NEURAL CORRELATES OF SEVERITY AND RECOVERY OF MEMORY FUNCTION FOLLOWING TRAUMATIC BRAIN INJURY

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A thesis submitted in conformity with the requirements
for the degree of Master of Science,
Graduate Department of Rehabilitation Science
University of Toronto

Your file Votre référence
ISBN: 978-0-494-38968-3
Our file Notre référence
ISBN: 978-0-494-38968-3

Abstract

Neural Correlates of Severity and Recovery of Memory Function Following Traumatic Brain Injury

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Impaired memory is one of the most predominant complaints reported by traumatic brain injury (TBI) survivors. To date, research has addressed focal and global neuropathologic effects of TBI that correlate with poor memory function, but not their impact on the recovery of memory impairment. This study aimed to investigate focal (hippocampal atrophy) and global (measured by ventricle-to-brain ratio or VBR) neuropathologic effects of brain injury on recovery of memory function. Learning and memory performance of 18 TBI patients were assessed at three time points: 1.5 (t1), 5 (t2) and 12 (t3) months post-injury. T1-weighted MR images were used to obtain hippocampal volumes and VBR. Memory performance at all three time points was significantly correlated with the left hippocampal volume. *Recovery* of memory function was significantly correlated with VBR (t1 to t2) and hippocampal volume (t1 to t3). Both focal and global effects of brain injury appear to influence memory recovery.

Acknowledgements

This thesis would not have been possible without many contributions from my supervisors, committee members, colleagues and lab mates. I would like to thank in particular my supervisors, Dr. Robin Green and Dr. Noor Kabani for their guidance, sharing their knowledge and all their patience throughout all this time and for helping me to see the light at the end of the tunnel. I would also like to thank my committee members, Dr. Cindi Morshead and Dr. Nancy Lobaugh for their expertise and for always being available to offer their guidance and advice on all areas of this research. Thanks to my lab mates, Adrienne Dorr, Vivek Singh, and Brenda Melo for putting up with me on a daily basis and for their willingness to lend a hand whenever needed. Special thanks to all of the participants for their time and effort without which, this study would have not been possible.

Finally, I would like to sincerely thank my family and friends for their ongoing support and encouragement throughout my endeavors. I owe much to my best friend, my husband Peter for making the journey with me.

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List of Abbreviations

AC: Anterior commissure

ANIMAL: Automated non-linear image matching and anatomic labelling

BDI: Beck Depression Inventory

CSF: Cerebro-spinal fluid

CT: Computed tomography

DAI: Diffuse axonal injury

DICOM: Digital Imaging and Communications in Medicine

fMRI: Functional magnetic resonance imaging

GCS: Glasgow Coma Scale

GM: Grey matter

HB: Hippocampus body

HC: Hippocampus

HH: Hippocampus head

HT: Hippocampus tail

IHLV: Inferior horn of the lateral ventricle

IQ: Intelligence quotient

LM (IR and DR): Logical Memory (Immediate Recall and Delayed Recall)

MINC: Medical Imaging NetCDF, where NetCDF stands for Network Common Data Form

MRI and MR: Magnetic Resonance Imaging and magnetic resonance

NP: Neuropsychological testing

PC: Posterior commissure

PET: Positron emission tomography

QC: Quality control

RAVLT (SD and LD): Rey Auditory Verbal Learning Test (Short Delay and Long Delay)

RM ANOVA: Repated measures analysis of variance

RVDLT: Rey Visual Design Learning Test

SPGR: spoiled-gradient recalled-echo

TBI: Traumatic brain injury

TLV: Trigone of the lateral ventricle

WM: White matter

WMS: Wechsler Memory Scale

VBR: Ventricle-to-brain ratio

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1.0 Introduction And General Overview

1.1 Clinical Consequences Of Traumatic Brain Injury

Traumatic Brain Injury (TBI) refers to damage to the brain resulting from forces exerted to the head or directly to the brain itself, in the case of penetrating injuries. It can cause debilitating sequelae to people of all ages. In Canada, TBI occurs primarily as a result of motor vehicle accidents and falls (OTR, 2004) and more than six thousand new brain injuries resulting in permanent disabilities are sustained each year (OBIA, 2002) .

TBI can cause a range of motor, cognitive, behavioural and psychosocial deficits, with sometimes devastating emotional and economic consequences for TBI victims and their families (Bigler, 1990; Bigler & Snyder, 1995). These deficits often lead to long-term disabilities (Strangman et al., 2005). The cognitive deficits that are most consistently reported in TBI include impairments to memory, attention, executive functioning and speeded information processing (Bigler, 1990; Fork et al., 2005; Levine et al., 2006; Strangman et al., 2005) with impaired memory being one of the most predominant complaints reported by TBI survivors and their families.

Recovery from cognitive sequelae may not be complete and recovery that does occur may take months to years. Cognitive deficits improve most during the first 6 to 12 months post-injury (Schretlen & Shapiro, 2003). Thereafter, recovery decelerates over time and may reach a plateau by two years post-injury, sometimes leaving patients with marked impairments (Schretlen & Shapiro, 2003). Thus, cognitive functioning may never return to pre-injury level, though it may improve enough to allow person to operate independently (Stein, Brailowsky & Will, 1995).

1.2 The Neuropathology Of TBI

The neuropathology of TBI comprises both focal lesions and non-specific diffuse injury (Bigler, 1990; Gennarelli, 1993). A great deal of focal damage is observed in the frontal and temporal lobes of the brain, near the bony surfaces of the inner skull (Bigler, 1990; Levine et al., 2006). Diffuse injury refers to smaller and more widespread lesions throughout the brain, predominantly affecting white matter but often affecting the smallest blood vessels of the brain as well (Bigler, 1990). The relative contributions of focal and diffuse brain damage vary from individual to individual, depending in large part on the nature of injury. For example, accidents involving powerful acceleration and deceleration forces, but no significant blow to the head may

have a higher ratio of diffuse to focal injury (i.e., car accidents where the TBI survivors are wearing seatbelts).

Morphologic changes, which are associated with worse cognitive performance, include brain atrophy, ventricular dilation and volume loss of cortical and subcortical structures (e.g., hippocampus, fornix and corpus callosum) (Bigler, 1990, 2001, Bigler et al., 1996; Tomaiuolo et al., 2004). Volume loss of the hippocampus, a structure that is especially vulnerable to a variety of brain insults (e.g., herpes encephalitis, hypoxia), has been repeatedly shown to be associated with memory impairment (Bigler et al., 1996, 1997; Kilpatrick et al., 1997; Serra-Grabulosa et al., 2005; Tate & Bigler, 2000; Tomaiuolo et al., 2004).

