SUBACUTE HIPPOCAMPAL ATROPHY FOLLOWING TRAUMATIC BRAIN INJURY: RELATIONSHIP TO ENVIRONMENTAL ENRICHMENT AND VOCATIONAL OUTCOME

by

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Abstract

Preliminary novel research findings indicate that a subset of individuals with moderate to severe traumatic brain injury show bilateral hippocampal atrophy progressing beyond the acute stage post-injury. The present study proposes a novel, integrated model of neuroprotection against subacute hippocampal atrophy (i.e., atrophy occurring beyond the initial 3 months post-injury) via environmental enrichment, drawing on theoretical models and research findings from the fields of environmental enrichment, brain and cognitive reserve, and neuroplastic models of functional recovery from brain injury. **Objectives:** (a) to examine the relationship between environmental enrichment factors and subacute hippocampal atrophy and (b) to examine the relationship between subacute hippocampal atrophy and return to productivity. **Design:** Retrospective observational within-subjects. **Participants:** Patients (N=21) with moderate to severe TBI. **Measures:** Primary predictors: Self-report ratings of environmental enrichment factors (i.e., hours of cognitive, physical, and social activities, meditation/prayer, and therapy). Primary outcome: hippocampal volume change between 5 months and 24+ months post-injury based on initial and follow-up MRI scans; Brain Injury Community Rehabilitation Outcome Scales-39 (BICRO-39). **Results:** Generalized environmental enrichment (i.e., an aggregate of cognitive, physical, and social activity) was significantly negatively correlated with subacute bilateral hippocampal atrophy (p<.05). Cognitive activity was the environmental enrichment

element that accounted for the greatest degree of variance (32%) in subacute bilateral hippocampal atrophy (p<.01). Frequency of meditation/prayer was significantly negatively correlated with right hippocampal subacute atrophy (<.05) after controlling for socioeconomic status and generalized environmental enrichment. Level of education and pre-injury occupational attainment did not correlate with subacute hippocampal atrophy. **Conclusion:** Findings suggest that a fixed degree of neural reserve at the time of brain injury may not confer neuroprotection against structural pathology in the manner suggested by the present study's proposed model of neuroprotection via environmental enrichment. Instead, findings suggest that in order for environmental enrichment to positively modulate susceptibility to subacute hippocampal atrophy post-TBI, environmental enrichment exposure must occur during the subacute phase post-injury rather than prior to injury.

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Chapter 1: INTRODUCTION

Traumatic Brain Injury: State of Knowledge

Each year in Canada, 50,000 individuals sustain traumatic brain injury, resulting in 34,000 hospitalizations per year (Toronto Rehabilitation Institute, 2005). Young adults, aged 15-24 years, account for the largest proportion of traumatic brain injuries, and given the substantial and longstanding disability associated with traumatic brain injury, many of these individuals require some sort of support services throughout the remainder of their lives (National Institute of Mental Health, 1998). Most patients discharged from inpatient rehabilitation continue to experience some degree of injury-related functional difficulties that impair their ability to return to work or reintegrate into the community, resulting in significant personal and financial costs to patients, their caregivers, and society as a whole (Brooks, Lindstrom, McCray, & Whiteneck, 1995; McGregor & Pentland, 1997; Morton & Wehman, 1995). A large proportion of individuals are unable to return to paid employment outside of the home (Brooks, McKinlay, Symington, Beattie, & Campsie, 1987; Rappaport, et al., 1994; Thomsen, 1984), and of those who do return to paid employment, only a minority return to jobs at a level consistent with their pre-injury status (Green, Colella, Hebert, et al., 2008; Lewin, Marshall, & Roberts, 1979). Social isolation, interpersonal difficulties, and low community integration are also common following traumatic brain injury (Dawson & Chipman, 1995; Hoofien, Gilboa, Vakil, & Donovick, 2001; Oddy, et al., 1985). Although improvements in functioning are seen up to 10 years post-injury (Sbordone & Long, 1996), mild to moderate functional impairments persist in the long-term. Despite a growing need for effective treatments, rehabilitation methods in traumatic brain injury have developed in an ad-hoc manner and are limited by a lack a unified theory and a paucity of empirical support (Bach-Y-Rita, 2000), largely because the mechanisms underlying recovery are as yet unknown (Gordon, et al., 2006).

Research into the mechanisms underlying traumatic brain injury recovery is limited by a number of factors, including small sample sizes, high attrition rates, heterogeneity of injury type (e.g., blast injury versus motor vehicle accident) and severity, and variability in location of focal injury within the brain. Further, given the unique and fundamental rehabilitation needs of each brain-injured individual, random assignment to experimental treatment conditions is at times unfeasible. Further, given the complex nature of human experience and environments, it is

impossible to experimentally control all of the diverse environmental, motivational, and experiential variables inherent in patients' lives.

Despite these limitations, research in traumatic brain injury thus far has provided extensive evidence regarding the nature of impairments and course of recovery in traumatic brain injury (Gordon, et al., 2006). At this point in time, there is a fairly good understanding of who gets injured and how, neuropathology in the acute stages of recovery (i.e., the first 3 months post-injury), patterns and predictors of cognitive and functional recovery, and reliable and valid measures for assessing outcome (Cicerone, et al., 2005; Gordon, et al., 2006). However, less is known about neuropathology and neuroplastic mechanisms operating beyond the acute stage of recovery (i.e., beyond the initial 3 months post-injury), and researchers are only beginning to examine neuroprotective factors and environmental enrichment factors that might promote neuroplastic recovery following traumatic brain injury. An increased understanding of neuroplastic mechanisms and factors moderating brain recovery would greatly inform the development of theoretically-driven and empirically-supported treatments aimed at reducing disability and promoting brain recovery.

Novel Findings: Traumatic Brain Injury as a Progressive Condition

Conventionally, traumatic brain injury has been viewed as a non-progressive brain disorder constituting a finite event with a predictable course and stable outcome (Lezak, Howieson, & Loring, 2004). Acute injury effects such as elevated intracranial pressure, brain swelling, edema, hydrocephalus, and hematomas typically resolve or stabilize within the first six weeks post-injury (Lezak, et al., 2004). During the acute stage post-injury (i.e., the initial 3 months post-injury), necrotic processes contribute to the death and disintegration of neuronal tissue that was severely damaged at the time of impact (Lezak, et al., 2004). Neuroimaging conducted during the first few months post-injury often shows evidence of reduced global brain volume, reflecting both resolution of acute injury effects (for example, reduction in brain swelling) as well as disintegration and clearing of damaged neuronal tissue (Katz & Mills, 1999). Conventionally, following resolution of these acute injury effects and disintegration of damaged tissue, it has been assumed that the brain stabilizes and that the condition is static (Lezak, et al., 2004). The fact that cognitive and functional recovery tends to plateau for many individuals after the first year post-injury (Christensen, et al., 2008; Ruttan, Martin, Liu, Colella, & Green, 2008)

has often been viewed as supporting this conventional view of traumatic brain injury being a non-progressive condition.

However, preliminary novel research findings indicate that a significant proportion of individuals show signs of progressive brain atrophy occurring beyond the acute stage of recovery post-injury (i.e., beyond the initial 3 months post-injury) (Greenberg, Mikulis, Ng, DeSouza, & Green, 2008; Ng, et al., 2008; Trivedi, et al., 2007), suggesting that traumatic brain injury may not be a stable condition as previously thought. For example, in a Canadian sample of 14 patients presenting with moderate to severe traumatic brain injury, 10 of the subjects showed significant progressive brain atrophy on MRI between 4.5 months and 2 years post-injury, (Ng, et al., 2008), well-beyond the likely resolution of acute injury effects. Progression of atrophy was seen in both focal and diffuse brain regions in this sample, and the degree of atrophy was nearly twice that seen in healthy controls over a similar period of time (Blatter, et al., 1995). Further, while rarely highlighted in the literature, a subset of individuals with traumatic brain injury also shows progressive cognitive and functional long-term declines over a period of years post-injury (Corkin, Rosen, Sullivan, & Clegg, 1989; Himanen, et al., 2006; Millis, et al., 2001; Till, Colella, Verwegen, & Green, 2008), supporting the notion that traumatic brain injury may not be a stable condition as previously thought. Indeed, findings of subacute brain atrophy and long-term cognitive and functional declines in a subset of patients suggest that traumatic brain injury may reflect a progressive degenerative disorder rather than a stable condition (Green, 2009).

Hippocampal Vulnerability to Subacute Atrophy

Given the preliminary nature of findings regarding atrophy progression, there is some confusion in the literature regarding the terms “acute” and “subacute” when referring to time windows post-injury. For the purpose of the present study, the acute phase post-injury refers to the initial 3 months post-injury, while the subacute phase refers to any time window beginning beyond the initial 3 months post-injury. Research findings thus far indicate that subacute cerebral volume loss (occurring beyond the initial 3 months post-injury) is diffuse, affecting a wide range of brain structures in both white matter and grey matter, regardless of the location of original focal lesion (Blatter, Bigler, Gale, & et al., 1997; Gale, Johnson, Bigler, & Blatter, 1995; Greenberg, Mikulis, Ng, DeSouza, & Green, 2008; MacKenzie, et al., 2002; Ng, et al., 2008; Trivedi, et al., 2007). The hippocampus appears to be particularly vulnerable to subacute atrophy

(Arciniegas, et al., 2001; Ariza, et al., 2006), likely due to persistent neuroinflammation during the acute and subacute stages post-injury (Gentleman, et al., 2004; McCarthy, 2003), and the unique pattern of neuronal connections within the hippocampus (Duvernoy, Cattin, & Naidich, 2005). Specifically, the hippocampal formation is comprised of six architecturally distinct regions that are linked via unidirectional projections (Amaral & Witter, 1995). The connections in the hippocampus have been referred to as an Achilles' heel of sorts (McCarthy, 2003) in that damage to one region of the hippocampus can lead to downstream damage to other regions via loss of activity-dependent survival factors or over-activity of excitatory glutamatergic projections from damaged areas (McCarthy, 2003). Given the important memory functions supported by the hippocampus, subacute atrophy in this structure is likely to have significant clinical implications for functional outcome. Indeed, studies suggest that in comparison to other cognitive functions, recovery of memory functions is one of the strongest moderator of return to work following traumatic brain injury (Green, Colella, Hebert, et al., 2008), suggesting that preservation of the hippocampus is likely to be integral to the successful re-integration of brain injury survivors into the community and workforce.

Neuroplastic Mechanisms in Subacute Atrophy

In the field of neuropsychology, it was originally believed that the brain was hard-wired following development. However, it is now well-accepted that changes in neurons and their structural and functional networks continue to occur in response to learning and experience throughout the lifespan (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). Neuroplasticity refers to the brain's capability of developing, modifying, strengthening, and adjusting neural pathways in response to internal and external stimuli (Grafman, 2000; Kolb & Whishaw, 1998; Mateer & Kerns, 2000). Neuroplastic changes can be both adaptive (positive) or maladaptive (negative) for the organism.

The presence of progressive subacute atrophy in a subset of traumatic brain injury patients likely reflects the operation of a number of maladaptive neuroplastic mechanisms and a paucity of counteracting adaptive neuroplastic mechanisms. At a molecular level, a host of biochemical cascades that occur following traumatic brain injury are likely to contribute to progressive cell death and to inhibit the recovery of damaged but potentially salvageable neurons (Gentleman, et al., 2004; Schmidt, Petrovic, Ropele, Enzinger, & Fazekas, 2007). At a cellular

and network level, gliosis (i.e., proliferation of astrocytes) and the development of glial scars at injury sites inhibits reconnection or reorganization of damaged neural networks (Galvin, et al., 2000). Additionally, under-stimulation of viable tissue by afferent projections from damaged tissue may lead to structural decay of potentially salvageable networks (Robertson & Murre, 1999). At the behavioural level, drawing on Mahncke's (2006) model of negative neuroplasticity and functional loss in normal aging, some patients may engage in maladaptive behaviours following brain injury that serve to promote these negative neuroplastic mechanisms. Specifically, cognitive, emotional, and physical impairments resulting from the brain injury may limit patients' ability to engage in the same schedule of activities as they did prior to their injury, and they may tend to avoid activities that are now increasingly challenging and frustrating due to their cognitive limitations. This reduced schedule of activity and avoidance of challenging activities can result in a negatively-reinforced cycle of behavioural inactivation and avoidance leading to inactivation of critical brain networks and associated loss of function (Blake, Heiser, Caywood, & Merzenich, 2006).

Proposing a Neuroprotective Model of Environment Enrichment and Subacute Hippocampal Atrophy

Despite the ominous implications of negative neuroplasticity in traumatic brain injury, findings from the fields of environmental enrichment, brain and cognitive reserve (BCR) theory, and models of neuroplastic recovery of function, provide optimism that behavioural interventions could potentially have neuroprotective effects and might counteract negative neuroplastic mechanisms in traumatic brain injury, thus halting or hindering subacute atrophy in vulnerable patients. Indeed, evidence from epidemiology and animal studies provides extensive convergent evidence that all brain disorders, even those in which genetics play a primary role, can be modulated by environmental factors (Spires & Hannan, 2005). For example, studies demonstrate that exposure to environmental enrichment (i.e., cognitive, physical, and social stimulation) is associated with a host of positive neuroplastic changes, including increases in brain size, cortical thickness, neuron size, dendrite branching, dendrite spine density, and number of synapses per neuron (Diamond, 2001; Grossman, Churchill, Bates, Kleim, & Greenough, 2002; Kolb, 1999; Kolb & Whishaw, 1998; Nudo, Milliken, Jenkins, & Merzenich, 1996; Rosenzweig & Bennett, 1996). In addition, functional neuroplastic changes associated with experience and behaviour

include reorganization of functional cortical networks, whereby intact neuronal networks assume the functions of damaged networks (Bayona, Bitensky, & Teasell, 2005; Buonomano & Merzenich, 1998; Johansson, 2000; Pascual-Leone, et al., 2005). Further, computational modeling suggests that vulnerable neural networks can be strengthened and repaired through Hebbian learning by way of exposure to non-specific environmental stimulation and targeted stimulation of attentional processes (Robertson & Murre, 1999). Based on these findings, seminal reviews of the literature conclude that brains that have received increased stimulation, via enhanced mental and physical activity, are better able to mount neuroprotective responses against neurodegenerative processes, traumatic insults, or other forms of adult-onset neural dysfunction (Nithianantharajah & Hannan, 2009).

The purpose of the present study was to examine the relationship between environmental enrichment and subacute hippocampal atrophy following moderate to severe traumatic brain injury. Specifically, the primary objective of this study was to examine the relationship between both pre-injury and post-injury environmental enrichment factors and subacute hippocampal atrophy. Consistent with recommendations in the literature (Gordon, et al., 2006), a second objective of the present study was to tie subacute hippocampal volume changes to functional outcome, namely return to productivity. Rather than focusing on the direct relationship between environmental enrichment and functional outcome in traumatic brain injury, the focus of the present study's second objective is on the relationship between the brain and function. By focusing on the relationship between the brain and function rather than the direct relationship between environment and function, the present study aims to elucidate neuroprotective mechanisms that might prevent or hinder subacute hippocampal atrophy and to explore whether this neuroprotection impacts real-world functioning.

In order to address these objectives, an integrated, dynamic, neuroprotective model of environmental enrichment and subacute hippocampal atrophy in traumatic brain injury was created. This model draws on theoretical models and research findings from the fields of environmental enrichment (Diamond, 2001; Green, 2006; Kolb & Gibb, 1991; Will, Galani, Kelche, & Rosenzweig, 2004), brain and cognitive reserve (Nithianantharajah & Hannan, 2009; Scarmeas & Stern, 2003; Stern, 2007), and neuroplastic recovery of function following brain injury (Mahncke, Bronstone, & Merzenich, 2006; Robertson & Murre, 1999; Teasell, Bayona, Salter, Hellings, & Bitensky, 2006). Environmental enrichment in humans is conventionally

viewed as being comprised of three primary elements: cognitive, physical, and social stimulation. The integrated neuroprotective model of environmental enrichment and subacute atrophy proposed in the present study posits a novel fourth element of environmental enrichment that is only beginning to be explored in the neuroplasticity and clinical rehabilitation literature, namely spiritual practice in the form of meditation and cognitively-related activities such as prayer. This novel, integrated neuroprotective model is the foundation of the current study and serves to facilitate understanding of the complex relationships among environmental enrichment, hippocampal subacute atrophy, and functional outcome following moderate to severe traumatic brain injury.

Objectives of the Current Study

Objective 1. Examine the relationship between pre- and post-injury environmental enrichment and subacute hippocampal atrophy.

Objective 1.1. Post-injury environmental enrichment and subacute hippocampal atrophy.

Environmental enrichment refers to exposure to complex and stimulating environments that promote greater neuronal growth and connectivity as well as related improvements in functional performance (Kolb & Gibb, 1991; Mohammed, et al., 2002). No studies have yet examined the relationship between post-injury environmental enrichment factors and subacute hippocampal atrophy in humans following traumatic brain injury. Further, no studies have yet directly compared within the same study the important question of whether specific elements of environmental enrichment have differential effects on neuroplasticity in humans. Indeed, while an engaged lifestyle could promote neuroplastic recovery following brain injury, it is clinically informative to know whether it is the cognitive, physical, or social aspects of one's lifestyle that is driving increases in neuronal growth and connectivity. Given the primarily cognitive functions supported by the hippocampus (Leuner & Gould, 2010), it is proposed that cognitive elements of environmental enrichment would have the greatest impact on neuroplasticity in this structure. Indeed, comparison studies in animals have demonstrated that cognitive training has a stronger effect than physical exercise alone on increasing synaptogenesis in the hippocampus (Moser, Trommald, & Andersen, 1994) and promoting the survival of newly-generated neurons in the

hippocampus and their integration into neural networks (Kempermann & Gage, 1998, 1999). Survival and integration of newly-generated neurons are likely to support the recovery of the hippocampus following traumatic brain injury, thus hindering the progression of subacute atrophy. However, the relative importance of post-injury cognitive enrichment in averting subacute hippocampal atrophy following traumatic brain injury remains an empirical question to be addressed in the present study.

A novel aspect of environmental enrichment that has yet to be studied in traumatic brain injury includes meditation (and related cognitive activity such as prayer). Consistent with Newberg and Iverson's (2003) neuropsychological model of meditation, in the present study meditation and prayer are defined as practices of self-regulating the body and mind by engaging a specific attentional set, involving activation of the prefrontal cortex, thalamus, and hippocampus (Newberg & Iversen, 2003); these practices are a subset of those used to induce relaxation or altered states such as trance-induction techniques (Vaitl, et al., 2005). There is accumulating evidence of the benefits of meditation on brain and behaviour (Green & Turner, 2010). Meditation shows particular effects on attentional functioning (Bishop, et al., 2004; Borgaro & Prigatano, 2002; Wenk-Sormaz, 2005) and on stress regulation (Carlson, Speca, Patel, & Goodey, 2003; Kabat-Zinn, et al., 1992; Nidich, et al., 2009), two factors that could play a role in subacute atrophy of the hippocampus. It is possible that meditation, as a proposed fourth element of environmental enrichment, may offer additive neuroprotective effects against subacute atrophy by means of: (a) activating and strengthening attentional networks, specifically prefrontal cortex, thalamus, and hippocampal networks, required to support neuroplastic recovery in other brain regions (Robertson & Murre, 1999); (b) specific activation of networks within the hippocampus (Newberg & Iversen, 2003) promoting maintenance of viable networks and hindering atrophy in this region; (c) reduction of cortisol, a chemical that has toxic effects on hippocampal neurons (McCarthy, 2003) and that reduces hippocampal dendritic branching and hippocampal neurogenesis (Brown, Rush, & McEwen, 1999; Gould, Tanapat, Rydel, & Hastings, 2000; Jacobs, 2002; Vollmayr, Simonis, Weber, Gass, & Henn, 2003); and (d) enhancing cerebrovascular integrity within the hippocampus, which is closely associated with neurogenesis in this region (Palmer, Willhoite, & Gage, 2000), possibly due to enhanced glucose availability to neurons, delivery of cytoprotective factors to neurons, and improved neuroimmune surveillance (Nithianantharajah & Hannan, 2009).

Treatment intensification is an area of increasing interest and research within traumatic brain injury neurorehabilitation and involves a combination of all primary elements of environmental enrichment, including cognitive, social, and physical stimulation. Preliminary findings in the field of stroke and traumatic brain injury rehabilitation provide strong support for the efficacy of treatment intensification in promoting cognitive, motor, and functional recovery following brain injury (Cifu, Kreutzer, Kolakowsky-Hayner, Marwitz, & Englander, 2003; Heinemann, et al., 1995; Spivack, Spettell, Ellis, & Ross, 1992). No studies have yet examined the relationship between treatment intensification and neuroplastic changes following traumatic brain injury; the possibility that treatment intensity may serve to avert subacute hippocampal atrophy remains an empirical question to be addressed in the present study.

Objective 1.2. Pre-injury environmental enrichment factors and subacute hippocampal atrophy.

Exposure to higher levels of education in development and early adulthood is associated with better cognitive recovery following traumatic brain injury (Kesler, Adams, Blasey, & Bigler, 2003). Few studies have yet explored the relationship between pre-injury environmental enrichment factors, such as level of education and pre-injury occupational attainment, and subacute atrophy following traumatic brain injury. Given that lower educational attainment is associated with poorer functional recovery following traumatic brain injury (Christensen, et al., 2008; Green, Colella, Christensen, et al., 2008; Kesler, et al., 2003; Till, et al., 2008), it is likely that pre-injury environmental enrichment such as higher education or pre-injury occupational attainment may be associated with reduced risk for subacute hippocampal atrophy.

Objective 2. Examine the relationship between hippocampal atrophy and return to productivity.

A recurrent recommendation in the literature on traumatic brain injury has been to tie brain changes to real-world functional outcomes (Gordon, et al., 2006). Rather than focusing on the direct relationship between environmental enrichment and functional outcome in traumatic brain injury, the focus of the present study's second objective is on the relationship between the brain and function. By focusing on the relationship between the brain and function rather than the direct relationship between environment and function, the present study aims to elucidate

neuroprotective mechanisms that might prevent or hinder subacute hippocampal atrophy and to explore whether this neuroprotection might impact real-world functioning.

In general, there are few imaging studies that show reliable correlations between subacute hippocampal atrophy and specific functional outcomes in traumatic brain injury (Levine, et al., 2006). Broad associations have been demonstrated between subacute global brain atrophy and poorer clinical outcome (Blatter, Bigler, Gale, & et al., 1997; Jellinger, 2004; Levin, Meyers, C.A., Grossman, R.G., & Sarwar, M., 1981; MacKenzie, et al., 2002; Mellick, Gerhart, & Whiteneck, 2003; National Institute of Mental Health, 1998). Despite the importance placed on vocational rehabilitation in traumatic brain injury, only one study (van der Naalt, Hew, van Zomeren, Sluiter, & Minderhoud, 1999) explicitly examined the relationship between subacute atrophy and vocational outcome. Results indicated that focal lesions and atrophy in predominantly frontotemporal areas and posttraumatic amnesia were associated with poorer vocational outcome. Specifically, only 42% of the individuals who showed lesions and subacute atrophy had returned to work at 6-12 months post-injury, while 86% of those without lesions or subacute atrophy had returned to work at 6-12 months post-injury, highlighting a possible relationship between subacute cerebral atrophy and vocational recovery. It is proposed that subacute atrophy of the hippocampus in particular may play an important role in vocational outcome following traumatic brain injury given that hippocampal atrophy is associated with poorer memory performance and poorer recovery of memory following traumatic brain injury (Ariza, et al., 2006; Bigler, et al., 1997; Green, 2009; Serra-Grabulosa, et al., 2005; Tate & Bigler, 2000) and given that recovery of verbal memory is one of the strongest cognitive predictors of return to pre-injury productivity following traumatic brain injury (Green, Colella, Hebert, et al., 2008).

Implications of the Present Study

Identification of environmental factors associated with subacute hippocampal atrophy in traumatic brain injury would greatly inform the development of effective treatments aimed at hindering or reversing atrophy (Cicerone, et al., 2005; Gordon, et al., 2006). Specifically, by demonstrating a negative relationship between environmental enrichment and subacute atrophy, and by identifying specific elements of environmental enrichment that are most strongly related to diminished subacute hippocampal atrophy, the present study would inform the development of

targeted behavioural interventions that are grounded in theory relating to neuroplasticity and neurological recovery and that are based on empirical evidence. Inclusion of real-world outcome measures, specifically return to productivity, further increases the practical utility of these findings in clinical practice. By identifying behavioural factors at 5 months post-injury that affect subacute atrophy between 5 months and 2 years post-injury, the present study has the potential of providing valuable preliminary information about effective timing of treatment interventions, which has been identified as an area of research lacking in the field of traumatic brain injury thus far (Bayley, Teasell, Marshall, Cullen, & Colantonio, 2006; Burns, Rivara, Johansen, & Thompson, 2003; Gordon, et al., 2006). The current norm in the field of traumatic brain injury rehabilitation is to provide intensive rehabilitation during the acute stage post-injury, following which the patient is typically discharged to the community with no follow-up care (Bach-Y-Rita, 2000; Mellick, Gerhart, & Whiteneck, 2003). This tendency may well reflect the financial limitations of the healthcare system as well as the conventional notion of traumatic brain injury being a stable condition (Lezak, et al., 2004). If the present study demonstrates evidence for subacute atrophy beyond the acute stage post injury, this would highlight that for a subset of individuals at least, maintenance of treatment beyond the acute stage post injury may be warranted to prevent the progression of atrophy. Finally, by identifying environmental enrichment associated with diminished progression of atrophy following traumatic brain injury, the present study has the potential to enhance academic understanding of the mechanisms by which organic recovery occurs following brain injury and the relationship between environmental enrichment and neuroplasticity in humans.

Definition of Terms

Acute stage post-injury: For the purpose of the present study, the acute stage is defined as the initial 3 months following the traumatic brain injury.

Brain and cognitive reserve: Changes occurring in the brain, in response to life experiences, which positively modulate susceptibility to brain disorders via neuroprotective and/or compensatory mechanisms (Nithianantharajah & Hannan, 2009).

Environmental enrichment: Exposure to complex and stimulating environments that promote greater neuronal growth and connectivity and related improvements in functional performance (Kolb & Gibb, 1991; Mohammed, et al., 2002).

Meditation: Practices of self-regulating the body and mind, thereby affecting mental events by engaging a specific attentional set that involves activation of the prefrontal cortex, thalamus, and hippocampus (Newberg & Iversen, 2003); these practices are a subset of those used to induce relaxation or altered states such as trance-induction techniques (Vaitl, et al., 2005).

Neuroplasticity: The brain's capability of developing, modifying, strengthening, and adjusting neural pathways in response to external and internal stimuli (Kolb & Whishaw, 1998). In the field of neuropsychology, it was originally believed that the brain was hard-wired following development. However, it is now a well-accepted notion that neuroplastic changes continue to occur in response to learning and experience throughout the lifespan. Behaviour and experience can result in neuroplastic changes that are adaptive (positive) or maladaptive (negative) for the organism.

Prayer. Self-induction of altered or transcendental states of consciousness (Johnstone, Yoon, Rupright, & Reid-Arndt, 2009) via engagement of a specific attentional set that involves activation of the prefrontal cortex, thalamus, and hippocampus (Newberg & Iversen, 2003).

Return to productivity. For the purpose of the present study, return to productivity refers to systematic engagement in paid work, volunteer work, formal schooling, or childcare (Gordon, et al., 2006; Powell, Beckers, & Greenwood, 1998).

Subacute atrophy: Diminished volume of cerebral tissue occurring beyond the acute stage following traumatic brain injury (i.e., beyond the initial 3 months post-injury).

Chapter 2: LITERATURE REVIEW

Current Knowledge in Traumatic Brain Injury Research

Overview

History of traumatic brain injury research. Unlike some conditions, such as heart disease, stroke, or diabetes, traumatic brain injury only recently has become a specialized focus of clinical care and research (Gordon, et al., 2006). Interest and research related to traumatic brain injury began to build in the late 1970's with the founding of the National Head Injury Foundation (now known as the Brain Injury Association of America), which served to advocate for traumatic brain injury survivors. Still, in 1981, fewer than 100 research articles on traumatic brain injury were published. This number grew exponentially to 1240 publications on traumatic brain injury-related issues in 2003 (Gordon, et al., 2006). The majority of research to date has addressed basic questions about epidemiology, patterns of impairments, secondary conditions associated with traumatic brain injury, and the natural course of recovery in traumatic brain injury.

Limitations of traumatic brain injury research. Unfortunately research findings to date in the field of traumatic brain injury are limited by small sample sizes, heterogeneity of samples, methodological inconsistencies between studies, and the markedly diverse patterns of impairments and courses of recovery seen among traumatic brain injury patients (Gordon, et al., 2006). The population of traumatic brain injury survivors is a particularly heterogeneous one given the complex and variable nature of injuries to brain. For example, there is great variability in the location of primary injury, severity of injury, secondary pathologies occurring in other regions of brain, and the presence of local versus diffuse pathologies. At the present time, there is no single measure of severity of injury. Two people with severe injuries may differ in terms of type of injury, location of injury, associated cognitive and behavioural problems, and outcome. As such, recovery course and rehabilitation needs tend to be unique to each individual.

In terms of methodology, randomized control treatment studies are lacking due to unique individual rehabilitation needs, small sample sizes, difficulty controlling for complex variables in heterogeneous samples, and ethical issues regarding provision or withholding of treatments (Cicerone, et al., 2005; Gordon, et al., 2006). Further, the complexity of brain injury makes it

difficult to determine appropriate inclusion/exclusion criteria for samples as well as the length of time required to determine if an intervention is effective. Research into outcomes or treatment of traumatic brain injury has been criticized for excessive reliance on psychometric measures of outcome that have limited ecological validity or that measure functioning at too broad a level, failing to tap into the subtle changes in functioning seen in later stages of recovery (Gordon, et al., 2006; Teasell, et al., 2007).

Knowns and unknowns. Based on research in traumatic brain injury to date, much is known about who gets injured and how, neuropathological changes in the early period post-injury, cognitive and functional recovery and outcomes, and predictors of outcome (Cohadon, Richer, & Castel, 1991; Dalby & Obrzut, 1991; Greenwald, Burnett, & Miller, 2003; Jager, Weiss, Coben, & Pepe, 2000; Thurman, 2001; Thurman, Alverson, Dunn, Guerrero, & Sniezek, 1999). Despite limitations outlined previously, a great deal of research has gone into the development of reliable and valid methods of assessing outcome in traumatic brain injury (Hall, et al., 1996; Powell, Heslin, & Greenwood, 2002; Powell, et al., 1998; Sander, et al., 1997; Seale, et al., 2002; Willer, Ottenbacher, & Coad, 1994). In contrast, there is limited understanding of patient characteristics or modifiable factors that might influence brain recovery. While neuroplastic mechanisms underlying brain recovery have been researched in the stroke literature (Grafman, 2000; Nudo, Barbay, & Kleim, 2000), less attention has been placed on neuroplastic mechanisms operating in the subacute phase of traumatic brain injury recovery. Research into these areas would provide valuable information to address the primary issue of clinical relevance in traumatic brain injury, namely the development and validation of theoretically-based and empirically-supported treatment methods, which are currently lacking in the field (Cicerone, et al., 2005; Gordon, et al., 2006; Ylvisaker, Hanks, & Johnson-Greene, 2002).

Research recommendations in the literature. Primary research questions that remain to be addressed in the literature include those pertaining to evaluation of the efficacy of interventions and the development of appropriate interventions for brain-injured populations (Bach-Y-Rita, 2000; Cicerone, et al., 2005; Gordon, et al., 2006; Ylvisaker, et al., 2002). In order to develop effective treatment methods for traumatic brain injury, it is important to first identify modifiable factors and behavioural interventions that will maximize recovery and prevent decline (Cicerone, et al., 2005; National Institute of Mental Health, 1998; Ylvisaker, et al., 2002). In addition, identification of the optimal intensity of rehabilitation is an area of research that has begun to be

addressed in the stroke rehabilitation literature (Johansson, 2000), but is yet lacking in the traumatic brain injury literature (Bayley, Teasell, Marshall, Cullen, & Colantonio, 2006; Burns, Rivara, Johansen, & Thompson, 2003). In particular, there are calls in the literature for research into the nature and time of rehabilitation, grounded in state of the art neuroimaging (Robertson, 2008), research into the mechanisms that underlie recovery versus decline following traumatic brain injury, and research tying functional changes to physical change in order to inform the development of treatments (Gordon, et al., 2006). As stated by Levine and colleagues (2006), the "mechanisms governing brain damage effects, including their trajectory over the recovery process, their rehabilitation and their high variability across traumatic brain injury patients…are not well understood". Researchers (Cicerone, 2004; Gordon, 2006; Ylvisaker, 2002) have also provided recommendations regarding the methodology of future research related to traumatic brain injury. Firstly, studies should incorporate both neuropsychological and real-world outcome measures that have demonstrated ecological validity, that tap into variety of specific domains of real-world functioning, and that are sensitive to the subtle changes in functioning seen in later stages of recovery (Gordon, et al., 2006).

