" – currently exist (e.g., Brain HQ™ , Lumosity™ , MindSparke™), and are designed to stimulate users to exercise various cognitive domains (234). These programs have demonstrated varied efficacy in enhancing cognition in cognitively vulnerable populations, including healthy older adults (164, 165, 178, 182-187), Alzheimer's disease (188), mild cognitive impairment (189, 190) and multiple sclerosis (191).

The documented efficacy of cognitive training programs, combined with the potential benefits of C-EE (their grounding paradigm), indicates that these programs have utility as clinical interventions for moderate-to-severe TBI patients. Moreover, because cognitive training is completed online, it is a therapy option accessible to moderate-to-severe TBI patients that may live in rural areas or have mobility restrictions that preclude routine hospital or clinic visitation for therapy purposes. Furthermore, because moderate-to-severe TBI patients are likely to require C-EE for extended periods of time to achieve clinical gains (consider the "use it or lose it" principles that have been proposed to guide clinical interventions (185)), online therapy provides a means to deliver therapy to patients continuously.

Despite the ease of access and delivery of computerized brain-games, these conveniences cannot be assumed to circumvent some of the unique feasibility challenges of the TBI population, such as cognitive impairment and manual motor restrictions. Therefore, it is important to assess the feasibility of an intervention, as otherwise it is not possible to know whether the intervention can be widely implemented in a clinical setting, where patient adherence, resource or personnel strains may be limiting factors. Feasibility studies also help evaluate safety, recruitment, retention, and assessment procedures, in addition to other aspects of study design, in preparation for subsequent, larger, definitive intervention studies (213-216, 218-222, 224, 225). Considerations of efficacy and feasibility are closely tied, and ultimately, the findings of feasibility studies should, in theory, be used to determine whether an intervention is suitable for further efficacy testing (214).

Recently, Lebowitz et al. (210) investigated the feasibility and preliminary efficacy of a commercially available C-EE program (created by the developers of Brain HQ™) in the context of TBI. Brain HQ™ is designed to improve attention, speed of processing, memory, executive function, and spatial navigation skills by providing stimulation that exercises and challenges these domains. This program has a strong empirical track record for improving cognitive performance in healthy, aging adults (164, 165, 178, 183-187), a population with conceptual similarities to TBI patients (156). In particular, these two populations share the similarity of being cognitively and neurologically vulnerable, potentially because age- or injury-related impairments reduce opportunities for social engagement, and therefore limit exposure to cognitively enriching environments (156). Lebowitz et al. (210) reported an 80% adherence rate, with patients showing improvements on self-report neuropsychological tests of memory, reaction time, and mathematical processing, with small-to-large effect sizes. Their study included patients for whom program use may have been highly feasible, however, because of the injury and demographic characteristics of the sample. Four of the patients were in the moderate (n = 2) and severe (n = 2) range, while five had mild TBIs. The average time post-injury was 9 years and 3 months (range: 6 months-22 years), and the mean education level was 19.0 years (range: 14-27 years). As well, the majority of their sample was female. It remains unknown whether more typical moderate-severe TBI patients (i.e., fewer years of education, mostly male) and patients who are earlier post-injury, would also find computerized cognitive training feasible. Interventions for patients with chronic moderate-to-severe TBI are needed, as these more

severely injured patients are the population most often linked to neural and cognitive decline, poor behavioural and psychosocial health outcomes, considerable economic burden, and long-term disability (6, 53).

Therefore, we investigated the feasibility of computerized cognitive training programs in in a case-series of patients drawn from a more severely injured and more demographically typical sample of TBI. The current study extended research the Lebowitz et al. (210) by investigating the feasibility obstacles that may be associated with *online* cognitive training program use. This is of value as online cognitive training offers the opportunity for routine, remote delivery of therapy to patients, irrespective of mobility and travel restrictions.

The objectives of this study were to build on the research by Lebowitz and colleagues (210) by establishing the feasibility of implementing an online C-EE-based intervention in predominantly male moderate-to-severe TBI patients with a university education. The following outcomes were employed: adherence and demand rates, acceptability of the program; and limited-efficacy testing intended to demonstrate behavioural trends on neuropsychological tests in the expected direction (214).

METHODS

Participants

The research ethics board at the University Health Network approved this study, and all patients provided written informed consent.

The study sample comprised 11 moderate-to-severe TBI patients recruited through a larger, ongoing longitudinal study in our laboratory that examines cognitive, motor, and neural recovery following moderate-to-severe TBI over the course of two years. Participants of the larger study were recruited through the In-Patient Neurorehabilitation Program, Acquired Brain Injury Service at Toronto Rehab-University Health Network, a large urban teaching hospital. Referrals to the In-Patient Neurorehabilitation Program are adult males and females aged 18 to

65 who are medically stable, with cognitive and neuro-physical impairments that are severe enough to warrant in-patient neurorehabilitation.

Inclusion criteria for the larger research study were as follows: Age between 18 and 65; acute care medical diagnosis of moderate-to-severe TBI; ability to communicate functionally in English; functional vision and hearing, and competency to provide informed consent, or have a substitute decision maker available to do so. Patients were excluded from the study if they had: prior history of TBI; co-morbid or past psychotic illness and/or central nervous system diseases (e.g., Huntington's disease, Alzheimer's disease); TBI secondary to another brain injury (e.g., a stroke resulting in a fall and a subsequent TBI); orthopedic injuries that affected upper extremity use; demonstrated suicidal ideation as measured on the Personality Assessment Inventory and a structured clinical interview addressing psychopathology; and metal plates or pins within the skull (which would preclude the neuroimaging component of the larger study).

The inclusion criteria for the current study were the same as those for the larger study, with the addition of access to an Internet-ready personal computer, as this was required for cognitive training. The present study shared all of the *exclusion* criteria of the larger study, with the exception of possession of cranial metal plates or pins (as we did not have any neuroimaging outcomes in the current study). Demographic and injury characteristics of our sample, ascertained through medical record review and clinical interview, are summarized in Table 1.

ID	Age	Sex	YOE	Time Post-Injury (Months)	Pre-Morbid IQ (WTAR)	GCS	PTA (Days)	LOC (Days)	Cause of Injury	Pre-Morbid Occupational Status
P1	57	M	15	60	-	-	-	150	MVC	-
P2	62	M	19	14	116	13 (ER)	7	27	Fall (Sport)	Employed (Full-time)
P3	40	M	19	2	116	14 (ER)	4	15	Fall (Sport)	Employed (Full-time)
P4	30	M	21	8	116	3	-	-	Fall	Employed (Full-time)
P5	55	F	13	17	105	3	7	-	MVC	Employed (Full-time)
P6	53	M	19	24	105	8	7	-	MVC	Employed (Full-time)
P7	37	M	17	17	116	3	21	24	Fall	Employed (Full-time)
P8	48	F	17	18	111	13 (ER)	14	-	Fall	Employed (Part-time); Student (Full-time)
P9	22	F	15	5	105	6	60	103	MVC	Student (Full-time)
P10	68	M	21	35	122	8	30	-	MVC	Retired
P11	22	F	14	8	113	6	9	-	MVC	Student (FT)

Table 1: Demographic and injury characteristics of our sample (n = 11) of moderate-to-severe TBI patients. **Abbreviations:** YOE, Years of Education; WTAR, Wechsler Test of Adult Reading; GCS, Glasgow Coma Scale; PTA, Post-Traumatic Amnesia; MVC, Motor Vehicle Collision; FT, Full-time; PT, Part-time.

All 11 patients in the present study were recruited over a 15-month period spanning from December, 2012 to March, 2014. They were a convenience sample of patients from the larger study who were identified as being willing and able to carry out the basic demands of the study.

During the window of recruitment for the present study, 36 patients were recruited into the larger study on recovery following TBI. Five of these patients withdrew from the study. Thus the 11 moderate-to-severe TBI patients were recruited from this remaining sample of 31 patients.

Design

This was a prospective, longitudinal case-series examining the feasibility of delivering an environmental enrichment intervention in-home to TBI patients *via* the Internet.

A sub-set of patients (n = 8) were available for neuropsychological testing. These patients were evaluated at two time-points (i.e., baseline and 12-week follow-up); each patient completed the same set of behavioural tests and questionnaires (with alternate forms, where available) at both testing sessions. All behavioural tests had alternative forms except the Sustained Attention to Response Test (SART; (235)). With the exception of tests of memory, where 5 patients completed the Rey Auditory Verbal Learning Test (RAVLT; (236)) and the remaining 3 completed the California Verbal Learning Test (CVLT; (237)), this sub-set of 8 patients completed the same set of neuropsychological tests. Each testing session lasted between 90-120 minutes, and all patients were tested individually.

The dependent measures for the present study are: daily and weekly adherence, weekly participation, Acceptability Scale reports, and neuropsychological test scores. We also included a secondary outcome variable, namely, the Sleep and Concussion Questionnaire (238). (See Appendix 1 for a copy of the Sleep and Concussion Questionnaire.)

Materials

Primary feasibility outcome measures:

(1) Adherence, participation and demand: We calculated two adherence rates: daily adherence and weekly adherence. Daily adherence was operationalized as the total amount of time patients used the cognitive training program per session, divided by the pre-determined

daily session length. This adherence rate allowed us to examine patterns in daily program usage (e.g., intensity of daily cognitive training in minutes per day). Weekly adherence was operationalized as the average amount of time trained in a given week at one of four levels, namely a percentage of 300, 200, 180, or 120 minutes. The rationale for presenting weekly adherence as a percentage of 300 minutes is that patients were required to use the cognitive training program for 300 minutes a week (i.e., 60 minutes/day, 5 days/week). Alternatively, weekly adherence is presented as a percentage of 200 minutes for cross-study comparison purposes, as this is the amount of time participants in the study by Lebowitz et al. (210) were required to train. Weekly adherence is also reported as a percentage of 120 minutes, as all participants in the study by Lebowitz et al. (210) committed at least two hours a week to cognitive training. Finally, weekly adherence is presented as a percent of 180 minutes, as a contact at the Posit Science Corporation (the developer of the Brain HQ™ program) suggested, after study initiation, that training for 45 minutes/day, 4 days/week, for a total of 180 minutes may maximize adherence rates. We also computed training participation, the number of days of cognitive training patients completed in a week.

(2) Retention and implementation: To examine retention and implementation, we documented the number of patients that discontinued cognitive training prior to the end of the 12-week study, and the week in which these patients suspended cognitive training.

(3) Acceptability: A tool was developed, namely the Acceptability Scale, for the current study to assess the acceptability of the intervention. This scale was comprised of thirteen items (see Appendix 2 for a copy of the Acceptability Scale), which were derived through a consensus driven approach. Specifically, a panel of nine experts in cognitive neurorehabilitation (and related disciplines that utilize cognitive therapies) developed an exhaustive list of somatic symptoms (e.g., fatigue, eyestrain) and psychological manifestations (e.g., confidence, sense of accomplishment) of cognitive training. During subsequent discussions, this group reached a consensus on which items to include in the final iteration of the *Acceptability Scale*, on the basis of the clinical relevance of each item to cognitive interventions.

The *Acceptability Scale* was self-administered, and for the current 12-week intervention, frequency of use was targeted at twice weekly. The purpose of this scale was to assess whether each session of the intervention resulted in post-training responses, either beneficial or adverse

By measuring changes in post-session training response, this questionnaire served as a self-report measure of the acceptability of cognitive training. On each Acceptability Scale, patients were required to report whether they felt, for example, less, same, or more fatigued following cognitive training, relative to how they felt immediately prior to a cognitive training session.