1.3 Measurement Of Neuropathology In TBI

Magnetic Resonance Imaging (MRI) and neuropsychological (NP) tests are commonly used tools for the assessment of neurological damage and cognitive impairments, respectively in TBI and for the relationship between them (Ariza et al., 2006; Bigler, 1996, 2001a; Bigler et al., 1996; Serra-Grabulosa et al., 2005; Tomaiuolo et al., 2004).

While NP tests are used to detect subtle cognitive deficits associated with injury, structural MRI allows for volumetric quantification of cortical and subcortical structures. It can help identify, localize and quantify gross structural changes associated with injury, including hemorrhages, contusion, and necrotic tissue (Bigler, 1990; Garnett, Cadoux-Hudson & Styles, 2001). It is a particularly useful technique in quantitative assessment of non-focal injury. For instance, Levine et al. (2006) have shown that MR based volume loss of both grey and white matter can be quantified in TBI patients despite the absence of large focal lesions. Furthermore, MRI is quite sensitive to brain damage, often revealing injuries that are not visualized by CT scanning (Lezak, 2004). Focal effects of brain injury can be assessed by volumetric quantification of regions of interest within the brain such as focal lesions, hippocampus or corpus callosum (Anderson, Bigler, & Blatter, 1995; Tate & Bigler, 2000; Tomaiuolo et al., 2004). Global neuropathologic changes, both in relation to focal and non-focal injuries in the brain can be assessed by measures such as total brain volume, total intracranial volume or ventricle-to-brain ratio (VBR) (Bigler et al., 1996, 2004).

1.4 Mechanisms Of Recovery After TBI

The brain has a substantial capacity to recover following an injury. The primary mechanism of recovery involves functional reorganization, where intact areas of the brain take over

functioning of the injured ones (Weiller, Ramsay, Wise, Friston & Frackowiak, 1993). Logically, the more intact resources that remain within the brain after injury, the greater is the potential capacity for recovery. Conversely, when damage is more extensive and widespread, as is often observed in diffuse axonal injury (DAI), the recovery potential is arguably diminished (Himanen et al., 2005; Smith, Meaney & Shull, 2003).

The mechanisms of recovery are not yet well understood (Levine et al., 2006). With regard to memory function - the focus of this thesis - human and animal studies have shown that memory impairment following TBI is associated with decreased hippocampal volume (Ariza et al., 2006; Bigler et al., 1996, 1997; Clausen et al., 2005; Hicks, Smith, Lowenstein, Saint Marie & McIntosh, 1993; Serra-Grabulosa et al., 2005). However, the impact of neurological factors on the *recovery* of memory function has not yet been examined.

1.5 Purpose And Hypotheses Of The Study

Given the dearth of knowledge regarding the neurological predictors of memory recovery, and the clinical importance of memory impairments to patients, the purpose of this research was to increase our understanding of memory recovery after TBI. Two broad types of neuropathology have been highlighted: focal vs. diffuse injury. The current study examined the potentially differing influences of focal and diffuse injury on memory recovery. Specifically, the study hypothesized that focal damage (as measured by hippocampal volume) would be strongly associated with degree of memory impairment (but not recovery) whereas global injury, as measured by VBR, would be associated with recovery of memory function (but not severity of memory impairment). The study examined these predictions in longitudinal, prospective, correlational design.

The intention of this research is to have an impact on the status of our scientific knowledge and on clinical practice. From a research standpoint it is anticipated that this study will generate further investigations in the area of impairment and recovery of memory function. From a clinical standpoint, better knowledge of mechanisms of TBI and recovery will contribute towards the development of new rehabilitation programs as well as timely intervention strategies. These in turn will have profound implications for minimizing the diverse impairments accompanied by a TBI, thereby improving the quality of life.

2.0 Background And Literature Review

2.1 Epidemiology Of Traumatic Brain Injury

The prevalence of TBI follows a bimodal distribution for age. The highest incidence of TBI occurs in young adults, aged 15-24 and in the elderly, aged above 70 years old (NIH Consensus Statement, 1998; OTR, 2004). In the younger group, there is a gender bias, with males sustaining TBI twice as often as females (NIH Consensus Statement, 1998). The medical and economic consequences of TBI are enormous, since the annual cost of TBI-related treatment in Canada is estimated at three billion dollars (OBIA, 2002). Recent data collected in Ontario show that the leading causes of TBI are: motor vehicle traffic incidents (46% of all TBI), falls (35%), unintentionally being struck by an object or person (10%) and assaults (6%) (OTR, 2004). Motor vehicle incidents cause TBI equally in all age groups; however, falls are most prevalent among elderly (OTR, 2004). A decrease in mortality and improved medical outcome in severe TBI patients has been observed over the past 25 years (Ghajar, 2000). Such changes are attributed to advances in medical and trauma care, brain imaging, as well as safety improvement in motor vehicles, workplace safety, and changing sporting equipment standards (Ghajar, 2000). As a result, many individuals who in the past would have died because of the brain injury now survive but are often left with a range of permanent disabilities.

2.2 Neuropathological Characteristics Of TBI

2.2.1 Focal vs. Diffuse Injury

TBI results from damage to the brain tissue caused by external mechanical forces that give rise to focal and diffuse injuries. Focal injuries, which are usually caused by direct blows to the head, include contusions, brain lacerations and hemorrhage, which can further lead to hematoma (Gennarelli, 1993). Contusions usually occur in inferior-anterior temporal and frontal lobes when the brain strikes and compresses again the bony surface ridges of the inner skull (Bigler, 1990; Levine et al., 2006). Contusions can occur in such areas regardless of the site or the direction of the initial impact (Bigler, 1990). In addition, focal damage may occur at the site opposite the point of impact due to oscillation of the brain within the skull, which is also called contre-coup (opposite site of contact) damage. For instance, when impact occurs in frontal lobe regions, damage may be also detected in parieto-occipital region. Damage associated with a site of focal injury, or a lesion, is not limited to a specific region, but rather may result in more widespread dysfunction throughout cortical and subcortical areas (Bigler, Yeo, & Turkheimer, 1989; Stein et al., 1995) through mechanisms such as transneuronal degeneration (Bigler, 1990;

Stein et al., 1995). As such, neuroanatomical abnormalities may extend beyond a lesion and lead to behavioural consequences associated with regions other than that of the brain area affected by the focal injury (Christodoulou et al., 2001).