Disability, Epidemiology, and Causes of Traumatic Brain Injury

Traumatic brain injury is the leading cause of death and disability for people under 40 years of age in Canada and the United States (Gennarelli, et al., 1994; Toronto Rehabilitation Institute, 2005), and it is the most common cause of brain damage in children & young adults (Grady, et al., 2002; Thurman, Alverson, Dunn, Guerrero, & Sniezek, 1999). In Canada, incidence of traumatic brain injury is estimated to be approximately 150:100,000 with 50,000 individuals in Canada sustaining traumatic brain injury per year on average (Toronto Rehabilitation Institute, 2005). Traumatic brain injury accounts for 34,000 hospitalizations in Canada each year. The vast majority (90%) of those hospitalized are diagnosed with moderate to severe traumatic brain injury; of those hospitalized, the annual mortality rate is 13,000. Those who survive traumatic brain injury tend to be young adults, aged 15-24, the greatest proportion of whom are left permanently or partially disabled (National Institute of Mental Health, 1998). In the majority of cases, traumatic brain injury results in significant and lifelong problems with interpersonal, emotional, and cognitive functioning. These difficulties often interfere with the individual's ability to return to work or reintegrate into the community, resulting in significant

personal and financial costs to patients, their caregivers, and society as a whole (Brooks, Lindstrom, McCray, & Whiteneck, 1995; McGregor & Pentland, 1997; Morton & Wehman, 1995).

According to the National Institute of Health's Consensus Statement (1998), falls are the most frequent cause of traumatic brain injuries overall (28%), particularly in infants, young children, and the elderly. Risk factors for fall-related traumatic brain injuries in the elderly include alcohol use, medication effects, and osteoporosis. Motor vehicle accidents are the second most common cause of traumatic brain injury, particularly severe traumatic brain injury, and account for 20% of all traumatic brain injuries in the general population. Violence-related incidents account for approximately 20% of all traumatic brain injuries and are almost equally divided between firearm and non-firearm related assaults. For active military personnel in war zones, blasts are the leading cause of traumatic brain injury (Salazar, Zitnay, Warden, & Schwab, 2000). Alcohol is associated with half of all traumatic brain injuries, either in the person causing the injury or the person who is injured (National Institute of Mental Health, 1998). Other factors associated with traumatic brain injury include residence in urban centres as opposed to rural areas, lower socioeconomic status, unemployment, and lower education level (Cohadon, Richer, & Castel, 1991).

Cognitive Recovery

Cognitive impairments following traumatic brain injury can occur singly or in combination and are variable in their effects on individuals due to heterogeneity in injury type, severity, or location. The pattern of cognitive deficits may also change in severity and presentation over time. For most individuals, speed of processing and memory tend to be the areas that are most impaired over the long-term (Christensen, et al., 2008; Ruttan, et al., 2008). Impairments in attention, expressive language, visual perception, and executive functions, such as problem solving, abstract reasoning, insight, judgment, planning, and organization are also common following injury (Green, et al., 2006; Lezak, et al., 2004).

There is marked variability between individuals in patterns of cognitive recovery following traumatic brain injury depending on a number of factors, most notably, the severity and location of injuries to the brain. Complete return to premorbid functioning is extremely rare; the vast majority of survivors of traumatic brain injury present with some form of lasting

impairment for which they need to learn to compensate (Conzen, et al., 1992; Hanks, Rosenthal, Novack, & et al., 2001; Himanen, et al., 2006; Hoofien, Gilboa, Vakil, & Donovick, 2001; Ruttan, Martin, Liu, Colella, & Green, 2008). The greatest rate of recovery tends to be in the first 5 months post-injury (Christensen, et al., 2008; Chu, et al., 2007; Dikmen, Reitan, & Temkin, 1983; Spikman, Timmerman, Zomeren van, & Deelman, 1999). The point of plateau of cognitive recovery varies across studies and individuals, but cognitive recovery typically plateaus between 6 to 18 months post-injury for most individuals (Ruttan, Martin, Liu, Colella, & Green, 2008). Some individuals continue to show improvements in cognitive functioning beyond the initial two years post-injury, albeit at a slower pace (Millis, et al., 2001; Olver, Ponsford, & Curran, 1996; Van Zomeren & Deelman, 1978). In addition, as previously mentioned, a small but significant subset of individuals show long-term declines in cognitive functioning despite an initial period of cognitive recovery (Himanen, et al., 2006; Till, Colella, Verwegen, & Green, 2008).

In terms of specific cognitive functions, traumatic brain injury tends to impact declarative memory (memory for factual information), and explicit memory (memory involving conscious learning) (Ruttan, et al., 2008). These deficits tend to be associated with damage to the medial temporal lobe structures, particularly the hippocampus, often as the result of secondary anoxic brain injury following traumatic brain injury (Ruff, Young, Guatille, & et al., 1991). Damage to the frontal lobe, which is common in traumatic brain injury, can impair one's ability to implement strategies to aid encoding and retrieval of new information, also contributing to poor memory performance (Stuss & Gow, 1992).

Primary predictors of cognitive recovery include age at injury, level of education, and history of substance abuse. In particular, older age at the time of injury is associated with poorer cognitive outcome and slower recovery rates, particularly recovery of processing speed (Himanen, et al., 2006; Millis, et al., 2001). Lower education and cognitive inactivity are also associated with a slower rate of cognitive recovery post-injury (Chu, et al., 2007; Kesler, et al., 2003; Salmond, Menon, Chatfield, Pickard, & Sahakian, 2006). Finally, history of substance abuse is also associated with poorer cognitive recovery post-injury (Till, et al., 2008).

Preliminary evidence suggests that intensification of treatment in the early stages post-injury may promote recovery and protect against cognitive and functional decline (Shiel, et al., 2001; Zhu, Poon, Chan, & Chan, 2001). In particular, a recent study showed that a greater

number of therapy hours at 4.5 months post-injury was associated with a decreased cognitive decline after 12 months post-injury in traumatic brain injured individuals (Till, et al., 2008). These preliminary findings provide hope that behavioural interventions, such as intensification of therapy, may support cognitive and neuroplastic recovery in the later stages following traumatic brain injury.

Functional Recovery

Issues in functional recovery research. In addition to the general limitations of traumatic brain injury research, such as heterogeneous samples and lack of prospective studies, functional outcome studies in traumatic brain injury are further limited by issues related to measurement of outcome. One of the strongest criticisms of outcome studies in traumatic brain injury is the reliance primarily on psychometric or neuropsychological measures of outcome to the frequent neglect of assessing real-world daily functioning (Gordon, et al., 2006; Ownsworth & McKenna, 2004). While neuropsychological outcomes have been investigated extensively, less attention has been paid to functional vocational outcomes (Ownsworth & McKenna, 2004). Some of the most widely-used measures of functional outcome following traumatic brain injury include the Barthel Index (Mahoney & Barthel, 1965) and the Functional Independence Measure (Uniform Data System for Medical Rehabilitation, 1993), which are broad measures of activities of daily living. These measures are limited by a ceiling effect, in that they are sensitive only to gross impairments in functioning and lack sensitivity to subtle impairments that may be present in the later stages of recovery (Powell, et al., 1998). Other commonly-used measures of global outcome in traumatic brain injury are the Glasgow Outcome Scale (Jennett, Snoek, Bond, & Brooks, 1981) and the Disability Rating Scale (Rappaport, Hall, Hopkins, Belleza, & Cope, 1994), which tap into global outcomes and lack sensitivity to different qualitative aspects of change.

One measure that is sensitive to a range of functional areas as well as subtle changes in functioning is the Community Integration Questionnaire (Willer, Ottenbacher, & Coad, 1994). The CIQ is a brief, 15-item inventory that assesses three factorally-determined dimensions of function post-brain injury, including home integration, social integration, and productive activities. It has good test-retest reliability (Willer, et al., 1994) and high inter-rater reliability between patients' self-report and caregivers' reports (Sander, et al., 1997). Limitations of the CIQ include a substantial ceiling effect on the Social and Home integration scales (Hall, et al.,

1996) and a lack of internal consistency and irregularities of distribution on the Productivity scale (Corrigan & Deming, 1995), suggesting that it should not be used independently as a measure of an individual's functioning.

A measure of functional outcome that overcomes many of the limitations of the scales outlined above is the Brain Injury Community Rehabilitation Outcome Scales-39 (Powell, et al., 1998). The BICRO-39 assesses eight factorally-determined dimensions of functioning, rated in terms of how much assistance is required to perform activities as well as frequency of engagement in certain activities of daily living. These domains include personal care, mobility, self-organization, contact with partner/own children, contact with parents/siblings, socializing, productive employment, and psychological well-being. The BICRO-39 provides a multidimensional assessment of functioning in people with acquired brain injury living in community settings and was designed specifically for assessment of change in functioning in both individuals and groups. Studies have demonstrated that the BICRO-39 has high content validity, good test retest reliability, and good construct validity, as well as good inter-rater reliability between patient and caregiver, supporting the validity of the patient's self-report (Powell, et al., 1998). All eight scales except the contact with parents/siblings scale and the contact with partner/child scales are sensitive to changes over time after acquired brain injury (Powell, et al., 1998). In contrast to the CIQ, the BICRO-39 scales were designed to minimize subjectivity by making items specific and concrete and by making rating criteria explicit in terms of frequencies or level of help required. While the CIQ social integration scale taps into the nature of social activities and relationships, the BICRO-39 socializing scale focuses on the frequency of contact with different groups of people.

Functional Outcome Findings. Many traumatic brain injury survivors show a general plateau in functioning after the first few years post-injury. However, some individuals show ongoing improvements in the long-term, and a small but significant proportion of traumatic brain injury survivors show gradual declines (Oddy, Coughlan, Tyerman, & Jenkins, 1985; Olver, Ponsford, & Curran, 1996). In general, while some improvements in functioning may be expected beyond the initial year post-injury, most studies demonstrate chronic functional difficulties in a wide range of domains, including independence in activities of daily living, social integration, productivity, and mobility. For example, in a sample of 95 adults with traumatic brain injury, 40% of individuals required supervision or assistance with activities of

daily living during the initial year post injury, and by the fifth year post-injury, only 25% of the sample had achieved full independence in their daily living activities (Corrigan & Deming, 1995). In a sample of 20 traumatic brain injury survivors, caregiver ratings suggested gradual improvements in cognition, mobility, behavioural regulation, social integration, and productivity between two years and 10 years post-injury (Sbordone & Long, 1996). However, despite improvements in functioning, caregivers in this sample still described mild to moderate impairments in patients' level of functioning in these areas at 10 years post-injury.

Return to productivity. Vocational outcome (i.e., return to homemaking, childcare, schooling, or vocational pursuits) following traumatic brain injury is an increasingly active area of research since its recent inclusion as an explicit component of rehabilitation in the World Health Organization's *International Classification of Functioning, Disability, and Health* (Shames, Treger, Ring, & Giaquinto, 2007). Vocational outcome is an important outcome variable of interest to researchers and clinicians for a number of reasons. Firstly, Western society places high value on work and productivity (Prigatano, 1999), and loss of employment can negatively affect an individual's sense of identity, autonomy, and psychological well-being (Bogan, Livingston, Parry-Jones, Buston, & Wood, 1997; Prigatano, 1989). Further, loss of employment due to disability following traumatic brain injury can lead to social isolation, financial strain, and caregiver burden (Dawson & Chipman, 1995; D. Hoofien, Gilboa, Vakil, & Donovick, 2001; Oddy, et al., 1985). Return to paid employment following injury often increases the opportunity for social interaction and enhances self-esteem (McCrimmon & Oddy, 2006; Wehman, Targett, West, & Kregel, 2005). From a research perspective, return to work is an outcome variable that can be assessed more reliably than many other subjective functional outcomes, such as quality of life, level of caregiver burden, and community integration (Sherer, Madison, & Hannay, 2000). Finally, given that traumatic brain injury cases are often handled within an insurance or medicolegal context, it is important to have clear and agreed-upon guidelines for predicting future vocational functioning following traumatic brain injury (Sherer, et al., 2000).

Given limitations such as heterogeneity of samples and injury location and severity, findings regarding vocational productivity following traumatic brain injury are variable across studies. Some prospective studies demonstrate improvements in productivity with increasing time since injury. For example, in a sample of 95 adults with traumatic brain injury, the

percentage of individuals who had returned to paid employment rose from 23% at 2 to 3 years post-injury to 56% at 4 to 5 years post-injury (Corrigan & Deming, 1995). In contrast to this finding, the majority of outcome studies demonstrate that following moderate to severe traumatic brain injury, fewer than half of individuals return to full-time, paid employment (Brooks, et al., 1987; Rappaport, et al., 1994; Thomsen, 1984), and only a small proportion return to the same level of productivity that they achieved prior to their injury, both in the early and later stages of recovery (Asikainen, Kaste, & Sarna, 1996; Dawson & Chipman, 1995; Green, Colella, Hebert, et al., 2008; Hoofien, et al., 2001; Paniak, Shore, Rourke, Finlayson, & Moustacalis, 1992).

During the first few years post injury, less than a third of individuals return to productivity at a level of difficulty, prestige, or pay that is commensurate with pre-injury levels (Asikainen, Kaste, & Sarna, 1996; Corrigan & Deming, 1995; Green, Colella, Hebert, et al., 2008; Ponsford, Olver, Curran, & Ng, 1995). For example, in a Canadian rehabilitation outpatient sample of 63 patients presenting with moderate to severe traumatic brain injury, at 12 months post-injury, only 30% of the sample (19 participants) had returned to their premorbid level of productivity in terms of paid employment, enrolment in formal educational programs, and/or homemaking roles (Green, Colella, Hebert, et al., 2008). In a Canadian hospital-based sample of 57 patients presenting with severe traumatic brain injury, at 2 years post injury, 42% had returned to paid employment, but only 4% of the sample had returned to jobs at a level of status, difficulty, and pay that was commensurate with pre-injury levels (Paniak, Shore, Rourke, Finlayson, & Moustacalis, 1992).

At later stages of recovery (i.e., greater than 5 years post-injury) following moderate to severe traumatic brain injury, less than half of individuals return to productive employment. For example, in a Canadian community sample of traumatic brain injury survivors, only 25% of the sample had returned to some sort of employment by 13 years post-injury, and just 17% of the sample had returned to paid positions (Dawson & Chipman, 1995). Similarly, in a sample of 76 patients with severe traumatic brain injury, at 14 years post-injury, 61% of the sample was employed, but only 24% of the sample was working in paid positions (Hoofien, et al., 2001). Worth noting is that no difference in measures of global intellectual functioning was found between the employed and unemployed groups in that study.

Predictors of return to productivity. Research suggests that pre-injury predictors of vocational outcome include pre-injury occupational status (Felmingham, 2001; Gollaher, 1998; Keyser-Marcus, 2002) and socioeconomic status (Hoofien, 2002). Injury variables predictive of vocational outcome include: injury severity (Wagner, 2002); duration of posttraumatic amnesia or loss of consciousness (Cattelani, Tanzi, Lombardi, & et al., 2002; Kreutzer, 2003; Sherer, et al., 2002); length of rehabilitation inpatient stay (Keyser-Marcus, 2002); and functional status at discharge (Fleming, Tooth, Hassell, & et al., 1999; Keyser-Marcus, 2002). Cognitive variables that most strongly predict vocational outcome include memory functioning and executive functioning (Green, Colella, Hebert, et al., 2008; Ownsworth & McKenna, 2004). Metacognitive and emotional variables that have been shown to be predictive of vocational outcome following traumatic brain injury include degree and history of psychopathology, pre-injury substance abuse, and emotional distress (Cattelani, 2002; Felmingham, 2001; Franulic, 2004; Kendall, 2003; Sherer, Bergloff, High, et al., 1999; Wagner, 2002). Finally, while social and environmental variables have been less studied, preliminary research suggests that participation in vocational rehabilitation is related to employment stability following traumatic brain injury (Kreutzer, 2003).

In summary, moderate to severe traumatic brain injury is associated with a host of long-term, functional impairments for the majority of individuals, with a small but significant proportion of individuals showing incremental recovery or gradual decline over the long-term. Low rates of employment are common post- injury, ranging from 25-61% at long-term follow up. The chronic and yet dynamic nature of functional impairments over the long-term suggests the need for long-term maintenance treatment beyond the typical acute rehabilitation care offered to patients, focused specifically on vocational rehabilitation and supported employment. Studies tying neuroimaging findings and neuroplastic changes to functional recovery, particularly vocational outcome, are lacking.

Treatment Methods and Efficacy

The overall goals of rehabilitation are to improve patient and family quality of life, to maximize functional and financial independence, and to reduce the need for care by the means of facilitating community re-integration, return to productivity, and psychosocial adjustment (Powell, et al., 1998). Seminal reviews of the state of traumatic brain injury rehabilitation

(Carney, et al., 1999; Chesnut, et al., 1999; Cicerone, et al., 2005; Gordon, et al., 2006; National Institute of Mental Health, 1998; Teasell, et al., 2007) reveal controversy within the field of brain injury rehabilitation. This controversy is the result of a number of factors. Primarily, the field of cognitive rehabilitation lacks an accepted theoretical framework, and the efficacy of cognitive rehabilitation lacks empirical support, both in terms of psychometric outcomes as well as real-world functional outcomes (Gordon, et al., 2006). Clinical neurorehabilitation has developed in an improvised manner that has lacked grounding in theoretically or empirically based methodologies (Bach-Y-Rita, 2000; Gordon, et al., 2006; Schallert, et al., 2000). In addition, available studies of cognitive rehabilitation efficacy tend to be methodologically weak and show conflicting results, partially due to the heterogeneity of patient samples and injuries as well as small sample sizes. Given the absence of empirical support or clear theoretical frameworks, the field of cognitive rehabilitation lacks standards of practice that are agreed upon by various researchers and practitioners.

Clinical studies have provided support for the efficacy of comprehensive-holistic rehabilitation programmes in improving community functioning following traumatic brain injury; however, methodological limitations of these studies limit the conclusions that can be made about the mechanisms underlying the programs or specific elements of the programs that most strongly contribute to recovery (Cicerone, 2004; Gordon, et al., 2006). Some controlled studies have demonstrated the effectiveness of specific interventions aimed at improving attention (Fasotti, Kovacs, Eling, & et al., 2000; Sohlberg, 2000), mild memory impairment (Berg, Koning Haanstra, & Deelman, 1991; Kaschel, 2002; Milders, Berg, & Deelman, 1995; Schmitter-Edgecombe, 1995), and executive functions (Cicerone, et al., 2005; Levine, et al., 2000). Despite the fact that memory deficits are among the most common deficits seen following traumatic brain injury and may cause the greatest disruption in real-world functioning (Cicerone, et al., 2005), few controlled studies have examined the efficacy of rehabilitation strategies aimed specifically at improving memory functioning post-injury. Overall, comprehensive reviews of the efficacy of cognitive rehabilitation suggest there is currently a paucity of studies/evidence to show that cognitive rehabilitation strategies result in significant lasting improvements in cognitive functions above and beyond those seen in the natural course of recovery (Carney, et al., 1999).

Traditional rehabilitation paradigm. The traditional approach to cognitive rehabilitation that dominated clinical work from the 1970s through to the 1990s focused on training and exercising discreet cognitive functions post traumatic brain injury, with the aim of strengthening these functions and then generalizing these skills from clinic-based tasks to real-world tasks (Ownsworth & McKenna, 2004). However, the efficacy of this traditional approach to cognitive rehabilitation has not been supported by research and is inconsistent with theoretical and empirical advances within the field of cognitive science and learning. Based on (a) the lack efficacy studies supporting the traditional cognitive rehabilitation paradigm, (b) theoretical and empirical advances in cognitive science, and (c) examination of developments being made in treatments in parallel populations, such as developmental disabilities, learning disabilities, and attention-deficit/hyperactivity disorder, the Joint Committee on Interprofessional Relationships for the American Speech, Language and Hearing Association (ASHA) and Division 40 (Neuropsychology) of the American Psychological Association (APA) have developed an alternative "contextualized" rehabilitation paradigm for the treatment of traumatic brain injury (Ylvisaker, Hanks, & Johnson-Greene, 2002). Rather than addressing underlying cognitive impairments directly, the primary focus of the contextualized paradigm involves addressing functional difficulties first, teaching the traumatic brain injured patient new ways of overcoming obstacles in their daily functioning. In order to clarify the nature of the contextualized paradigm of cognitive rehabilitation, the following definitions related to disability and rehabilitation are provided (Powell, et al., 1998). Impairment refers to the underlying damage to psychological, physiological, or anatomical structures. Disability refers to a reduction in ability to perform functional activities of everyday life in a normal manner. Handicap refers to a reduction in participation in key roles, such as social, familial, educational, or vocational roles (e.g., loss of job due to communication or memory impairments).

Within the traditional rehabilitation paradigm, the focus of treatment is on improving underlying neuropsychological deficits. If this fails, then compensatory strategies may be implemented to overcome permanent impairments in specific cognitive functions. The traditional paradigm holds that specific cognitive processes, such as memory or attention, can be strengthened individually through engagement in specific cognitive exercises within a clinical setting. Once these specific cognitive functions have been strengthened, they can then be applied to improve aspects of the individual's daily functioning in real-world situations. As mentioned

previously, there is only limited research to support the efficacy of these strategies in improving individuals' level of real-world functioning, in terms of community re-integration or return to productivity (Ylvisaker, et al., 2002).

Contextualized rehabilitation paradigm. In contrast to the traditional paradigm, the framework of the contextualized paradigm of cognitive rehabilitation proposed by Ylvisaker and colleagues (2002) is grounded in a wide range of activities within the patient's real life outside of the clinical setting. The primary focus of the contextualized paradigm is on reduction of handicap (i.e., increased participation in life roles), reduction of disability (increasing functional activity), and lastly, amelioration of underlying neuropathological and cognitive impairments. Treatment within the contextualized paradigm of cognitive rehabilitation is primarily focused on practicing functional tasks within the context of the patient's real-life demands outside of the clinic setting. Learning or relearning of skills is always embedded in real-life contexts, and the primary goal of learning is to reduce the patient's level of handicap or disability while not necessarily aiming to reduce underlying cognitive deficits. The contextualized paradigm can be viewed as an inversion of the traditional hierarchy of cognitive rehabilitation, in that the initial aspect of treatment focuses on handicap-oriented interventions (e.g., modifying the patient's daily routine at home in ways that allow them to maintain their pre-injury roles within relationships and at work). Within the contextualized paradigm, amelioration of underlying cognitive deficits is not directly addressed as a primary focus of treatment. However, with repeated successful implementation of compensatory strategies within real-life situations (such as using memory books to aid recall in work situations, or using word finding techniques in daily social interactions), these strategies become over-learned, less consciously-employed, and internalized, and in this way, the underlying cognitive impairments themselves may be reduced.

Developments within the field of cognitive science support the notion that engaging in contextualized, repeated, supported behaviours leads indirectly to amelioration of specific cognitive functions as well as improved daily functioning in various populations. This paradigm shift of contextual learning has occurred largely within the field of vocational rehabilitation; supported employment services is one of the interventions for traumatic brain injury that is most strongly supported by empirical findings (Chesnut, 1999). Theoretical and empirical developments within learning and cognition suggest that cognitive development is characterized by a systematic pattern of growth from (a) concrete to abstract thinking (i.e., context-bound to

contextless skills), (b) real-life, concrete routines to more abstract organizing schemes, and (c) involuntary, nonstrategic processing to more controlled, strategic processing (Flavell, Miller, & Miller, 2001). Indeed, cognitive growth in children and developmentally-delayed adults has been shown to be maximally achieved by interventions that focus on learning in concrete, real-life situations that are meaningful to the individual, and gradually assisting the individual in a supported way, to apply these learnings to an increasingly widening range of situations (Horner, Dunlap, & Koegel, 1988; Kavale, 1999; Koegel, Koegel, & Dunlap, 1997). The majority of published studies examining cognitive rehabilitation efficacy has examined the traditional approach to cognitive rehabilitation. At the present time, there is little direct empirical evidence to support the efficacy of the contextualized model of cognitive rehabilitation.

Recommendations for empirically-based neurorehabilitation research. Researchers have provided the following recommendations for future research into traumatic brain injury rehabilitation efficacy: (a) real-world outcome measures, such as measures of vocational outcome post-treatment, should be incorporated; (b) analyses of outcome should control for demographic and injury characteristics that affect outcome, such as injury severity; and (c) the outcome should be measured over substantial periods of time, such as years post-injury (Cicerone, Mott, T., Azulay, J., et al. , 2004; Gordon, et al., 2006; Ylvisaker, et al., 2002). Seminal reviews of the state of the science in traumatic brain injury research suggest that to optimize rehabilitation for traumatic brain injury, therapies should be varied and must not be repetitive (Nudo, Barbay, & Kleim, 2000) and should involve the acquisition of new skills in order to drive changes in functional neural maps. Given that in some cases, intensive therapy during the acute phase of recovery can have deleterious effects on the brain following injury (Johansson, 2000), review authors highlight the importance of identifying the optimal intensity and timing of rehabilitation (Gordon, et al., 2006). Some authors caution that early interventions may exacerbate damage to vulnerable brain tissue and suggest that extended duration of therapy beyond acute phase may be warranted (Bach-Y-Rita, 2000). Finally, cognitive rehabilitation researchers have recommended that rehabilitation strategies should be embedded in real-life situations and contexts in order to maximize far transfer of learned skills and to impact real-life functioning (Mateer & Sira, 2006; Murre & Robertson, 1999).

Acute Neuropathology in Traumatic Brain Injury

Severity Specifiers in Traumatic Brain Injury

Level of severity of traumatic brain injury is typically measured by length of posttraumatic amnesia (PTA), depth and duration of coma, and presence of neurological signs, such as focal brain contusions or other damage revealed by neuroimaging. Posttraumatic amnesia refers to loss of memory following head injury and is the period of time between sustaining a head injury and regaining continuous day-to-day memory for events. This condition typically lasts approximately four times the duration of the coma (Katz & Mills, 1999; Prigatano, et al., 1998). Depth of coma is usually measured immediately following resuscitation using the Glasgow Coma Scale (Jennett, et al., 1981). Acute care length of stay is another measure of injury severity that has been shown to predict outcome following traumatic brain injury (Green, Colella, Christensen, et al., 2008).

Mechanisms of Primary Injury

In traumatic brain injury, damage to the brain is a function of more than the magnitude of force applied to the skull. Pathophysiology in traumatic brain injury varies as a function of a number of factors, including: penetration or non-penetration of brain tissue; movement or lack of movement of the skull; linear and rotational inertia of brain tissue in relation to skull movement; destructive events secondary to the initial trauma, including hemorrhage, swelling, and hypoxia; and complicating injuries elsewhere in the body (Graham, Adams, Nicoll, Maxwell, & Gennarelli, 1995). Brain areas most vulnerable to initial damage include the orbitofrontal, medial- and anterior-temporal, and dorsolateral frontal areas (Graham, et al., 1995; Katz & Mills, 1999). In injuries involving a blow to the head, damage is caused by both the direct impact of the missile and by shock waves and pressure effects, which combine to produce focal and diffuse damage within the brain. Dangers following impact include hypotension, decreased blood volume, contusions, hematomas (areas of bleeding within the brain), infection, and seizures; a combination of these acute secondary effects occurs in up to 80% of traumatic brain injury patients during the first 24 hours post-injury (Greenwald, Burnett, & Miller, 2003; Lezak, et al., 2004).

Traumatic brain injury can involve either acceleration or non-acceleration injuries. Non-acceleration injuries are relatively rare and occur when the stationary head is struck by a moving object. Such non-acceleration injuries tend to cause less severe brain damage than acceleration injuries (Pang, 1985). Acceleration (or acceleration-deceleration) injuries occur when the movement of the skull and movement of the brain itself contribute to destructive forces within the brain. While in most cases, the moving head strikes an object (such as a car windshield), serious damage can occur with no contact whatsoever, as in the case of whiplash injuries. The brain is not affixed to the inner surface of the skull. As such, when a stationary skull is suddenly accelerated, or a moving skull is suddenly decelerated, the brain compresses against the skull at one side or the other, depending on the direction of the force. When acceleration of the skull results from an external blow, the compression of brain tissue and focal damage at the site of impact is referred to as a coup injury (Drew & Drew, 2004). As the brain rebounds backward striking the opposite side of the skull, compression and focal damage are caused to the opposite side of the brain. This is referred to as a contrecoup injury.

An aspect of acceleration/deceleration injuries that causes the most pervasive damage is the impact of rotational acceleration forces on the brain (Holbourn, 1943). This may account for many of the common sites of focal injury and also for the diffuse injury to axons throughout the brain following most moderate to severe head injuries (Besenski, 2002; Fujiwara, et al., 1993; Higgens & Unterharnscheidt, 1969). When the movement of the skull is abruptly halted by an impact with an external object (e.g., a windshield), the brain continues to rotate within the skull. These rotational forces can cause the brain to tear against bony prominences on the inner surface of the skull, such as the sharp wings of the sphenoid bone separating the frontal and temporal cortices and the crista galli separating the right from left ventromedial prefrontal cortex (Besenski, 2002). In addition, differential movement of brain tissue of varying density can lead to tearing and shearing of axons throughout the brain and particularly at intersections between brain areas of varying density (Besenski, 2002; Kilbourne, et al., 2009).

Diffuse Axonal Injury

Diffuse pathology in traumatic brain injury is characterized by diffuse microscopic damage to axons throughout the brain, particularly at the intersections between grey matter and white matter in cortical and subcortical areas (Adams, et al., 1989). The initial cause of damage

in diffuse axonal injury is the tearing of axons during acceleration injuries. As previously mentioned, acceleration, particularly rotational acceleration, causes axonal shearing as the movement of the brain lags relative to the skull. In addition, when the brain is accelerated, brain tissues of differing densities and distances from the axis of rotation slide over one another, stretching axons that traverse junctions between the areas of different density, especially grey-white matter junctions (Levine, et al., 2006; Meythaler, Peduzzi, Eleftheriou, & Novack, 2001). Two thirds of diffuse axonal injury lesions occur in areas where grey and white matter meet (Hammoud & Wasserman, 2002; Levine, et al., 2006). Axons are normally elastic, but when rapidly stretched they become brittle, and the axonal cytoskeleton can be broken. Three types of axonal strain can occur, including compressive (pushing together), tensile (pulling apart), and shearing (deformation parallel to adjacent layers), with tensile and shearing strains contributing most to diffuse axonal injury (Adams, et al., 1989).

Diffuse axonal injury is characterized by eventual axonal separation, in which the axon is torn at the site of stretch and the part distal to the tear degrades. Axonal injury was previously believed to be due primarily to mechanical forces; however, it is now understood that secondary biochemical processes are largely responsible for the damage to axons (Arundine, Aarts, Lau, & Tymianski, 2004; Wolf, Stys, Lusardi, Meaney, & Smith, 2001). These biochemical cascades occur in response to the primary injury and take place hours to days after the initial injury. Over the first few days post-injury, axonal transport continues up to the point of the tear in the cytoskeleton, but no further, leading to a buildup of transport products, local swelling and degradation. As well, distal to the swellings, axons and myelin degenerate (Cervos-Navarro & Lafuente, 1991). During the first weeks post-injury, microglia surround and “clear” areas of damaged axons. Wallerian degeneration, in which the part of the axon distal to the break degrades, takes place within weeks and months following injury (LoPachin & Lehning, 1997). As myelin breaks down and detaches from cells, nearby cells begin phagocytic activity, engulfing and eliminating debris (Hughes, Wells, Perry, Brown, & Miller, 2002). Glial scars may also form at these sites of injury, serving an adaptive purpose by preventing the spread of damage to healthy surrounding tissue, but also preventing complete reparation of the damaged area by hindering neuronal axon extensions from forming in these areas (Stichel & Muller, 1998).

Due to its microscopic scale, diffuse axonal injury is often not detectable on macroscopic imaging, such as CT scans. In contrast, MRI scanning tends to be more sensitive to diffuse axonal injury effects (Meythaler, et al., 2001). For example, 30% of subjects with traumatic brain injury show normal CT scans but have signs of diffuse axonal injury on MRI (Corbo & Tripathi, 2004). However, even MRI may fail to show evidence of diffuse axonal injury, given that MRI identifies the injury using signs of edema, which may not be present (Corbo & Tripathi, 2004). Even skilled radiologists tend to underestimate diffuse axonal pathology on MRI (Gentry, 1990). Diffusion tensor imaging (DTI) tends to be more sensitive than CT or MRI for characterizing microstructural brain injury contributing to regional white matter loss in traumatic brain injury (Bendlin, et al., 2008; Greenberg, et al., 2008; Huisman, et al., 2004; Lazar, et al., 2003).

Consequences of diffuse axonal injury. Immediately following traumatic brain injury, the initial damage to axons disrupts axonal transport and brain connectivity, causing confusion, loss of consciousness, or coma due to disruption of ascending fibers involved in arousal (Gennarelli, et al., 1982). A confusional state characterized by posttraumatic amnesia may then result. Although many areas of cognition are affected by diffuse axonal injury, primary impairments include attention and speed of processing (Mathias, et al., 2004; Meythaler, et al., 2001; Smith, Meaney, & Shull, 2003). Given that axonal damage in diffuse axonal injury is largely a result of secondary biochemical cascades and has a delayed onset, a person with diffuse axonal injury who initially appears well may deteriorate later (Meythaler, et al., 2001).