Evidence of feasibility of the intervention as measured by the Acceptability Scale would be given by: (1) no change or reductions in endorsements of adverse items pre- vs. post-testing (e.g., headachy, dizzy, foggy); and (2) an increase in endorsements of positive items (e.g., confidence, mentally sharp).

We also measured the completion rate of the Acceptability Scale. This was operationalized as the number of Acceptability Scales completed by each patient divided by the total number questionnaires each patient was required to complete, which was 24. This allowed us to assess how feasible it is to administer this scale twice weekly following cognitive training.

(4) Neuropsychological outcomes for limited efficacy testing: Neuropsychological tests were selected for demonstrated validity and reliability with moderate-severe TBI patients, including test-retest reliability. The tests were also selected for their wide use in the literature and in our studies to allow for comparison with previous TBI studies. The tests measured the following cognitive domains that are frequently disrupted in TBI: speed of processing, simple and complex attention, executive functioning, and memory. The domains were also selected because they overlap with those domains the intervention is designed to train. Neuropsychological tests were administered in pencil-and-paper format, except for the SART (235) (which is computerized) and the Grooved Pegboard (236) and Visual Span (239) (which each require the use of an instrument). See Table 2 for a full list of the neuropsychological tests included in our battery.

DOMAIN	NEUROPSYCOLOGICAL TEST	FUNCTION MEASURED
Simple attention	Digit span forwards (239)	Auditory verbal attention span
	Spatial span forwards (239)	Visual attention span
Complex attention	SART (235)	Sustained attention
	Stroop – Interference (240)	Selective attention
Speed of processing	Grooved pegboard (dominant and non-dominant) (236)	Speed of processing
	Trails A (241)	Simple visual attention and speed of processing
Executive functioning	Trails B (241)	Mental flexibility, set shifting
	Stroop – Colour Word Score (240)	Executive interference
	Spatial span backwards (239)	Visuospatial working memory
	Digit span backwards (239)	Auditory verbal working memory
Memory*	CVLT (237)	Verbal learning and memory
	RAVLT (236)	Verbal learning and memory

Table 2: Comprehensive list of the neuropsychological tests employed in our study. *Some patients received baseline and/or follow-up testing as part of the Toronto Rehab Recovery Study. These patients were tested on the RAVLT. Others, tested as part of the present study, were tested on the CVLT.

Secondary outcome variable:

Sleep and Concussion Questionnaire: Sleep quality and sleep patterns were measured using the Sleep and Concussion Questionnaire (238) that was designed to measure sleep disturbances through patient self-report. We wanted to measure the effects of sleep, as sleep has been shown to influence cognitive outcomes (242, 243). This questionnaire contains four items with multiple sub-components. Specifically, the Sleep and Concussion Questionnaire evaluates: (1) changes in self-reported quality and frequency of sleep; (2) whether injury-related factors (e.g., pain, mood changes, restlessness, worrying) affect sleep quality; (3) changes in wakefulness and ease of falling asleep; and (4) whether the injury resulted in an increased frequency or need for daytime sleep. The scores on these four items are aggregated to provide a single, overall score, which ranges from 0-31. The magnitude of the total score permits an analysis of changes in pre- post-injury sleep quality and frequency. Total scores between 8-15, 16-22, 23-31 indicate, respectively, sub-clinical, moderate, and severe changes in sleep patterns. Scores below 8 indicate no changes in pre- post-injury sleep patterns.

Intervention

The cognitive training program, Brain HQ™ from Posit Science (192), is designed to improve attention, speed of processing, memory, executive function, and spatial navigation skills. Specifically, the program is designed to harness the brain's inherent neuroplasticity (or ability to change when stimulated), and improve cognition by providing stimulation to exercise and challenge the aforementioned cognitive domains and improve their functioning.

The Brain HQ™ (192) homepage allows patients to review their performance to date, and also access any games in the aforementioned cognitive domains. This homepage also offers a help feature, which helps users troubleshoot and navigate any difficulties. However, in the present study, the experimenters were available on an *ad hoc* basis to assist patients with any technical difficulties.

Patients are able to switch between training exercises at any time. Each training exercise is comprised of multiple levels that a patient advances through, and each training exercise adjusts its difficulty to maintain continual challenge for the user. For example, if a patient returns to a training exercise that previously was not successfully completed due to its difficulty, the exercise will be available to the patient at an easier level upon subsequent use. It should be noted that within each cognitive domain, an overall domain-specific percentile score is also provided. Percentiles are computed relative to other users of Brain HQ™ (192).

In general, prior to starting a brain game, written instructions are displayed to the user at the top of the page, which are often accompanied by a demonstration or tutorial. Some games have an auditory component, wherein patients need to follow or filter auditory cues in order to complete the game objective. Other tasks do not have an auditory component, but rather require the patient to follow visual cues. All games are designed to entertain users through the delivery of cognitively engaging stimulation. (See Appendix 3 for screenshots of the Brain HQ™ program.)

The amount of time participants train each day is documented through the administrating experimenter's Brain HQ™ account; domain-specific usage information can also be collected. Brain HQ™ (192) provides real-time feedback on user performance. For example, upon completing a level, patients are given a percentile rank for their score, and also a number of "stars", or in-game rewards that reflected level of performance. The number of stars a patient receives is based on how many standard deviations above or below the mean their performance was relative to other users of Brain HQ™ . Upon completing a training exercise a subsequent time, the subject is informed how their more recent performance compared to their baseline.

Procedures

Patients were evaluated at baseline and again at 12-week follow-up on all outcome measures: the neuropsychological battery and Sleep and Concussion Questionnaire (238). Following baseline assessment, a Brain HQ™ (192) account was set up for each patient. Two patients were guided by the experimenters through an initial log-in and tutorial (i.e., demonstration of how to use the program and access its various components) during an in-home

assessment in their own homes. For the remaining 9 patients, this process was completed over the phone. Throughout the 12-week intervention, the experimenters remained accessible to patients (specifically, patients were provided with the emails and direct telephone lines of the experimenters). The experimenters called patients on a weekly basis to ensure that technical difficulties were not encountered, and to remind patients to participate in cognitive training.

For the first week of the intervention, patients were asked to alternate between 30 and 60 minutes of daily cognitive training and then select the length of sessions for all subsequent training sessions, that is, 30 or 60 minutes. For weeks 2-12 of the study, patients were asked to continue using the training program five days a week for the remainder of the study at the intensity level self-selected in week 1. Patients were asked to access games from each cognitive domain with relatively equal frequency, and they were informed that game selection was not monitored or enforced.

Each week during the 12-week study, the experimenters called patients to provide a reminder to patients to carry out the intervention, and to provide support for any technical difficulties with the program.

Patients were also requested to complete an Acceptability Scale twice weekly to measure self-reported changed in post-training training responses. More specifically, patients were asked to complete The Acceptability Scale immediately following a session of cognitive training.

Patients completed the intervention in-home over their own Internet connection. Although patients were expected to begin the intervention immediately after baseline testing, there was an average delay 28.0 ± 38.9 days (range: 2-93 days) between testing and intervention initiation. Patients were scheduled for follow-up testing 12 weeks after beginning the intervention. On average, however, the time between completion of training and follow-up testing was 40.6 ± 42.5 days (range: 11-111 days). It should be noted that because the time lapse between the two testing sessions was greater than the duration of the 12-week intervention, the results were biased towards Type II error, as intervention effects were not measured immediately after training and may have lessened by follow-up.

Data analyses

Descriptive statistics were performed to characterize subjects for each feasibility variable, including daily and weekly adherence rates, participation, and retention and implementation rates. Acceptability of the intervention was assessed through descriptive analysis of Acceptability Scale data, which was reported by patient and item.

All neuropsychological tests were scored against normative data. Pre- post-standard/scales scores were computed and transformed to a Z-score in order to compute a difference score for each variable for each neuropsychological test, and to aggregate sub-scales. A pre- post-intervention change score for the Sleep and Concussion Questionnaire was also computed.

RESULTS

Recruitment

All 11 participants invited to participate from the convenience sample were recruited to the study, producing a 100% recruitment rate. These patients were identified for their probable willingness and ability to participate, and thus recruitment was heavily biased towards participation.

Retention rate was 63.6%. Four of the 11 patients dropped out of the study prior to completion of the 12-week intervention, citing the following reasons and at the following time points: (1) returning to graduate school and could no longer commit time to the study, dropping out after week 1; (2) loss of Internet and computer access after week 6; (3) part-time return to work, dropping out after week 10; (4) lack of time and lack of interest, with dropout after week 10.

Adherence

Figure 1 illustrates *weekly adherence* across the 12-weeks of intervention (colored curves), and the number of active study patients in a given study week (columns). The average weekly adherence rates as a percentage of 300, 200, 180, and 120 minutes, were, respectively, 42.6% (SD = 5.6%), 64.0% (SD = 8.4%), 71.1% (SD = 9.4%), and 106.6% (SD = 14.1%). Our protocol required patients to train for 300 minutes a week; however, this training duration was associated with a modest adherence rate. To achieve 100% adherence, on average, it would be necessary for patients to train between 120 and 180 minutes per week. It should be noted that all but one patient (P11) opted to train for 60 minutes per day. Adherence rates for this patient are adjusted to account for the difference in pre-determined training session length.

As can be seen, there were notable fluctuations in adherence from week to week, although no systematic overall increase or decrease with time, despite variations in the number of active patients in the study in any given week. On average, there were 8.3 patients in the intervention in any given week. Reductions in participants in a given week were attributable to attrition (n = 4), as noted above, and/or to vacations (n = 2), with a gradual overall reduction in sample size across time due to attrition. Of the two patients who intermittently missed cognitive training due to vacation, one (P10) missed 1 week of participation and the second (P8) missed 4 consecutive weeks. Both of these participants, however, ultimately remained in the study until week 12, and were thus not classified as “drop-outs”.

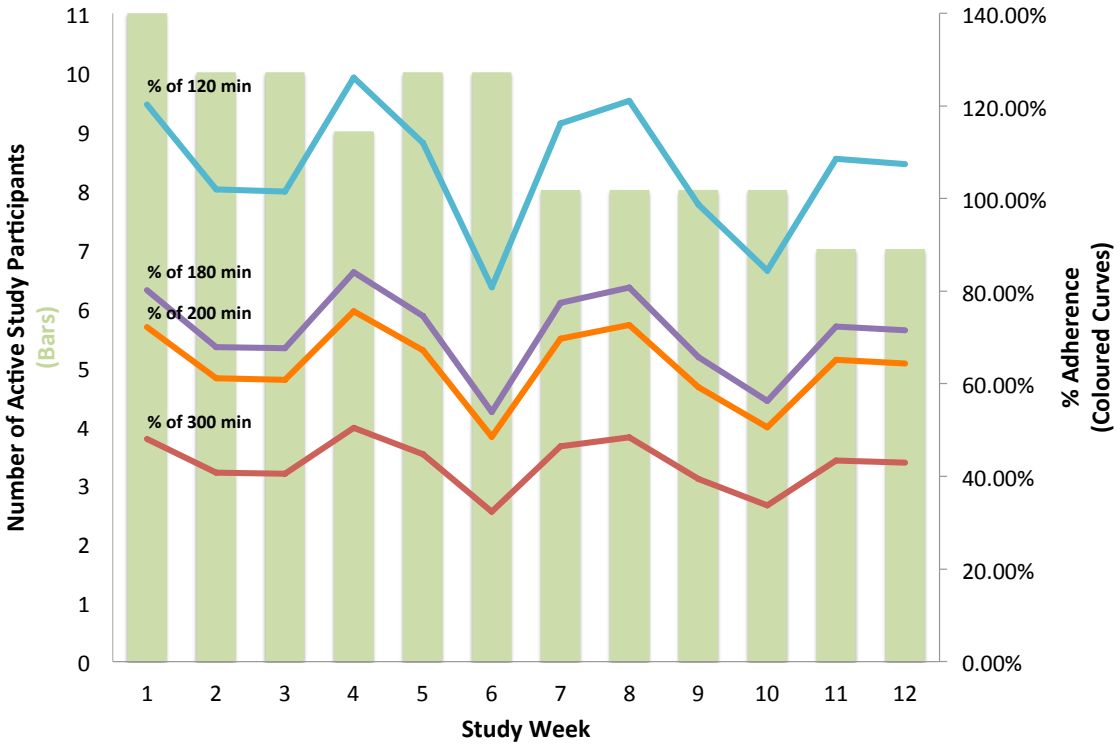

Figure 1: (i) Mean weekly adherence as percentage of 300, 200, 180, or 120 minutes and (ii) number of active study participants across weeks. The curved lines represent mean weekly adherence rates, collapsed across patients. The bars represent the number of active study participants in a given week.