Diffuse injury, including diffuse axonal injury (DAI), is associated with sudden movement of the head, involving acceleration/deceleration forces (e.g., motor vehicle crashes, sports-related high speed collisions) (Meythaler, Peduzzi, Eleftheriou, & Novack, 2001). DAI is recognized as a consistent and important characteristic of TBI (Povlishock, 1993), which can occur in the absence of any direct impact to the head (Bigler, 1990; Lezak, 2004). It is characterized by widespread damage to the white matter caused by strain and shearing to the axons occurring when the brain rotates and moves within the skull (Bigler, 1990, 2001; Povlishock, 1993; Salmond et al., 2006). White matter is composed of the axons, which connect various grey matter areas (nerve cell bodies) within the brain to each other and carry nerve impulses between neurons. Thus, microscopic axonal and neuronal disruptions within white matter may disconnect the cortex from subcortical structures and disrupt connections between the structures (Lezak, 2004). DAI is a predominant pattern of TBI injury (Bigler, 1990).

Neuronal damage or death may be caused not only by primary axotomy from mechanical forces, but also may result from trauma induced biochemical events (Meythaler et al., 2001; Povlishock, 1993). These biochemical events include excitotoxic damage that is caused by massive release of excitatory amino acids such as glutamate (Di, Harpold, Watson & Bullock, 1996; Hopkins, Tate, & Bigler 2005; Levin & Grafman, 2000; Meythaler et al., 2001). These injury-related pathological changes in the brain take time to be fully expressed as often neurons do not die immediately when their axons are affected, but may die many days later (Bigler, 2001; Fawcett, Rosser & Dunnett, 2001). DAI can be identified, using electron microscopy, as early as 1 hour post-injury (Bigler, 2001), but studies show that cell death in some structures occurs for up to a month (Conti, Raghupathi, Trojanowski, & McIntosh, 1998).

Diffuse injury can occur in isolation or together with focal damage (Levin, 2003). The former is more widespread and may be responsible for a greater share of disability (Bigler, 1990; Levine et al., 2006); however, both types of injury, focal and diffuse, may lead to interruption or disconnection of the local and long-distance circuits within the brain that transmit information and control various actions (Bigler, 1990; Stein et al., 1995). Neurons that are not directly damaged may also degenerate and hence, the effects of brain injury may be remote from the original site of the injury (Stein et al., 1995; Fawcett et al., 2001).

2.2.2 Global Pathological Consequences Of TBI: Brain Damage And Ventricular Enlargement

Structural brain abnormalities in TBI patients have been studied extensively (Anderson & Bigler, 1995; Anderson, Wood, Bigler, & Blatter, 1996; Bigler, 2001; Bigler et al., 1996; Gale, Johnson, Bigler, & Blatter, 1995; Levine et al., 2006). In addition to circumscribed focal injury, larger brain abnormalities include overall brain atrophy, such as reduction of grey and white matter, enlargement of ventricles, and size reduction of subcortical medial temporal lobe structures, such as hippocampus and fornix (Bergeson et al., 2004; Tate & Bigler, 2000; Yount et al., 2002).

In addition to volume loss of both grey and white matter (Bigler, 2001; Blatter et al., 1997; Bramlett & Dietrich, 2002; Levine et al., 2006) numerous studies have demonstrated ventricular enlargement following TBI (Anderson & Bigler, 1995; Bigler, 1996; Blatter et al., 1995, 1997; Bramlett & Dietrich, 2002 ; Gale et al., 1995; Gale, Johnson, Bigler, & Blatter, 1994; Macnamara et al., 1992; Yount et al., 2002). The ventricular system of the brain comprises spaces within the brain, filled with cerebrospinal fluid (CSF) and surrounded by brain parenchyma. It has been found that the size of the ventricles increases with normal aging and abnormally so under certain neurological conditions, such as TBI, schizophrenia and dementias (e.g., Alzheimer's disease). Ventricular enlargement, provided there is no increase in pressure or obstructions of any of the foramens or the aqueduct, may result from shrinkage of brain parenchyma caused by damage and death of neurons (Lezak, 2004). As a result, in an event of brain volume loss, a subsequent increase in ventricular volume may be observed (Bigler, 2001). This phenomenon is called hydrocephalus ex vacuo (Bigler, 2001). Such systematic changes in the brain and ventricular volumes, may be observed over time in patients with TBI (Blatter et al., 1997). For instance, compared to normal control subjects, Blatter and colleagues (1997) demonstrated a 62% increase in ventricular volume that corresponded to approximately a 2.97% reduction in brain volume measured in MR scans in moderate to severe brain injury patients around 10.5 months post-injury. Such brain volume decrease and ventricle enlargement was associated with both focal and diffuse mechanisms of injury, and both were found to be greater in TBI than seen in the normal population (Blatter et al., 1997).

Similarly, Bigler et al. (1996) reported a significant reduction in brain volume and marked increase in ventricular volume in TBI patients imaged more than 90 days post-injury in comparison with a control group. In this study the mean total brain volume, including grey and white matter, of control subjects (1.335.14 cm^3) was significantly ($p = .0001$) larger in comparison to TBI patients (1.309.36 cm^3). In addition, the ventricular volume (the mean and

standard deviation of the volume of the third ventricle only were reported) was significantly ($p = .0001$) larger in TBI (1.53 cm^3) in comparison to normal control subjects (0.78 cm^3).

In the more recent study, MacKenzie and colleagues (2002) reported loss of the total brain parenchyma, measured by quantitative MRI, in mild to moderate TBI patients being on average 0.528 cm^3 a day in comparison to healthy control subjects, where the magnitude of loss was 0.106 cm^3 a day. These observations need to be viewed as preliminary, however, because of the small sample size ($n = 7$ for TBI patients and $n = 4$ for the normal control subjects).

Ventricular enlargement has been also documented when comparing pre-and post-injury scans of TBI patients (Bigler, Kurth, Blatter, & Abildskov, 1992; Macnamara et al., 1992). For instance, Bigler and colleagues (1992) reported a significant increase (by 70%) in ventricular size in a case study of a severe head injury patient, for whom pre-and two post-injury (at 42 days and 10 months) MR scans were available. The largest proportion of the increase was observed to take place within 42 days post-injury, with little further degeneration at 10 months post-injury.