Recent neuroimaging studies provide convergent evidence to suggest that diffuse axonal injury leads to widespread volume loss of both grey and white matter in patients with moderate to severe traumatic brain injury, even when patients with focal lesions are excluded from the sample (Blatter, et al., 1997; Levin, 1981; MacKenzie, et al., 2002). However, as yet, only broad relationships have been demonstrated between grey and white matter volume loss and clinical outcome. Generally, neuroimaging studies suggest that greater grey and white matter volume loss is associated with poorer global functional outcome, slowed processing speed, and impaired memory following traumatic brain injury (Bigler, et al., 2010; Corkin, Amaral, Gonzalez, Johnson, & Hyman, 1997; Green, 2009; Hofman, et al., 2001; Levin, 1981; Mathias, et al., 2004; Serra-Grabulosa, et al., 2005).

Acute focal pathology and secondary injury effects. Focal pathology in traumatic brain injury is most often characterized by focal cortical contusions, deep hemorrhages in the basal ganglia, and focal hypoxic (deprivation of oxygen) and/or ischemic (restriction of blood flow) lesions or strokes (Levine, et al., 2006; van der Naalt, et al., 1999). Regardless of the site of impact in traumatic brain injury, focal cortical contusions often cause localized damage in frontal and anterior temporal areas, where the brain is confined by bony ridges of the inner skull (Ommaya & Gennarelli, 1974). These areas mediate self-monitoring and self-regulation, emotional functioning, and social functioning, which are areas of functioning commonly affected in moderate to severe traumatic brain injury (Stuss & Gow, 1992; Varney & Menefee, 1993). Deep hemorrhages, or collections of blood within the brain, are less common than cortical contusions, but can have significant effects on basal ganglia, contributing to deficits in motor control and learning (Graham, et al., 1995; Greenwald, et al., 2003). Focal hypoxic-ischemic injury is common during the early days post-injury as blood flow to the brain is disrupted and reduced by elevated intracranial pressure, hemorrhages within the brain, and constriction of blood vessels in the cortex (Lezak, et al., 2004). The basal ganglia and hippocampus are particularly vulnerable to hypoxic-ischemic injury (Amaral & Witter, 1995; Geddes, LaPlaca, & Cargill, 2003; McCarthy, 2003); damage to these structures likely contributes to memory problems after traumatic brain injury (Bigler, Blatter, Gale, et al., 1996; Serra-Grabulosa, et al., 2005).

Focal injuries and acute secondary effects of traumatic brain injury tend to resolve within the first six weeks post-injury (Lezak, et al., 2004), but may take months to resolve for some individuals (Haymaker, 1982). Reduction of brain volume commonly observed on imaging in the early stage post-injury is deemed to reflect both resolution of acute injury effects (such as reduced brain swelling and resolution of hematomas) as well as disintegration and clearing of neurons that were severely damaged in the course of the initial impact (Katz & Mills, 1999; Lezak, et al., 2004). Prolonged duration of coma, diffuse as opposed to focal damage, and history of substance abuse tend to be associated with greater reductions in global brain volume during the initial weeks and months post-injury (Bigler, Blatter, Johnson, et al., 1996; Levin, 1995; Trivedi, et al., 2007). Reduction in global brain volume, hippocampal volume, and corpus callosum volume during the acute stage post-injury have also been associated with poorer functional outcomes (Tate & Bigler, 2000; Verger, et al., 2001).

Subacute Cerebral Atrophy in Traumatic Brain Injury

Overview

Up until recently, clinicians and researchers have generally assumed that the brain remains relatively stable once the acute effects of injury have resolved (Lezak, et al., 2004). However, novel preliminary findings suggest that in a subset of individuals, the brain does not remain stable following resolution of acute pathologies post-injury, but instead shows signs of progressive atrophy in the subacute phase post-injury (i.e., beyond the initial 3 months post-injury) (Greenberg, et al., 2008; Ng, et al., 2008; Trivedi, et al., 2007; van der Naalt, et al., 1999). This subacute atrophy tends to be seen throughout diffuse areas of the brain, in both white matter and grey matter, regardless of original sites of focal injury (Blatter, et al., 1997; Gale, et al., 1995; Greenberg, et al., 2008; MacKenzie, et al., 2002; Ng, et al., 2008; Trivedi, et al., 2007). The hippocampus appears to be particularly vulnerable to atrophy during the subacute stage post-injury, likely due to the vulnerability of this structure to negative neuroplastic mechanisms at the molecular, cellular, and neural network levels following traumatic brain injury (McCarthy, 2003). Indeed, preliminary findings suggest the presence of even greater hippocampal atrophy than whole brain atrophy in the subacute stages post-injury regardless of original injury location severity (Arciniegas, et al., 2001; Ng, et al., 2008). Interestingly, degree of hippocampal loss appears to be equally distributed bilaterally regardless of which hemisphere was more damaged at initial injury (Arciniegas, et al., 2001; Ariza, et al., 2006). One study examined differential degree of subacute atrophy between the anterior (head), middle (body), and posterior (body) regions of the hippocampus and found that atrophy was mainly occurring in the head of the hippocampus, while the tail and body of the hippocampus were not significantly affected (Ariza, et al., 2006).

Studies of Subacute Cerebral Atrophy

Given the preliminary nature of findings regarding atrophy progression, there is some confusion in the literature regarding the terms “acute” and “subacute” when referring to time windows post-injury. For the purpose of the present study, the acute phase post-injury refers to the initial 3 months post-injury, while the subacute phase refers to any time window beginning beyond the initial 3 months post-injury. An important limitation of many of the human studies of

subacute atrophy is that initial imaging has often been conducted prior to the likely resolution of the acute secondary effects of injury, such as brain swelling due to edema, hydrocephalus, or hematomas. For example, in one study, initial MRIs were conducted as early as four weeks post-injury, at which time 8% of the sample still showed signs of edema (van der Naalt, et al., 1999). In some studies, initial imaging was conducted only days post-injury (Hofman, et al., 2001; MacKenzie, et al., 2002). In such studies, where early initial imaging was conducted at less than 3 months post-injury, it is impossible to determine the extent to which volume reductions reflect resolution of acute injury effects (such as reduced brain swelling) or reflect progressive deterioration of neuronal tissue. Some previous studies of subacute atrophy are further limited by inter-individual overlap within the same sample in terms of the time window between initial and follow-up imaging (MacKenzie, et al., 2002; Wilson, et al., 1988), making it difficult to ascertain the specific time window in which changes were likely to be occurring across individuals in the sample. Following is a review of the findings and limitations of some of the prominent studies of subacute atrophy following traumatic brain injury.

Studies using early initial magnetic resonance imaging (MRI). In a sample of 25 adults with closed head injury, comparison of MRI scans conducted immediately following injury and at 5-18 months post-injury revealed significant atrophy as measured by ventricular enlargement between initial and follow-up imaging (Wilson, et al., 1988). Consistent with limitations outlined above, given that initial neuroimaging was conducted when acute injury effects had not yet resolved, it is impossible to determine the degree to which the ventricular changes seen in this study represented resolution of acute injury effects versus atrophy of cerebral tissue during the subacute stages post-injury.

In a sample of 67 adults with mild to moderate traumatic brain injury, comparison of MRI scans conducted at 1-3 months post-injury and again at 6-12 months post-injury revealed significant atrophy around the site of the original injury lesion in approximately 50% of patients (van der Naalt, et al., 1999). Again, given that initial MRIs in this study were conducted as early as one month post-injury, it is impossible to determine the degree to which atrophy reflected resolution of acute injury effects versus cerebral tissue atrophy in subacute stages post-injury.

In a sample of 7 patients with mild to moderate traumatic brain injury, initial MRI scans conducted as early as 7 days post-injury were compared to MRI scans conducted 3 months post-

injury, revealing significant reductions in volume of brain parenchyma compared to normal controls (MacKenzie, et al., 2002). Once again, given the early timing of initial imaging, it is impossible to ascertain whether volume decreases reflected resolution of brain swelling or degeneration of neuronal tissue.

In a sample of 24 patients with severe traumatic brain injury, MRI scans conducted at 12 months post-injury were compared with MRIs conducted at 8 weeks post-injury (Sidaros, et al., 2009). In comparison to healthy controls, traumatic brain injury subjects showed significant atrophy across a broad range of brain regions, including the brain stem, cerebellar peduncles, thalamus, internal and external capsules, putamen, inferior and superior longitudinal fasciculus, corpus callosum, and corona radiata. Similar to earlier studies, the early timing of the initial assessment makes it impossible to determine the degree to which the atrophy observed in this study reflects resolution of acute injury effects or cerebral atrophy during the subacute phase post-injury.

Studies using later initial magnetic resonance imaging (MRI). In a sample of 37 adults with traumatic brain injury ranging from mild to severe, MRI scans conducted at 2.5 months post-injury were compared with MRI scans conducted at 13 months post-injury, revealing significantly greater percentage of brain volume loss than seen in normal controls (Trivedi, et al., 2007). This study represents a methodological improvement on previous studies in that the majority of initial imaging was conducted at 2.5 months post-injury when acute effects were more likely to have resolved. However, for some of the individuals in this sample, initial imaging was conducted as early as 7 weeks post-injury, at which time swelling and edema may have still been present, raising the likelihood of overestimation of actual cerebral tissue loss in that sample.

In a Canadian rehabilitation sample of 14 patients presenting with moderate to severe traumatic brain injury, MRI scans conducted at more than 2 years post-injury were compared to MRI scans conducted at 4.5 months post-injury (Ng, et al., 2008). Measures of volume changes included expert ratings of visible signs of lesion progression as well as volumetric analysis of cerebrospinal fluid volume change. Results from expert visual ratings and volumetric analysis revealed evidence of significant cerebral atrophy occurring in 85% of the subjects in the sample. The degree of global brain atrophy was almost twice the degree seen in healthy controls (Blatter, et al., 1995), and degree of hippocampal atrophy was nearly twice the degree seen in healthy

controls (Bigler, et al., 1997). The study by Ng and colleagues (2008) addressed limitations of previous studies by conducting initial imaging at 4.5 months post-injury, well beyond the likely resolution of acute injury effects. As such, this study provided stronger evidence that volume changes reflected actual atrophy of cerebral tissue rather than resolution of acute injury effects such as brain swelling or edema.

Preliminary findings of a study being conducted currently at the Toronto Rehabilitation Institute provide further evidence of cerebral atrophy occurring during the subacute stages following moderate to severe traumatic brain injury (Green, 2009). In this study of 33 adults with moderate to severe traumatic brain injury, comparison of MRI scans conducted at 4.5 months and 12 months post-injury revealed evidence of significant bilateral hippocampal atrophy compared with healthy controls.

Studies of diffusion-tensor imaging (DTI). Some studies have used diffusion tensor imaging (DTI) to examine differential changes in grey matter and white matter that might be contributing to overall brain volume loss over time. Diffusion tensor imaging (DTI) is useful for characterizing microstructural brain injury contributing to regional white matter loss in traumatic brain injury. In a study of 13 subjects from a Canadian rehabilitation hospital, comparison of diffusion tensor imaging (DTI) conducted at 4.5 months and again at two years post-injury revealed significant progression of white matter damage with the greatest impact seen in frontotemporal regions (Greenberg, et al., 2008). In another study of 46 adults with moderate to severe traumatic brain injury, comparison of diffusion tensor imaging (DTI) conducted at 2 months and again at 12.7 months post-injury revealed significantly greater deterioration of grey matter and white matter in patients compared to controls (Bendlin, et al., 2008). In traumatic brain injury subjects, deterioration was seen across all major fibre bundles in the brain, including the corpus callosum, cingulum, the superior and inferior longitudinal fascicules, the uncinate fasciculus, and brain stem fibre tracts.

Predictors and Potential Modifiers of Subacute Atrophy

Research is limited regarding predictors of subacute atrophy in traumatic brain injury. Preliminary studies suggest that injury severity, as measured by coma duration, posttraumatic amnesia duration, or Glasgow Coma Scale scores, is associated with degree of subacute atrophy following traumatic brain injury (Gale, et al., 1995; Kesler, et al., 2003; Trivedi, et al., 2007; van

der Naalt, et al., 1999; Wilde, Bigler, Pedroza, & Ryser, 2006), although one study demonstrated no association between coma duration and subacute global atrophy (Tomaiuolo, et al., 2004; Tomaiuolo, et al., 2005). Less is known about other predictors of atrophy following traumatic brain injury.

Increasing age at injury may place an individual at increased risk for subacute atrophy during the subacute phases of recovery. Indeed, animal studies have demonstrated that older brains show a greater degree of subacute atrophy following traumatic brain injury (Onyszchuk, He, Berman, & Brooks, 2008; Petcu, et al., 2008; Popa-Wagner, Carmichael, Kokaia, Kessler, & Walker, 2007; Yager, Wright, Armstrong, Jahraus, & Saucier, 2006). In human studies, there is no direct evidence that greater age at injury is associated with greater degree of subacute atrophy. However, given findings that older age is associated with slower rate of recovery of speed of processing following traumatic brain injury (Christensen, et al., 2008), and given that in normal aging, increasing age is associated with increasing neuronal loss and less white matter integrity (Blatter, et al., 1995), one might extrapolate that less initial white matter integrity at the time of injury would constitute diminished brain reserve available to support restitution of damaged white matter networks. As such, older brains at the time of injury would be more vulnerable to cerebral atrophy following injury than younger brains.

Given the preliminary nature of findings regarding the presence of subacute cerebral atrophy, environmental factors modifying the degree of atrophy have not yet been examined directly. However, experimental studies in the animal literature demonstrate a positive relationship between environment enrichment (i.e., exposure to cognitively, physically, and socially stimulating environments) and a host of positive plastic changes, such as increased hippocampal neurogenesis (Kempermann, Brandon, & Gage, 1998; Kempermann & Gage, 1999) and increases in dendritic spine density and number of synapses (Kozorovitskiy, et al., 2005). Observational studies of environmental enrichment in humans also show an association between engagement in stimulating activities and similar positive neuroplastic changes, although the causal direction of this relationship is unclear (Fritsch, et al., 2007; Hultsch, Hertzog, Small, & Dixon, 1999; Jacobs, Schall, & Scheibel, 1993). The present study posits that exposure to environmental enrichment may contribute to positive neuroplastic changes following traumatic brain injury, which may serve to hinder or halt progression of subacute atrophy in vulnerable

patients. This supposition has not yet been addressed directly in the empirical literature on traumatic brain injury in humans.

Clinical Outcomes Associated with Subacute Atrophy

Regardless of location or tissue type, injuries of greater severity are generally associated with a greater degree of subacute atrophy (Gale, et al., 1995; Kesler, et al., 2003), and injuries of greater severity are negatively correlated with outcome (Dikmen, Machamer, Temkin, & McLean, 1990; Felmingham, Baguley, & Crooks, 2001; Green, Colella, Christensen, et al., 2008; Henry-Feugeas, et al., 2000; Hoofien, 2002). The few studies that have directly examined specific relationships between degree of subacute cerebral atrophy and functional outcome have typically focused on either global subacute atrophy or else subacute atrophy in the corpus callosum and/or hippocampus, as these two subregions tend to be particularly vulnerable to the deleterious effects of traumatic brain injury (Gale, et al., 1995; Gentry, Thompson, & Godersky, 1988; Levin, et al., 1990; McCarthy, 2003; Meythaler, et al., 2001).

Total brain subacute atrophy and functional decline. Studies of total brain subacute atrophy and functional outcome have demonstrated broad associations between greater degrees of grey and white matter atrophy and poorer clinical outcomes (Jellinger, 2004; Levin, Meyers, C.A., Grossman, R.G., & Sarwar, M., 1981; MacKenzie, et al., 2002; Mellick, Gerhart, & Whiteneck, 2003; National Institute of Mental Health, 1998). A single study examined the relationship between subacute atrophy and vocational outcome as a specific outcome measure. In that study, 67 adults with mild to moderate traumatic brain injury underwent MRI scans at 1-3 months post-injury and again at 6-12 months post-injury (van der Naalt, et al., 1999). Results indicated that focal lesions and atrophy in predominantly frontotemporal areas and posttraumatic amnesia were associated with poorer vocational outcome. Of the individuals showing lesions and subacute atrophy in that sample, only 42% had fully returned to work at 6-12 months post-injury as opposed to 86% of individuals without lesions or atrophy who returned to work.

Regarding the cognitive impact of subacute atrophy following traumatic brain injury, a broad relationship has been demonstrated between increased ventricular volume (a measure of global cerebral atrophy) and poorer neuropsychological outcomes post traumatic brain injury (Anderson & Bigler, 1995; Gale, et al., 1995). More specifically, greater degree of white and grey matter subacute atrophy is associated with greater deficits in attention (Gale, Baxter,

Roundy, & Johnson, 2005), speed of processing (Levine, et al., 2006; Mathias, et al., 2004) and memory (Anderson & Bigler, 1995; Blatter, et al., 1997; Cullum & Bigler, 1986; Levin, Meyers, C.A., Grossman, R.G., & Sarwar, M., 1981; Serra-Grabulosa, et al., 2005).

Corpus callosum subacute atrophy and functional decline. Degree of subacute atrophy in the corpus callosum typically increases with increasing time from injury (B. Levine, et al., 2006; Sidaros, et al., 2009). Subacute atrophy of the corpus callosum is assumed to result from the progressive degenerative effects of diffuse axonal injury, which leads to Wallerian deterioration of white matter (Sidaros, et al., 2009). As yet, the clinical impact of corpus callosum atrophy remains unclear, but in general, progressive thinning of the corpus callosum in the subacute stage post-injury has been associated with poorer global functional outcome (Azouvi, et al., 1993; Sidaros, et al., 2009). Little is known about the specific cognitive impact of corpus callosum atrophy in traumatic brain injury, but preliminary studies suggest an association between greater corpus callosum atrophy and impairments in episodic learning and memory (Tomaiuolo, et al., 2004; Tomaiuolo, et al., 2005).

Hippocampal subacute atrophy and functional decline. There are few imaging studies showing reliable correlations between subacute hippocampal atrophy and specific functional outcomes in traumatic brain injury (Levine, et al., 2006). Research thus far has focused primarily on cognitive rather than functional correlates of subacute atrophy in traumatic brain injury. In terms of cognitive correlates, studies provide convergent evidence to suggest that subacute hippocampal atrophy is associated with poorer memory performance and poorer recovery of memory following traumatic brain injury (Ariza, et al., 2006; Bigler, et al., 1997; Green, 2009; Serra-Grabulosa, et al., 2005; Tate & Bigler, 2000). A single study that examined differential effects of atrophy in the hippocampal head, body, and tail showed a significant correlation between atrophy of the left hippocampal head and impaired verbal learning and memory and a trend for atrophy in the right hippocampal tail associated with impaired visual memory (Ariza, et al., 2006). Despite the major role that memory plays in vocational functioning and that memory deficits are a primary predictor of successful return to productivity following traumatic brain injury (Green, Colella, Hebert, et al., 2008), no studies have explicitly examined the relationship between subacute hippocampal atrophy and vocational outcome following traumatic brain injury. Due to its prominent role in learning and memory, damage to the hippocampus is likely to have

significant functional limitations in traumatic brain injury, warranting further investigation of functional impacts of progressive hippocampal atrophy.

Neuroplastic Mechanisms in Traumatic Brain Injury

Overview

Neuroplasticity refers to the brain's capability of developing, modifying, strengthening, and adjusting neural pathways in response to internal and external stimuli (Grafman, 2000; Kolb & Whishaw, 1998; Mateer & Kerns, 2000). In the field of neuropsychology, it was originally believed that the brain was hard-wired following development. However, it is now a well-accepted notion that neuroplastic changes continue to occur in response to learning and experience throughout the lifespan (Pascual-Leone, et al., 2005). Behaviour and experience can result in neuroplastic changes that are adaptive (positive) or maladaptive (negative) for the organism. A study of hippocampal volumes of taxi drivers in London, England provides a compelling example of positive neuroplasticity, wherein longstanding taxi drivers were found to have significantly larger posterior hippocampal volumes than matched controls (Maguire, et al., 2000). In contrast, negative neuroplasticity is exemplified in studies showing diminished connectivity of neural networks and increased cerebral atrophy associated with normal aging (Coffey, Saxton, Ratcliff, Bryan, & Lucke, 1999; Whalley, Deary, Appleton, & Starr, 2004).

Negative Neuroplastic Mechanisms in Traumatic Brain Injury

Studies demonstrate a number of negative neuroplastic mechanisms occurring at the molecular, cellular, and neural network levels following traumatic brain injury. These mechanisms may underlie the progression of atrophy during the subacute phase following traumatic brain injury, although this remains an empirical question requiring further study. Behavioural mechanisms on the part of brain-injured patients may further promote such negative neuroplastic mechanisms following injury.

Molecular mechanisms. At the molecular level, traumatic brain injury is associated with prolonged glutamate excitotoxicity (Matsushita, Shima, Nawashiro, & Wada, 2000; Yamamoto, et al., 1999), elevated cortisol (McCarthy, 2003), diminished expression of brain derived neurotrophic factor (BDNF) (Chen, et al., 2005) and accumulation of amyloid precursor protein

and amyloid beta peptides (Smith, Chen, Iwata, & Graham, 2003), all of which are likely to inhibit neuronal recovery and promote cerebral tissue degeneration following injury. Firstly, the extracellular upregulation of glutamate following traumatic brain injury results in prolonged excitotoxicity, leading to chronic neuroinflammation and persistent apoptosis (i.e., programmed cell death) in diffuse areas of the brain over months or even years post-injury (Gentleman, et al., 2004; Schmidt, Petrovic, Ropele, Enzinger, & Fazekas, 2007). Hippocampal neurons are particularly vulnerable to the effects of excitotoxicity as well as cortisol following brain injury (McCarthy, 2003), which may contribute to the relatively greater hippocampal than whole brain atrophy seen during the subacute phase (Ariza, et al., 2006; Ng, et al., 2008). Secondly, given that BDNF supports the survival of existing neurons and promotes the growth and differentiation of new neurons and synapses (Huang & Reichardt, 2001), diminished BDNF following traumatic brain injury is likely to impede regeneration and repair of damaged neurons and neural circuits, failing to protect against negative plastic mechanisms that may be contributing to subacute atrophy. Finally, elevated levels of amyloid precursor protein, a regulator of synapse connectivity (Priller, et al., 2006) and neuroplasticity (Turner, O'Connor, Tate, & Abraham, 2003), has been shown to impeded synaptogenesis in the hippocampus (Matsuyama, Teraoka, Mori, & Tomiyama, 2007), which may further impede the successful integration of newborn cells in the hippocampus and reconnection of damaged neural circuits following injury. Further, accumulation of amyloid beta peptides, associated with the amyloid beta plaques seen in Alzheimer's disease, may contribute to chronic apoptosis and progressive cell death (Kadowaki, et al., 2005; Smith, Chen, et al., 2003). In sum, prolonged glutamate excitotoxicity (Matsushita, et al., 2000; Yamamoto, et al., 1999), elevated cortisol (McCarthy, 2003), diminished expression of brain derived neurotrophic factor (BDNF) (Chen, et al., 2005) and accumulation of amyloid precursor protein and amyloid beta peptides (Smith, Chen, et al., 2003) following traumatic brain injury are likely to impede the survival and integration of newborn neurons in the hippocampus, promote apoptotic cell death, and inhibit the reconnection and repair of damaged neural circuits following injury. In combination, these molecular mechanisms occurring following traumatic brain injury are likely to underlie the cerebral tissue degeneration seen during the subacute phase post-injury in a subset of patients.

Cellular mechanisms. A primary cellular degenerative mechanism following brain injury is apoptosis, or programmed cell death. Apoptosis refers to a biochemical process in which

macrophages locate, engulf, and break down damaged cells. In contrast to necrosis, which refers to traumatic cell death resulting from acute traumatic injury, apoptosis is often an adaptive process allowing for beneficial clearing of damaged cells, adaptive differentiation of cells, and prevention of excessive proliferation of cells. For instance, in embryonic development, apoptosis is the process by which a mass of embryonic tissue differentiates into different body structures and organs. The process of apoptosis also plays an adaptive role in preventing the spread of certain diseases like cancer, in that it typically prevents cells from continuing to divide and developing into cancerous tumours. In the case of traumatic brain injury, apoptotic mechanisms are initiated by excitotoxicity beginning in the region of damaged tissue. Excitotoxicity refers to the influx of excessive calcium into the cell, leading to imbalances in proteins that regulate cell viability, which leads to eventual cell death (Choi, 1992; Koliatsos & Ratan, 1999). The biochemical process involved in apoptosis affects the structure and functional viability of affected cells, by way of changes to the cell membrane, cell shrinkage, and fragmentation of the cell nucleus, chromosomes, and DNA. In the case of brain injury, apoptosis serves to remove damaged cells and their debris, thus preventing damaged cells from depleting the nutrients available to surrounding healthy neurons. However, in the case of traumatic brain injury, apoptosis can spread from areas of damaged tissue to adjacent areas of healthy tissue (i.e., the penumbra), leading to death of viable healthy brain tissue.

Neural network mechanisms. For the purposes of understanding mechanisms of atrophy in brain injury, it is worth noting that cerebral tissue following brain injury can be divided into three types: (a) the core of a lesion wherein traumatically-damaged cells deteriorate through a process of necrosis; (b) intact, undamaged neuronal tissue; and (c) the penumbra (i.e., intermediate tissue between areas of damaged and undamaged tissue). Neurons in the penumbra may have been injured during the course of the traumatic event, but are still structurally intact and functionally viable. Brain tissue in the penumbra is particularly vulnerable to degeneration secondary to either apoptotic mechanisms and neuroinflammation spreading from the lesion site (Dirnagl, Iadecola, & Moskowitz, 1999; Johansson, 2000) or under-stimulation from damaged neurons at the lesion site (Johansson, 2000; Robertson & Murre, 1999).

Unsuccessful repair of damaged networks and structural decay of viable neural networks following injury may lead to progression of cerebral atrophy in the subacute phase following traumatic brain injury. As described earlier, a primary mechanism of injury in traumatic brain

injury involves diffuse axonal injury (injury to neuronal axons that make up white matter tracts) and Wallerian degeneration of axons over time. Wallerian degeneration of axons may persist for years post-injury and may be accompanied by deposition of myelin debris and formation of gliosis (i.e., neuronal scar tissue) (Cervos-Navarro & Lafuente, 1991; Galvin, et al., 2000). In the case of neuronal death, the myelin sheath is often the last of the debris to be cleared by macrophages in the process of apoptosis. Animal studies have demonstrated that myelin debris may be present as long as 22 months post-injury (Hughes, Wells, Perry, Brown, & Miller, 2002). Subsequently, restitution of damaged networks or establishment of new neuronal connections may thus be hindered in areas where myelin debris forms gliosis or scar tissue, physically and biochemically hindering the development of connections between neurons in these areas. Diminished expression of brain-derived neurotrophic factor (BDNA) following traumatic brain injury (Chen, et al., 2005) may further limit the attraction of proximal axons to re-establish connections between viable neurons.

In addition to myelin debris hindering the restitution of damaged networks, under-stimulation of viable neural networks can lead to the functional and structural deterioration of those networks (Johansson, 2000; Robertson & Murre, 1999). Robertson and Murre's (1999) computational model of neural networks and brain damage posits that when a neural circuit loses a certain number of connections (i.e., through damage), the circuit is left in a critical state in which the network could either collapse and lose functional connectivity altogether or else be rescued and recover its original patterns of functional connection. Based on this model, a primary mechanism of neuronal degeneration in traumatic brain injury may be the under-stimulation of structurally intact and functionally viable neurons by damaged axonal projections from lesion sites or diffuse axonal injury. Indeed, some researchers posit that diffuse damage to axons in white matter contributes to downstream loss of activation to grey matter that is innervated by the damaged axons (Levine, et al., 2006). Grey matter degeneration is thus hypothesized to be the result of under-stimulation by damaged white matter tracts that previously innervated the grey matter.

Behavioural mechanisms influencing negative neuroplasticity. Drawing on Mahncke's (2006) theoretical model of negative neuroplasticity and functional loss in normal aging, negative neuroplastic changes in traumatic brain injury may influence, and be influenced by, patients' experiences and behaviour following brain injury. Two core behavioural factors drawn

from Mahncke's model that may contribute to negative neuroplastic changes in traumatic brain injury include a reduced schedule of activity and negative learning. There are a number of factors following traumatic brain injury that can hinder an individual from engaging in the variety of cognitively, socially, and physically stimulating activities that might promote neuroplastic recovery. For example, cognitive deficits may make it difficult for the individual to return to the same job or level of productivity as prior to their injury, which limits their exposure to the cognitive challenges and social stimulation that might promote positive neuroplastic changes. Physical deficits may also interfere with social engagement given the environmental and transportation barriers and social stigma faced by persons with physical disabilities (Ownsworth & McKenna, 2004). Other factors include emotional difficulties or personality changes secondary to injury, which may place a strain on interpersonal relationships, leading to diminished exposure to stimulating social interaction. In these ways, impairments associated with traumatic brain injury can preclude an individual from returning to work or social roles that could potentially promote positive neuroplastic changes. In sum, injury-related impairments can contribute to a reduced schedule of activity and diminished stimulation of brain networks, increasing the likelihood of negative neuroplastic changes due to diminished brain activation. Negative learning may also lead patients to actively avoid activities that they find to be more challenging or frustrating since their injury. Many activities that were previously enjoyed or completed with ease may be experienced as difficult and frustrating by a person with cognitive impairments. Novel tasks encountered in daily life that require learning, memory, speeded information processing, or problem solving are likely to be particularly difficult for individuals following traumatic brain injury (Christensen, et al., 2008; Hellawell, Taylor, & Pentland, 1999; Ruttan, et al., 2008), and as such, may be avoided, resulting in a negatively-reinforced cycle of avoidance of challenging activities leading to diminished activation of brain networks and associated negative neuroplastic changes (Blake, Heiser, Caywood, & Merzenich, 2006).

Adaptive Neuroplastic Mechanisms in Traumatic Brain Injury

Despite novel findings of subacute cerebral atrophy (Greenberg, et al., 2008; Ng, et al., 2008; Trivedi, et al., 2007), a subset of patients show some degree of functional improvements beyond the initial two years post-injury (Bendlin, et al., 2008; Sidaros, et al., 2009), raising the possibility of positive neuroplastic changes contributing to functional improvements. Indeed,

preliminary findings in studies with humans show increased integrity of white matter tracts concurrent with functional improvements in a subset of patients (Sidaros, et al., 2009). During the subacute stages post-injury (i.e., after the initial 3 months), adaptive, experience-dependent neuroplastic recovery mechanisms may include both structural and functional neuroplastic mechanisms (Gainotti, 1993; Rosen, Burstein, & Galaburda, 2000). At a structural level, axonal sprouting has been demonstrated both within lesion sites and in distal areas of the brain following brain injury (Raineteau & Schwab, 2001), which may contribute to the establishment of new neural networks or restitution of damaged networks (Robertson & Murre, 1999). In addition, there is increasing evidence for neurogenesis occurring in the dentate gyrus of the hippocampus in adults, (Ericksson, et al., 1998; Gould, Tanapat, Rydel, & Hastings, 2000; B. L. Jacobs, 2002; Lichtenwalner & Parent, 2006), which may underlie functional recovery following traumatic brain injury (Gaulke, et al., 2005; Ramaswamy, Goings, Soderstrom, Szele, & Kozlowski, 2005; Yu, Zhang, Liebl, & Kernie, 2008). Adaptive vascular changes associated with environmental enrichment include increased angiogenesis and active vascular recruitment within the hippocampus (Ekstrand, Hellsten, & Tingstrom, 2008), both of which are closely associated with neurogenesis in this region (Palmer, Willhoite, & Gage, 2000), possibly due to enhanced glucose availability to neurons, delivery of cytoprotective factors, and improved neuroimmune modulation (Nithianantharajah & Hannan, 2009). At the level of functional organization, evidence suggests that the viable brain tissue both adjacent to, and distal from, a lesion may assume the functions of damaged networks within the lesion (Gainotti, 1993). In addition to reorganization of functional cortical maps, in which new networks assume the functions of damaged networks, it is possible that damaged networks themselves can be repaired and restored (Robertson & Murre, 1999) through Hebbian (1947) activation mechanisms.

Neuroprotection:
Brain and Cognitive Reserve

Brain and Cognitive Reserve

The concepts of “brain reserve” and “cognitive reserve” were originally developed to explain why adults who were exposure to higher levels of mental and physical activity (e.g., education, occupational achievement, physical exercise) showed a lower risk for developing the

behavioural manifestations of dementia. Brain reserve refers to structural brain capacity, which may be influenced by genetics but can also be induced by enhancement of mental and physical activity (Katzman, et al., 1988; Satz, 1993). According to brain reserve theory, exposure to stimulating lifestyle factors contributes to the development of more complex and interconnected neural networks, which may protect against the progression of neurodegenerative disease processes. Cognitive reserve is a more limited construct and refers to how innate intelligence and exposure to mental, physical, and social enrichment may confer an individual with greater ability to compensate for brain pathology through differential recruitment of alternative brain networks or alternative cognitive strategies to overcome brain pathology (Scarmeas & Stern, 2003; Stern, 2003; Whalley, et al., 2004). More recently, the concepts of brain reserve and cognitive reserve have been integrated into a unified concept of brain and cognitive reserve (BCR), defined as "changes occurring in the brain, in response to life experiences, which positively modulate susceptibility to brain disorders…via neuroprotective and/or compensatory mechanisms" (Nithianantharajah & Hannan, 2009).