Figure 2 presents the ranges of the mean *weekly adherence* rates (as a percentage of 300 minutes; coloured curve) in order to illustrate variability across patients in amount of time spent using the cognitive training program in a given week. Overall weekly adherence rates for individual patients ranged from 7.7-90.1%, demonstrating considerable variability in weekly adherence between patients. In weeks 1, 4, and 8, the upper limit of the mean adherence range exceeded 100%, largely because some patients independently opted to train for more than 5 days a week.

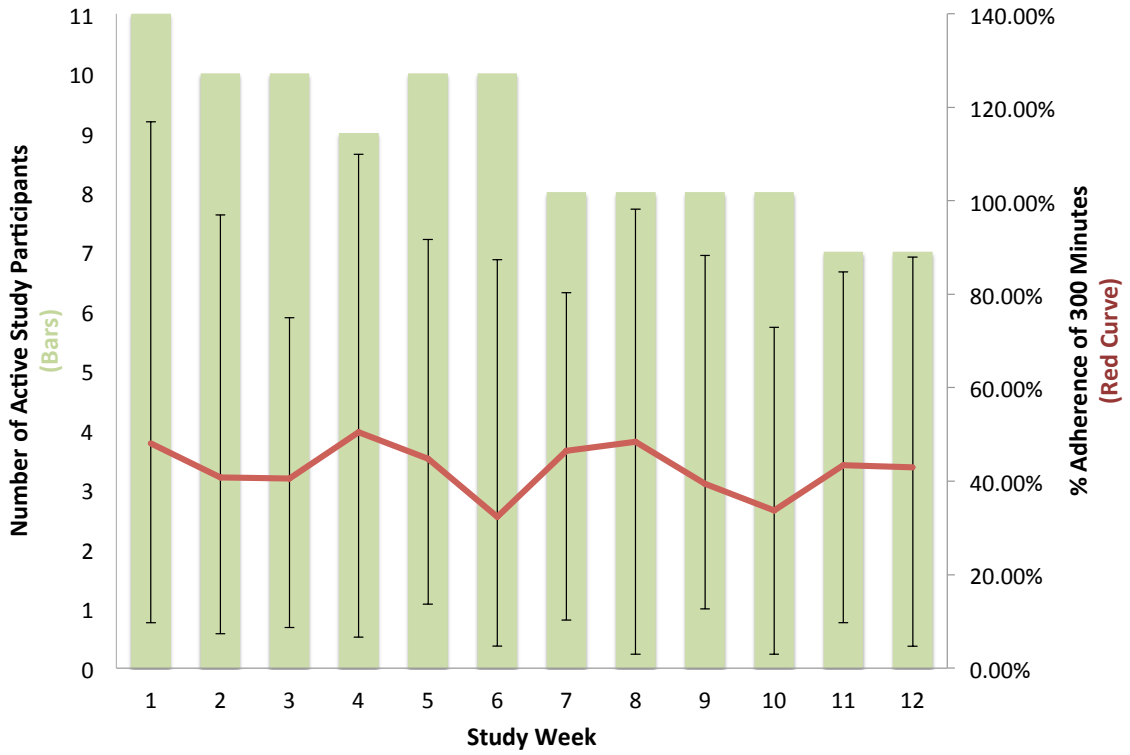

Figure 2: Variability in weekly adherence rates between patients. The red line represents mean weekly adherence rates as a percentage of 300 minutes; error bars represent the range in individual weekly adherence rates in a given week.

Average *daily adherence* for each patient in each study week is illustrated in Figure 3 using a "heat map", with the highest number of minutes trained per day represented in burgundy. Training participation (i.e., the number of days/week trained) per participant is also illustrated. The aim of this figure was to demonstrate the frequency of extra days trained. Four of 11 patients (P2, P4, P9 and P11) trained 6 days a week at least once, and one patient (P9) trained 7 days a week 5 times.

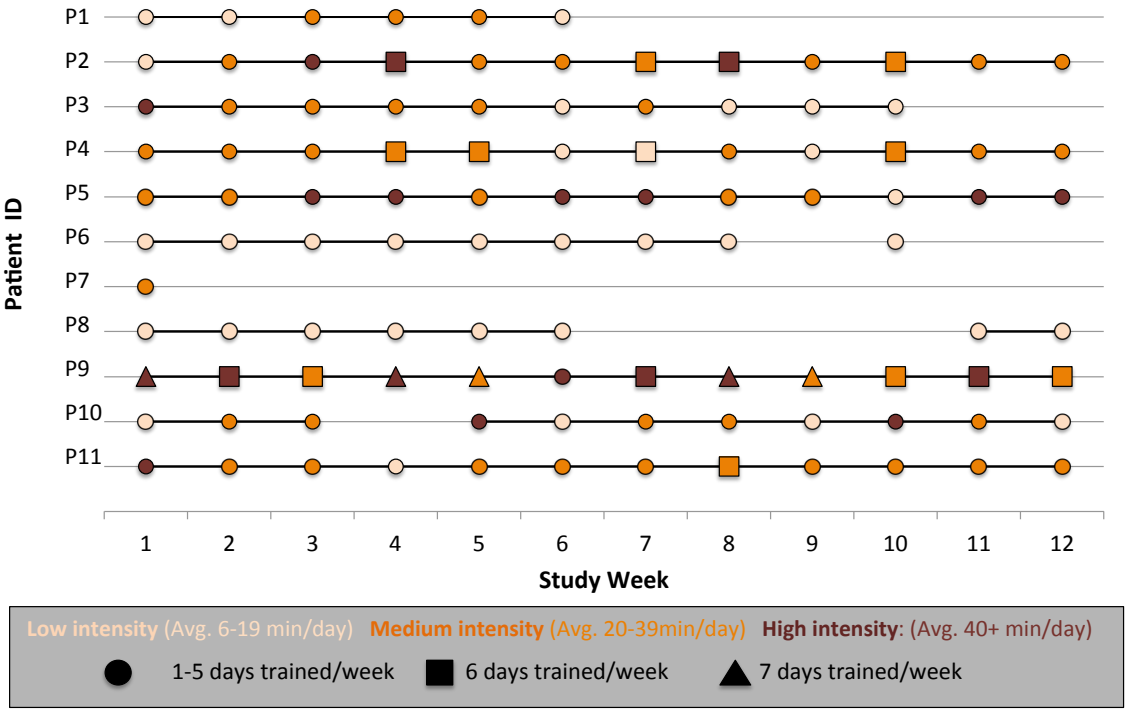

Figure 3: (i) Mean daily adherence (average minutes trained/day collapsed across week) and (ii) supplemental training (i.e., excess of 5 days/week). Maximum weekly adherence is represented by red triangles (i.e., 7 days/week and, on average, > 40 minutes trained/day). Minimum weekly adherence is represented by no symbol (i.e., 0 days trained/week) followed by the beige circle (1-5 days per week at, on average, 6-19 minutes/day).

Figure 4 allows us to gain a more fine-grained understanding of the relationship between participation level and *weekly adherence*. For each participant, we plotted weekly adherence findings (as a percentage of 300 minutes; red marker), the total number of weeks trained (total column height), and number of weeks at each participation level (coloured, stacked columns). Again, the data suggest that for each participant, higher weekly participation is associated with higher weekly adherence. For example, P9 and P11 showed high participation rates and high weekly adherence rates while P6, P8, and P10 had low weekly participation and low weekly adherence rates.

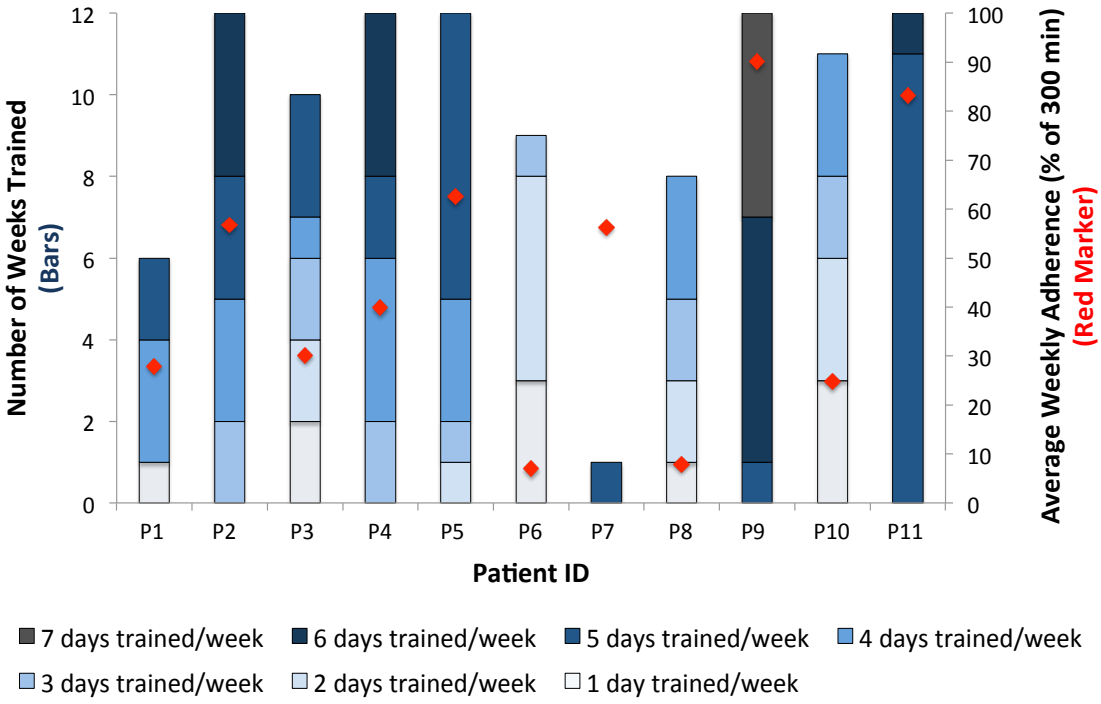

Figure 4: Weekly training participation (number of days trained/week) plotted against average weekly adherence rates (as a percentage of 300 minutes; red marker), by patient. The left y-axis denotes the number of weeks patients trained at a participation level (e.g., P1 performed cognitive training 1 day/week for 1 week, 4 days/week for 3 weeks, and 5 days/week for 2 weeks). The right y-axis denotes average weekly adherence, as a percentage of 300 minutes.

We advised patients to commit an equal amount of time to train each cognitive domain. However, patients ultimately used the cognitive training program independently, and self-governed how often they would train each cognitive domain. Once patients completed the 12-week intervention, we computed the percentage of time they committed to each cognitive domain over the course of the study. These findings are provided in Table 3.