2.2.3 Hippocampal Injury In TBI

General Introduction

The hippocampus, a bilateral structure located in the medial temporal lobe, is a critical structure of the temporal lobe memory system (Squire & Zola-Morgan, 1991). The hippocampus appears to be particularly vulnerable to injury, regardless of the point of impact or severity of damage (Bigler, 1996; Bigler et al., 1996, 1997; Geddes, LaPlaca & Cargill, 2003; Hicks et al., 1993; Tate & Bigler, 2000). Temporal lobe is especially vulnerable to injury because of its position in the skull (middle cranial fossa) (Bigler et al., 1997). As such hippocampus is exposed to direct injury that may cause mechanical deformation, but it is also vulnerable to excitotoxic reaction, and DAI involving hippocampal input and output fibers (Bigler, Anderson, & Blatter, 2002; Gale et al., 1995; Goldstein & Levin, 1990; Kotapka, Graham, Adams, & Gennarelli, 1994). The prevalence of hippocampal lesions due to trauma has been demonstrated by Kotapka et al. (1994) in post-mortem examination of human head injury. The major neuro-pathological findings in these fatal head injures consisted of cortical contusions, DAI and hypoxic brain damage. Despite different mechanisms of injury, hippocampal lesions were found in 12 out of 14 studied injured brains.

It has been well established that trauma results in hippocampal atrophy (Ariza et al., 2006; Bigler et al., 1996, 1997; Hopkins et al., 2005; Serra-Grabulosa et al., 2005; Tomaiuolo et al., 2004). A number of MRI studies have shown positive associations between the hippocampal

volume and memory performance in various populations such as TBI (Ariza et al., 2006; Bigler et al., 1996, 1997; Hopkins et al., 2005; Tate & Bigler, 2000; Tomaiuolo et al., 2004; Serra-Grabulosa et al., 2005), patients with dementia (Bigler et al., 2000; Petersen et al., 2000), epilepsy (Kilpatrick et al., 1997), carbon monoxide poisoning (Hopkins et al., 2005), developmental amnesia (Isaacs et al., 2003) and animal models of brain injury (Clausen et al., 2005; Hicks et al., 1993). In addition, studies have demonstrated the critical role of the hippocampus in memory with lateralizing implications where verbal memory and learning appears to be mediated by the left hippocampus and visual memory by the right hippocampus (Bigler et al., 1996; Cullum, Kuck, & Ruff, 1990; Kilpatrick et al., 1997; Lezak, 2004; Petersen et al., 2000; Tomaiuolo et al., 2004; Salmond et al., 2006; Squire & Butters, 1992).

Animal Studies Of The Hippocampus And TBI

A variety of animal models have been developed to study the pathophysiology of TBI (Bigler, 1996; Dixon et al., 1987; Povlishock, 1992). One of the most frequently employed models of TBI pathology, producing both focal and diffuse brain injury, is the fluid-percussion injury model, developed by Dixon et al. (1987). In this model saline is rapidly injected into the closed cranial cavity, resulting in brief displacement and deformation of neural tissue (Dixon et al., 1987; Hicks et al., 1993). Fluid-percussion injury model has been well characterized and has been shown to reproduce many relevant features of TBI typical for high-velocity-impact head injury (Bigler, 1996; Hicks et al., 1993). Hippocampal atrophy as a consequence of TBI has been well documented in animal models (Clausen et al., 2005; Conti et al., 1998; Hicks et al., 1993). Hicks et al. (1993) have shown that mild lateral fluid-percussion brain injury in rat results in significant memory deficits, compared to control animals, as early as 48 hours post-injury, which is associated with loss of hippocampal neurons. Furthermore, studies have shown that neuronal degeneration in hippocampus and other structures after lateral fluid-percussion injury can be detected as early as 10 min after the injury (Conti et al., 1998; Hicks et al., 1996). Clausen et al. (2005) assessed relationship between memory dysfunction and regional hippocampal morphological changes after a different type of brain damage, including controlled cortical contusion, in rats. They have found that severe cortical contusion caused bilateral morphological changes in the hippocampus, which correlated with impairment in spatial learning task as assessed by Morris Water Maze performance.

Human Studies Of The Hippocampus And TBI

Changes in the hippocampal volume have also been extensively studied in a human model. For instance, Bigler and colleagues (1997) studied changes in hippocampal volume, quantified

in MR scans, in normal aging and TBI. In normative groups from age 16 to 65, both left and right hippocampal volumes decreased slightly but not significantly (from 2.63 cm^3 to 2.42 cm^3, and from 2.68 cm^3 to 2.51 cm^3, left and right respectively, volumes corrected for head size). Also, the left and right hippocampi remained symmetric and stable in size when compared in groups of participants from 16 to 65 years old over the five-decade time span (Bigler et al., 1997).

When compared with normal controls however, patients with TBI, showed significant hippocampal atrophy. The observed reduction in hippocampal volume appeared to be time dependent following injury, as the bilateral hippocampus volume in the early-TBI group (2.43 cm^3 and 2.48 cm^3, left and right respectively), assessed less than 100 days post-injury did not differ significantly from that of control subjects (2.54 cm^3 and 2.60 cm^3, left and right respectively). However, compared to normal controls, hippocampal volumes were significantly (by 9%) smaller ($p = .001$ and $p = .014$ left and right respectively) in the late-TBI group assessed more than 100 days post-injury (2.35 cm^3 and 2.47 cm^3, left and right respectively).

In addition, Bigler et al. also assessed the relationship between hippocampal volumes and memory function. For a subgroup of TBI patients who were assessed 71 to 210 days after injury, the relationship between verbal memory performance and hippocampal volumes was particularly strong ($r = 0.703$, $p < .01$). The authors concluded that hippocampal volume in the sub-acute phase of recovery may be predictive of long-term cognitive function, as during this time frame (2.5 to 7 months) a large portion of the deterioration resulting from TBI will take place (Bigler et al., 1997).

A previous study by Bigler et al. (1996) examined the relationship between focal (measured hippocampal damage) versus global (assessed with VBR) brain pathology measurement and memory impairment in TBI. Memory performance was related significantly to the degree of hippocampal damage ($r = 0.47$, $p = .003$), but not to VBR. In addition, verbal memory performance was correlated higher with the left hippocampus as opposed to the right. Comparison with normal controls identified greater atrophy in the left hippocampus as opposed to the right. The average volume of the left and right hippocampus was 2.50 cm^3 and 2.55 cm^3 respectively in control subjects and 2.29 cm^3 and 2.43 cm^3 in TBI patients. The memory-hippocampus relationship became significant only at later point in time after the injury, around 90 days post-trauma Bigler et al. (1996).