Research investigating the BCR model examines the relationship between exposure to environmental factors and changes in brain structure and function (Nithianantharajah & Hannan, 2009). Direct measures of BCR include such things as brain volume, synaptic count, and dendritic branching. In human studies, indirect measures of BCR include level of education or premorbid intelligence (Stern, 2002). Much of the evidence supporting the BCR model draws on literature in the areas of normal aging (Corral, Rodriguez, Amenedo, Sanchez, & Diaz, 2006; Fritsch, et al., 2007) and traumatic brain injury (Kesler, et al., 2003). In the literature on aging, some studies have suggested that individuals with greater brain volumes show a lower rate of cognitive decline associated with normal aging (Coffey, Saxton, Ratcliff, Bryan, & Lucke, 1999; Cummings, Vinters, Cole, & Khachaturian, 1998; Drachman, 2002; Tisserand, Bosma, Van Boxtel, & Jolles, 2001). Some studies have also suggested that higher level of education, an indirect measure of BCR, is also associated with a slower rate of cognitive decline associated with normal aging and dementia (Scarmeas & Stern, 2004; Stern, Albert, Tang, & Tsai, 1999). However, recent comprehensive reviews of the literature suggest that while level of education is associated with higher levels of cognitive functioning at various age points, level of education does not moderate the actual rate of cognitive decline in normal aging (Salthouse, 2006). It should be noted that a primary limitation of research into BCR is that the direction or causality of

the relationship between behaviour/experience and brain changes is unclear and may well be reciprocal (Pascual-Leone, et al., 2005).

The model of brain and cognitive reserve (BCR) has not been addressed in traumatic brain injury as frequently or explicitly as in the literature on aging. The concept of BCR is a useful construct that might explain the different patterns and rates of recovery in individuals who have sustained traumatic brain injury of similar severity and location. Indirect measures of BCR, such as pre-injury level of education, pre-injury employment status, and premorbid intelligence are predictive of better overall functional recovery following traumatic brain injury (Green, Colella, Christensen, et al., 2008; Hoofien, 2002; MacMillan, Hart, Martelli, & Zasler, 2002; Novack, Bush, Meythaler, & Canupp, 2001). In contrast, factors that would theoretically lower BCR, such as age at injury, pre-injury history of substance abuse, psychiatric conditions, or additional neurological insult are associated with slower rates of recovery and greater cognitive decline following traumatic brain injury (Green, Colella, Christensen, et al., 2008; Ropacki & Elias, 2003; Till, et al., 2008), thus supporting the hypothesis BCR may have a neuroprotective effect in traumatic brain injury.

Influencing Neuroplasticity: Environmental Enrichment and Guided Recovery of Function

Environmental Enrichment

At a basic level, environmental enrichment refers to the complexity of an organism's environment and conventionally involves a combination of cognitive, physical, and/or social stimulation (Rosenzweig, Bennett, Hebert, & Morimoto, 1978). The term was originally adapted from early animal research conducted by Hebb, in which he demonstrated that exposing rodents to physical and/or social stimulation improved their cognitive abilities (Hebb, 1947). Since Hebb's original studies, numerous animal studies have provided convergent evidence that exposure to complex environments has positive behavioural effects in both intact and brain-injured animals (Hamm, Temple, O'Dell, Pike, & Lyeth, 1996; Passineau, Green, & Dietrich, 2001). Further, numerous studies have demonstrated that environmental enrichment has demonstrated positive neuroplastic changes associated with environmental enrichment in both

healthy and brain-injured animals (Kolb & Whishaw, 1998; Passineau, Green, & Dietrich, 2001; Rosenzweig & Bennett, 1996).

Animal Studies of Environmental Enrichment

Early research into environmental enrichment was conducted with animals, beginning with Hebb's seminal study in which he demonstrated that pet rats allowed to run free in his home performed significantly better on learning and problem-solving tasks than did rats housed in standard laboratory cages (Hebb, 1947). The parameters of environmental enrichment have been more clearly delineated since Hebb's original study, and typically involve experimental manipulation of discreet aspects of enrichment, including exposure to social groups, access to a variety of foods, novel toys, scented objects, and running wheels, which tap into important social, cognitive, and physical components of enrichment. The models for standardized enrichment studies in rodents use a number of specific parameters of enrichment (Will, Galani, Kelche, & Rosenzweig, 2004) which are outlined as follows: the standard housing condition consists of three to six rodents kept in one standard laboratory cage without objects; the physical enrichment environment consists of the standard housing condition plus access to running wheels; and the generalized enriched environment condition consists of 8-12 rodents kept in one larger-than-normal cage with access to a variety of objects and toys that are changed daily, allowing for sensory and physical interaction with novel stimuli. In the impoverished condition, rodents are kept isolated in a single smaller cage without objects.

Environmental enrichment and functional outcome in animals. Animal research since the 1960's has provided extensive convergent evidence that exposure to enriched environments in the laboratory results in improvements in learning, memory, and motor functioning, both in healthy animals (Lambert, Fernandez, & Frick, 2005; Will, et al., 2004) and animals with fluid-percussion-produced traumatic brain injury (Hamm, Temple, O'Dell, Pike, & Lyeth, 1996; Passineau, Green, & Dietrich, 2001). However, in contrast to the generalized positive effects of environmental enrichment on learning and behaviour in healthy animals, these effects in brain-injured animals tend to be lesion-specific, task-specific, and age-specific (Will et al., 2004). In terms of lesion-specificity, exposure to general environmental enrichment has positive effects on recovery of learning and memory in the case of lesions to the hippocampus but not in the case of lesions to the afferent-efferent systems of the hippocampus (Kelche, Dalrymple-Alford, & Will,

1987; Kelche, Roeser, Jeltsch, Cassel, & Will, 1995) or specific components of the hippocampal formation, such as the subiculum or entorhinal cortex (Galani, Coutureau, & Kelche, 1998). In terms of task-specificity, the effects of environmental enrichment on task performance can vary significantly depending on even subtle differences in the degree of sensory, motor, spatial, temporal, or motivational demands of tasks (Dalrymple-Alford & Benton, 1984; Kessner, 1986). Finally, younger animals tend to show greater functional benefits from exposure to environmental enrichment following brain injury than older animals (Kolb, 1999).

One area of particular interest is the relative contribution of different elements of environmental enrichment to behavioural outcome. Overall, animal studies suggest that general environmental enrichment has greater positive effects on recovery of learning, memory, and motor functioning than either physical enrichment or social enrichment alone (Hamm, et al., 1996; Will, et al., 2004). Some authors suggest that the greater impact of generally enriched environments on functional recovery may be due to the diverse and novel learning opportunities inherent in a more complex environment (Rosenzweig & Bennett, 1996; Will, et al., 2004).

Environmental enrichment and neuroplasticity in animals. The animal literature provides extensive convergent evidence of positive structural brain changes in response to environmental enrichment exposure in both healthy and brain-injured animals, including increased cortical thickness (Ip, Giza, Griesbach, & Hovda, 2002), increased number of neurons and glial cells (Diamond, et al., 1964; Diamond, et al., 1966), increased number and size of synapses (Briones, Klintsova, & Greenough, 2004; Rosenzweig & Bennett, 1996), increased dendritic branching, (Kolb & Whishaw, 1998), and increased capillary density and branching (Borowsky & Collins, 1989; Sirevaag & Greenough, 1987). Adaptive vascular changes associated with environmental enrichment in healthy animals include increased angiogenesis and active vascular recruitment within the hippocampus (Ekstrand, et al., 2008), which are closely associated with neurogenesis in this region (Palmer, et al., 2000). Preliminary findings over the past 15 years suggest that in healthy animals, exposure to environmental enrichment results in increased neurogenesis in adult animals (Fan, Liu, Weinstein, Fike, & Liu, 2007). It is unclear at this time whether similar effects on neurogenesis occur in the injured brain in response to environmental enrichment (Rakic, 2002). Positive neuroplastic changes at the molecular level are also associated with environmental enrichment, including elevated expression of brain derived neurotrophic factor

(BDNF), nerve growth factor (NGF), and glial cell derived neurotrophic factor (Ickes, et al., 2000; Smith & Zigmond, 2003).

In terms of promoting neuronal recovery following brain injury, evidence from animal studies suggests that exposure to environmental enrichment is associated with positive neuroplastic recovery following brain injury. For example, studies of brain-injury in rats revealed reduced atrophy and degeneration at and around the sites of cortical lesions (Passineau, et al., 2001), and reduction in apoptotic cell death by 45% in the rat hippocampus (Young, Lawlor, Leone, Dragunow, & During, 1999). Proposed mechanisms by which environmental enrichment promotes neuronal recovery following injury include activation of transcription factor and induction of neurotrophic growth factor expression (Mohammed, et al., 2002; Young, et al., 1999).

While studies have examined the differential effects of specific environmental enrichment elements on neuroplasticity in healthy animals, little is known about the differential impact of these elements on neuroplastic changes in brain-injured animals. In healthy animals, comparison studies have demonstrated that cognitive training has a stronger effect than physical enrichment alone on neuroplastic changes such as increased synaptogenesis in the hippocampus (Moser, et al., 1994) and cerebellum (Kleim, Lussnig, Schwarz, Comery, & Greenough, 1996) as well as gliogenesis (Gomez-Pinilla, So, & Kesslak, 1998). Both physical exercise alone and cognitive training result in increased cortical thickness in healthy animals (Anderson, Eckburg, & Relucio, 2002). In contrast to cognitive training, physical enrichment alone does not appear to affect synaptogenesis or to promote neuroprotection (Will, et al., 2004). Regarding neurogenesis, evidence suggests that physical exercise alone has a significant positive effect on actual proliferation of progenitor cells (Brown, et al., 2003), while cognitive training appears to promote the survival and integration of newly-generated neurons into existing neural networks (Kempermann, et al., 1998; Kempermann & Gage, 1999).

Human Studies of Environmental Enrichment

Research into the effects of environmental enrichment on brain structures, cognition, and functioning in humans is complicated by the marked diversity and complexity of environmental enrichment elements in human lives. Given the ethical limitations in conducting experimental studies of environmental enrichment in humans, much of the findings regarding environmental

enrichment in humans come from longitudinal, observational studies or else indirectly from findings in the field of developmental psychology. While randomized control trials with humans in this area are lacking, there is some evidence from observational and longitudinal studies in humans to support Schooler's (1987) environmental complexity theory, which posits that exposure to more complex environments leads to improvements in cognitive functioning. In general, positive correlations have been demonstrated between engagement in cognitively, socially, and physically-stimulating environments and cognitive functioning in healthy adults in both mid to late life (Arbuckle, Gold, & Andres, 1986; Christensen, et al., 1996; Craik, Byrd, & Swanson, 1987; Dik, Deeg, Visser, & Jonker, 2003; Elwood, et al., 1999; Erber & Szuchman, 1996; Gallacher, et al., 1999; Hill, Wahlin, Winblad, & Backman, 1995; Hultsch, Hammer, & Small, 1993; Luszcz, Bryan, & Kent, 1997; van Boxtel, Langerak, Houx, & Jolles, 1996).

Environmental enrichment and function in humans. Research on functional changes associated with environmental enrichment in humans draws from literature on human development, cognitive reserve, and neurological recovery. In general, findings suggest that exposure to environmental enrichment is associated with improvements in cognition and functioning in humans. For example, studies of human development demonstrate that social and cognitive deprivation in early development is associated with delays in cognitive and social development and poor psychological functioning in adulthood (Kaler & Freeman, 1994; Rutter, et al., 1999; Windsor, Glaze, & Koga, 2007). Further, exposure to higher levels of education in development and early adulthood is associated with a lower risk of behavioural manifestations of dementia (Hall, et al., 2007; Koepsell, et al., 1998) and better functional recovery following stroke (Elkins, et al., 2006) and traumatic brain injury (Kesler, et al., 2003). The question remains, however, regarding the direction of causality in environmental enrichment research in humans. Is it that elderly adults with intact cognitive abilities seek out cognitively-challenging activities, or is it that engagement in cognitive-stimulating activities promotes cognitive functioning in elderly adults? Likewise, is it that physically and cognitively independent elderly adults are sufficiently independent to maintain an active lifestyle, or does engagement in an active lifestyle promote functional independence in elderly adults? At this point in time, there is insufficient evidence to clarify these questions given the lack of randomized control trials in this field. In general, a critical review of the literature suggests a reciprocal relationship between intellectual functioning and engagement in an active lifestyle in that higher intelligence appears

to contribute to increased engagement in cognitively-stimulating activities, which subsequently contributes to diminished cognitive declines associated with normal aging (Schooler & Mulatu, 2001).

Within the neurological recovery literature, particularly the stroke literature, there has been increasing interest in examining the effect of treatment intensification on neurological recovery. Treatment intensification refers to increased frequency of neurological rehabilitation therapies and is based on the theory that (a) increased cognitive stimulation improves cognition and, conversely, that under-stimulation of cognition can cause or accelerate cognitive deterioration (Timothy A. Salthouse, 1991; Salthouse, Berish, & Miles, 2002), and that (b) general environmental enrichment (i.e., a cognitively, socially, physically, and spiritually engaged lifestyle) maintains cognitive and functional abilities and hinders cognitive and functional decline (Hultsch, et al., 1999). Preliminary findings in the field of stroke and traumatic brain injury recovery provide strong support for the efficacy of treatment intensification in promoting cognitive, motor, and functional recovery and preventing decline. For instance, in the stroke literature, several randomized control trial studies have demonstrated significant relationships between treatment intensification and functional improvement following stroke (Cifu & Stewart, 1999; Kwakkel, et al., 2004; Kwakkel, et al., 1997; Langhorne, et al., 1996; Teasell, Bayona, Salter, Hellings, & Bitensky, 2006).

Within the traumatic brain injury literature, few studies have examined explicitly the impact of treatment intensification on functional recovery, and none have examined the relationship between treatment intensification and neuroplastic changes post-injury. The results of observational studies and two randomized control trials addressing this issue have demonstrated positive effects of treatment intensification on functional outcome following traumatic brain injury (Carney, et al., 1999b; Teasell, et al., 2007). For instance, the results of two randomized control trials provide strong preliminary evidence that increased frequency of inpatient rehabilitation therapy was associated with greater degrees of functional recovery in the first few months following traumatic brain injury (Shiel, et al., 2001; Zhu, et al., 2001). Preliminary observational findings supporting maintenance of treatment intensification effects suggest that increased frequency of rehabilitation treatment at 4.5 months following traumatic brain injury is associated with better functional recovery and less cognitive decline at more than one year post-injury (Till, et al., 2008). The results of other observational studies on treatment

intensification in traumatic brain injury demonstrate that increased frequency of rehabilitation therapies is associated with improved functional recovery in the first year post-injury (Cifu, Kreutzer, Kolakowsky-Hayner, Marwitz, & Englander, 2003; Heinemann, et al., 1995; Spivack, Spettell, Ellis, & Ross, 1992) with the FIM and Rachos Los Amigos being the primary functional outcome measures in these studies. One of these observational studies (Heinemann, Hamilton, Linacre, Wright, & Granger, 1995) examined the differential effects of specific treatment modalities on functional recovery between hospital admission and discharge as measured by the FIM. When the predictive capabilities of physical, occupational, speech, and psychological therapies were examined individually, only psychological therapies significantly predicted functional recovery, specifically cognitive recovery, after controlling for level of functioning on admission, length of hospital stay, and age. However, the lack of findings in this study regarding efficacy of intensification of occupational, physical, and speech therapies in predicting functional improvement may reflect ceiling effects and lack of sensitivity to different aspects of recovery characteristic of the FIM used in this study to assess outcome.

Environmental enrichment and neuroplasticity in humans. With respect to environmental enrichment and neuroplastic changes in humans, several studies provide convergent evidence that engagement in cognitively-demanding tasks is associated with increased cerebral volume in brain areas that are functionally-related to the demands of the task (Draganski, et al., 2004; Draganski, et al., 2006; Ilg, et al., 2008). For example, one study involving repeated MRI scans of medical students demonstrated significant grey matter increases in the posterior and lateral parietal cortex bilaterally during periods of intense studying for medical exams, while no significant structural changes were observed during a subsequent semester break 3 months following the examination (Draganski, et al., 2006). Indirect evidence for positive neuroplastic changes associated with enriched environment includes studies showing a significant association between exposure to higher levels of education and greater dendritic branching in humans (Jacobs, et al., 1993). The developmental literature also demonstrates that social and cognitive deprivation during early development is associated with reduced activity across many brain systems, including the orbital prefrontal cortex, amygdala, hippocampus, temporal cortex, and brain stem (Chugani, et al., 2001) as well as diminished white matter connectivity between cortical regions (Eluvathingal, et al., 2006). No studies have yet examined the impact of

environmental enrichment on subacute atrophy in traumatic brain injury or the differential effects of specific elements of environmental enrichment on neuroplasticity in humans.

Meditation and Prayer: A Novel Element of Environmental Enrichment

Conventionally, environmental enrichment has been conceptualized as being composed of three primary elements: cognitive, physical, and social stimulation (the animal literature has also investigated novel and sensory stimuli as an additional element of enrichment) (Kolb & Gibb, 1991; Scarmeas & Stern, 2003; Stern, 2003). However, a fourth fundamental aspect of human experience that has been largely ignored in the environmental enrichment literature pertains to human spirituality in the form of meditation and/or prayer, an area that has only begun to be addressed in clinical practice and in the empirical literature on neuroplasticity. Consistent with Newberg and Iverson's (2003) neuropsychological model of meditation, for the purpose of the present study meditation and prayer are defined as practices of self-regulating the body and mind, thereby affecting mental events by engaging a specific attentional set that involves activation of the prefrontal cortex, thalamus, and hippocampus and deactivation of the posterior superior parietal lobule; these practices are a subset of those used to induce relaxation or altered states such as trance-induction techniques (Vaitl, et al., 2005).

Meditation. Positive neuroplastic changes associated with meditation have been demonstrated in the cerebral cortex, temporal lobe (Hoelzel, et al., 2008; Lazar, et al., 2000; Lou, et al., 1999), hippocampus, and brain stem of healthy adults. Within the cortex, neuroimaging studies show consistent findings of localized effects of meditation, with specific activation seen in frontal and prefrontal areas as well as the insula, all of which are associated with attention regulation (Cahn & Polich, 2006; Gusnard & Raichle, 2001; Lazar, et al., 2005; Manna, et al., 2010; Raichle, et al., 2001). Long-term meditation practice is associated with increased cortical thickness, and degree of cortical thickness is positively correlated with frequency of practice (Brefczynski-Lewis, Lutz, Schaefer, Levinson, & Davidson, 2007; Lutz, Greischar, Rawlings, Ricard, & Davidson, 2004). Preliminary studies have demonstrated specific activation of the hippocampus and hypocampal gyrus during meditation practice (Buckner & Carroll, 2007; Holzel, et al., 2007; Lazar, et al., 2000; Lou, et al., 1999; Newberg & Iversen, 2003). Further, preliminary studies have demonstrated increased grey matter concentration within the brainstem (Vestergaard-Poulsen, et al., 2009), left anterior temporal gyrus, and right hippocampus

(Hoelzel, et al., 2008) of long-term meditators, with years of meditation practice predicting degree of grey matter concentration in the anterior temporal gyrus and right hippocampus. These structural and functional brain changes associated with meditation suggest that meditation may be an important, but as yet ignored, aspect of environmental enrichment that may contribute to brain and cognitive reserve, with possible neuroprotective effects.

Evidence supporting this notion that meditation may have neuroprotective effects includes findings that meditation training is associated with reductions in physiological, subjective, and affective symptoms of anxiety and stress (Carlson, Speca, Patel, & Goodey, 2003; Eppley, Abrams, & Shear, 1989; Kabat-Zinn, et al., 1992) and associated reductions in cortisol and catecholamine levels (Carlson, et al., 2003; Infante, et al., 1998; Kamei, et al., 2000), hormones that can have negative effects on neuronal integrity within the hippocampus in particular (McCarthy, 2003). Reduced neurophysiological reactivity and reduced cortisol responses to stressful stimuli have been demonstrated in long-term meditators (Goleman, 2003; Kabat-Zinn, 1990). Given the vulnerability of hippocampal neurons to the toxic effects of cortisol released following traumatic brain injury (McCarthy, 2003), it is possible that engagement in meditation practice may contribute indirectly to neuroprotection of the hippocampus in the subacute phases post-injury. Additionally, controlled studies have demonstrated an association between meditation practice and reduction of cerebrovascular risk factors, including reductions in blood pressure and artherosclerosis (Walton, Schneider, & Nidich, 2004).

Prayer. The emerging field of neurotheology has begun to explore the relation between spirituality, spiritual experiences, and neurological processes (Giordano & Engebretson, 2006). Neuroimaging studies indicate that brain regions that are activated during prayer and spiritual experiences are similar to those activated during engagement in meditation. Specifically, functional neuroimaging studies of Buddhist monks and Franciscan nuns engaged in meditation or prayer revealed increased blood flow in the frontal lobes, cingulate gyri, and thalamus (Newberg, et al., 2001; Newberg, Alavi, Baime, Mozley, & d'Aquili, 1997; Seybold, 2007). Similar to meditation, engagement in prayer has been shown to be associated with increased activity in frontal and prefrontal regions (Aftanas & Golocheikine, 2001; Azari, et al., 2001; Newberg & Iversen, 2003) associated with attention regulation. Consistent with the literature on the protective effects of meditation, a review of the literature on prayer suggests that prayer is

associated with reductions in stress, anxiety, and depression as well as improvements in physical health, and these positive associations have been demonstrated across a range of populations (i.e., medical, psychiatric, and healthy samples) and age groups (Koenig, 2009). Evidence supporting the indirect neuroprotective effects of prayer includes findings that prayer and engagement in spiritual care practices are associated with lower blood pressure (Koenig, et al., 1998), enhanced cerebrovascular integrity, and improved immune functioning (Koenig, et al., 1997), which may increase the availability of glucose and delivery of cytoprotective factors to neurons as well as have positive effects on neuroimmune surveillance (Nithianantharajah & Hannan, 2009). Studies of young adults indicate that increased frequency of engagement in spiritual/prayer practice is associated with lower cortisol response to stressful stimuli and lower blood pressure (Tartaro, Luecken, & Gunn, 2005), which may have indirect neuroprotective effects in the hippocampus during the subacute phase following traumatic brain injury by way of reducing cortisol levels, a chemical to which hippocampal neurons are particularly vulnerable (McCarthy, 2003).

Limitations in meditation and prayer research. Empirical research into the neuroplastic effects of meditation and prayer is limited by the heterogeneity of types of meditation and prayer practice as well as heterogeneity in the expertise of the practitioners. Recommendations in the empirical literature on prayer and meditation include further study of the mechanisms by which prayer and meditation training might impact neurophysiology, neuroplasticity, and regulation of mental functions and increased longitudinal studies of brain changes over time associated with meditation and prayer.

Relevance of meditation and prayer to subacute atrophy. Given that meditation and prayer have numerous indirect protective effects on brain structure and function, mental health, and physical health conditions, it is proposed that spirituality (in the form of meditation and prayer practice) constitutes an important fourth element of environmental enrichment in humans, which may contribute to brain and cognitive reserve, thereby contributing to neuroprotection against subacute atrophy following traumatic brain injury. It is proposed that neuroprotective mechanisms involved in meditation and prayer may consist of: (a) activation and strengthening of attentional networks in frontal regions that support neuroplastic recovery of functional networks in other brain regions (Robertson & Murre, 1999); (b) specific activation of networks within the hippocampus (Newberg & Iversen, 2003) promoting maintenance of viable networks

and hindering atrophy in this region; (c) reduction of cortisol, a chemical that has toxic affects on hippocampal neurons (McCarthy, 2003) and that reduces hippocampal dendritic branching and hippocampal neurogenesis (Brown, Rush, & McEwen, 1999; Gould, Tanapat, Rydel, & Hastings, 2000; Jacobs, 2002; Vollmayr, Simonis, Weber, Gass, & Henn, 2003); and (d) enhancing cerebrovascular integrity, which is closely associated with neurogenesis in the hippocampus (Palmer, et al., 2000) possibly due to enhanced glucose availability to neurons, delivery of cytoprotective factors to neurons, and improved neuroimmune surveillance (Nithianantharajah & Hannan, 2009).

Implications of Environmental Enrichment and Neuroplasticity for Recovery from Brain Damage

Much of the research in neuroplastic recovery from brain damage comes from the literature on stroke, based on a conceptual framework of reorganization of functional cortical maps (Johansson, 2000; Nudo, et al., 2000). Within this framework, changes in cortical map organization are the result of both neuronal degeneration at the site of the lesion or injury as well as subsequent degeneration of adjacent tissue and even tissue in areas distal to the lesion. This framework is supported by neuroimaging evidence of brain atrophy in areas outside of the original lesion site in stroke (Johansson, 2000), as well as by computational models of plasticity in neural networks (Robertson & Murre, 1999).

Neuroplasticity and guided recovery of function. Based on computational neural network modeling of brain injury as well as clinical research findings, Robertson and Murre (1999) have developed a comprehensive model of neuroplastic and functional recovery following brain injury. The primary focus of the model is the concept of either rescue or collapse of damaged neural circuits in brain injury. In particular, Robertson and Murre (1999) propose that when a neural circuit loses a certain number of connections, the circuit is left in a critical state in which the network could either collapse and lose functional connectivity altogether or else be rescued and recover the original patterns of functional connection. The primary mechanism by which restitution or rescue of a network might occur is by means of simultaneous activation of two neurons or groups of neurons that have been disconnected due to injury. Therefore, the primary focus of rehabilitation based on this model would be restitution of damaged neural circuits through reactivation of the circuits.

The central hypothesis underlying Robertson and Murre's (1999) model of guided recovery of function is that normal learning and experience lead to neuroplastic changes in functional neural maps (Bayley, Teasell, Marshall, Cullen, & Colantonio, 2006; Merzenich, et al., 1996; Nudo, Milliken, Jenkins, & Merzenich, 1996; Pascual-Leone, et al., 2005). The assumption underlying this hypothesis is that the mechanisms involved in normal learning may also underlie restitution of damaged neural circuits following brain injury (Bayley, et al., 2006; Kolb, 1999; Kolb & Gibb, 1991; Kolb & Whishaw, 1998). In the brain, learning occurs by three primary neuroplastic mechanisms: (a) changing the strength of connections between neurons and neural networks, (b) adding or removing connections, or (c) by adding new cells (i.e., neurogenesis).

Similar to normal learning, the primary mechanism proposed to underlie guided recovery of function following brain injury is Hebbian learning, in which simultaneous activation of adjacent neurons or groups of neurons leads to increased connectivity between those neurons or groups of neurons. In colloquial terms, "cells that fire together, wire together" (Hebb, 1947). According to Robertson and Murre's (1999) model, in order for damaged neurons to be simultaneously activated, they must be separately connected to one functionally intact larger circuit. According to this model, with several repetitions of simultaneous stimulation within the context of this larger network, the damaged neurons will become reconnected. Evidence supporting Hebbian learning includes findings that electrical stimulation of cortical cells in temporal proximity increases the strength of synaptic connections between them (Dinse, Recanzone, & Merzenich, 1993). Conversely, non-synchronous activation of adjacent neurons may lead to inhibition of synaptic connections between them (Fitzsimonds, Song, & Poo, 1997; Singer, Valenta, Kotai, Drobny, & Weisz, 1990).

Within Robertson and Murre's (1999) model, stimulation and restitution of neural networks may be achieved by means of (a) exposure to non-specific (i.e., generalized) social and behavioural stimulation as well as (b) targeted stimulation of circuits involved in higher mental processes, such as attention. Indeed, attention has been shown to mediate synaptic activity associated with specific tasks (Buchel & Friston, 1997; Pascual-Leone, Grafman, & Hallett, 1995), whereby activity-dependent reorganization in sensory and motor maps requires active attention to the relevant stimuli; passive stimulation of the relevant circuits while attention is deployed elsewhere does not result in plastic reorganization of the stimulated circuits

(Recanzone, Schreiner, & Merzenich, 1993). Based on Robertson and Murre's (1999) model of plasticity and guided recovery of function, the primary goal of neurorehabilitation, particularly in the early stages post-injury, should be the restitution of damaged neural circuits through reactivation of the circuits by means of exposure to non-specific environmental enrichment as well as targeted stimulation of attention.

Proposing a Neuroprotective Model of Environment Enrichment and Subacute Hippocampal Atrophy

The presence of progressive subacute atrophy in a subset of traumatic brain injury patients reflects the operation of a number of negative neuroplastic mechanisms and a paucity of counteracting positive neuroplastic mechanisms. Specifically, at the molecular level, subacute atrophy is likely associated with prolonged glutamate excitotoxicity (Matsushita, et al., 2000; Yamamoto, et al., 1999), elevated cortisol (McCarthy, 2003), diminished expression of brain derived neurotrophic factor (BDNF) (Chen, et al., 2005) and accumulation of amyloid precursor protein and amyloid beta peptides (Smith, Chen, et al., 2003), all of which are likely to inhibit recovery of damaged neurons and to contribute to cell death via apoptotic mechanisms. At a cellular and network level, gliosis at injury sites likely inhibits reconnection or reorganization of functional networks, and under-stimulation of viable tissue by afferent projections from damaged tissue likely leads to structural decay of networks and atrophy of associated tissue.

Drawing on Mahncke's (2006) theoretical model of negative neuroplasticity and functional loss in normal aging, these negative neuroplastic mechanisms proposed to underlie subacute atrophy may be promoted by patients' experiences and behaviour following brain injury. Specifically, two core behavioural factors drawn from Mahncke's model that may be contributing to negative neuroplastic changes in traumatic brain injury include a reduced schedule of activity and negative learning. There are a number of factors following traumatic brain injury that can hinder an individual from engaging in the variety of cognitively, socially, and physically stimulating activities that might promote neuroplastic recovery. Cognitive deficits may make it difficult for the individual to return to the same job or level of productivity as prior to their injury, which limits their exposure to the cognitive challenges and social stimulation that might promote positive neuroplastic changes. Physical deficits may also interfere with social engagement given the environmental and transportation barriers and social stigma faced by

persons with physical disabilities (Ownsworth & McKenna, 2004). Emotional difficulties or personality changes secondary to injury may place a strain on interpersonal relationships, leading to diminished exposure to stimulating social interaction. In these ways, impairments associated with traumatic brain injury can preclude an individual from returning to work or social roles that could potentially promote positive neuroplastic changes. In this way, injury-related impairments may contribute to a reduced schedule of activity and associated diminished stimulation of brain networks, increasing the likelihood of negative neuroplastic changes following injury. Negative learning may also lead patients to actively avoid activities that they find to be more challenging or frustrating since their injury. Many activities that were previously enjoyed or completed with ease may be experienced as difficult and frustrating by a person with cognitive impairments. Novel tasks encountered in daily life that require learning, memory, speeded information processing, or problem solving are likely to be particularly difficult for individuals following traumatic brain injury (Christensen, et al., 2008; Hellawell, et al., 1999; Ruttan, et al., 2008), and as such, may be avoided, resulting in a negatively-reinforced cycle of avoidance of challenging activities leading to diminished activation of brain networks and associated negative neuroplastic changes (Blake, et al., 2006).

Despite the ominous implications of this negative plasticity model of subacute atrophy, findings from the fields of environmental enrichment and brain and cognitive reserve (BCR), as well as models of neuroplastic recovery of function, provide optimism that exposure to environmental enrichment has neuroprotective effects that could counteract negative neuroplastic mechanisms and halt or hinder subacute atrophy while promoting recovery. Indeed, evidence from epidemiology and animal model studies provides extensive convergent evidence that all brain disorders, even those in which genetics play a primary role, can be modulated by environmental factors (Spires & Hannan, 2005). For example, animal studies demonstrate that exposure to environmental enrichment (i.e., cognitive, physical, and social stimulation) is associated with a host of positive neuroplastic changes, including increases in brain size, cortical thickness, neuron size, dendrite branching, dendrite spine density, and number of synapses per neuron (Diamond, 2001; Grossman, Churchill, Bates, Kleim, & Greenough, 2002; Kolb, 1999; Kolb & Whishaw, 1998; Nudo, Milliken, Jenkins, & Merzenich, 1996; Rosenzweig & Bennett, 1996). In addition, functional neuroplastic changes associated with experience and behaviour include reorganization of functional cortical networks, whereby intact neuronal networks assume

the functions of damaged networks (Bayona, et al., 2005; Buonomano & Merzenich, 1998; Johansson, 2000; Pascual-Leone, et al., 2005). Furthermore, computational modeling suggests that vulnerable neural networks can be strengthened and repaired through Hebbian learning by way of exposure to non-specific environmental stimulation and targeted stimulation of attentional processes (Robertson & Murre, 1999). Based on these findings, seminal reviews of the literature conclude that brains that have received increased stimulation, through enhanced mental and physical activity, are better able to mount neuroprotective responses against neurodegenerative processes, traumatic insults, or other forms of adult-onset neural dysfunction (Nithianantharajah & Hannan, 2009).