Domain	Percentage of time committed to each domain							
	P3	**P4**	**P5**	**P7**	**P8**	**P9**	**P10**	**P11**
Attention	16.1	14.4	15.1	21.9	23.2	20.1	22.9	21.5
'Brain Speed' (Speed of Processing)	21.3	15.1	14.0	10.8	20.0	14.8	19.4	15.1
'Intelligence' (Executive Functioning)	29.9	4.0	8.5	19.2	10.9	16.5	12.8	34.7
Memory	17.4	57.4	20.8	17.3	16.5	24.1	14.5	14.5
'People Skills' (Social Cognition)	4.2	9.0	13.0	15.3	4.4	12.3	13.1	5.9
'Navigation' (Spatial Navigation)	11.1	0.1	28.6	15.5	25.0	16.3	17.1	8.2

Table 3: Percentage of time patients committed to training each cognitive domain.

Acceptability Scale Feasibility: Completion Rate and Scale Performance

Participants were asked to complete the Acceptability Scale twice weekly over the course of the study; therefore, the total number of possible Acceptability Scale completions was 24. Six of 11 patients completed at least one scale over the course of the study (yielding a completion rate of 54%) and each of these 6 completed the scale at least once/week for each week of the study, with an average of 18.5 (range = 14-23) scales completed by each patient.

With regard to the piloting of this scale for future validity and reliability testing, the items on the scale were endorsed in a coherent manner. For example, no patients reported reductions in somatic symptoms such as fogginess, headaches, and eye strain, although increases were reported. Cognitive capacity items (e.g., ability to think clearly, sharply, faster) and psychological self-efficacy items (e.g., confidence, sense of accomplishment) showed

predominantly increases, as expected.

Acceptability Scale Findings

Figure 5a illustrates, for each patient who completed the Acceptability Scales, the mean increases in ratings (organized by adverse vs. positive items). Conversely, figure 5b demonstrates the mean decreases on Acceptability Scale items, by patient.

With respect to a worsening of overall well-being or reduced acceptability (i.e., decreases in positive or increases in adverse items), on average, fatigue and eye strain showed increases of at least 25%. In two patients, increased boredom immediately following cognitive training was reported on less than 10% of all Acceptability Scales. Five patients reported a decreased sense of accomplishment and confidence in abilities, albeit at a frequency of 15% or less.

In regard to enhancement of overall well-being or increased acceptability (i.e., increases in positive or decreases in adverse items, or increased acceptability), each patient reported an increased sense of accomplishment and confidence on at least, respectively, 15% and 5% of all Acceptability Scales. Moreover, five patients reported decreased boredom on 15-100% of all Acceptability Scales.

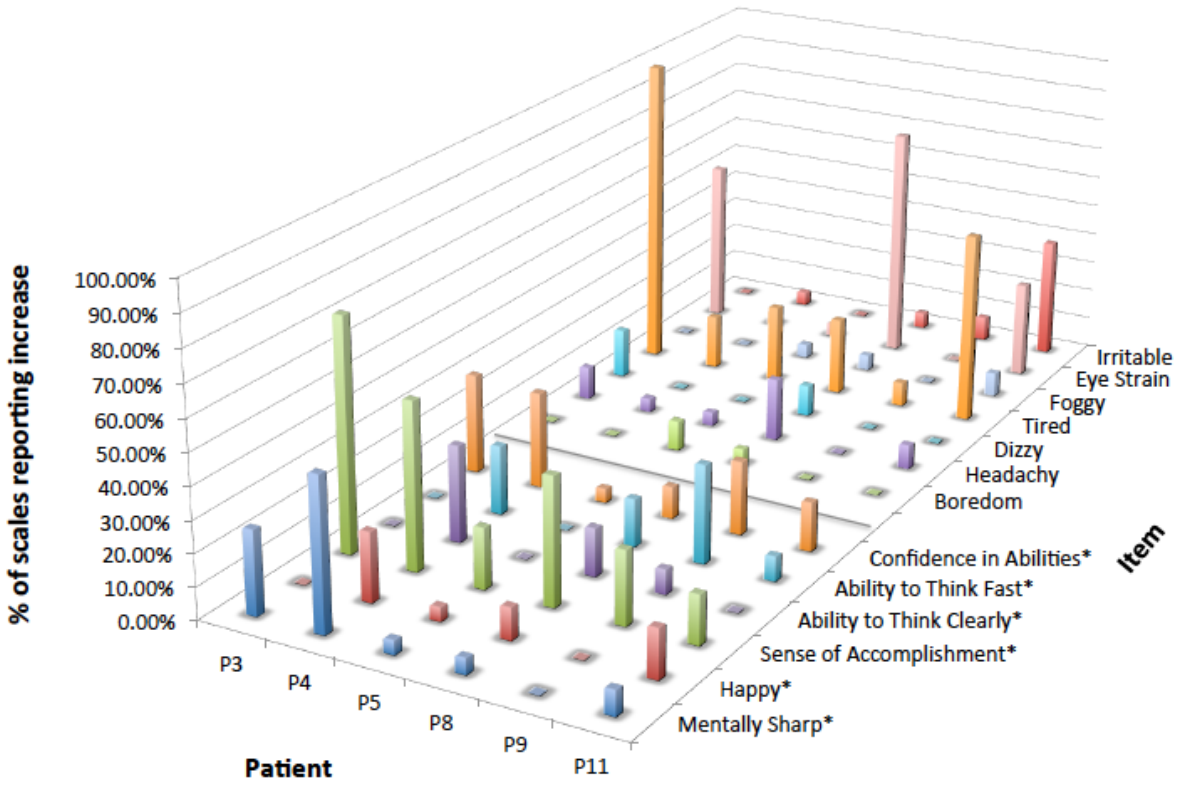

Figure 5a: Percentage of Acceptability Scales reporting a pre- vs. post-training increases on each Acceptability Scale item, by patient. **Note:** *denotes a positive item.

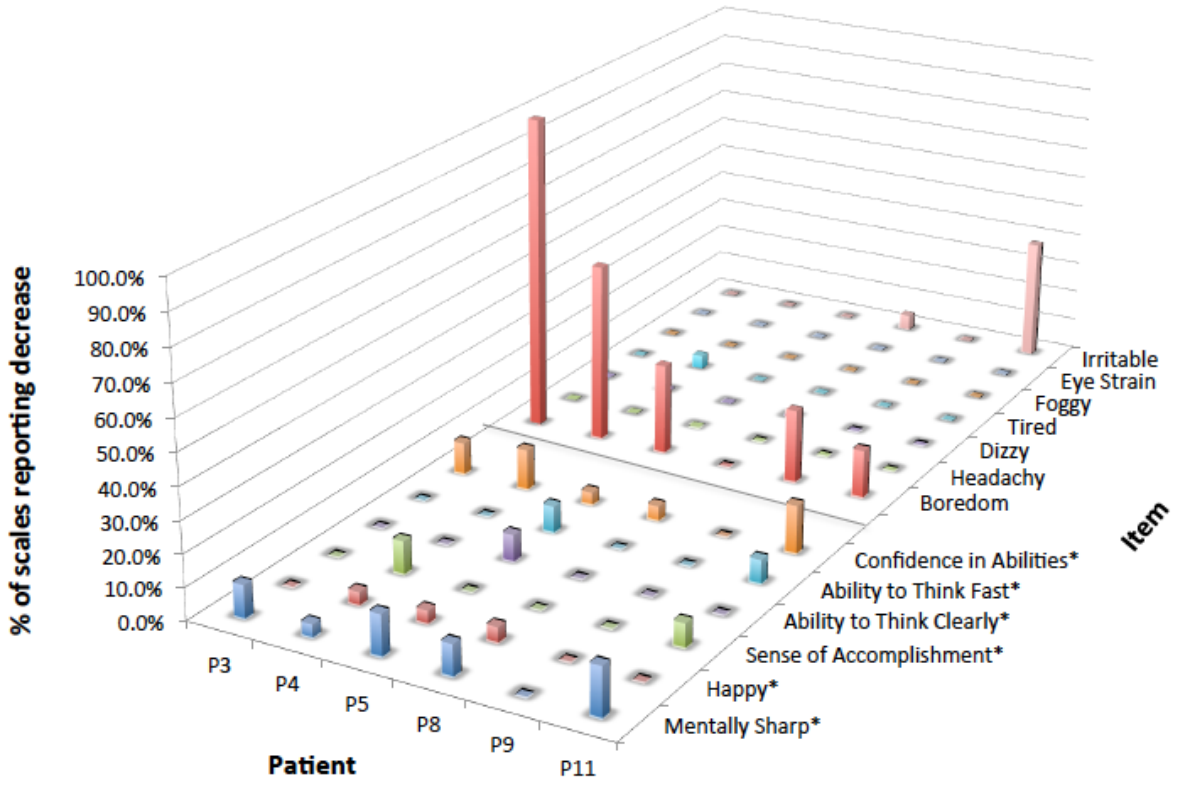

Figure 5b: Percentage of Acceptability Scales reporting a pre- vs. post-training decreases on each Acceptability Scale item, by patient. **Note:** *denotes a positive item.

Limited-Efficacy Testing

When evaluating pre- post-intervention performance across cognitive domains, most patients showed improvements or no change (Table 4). Five patients (P4, P5, P7, P9, and P10) showed domain increases of at least 0.5 Z-scores in at least one domain, and 3 patients (P7, P9, and P10) showed increases of 1.0 Z-score or more in at least one domain. P4 and P8 showed declines in the memory domain of over 0.5 Z-scores. P8 also showed considerable declines on complex attention, as did P3, P4, and P11. Of note, P8 was the patient who missed 4 weeks of intervention and otherwise showed modest adherence. Conversely, P9 had the highest weekly

adherence rate and showed the largest magnitude of improvement. However, the pattern suggested by these data is potentially mitigated by time post-injury, with P9 much earlier post-injury (i.e., 5-months post-injury) and possibly still spontaneously recovering, with P4 well into the chronic stages of injury, at 17 months post-injury.

Domain	P3	P4	P5	P7	P8*	P9	P10*	P11*
Speed of Processing	0.14	**0.66**	**0.62**	-0.01	0.00	**1.37**	0.34	0.22
Simple Attention	0.00	0.17	**0.50**	**1.33**	0.34	**0.50**	**-1.17**	**-0.50**
Complex Attention	**-1.32**	**-1.91**	-0.04	0.05	**-1.06**	**1.00**	-0.28	**-0.84**
Executive Functioning	-0.06	0.46	**0.58**	**0.65**	-0.05	**0.94**	**1.06**	0.20
Memory	-0.12	**-0.52**	0.43	**1.92**	**-0.81**	**1.04**	0.47	0.14
Clinical note	Visual field cut	Sleep deficit	High adherence	Early drop-out	Low adherence	High adherence	Moderate adherence	Clinically depressed

Table 4: Pre- post-intervention improvements in speed of processing, simple attention, complex attention, executive functioning, and memory. Numbers represent the magnitude of the pre- post-intervention Z-score change on a particular domain, with green, red, and grey font representative of improvements, declines, and no change, respectively. **Note:** Only Z-score differences of a magnitude of 0.5 or greater are provided in coloured font, as changes below this threshold may be clinical insignificant (as per expert clinical opinion). *Patient completed the CVLT in lieu of the RAVLT.

Seven patients completed the Sleep and Concussion Questionnaire at baseline and follow-up. Three patients (P3, P4, and P11) showed declines in sleep quality, whereas three

others showed improvements (P5, P8, and P10). Of the patients that showed declines on this measure, two (P3 and P11) had sleep impairments of moderate severity at the end of the study. The remaining patient showed no changes on the Sleep and Concussion Questionnaire.