A more recent study by Ariza and colleagues (2006) examined hippocampal damage, using structural MRI, and memory performance in moderate to severe TBI. The study investigated whether damage varied according to the hippocampal area involved, such as the hippocampus

head, body or tail. TBI patients were scanned on average 10 months post-injury and underwent memory assessment, on average 8 months post-injury. Both left and right hippocampal volumes were significantly ($p = .007$ and $p = .003$, respectively) lower in TBI (2148 mm^3 and 2201 mm^3, respectively) than in control group (2367 mm^3 and 2462 mm^3, respectively). Thus, the percent difference in the left and right hippocampal volumes was 9.21% and 10.61%. The hippocampal head was the region with the largest degree of atrophy. Moreover, TBI patients performed significantly worse than controls (performance was decreased up to 39%) on all memory tests. In addition, left hippocampal head volume correlated significantly with verbal memory measured by Rey Auditory Verbal Learning Test ($r = 0.50$, $p = .031$).

2.3 Magnetic Resonance Imaging In TBI

2.3.1 General Introduction

MRI allows for in-vivo observation of the intact and injured brains. It has been used widely in studying and diagnosing TBI, and proved to be a useful technique in assessment of severity and clinical outcome (Garnett et al., 2001).

Structural MRI can help identify and localize gross structural changes associated with injury, including hemorrhage, contusion and necrotic tissue (Bigler, 2001; Garnett et al., 2001). DAI, however, is not readily visualized in vivo, but by indirect observations of its consequences, such as ventricular dilation, global brain atrophy, and atrophy of white matter structures such as corpus callosum (Bigler, 2001; Levin, 2003; Levine et al., 2006). These changes in the brain can be measured by structural MRI, providing quantitative versus qualitative assessment of brain neuropathology. For instance, Levine et al. (2006) showed that MR based volume loss of both grey and white matter can be quantified in TBI patients despite the absence of large focal lesions. Structural effects of injury studied by MRI can then be related to cognitive outcome and as such, neuroimaging can provide information complementary to cognitive testing in the assessment of TBI and understanding mechanisms of injury and recovery (Munoz-Cespedes, Rios-Lago, Paul, & Maestu, 2005). As structural changes may take time to develop, MRI completed immediately after injury is often normal, and thus correlations between brain and behaviour early post-injury may not be strong (Bigler et al., 1996, 1997; Garnett et al., 2001; Meythaler et al., 2001).

2.3.2 MRI Measurement Of Focal And Global Indices Of Neuropathologic Changes In TBI

Focal effects of brain injury can be examined using volumetric quantification of the brain structures (Anderson, Bigler, & Blatter, 1995; Anderson et al., 1996; Bigler, 2001, 2001a; Pierallini et al., 2000; Tate & Bigler, 2000; Tomaiuolo et al., 2004). Brain structures can be automatically or semi-automatically segmented or manually traced in MRI scans in order to obtain their volumes. For example, TBI induced hippocampal or corpus callosum atrophy, has been well established using MR volumetric quantification of these structures (Bigler at al., 1996, 1997; Hopkins et al., 2005; Tomaiuolo et al., 2004). Furthermore, a number of studies have examined lesions, quantifying their size, and determining their type and location as predictors of neuropsychological outcome (Anderson et al., 1995, 1996; Pierallini et al., 2000).

In contrast, global indices of neuropathologic changes in TBI address generalized, nonspecific brain integrity. These global measures include total brain volume, total intracranial volume and the VBR (Bigler et al., 2004; Blatter et al., 1997). These volumes are obtained using tissue segmentation algorithms where every voxel in a volume is assigned a tissue label of grey and white matter or CSF, based on image intensity (Bigler et al., 1996; Blatter et al., 1997; Hopkins et al., 2005; Levine et al., 2006). The global atrophy measures have been highly correlated with neuropsychological outcome (Bigler et al., 2004).

2.3.3 Ventricle-to-Brain Ratio (VBR)

VBR is one of the best documented and most extensively used measures of the global brain atrophy (Anderson et al., 1996; Bergeson et al., 2004; Bigler et al., 2004; Blatter et al., 1995; Gale et al., 1995; Johnson, Bigler, Burr, & Blatter, 1994; Resnick et al., 2000; Yount et al., 2002). VBR is calculated by taking a percent ratio of ventricular volume (lateral ventricle, third and fourth ventricle) to total brain volume including total grey matter and white matter of the cerebral hemispheres and cerebellum (Anderson et al., 1996; Bigler et al., 2004; Blatter et al., 1995). As such, VBR reflects both the expansion of the ventricular system resulting from injury and decreased brain volume (Bigler et al., 2004). Since the ventricular volume constitutes the numerator and the decreasing brain volume the denominator, increasing VBR reflects greater atrophy (Bigler et al., 2004). Increased VBR has been associated with worse cognitive performance (Bigler 2001; Bigler et al., 2004; Blatter et al., 1997). In a large normative study of the human brain, Blatter et al. (1995) demonstrated that for ages 16 to 54, the VBR is relatively stable with average VBR being approximately 1.32 (uncorrected for head size) while Anderson et al. (1996) have shown the average VBR in normal controls being 1.28 (corrected for head size). In addition, Anderson, et al. (1996) examined the relationship between injury severity,

measured by Glasgow Coma Scale (GCS) and VBR. Based on GCS patients were separated into two groups: mild-moderate (GCS > 9) and moderate-severe injury (GCS ≤ 9). Patients with moderate to severe injury had a significantly higher VBR (mean = 3.14) in comparison to patients with mild-moderate injuries (mean VBR = 1.56).

Bigler et al. (1996) have reported significantly higher VBR in TBI patients when compared to normal controls. In this study two groups of TBI patients were examined: TBI assessed less that 90 days post-injury and TBI assessed more that 90 days post-injury. Both groups had significantly higher VBR when compared to normal controls (mean = 1.29). In addition, TBI > 90 days had significantly higher VBR (mean = 2.43) compared to TBI < 90 days post-injury (1.85).

Significantly increased VBRs were also reported at later points after the injury (Gale et al., 1994; Yount et al., 2002). For instance, Gale et al. (1994) showed on average a 2.76 increase in VBR in TBI patients (3.50), who were scanned on average 26 months post-injury, in comparison to the healthy control subjects (1.27). Furthermore, Yount and colleagues (2002) reported significantly increased VBRs and reduced total brain volumes in TBI patients who underwent MRI at an average of 22 months post-injury when compared to normal controls. However, the magnitude of impairment cannot be determined from this study because means and standard deviations for the VBR and total brain volumes were not reported.

The relationship between VBR and performance on a variety of NP tests (i.e., tests of mental status/orientation, mini-mental status exam, language, memory, processing speed, executive functioning and intelligence) and other global brain atrophy measures (i.e., total brain volume, total intracranial volume, total ventricular volume, ventricle-to-cranial ratio) have been also assessed (Bigler et al., 2004). Results of this study indicate that VBR demonstrates robust correlations with neuropsychological performance. The authors concluded that use of a single global brain measure such as VBR is sufficient in studies examining global indicators of brain atrophy in relation to cognitive function (Bigler et al., 2004). As such, VBR was used in the current study as a measure of global atrophy.