The present study proposes a novel, integrated neuroprotective model of environmental enrichment and subacute hippocampal atrophy in traumatic brain injury. This model draws on theoretical models and research findings from the literature on environmental enrichment (Diamond, 2001; Green, 2006; Kolb & Gibb, 1991; Will, et al., 2004), brain and cognitive reserve (Nithianantharajah & Hannan, 2009), and neuroplastic recovery of function in brain injury (Mahncke, et al., 2006; Robertson & Murre, 1999; Teasell, et al., 2006). Environmental enrichment in humans is conventionally viewed as being comprised of three primary elements: cognitive, physical, and social stimulation. The integrated neuroprotective model of environmental enrichment and subacute atrophy proposed in the present study posits a novel fourth element of environmental enrichment that is only beginning to be explored in the neuroplasticity and clinical rehabilitation literature, namely spiritual practice in the form of meditation and/or prayer. This novel, integrated neuroprotective model is the foundation of the current study and serves to facilitate understanding of the complex relationships among environmental enrichment, hippocampal subacute atrophy, and functional outcome following moderate to severe traumatic brain injury. This model is represented in Figure 1.

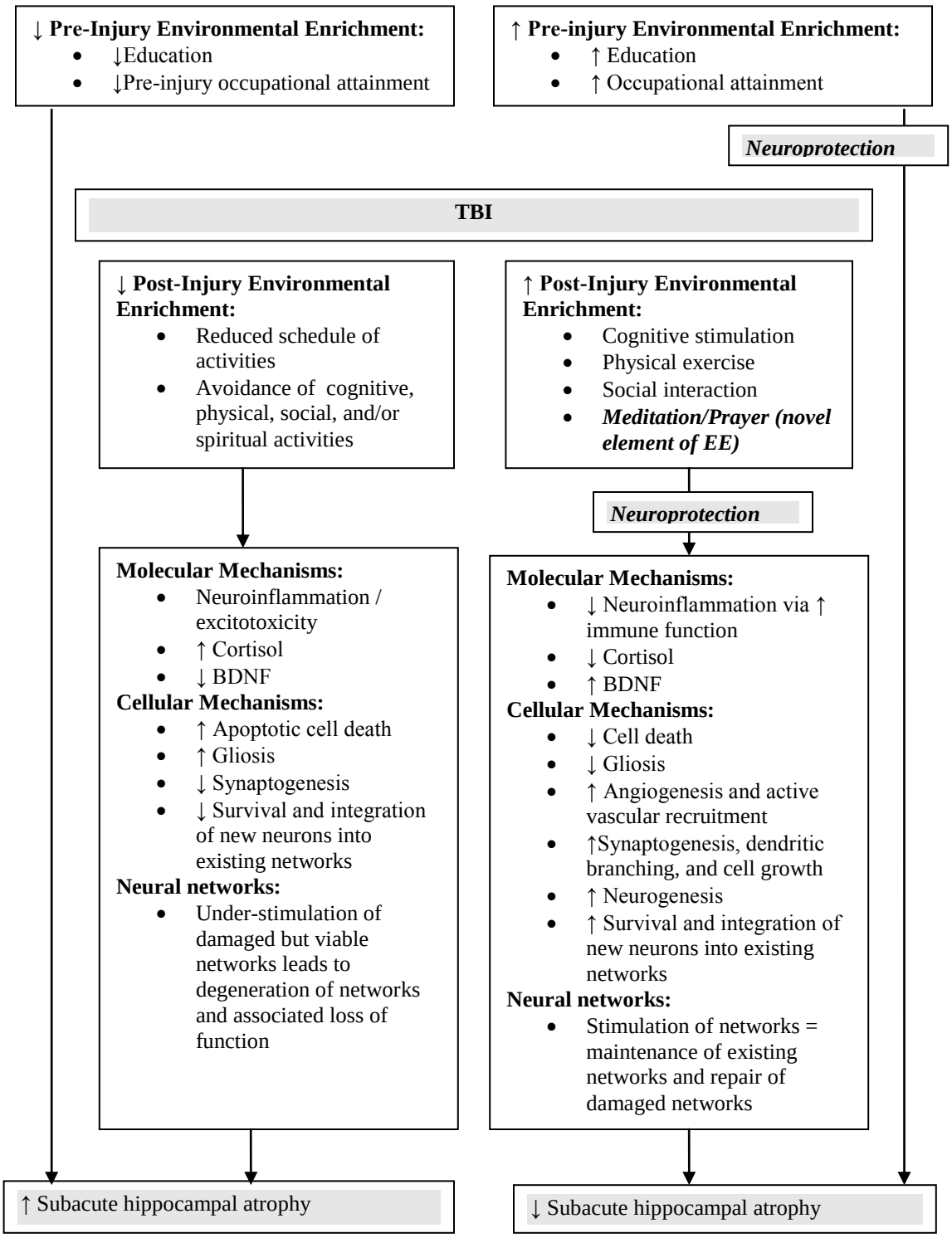

Figure 1. **Proposed model of neuroprotection against subacute hippocampal atrophy via environmental enrichment.**

Rationale and Assumptions of the Present Study

Study Rationale

The present study's data regarding clinical and control participants' hippocampal volumes at 5 months and 24+ months post-injury were obtained from an existing database at the Toronto Rehabilitation Institute; the MRI data had been collected previously for a larger study regarding the natural history and mechanisms of recovery following traumatic brain injury. The present study aimed to replicate the relatively few recent studies demonstrating subacute atrophy following traumatic brain injury in humans. Only a few studies addressing this question have conducted initial imaging at greater than 4.5 months post-injury. By using an initial imaging window beyond the acute recovery stage, the present study aimed to demonstrate that atrophy seen over time represents actual atrophy of neuronal tissue rather than resolution of acute effects of injury, such as reduction of brain swelling or resolution of hematomas. For clinical participants drawn from the database of the larger study, initial scanning had been conducted at 3.6 to 5.2 months post injury, well beyond the likely resolution of acute injury effects, and follow-up scans had been conducted between 1.9 to 4.6 years post-injury for all subjects. As such, there was no overlap in time windows between subjects.

Functional outcomes of traumatic brain injury are often assessed using measures of broad, global outcomes, such as the Barthel Index (Mahoney & Barthel, 1965) or the Functional Independence Measure (Uniform Data System for Medical Rehabilitation, 1993). However, such broad outcome measures lack sensitivity to specific areas of functioning, such as return to varying types of productivity post-injury. Further, many previous studies of vocational outcome have not taken into account or differentiated between types of productivity (e.g., paid employment, homemaking, academic involvement, volunteer work, childcare) and have failed to compare post-injury productivity to pre-injury levels. The present study addressed these limitations by utilizing data that tapped into a wide range of types of productivity, including paid employment, volunteer work, childcare, and engagement in school. In addition, the present study examined return to productivity relative to premorbid productivity. To date, only one study has examined specifically and explicitly the relationship between subacute atrophy and vocational outcome following traumatic brain injury. Evidence of such relationships would offer valuable

information about the functional impacts of cerebral atrophy on day-to-day functioning of brain-injured individuals.

Assumptions Underlying the Current Study

Assumption 1. The present study is based on the Hebbian principle of learning and neuroplasticity which posits that "neurons that fire together wire together" (Hebb, 1947). Specifically, Hebb posited that "when an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased." Based on this principle, repeated activation of a functional neural network is assumed to strengthen the connections within that network. Conversely, inactivation of a neural network is assumed to weaken the network connections and may lead to degeneration of the network altogether and loss of the functions supported by that network. Finally, damage to one neural circuit can lead to downstream degeneration of viable circuits that are innervated by projections from the damaged circuit.

Assumption 2a. Environmental experience and behaviour lead to neuroplastic changes. In particular, increased environmental enrichment leads to positive neuroplastic changes such as an increased number of synapses, increased dendritic branching, increased maintenance of intact networks, and increased recovery of damaged networks in humans. Conversely reduced exposure to environmental enrichment leads to negative neuroplastic changes in humans.

Assumption 2b. Brains that have received increased stimulation, through enhanced mental and physical activity, are better able to mount neuroprotective responses against neurodegenerative processes, traumatic insults, or other forms of adult-onset neural dysfunction, consistent with the concept of brain and cognitive reserve (Nithianantharajah & Hannan, 2009).

Assumption 3. Neuroplastic changes are associated with functional consequences following traumatic brain injury.

Assumption 4. What remains unclear from preliminary research findings of subacute atrophy in humans is at what stage the majority of subacute atrophy actually occurs. As a result of practical limitations related to availability of imaging data for the present study, the time window for initial and follow-up MRI scans was 5 months and 2-5 years post-injury. Given the

unavailability of imaging data at intermediate time points (for example, 12 months post-injury), it is unclear whether the majority of atrophy occurred in the first 12 months post-injury or occurred in a gradual linear manner between 5 months and 2-5 years post-injury. Based on evidence from human functional recovery studies showing cognitive decline in a subset of individuals between 12 months and 5 years post-injury (Millis, et al., 2001), and based on animal study findings of progressive neurodegeneration during multiple time windows in the chronic phase post-injury (Rodriguez-Paez, Brunschwig, & Bramlett, 2005; Smith, et al., 1997), it is assumed that subacute cerebral atrophy seen in the present study represented a gradual progression of atrophy between initial and follow-up imaging.

Objectives and Hypotheses

The following hypotheses are proposed in accordance with the previously-outlined objectives of the present study.

Objective 1. Examine the relationship between environmental enrichment and subacute hippocampal atrophy.

Objective 1.1. Post-injury environmental enrichment and subacute hippocampal atrophy.

Hypothesis 1.1a. Generalized environmental enrichment. Given that exposure to environmental enrichment (i.e., cognitive, physical, and social stimulation) is associated with a host of positive neuroplastic changes, including increases in brain size, cortical thickness, neuron size, dendrite branching, dendrite spine density, and number of synapses per neuron (Diamond, 2001; Grossman, Churchill, Bates, Kleim, & Greenough, 2002; Kolb, 1999; Kolb & Whishaw, 1998; R. J. Nudo, Milliken, Jenkins, & Merzenich, 1996; Rosenzweig & Bennett, 1996), and given evidence that brains that have received increased stimulation, via enhanced mental and physical activity, are better able to mount neuroprotective responses against neurodegenerative processes, traumatic insults, or other forms of adult-onset neural dysfunction (Nithianantharajah & Hannan, 2009), it was hypothesized that greater generalized environmental enrichment (i.e., frequency of cognitive, physical, and social engagement) between 5-12 months post-injury would predict less bilateral hippocampal atrophy between 5-24+ months post-injury.

Hypothesis 1.1b. Cognitive activity. Given the primarily cognitive functions supported by the hippocampus (Leuner & Gould, 2010), and given that comparison studies in animals have demonstrated that cognitive training has a stronger effect than physical exercise alone on increasing synaptogenesis in the hippocampus (Moser, et al., 1994) and promoting the survival of newly-generated neurons in the hippocampus and their integration into neural networks (Kempermann, Brandon, & Gage, 1998; Kempermann & Gage, 1999), it was hypothesized that, of the three conventional elements of environmental enrichment (i.e., cognitive, physical, and social activities), cognitive activity between 5-12 months would account for the greatest amount of variance in predicting bilateral hippocampal atrophy between 5-24+ months post-injury.

Hypothesis 1.1c. Meditation/prayer. Consistent with Newberg and Iverson's (2003) neuropsychological model of meditation, given (a) that meditation and prayer practice involves activation of a specific attentional network including activation of the prefrontal cortex, thalamus, and hippocampus (Buckner & Carroll, 2007; Holzel, et al., 2007; Lazar, et al., 2000; Lou, et al., 1999; Newberg & Iversen, 2003); (b) evidence of increased grey matter concentration and volumes within the right hippocampus (Hoelzel, et al., 2008; Luders, Toga, Lepore, & Gaser, 2009) of long-term meditators, with years of meditation practice predicting degree of grey matter concentration in the right hippocampus; (c) evidence of an association between meditation and reduced cortisol, a chemical that has toxic affects on hippocampal neurons (McCarthy, 2003) and that reduces hippocampal dendritic branching and hippocampal neurogenesis (Brown, et al., 1999; Gould, et al., 2000; Jacobs, 2002; Vollmayr, et al., 2003); and (d) evidence of an association between meditation/prayer and reduction of cerebrovascular risk factors (Koenig, et al., 1997; Walton, et al., 2004), it was hypothesized that greater frequency of meditation/prayer between 5-12 months would predict less atrophy of the right hippocampus between 5-24+ months post-injury after controlling for frequency cognitive, physical, and social engagement.

Hypothesis 1.1d. Therapy hours. Given preliminary evidence supporting the efficacy of treatment intensification in promoting cognitive, motor, and functional recovery and preventing decline following traumatic brain injury and stroke (Cifu & Stewart, 1999; Kwakkel, et al., 2004; Kwakkel, et al., 1997; Langhorne, et al., 1996; Teasell, Bayona, Salter, Hellings, & Bitensky, 2006), it was hypothesized that a greater number of therapy hours per week between 5-12 months would predict less bilateral hippocampal atrophy between 5-24+ months post-injury.

Objective 1.2. Pre-injury environmental enrichment factors and subacute hippocampal atrophy.

Hypothesis 1.2a. Years of education. Given (a) evidence of an association between higher levels of education and better cognitive and functional recovery following traumatic brain injury (Christensen, et al., 2008; Green, Colella, Christensen, et al., 2008; Kesler, et al., 2003; Till, et al., 2008) and (b) evidence for a significant association between exposure to higher levels of education and greater dendritic branching in humans (Jacobs, et al., 1993), it was hypothesized that greater years of education would predict less bilateral hippocampal atrophy between 5-24+ months post-injury.

Hypothesis 1.2b. Pre-injury occupational attainment. Although no human studies have yet explored the relationship between pre-injury occupational attainment and subacute atrophy following traumatic brain injury, based on evidence of an association between pre-injury occupational status and functional outcome (Felmingham, 2001; Gollaher, 1998; Keyser-Marcus, 2002) following traumatic brain injury, it was hypothesized that higher pre-injury occupational attainment would predict less bilateral hippocampal atrophy between 5-24+ months post-injury.

Objective 2. Examine the relationship between subacute hippocampal atrophy and return to productivity.

Hypothesis 2. Bilateral hippocampal atrophy and return to productivity. There are few imaging studies that show reliable correlations between subacute hippocampal atrophy and specific functional outcomes in traumatic brain injury (Levine, et al., 2006). However, given (a) preliminary evidence of subacute atrophy associated with poorer vocational outcome (van der Naalt, et al., 1999); (b) evidence of broad associations between subacute global brain atrophy and poorer clinical outcome (Blatter, Bigler, Gale, & et al., 1997; Jellinger, 2004; Levin, Meyers, C.A., Grossman, R.G., & Sarwar, M., 1981; MacKenzie, et al., 2002; Mellick, Gerhart, & Whiteneck, 2003; National Institute of Mental Health, 1998); and (c) evidence of an association between subacute hippocampal atrophy and poorer recovery of memory following traumatic brain injury (Ariza, et al., 2006; Bigler, Blatter, Gale, et al., 1996; Green, 2009; Serra-Grabulosa, et al., 2005; Tate & Bigler, 2000), it was hypothesized that bilateral hippocampal atrophy between 5-24+ months post-injury would be negatively correlated with return to productivity at 24+ months post-injury.

Chapter 3: METHODS

Participants

The 21 clinical participants in this study were part of a larger research study being conducted at the Toronto Rehabilitation Institute, a large publicly-funded inpatient neurorehabilitation hospital. The focus of the larger study was to investigate the natural history and mechanisms of recovery following traumatic brain injury. The neurorehabilitation hospital has a province-wide catchment area, is located in an urban center, and sees patients both with and without motor-vehicle or private insurance. Participants underwent prospective assessments at 5 months, 12 months, and 24+ months post-injury.

Inclusion criteria consisted of the following: (a) acute care medical diagnosis of traumatic brain injury; (b) posttraumatic amnesia of 1 hour or more and/or Glasgow Coma Scale score of 12 or less either at emergency or at the scene of the accident and/or positive CT or MRI findings; (c) between 17 and 80 years old; (d) able to follow simple commands in English based upon Speech Language Pathologist intake assessment; and (e) competent to provide informed consent for study or availability of a legal decision maker (Appendix A). Exclusion criteria included: (a) orthopaedic injuries affecting both upper extremities; (b) diseases primarily or frequently affecting the central nervous system, including dementia of Alzheimer's type, Parkinson's disease, multiple sclerosis, Huntington's disease, lupus, or stroke; (c) a history of psychotic disorder; (d) non-emergence from posttraumatic amnesia by 6 weeks post-injury, as measured by the Galveston Orientation Amnesia Test; (e) traumatic brain injury secondary to another neurological event, such as a fall due to stroke; and (f) failure on a symptom validity test (Test of Memory Malingering) at any of the assessments.

The demographic and injury characteristics of the clinical sample are shown in Table 1. The mean age of the clinical sample was 35 years, with the minimum being 19 years of age and the maximum 58 years of age. Males made up the majority of the clinical sample with a ratio of 13:8 for males:females. The mean level of education for the clinical sample was 13 years (*SD*=3) and participants' education ranged from grade 8 to graduate studies. The clinical sample consisted of individuals with moderate to severe traumatic brain injury with a mean GCS score of 8 (*SD*=4; range=3-13), mean duration of posttraumatic amnesia being 4.4 days (*SD*=1.1; range=1-6), and mean acute care length of stay being 34 days (*SD*=19; range=14-88). Of the 21

clinical participants, 16 participants had insurance coverage at 12 months post-injury, and 6 participants were involved in litigation at 12 months.

The control group consisted of 10 healthy adults with no history of neurological or psychiatric conditions. The mean age of the control group was 38 years (*SD*=12 years; range=21-60 years). The mean education of the control group was 18 years (*SD*=2; range=14-21 years).

Table 1

Demographics

Age/sex (Mean=35 years; *SD*=13)	**Education (Mean=13 years; *SD*=3)**	**Injury type**	**GCS (Mean=8; *SD*=4)**	**PTA (Mean=4.4 days; *SD*=1.1)**	**%Change in bilateral hippocampal volume (Mean= -2.82%; *SD*=4.06)**	**Hippocampal volume change z-score (compared to control sample) (Mean= -6.25; *SD*=8.73)**
42/M	17	Fall	5	5	-9.89	-21.46
47/M	19	Fall	13	4	-9.12	-19.80
51/F	16	Fall	10	3	-8.69	-18.87
20/M	12	Struck	4	1	-6.85	-14.93
32/M	15	Fall	13	5	-6.58	-14.2
21/M	9	MVA	8	5	-5.27	-11.52
44/F	16	Fall	6	4	-4.06	-8.92
58/M	12	MVA	13	4	-3.37	-7.44
57/F	12	MVA	13	6	-3.27	-7.23
24/F	8	MVA	3	6	-3.22	-7.11
28/F	17	Fall	3	5	-3.10	-6.86
41/M	9	MVA	13	4	-2.82	-6.25
22/M	9	Fall	4	5	-1.85	-4.18
20/M	12	MVA	5	5	-1.21	-2.78
28/F	15	MVA	7	5	-1.01	-2.36
19/M	9	MVA	Unknown	4	-0.97	-2.28
52/F	12	MVA	13	4	-0.61	-1.51
40/F	12	MVA	3	4	1.53	3.11
31/M	14	MVA	6	6	2.77	5.76
42/M	11	MVA	3	4	2.98	6.22
25/M	16	Fall	7	4	5.43	11.48

With respect to anxiety, BAI scores (averaged across three time points: 5 months, 12 months, and 24+ months post-injury) of the clinical sample ranged from 0 (none) to 23 (moderate anxiety) (mean=7; *SD*=7). In particular, 15 of the 21 clinical participants reported minimal to no anxiety, 6 reported mild to moderate anxiety, and none reported severe anxiety. In terms of depression, BDI-II scores in the clinical sample ranged from 0 (none) to 25 (severe depression) (mean=9; *SD*=7). In particular, 13 of the 21 clinical participants reported minimal to

no depression, while 7 participants reported mild to moderate depression, and no participants reported severe depression. Unsurprisingly, BAI and BDI-II scores correlated significantly (r=.86, p<.001). Of the 21 clinical participants, 7 participants were taking SSRI's and/or lithium at 5, 12, and/or 24+ months post-injury. Those taking SSRI's and/or lithium also presented with higher levels of depression on the BDI-II (τ=.45, p<.05). Only 3 of the 21 clinical participants met criteria for likely substance abuse at 5 to 12 months post-injury, defined as greater than moderate alcohol use (i.e., greater than 3 ounces of alcohol per day on average) or regular marijuana use (i.e., marijuana use 4 days per week on average) (Lezak, et al., 2004).

Measures

Control Variables: Demographic Characteristics and Injury Variables

A number of control variables were examined in order to rule out their potential effects on hippocampal changes or return to productivity. These included age at injury, estimated premorbid intelligence (based on scores on the Wechsler Test of Adult Reading administered at 12 months post-injury), injury severity (measured as Glasgow Coma Scale scores, duration of posttraumatic amnesia, and duration of acute care length of stay), level of disability at acute care discharge (based on Functional Independence Measure scores at acute care discharge), medications (SSRI and/or lithium post-injury), insurance and/or litigation involvement post-injury, substance abuse history (defined as greater than 3 ounces of alcohol per day on average or marijuana/other substance use 4 days per week on average) (Lezak, et al., 2004), psychological distress (based on Beck Depression Inventory-II and Beck Anxiety Inventory scores). Given that BDI-II and BAI scores correlated significantly with one another (r=.86, p<.001), BDI-II was used as a primary measure of psychological distress.

Demographic and injury variables. Information regarding age at injury, socioeconomic status, injury severity, and level of disability at acute care discharge was obtained from review of patients' medical records. Acute care length of stay was calculated based on admission and discharge dates from the acute care hospital.

Semi-structured interview. A semi-structured interview (Appendix B) was administered to participants and their caregivers to obtain information regarding medications, insurance and/or litigation involvement, and substance abuse history, defined as greater than moderate alcohol use

(i.e., greater than 3 ounces of alcohol per day on average) or regular marijuana/other substance use (i.e., 4 days per week on average) (Lezak, et al., 2004).

Beck Depression Inventory-II (BDI-II). The BDI-II (Beck, Steer, & Brown, 1996) is a brief self-report inventory that assesses for the presence and severity of symptoms of depression. It is composed of items relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex. The BDI-II was administered to participants at 5, 12, and 24+ months post-injury to assess for the presence and severity of symptoms of depression. Scores were averaged across these three time points.

Beck Anxiety Inventory (BAI). The BAI (Beck, 1993) is a 21-item self-report inventory that assesses for the presence and severity of symptoms of anxiety. Each item is descriptive of subjective, somatic, or panic-related symptoms of anxiety. The BAI was administered to participants at 5, 12, and 24+ months post-injury to assess for the presence and severity of symptoms of depression. Scores were averaged across these three time points.

Wechsler Test of Adult Reading (WTAR). The WTAR (Wechsler, 2001) is a reading test composed of a list of 50 words that have atypical grapheme to phoneme translations. The intent in using words with irregular pronunciations is to minimize the current ability of the participant to apply standard pronunciation rules and assess previous learning of the word. Estimated premorbid intelligence quotient was estimated for each participant using the Wechsler Test of Adult Reading administered at 12 months post-injury. The WTAR has been shown to have good psychometric properties for predicting premorbid intelligence in traumatic brain injury samples (Green, Melo, et al., 2008; Wechsler, 2001), although some researchers suggest that in cases of severe traumatic brain injury, reading tests such as the WTAR may under-estimate premorbid intellectual functioning to some degree, particularly if administered during the initial few months post-injury (Freeman, Godfrey, Harris, & Partridge, 2001; Mathias, Bowden, Bigler, & Rosenfeld, 2007; Riley & Simmonds, 2003).

Independent Variables: Environmental Enrichment Factors

Post-injury environmental enrichment. Assessment of post-injury environmental enrichment was based on participants' self-reported frequency of engagement in a variety of

activities involving cognitive, physical, and social demands as well as meditation/prayer engagement. Given the absence of reliable or valid published measures of environmental enrichment in humans, environmental enrichment activities were listed on a self-report questionnaire designed for the purpose of the present study, entitled the Lifestyle Activities Questionnaire (LAQ) (Appendix D). Participants were asked to rate the frequency at which they engaged in each of the activities listed on an ordinal scale. Cognitive, physical, and social activities on the LAQ were obtained from a theoretically-derived and empirically-tested inventory developed by Salthouse and colleagues (Salthouse, Berish, & Miles, 2002), which was constructed by specifying 22 common activities that a sample of 1200 adults, ranging from the age of 18-97 years, rated in terms of their cognitive demand (where 1=low demand, corresponding to sleeping, and 5=high demand, corresponding to working on a tax form). Additional activities on the LAQ that were not on Salthouse's inventory included items pertaining to engagement in prayer and/or meditation and frequency of engagement in sports or physical activity at the gym.

In order to create meaningful aggregates of environmental enrichment, ordinal scores on the LAQ were transformed into weighted scores that corresponded to hours per week. Specifically, ratings of "didn't do at all" and "less than once a week" were transformed to a score of 0; "once or twice a week" was transformed to 1; "several times a week" was transformed to 3; "an hour or so most days" was transformed to 7; and "several hours a day" was transformed to 20. Ordinal self-reported ratings of frequency of activities were deemed to be most easily understood by patients and least likely to result in missing data due to patients' potential difficulty calculating number of hours each week. Transformation of ordinal scores into weighted scale scores was done to provide a meaningful and ecological aggregate of environmental enrichment that retained information about idiosyncratic types, frequencies, and durations of activities endorsed among individuals in the sample. This method was deemed to be an improvement on previous methods of aggregating environmental enrichment activities, in which individuals were classified as "active" if they endorsed doing even one mentally-challenging activity for one hour per week or more (Bosma, et al., 2002; Richards, Hardy, & Wadsworth, 2003).

A semi-structured interview (Appendix C) was administered to participants and their caregivers to obtain information regarding frequency/hours of engagement in therapy between 5-12 months post-injury.

Pre-injury environmental enrichment. Information regarding pre-injury level of education and pre-injury occupational level was obtained during a semi-structured interview (Appendix B) with patients and caregivers. Ratings of pre-injury occupational level consisted of a dichotomous rating of higher-cognitive-demand occupations (i.e., professions such as dentist or teacher or university student) or lower-cognitive-demand occupations (i.e., skilled trades or homemaking).

Dependent Variables: Hippocampal Volume and Return to Productivity

Hippocampal volume. Data regarding clinical and control participants' hippocampal volumes at 5 months and 24+ months post-injury were obtained from an existing database at the Toronto Rehabilitation Institute; the MRI data had been acquired previously for a larger study of the natural history and mechanisms of recovery following traumatic brain injury. All clinical and control participants' MRI head scans had been conducted at the Toronto General Hospital, part of the University Health Network (UHN). From the MRI scans, hippocampi had been manually outlined by two trained operators at the Brain Stimulation and Neuroimaging Lab of the Alfred and Monash University's Department of Medicine based on the protocol suggested by Pruessner and colleagues (Pruessner, et al., 2000). All raw hippocampal volumes were expressed in mm^3. For the purpose of the present study, hippocampal volume change between 5 months (T1) post-injury and 24+ months (T2) post-injury was measured using the following formula:

$$\text{Hippocampal volume change} = \frac{(\text{Vol T2} - \text{Vol T1})}{(\text{Vol T2} + \text{Vol T1}) / 2} * 100$$

Return to productivity. Two separate measures of return to productivity were used. Firstly, a dichotomous classification of return to premorbid level of productivity was made for all patients. Activities included paid employment (full or part-time), volunteer employment, schooling, parenting, home-making, and active retirement (i.e., participation in cultural and physical activities). Information on pre-morbid and current activities was collected from patients, and corroborated by caregivers. Two trained clinicians ascertained the match, or lack thereof, between current and previous primary role. In all cases, clear consensus was reached, with

patients either returning to prior role at the same level of activity or not returning at all. The second measure of return to productivity consisted of participants' scores on the Productive Employment subscale of the Brain Injury Community Rehabilitation Outcome Scales (BICRO-39; (Powell, et al., 1998) (Appendix E) a factorally-determined subscale of hours of engagement in productive employment activities, including paid work, unpaid or volunteer work, studying or training, and looking after children. The BICRO-39 has been shown empirically to have content validity, good test retest reliability, good construct validity, and good inter-rater reliability (patient and caregiver) (Powell, et al., 1998).

Design and Procedures

The study involved retrospective examination of data that had been collected prospectively for the purposes of a larger research study regarding the natural history and mechanisms of recovery following traumatic brain injury. The procedure for MRI acquisition and analysis and the time window between initial and follow-up MRI scans were the same between the clinical and control groups. For clinical participants, initial MRI scans were acquired at a mean of 4.5 months (*SD*=0.4; range=3.6-5.2 months) post-injury and follow-up MRI scans were acquired at 2.5 years (*SD*=0.6; range=1.9-4.6 years) post-injury. Ratings of environmental enrichment were obtained at 4.5 months (*SD*=0.4; range=3.6-5.2 months) post-injury and again at 12.1 months (*SD*=0.7; range=10.6-13.0 months) post-injury. Ratings of return to productivity were obtained at 2.5 years (*SD*=0.6; range=1.9-4.6 years) post-injury.

Chapter 4: RESULTS

Preliminary Analyses

All analyses were conducted using SPSS for Windows, student version 18.0. Prior to analysis, raw data were examined for data entry errors, missing values, and satisfaction of univariate assumptions. In order to investigate the research questions, both descriptive and inferential statistical analyses were employed.

Multiple Comparisons

The small sample size precluded inclusion of more than three variables in any one statistical model in the present study. As such, examination of the hypotheses required multiple separate analyses. Some researchers advocate for the use of a Bonferroni-Holm correction (Holm, 1979) to reduce the likelihood of a Type I error resulting from multiple comparisons (Curtin & Schulz, 1998; Holm, 1979). When the conservative Bonferroni-Holm correction was applied to the present study analyses, none of the primary analyses achieved significance at the .005 level. While reducing the likelihood of a Type I error, the conservative nature of the Bonferroni and/or Bonferonni-Holms correction increases the likelihood of a Type II error (Norman & Streiner, 2000), thus increasing the possibility of missing actual relationships that might be occurring among variables in the present study. Failure to identify actual relationships occurring among variables in the present study was deemed incompatible with the over-arching aim of the present study. This over-arching aim was to elucidate the relationship between environmental enrichment and hippocampal subacute atrophy, the purpose of which was to inform the development of a novel theoretical model of subacute cerebral atrophy, which is currently only in the preliminary stages of development. Given that little is known about relationships between environmental enrichment and subacute hippocampal atrophy in humans, and given the paucity of theoretical models of subacute hippocampal atrophy in humans, a Bonferonni correction was deemed to be excessively conservative and inappropriate for the exploratory aims of the present study. Furthermore, some researchers propose that Bonferonni corrections are appropriate to use when searching for significance without a priori hypotheses (Prenger, 1998), which does not apply given the directional and a priori nature of the present study's hypotheses.

Assessment of Normality of Distributions, Outliers, and Colinearity

All scaled variables were screened for univariate normality using skewness and kurtosis values. Variables were considered non-normal if corresponding *z* scores exceeded a conservative critical value ($z > 3.08$, $p < .001$) (Tabachnick & Fidell, 2001). Values were within the acceptable range for all scaled variables.

The presence of univariate outliers was assessed by transforming raw scaled data into standardized scores (i.e., *z* scores) and examining these scores for extreme values. Scores were considered true outliers if their corresponding *z* values exceeded 3.08, $p < .001$ (Tabachnick & Fidell, 2001). No participant exceeded this critical value for any of the scaled variables. Multicollinearity of control variables and independent variables were assessed using Pearson correlation matrices. No control variables or independent variables met criteria for multicolinearity (e.g., $r > .90$) (Tabachnick & Fidell, 2001).

Hippocampal Volume Change

To determine degree of hippocampal volume change, a t-test was conducted to compare the mean bilateral hippocampal volume change of the participants to the mean bilateral hippocampal volume change for a group of healthy controls. The test was significant, $t(21.08) = 3.24$, $p < .05$, with traumatic brain injury participants showing a 2.82% decrease in hippocampal volume on average (*SD*=4.06%) compared to healthy controls, who showed a 0.09% mean increase (*SD*=0.47%) in hippocampal volume over time. Effect size calculation demonstrated a considerable difference in the mean difference in degree of atrophy between the clinical and control groups ($d = -1.01$). No significant difference in the time window between initial and follow-up scanning was seen between the clinical group (mean=26 months; *SD*=8 months) and control group (mean=25 months; *SD*=10 months), $t(21.05)=0.35$, $p=.73$. Similarly, there was no significant between-group difference in age between the clinical group (mean=35 years; *SD*=13) and control group (mean=38, *SD*=12), $t(26.74)=-.58$, $p=.57$. A significant difference was seen in education level between the clinical group (mean=13 years; *SD*=3) and the control group (mean=18 years; *SD*=2), $t(31.30)=-.53$, $p < .001$. Given the higher mean education level of the control group, a correlation analysis was conducted to rule out a relationship between education and hippocampal change in the control group. The correlation was not significant and the effect

size was minimal, suggesting no significant relationship between education and hippocampal volume change in controls.