DISCUSSION

This was the first study to evaluate the feasibility of an *online* C-EE intervention for moderate-to-severe TBI patients. We report modest adherence and high program acceptability, with many patients demonstrating improvements in the expected direction on neuropsychological testing. With regard to patient retention, the findings were comparable to – or arguably better than – the drop-out rates of other longitudinal studies of TBI (see low retention rates of American Model Systems studies (244)). Importantly, in 3 of 4 cases, the stated reasons for dropping out of the study (i.e., return-to-work, return-to-school, and loss of Internet and computer access) were unrelated to the acceptability of the intervention. However, a fourth patient (P6) dropped out of the study due to lack of interest in cognitive training. This patient had the lowest weekly adherence rate and the second lowest daily adherence rate. Future pilot research should evaluate whether early low adherence is a predictor of attrition. A full-scale study might want to incorporate a pre-treatment screening period in which adherence levels are evaluated in order to exclude patients with a low probability of program compliance/retention, unless this kind of variability is desirable in the study.

The majority of the cases in this series did not consistently participate in cognitive training 5 days a week (Figures 3 and 4). Acceptability Scale findings suggested a positive and non-aversive user experience (Figures 5a & 5b). Thus, given the characteristic initiation impairments of this patient population (245), it may be the case that rather than changing the intervention itself, additional support or motivation is required to increase adherence and participation. This assertion is supported by information that one patient volunteered during a weekly telephone check-in. P9, one of the most adherent patients, reported that two of her family members independently purchased Brain HQ™ licenses. All three family members would regularly use Brain HQ™ on different computers at the same time, serving both to motivate P9

and also to facilitate the creation of structure through routine program use. P9 also volunteered that family member support was a factor that contributed to regular cognitive training. Foster et al. (246) encouraged family members of patients with moderate-to-severe TBI to engage in the rehabilitation process at an early stage, and others have suggested that family support may contribute to improved outcomes (247-249). While this case series encouragingly showed that even in the absence of family support some degree of regular adherence was shown, future trials with moderate-to-severe TBI patients would likely benefit from incorporation of family member support into the study protocol. Alternate methods of motivation and structure, such as a regular phone call or email from the overseeing clinician, may also improve adherence and participation. Rewards for regular participation might also be considered (250).

Poor adherence may also be a function of TBI sequelae. For example, prospective memory impairment is widely documented following TBI (251). These memory impairments may limit the ability of participants to perform future tasks at the appropriate time (251). Therefore, poor prospective memory may explicate low adherence and participation, as patients may not have remembered to participate in cognitive training on a daily basis. Although we document no explicit reports of patients forgetting to participate in cognitive training, patients occasionally did not remember to attend their weekly calls and/or complete Acceptability Scales. This suggests that prospective memory impairments may have been a complication in our sample. Wilson et al. (207) found that the provision of daily reminders (intended to help TBI patients complete daily tasks, such as attending appointments) delivered over a paging system significantly reduced everyday memory and planning problems. Other studies have demonstrated the efficacy of a text-messaging system (wherein clinicians or therapy administrators text patients daily reminders concerning their rehabilitation goals) in improving recall of rehabilitation-specific goals (252). Automated reminders installed into a personal digital assistant (253) or smartphone (254) may also serve as effective prospective memory aids for TBI patients. Therefore, there are many mediums through which clinicians or therapy administrators can quickly and reliably send patients daily reminders about cognitive training, potentially increasing increase adherence and participation.

Patients with moderate-severe TBI also frequently display impairments in initiating, planning, and implementing plans (255). Such executive impairments are among the most common and disabling consequences of brain injury, as they may have a negative influence on a

host of functions (such as initiation, reasoning, and aspects of attention and mental flexibility) that are required for successful daily living (245). It is possible that executive impairments, to some degree, were the underlying cause of modest adherence across our sample. For example, if patients experienced deficits in planning and plan-implementation, committing 60 minutes for cognitive training, 5 days a week, for 12 weeks may be unmanageable, especially without daily reminders. In order to mitigate the potential effects of executive dysfunction on adherence rates, it is possible that patients may require concurrent (or perhaps antecedent) therapy for the rehabilitation of executive functions, such as Goal Management Training (GMT; (256)). Providing GMT prior to or in combination with cognitive training (i.e., C-EE) may not only be of additional clinical benefit to patients, but it may also promote adherence and allow patients to maximize potential gains from cognitive training. A recent review of the literature concluding that metacognitive therapies, such as GMT, have demonstrated efficacy in improving executive impairments in TBI patients provides further rationale for a combination therapy approach (86). By rehabilitating the planning and plan-implementation domains that are commonly impaired following TBI, overall adherence (and associated exposure to cognitive training) may be improved. Future studies should explore the baseline executive impairments in their sample, and consider administering GMT and C-EE in combination, at least to patients with considerable executive impairments. Therefore, to improve adherence rates, it may be necessary to provide patients with additional family and clinical support, in adjunct with supplemental therapy that can address some of the memory and executive dysfunction widely documented following moderate-to-severe TBI.

Another means of improving adherence may be to decrease training demands. This can be accomplished by reducing the length of each training session, or reducing the number of requisite training days. Our data suggest that it is unlikely that reducing the number of days of requisite training would improve overall adherence, given that daily adherence tended to be higher when patients trained more regularly (Figures 3 & 4). However, our data show that the length of a given session of cognitive training lasted, on average, just under 30 minutes. Had we required patients to use the cognitive training program for 45 minutes a day instead of 60, it is possible that daily adherence would increase; patients may be able and willing to complete an additional 15 minutes of required training, whereas training for another half hour may not seem achievable. The effect of varying session length on adherence should be a focus of future studies.

With respect to the acceptability of cognitive training, on Acceptability Scales, patients frequently reported that cognitive training resulted in post-intervention fatigue (Figure 5a). One patient, P3, consistently reported post-training fatigue, while other patients reported fatigue intermittently. As P3 was 2-months post-injury when starting cognitive training, this patient was likely participating in other physical and occupational therapies; the combination of routine therapy and cognitive training may have contributed to this patient's overall sense of fatigue. Moreover, studies show that fatigue is most common during early recovery following TBI (257), and that considerable recovery in level of fatigue occurs within the first year of injury (258). P3, very early in his recovery, may have therefore been vulnerable to post-trauma fatigue common in many TBI patients. Moreover, sleep impairments are also common following TBI, with nearly half of all patients presenting with sleep disorder 3-months post-injury (242). Therefore, post-injury sleep disorders may have also contributed to P3's reports of fatigue. Indeed, this patient reported a reduction of sleep quality on the Sleep and Concussion Questionnaire from baseline to follow-up, and had a sleep impairment of moderate clinical severity at the end of the study.

However, it should be recognized that fatigue may not necessarily be a maladaptive outcome of cognitive training. It may be the case that to experience the benefits of cognitive training, it is necessary to expend a fatigue-inducing amount of cognitive effort. In some contexts, post-training fatigue is often a positive symptom; consider that following intensive physical training, muscle fatigue is an indicator of an effective workout. To determine whether the process of improving cognitive performance is inherently fatiguing, the Acceptability Scale should be empirically validated and used in subsequent controlled clinical trials involving cognitive training. This may permit an analysis of whether the patients that experienced the greatest cognitive gains were also those who found cognitive training fatiguing.

The second most prevalent post-training reaction was eyestrain (Figure 5a). As with fatigue, some patients (P3 and P8) reported increases in post-training eyestrain more frequently than others. To mitigate the effects of eyestrain, patients can be advised to follow the 20/20/20 guideline for reducing eyestrain (259). Specifically, as per this guideline, patients would be instructed to look away from their computers every 20 minutes, and for 20 seconds, and focus on an object that is at least 20 feet away (259). Instructing patients to follow this rule at study initiation (and during any subsequent reminder emails or calls) may reduce reports of eyestrain, and further increase the acceptability of the intervention.

It should be noted that our acceptability findings may have been limited by the Acceptability Scale itself. The validity and reliability of this scale has not been established, as the instrument was developed for the purposes of this study. Therefore, we cannot interpret what magnitude of percent change on an Acceptability Scale item is clinically relevant, and whether all items on the Acceptability Scale are equally sensitive to training effects. Future studies should corroborate our acceptability findings using measure with demonstrated validity and reliability in TBI.

On neuropsychological outcomes, improvements were noted across many patients (Table 4). It is important to note that although promising, neuropsychological findings must be cautiously interpreted given the lack of a control group and heterogeneity across patients in our study. Improvements were most consistently observed, across patients, in certain cognitive domains (i.e., speed of processing and executive function). However, it is important to note that the complex attention domain included SART False Press (235) errors as one of the outcome measures. Seven patients declined on this measure, although their SART Reaction Times improved. This suggests that cognitive training may introduce a response bias, wherein accuracy is sacrificed for speed. Alternatively, these findings may suggest that the SART (235) was insensitive to intervention effects. Therefore, complex attention findings may be confounded as per above and the effect of cognitive training on complex attention requires further investigation.

Some neuropsychological findings may be explicable by patient adherence. For example, the patient (P9) that showed the greatest gains on speed of processing and complex attention, in addition to clinically significant improvements across all other cognitive domains, was among the most adherent patients. Likewise, P5 demonstrated high adherence and showed steady improvements in neuropsychological functioning across domains. In contrast, P8, one of the least adherent patients, demonstrated pre- post-intervention declines on neuropsychological testing (Table 4). Our findings, therefore, suggest that performance on neuropsychological testing may be a function of adherence. Future, controlled studies should explore the effect of adherence levels on cognitive performance.

However, neuropsychological findings may also be explicable by other clinically salient features. P11, although among the most adherent patients, was clinically depressed. This patient demonstrated pre- post-intervention declines on measures of attention. Given that clinical

depression has been shown to have an influence on attentional capacities (260-262), the attentional declines in P11 may be explicable by depressive symptomology. Moreover, P4 reported considerable declines in sleep quality on the Sleep and Concussion Questionnaire. Given that sleep quality has been implicated with learning and memory (263-265), poor sleep quality may have contributed to declines in memory performance in this patient. It is interesting to note, however, that Lebowitz et al. (210) reported that the largest intervention effect sizes were associated with memory tests. Moreover, in studies where aging adults (a population that conceptually resembles the TBI population in many ways; (156)) participated in cognitive training, modest-to-large effect sizes were associated with measures of memory (164, 165). Therefore, although our neuropsychological results are preliminary, they suggest that moderate-to-severe TBI patients benefit from cognitive training, with respect to memory, differently than mild TBI patients (who predominated the study by Lebowitz et al. (210)) and healthy, aging adults.

It is also important to note that the patient that demonstrated gains across all cognitive domains (P9) was also in the early stages of injury (Tables 1 & 4). Given that it has been demonstrated that the most accelerated rate of cognitive recovery occurs within the first 5 or 6 months post-injury (20), P9's baseline to follow-up gains may be explicable by spontaneous recovery. Although P3 was 2-months post-injury when starting cognitive training, this patient demonstrated more modest gains on neuropsychological test performance. However, as mentioned above, this patient experienced a reduction in sleep quality, which may have limited scope for cognitive recovery. To contextualize these findings, more chronic patients (e.g., P5) also demonstrated gains in neuropsychological performance in attention, executive functioning, and memory (Tables 1 & 4); these improvements, unlike the improvements of P9, are not attributable to spontaneous recovery, and may more accurately reflect the magnitude of intervention effects.

One limitation of the present study is the use of a convenience sample. Although this sample derives from a larger pool of TBI patients (who are more representative of the moderate-to-severe TBI population), sampling bias may nonetheless influence our study. Moreover, given our modest sample size, conclusions must be cautiously interpreted. With respect to feasibility, our Acceptability Scale findings are based on the reports of a sub-set of patients, which may not

be representative of our sample at large. It is also important to note that the Acceptability Scale does not have demonstrated validity and reliability, and this may limit our acceptability findings.