2.4 Cognitive Functioning And TBI

2.4.1 General Brain-Behaviour Relationships After TBI

Focal damage results in impairment of cognitive functions normally mediated by the cortex at the site of the lesion (Lezak, 2004). Since, frontal and temporal lobes are areas most susceptible to brain damage in TBI, difficulties with functions associated with these areas are most predominant. Therefore, executive functions and high-level functions such as problem-

solving, strategic decision making, judgment, and learning and memory are often compromised. As well, personality and psychosocial functioning difficulties are commonly observed in conjunction with these focal injuries (Levine et al., 1998; Lezak, 2004). DAI has been associated with deficits in mental speed, attentional functions, cognitive efficiency, and concentration, as well as irritability and fatigue (Lezak, 2004). Thus, patients with diffuse damage perform poorly on tasks that require concentration and mental tracking (e.g., arithmetic and reasoning problems) and tasks requiring selective or divided attention. Most TBI patients, suffer from both focal and diffuse injury, hence their cognitive performance exhibits symptoms associated with focal and diffuse damage (Lezak, 2004). However, diffuse injury in the absence of focal lesions can result in cognitive deficits similar to those caused by focal injury alone (i.e., deficits in executive functions, speed of processing and attention) (Bigler, 2001; Fork et al., 2005; Levine et al., 1998, 2005; Strangman et al., 2005). The severity of cognitive deficits increases with severity of brain injury, as determined by length of coma and GCS (Dikmen, Machamer, Winn, & Temkin, 1995; Schretlen & Shapiro, 2003).

Cognitive and behavioural impairments are more closely associated with chronic disability than physical impairments (Levine et al., 2005). Deficits in learning and memory, both verbal and non-verbal, are particularly common and according to some, the most debilitating consequences of TBI (Vakil, 2005).

2.4.2 Memory Impairments And Their Assessment Following TBI

Extensive research over many decades has shown that the hippocampus, a part of the limbic system, plays a crucial role in learning and memory (de Haan, Mishkin, Baldeweg & Vargha-Khadem, 2006; Squire & Zola-Morgan, 1991; Squire, 1992). Lesion studies of patients with neurological damage, functional imaging studies in humans, and experimental work with nonhuman primates and rats have all provided conclusive evidence for the role of the hippocampi in learning and memory (Bigler, 1996; Bigler et al., 1996, 1997; Hicks et al., 1993; Kotapka et al., 1994; Lezak, 2004; Squire & Zola-Morgan, 1991; Tate & Bigler, 2000). As discussed above, the hippocampus shows significant atrophy after TBI, and the memory impairments so commonly observed in TBI are underlined in large part by hippocampal damage (Bigler, 1996; Bigler et al., 1996, 1997; Hicks et al., 1993; Hopkins et al., 2005; Tate & Bigler, 2000; Serra-Grabulosa et al., 2005; Tomaiuolo et al., 2004).

With regard to the assessment of memory function after TBI, there are a number of neurosychological measures with strong psychometric properties and demonstrated validity for the TBI population.

One of the most frequently used measures of verbal memory performance is the Wechsler Memory Scale (WMS) Logical Memory (LM) (Wechsler, 1997). This test examines memory for organized, meaningful information (stories) and both immediate and delayed recall of auditorily presented short stories. Impaired performance on WMS was reported in many studies of TBI. For example, one study compared TBI performance to trauma controls at 1 year post-injury and observed significant impairments (by 16% to 20%) in the TBI group on measures of immediate and delayed recall (Dikmen et al., 1995). In another study, even at 30 years post-injury, the WMS was able to discriminate between TBI patients and normal controls (Himanen, et al., 2006). In this study performance of the TBI group was lower by 18% and 24% on measures of immediate and delayed recall respectively. WMS performance was correlated with the left hippocampal volume as measured by MRI in a number of studies (Bigler et al., 1996, 1997; Petersen et al., 2000).

Verbal learning is often assessed using word-list learning tasks such as the Rey Auditory Verbal Learning Test (RAVLT) (Cullum et al., 1990; Lezak, 2004) and the California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987). RAVLT has been extensively used in assessment of verbal learning and memory. This test allows for assessment of learning, immediate and delayed recall, and recognition (Lezak, 2004) and it is a good test for characterization of memory impairment (Vakil, Blachstein, Rochberg, & Vardi, 2004). The RAVLT has been shown to be sensitive to memory impairments in TBI patients in many studies. For instance, impaired performance on RAVLT was observed in TBI patients assessed at 9.5 years post-injury relative to control subjects (Serra-Grabulosa et al., 2004), where TBI patients' performance was reduced from 27% to 35% on measures of learning (RAVLT total) and long term recall (RAVLT long delay). As well, significant correlations between MR measured hippocampal atrophy and deficient performance on RAVLT tests (RAVLT total, delayed recall and final delayed recall) were reported ($r = 0.60$, $p < .05$; $r = 0.90$, $p < .001$; $r = 0.70$, $p < .001$, respectively) (Kilpatrick et al., 1997).

Non-verbal or visuo-spatial memory is assessed in TBI using both familiar and unfamiliar objects, for example, faces, scenes and geometric figures (Lezak, 2004). One commonly used test is the Rey Visual Design Learning Test (RVDLT), a visuospatial analogue to the RAVLT test. In this test, geometric figures are presented and immediate recall, delayed recall and recognition are measured for the figures (Lezak, 2004; Spreen & Strauss, 1991).

Given the strong psychometric properties of the WMS-III Logical Memory, the RAVLT and the RVDLT and their sensitivity to memory impairment in patients with TBI, these tests were used in the current study.

2.5 Recovery Following TBI

2.5.1 Neuroplasticity

Neural cell death and dysfunction caused by mechanical and excitotoxic damage contribute to cognitive deficits following TBI (Sun et al., 2007). Nevertheless, after the resolution of acute changes (i.e., edema), substantial spontaneous recovery occurs, indicating that there are inherent repair mechanisms existing in the brain (Sun et al., 2007).

Until recent decades, the adult brain was thought to have very little capacity to change and to repair itself in response to injury (Munoz-Cespedes et al., 2005). However, in the past two decades, scientists have found that the brain has the ability to change at the microscopic level both with age and in response to injury. This cortical reorganization of the brain is also referred to as brain plasticity. Plasticity refers to the brain's ability to learn, remember and forget, and to its capacity to reorganize in response to injury (Buonomano & Merzenich, 1998; Kolb, 1999). Plastic changes are believed to be a part of normal brain development as well as an adaptive mechanism following an injury.