Return to Productivity

Descriptive statistics were performed to clarify patterns of return to productivity within the clinical sample. At 24+ months post-injury, only 8 of the 21 clinical participants had returned to premorbid productivity level. At 24+ months, only 11 of the 21 clinical participants were engaged in productive activities, namely paid work, volunteer work, school, or childcare, for at least 20 hours per week or more. Of the 21 clinical participants, 7 participants reported no engagement in any of these productive activities at 24+ months.

Control Variable Analyses

Correlations were performed to examine relationships between the following control variables and environmental enrichment, hippocampal volume change, or return to productivity. These control variables included age at injury, estimated premorbid intelligence, injury severity (measured as Glasgow Coma Scale scores, duration of posttraumatic amnesia, and duration of acute care length of stay), level of disability at acute care discharge (based on Functional Independence Measure scores), medications (SSRI and/or lithium post-injury), insurance and/or litigation involvement post-injury, substance abuse history, and psychological distress (based on Beck Depression Inventory-II and Beck Anxiety Inventory scores). Given that BDI-II and BAI scores correlated significantly with one another (r=.86, p<.001), BDI-II was used as a primary measure of psychological distress. In order to examine whether WTAR scores, a measure of premorbid intelligence, were suppressed in cases of severe injury, a correlation analysis was conducted between WTAR scores at 12 months post-injury and three measures of injury severity: Glasgow Coma Scale scores, duration of posttraumatic amnesia, and acute care length of stay. No significant correlations were found between WTAR scores and any of these three measures of injury severity, and the effect sizes were minimal.

With the exception of a significant positive correlation between socioeconomic status and frequency of engagement in meditation/prayer (r=.48, p<.05), the results of these correlation analyses revealed no significant correlations between any of the control variables and any of the environmental enrichment variables or measures of hippocampal atrophy. With the exception of

BDI-II scores and insurance involvement, no control variables correlated significantly with return to productivity. BDI-II scores correlated positively with BICRO-39 Productive Employment scores (μ=.54, p<.05), whereby those with higher levels of psychological distress were functioning at a lower level of productivity at 24+ months post-injury; similarly, BDI-II scores correlated negatively with return to premorbid occupational level (τ= -.45, p<.05), whereby those with higher levels of psychological distress were less likely to return to premorbid occupational levels at 24+ months post-injury. Specifically, all of the participants with moderate depression scores (N=6) had not returned to premorbid productivity levels, while only 6 of the 13 participants with depression scores in the mild range or less had not returned to work. With regards to insurance, those who had insurance coverage at 12 months post-injury had lower productivity levels (τ=-.48, p<.05) and were less likely to return to premorbid levels of productivity (τ= -.48, p<.05). In particular, of the 16 participants who had insurance coverage, only 25% (N=4) returned to premorbid levels of productivity, while 80% (N=4) of the 5 participants without insurance coverage returned to premorbid productivity levels. Based on these findings, BDI-II scores and insurance involvement were included in subsequent statistical models of return to productivity. It is worth noting that of the 16 participants who had insurance coverage, 14 participants had sustained motor vehicle accidents as opposed to the remaining 4 participants who had sustained falls and 1 participant who had been struck by a small object. Since those who sustained brain injuries in the course of a motor vehicle accident may have sustained more severe injuries, this raises the possibility that those with insurance coverage had more severe injuries. However, a correlational analyses revealed no significant correlations between insurance involvement and measures of injury severity, including Glasgow Coma Scale score (τ=.09; p=.66), duration of posttraumatic amnesia (τ=.21; p=.33), or acute care length of stay (τ=-.12; p=.54), suggesting no significant relationship between insurance involvement and injury severity in the present sample.

Analyses of Hypotheses

1. Environmental Enrichment and Subacute Hippocampal Atrophy.

1.1 Post-injury environmental enrichment and hippocampal atrophy.

Hypothesis 1.1a. Generalized environmental enrichment. A Pearson correlation was conducted to examine the relationship between an aggregate of generalized environmental enrichment (i.e., a sum total of the cognitive, physical, and social items on the LAQ) and bilateral hippocampal atrophy. A significant negative correlation was found between an aggregate of generalized environmental enrichment and bilateral hippocampal atrophy (r=-.56, p<.05) (Appendix F).

Hypothesis 1.1b. Cognitive enrichment. In order to determine whether cognitive activity accounted for a greater degree of variance than physical or social activity in predicting bilateral hippocampal atrophy, a hierarchical linear regression was conducted, entering cognitive activity first followed by social and physical activity. Pearson correlations revealed significant negative correlations between bilateral hippocampal atrophy and cognitive activity (r=-.57, p<.01) and between bilateral hippocampal atrophy and social activity (r=-.41, p<.05) but no significant correlation between bilateral hippocampal atrophy and physical activity. The results of a hierarchical regression revealed that cognitive activity accounted for 32% of the variance in bilateral hippocampal atrophy (R^2=.32, p=.01), while neither social activity nor physical activity accounted for additional variance in bilateral hippocampal atrophy.

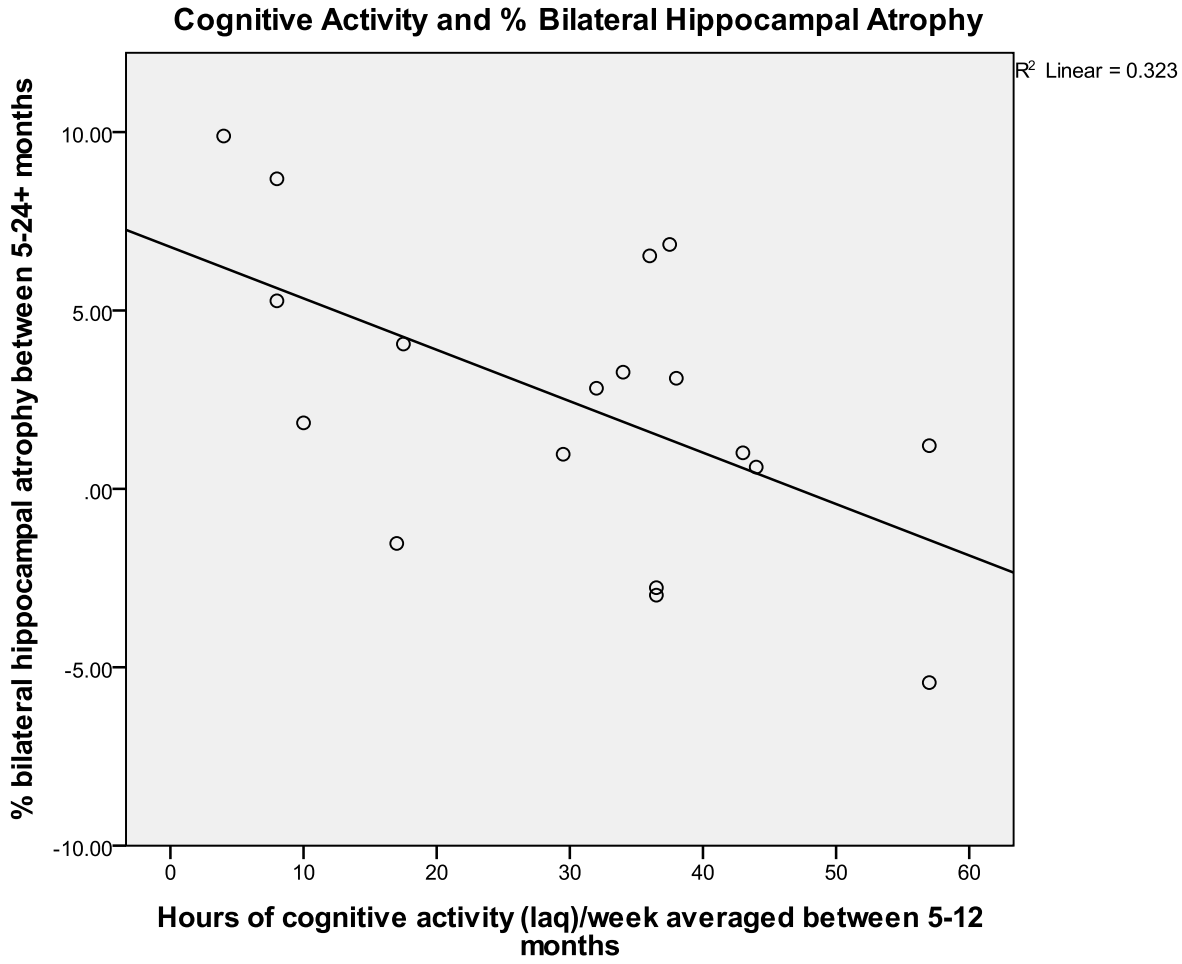

Figure 2. **Cognitive activity and percent bilateral hippocampal atrophy.**

Hypothesis 1.1c. Meditation/prayer. Regarding the relationship between meditation/prayer and right hippocampal atrophy, Pearson correlation analyses revealed a non-significant trend for greater frequency of meditation/prayer associated with less right hippocampal atrophy (r=-.36, p=.07) (Appendix G). As a group, participants who engaged in meditation and/or prayer showed less right hippocampal atrophy (mean=1.4% decrease in volume) than those who did not engage in meditation and/or prayer (mean=6.6% decrease in volume); the size of this group difference was moderate (d=0.41) but was not statistically significant.

Correlation analyses revealed no significant correlation between frequency of meditation/prayer and either generalized environmental enrichment (r=.09, p=.73) or cognitive

enrichment (r=-.01, p=.98). Correlation analysis revealed a significant positive correlation between socioeconomic status and frequency of meditation/prayer (r=.48, p<.05) whereby those of higher socioeconomic status engaged in meditation/prayer more frequently than those of lower socioeconomic status.

In order to investigate the incremental effects of meditation/prayer on right hippocampal atrophy after controlling for socioeconomic status and generalized environmental enrichment, a hierarchical linear regression was conducted entering an aggregate of LAQ items (i.e., sum of LAQ cognitive, physical, and social items) followed by socioeconomic status followed by meditation/prayer score. The results of the regression analysis revealed that frequency of engagement in prayer/meditation accounted for 30% of the variance in right hippocampal atrophy beyond that accounted for by generalized environmental enrichment and socioeconomic status (R^2 *change*=.30, p<.05). Partial correlation analyses revealed that increased frequency of meditation/prayer correlated significantly with decreased right hippocampal atrophy after controlling for socioeconomic status and generalized environmental enrichment (r=-.60, p<.05).

Hypothesis 1.1d. Therapy intensity. A Pearson correlation was conducted to examine the relationship between hours of therapy per week between 5-12 months post-injury and bilateral hippocampal atrophy between 5 months and 24+ months post-injury. The results of the correlation analysis were not significant and the effect size was small (r=-.15, p=.53) (Appendix H). Of note, correlation analyses revealed no significant correlations between therapy hours and any of the measures of injury severity or level of disability, including Glasgow Coma Scale scores, duration of posttraumatic amnesia, acute care length of stay, or FIM scores at acute care discharge. However, correlation analyses revealed non-significant trends whereby greater hours of therapy between 5-12 months post-injury were associated with lower FIM scores at acute care discharge (r=-.43, p=.08) and higher BDI-II scores between 5, 12, and 24+ months post-injury (r=.41, p=.07). Subsequent partial correlation analyses revealed no significant correlation between therapy hours and bilateral hippocampal atrophy after controlling for FIM scores at discharge or BDI-II scores between 5, 12, and 24+ months post-injury (r=.12, p=.65).

1.2. Pre-Injury environmental enrichment and subacute hippocampal atrophy.

Hypothesis 1.2a. Years of education. A Pearson correlation revealed no significant relationship between years of education and subacute bilateral hippocampal atrophy (r=.30,

p=.20) (Appendix I). Partial correlation analyses also revealed no significant correlation between years of education and bilateral hippocampal atrophy after controlling for estimated premorbid intelligence based on WTAR scores.

Hypothesis 1.2b. Pre-injury occupational attainment. A Kendall's tau correlation was conducted to investigate the relationship between pre-injury occupational attainment and bilateral subacute atrophy. The results of the correlation revealed no significant relationship between pre-injury occupational attainment and bilateral subacute atrophy (τ=-.05, p=.78) (Appendix J).

2. Subacute Hippocampal Atrophy and Return to Productivity

Hypothesis 2. Bilateral hippocampal atrophy and return to productivity. In order to examine the relationship between degree of bilateral hippocampal atrophy and level of productivity at 24+ months after controlling for BDI-II scores and insurance involvement, a hierarchical regression was conducted, in which BDI-II score and insurance involvement were entered first followed by bilateral hippocampal volume change. Partial correlations revealed no significant correlation between bilateral hippocampal atrophy and BICRO-39 Productive Employment scores, although a trend was seen for greater bilateral hippocampal atrophy associated with return to a higher level of productivity (r=.33, p=.07) (Appendix K). The results of the regression analysis revealed that BDI-II scores and insurance involvement accounted for 36% of the variance in BICRO-39 Productive Employment scores (R^2=.36, p<.05), while bilateral hippocampal atrophy did not account for additional variance in level of productivity (R^2 *change*=.03, p=.41). In order to examine the relationship between bilateral hippocampal atrophy and return to premorbid occupational level, a Kendall's tau correlation analysis was conducted, the results of which showed no significant correlation between bilateral hippocampal atrophy and return to premorbid occupational level (τ=.07, p=.72) (Appendix L).

Table 2

Summary of Findings

Study objective	Hypothesis	Findings
1.1. Examine the relationship between post-injury environmental enrichment and subacute hippocampal atrophy.	***Hypothesis 1.1a.*** Greater generalized environmental enrichment (i.e., frequency of cognitive, physical, and social engagement) between 5-12 months post-injury will predict less bilateral hippocampal atrophy between 5-24+ months post-injury.	***The hypothesis was supported:*** Generalized environmental enrichment was negatively correlated with degree of subacute bilateral hippocampal atrophy (r=-.56, p<.05), whereby greater generalized environmental enrichment was associated with less bilateral hippocampal atrophy.
	Hypothesis 1.1b. Of the three conventional elements of environmental enrichment (i.e., cognitive, physical, and social activities), cognitive activity between 5-12 months will account for the greatest amount of variance in predicting bilateral hippocampal atrophy between 5-24+ months post-injury.	***The hypothesis was supported:*** Cognitive activity was negatively correlated with subacute bilateral hippocampal atrophy (r=-.57, p<.01), whereby greater cognitive activity was associated with less subacute bilateral hippocampal atrophy. Further, cognitive activity accounted for 32% of the variance in subacute bilateral hippocampal atrophy (R^2=.32, p=.01), while neither social activity nor physical activity accounted for additional variance in bilateral hippocampal atrophy.
	Hypothesis 1.1c. Greater frequency of meditation/prayer between 5-12 months will predict less atrophy of the right hippocampus between 5-24+ months post-injury after controlling for frequency cognitive, physical, and social engagement.	***The hypothesis was supported:*** Partial correlation analyses revealed that increased frequency of meditation/prayer correlated significantly with decreased right hippocampal atrophy after controlling for socioeconomic status and generalized environmental enrichment (r=-.60, p<.05). Frequency meditation/prayer accounted for 30% of the variance in right hippocampal atrophy beyond that accounted for by generalized environmental enrichment and socioeconomic status (R^2 *change*=.30, p<.05).

Study objective	Hypothesis	Findings
	Hypothesis 1.1d. Greater number of therapy hours per week between 5-12 months will predict less bilateral hippocampal atrophy between 5-24+ months post-injury.	***The hypothesis was not supported:*** Hours of therapy per week between 5-12 months post-injury was not correlated with subacute hippocampal atrophy.
Objective 1.2. Examine the relationship between pre-injury environmental enrichment factors and subacute hippocampal atrophy.	***Hypothesis 1.2a.*** Higher years of pre-injury education will predict less bilateral hippocampal atrophy between 5-24+ months post-injury.	***The hypothesis was not supported:*** Years of education was not correlated with subacute hippocampal atrophy.
	Hypothesis 1.2b. Higher pre-injury occupational attainment will predict less bilateral hippocampal atrophy between 5-24+ months post-injury.	***The hypothesis was not supported:*** Pre-injury occupational attainment was not correlated with subacute hippocampal atrophy.
Objective 2. Examine the relationship between subacute hippocampal atrophy and return to productivity.	***Hypothesis 2.*** Bilateral hippocampal atrophy between 5-24+ months post-injury will be negatively correlated with return to productivity at 24+ months post-injury.	***The hypothesis was not supported:*** Subacute bilateral hippocampal atrophy was not correlated with level of productivity at 24+ months and did not account for variance in BICRO-39 Productive Employment scores after accounting for BDI-II scores and insurance involvement. Further, degree of subacute bilateral hippocampal atrophy was not correlated with return to premorbid occupational level.

Chapter 5: DISCUSSION

Overview

The purpose of this study was to examine the relationship between environmental enrichment factors and subacute hippocampal atrophy following moderate to severe traumatic brain injury. The primary objective of this study was to examine the relationship between post- and pre-injury environmental enrichment factors and subacute hippocampal atrophy. A second objective was to tie subacute hippocampal volume changes to functional outcome, namely return to productivity. Rather than focusing on the direct relationship between environmental enrichment and functional outcome in traumatic brain injury, the focus of the present study's second objective was on the relationship between the brain and function. By focusing on the relationship between the brain and function rather than the direct relationship between environment and function, the present study aimed to elucidate neuroprotective mechanisms that might prevent or hinder subacute hippocampal atrophy and to explore whether such brain changes impact real-world functioning.

In order to address these objectives, an integrated neuroprotective model of environmental enrichment and subacute hippocampal atrophy in traumatic brain injury was created. This model draws on theoretical models and research findings from the literatures on environmental enrichment (Diamond, 2001; Green, 2006; Kolb & Gibb, 1991; Will, et al., 2004), brain and cognitive reserve (Nithianantharajah & Hannan, 2009), and neuroplastic recovery of function in brain injury (Mahncke, et al., 2006; Robertson & Murre, 1999; Teasell, et al., 2006). The integrated neuroprotective model of environmental enrichment and subacute atrophy proposed in the present study posits a novel fourth element of environmental enrichment that is only beginning to be explored in the neuroplasticity and clinical rehabilitation literature, namely meditation (and related cognitive activity such as prayer). Consistent with Newberg and Iverson's (2003) neuropsychological model of meditation, in the present study meditation and prayer are defined as practices of self-regulating the body and mind by engaging a specific attentional set, involving activation of the prefrontal cortex, thalamus, and hippocampus (Newberg & Iversen, 2003); these practices are a subset of those used to induce relaxation or altered states such as trance-induction techniques (Vaitl, et al., 2005). This novel integrated neuroprotective model was the foundation of the current study and facilitates understanding of

the relationships among environmental enrichment, hippocampal subacute atrophy, and functional outcome in moderate to severe traumatic brain injury.

Findings Regarding Environmental Enrichment and Subacute Hippocampal Atrophy

Pre- and Post-Injury Environmental Enrichment

Generalized environmental enrichment. As expected, the results of this study indicated that generalized environmental enrichment (i.e., engagement in a variety of cognitive, physical, and social activities) during the initial year following traumatic brain injury was associated with less subacute bilateral hippocampal atrophy between 5 months and 24+ months post-injury. This finding is consistent with the results of animal studies that show an association between generalized environmental enrichment and positive neuroplastic recovery following lab-induced brain injury, including reduced atrophy and degeneration at and around the sites of cortical lesions (Passineau, et al., 2001) and reduction in apoptotic cell death in the hippocampus (Young, et al., 1999). The findings of the present study are consistent with the dynamic model of brain and cognitive reserve, whereby exposure to environmental enrichment positively modulates susceptibility to brain disorders via a combination of neuroprotective and/or compensatory mechanisms (Nithianantharajah & Hannan, 2009). Findings of a negative correlation between generalized environmental enrichment and bilateral subacute hippocampal atrophy are also consistent with Mahncke's (2006) model of brain plasticity and functional loss in the aged, whereby a reduced schedule of activities and avoidance of challenging activities is proposed to lead to under-stimulation of critical neural networks and loss of associated functions. In addition, these findings are consistent with Robertson and Murre's (1999) computational model of brain plasticity and guided recovery of function, whereby damaged but potentially viable circuits may be repaired via exposure to generalized environmental stimulation and Hebbian learning mechanisms.

Cognitive activity. As expected, the results of the present study indicated that of the three conventional elements of environmental enrichment (i.e., cognitive, physical, and social activity), cognitive activity accounted for the greatest degree of variance in subacute bilateral hippocampal atrophy while physical and social activity did not account for significant variance

in bilateral hippocampal atrophy beyond that accounted for by cognitive activities. These findings are consistent with comparison studies in animals demonstrating that cognitive training has a stronger effect than physical exercise alone on increasing synaptogenesis in the hippocampus (Moser, Trommald, & Andersen, 1994) and promoting the survival of newly-generated neurons in the hippocampus and their integration into existing neural networks (Kempermann, et al., 1998; Kempermann & Gage, 1999). Although the observational design of the present study precludes conclusions regarding causality, it is possible that cognitive activity supported the survival and integration of newly-generated neurons and thus hindered the progression of subacute atrophy in cognitively-active participants in the present study.

Findings of a negative correlation between hours of cognitive activity and subacute bilateral hippocampal atrophy are consistent with the dynamic model of brain and cognitive reserve (Nithianantharajah & Hannan, 2009) and with Mahncke's (2006) model of brain plasticity and functional loss in the aged, whereby a reduced schedule of activities and avoidance of cognitively-challenging activities are proposed to lead to under-stimulation of critical neural networks and loss of associated functions. Further, these findings are consistent with Robertson and Murre's (1999) computational model of brain plasticity and guided recovery of function, whereby damaged but potentially viable circuits may be repaired via cognitive activity, cognitive arousal, and Hebbian learning mechanisms. Finally, the present study's findings of an association between cognitive activity and hippocampal changes are consistent with findings in the cognitive-training literature, which show convergent evidence that engagement in cognitively-demanding tasks is associated with increased cerebral volume in brain areas that are functionally-related to the demands of the task (Draganski, et al., 2004; Draganski, et al., 2006; Ilg, et al., 2008). Given the primarily cognitive functions supported by the hippocampus (Leuner & Gould, 2010), these findings support the notion that cognitive elements of environmental enrichment would have a greater impact than physical or social elements on neuroplasticity in this structure.

Meditation/prayer. Initial correlation analyses revealed a non-significant trend for greater frequency of meditation/prayer associated with less right hippocampal atrophy (r=-.36, p=.07). As a group, participants who engaged in meditation and/or prayer showed less right hippocampal atrophy (mean=1.4% decrease in volume) than those who did not engage in meditation and/or prayer (mean=6.6% decrease in volume); the size of this group difference was moderate (d=0.41)

but was not statistically significant. However, further analyses revealed a significant relationship between meditation/prayer and socioeconomic status, whereby those who engaged in meditation and/or prayer were more likely to come from higher socioeconomic backgrounds, highlighting the importance of controlling for socioeconomic status when examining the relationship between meditation/prayer and subacute right hippocampal atrophy. Further, given the significant relationship between generalized environmental enrichment and subacute hippocampal atrophy, it was important to determine whether meditation/prayer accounted for significant variance in right hippocampal atrophy beyond that accounted for by generalized environmental enrichment. Interestingly, after controlling for socioeconomic status and generalized environmental enrichment, meditation/prayer accounted for 30% of the variance in right hippocampal atrophy beyond that accounted for by generalized environmental enrichment and socioeconomic status (R^2 *change*=.30, $p<.05$). Partial correlation analyses revealed that increased frequency of meditation/prayer correlated significantly with decreased right hippocampal atrophy after controlling for socioeconomic status and generalized environmental enrichment (r=-.60, $p<.05$).

These findings are consistent with Newberg and Iverson's (2003) neuropsychological model of meditation, whereby meditation engages a specific attentional set that involves activation of the prefrontal cortex, thalamus, and hippocampus. These findings are also consistent with empirical findings of specific activation of the hippocampus and hypocampal gyrus during meditation practice (Buckner & Carroll, 2007; Holzel, et al., 2007; Lazar, et al., 2000; Lou, et al., 1999; Newberg & Iversen, 2003) and increased grey matter concentration within the right hippocampus (Hoelzel, et al., 2008), the degree of which is associated with years of practice. In particular, the present study findings provide preliminary support for the proposition of the present study that meditation/prayer practice may have neuroprotective effects against subacute hippocampal atrophy via: (a) activation and strengthening of attentional networks in frontal regions that support neuroplastic recovery of functional networks in other brain regions (Robertson & Murre, 1999); (b) specific activation of networks within the hippocampus (Newberg & Iversen, 2003) promoting maintenance of viable networks and hindering atrophy in this region; (c) reduction of cortisol, a chemical that has toxic affects on hippocampal neurons (McCarthy, 2003) and that reduces hippocampal dendritic branching and hippocampal neurogenesis (Brown, et al., 1999; Gould, et al., 2000; Jacobs, 2002; Vollmayr, et al., 2003); and (d) enhancing cerebrovascular integrity within the hippocampus, which is closely

associated with neurogenesis in this region (Palmer, et al., 2000) possibly due to enhanced glucose availability to neurons, delivery of cytoprotective factors to neurons, and improved neuroimmune surveillance (Nithianantharajah & Hannan, 2009). Finally, the present study findings provide modest, partial support for the notion that meditation and prayer may constitute an important fourth element of environmental enrichment in humans, which has been largely ignored in the clinical practice and neuroplasticity literature thus far.

Treatment intensification. The present study revealed no significant relationship between treatment hours per week during the first year post-injury and degree of subacute hippocampal atrophy, thus failing to support the proposition that treatment intensification may confer neuroprotection of the hippocampus following traumatic brain injury. The absence of significant findings is inconsistent with previous findings in the field of stroke and traumatic brain injury recovery, which show convergent support for the efficacy of treatment intensification in promoting cognitive, motor, and functional recovery and preventing functional decline (Cifu & Stewart, 1999; Kwakkel, et al., 2004; Kwakkel, et al., 1997; Langhorne, et al., 1996; Teasell, Bayona, Salter, Hellings, & Bitensky, 2006). The lack of significant findings regarding treatment intensity in the present study may be due to the heterogeneous nature of treatment across individuals and across practitioners. Additionally, given the findings that cognitive rather than physical and social stimulation was associated with subacute atrophy in the present study, it may be that only the cognitive aspects of rehabilitation treatment were contributing to hippocampal change in the study sample.

Education and pre-injury occupation level. Unexpectedly, the results of the present study showed no significant relationship between hippocampal atrophy and pre-injury environmental enrichment factors including level of education or pre-injury occupational attainment. This finding was surprising given the extensive evidence of a positive correlation between level of education and cognitive functioning in normal aging (Corral, et al., 2006; Fritsch, et al., 2007), dementia (C. B. Hall, et al., 2007; Koepsell, et al., 1998), stroke recovery (Elkins, et al., 2006), and traumatic brain injury recovery (Kesler, et al., 2003). Interestingly, these findings suggest that while pre-injury environmental enrichment factors may confer cognitive reserve against cognitive or functional decline in the face of increasing neuropathology, these static pre-injury environmental enrichment factors may not protect against the structural progression of neuropathology itself.

Implications of Environmental Enrichment Findings for a Dynamic Neuroprotective Model of Environment Enrichment and Subacute Hippocampal Atrophy

The present study findings showed strong evidence to support the proposed novel model of post-injury environmental enrichment offering neuroprotection against subacute hippocampal atrophy following traumatic brain injury. However, contrary to the proposed model, the study findings suggest that static pre-injury environmental enrichment factors may not protect against the structural progression of subacute hippocampal atrophy following traumatic brain injury, while active post-injury environmental enrichment, particularly cognitive enrichment, does appear to be associated with diminished structural progression of subacute hippocampal atrophy. This surprising finding suggests that a fixed degree of neural reserve at the time of brain injury may not confer neuroprotection against structural pathology in the manner suggested by the conventional theories of brain reserve (Satz, 1993; Stern, 2002). In particular, these findings suggest that in order for environmental enrichment to positively modulate susceptibility to brain disorders via neuroprotective and/or compensatory mechanisms, environmental enrichment exposure must occur post-injury, during the period of progression of neuropathology (Nithianantharajah & Hannan, 2009) rather than preceding the onset of neuropathology. However, it should be noted that, consistent with primary limitations in the literature on brain and cognitive reserve, the direction or causality of the relationship between behaviour/experience and brain changes is unclear. Indeed, the relationship between experience/behaviour and brain changes appears to be reciprocal (Pascual-Leone, et al., 2005). Figure 2 illustrates a revised model of neuroprotection against subacute hippocampal atrophy via environmental enrichment, whereby post-injury environmental enrichment factors play a significant neuroprotective role in reducing susceptibility to subacute atrophy while pre-injury environmental enrichment do not.

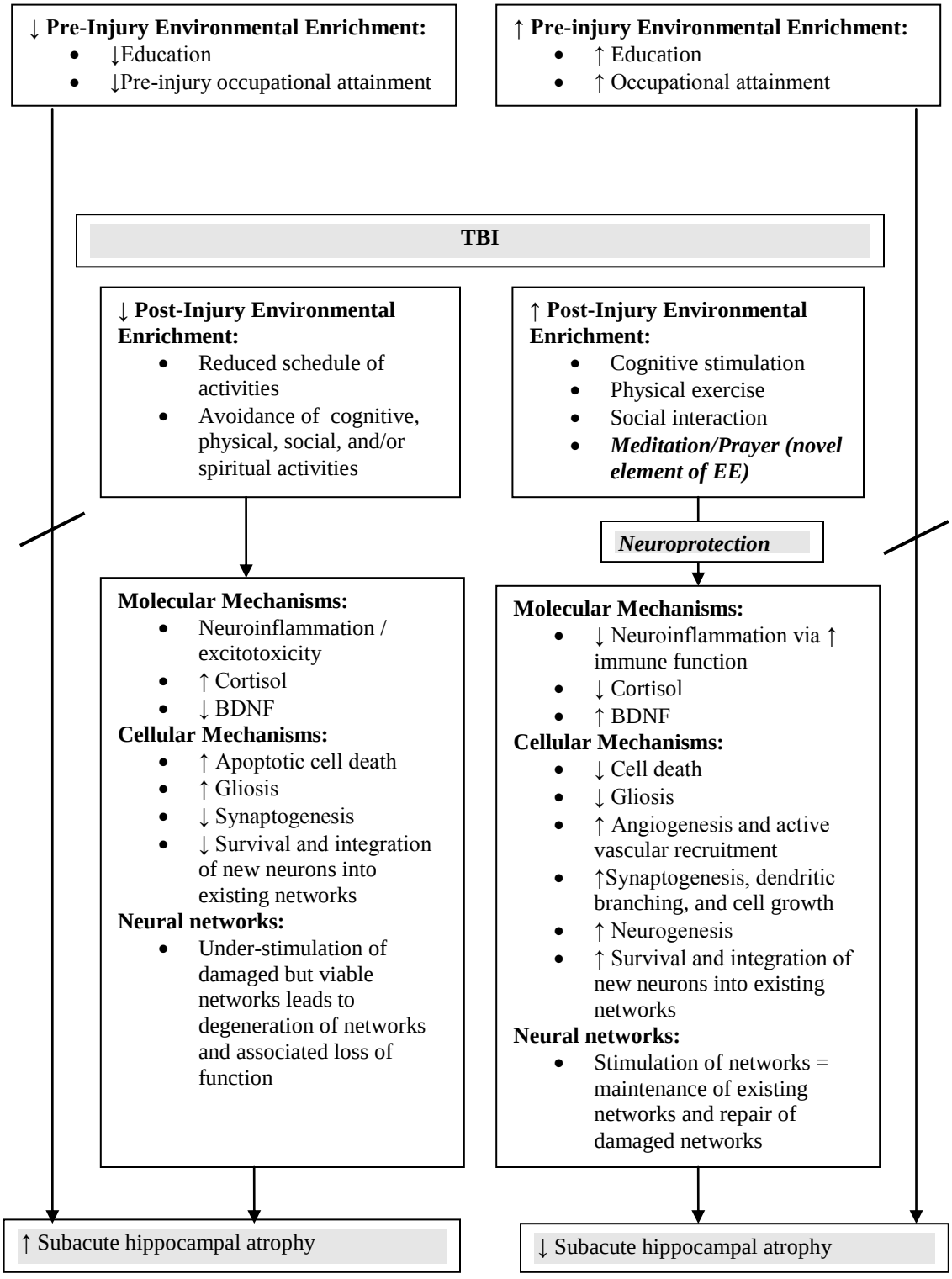

Figure 3. **Revised model of neuroprotection against subacute hippocampal atrophy via environmental enrichment.**

Proposed Neuroplastic Mechanisms Underlying the Relationship of Cognitive Enrichment and Subacute Hippocampal Atrophy

Consistent with the neuroprotective model of environmental enrichment and subacute hippocampal atrophy proposed in the present study, the bilateral subacute hippocampal atrophy seen in the present sample likely reflects the operation of a number of maladaptive neuroplastic mechanisms operating at the molecular, cellular, neural network, and behavioural levels. It is proposed that in the present study, participants' involvement in cognitively-stimulating activities served to promote positive neuroplastic mechanisms that counteracted the negative neuroplastic mechanisms operating following traumatic brain injury, and thus served to halter or hinder subacute hippocampal atrophy in cognitively-active participants.