Nonetheless, our findings show that online cognitive training is a feasible online intervention for moderate-to-severe TBI patients, and that a number of modifications might enhance feasibility. These findings are promising, and suggest that this intervention is suitable for future, large-scale efficacy testing. However, to improve adherence, future trials should consider providing family member or clinician support to patients. Alternatively, the provision of supplemental therapy that targets memory and executive impairments may improve adherence. Furthermore, encouraging patients to take routine training breaks may increase acceptability.

In conducting limited-efficacy testing, we also demonstrated that intervention effects were largely in the expected direction. Future, controlled trials are required to determine whether the intervention leads to significant improvements in cognitive functioning. These studies should also determine intervention effect sizes to permit sample size calculations that can inform the design of large-scale efficacy trials.

CONCLUSIONS

Our study demonstrates that online cognitive training is a feasible and potentially efficacious intervention for moderate-to-severe TBI patients. This intervention has considerable clinical utility, given that it can be administered remotely to patients that cannot routinely visit hospitals or clinics for therapy. When considered in the context of current literature documenting the post-TBI cognitive and neural benefits of C-EE, our feasibility findings suggest that online cognitive training is a tele-rehabilitation strategy that may help promote recovery following moderate-to-severe TBI.

Chapter 3
General Discussion

This was the first study to evaluate the feasibility of an *online* C-EE intervention for moderate-to-severe TBI patients. I report modest adherence and high program acceptability, with many patients demonstrating improvements in the expected direction on neuropsychological testing. With regard to patient retention, the findings were comparable to – or arguably better than – the drop-out rates of other longitudinal studies of TBI (see low retention rates of American Model Systems studies (244). Importantly, in 3 of 4 cases, the stated reasons for dropping out of the study (i.e., return-to-work, return-to-school, and loss of Internet and computer access) were unrelated to the acceptability of the intervention. However, a fourth patient (P6) dropped out of the study due to lack of interest in the cognitive training program. This patient had the lowest weekly adherence rate and the second lowest daily adherence rate. Future pilot research should evaluate whether early low adherence is a predictor of attrition. A full-scale study might want to incorporate a pre-treatment screening period in which adherence levels are evaluated in order to exclude patients with a low probability of program compliance/retention, unless this kind of variability is desirable in the study.

However, given that I report a drop-out (P6) due to lack of interest in cognitive training, my findings may nonetheless suggest a need to screen patients for apathy at the time of recruitment, with an instrument such as the Apathy Evaluation Scale (266). Early screening for apathy, and potentially incorporating apathy as an exclusion criterion of future studies, may preclude the enrolment of patients unlikely to complete – and therefore benefit from – cognitive training. Conversely, if resources permit, identifying apathetic patients at study onset may allow early arrangements to be made wherein additional clinical support can be provided to apathetic patients, in an attempt to prevent premature drop-out due to lack of interest in the study. It is interesting to note, however, that P6 had the lowest weekly adherence rate and second lowest daily adherence rate. Future pilot research should evaluate whether early low adherence is a predictor of attrition. A full-scale study might want to incorporate a pre-treatment screening

period in which adherence levels are evaluated in order to exclude patients with a low probability of compliance/retention, unless this kind of variability is desirable in the study.

An additional patient, P8, did not drop out of the study, but missed the highest number of weeks of therapy (4 consecutive weeks; Figure 3). This patient, interestingly, had the second lowest weekly adherence rate and the lowest daily adherence rate, bolstering the potential value of a pre-treatment screening period. Although P8 did not drop-out of the study (or cite a lack of interest in the study), this patient did miss 4 weeks of cognitive training, between weeks 7-10, due to vacation. In addition, throughout the study, this patient was involved in a legal dispute (unrelated to the brain injury). Although this patient's legal dispute was unrelated to TBI, studies have demonstrated that litigation contributes to poorer outcomes following brain injury (267, 268). It is possible that the combination of mid-intervention training suspension and legal complications were contributing factors to P8's low adherence and declines in pre- to post-intervention cognitive performance in complex attention and memory (Table 4).

The majority of the cases in this series did not consistently participate in cognitive training 5 days a week (Figures 3 and 4). Acceptability Scale findings suggested a positive and non-aversive user experience (Figures 5a & 5b). Thus, given the characteristic initiation impairments of this patient population (245), it may be the case that rather than changing the intervention itself, additional support or motivation is required to increase adherence and participation. This assertion is supported by information that one patient volunteered during a weekly telephone check-in. P9, one of the most adherent patients, reported that two of her family members independently purchased Brain HQ™ licenses. All three family members would regularly use Brain HQ™ on different computers at the same time, serving both to motivate P9 and also to facilitate the creation of structure through routine program use. P9 also volunteered that family member support was a factor that contributed to regular cognitive training. Foster et al. (246) encouraged family members of patients with moderate-to-severe TBI to engage in the rehabilitation process at an early stage, and others have suggested that family support may contribute to improved outcomes (247-249). While this case-series encouragingly showed that even in the absence of family support some degree of regular adherence was shown, future trials with moderate-to-severe TBI patients would likely benefit from incorporation of family member support into the study protocol. Alternate methods of motivation and structure, such as a regular

phone call or email from the overseeing clinician, may also improve adherence and participation. Rewards for regular participation might also be considered (250).

Findings from the present study and the current literature suggests that there are several further factors that may potentially influence adherence that warrant further exploration:

(1) Fatigue: Some patients who endorsed reduced boredom and an increased sense of accomplishment also reported increased fatigue (Figures 5a & 5b). Fatigue may be a barrier to high adherence or in fact, a necessary byproduct of high effort and engagement. As the adherence of patients who most frequently reported fatigue varied considerably (Figures 3, 4, 5a & 5b), future studies should investigate whether fatigue precludes high adherence or indicates of high-effort, high-reward cognitive training.

(**2) Apathy:** recent research suggests that apathy is present in half of all moderate-to-severe TBI patients at some point following their injury, and that this apathy may negatively influence rehabilitation outcomes (269). In our study, P6 overtly expressed a lack of interest in the cognitive training program, it is possible that apathy was a behavioural complication in our sample, perhaps more ostensibly in some cases than in others. Providing motivational support to apathetic patients may improve adherence.

(3) Reduced self-awareness: Reduced self-awareness is a well-documented consequence of more severe TBIs (270, 271). Therefore, limited self-awareness may make it difficult for patients to recognize the benefits of daily cognitive training. To increase adherence in the context of apathy and reduced self-awareness, it may be necessary to remind patients on a daily basis, *via* telephone, email or text message, to participate in cognitive training. Empirically testing which of these techniques confers the strongest environmental support to offset these prevalent impairments in this population would be of clinical value. It should be noted that patients in our study declined to have daily reminders. Therefore, we cannot know from our study whether or not this adversely affected outcomes. However, given that some patients may decline certain forms of environmental support, it would be of additional clinical value to empirically ascertain for whom supports are needed and for whom they are redundant, and what the dose-response is for different patient types. This would permit tailoring of rehabilitation to suit levels of patient motivation and self-awareness, which may improve outcomes (272).

Alternatively, some studies report that a more potent strategy for achieving behavioural change may be to conduct motivational interviews with TBI patients on a routine basis (273). Such interviewing, which can be performed over the phone, would involve encouraging patients to intensively participate in cognitive training. More specifically, it would involve motivating patients to commit to a behavioural change (e.g., intensified cognitive training) that may produce neural and cognitive benefits. This would be achieved by highlighting patients' recent successes (e.g., a new high score in a certain domain), exploring barriers to change, and ultimately helping resolve issues of ambivalence (274). Although motivational interviewers need to be specially trained, this training can be completed online, through, for example, the University of Toronto affiliated Center for Addiction and Mental Health (CAMH) educational module (275). Once an individual is trained to conduct motivational interviews, this individual can then interview many patients over the phone in a given week, precluding the need for costly and logistically challenging face-to-face patient consultation. Moreover, these interviews may only be required for the initial weeks of cognitive training, or until patients become accustomed to intensive cognitive training. Most importantly, research suggests that telephone-based motivational interviewing for TBI patients results in improved outcomes (276, 277), and that motivational interviewing can reduce apathy (278) and increase self-awareness (279) in TBI patients.

Poor adherence may also be a function of other TBI sequelae. For example, prospective memory impairment is widely documented following TBI (251). These memory impairments may limit the ability of participants to perform future tasks at the appropriate time (251). Therefore, poor prospective memory may explicate low adherence and participation, as patients may not have remembered to participate in cognitive training on a daily basis. Although we document no explicit reports of patients forgetting to participate in cognitive training, patients occasionally did not remember to attend their weekly calls and/or complete Acceptability Scales. This suggests that prospective memory impairments may have been a complication in our sample. Wilson et al. (207) found that the provision of daily reminders (intended to help TBI patients complete daily tasks, such as attending appointments) delivered over a paging system significantly reduced everyday memory and planning problems. Other studies have demonstrated the efficacy of a text-messaging system (wherein clinicians or therapy administrators text

patients daily reminders concerning their rehabilitation goals) in improving recall of rehabilitation-specific goals (252). Automated reminders installed into a personal digital assistant (253) or smartphone (254) may also serve as effective prospective memory aids for TBI patients. Therefore, there are many mediums through which clinicians or therapy administrators can quickly and reliably send patients daily reminders about cognitive training, potentially increasing increase adherence and participation.

Patients with moderate-severe TBI also frequently display impairments in initiating, planning, and implementing plans (255). Such executive impairments are among the most common and disabling consequences of brain injury, as they may have a negative influence on a host of functions (such as initiation, reasoning, and aspects of attention and mental flexibility) that are required for successful daily living (245). It is possible that executive impairments, to some degree, were the underlying cause of modest adherence across our sample. For example, if patients experienced deficits in planning and plan-implementation, committing 60 minutes for cognitive training, 5 days a week, for 12 weeks may be unmanageable, especially without daily reminders. In order to mitigate the potential effects of executive dysfunction on adherence rates, it is possible that patients may require concurrent (or perhaps antecedent) therapy for the rehabilitation of executive functions, such as Goal Management Training (GMT; (256)). Providing GMT prior to or in combination with cognitive training (i.e., C-EE) may not only be of additional clinical benefit to patients, but it may also promote adherence and allow patients to maximize potential gains from cognitive training. A recent review of the literature concluding that metacognitive therapies, such as GMT, have demonstrated efficacy in improving executive impairments in TBI patients provides further rationale for a combination therapy approach (86). By rehabilitating the planning and plan-implementation domains that are commonly impaired following TBI, overall adherence (and associated exposure to cognitive training) may be improved. Future studies should explore the baseline executive impairments in their sample, and consider administering GMT and C-EE in combination, at least to patients with considerable executive impairments. Therefore, to improve adherence rates, it may be necessary to provide patients with additional family and clinical support, in adjunct with supplemental therapy that can address some of the memory and executive dysfunction widely documented following moderate-to-severe TBI.

Another means of improving adherence may be to decrease training demands. This can be accomplished by reducing the length of each training session, or reducing the number of requisite training days. Our data suggest that it is unlikely that reducing the number of days of requisite training would improve overall adherence, given that daily adherence tended to be higher when patients trained more regularly (Figures 3 & 4). However, our data show that the length of a given session of cognitive training lasted, on average, just under 30 minutes. Had we required patients to use the cognitive training program for 45 minutes a day instead of 60, it is possible that daily adherence would increase; patients may be able and willing to complete an additional 15 minutes of required training, whereas training for another half hour may not seem achievable. The effect of varying session length on adherence should be a focus of future studies.