It has been widely confirmed that neuroplasticity in both the intact and injured brain is greatly influenced by behavioural experience (Kolb, 1999; Munoz-Cespedes et al., 2005). Plastic changes following extensive training have been reported. For example, Elbert et al., (1995) reported enlarged cortical representations of the left hand digits of string players. Similarly, expanded sensorimotor cortical representation of the right index (reading) finger in Braille readers have been reported (Pascual-Leone & Torres, 1993). Furthermore, there is a capacity for local neuroplastic change in specific brain structures in response to environmental demands. For instance, extensive navigation experience was positively associated with increased volume of posterior hippocampi in a study of London taxi drivers (Maguire et al., 2000).

2.5.2 Functional Reorganization

One of the mechanisms of neuroplasticity is functional reorganization, where intact areas of the brain take over functioning of the injured ones (Weiller et al., 1993). Recovery of cognitive functions after TBI is supported by functional reorganization of the brain (Munoz-Cespedes, 2005). Functional reorganization involves the formation of novel neural networks wherein synaptic changes, support the formation of new connections between neurons, strengthen the existing ones and eliminate weaker ones (Kolb, 1999). Neurophysiologic and neuroanatomic studies in both animals and humans conducted over the past 20 years have shown that damage to the brain results in cortical reorganization that varies depending on age, extent and location of injury, and the presence of rehabilitation; studies have established that cortical maps of adult

animals are dynamic (Bounomano & Merzenich, 1998; Nudo, Plautz, & Frost, 2001; Shih & Cohen, 2004).

The function of *intact* and injured cortical areas during recovery from brain injury has been studied using techniques such as positron emission tomography (PET), functional MRI (fMRI), transcranial magnetic stimulation and magnetoencephalography (Nudo et al., 2001). Functional re-organization is most explicitly seen in studies of patients with focal lesions. Here, extra activation is shown in areas adjacent to lesions or in areas contralateral to damaged regions, which would normally be involved in task performance (Levine et al., 2002). Levine et al., (2002) studied performance on verbal encoding and retrieval tasks in a group of six moderate-to-severe TBI survivors who sustained injury approximately four years prior to scanning. Although not significantly different, on average TBI patients' memory performance was worse than that of control subjects. When compared, both TBI patients and normal controls engaged frontal, temporal and parietal regions known to be involved in memory retrieval. However, in addition, TBI patients showed increases in frontal, anterior cingulate and occipital activity, as measured by PET, and showed activity in the contralateral homologous regions that was not observed in the healthy controls. Furthermore, TBI patients showed reduced activation in some regions such as thalamus. Overall, compared to normal control subjects, TBI patients showed more widespread activation and reduced cortical focus of activation in response to memory retrieval task. The overall pattern of activation was consistent across patients despite variability in focal injury and consistent with morphologic changes in the brain due to DAI (e.g., brain atrophy and ventricular enlargement). The authors concluded that in comparison to controls, TBI patients employed altered functional neuroanatomical networks while performing memory tasks, and these changes were associated with DAI (Levine et al., 2002). In addition, Christodoulou et al. (2001) examined patterns of brain activation while performing a working memory task in persons with moderate-to-severe TBI and healthy controls using fMRI. Both groups displayed cerebral activation in similar regions of the frontal, parietal and temporal lobes. However, TBI patients displayed altered cerebral activation overall, which was more widespread in these same regions and also more lateralized to the right hemisphere. These findings again suggest reorganization during recovery from brain injury (Christodoulou et al., 2001).

As mentioned above, behavioural experiences mediate physiological and neuroanatomic changes in the brain (Munoz-Cespedes et al., 2005; Nudo et al., 2001). Hence, behavioural rehabilitation is widely used in the treatment of TBI patients with the aim of enhancing

reorganization. Although rehabilitation results in greater functional gains, spontaneous recovery of function to some degree occurs, even in the absence of rehabilitation (Bach-y-Rita, 2003).

Changes in cortical area due to rehabilitation were presented in studies with patients after stroke or other brain damage (Nudo et al., 2001). For instance, it was found that the size of the cortical representation of the affected limbs and associated functional improvement in patients exhibiting motor deficits following neurologic injury, such as TBI or stroke, depended on the use of those limbs (Buonomano & Merzenich, 1998; Johansen-Berg et al., 2002; Kim, Park, Ko, Jang, & Lee, 2004; Nudo et al., 2001). Cortical changes detected by fMRI that are associated with subsequent functional improvements were reported following constraint-induced movement therapy in stroke patients. In this type of therapy the unimpaired limb is constrained while the use of the more affected one is promoted (Johansen-Berg et al., 2002; Kim et al., 2004; Nudo et al., 2001). These changes involved significant enlargements of the cortical areas representing an impaired limb in the affected and unaffected hemisphere and increased activity in the motor cortical areas in undamaged hemisphere associated with movement of a recovered limb (Johansen-Berg et al., 2002; Kim et al., 2004; Nudo et al., 2001). For instance, Johansen-Berg et al. (2002) performed serial fMRI on a group of stroke patients prior to and following a course of rehabilitation therapy. Seven patients, at least 6 months post-stroke were scanned twice before and twice after 2 weeks of constraint-induced movement therapy. Therapy-related improvement in hand function was associated with an increase in brain activity on fMRI in the premotor cortex and secondary somatosensory cortex contralateral to the affected hand, and in the bilateral superior posterior regions of the cerebellar hemispheres.

In conclusion, since the effects of brain injury are quite widespread, many areas of the brain participate in the repair processes, and recovery may continue for years after the injury (Stein et al., 1995). In DAI recovery may be restricted to localized plasticity in the grey matter and repair of damaged axons that did not disconnect (Smith et al., 2003). It is possible, that the effects of focal damage are easier to compensate by plastic mechanisms than the extensive effects of DAI (Himanen et al., 2005).

2.5.3 Recovery Of Cognitive Functions Following TBI

In general, studies report that the extent of neuropathologic abnormalities in the brain is directly associated with the degree of the neuropsychological impairment (Bigler, 2001). However, considering individual differences, the variable nature of damage, course of recovery from injury is difficult to predict and can vary greatly from patient to patient (Bigler, 2001).

Research on behavioural and neural recovery following brain damage is limited (Munoz-Cespedes et al., 2005; Stein et al, 1995). Specifically, there are few studies in the literature that correlate behavioural and imaging data in the area of recovery (Munoz-Cespedes et al., 2005).