Cognitive activity promotes positive molecular and cellular neuroplastic changes. At a molecular level, prolonged glutamate excitotoxicity (Matsushita, et al., 2000; Yamamoto, et al., 1999), elevated cortisol (McCarthy, 2003), diminished expression of brain derived neurotrophic factor (BDNF) (Chen, et al., 2005) and accumulation of amyloid precursor protein and amyloid beta peptides (Smith, Chen, et al., 2003) following traumatic brain injury are likely to impede the survival and integration of newborn neurons in the hippocampus, promote apoptotic cell death, and inhibit the reconnection and repair of damaged neural circuits following injury. In combination, these molecular mechanisms are likely to underlie the subacute hippocampal volume loss seen in a subset of patients in the present study. Based on findings from the animal literature, cognitive enrichment is associated with a host of positive plastic changes at the molecular and cellular levels, including the following: increased survival and integration of newly-generated neurons into existing hippocampal networks (Kempermann, Kuhn, & Gage, 1997; Moser, et al., 1994; Steiner, Zurborg, Horster, Fabel, & Kempermann, 2008); elevated hippocampal synaptogenesis and synaptic plasticity (Duffy, Craddock, Abel, & Nguyen, 2001; Foster & Dumas, 2001; Herring, et al., 2009; Moser, et al., 1994); increased brain derived neurotrophic factor (Rossi, et al., 2006); decreased pro-inflammatory and pro-oxidative mediators and decreased apoptotic caspases (Herring, et al., 2010); and adaptive altered expression of neurotransmitter receptors (Laviola, Hannan, Macri, Solinas, & Jaber, 2008), transcription factors (Rampon, et al., 2000), cytoskeletal proteins (McNair, Broad, Riedel, Davies, & Cobb, 2007; Rampon, et al., 2000), and regulators of synaptogenesis (McNair, et al., 2007; Rampon, et al., 2000). Structurally, exposure to cognitive enrichment is associated with

increases in neuron size, dendrite branching, dendrite spine density, and number of synapses per neuron (Diamond, 2001; Grossman, Churchill, Bates, Kleim, & Greenough, 2002; Kolb, 1999; Kolb & Whishaw, 1998; R. J. Nudo, Milliken, Jenkins, & Merzenich, 1996; Rosenzweig & Bennett, 1996). It is posited that these positive molecular and cellular neuroplastic changes associated with cognitive enrichment conferred cognitively-active individuals in the present study with neuroprotection against subacute hippocampal atrophy following injury.

Cognitive activity activates critical neural networks. At a neural network level, negative plastic mechanisms operating following traumatic brain injury may include neuronal degeneration in the hippocampus due to under-stimulation of structurally intact and functionally viable neurons by damaged axonal projections from lesion sites or diffuse axonal injury (Johansson, 2000; Robertson & Murre, 1999). Indeed, some researchers posit that diffuse damage to axons in white matter contribute to downstream loss of activation to grey matter that is innervated by the damaged axons (Levine, et al., 2006). In addition, the bilateral distribution of atrophy seen in the present study may reflect damage to the inter-hemispheric association fibres connecting the left and right hippocampi (Duvernoy, et al., 2005), in that damage to one hemisphere of the hippocampus may negatively impact afferent connections to the hippocampus of the other hemisphere, resulting in secondary damage from under-stimulation. At a behavioural level, a reduced schedule of activity and negative learning may also lead patients to actively avoid activities that they find to be more challenging or frustrating since their injury. Many activities that were previously enjoyed or completed with ease may be experienced as difficult and frustrating by a person with cognitive impairments. Novel tasks encountered in daily life that require learning, memory, speeded information processing, or problem-solving are likely to be particularly difficult for individuals following traumatic brain injury (Christensen, et al., 2008; Hellawell, et al., 1999; Ruttan, et al., 2008), and as such, may be avoided, resulting in a negatively-reinforced cycle of avoidance of challenging activities leading to diminished activation of brain networks and associated negative neuroplastic changes (Blake, et al., 2006).

Based on neuroplastic models of recovery following stroke (Teasell, Bayona, Salter, Hellings, & Bitensky, 2006) and computational models of plastic and functional recovery following brain injury (Robertson & Murre, 1999), cognitive stimulation is likely to activate critical neural networks, serving to maintain existing networks and to strengthen and repair damaged but salvageable networks via increased connectivity due to Hebbian learning

(Robertson & Murre, 1999). Thus, it is posited that cognitive activity in the present study resulted in increased activation of critical neural networks within the hippocampus, leading to the maintenance and repair of hippocampal networks and tissue, and thus, conferring cognitively-active individuals with neuroprotection against neuronal decay.

In sum, the neuroplastic mechanisms outlined above offer an integrative and coherent explanation of the neuroplastic mechanisms believed to underlie the significant correlation found between cognitive activity and subacute hippocampal atrophy in the present study. These findings concur with seminal reviews of the brain and cognitive reserve literature, which conclude that brains that have received increased stimulation, through enhanced mental and physical activity, are better able to mount neuroprotective responses against neurodegenerative processes, traumatic insults, or other forms of adult-onset neural dysfunction (Nithianantharajah & Hannan, 2009).

Implications of Environmental Enrichment Findings for Rehabilitation

The results of the present study suggest that engagement in cognitively-challenging activities post-injury may promote positive neuroplastic changes and possibly hinder or halt hippocampal atrophy in the subacute stages post-injury. At minimum, the present findings suggest that engagement in cognitively-challenging activities is not associated with deleterious effects on the hippocampus following traumatic brain injury. Engagement in appropriately challenging activities (i.e., activities that are challenging, engaging, achievable, and that promote a sense of accomplishment and/or pleasure), including cognitively, socially, physically, and spiritually stimulating activities, is likely to contribute to higher quality of life post-injury and may support the maintenance of a positive sense of self-efficacy post-injury (Cicerone, Mott, Azulay, & Friel, 2004; Holladay, 2003).

Developments within the field of cognitive science support the notion that engaging in contextualized, repeated, cognitively-challenging activities leads indirectly to amelioration of specific cognitive functions as well as improved daily functioning in various populations (Chesnut, et al., 1999; Horner, et al., 1988; Kavale, 1999; Koegel, et al., 1997). The present study findings provide preliminary empirical support for the contextualized model of cognitive rehabilitation proposed by Ylvisaker and colleagues (2002), in which therapeutic activities embedded in the patient's real life outside of the clinical setting may lead to cognitive and

organic recovery following brain injury. Cognitive rehabilitation researchers have recommended that rehabilitation strategies should be embedded in real-life situations and contexts in order to maximize far transfer of learned skills and to impact real-life functioning (Mateer & Sira, 2006; Murre & Robertson, 1999). Consistent with these recommendations and with Ylvisaker and colleagues' (2002) contextualized model of rehabilitation, the majority of activities examined in the present study were activities that are embedded in real-life contexts and that are accessible to most individuals in their daily lives, thus increasing the practical utility of the present study findings.

Implications of Environmental Enrichment Findings for Counselling

The present study findings have interesting implications for psychotherapeutic and counselling interventions post-injury. Psychotherapeutic intervention is frequently indicated in post-injury rehabilitation given the significantly elevated risk for depression and interpersonal difficulties following traumatic brain injury (Seel & Kreutzer, 2003). At this time, however, few studies have examined the efficacy of psychotherapeutic interventions in this population as a primary research question (Gordon, et al., 2006; Prigatano, 1999a). Preliminary studies suggest that cognitive behaviour therapy may be an effective mode of psychotherapy for the treatment of depression in traumatic brain injury populations (Bradbury, et al., 2008; Tiersky, 2005). In terms of format and content, cognitive behaviour therapy appears to be an ideal psychotherapeutic modality for brain-injured adults, in that it is concrete and direct, involves over-learning of concepts and repeated practice of new behaviours, is record-based (which may aid in memory problems), and encourages applicability and generalizability of skills learned in sessions to various situations in the client's real-life experience (Mateer & Sira, 2006; Mateer, Sira, & O'Connell, 2005). These characteristics of cognitive behaviour therapy allow for accommodation of the cognitive limitations resulting from traumatic brain injury.

The present study findings raise the possibility that cognitive behaviour therapy may not only accommodate cognitive deficits but could potentially promote neuroplastic recovery following brain damage. Specifically, it is likely that the cognitive challenges and stimulation inherent in cognitive behaviour therapy may serve to activate critical brain networks and hinder the loss of viable networks following injury, consistent with neuroplastic models of recovery proposed by previous authors (Mahncke, et al., 2006; Nithianantharajah & Hannan, 2009;

Robertson & Murre, 1999) and in the present study. Partial support for this proposition is provided by one observational study (Heinemann, et al., 1995) that examined the differential effects of specific treatment modalities on functional recovery in traumatic brain injury between hospital admission and discharge. When the predictive power of physical, occupational, speech, and psychological therapies were examined individually, only psychological therapies significantly predicted functional recovery, specifically cognitive recovery, after controlling for level of functioning on admission, length of hospital stay, and age. While these findings are preliminary, it may be that psychotherapeutic interventions following traumatic brain injury have a more wide-ranging impact on recovery than previously thought. Indeed, the possibility that psychotherapeutic intervention may promote not only emotional and functional recovery but also neuroplastic and cognitive recovery following injury remains an interesting empirical question to be examined in future studies.

Findings Regarding Hippocampal Atrophy and Return to Productivity

Return to Productivity

The present study is one of the first to examine explicitly the relationship between subacute hippocampal atrophy and return to productivity following traumatic brain injury. The absence of significant correlations between bilateral subacute hippocampal atrophy and return to productivity in the present study is somewhat inconsistent with previous findings that subacute atrophy in frontotemporal areas (between 1-3 months and 6-12 months post-injury) combined with duration of posttraumatic amnesia was associated with poorer vocational outcome (van der Naalt, et al., 1999). Furthermore, the absence of significant findings regarding bilateral hippocampal subacute atrophy and return to productivity is somewhat inconsistent with findings that subacute cerebral atrophy in global brain regions is associated with poorer global functional outcomes (Blatter, Bigler, Gale, & et al., 1997; Jellinger, 2004; Levin, Meyers, Grossman, & Sarwar, 1981; MacKenzie, et al., 2002; Mellick, Gerhart, & Whiteneck, 2003; National Institute of Mental Health, 1998).

It is possible that by summing right and left hippocampal changes, the present study failed to detect discreet relationships between left hippocampal changes and occupations relying

strongly on verbal memory skills, and right hippocampal changes and occupations relying strongly on visual memory skills. For instance, for individuals returning to jobs that require visual skills (e.g., cab driving or forklift driving), it could be that right hippocampal subacute atrophy, which may be associated with visual memory, might account for greater variance in return to productivity than left hippocampal subacute atrophy, which may be implicated in verbal memory (Ariza, et al., 2006). Further investigation of the differential cognitive demands of patients' occupations and their relationship with subacute atrophy of functionally-associated brain regions may reveal more discreet relationships between specific brain structures and productivity outcomes in future studies.

Alternatively, recent trends in the cognitive neuroscience literature suggest that specific cognitive functions, such as memory, might best be understood as involving a complex interplay between networks in different brain regions rather than involving activation of a single brain structure, such as the hippocampus alone (Bigler, et al., 2010; Diehl, et al., 2008; Gaffan, 2005). Indeed, some studies suggest that damage to white matter tracts of the temporal stem, which innervate and enervate the hippocampus, can cause a similar pattern of memory impairments as is seen in the case of damage to the hippocampus proper (Bigler, et al., 2010; Corkin, et al., 1997; Gaffan, Parker, & Easton, 2001; Horel, 1994). Thus, it may be that for some individuals at least, neurodegeneration across brain regions other than the hippocampus accounts for the greatest degree of variance in vocational outcome following traumatic brain injury. Indeed, in addition to memory, another primary cognitive predictor of return to productivity includes speed of processing (Rassovsky, et al., 2006), and it may be that subacute atrophy in brain regions supporting processing speed, such as white matter tracts of the corpus callosum, or else measures of whole brain atrophy such as ventricle-to-brain ratio, might better predict return to productivity than subacute atrophy of the hippocampus, which is not strongly implicated in processing speed (Leuner & Gould, 2010).

Implications of Return to Productivity Findings for Vocational Rehabilitation Methods

While the present study findings failed to identify a strong relationship between brain changes and functional outcome following traumatic brain injury, the study does provide valuable information about patterns of vocational recovery following moderate to severe brain injury, which can be used to inform vocational rehabilitation methods. Consistent with the

findings of previous studies (Asikainen, Kaste, & Sarna, 1996; Corrigan & Deming, 1995; Green, Colella, Hebert, et al., 2008; Ponsford, Olver, Curran, & Ng, 1995), less than half of participants in the present study returned to pre-injury levels of productivity at 2-5 years post-injury, and a third of the sample reported no engagement in productive or vocational activities at 2-5 years post-injury, including paid employment, volunteer work, schooling, or childcare. These findings illustrate the marked vocational impairments and lack of social re-integration faced by many individuals following brain injury, highlighting the need for effective vocational rehabilitation methods for these individuals. Unfortunately, the field of vocational rehabilitation in traumatic brain injury currently lacks a unified theoretical framework to guide treatment (Gordon, 2006).

In order to develop a unified theoretical framework and effective vocational rehabilitation methods, it is important to first ascertain the factors most strongly associated with individuals' return to productivity. While the absence of significant correlations between hippocampal volume change and level of productivity in the present study may be due to insufficient power, it is also possible that factors other than brain changes were influencing productivity levels in this sample. Control variable analyses suggested that age at injury, estimated premorbid intelligence, injury severity, level of disability at acute care discharge, medications, litigation involvement post-injury, and substance abuse history were not associated with return to productivity in the present sample. Not surprisingly, control variable analyses revealed that high levels of psychological distress were associated with poorer return to productivity in the present clinical sample. This raises the possibility that psychological adjustment and emotional regulation may play a stronger role than organic brain recovery in determining people's ability to return to pre-injury vocational roles. This would suggest that addressing psychological issues and emotional health should be a primary focus of vocational rehabilitation. Indeed, evidence indicates that degree of psychopathology, behavioural problems, emotional distress, and self-esteem are primary predictors of successful vocational rehabilitation (Cattelani, 2002; Felmingham, 2001; Franulic, 2004; Kendall, 2003; Sherer, 1999; Wagner, 2002), and behavioural interventions addressing these issues have been shown to be associated with improved vocational and community re-integration following brain injury (Cicerone et al., 2004; Feeney et al., 2001; Heinemann, 2004; Seale, 2002).

Another factor associated with return to productivity in the present sample was insurance involvement. Specifically, those with insurance coverage were less likely to return to pre-injury occupational levels and showed lower levels of productivity overall at 2-5 years post-injury. One explanation for this finding is that monetary gains associated with insurance involvement reduced individuals' incentive to return to paid employment. An alternative explanation is that those who had insurance involvement were likely to be more disabled, and thus unable to return to productive activities. However, control variable analyses revealed no significant relationships between level of disability upon acute care discharge and level of productivity at 2-5 years post-injury, suggesting that disability was not related to productivity.

Drawing on Turk's (2002) biopsychosocial disease model, there are a number of psychosocial factors that could be contributing to participants' vocational outcome in the present study, including maladaptive attitudes and beliefs, self-efficacy, and coping styles. Self-efficacy is defined as a personal conviction that one can successfully perform required behaviours in a given situation (Bandura, 1977). Bandura's self-efficacy model proposes that given sufficient motivation to engage in a behaviour, a person's self-efficacy beliefs will determine whether that behaviour will be initiated, how much effort will be expended, and how long the effort will be sustained in the face of obstacles and adverse experiences. Within this framework, coping behaviours are mediated by people's beliefs that situational demands will not exceed their coping resources. Following brain injury, individuals with weak efficacy expectancies would, therefore, be less likely to employ coping responses or persist in vocational rehabilitation efforts in the face of obstacles than would individuals with positive efficacy expectations. Self-efficacy and coping styles were not directly assessed in the present study, and the relationship between these factors and vocational outcome is an important empirical question to be addressed in future studies.

There are a number of environmental and social factors that may have influenced participants' return to productivity, which were not directly assessed in the present study. Specifically, Ownsworth and McKenna (2004) have proposed that provision of financial incentives for return to work, employer education and training, family education, and supported employment programmes are important factors to be addressed in order to optimize the success of vocational rehabilitation. It is possible that these factors may have played a stronger role than organic brain recovery in influencing participants' level of productivity in the present study. Additionally, the presence of environmental barriers, such as lack of access to transportation or

inaccessible workplaces, may also have contributed to lower levels of productivity for some participants in the present study. Indeed, preliminary evidence suggests that driving independence is associated with better employment stability following traumatic brain injury (Kreutzer, 2003), suggesting that transportation access may be an important focus for vocational rehabilitation. Finally, while socioeconomic status and age were not correlated with productivity or vocational outcome in the present study, it is possible that other aspects of identity and diversity, such as membership in a visible minority group, may have impacted participants' re-integration into vocational roles in ways that were not directly assessed in the present study. Research regarding the impact of identity and diversity issues in traumatic brain injury is very limited. While some evidence suggests that persons belonging to a visible minority group may have poorer vocational outcomes following traumatic brain injury, findings in this area are contradictory (Burnett, 2003; Kreutzer, 2003). Issues related to identity and diversity have not yet been addressed extensively in the published literature on traumatic brain injury rehabilitation, but these are likely to be important factors influencing vocational recovery.

In conclusion, the results of the present study raise the possibility that psychosocial and environmental factors may have a greater influence than organic brain recovery on return to productivity following traumatic brain injury. Specifically, the results of the present study suggest that interventions that address psychological distress should be an important component of vocational rehabilitation. Additionally, there are a number of psychosocial and environmental factors that were not directly assessed in the present study but which are likely to influence return to productivity following traumatic brain injury. These psychosocial and environmental factors should be incorporated into vocational rehabilitation theory and practice and include maladaptive attitudes and beliefs, self-efficacy, coping styles, provision of financial incentives for return to work, employer education and training, family education, supported employment, addressing/overcoming transportation or accessibility barriers, and issues of identity and diversity.

Strengths and Limitations of the Present Study

Strengths

Theory. The present study is the first to examine the relationship between environmental enrichment factors and subacute cerebral atrophy following traumatic brain injury in humans. Environmental enrichment factors are an important area of study given that these constitute modifiable factors that can be manipulated to influence brain recovery, thus informing the development of effective behavioural rehabilitation methods.

One of the primary strengths of the present study involves integration of the existing body of research related to traumatic brain injury into a comprehensive and unifying theory, something which is currently lacking in the field of traumatic brain injury research (Bach-Y-Rita, 2000; Cicerone, et al., 2005; Gordon, et al., 2006). The present study also extends existing theories of environmental enrichment to incorporate a novel element of environmental enrichment, namely spiritual practice in the form of meditation and/or prayer. By examining the relationship between meditation/prayer and subacute hippocampal atrophy, the present study highlights the potential utility of spiritual care practice in clinical neurorehabilitation settings and also expands on academic knowledge about neuroplastic mechanisms involved in meditation and prayer.

Methodology. All participants in the present study completed the full course of assessments and imaging, which constitutes a marked improvement on high attrition rates typical of previous studies of traumatic brain injury recovery. Additionally, many previous studies of subacute cerebral atrophy have lacked a control group or else used control data from other studies as a normative reference group. The present study included control data collected at the same time as clinical data, ensuring consistency in imaging equipment and timing of MRIs as well as ensuring that control subjects were drawn from the same population as traumatic brain injury participants (i.e., the same hospital catchment area, Canadian population).

Regarding timing of neuroimaging, few studies addressing subacute cerebral atrophy post traumatic brain injury have conducted initial imaging at greater than 4.5 months post-injury. By selecting an initial imaging window beyond the acute recovery stage, the present study aimed to demonstrate that atrophy seen over time represented actual atrophy of neuronal tissue rather than

resolution of acute effects of injury, such as reduction of brain swelling or resolution of hematomas. An additional limitation of previous imaging studies was that the time window of initial imaging for some subjects sometimes overlapped with the time window of follow-up imaging for other subjects in the same sample (MacKenzie, et al., 2002; Wilson, et al., 1988), making it difficult to ascertain the specific time frame in which changes were likely to be occurring. The present study addressed this limitation in a manner consistent with recent studies of atrophy progression (Greenberg, et al., 2008; Ng, et al., 2008) in that time-windows between initial and follow-up imaging were determined a priori and were consistent across subjects. Initial scanning was conducted at 3.6 to 5.2 months post injury, well beyond resolution of acute injury effects, and follow-up scans were conducted between 1.9 to 4.6 years post injury for all subjects. As such, there was no overlap in time windows between subjects.

Cognitive rehabilitation researchers have recommended that rehabilitation strategies should be embedded in real-life situations and contexts in order to maximize far transfer of learned skills and impact real-life functioning (Mateer & Sira, 2006; Murre & Robertson, 1999). The present study has focused on environmental enrichment factors that are, as recommended, embedded in real-life situations and have examined activities that are available to most individuals in their daily lives. In this way, findings regarding specific environmental enrichment activities from the present study can be generalized to typical daily activities available in patients' lives, increasing the practical utility of this study's findings.

Measures. Research into environmental enrichment in humans is complicated by the marked diversity and complexity of environmental enrichment elements in human lives. Given the ethical limitations in conducting experimental studies of environmental enrichment in humans, much of the findings regarding environmental enrichment in humans come from longitudinal, observational studies or else indirectly from findings in the field of developmental psychology. Measurement of environmental enrichment in the present study assessed a wide range of cognitive, physical, and social activities, and items were obtained from a theoretically-derived and empirically-tested inventory developed by Salthouse and colleagues (Salthouse, et al., 2002), which was constructed by specifying 22 common activities that a sample of 1200 adults, ranging from the age of 18-97 years, rated in terms of their cognitive demand (where 1=low demand, corresponding to sleeping, and 5= high demand, corresponding to working on a tax form). The sum of average hours for the 22 activities on Salthouse's (2002) questionnaire

was 100, corresponding to a 14 hour day, suggesting that activities included in the questionnaire accounted for a large proportion of the average respondent's non-sleeping time during the week. As such, environmental enrichment factors assessed in the present study were deemed to tap into a wide range of activities throughout the full course of participants' waking hours. This contrasts to measurement of environmental enrichment in previous studies, in which questionnaires have included as few as four activities (Kliegel, Zimprich, & Rott, 2004). The method of aggregating scores of environmental enrichment in the present study was deemed an improvement on that of previous studies, in that aggregate scores took into account a variety of idiosyncratic activities and the sum of hours engaged in these different activities. In contrast, ratings of environmental enrichment in previous studies have sometimes involved dichotomous ratings of frequency, whereby as little as one hour per week of environmental enrichment was rated as high environmental enrichment (Bosma, et al., 2002). Ratings of environmental enrichment in other studies have also involved dichotomous ratings of simply the number rather than duration or frequency of activities, whereby environmental enrichment was rated as high if an individual reported engaging in as little as one activity, regardless of the nature of the activity or degree of involvement (Richards, Hardy, & Wadsworth, 2003). By using an aggregate that takes into account both number of hours and number of activities, the present study employs a more rigorous and representative measure of environmental enrichment than previous studies of self-reported environmental enrichment.

Most previous studies of functional outcome in traumatic brain injury have employed measures of broad, global outcomes, such as the Barthel Index (Mahoney & Barthel, 1965) or the Functional Independence Measure (Uniform Data System for Medical Rehabilitation, 1993). However, such broad outcome measures lack sensitivity to discreet areas of functioning, such as return to varying types of productivity post-injury. Further, many previous studies of vocational outcome have not taken into account or differentiated between types of productivity (e.g., paid employment, homemaking, schooling, volunteer work, childcare) and have failed to compare productivity to premorbid levels. The present study addressed these limitations by assessing a wide range of types of productivity, including paid employment, volunteer work, childcare, and engagement in school. In addition, the present study assessed return to productivity relative to premorbid productivity, an important factor when attempting to determine functional outcome in an accurate and meaningful manner (Gordon, et al., 2006).

Analyses. The present study demonstrated that control variables, including age, estimated premorbid intelligence, injury severity, level of disability, level of psychological distress, substance abuse, and insurance or litigation involvement, did not correlate with participants' level of engagement in various environmental enrichment activities. These control variable analyses constitute a marked improvement on many previous studies of environmental enrichment, which have often failed to control for some or all of these factors that could be influencing a person's motivation or ability to engage in various environmental enrichment activities. For instance, is it that cognitively-intact individuals seek out cognitively-challenging activities, or is that cognitively-stimulating activities improve cognitive functioning? The observational nature of the present study and the correlational nature of the analyses preclude conclusions regarding causality or directionality of the relationship between environmental enrichment and hippocampal change. However, by controlling for factors that might influence participants' motivation or ability to engage in activities, one can be more confident that it is environmental enrichment that may be driving subacute hippocampal change rather than hippocampal change conferring greater cognitive strength, allowing for greater engagement in environmental enrichment activities. Similarly, by ruling out correlational relationships between these control variables and hippocampal change, the present study provided stronger evidence to suggest that hippocampal volume change was related to environmental enrichment rather than being primarily related to injury factors such as injury severity, medication, psychological distress, or substance abuse.

Limitations

Methodology. A primary limitation of the present study pertained to the small sample size, consistent with most clinical studies of traumatic brain injury recovery. The small number of participants in the present study reduced the power of analyses. In addition, the small sample size limits the generalizability of the study findings to the broader population of traumatic brain injury. The sample consisted of participants presenting with moderate to severe traumatic brain injury, and caution is warranted in generalizing these findings to populations with mild traumatic brain injury. It should be noted as well that the mean education level of the control group was higher than that of the clinical group. It is possible that the discrepancy in education level

between the control and clinical groups may have resulted in an over-estimation of the magnitude of difference in rates of hippocampal volume change between the two groups.

With respect to the design of the study, the observational nature of the present study precludes conclusions regarding causality or direction of the relationship between environmental enrichment and hippocampal subacute atrophy, or between hippocampal subacute atrophy and return to productivity. Salthouse and colleagues (2002) highlight the critical characteristics of research necessary to determine causal and directionality of relationships between environmental enrichment and outcomes. Specifically, random assignment to experimental and control groups is ideal in order to minimize influences associated with pre-existing individual differences, such as initial level of cognitive ability and amount of education. Further, rigorous control of enrichment groups, in terms of type and amount of environmental enrichment, is required. Finally, long-term objective monitoring of the amount and frequency of environmental enrichment activities would be required for an ideal study. Given that objective monitoring of patients' lifestyle activities is at times unfeasible, an alternative option for measuring environmental enrichment with greater accuracy than retrospective self-report would involve methods such as experience sampling (Csikszentmihalyi & Larson, 1987). Experience sampling involves participants making written notation of their activities in real time at specific points of time throughout their day. In addition to increasing accuracy of self-report ratings of frequency, duration, and type of environmental enrichment activities, experience sampling methods allow for analysis of reliability of engagement in activities.

Another limitation inherent in the assessment of environmental enrichment pertains to inter-individual differences in motivation, interest, and ability to engage in specific environmental enrichment activities. For instance, one individual may find solving crossword puzzles to be a cognitively-challenging, stimulating, and enjoyable task, while another individual may find crossword puzzles to be excessively difficult and thus stressful, or else excessively easy and thus boring or un-stimulating. Given these limitations inherent in environmental enrichment research, the vast majority of research relevant to the cognitive enrichment concept in particular has been based on approximations to the ideal research study, with each study tending to lack one of the critical characteristics (Salthouse, 2006).

Recommendations for Future Research

The present study is exploratory in that it is the first study to examine environmental enrichment factors and their relationship with hippocampal subacute atrophy following traumatic brain injury. Validation of the present study findings through replication with larger samples of traumatic brain injury patients is required. The findings presented here can be used to generate testable hypotheses regarding the directional impact of specific environmental enrichment factors on subacute cerebral atrophy and functional outcome post traumatic brain injury, questions that have significant implications for the development of effective rehabilitation methods. The novel and unifying model of neuroprotection of environmental enrichment against subacute hippocampal atrophy presented here requires further validation. Specifically, it will be important to determine the extent to which pre-injury environmental enrichment factors, such as education level, or genetically-influenced factors, such as premorbid intelligence, contribute to neuroprotection against subacute cerebral atrophy.

In order to inform the relationship between environmental factors and neuroplasticity, it will be important to extend these findings to other neurologically-compromised populations, such as patients presenting with stroke and dementia. Random assignment to controlled experimental groups is recommended as outlined in the previous section. Experimental control of environmental enrichment exposure would allow for examination of the specific effects of duration, frequency, and type of environmental enrichment activities that have the greatest effect on plastic changes. While the present study showed no significant correlation between treatment intensity and subacute hippocampal atrophy, examination of the differential effects of specific types of therapies (e.g., physiotherapy versus cognitive rehabilitation) would provide useful information about the potential efficacy of various treatments. Control groups should be well-matched for education in order to rule out education effects on brain volumes in healthy controls.

Studies of specific types of meditation are recommended. It will be important to differentiate between the effects of pre-injury meditation versus post-injury meditation, and to examine differences between novice and experienced meditators. Future studies of relationships between meditation/prayer and neuroplasticity should recruit individuals who engage in a uniform practice of meditation on a frequent basis.

Summary and Conclusions

The results of the present study extend upon previous findings of subacute hippocampal atrophy following traumatic brain injury by demonstrating a significant relationship between environmental factors and degree of subacute hippocampal atrophy. The present study also provides partial evidence to support the validity of a novel element of environmental enrichment, namely meditation and/or prayer. Finally, the present study highlights the importance of further examination of hippocampal subacute changes that might influence patients' return to productivity following traumatic brain injury. By proposing and examining a novel, integrated model of neuroprotection following traumatic brain injury, the present study serves to facilitate understanding of the complex relationships among environmental enrichment, hippocampal subacute atrophy, and functional outcome following moderate to severe traumatic brain injury. Findings from the present study provide preliminary support for the utility of increased engagement in cognitively-challenging activities following brain injury in order to facilitate neuroplastic recovery. The findings also provide preliminary partial support to suggest that engagement in spiritual practices, such as meditation and/or prayer may offer additional protection against cerebral atrophy following traumatic brain injury, an area that requires further investigation. If confirmed, the findings that increased cognitive engagement and spiritual practice may hinder subacute atrophy would greatly inform the development of empirically-supported treatments for traumatic brain injury, which are currently lacking in the field of neurorehabilitation. The present study also provides a unifying theory of neuroplastic recovery following traumatic brain injury, which the field of traumatic brain injury neurorehabilitation has lacked thus far. An enhanced understanding of environmental enrichment and other modifiable environmental factors provides valuable insight into the mechanisms of recovery following brain injury and informs the eventual development of novel therapeutic interventions that confer neuroprotection, and thus halt or hinder subacute atrophy in vulnerable patients.

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Appendix A

Consent Form

CONSENT FORM: RECOVERY FROM TRAUMATIC BRAIN INJURY

(Full Title: Cognitive Versus Motor Recovery After Traumatic Brain Injury: Is There Competition for Limited Neural Resources?)

Principal Investigator:

Dr. Robin Green, Toronto Rehabilitation Institute

Dr. David Mikulis, Toronto Western Hospital

Research Coordinator: Brenda Colella, Toronto Rehabilitation Institute

Introduction

You have been invited to participate in a research project on the Neuro Rehabilitation Program. The project looks at the assessment and mechanisms of recovery following a brain injury. This consent form should give you the basic idea of what the research is about and what participation will involve. If you would like more information, please ask.

Study Procedures

If you agree to participate in the study, you will be asked to carry out some cognitive tests (e.g., learning, reading, drawing) and physical testing (e.g., strength, balance) in addition to what you would usually do during your therapies. While you are an in-patient, this will take an extra day of your time sometime over the next few weeks. (The study will not affect your length of stay at Toronto Rehab.) Following discharge, you will be asked to come in for testing at approximately 5 months and 12 months after your injury. On those occasions, we will also give you a questionnaire to complete. The questionnaire asks questions about your home environment, such as the types of activities you are involved in and the degree of social/clinical support that you have. We will also contact you by telephone on three occasions to ask you if there are any updates to the questionnaire. All of the assessments are very similar to your routine clinical assessments. We will pay for any travel expenses.

You will also receive a magnetic resonance imaging (MRI) scan at the Toronto General Hospital. This is a brain scan, similar to the CT scan that you received in acute care. This will

take approximately one hour of your time and will be carried out about 5 months after your injury. You will be asked some questions to see if you can participate safely in an MRI scan. You will still be able to participate in the rest of the study if you cannot participate in the MRI scan.