With respect to the acceptability of cognitive training, on Acceptability Scales, patients frequently reported that cognitive training resulted in post-intervention fatigue (Figure 5a). One patient, P3, consistently reported post-training fatigue, while other patients reported fatigue intermittently. As P3 was 2-months post-injury when starting cognitive training, this patient was likely participating in other physical and occupational therapies; the combination of routine therapy and cognitive training may have contributed to this patient's overall sense of fatigue. Moreover, studies show that fatigue is most common during early recovery following TBI (257), and that considerable recovery in level of fatigue occurs within the first year of injury (258). P3, very early in his recovery, may have therefore been vulnerable to post-trauma fatigue common in many TBI patients. Moreover, sleep impairments are also common following TBI, with nearly half of all patients presenting with sleep disorder 3-months post-injury (242). Therefore, post-injury sleep disorders may have also contributed to P3's reports of fatigue. Indeed, this patient reported a reduction of sleep quality on the Sleep and Concussion Questionnaire from baseline to follow-up, and had a sleep impairment of moderate clinical severity at the end of the study.

However, it should be recognized that fatigue may not necessarily be a maladaptive outcome of cognitive training. It may be the case that to experience the benefits of cognitive training, it is necessary to expend a fatigue-inducing amount of cognitive effort. In some contexts, post-training fatigue is often a positive symptom; consider that following intensive physical training, muscle fatigue is an indicator of an effective workout. To determine whether the process of improving cognitive performance is inherently fatiguing, the Acceptability Scale should be empirically validated and used in subsequent controlled clinical trials involving

cognitive training. This may permit an analysis of whether the patients that experienced the greatest cognitive gains were also those who found cognitive training fatiguing.

The second most prevalent post-training reaction was eyestrain (Figure 5a). As with fatigue, some patients (P3 and P8) reported increases in post-training eyestrain more frequently than others. To mitigate the effects of eyestrain, patients can be advised to follow the 20/20/20 guideline for reducing eyestrain as proposed by the Ontario Chiropractic Association (259). Specifically, as per this guideline, patients would be instructed to look away from their computers every 20 minutes, and for 20 seconds, and focus on an object that is at least 20 feet away (259). Instructing patients to follow this rule at study initiation (and during any subsequent reminder emails or calls) may reduce reports of eyestrain, and further increase the acceptability of the intervention.

It is important to note that reports of reduced post-training boredom were more frequent than reports of increased boredom immediately following cognitive training (Figure 5b). Moreover, P3, the patient that consistently reported that cognitive training induced fatigue, also consistently reported feeling less bored following cognitive training. This shows that P3 was not biased towards endorsing negative items, as this patient also endorsed positive items (i.e., reduction in boredom) with the same frequency. Additionally, these findings suggest that expending cognitive effort (and experiencing the associated fatigue) may be necessary to experience gains of cognitive training, including reduced boredom.

It should be noted that my acceptability findings may have been limited by the Acceptability Scale itself. The validity and reliability of this scale has not been established, as the instrument was developed for the purposes of this study. Therefore, I cannot interpret what magnitude of percent change on an Acceptability Scale item is clinically relevant, and whether all items on the Acceptability Scale are equally sensitive to training effects. Future studies should corroborate our acceptability findings using measure with demonstrated validity and reliability in TBI.

On neuropsychological outcomes, improvements were noted across many patients (Table 4). It is important to note that although promising, neuropsychological findings must be cautiously interpreted given the lack of a control group and heterogeneity across patients in our study. Improvements were most consistently observed, across patients, in certain cognitive

domains (i.e., speed of processing and executive function). However, it is important to note that the complex attention domain included SART False Press (235) errors as one of the outcome measures. Seven patients declined on this measure, although their SART Reaction Times improved. This suggests that cognitive training may introduce a response bias, wherein accuracy is sacrificed for speed. Alternatively, these findings may suggest that the SART (235) was insensitive to intervention effects. Therefore, complex attention findings may be confounded as per above and the effect of cognitive training on complex attention requires further investigation.

Some neuropsychological findings may be explicable by patient adherence. For example, the patient (P9) that showed the greatest gains on speed of processing and complex attention, in addition to clinically significant improvements across all other cognitive domains, was among the most adherent patients. Likewise, P5 demonstrated high adherence and showed steady improvements in neuropsychological functioning across domains. In contrast, P8, one of the least adherent patients, demonstrated pre- post-intervention declines on neuropsychological testing (Table 4). Our findings, therefore, suggest that performance on neuropsychological testing may be a function of adherence. Future, controlled studies should explore the effect of adherence levels on cognitive performance.

However, neuropsychological findings may also be explicable by other clinically salient features. P11, although among the most adherent patients, was clinically depressed. This patient demonstrated pre- post-intervention declines on measures of attention. Given that clinical depression has been shown to have an influence on attentional capacities (260-262), the attentional declines in P11 may be explicable by depressive symptomology. Moreover, P4 reported considerable declines in sleep quality on the Sleep and Concussion Questionnaire. Given that sleep quality has been implicated with learning and memory (263-265), poor sleep quality may have contributed to declines in memory performance in this patient. It is interesting to note, however, that Lebowitz et al. (210) reported that the largest intervention effect sizes were associated with memory tests. Moreover, in studies where aging adults (a population that conceptually resembles the TBI population in many ways; (156)) participated in cognitive training, modest-to-large effect sizes were associated with measures of memory (164, 165). Therefore, although our neuropsychological results are preliminary, they suggest that moderate-to-severe TBI patients benefit from cognitive training, with respect to memory, differently than

mild TBI patients (who predominated the study by Lebowitz et al. (210)) and healthy, aging adults.

It is also important to note that the patient that demonstrated gains across all cognitive domains (P9) was also in the early stages of injury (Tables 1 & 4). Given that it has been demonstrated that the most accelerated rate of cognitive recovery occurs within the first 5 or 6 months post-injury (20), P9's baseline to follow-up gains may be explicable by spontaneous recovery. Although P3 was 2-months post-injury when starting cognitive training, this patient demonstrated more modest gains on neuropsychological test performance. However, as mentioned above, this patient experienced a reduction in sleep quality, which may have limited scope for cognitive recovery. To contextualize these findings, more chronic patients (e.g., P5) also demonstrated gains in neuropsychological performance in attention, executive functioning, and memory (Tables 1 & 4); these improvements, unlike the improvements of P9, are not attributable to spontaneous recovery, and may more accurately reflect the magnitude of intervention effects.

One limitation of the present study is the use of a convenience sample. Although this sample derives from a larger pool of TBI patients (who are more representative of the moderate-to-severe TBI population), sampling bias may nonetheless influence my study. Moreover, given my modest sample size, conclusions must be cautiously interpreted. With respect to feasibility, my Acceptability Scale findings are based on the reports of a sub-set of patients, which may not be representative of our sample at large. It is also important to note that the Acceptability Scale does not have demonstrated validity and reliability, and this may limit our acceptability findings.

Nonetheless, my findings show that cognitive training is a feasible online intervention for moderate-to-severe TBI patients, and that a number of modifications might enhance feasibility. These findings are promising, and suggest that this intervention is suitable for future, large-scale efficacy testing. However, to improve adherence, future trials should consider including means to provide family member or clinician support to patients. Alternatively, the provision of supplemental therapy that targets memory and executive impairments may improve adherence. Furthermore, encouraging patients to take routine training breaks may increase acceptability.

In conducting limited-efficacy testing, I also demonstrated that intervention effects were largely in the expected direction. Future, controlled trials are required to determine whether the

intervention leads to significant improvements in cognitive functioning. These studies should also determine intervention effect sizes to permit sample size calculations that can inform the design of large-scale efficacy trials. In addition, future studies should manipulate training session duration and explore the associated effects on adherence and behavioural and neural outcome measures.

Chapter 4
General Conclusions

My findings show that cognitive training is a feasible online intervention for moderate-to-severe TBI patients. Many patients demonstrated improvements on behavioural outcomes in the predicted direction. These findings are promising, and suggest that this intervention is suitable for future, large-scale efficacy testing.

Moreover, cognitive training may be of particular benefit to patients who have been discharged from in-patient therapy, but have not yet resumed occupation. During this transition, patients may be minimally enriched, as they receive no therapy- or vocation-related cognitive stimulation. It is also during this time that patients are vulnerable to neural decline. Specifically, given that frequency of cognitive activity at 5-months post-injury has been shown to negatively correlate with bilateral hippocampal atrophy from 5- to 28-months post-injury (54), a dearth of cognitive stimulation early post-TBI may result in downstream neural decline, and, as a result, poorer behavioural and functional outcomes (56, 57, 61, 62, 64, 71). Cognitive training can "fill the gap" between therapy and vocation, minimizing patient vulnerability to neurodegeneration and associated cognitive and functional decline.

Furthermore, post-TBI neural decline may be progressive as shown by recent studies (6, 53). Moderate-to-severe TBI patients may therefore require life-long therapy. My findings show that online cognitive training is a feasible option for providing TBI patients with cognitive enrichment on an ongoing basis, which may mitigate cognitive decline and offset neural atrophy through continual cognitive stimulation.

Future directions

The findings of the present study can be used to inform future studies involving online cognitive training for moderate-to-severe TBI patients. In particular, screening for apathy,

awareness of cognitive and other impairments should be performed at study onset, to identify patients who may not be suitable for the study or require additional therapy to promote adherence. Moreover, in order to increase adherence, future studies should examine the effect of providing patients with additional supports. In particular, the effect of daily telephone or email reminders, family member support and motivational interviewing on training adherence deserve study. Future studies should also be comprised of multiple experimental groups (with each group required to partake in cognitive training for different durations) to explore the effect of varying training intensity on adherence, and ultimately, behavioural outcomes.

To permit an examination of intervention effect sizes, future studies should ensure that all patients begin the intervention at the same time in their recoveries. At minimum, future trials should be focused exclusively on sub-acute or chronic TBI populations, or sub-divide their population by time-post injury. In addition, future studies should include a control group of patients that receive standard care or use of historical control data for comparison purposes to determine whether cognitive training enhances recovery beyond that which occurs naturally without intervention. Studies involving an active control group (e.g., a group that attended educational sessions on TBI) may also reveal whether C-EE, or any routine cognitive activity in general, is required to produce behavioural effects.

Overall conclusions

In this thesis, I demonstrate the feasibility of an online cognitive training intervention for moderate-to-severe TBI patients. Modest adherence rates that varied considerably across patients were observed. Providing moderate-to-severe TBI patients with additional supports, such as daily cognitive training reminders or additional therapy to rehabilitate executive function impairments, may increase adherence rates. Nonetheless, I report high acceptability of the cognitive training program. The most persistent post-training symptoms, including fatigue and eyestrain, may be reduced, respectively, by instructing patients to fragment longer training sessions into multiple smaller bouts of training and shifting focus from the computer screen to a distant object intermittently.

In conducting limited-efficacy testing, it was also demonstrated that intervention effects were largely in the expected direction. Future, controlled trials are required to determine whether the intervention leads to significant improvements in cognitive functioning. These studies should also determine intervention effect sizes to permit sample size calculations that can inform the design of large-scale efficacy trials.

In sum, this study demonstrates that online cognitive training is a feasible and potentially efficacious intervention for moderate-to-severe TBI patients. This intervention has considerable clinical utility, given that it can be administered remotely to patients that cannot routinely visit hospitals or clinics for therapy. When considered in the context of current literature documenting the post-TBI cognitive and neural benefits of C-EE, my feasibility findings suggest that online cognitive training is a tele-rehabilitation strategy that may help promote recovery following moderate-to-severe TBI.