With your permission, the researchers will use some of the information from your medical and neuropsychological records at Toronto Rehab for the present study including past medical history, injury-related information, clinical assessments/tests completed at Toronto Rehab, and address/telephone number.

Demographic and neuropsychological information obtained from similar research studies that you were involved in at Toronto Rehab with Dr. Green may be used in the present study to decrease duplication of questioning.

Risks and Discomforts

The study assessments involve no more risk to you than there are in your routine therapies/clinical assessments. If you become tired, you can stop and rest. If you have a pacemaker or metal inside your brain (e.g., surgical clips), you cannot receive an MRI scan. If you are claustrophobic, you might find the MR scan uncomfortable. Since the MR technicians are in constant communication with you during the MR scan, the scan can be stopped at any time.

Benefits

One benefit of your participation is that you will receive additional assessments, which may be helpful to your rehabilitation. Your recovery from brain injury will be monitored through these assessments and you will receive clinical feedback about your recovery. If you give your permission, the results of these assessments can be provided to your therapists, which may enhance your clinical care. This study will help us to better understand the way patients recover from brain injury.

Confidentiality

The information obtained for this research study will be kept locked in a secure area and will only be made available to researchers involved in the study and to your therapist, if you wish. Any information that identifies you personally (e.g., name, address) will be removed before the results from the study are published.

Participation

You are free to choose *not* to participate in this study. You are also free to withdraw from the study at any time without affecting your health care.

Your Rights

If you have questions concerning the study, you can call Dr. Robin Green at 416-597-3422 ext. 7606. If you have any questions concerning your rights as they relate to participation in the study, you can call Dr. Gaetan Tardif, Chair of the Research Ethics Board, Toronto Rehab Institute at 416-597-3422 ext. 3730. You will receive a copy of this consent form.

Consent

I have had the opportunity to discuss this study and my questions have been answered to my satisfaction. I give permission for the research team to access to my health records for the purposes of this study. I voluntarily consent to participate in this study.

Participant name: _____

Signature: _____ Date_____

Or For legal decision maker:

I have had the opportunity to discuss this study and my questions have been answered to my satisfaction. I voluntarily consent to have_____ participate in this study. I understand that his/her wish to participate or not participate in study procedures will be respected. If he/she becomes competent to provide informed consent, his/her consent will be sought to continue in the study.

_____	_____	_____
Legal decision maker	Relationship to participant	Date

Person who obtained consent: _____

Signature: _____ Date_____

Appendix B

Semi-Structured Clinical Interview

INTAKE INTERVIEW & CHART REVIEW

Patient Name:

Current age:

Date of birth:

Date of injury:

Date of interview:

Date(s) of current assessment:

PURPOSES OF ASSESSMENT

To provide a profile of current cognitive functioning

To determine any change in level of cognitive functioning since the previous evaluation at this service

To identify cognitive strengths and weaknesses to aid rehabilitation planning

BACKGROUND/HISTORY

Accident Details (from medical records, except where otherwise noted):

Presenting brain injury:

Nature of accident:

Glasgow Coma Scale: **at scene** **at emergency**

Duration of PTA:

Acute Care LOS- Total days:

Pt. admitted at _____ hospital on_____.

Pt. was discharged from acute care on _____(date) and went: 1-home / 2-to_____ hospital awaiting a rehab bed or 3- was transferred directly from _____ to Toronto Rehab.

Date of admission at Toronto Rehab: _____

Neurosurgical interventions:

Other significant medical symptoms associated with accident:

Medications at time of assessment:

Summary of neuroimaging findings:

Past medical history (from patient, except where otherwise noted):

Past neurological history: (brain injury, concussion, stroke, brain tumour)

Past medical history: (How does it affect you?)

❑ Kidney disease	❑ Heart Disease	❑ Diabetes
❑ Epilepsy	❑ Hematological	❑ Hypertension
❑ Respiratory	❑ Thyroid Disease	❑ Circulatory disease
❑ Other:	❑ Digestive	❑ Cancer

Past psychiatric history: (Have you ever been hospitalized? Anx./dep./schiz)

Significant family history (neurological/psychiatric):

Alcohol [ ] No [ ] Yes How many drinks? *per* [ ] day [ ] week [ ] month Type?

Cigarettes [ ] No [ ] Yes How many? ____ *per* [ ] day [ ] week

Recreational Drugs: no Describe type(s) of drug, frequency of use: _____

Visual Problems/Glasses: **Hearing Problems/Hearing Aids:**

Psychosocial history (from patient, except where otherwise noted):

Education (highest grade/diploma/degree completed)**:** (Yr. graduated-?average, below or above average student? favourite subjects? Best grades? Skipped or retained? LD Dx? ADD? Special placement?

Early development: (Birth complications/developmental milestones)

Occupation before injury: (How long did you work at your last job? A brief description or skills needed-)

Hobbies:

First language: **Country of origin:**

Family status:

Handedness : R L Both

Summary of current complaints :

Sensori-motor : (ability to move hands, fingers, legs, numbness, tingling)

Orthopedic injuries: Pain: **(in any part of your body? headaches?)**

Sensory visual: [ ] recognize people

Sensory hearing:

Reading:

Writing:

Speaking: [ ] word finding difficulty

Comprehension: (trouble understanding what people say?)

Paying attention: [ ] focus [ ] pay attention

Solving problems: (Ability to choose safe and correct options?)

Memory: (Any change from before the accident? Learn new info? Can u remember therapists' names or what you did in your last session? Spatial navigation, STM, LTM, does cueing help?

Mood: (Are you sad, crying more, angry, anxious?)

Visual perceptual: (eye sight/blurry)

Eating: (Appetite; lost or gained weight?)

Perceived changes in taste or smell:

Sleeping:

Did you drive before the injury? (Have your acute care doctors mentioned anything to you about your driver's license after the injury?)

Other:

What are your goals?

GP
Legal
Insurance company:
Case manager:
TR team:
OT-
PT-
SLP-
SW-
RT-

Appendix C

Semi-Structured Interview Regarding Therapy Hours

1. **PHYSIOTHERAPY (PT)**

Therapist:_____ Contact #:_____

Date of Assessment	Treatment Start Date	End Date		No. weeks	No. hrs/week	Nature of therapy
		□ *ongoing*				
		□ *ongoing*				
		□ *ongoing*				
		□ *ongoing*				
		□ *ongoing*				
		□ *ongoing*				

2. OCCUPATIONAL THERAPY (OT)

Therapist:_____ Contact #:_____

Date of Interview	Treatment Start Date	End Date		No. weeks	No. hrs/week	Nature of therapy
		□ *ongoing*				
		□ *ongoing*				
		□ *ongoing*				
		□ *ongoing*				
		□ *ongoing*				
		□ *ongoing*				

3. SPEECH-LANGUAGE THERAPY (SLP)

Therapist:_____ Contact #:_____

Date of Assessment	Treatment Start Date	End Date		No. weeks	No. hrs/week	Nature of therapy
		□ *ongoing*				
		□ *ongoing*				
		□ *ongoing*				
		□ *ongoing*				
		□ *ongoing*				
		□ *ongoing*				

4. NEUROPSYCHOLOGY

Therapist:_____ Contact #:_____

Date of Assessment	Treatment Start Date	End Date		No. weeks	No. hrs/week	Nature of therapy
		□ *ongoing*				
		□ *ongoing*				
		□ *ongoing*				
		□ *ongoing*				
		□ *ongoing*				
		□ *ongoing*				

5. COUNSELING

Therapist:_____ Contact #:_____

Date of Assessment	Treatment Start Date	End Date		No. weeks	No. hrs/week	Type: Single / Couple/ Group	Nature of therapy
		□ *ongoing*					
		□ *ongoing*					
		□ *ongoing*					
		□ *ongoing*					
		□ *ongoing*					
		□ *ongoing*					

Are you attending any other type of outpatient program?

Check all that apply:

[ ] Psychiatrist [ ] single [ ] couple [ ] group hrs/wk_____ Dates:_
[ ] Psychologist [ ] single [ ] couple [ ] group hrs/wk_____ Dates:_
[ ] Specialized Program [ ] single [ ] couple [ ] group hrs/wk_____ Dates: _
[ ] Therapy Support Worker [ ] single [ ] couple [ ] group hrs/wk_____ Dates: _
[ ] Other _____ [ ] single [ ] couple [ ] group hrs/wk_____ Dates: _
[ ] Respite Care [ ] single [ ] couple [ ] group hrs/wk_____ Dates: _
[ ] Regular family / friend therapy:_____ hrs/wk_____ Dates:_____
[ ] Self therapy (e.g., home programs that are self-initiated):_____

Appendix D

Lifestyle Activities Questionnaire (LAQ)

This questionnaire is designed to give us an idea how you spent your time and what kinds of activities you are participating in. Please read each item carefully and answer each question by placing a check (✔) in the corresponding box.

How often did you spend your time…	***Several hours a day***	***An hour or so most days***	***Several times a week***	***Once or twice a week***	***Less than once a week***	***Didn't do at all***
1. Writing emails, letters or phoning people	5	4	3	2	1	0
2. Spending time on the internet	5	4	3	2	1	0
3. Reading non-fiction (e.g., newspaper, magazines, etc.)	5	4	3	2	1	0
4. Reading fiction (e.g., novels)	5	4	3	2	1	0
5. Reading work-related material, such as union or association newsletters, technical reports, etc.	5	4	3	2	1	0
6. Watching news programs on television	5	4	3	2	1	0
7. Watching documentary or educational programs on television	5	4	3	2	1	0
8. Watching regular television shows (e.g., sitcoms, soap operas, game shows, etc) or sports on television	5	4	3	2	1	0
9. Going out for a walk	5	4	3	2	1	0
10. Listening to music or radio programs	5	4	3	2	1	0
11. Doing crossword or jigsaw puzzles	5	4	3	2	1	0
12. Playing board games (e.g., Scrabble, Trivial Pursuit, chess, checkers, or similar type board games)	5	4	3	2	1	0
13. Playing cards (e.g., bridge, poker)	5	4	3	2	1	0
14. Playing computer games	5	4	3	2	1	0
15. Taking part in sports. Please specify what activities:	5	4	3	2	1	0
16. Playing a musical instrument or singing	5	4	3	2	1	0
17. Doing art (e.g., painting, drawing, photography)	5	4	3	2	1	0
18. Pursuing an active hobby. Please specify:	5	4	3	2	1	0
19. Going to the theatre, concerts, cinema, art gallery, etc.	5	4	3	2	1	0
20. Going out to a restaurant or pub with another person	5	4	3	2	1	0
21. Going out to visit or meet with people	5	4	3	2	1	0
22. Going to the library	5	4	3	2	1	0
23. Going to parties	5	4	3	2	1	0
24. Watching a sports event (spectator)	5	4	3	2	1	0
25. Shopping for pleasure	5	4	3	2	1	0
26. Attending public lectures or talks (e.g., educational, political, etc.)	5	4	3	2	1	0
27. Taking general interest courses (e.g., language, photography, cooking, etc.)	5	4	3	2	1	0

How often did you spend your time…	***Several hours a day***	***An hour or so most days***	***Several times a week***	***Once or twice a week***	***Less than once a week***	***Didn't do at all***
28. Socializing with people / family at home	5	4	3	2	1	0
29. Participating in religious activities (e.g., go to church, temple, mosque, etc.)	5	4	3	2	1	0
30. Participating in organizational activities (e.g., professional associations, politics, service groups)	5	4	3	2	1	0
31. Engaging in prayer and/or meditation	5	4	3	2	1	0

Appendix E

Brain Injury Community Rehabilitation Outcome Scales-39 (BICRO-39)[1]

Date:_____ Date of your brain injury: _____
Name: _____ Date of Birth: _____ Gender: _____

This questionnaire helps us understand how much your life has changed as a result of your brain injury. It will also help us to monitor your progress during treatment. The questionnaire has eight sections which ask about your independence in personal care, mobility, self-organisation, contact with your partner and your own children, contact with your parents and siblings, socialising, productive employment and psychological well-being.

Please go through the questionnaire and answer all questions according to how you are NOW.

Thank you very much.

PERSONAL CARE

How much help or assistance from other people do you need with …

	don't do at all	constant help	a lot of help	some help	prompts only	no help/ prompts
1) getting into and out of bed	5	4	3	2	1	0
2) moving from room to room	5	4	3	2	1	0
3) getting to the toilet	5	4	3	2	1	0
4) using the toilet	5	4	3	2	1	0
5) reaching and using the phone	5	4	3	2	1	0
6) reaching and using TV or radio	5	4	3	2	1	0

MOBILITY

How much help or assistance from other people do you need with …

	don't do at all	constant help	a lot of help	some help	prompts only	no help/ prompts
7) using public transport	5	4	3	2	1	0
8) going to local shops	5	4	3	2	1	0
9) doing laundry (washing,drying,ironing)	5	4	3	2	1	0
10) cleaning the home (inc. vacuuming)	5	4	3	2	1	0
11) shopping (for food,household needs)	5	4	3	2	1	0

How often do you …

	don't do at all	once or twice a year	several times a year	about once a month	several times a month	once a week or more
12) go out for a walk or to a park	5	4	3	2	1	0

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SELF-ORGANISATION

How much help or assistance do you need from other people with …

	don't do at all	constant help	a lot of help	some help	prompts only	no help/ prompts
13) keeping track of money	5	4	3	2	1	0
14) dealing with your own bank account	5	4	3	2	1	0
15) paying household bills	5	4	3	2	1	0
16) writing official letters (e.g., bank)	5	4	3	2	1	0
17) writing private letters	5	4	3	2	1	0
18) managing appointments	5	4	3	2	1	0

CONTACT WITH PARTNER/OWN CHILDREN

How often do you spend some time with …

	not applicable or never	once or twice a year	several times a year	once or twice a month	once or twice a week	most or all days
19) your partner or spouse	5	4	3	2	1	0
20) your children	5	4	3	2	1	0

CONTACT WITH PARENTS/SIBLINGS

How often do you spend some time with…

	not applicable or never	once or twice a year	several times a year	once or twice a month	once or twice a week	most or all days
21) your mother	5	4	3	2	1	0
22) your father	5	4	3	2	1	0
23) a sister or brother	5	4	3	2	1	0

SOCIALISING

How often do you spend time …

	don't do at all	less than once a week	once or twice a week	several times a week	an hour or so a day	several hours a day
24) socialising with people/family at home	5	4	3	2	1	0

How often do you spend some time with …

	not applicable or never	once or twice a year	several times a year	once or twice a month	once or twice a week	most or all days
25) relatives other than immediate family (i.e., not parents, brothers, sisters, partner, own children)	5	4	3	2	1	0
26) your closest friend	5	4	3	2	1	0
27) another long-standing friend	5	4	3	2	1	0
28) a colleague (outside work time)	5	4	3	2	1	0
29) new acquaintance(since brain injury)	5	4	3	2	1	0

PRODUCTIVE EMPLOYMENT

How much time do you spend…

	don't do at all	less than an hour a week	1-4 hours a week	5-10 hours a week	11-20 hours a week	more than 20 hours a week
30) doing paid work	5	4	3	2	1	0
31) doing unpaid or voluntary work	5	4	3	2	1	0
32) studying, training, doing courses	5	4	3	2	1	0
33) looking after children	5	4	3	2	1	0

PSYCHOLOGICAL WELL-BEING

How often do you…

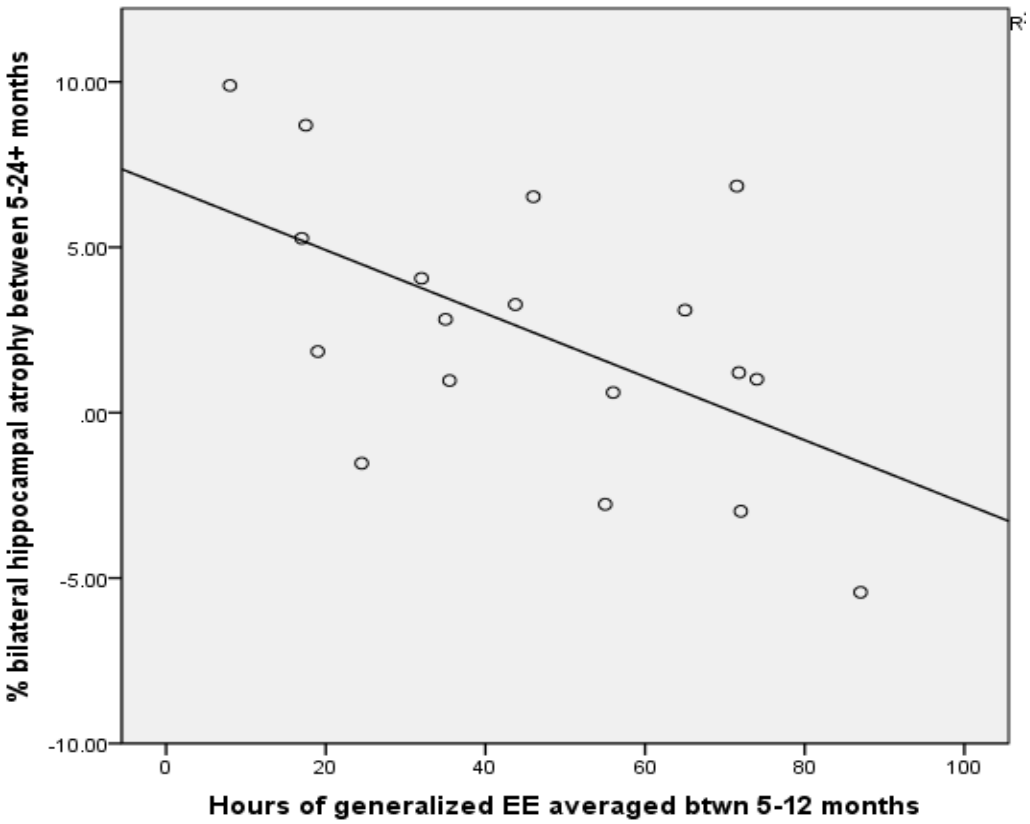
	almost always	very often	often	sometimes	hardly ever	never
34) get impatient with yourself?	5	4	3	2	1	0
35) get angry with other people?	5	4	3	2	1	0
36) feel hopeless about your future life?	5	4	3	2	1	0
37) feel lonely?	5	4	3	2	1	0
38) feel worn out?	5	4	3	2	1	0
39) feel bored?	5	4	3	2	1	0

TOTAL SCORES : (for completion by therapist/assessor)

Scale	***Average Item Score***	***Comments***
Personal Care		
Mobility		
Self-Organisation		
Contact with Partner/own Children		
Contact with Parents/Siblings		
Socialising		
Productive Employment		
Psychological Well-Being		

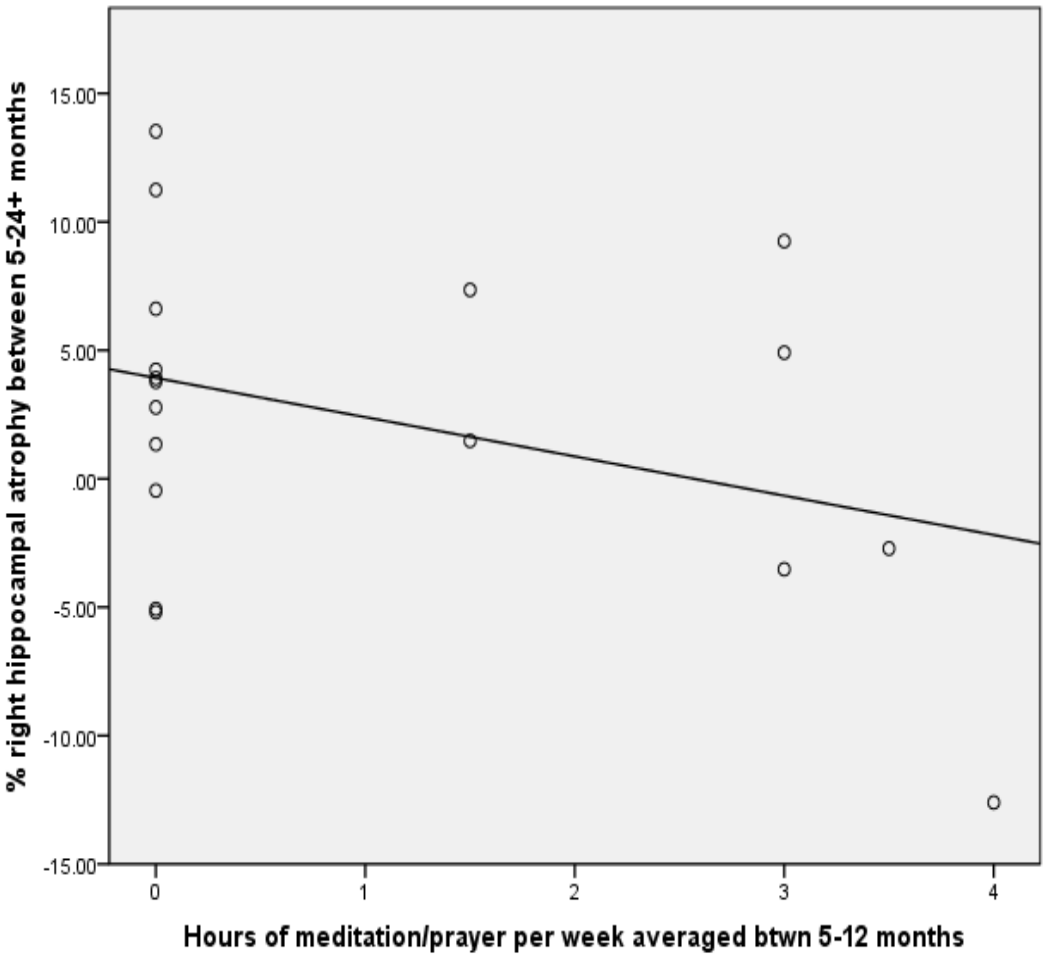
Appendix F

Generalized Environmental Enrichment and Bilateral Hippocampal Atrophy



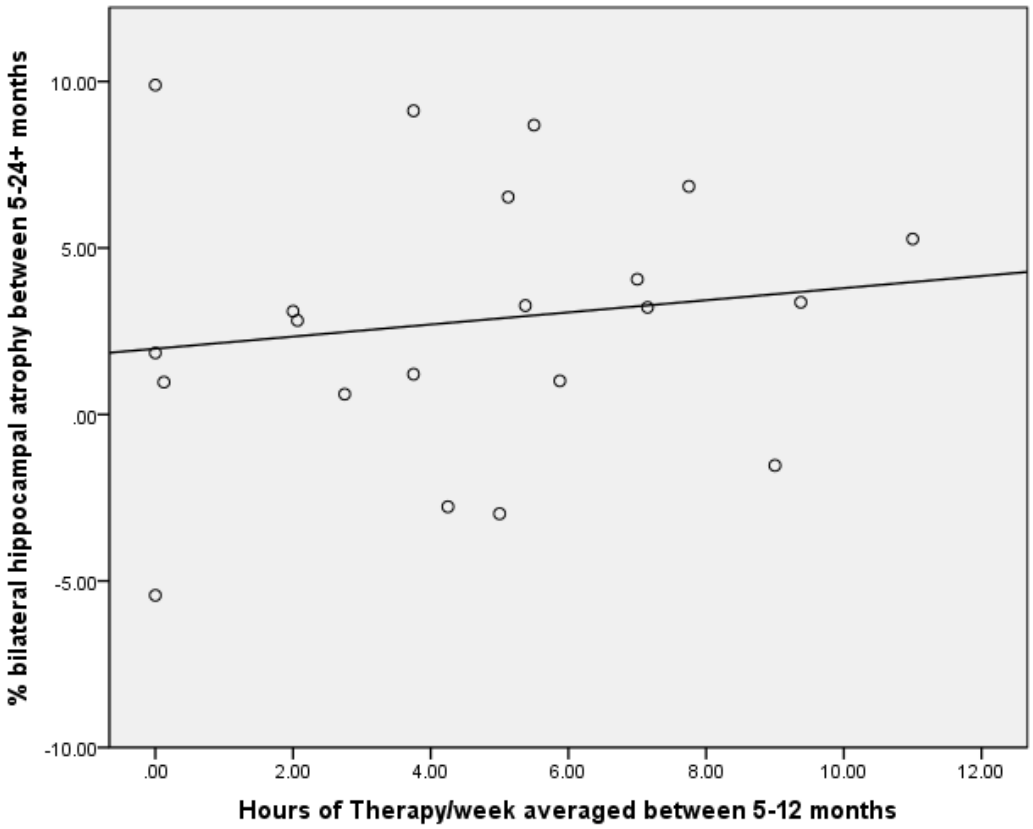
Appendix G

Meditation/Prayer and Right Hippocampal Atrophy



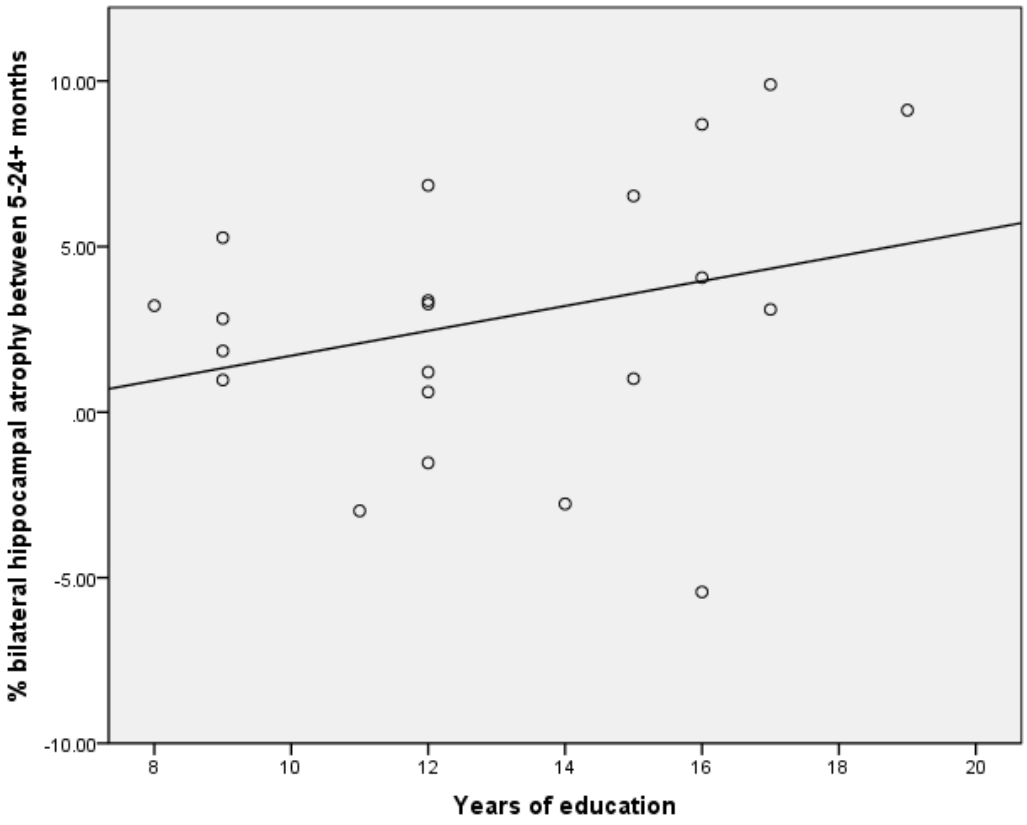
Appendix H

Therapy Hours and Bilateral Hippocampal Atrophy



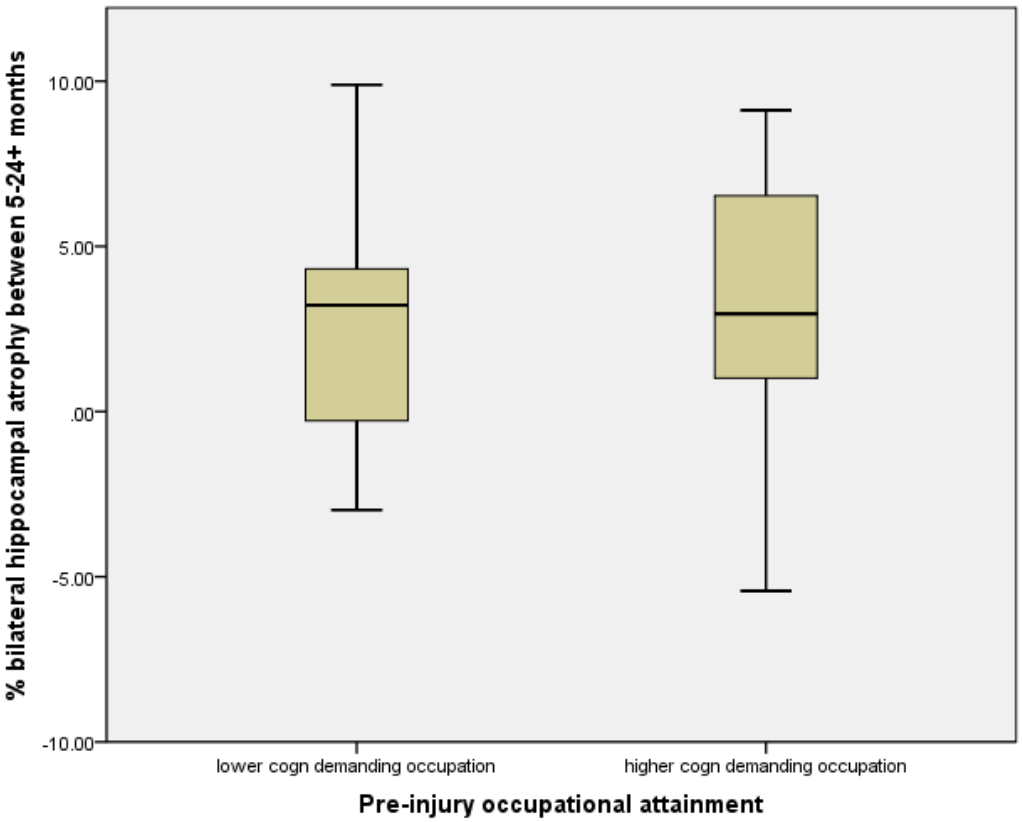
Appendix I

Years of Education and Bilateral Hippocampal Atrophy



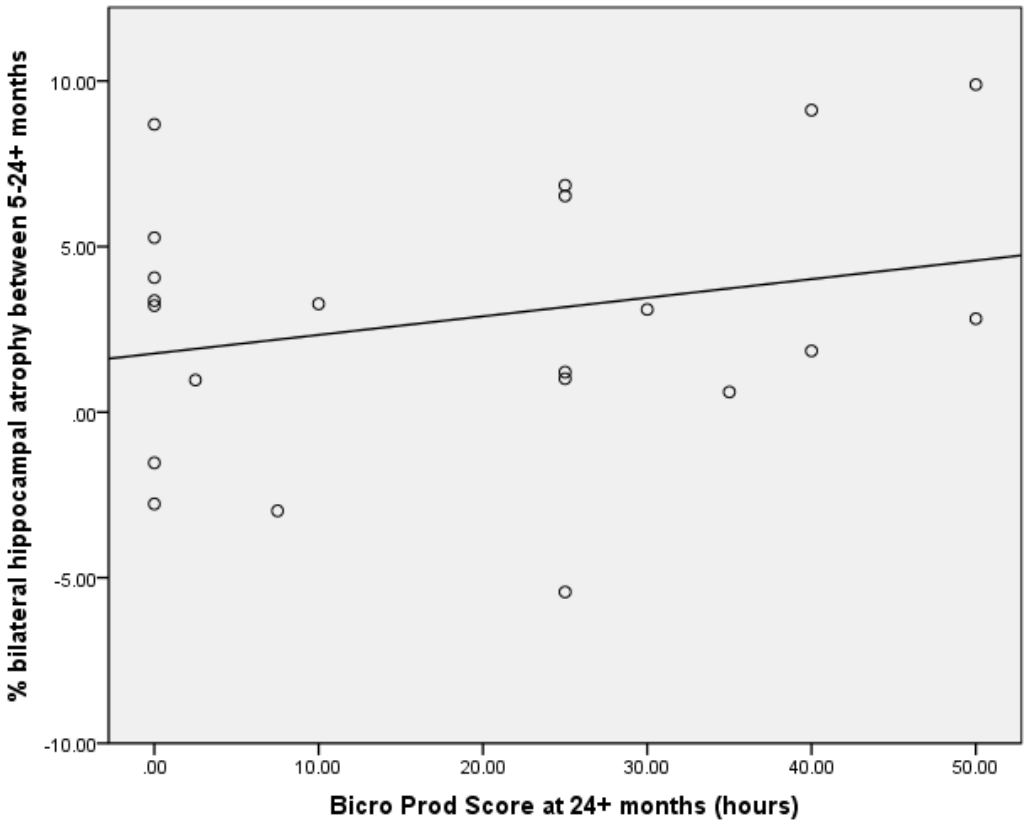
Appendix J

Pre-injury Occupational Attainment and Bilateral Hippocampal Atrophy



Appendix K

BICRO Productive Employment Scores and Bilateral Hippocampal Atrophy



Appendix L

Dichotomous Rating of Return to Pre-Injury Occupational Level and Bilateral Hippocampal Atrophy