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Appendices

APPENDIX 1: Study Questionnaire
Sleep and concussion Questionnaire

APPENDIX 2: Acceptability Scale

APPENDIX 3: Brain HQ™ Screenshots
Homepage
Memory Homepage
Memory Game Sample

APPENDIX 1

Study Questionnaire

Sleep and Concussion Questionnaire (238) (*2 pages*)

Sleep and Concussion Questionnaire (Draft May 2013)
Catherine Wiseman-Hakes, Marie-Christine Ouellet

Name: _____ **Date:** _____

1a) Has your sleep changed *since your injury*? Yes _____ No _____

No change since before my injury (0) ____

Yes: (1: Mild change) _____

Yes: (2: Moderate change) _____

Yes (3: Severe change) _____

1b) If you have filled out this form before, has your sleep changed *since the last time you completed it? Yes* _____ *No* _____

Yes (0: My sleep is improved) _____

Yes (1: My sleep is worse) _____

No (0: My sleep is the same as last time) _____

1c) *If you answered yes*, please indicate the type of change (If you have completed this questionnaire before you may choose 2 answers)

I sleep more than before my injury (1) _____

I sleep less than before my injury (1)____

I sleep the same amount but is less restful (1) _____

I sleep better than the last time I completed this questionnaire (0) _____

2. Please rate the severity of the changes to your sleep *since your injury or the last time you completed this questionnaire*

	Not a Problem	Mild	Mod	Severe
2a) I fall asleep earlier than usual	0	1	2	3
2b) I have difficulty falling asleep:	0	1	2	3
2c) I have difficulty staying asleep:	0	1	2	3
2d) I have difficulty waking in the morning:	0	1	2	3
2e) I have a problem with waking up too early:	0	1	2	3

3. My sleep is affected by: (check all that apply:)

Nothing (0) ____ Pain (1) ____ Mood (1) ___ Feeling restless (1) ____ Worrying (1) ___Other (1)____

If other please explain: _____

4. Please rate the severity of changes to your day-time function *since your injury*

4a) I feel more tired during the day: Never (0) __ Mild (1) ___ Mod (2) ___ Severe (3) ___

4b) I need to nap during the day: Never (0) ___ Sometimes (1) ___ Often (2) ___ Always (3) ___

APPENDIX 2

Acceptability Scale

Symptom Scale for Toronto Rehab Intervention

Name: _____

Date: _____

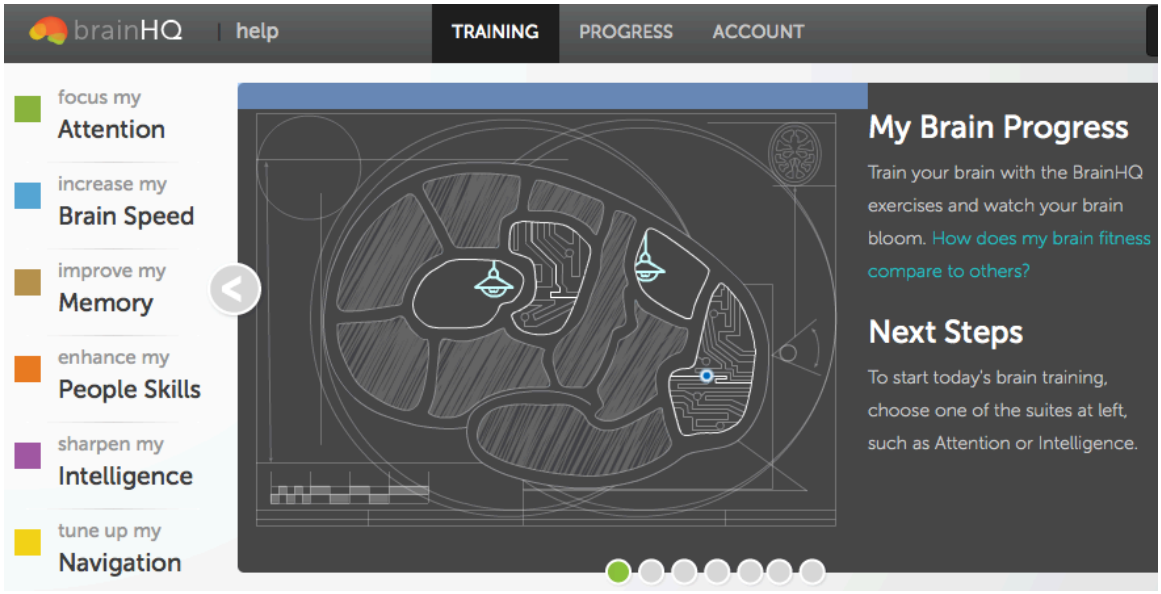
After completing the Brain HQ session, please rate the extent to which you are experiencing any of the following. Please simply compare yourself to how you felt before starting.

	Less	Same	More
Mentally sharp			
Headachy			
Tired			
Dizzy/Lightheaded			
Foggy			
Irritable			
Happy/content			
Experiencing eye strain			
Sense of accomplishment			
Able to think clearly			
Able to think fast			
Confidence in abilities			
Bored			

APPENDIX 3

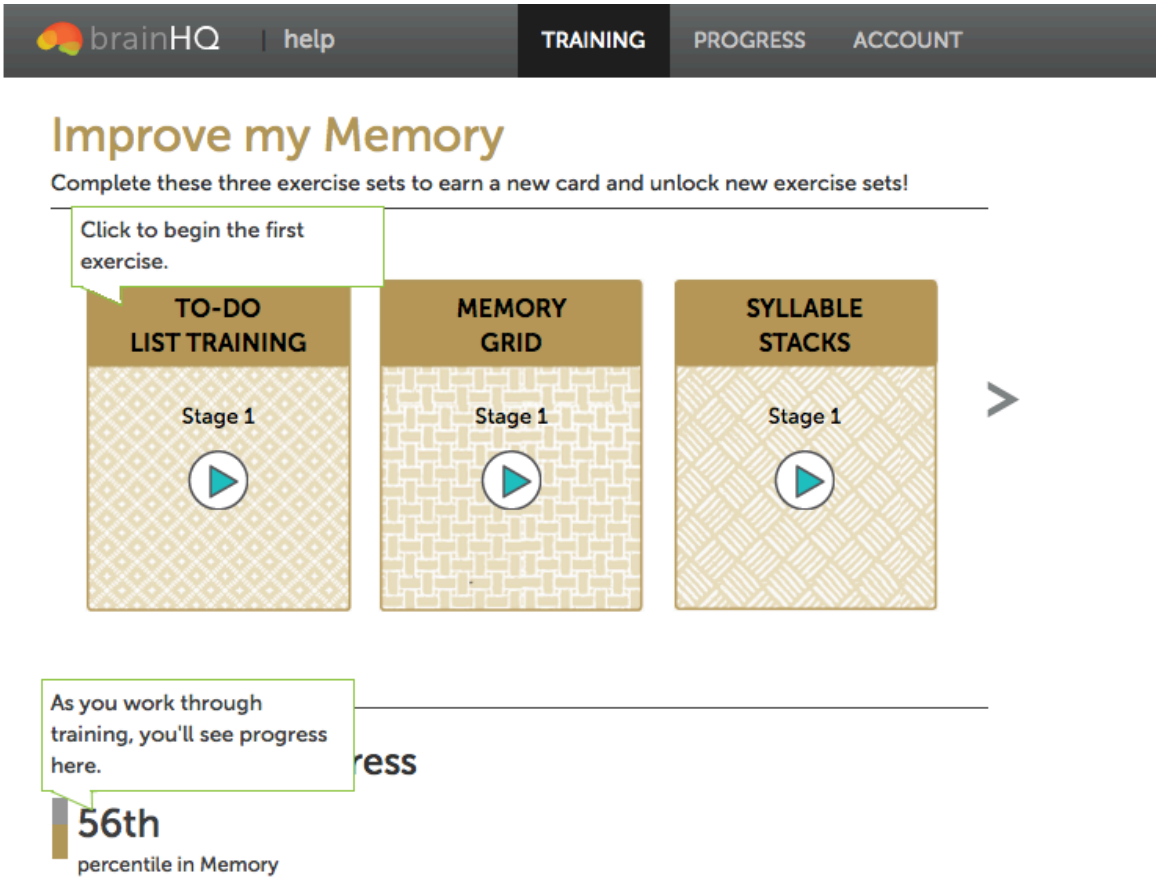
Brain HQ™ (192) Screenshots

Brain HQ™ Homepage



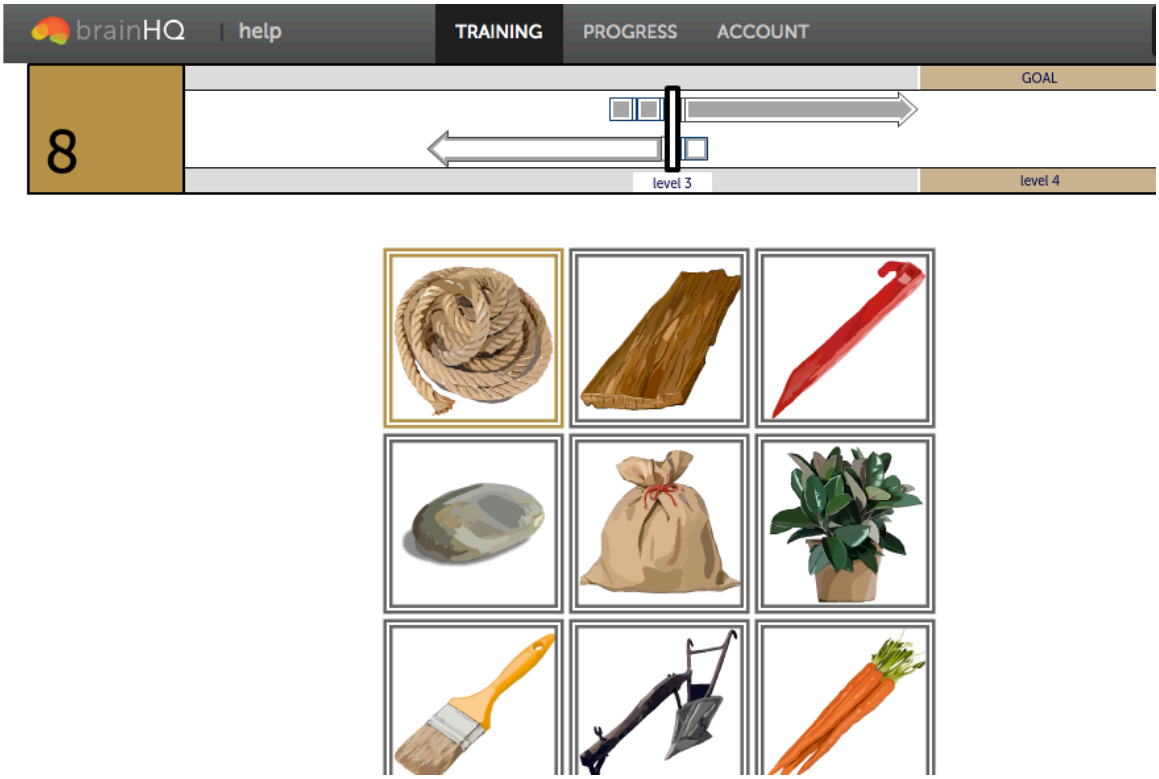
Screen shot of the Brain HQ™ homepage.

Memory Domain Homepage



Screen shot of the Brain HQ™ memory home page. The home pages for the other cognitive domains are similar to the memory home page.

Sample Memory Game



Screen shot of a memory game in the memory domain. In this particular game, patients are required to remember the spatial placement of the various items. The top left corner lists the number of trials patients are required to complete. The top-middle section of the screen provides patients with real-time feedback on their performance. Other games from the memory domain (and other cognitive domains) are set up similarly.