Recovery from cognitive sequelae is often incomplete (Dikmen et al., 1995; Himanen et al., 2006; Millis et al., 2001; Schretlen & Shapiro, 2003). Individuals with TBI show variability in their recovery with regard to the extent and rate, and a number of factors may differentially influence recovery, including age, sex, severity of injury, and pre-injury level of functioning (Dikmen et al., 1995; Millis et al., 2001). Recovery, following TBI may require a long period of time. Many individuals who suffer disabling brain injuries show remarkable recovery, but others are left with permanent disabilities (Bigler, 2001a; Dikmen et al., 1995; Himanen et al., 2006; Schretlen & Shapiro, 2003). Although, in many cases of moderate and severe TBI, cognitive function may never return to normal level, it may improve enough to allow a person to function independently nonetheless (Schretlen & Shapiro, 2003; Stein et al., 1995).

Schretlen & Shapiro (2003) conducted a meta-analysis of 39 studies of cognitive recovery after TBI. They found that cognitive functioning after mild head injury recovers most rapidly during the first few weeks and returns to baseline within 1-3 months. In moderate-to-severe TBI, cognitive functioning continues to improve during the first 2 years post injury, but for many patients it remains impaired beyond this time (Schretlen & Shapiro, 2003).

Memory has been found to recover at a different rate when compared with other cognitive domains, such as attention, speed of processing or executive function (Kersel, Marsh, Havill, & Sleigh; Millis et al., 2001; Novack, Alderson, Bush, Meythaler, & Canupp, 2000; Vakil, 2005). Improvement in memory function has been found from 6 to 12 months post-injury (Kersel et al., 2001; Novack et al., 2000), and also from 6 months to 2 years (Lannoo, Colardyn, Jannes, & de Soete, 2001). However, despite substantial improvements, deficiency in memory and learning have been found to exist even ten (Zec et al., 2001) and thirty years post-injury (Himanen et al., 2006). Zec et al. (2001) found that TBI patients tested at 10 years post injury performed significantly more poorly on a variety of memory tests when compared to either the spinal cord injury group or the normal control group (the spinal cord injury and normal control groups were not significantly different on any of the memory measures). For example, the TBI group remembered approximately 30-40% fewer words than the normal control group as measured by RAVLT (25-34% fewer words compared to the spinal cord injury group). In addition, there was approximately a 59% difference in verbal memory performance measured by WMS in comparison to the normal control and spinal cord injury groups (Zec et al., 2001). Dikmen and colleagues (1995) examined NP outcome, with measures of memory, attention, concentration,

flexibility, speed of processing, verbal skills, verbal and performance intelligence, at 1 year post TBI. They found significant differences relative to trauma control subjects on a variety of memory measures, where TBI patients' performance was up to 20% poorer. The degree of impairment was dependent on the severity of injury (measured by GCS), with mild TBI unassociated with persistent neuropsychological impairments, and more severe injury associated with impairments on measures of attention and memory at the 1-year time-point (Dikmen et al., 1995). Another study looked at recovery of cognitive functions, including memory, from one to five years post-TBI (Millis et al., 2001). Significant variability in outcome at 5 years post-injury was found, ranging from no impairment to severe impairment. With respect to recovery from 1 to 5 years, it was also variable as 22% of subjects improved, 15% declined and 62% of the subjects showed no change in NP performance, indicating a non-uniform recovery pattern among individuals with TBI (Millis et al., 2001).

Overall, the recovery course of memory function is variable and different memory domains of memory appear to recover to different degrees and at different rates (Prigatano, 1990).

In conclusion, TBI represents a distinct combination of focal and diffuse damage, where focal damage is usually overlaid on more widespread diffuse injury. The brain has a substantial capacity to recover following an injury, and the primary mechanism of injury involves functional reorganization, where intact areas of the brain take over functioning of the injured ones. As such, the more intact resources that remain after a brain injury, the greater is the potential capacity for recovery. However, when damage is more spread out, as it is often observed in DAI, the recovery may be more limited (Himanen et al., 2005; Smith et al., 2003).

2.6 Current Study

TBI disrupts a range of cognitive functions, particularly memory, which is of marked concern for TBI sufferers. TBI also causes both diffuse and focal injury. Diffuse injury refers primarily to DAI, and its extent can be measured with VBR. Focal injury includes lesions in discrete areas of the brain as well as volume loss to structures. One of these structures is the hippocampus, which plays an important role in memory.

The recovery of cognitive functions is supported by functional reorganization of the brain where intact areas of the brain take over functioning of the injured ones (Weiller et al., 1993). Since functional reorganization depends on the presence of the intact brain, it logically follows that the more intact resources that remain within the brain after injury, the greater is the potential capacity for recovery. By extension, the potential for recovery is reduced when damage is more extensive and widespread (i.e., due to DAI, for example). Hence, a higher VBR

- an index of widespread injury - should be negatively associated with degree of recovery of cognitive functioning, including memory function .

There is a great deal of research relating the hippocampus to memory in healthy and brain-injured individuals; however, the relationship between hippocampal volume and memory recovery (i.e., change from one time point to another) has not been yet examined. As well, a number of studies have examined VBR as a predictor of outcome (i.e., functioning at a single point in time), but no studies have examined VBR as a predictor of memory recovery (change over time).

The objective of this study was to investigate the effects of focal injury (specifically hippocampal volume) and global injury (measured by VBR) on recovery of memory function.

Quantitative neuroimaging methods integrated with NP testing were utilized in order to achieve this objective. Memory function was assessed within the modalities of verbal memory, visual memory and verbal learning. Verbal learning and memory performances were measured with the RAVLT and WSM – III LM test. Visuo-spatial learning and memory were assessed by RVDLT. Performance was measured at three times post injury, 1.5 months (t1), 5 months (t2) and 12 months (t3). Recovery of memory function was measured from t1 to t2, from t2 to t3 and from t1 to t3. The focal neuropathologic indices used were MR based volumetric measurements of the left and right hippocampus. The global neuropathologic effects of TBI was indexed by VBR.

The following hypotheses were tested:

1. Severity of memory impairment will be more strongly correlated with the degree of hippocampal volume than with VBR.
2. *Recovery* of memory function will be more strongly associated with VBR than with hippocampal volume.

3.0 Methods

This research project represents a sub-component of the TBI Recovery Study conducted at the Toronto Rehabilitation Institute.

3.1 Participants

Eighteen adult participants were recruited from the Acquired Brain Injury, In-patient service of the NeuroRehabilitation Program at the Toronto Rehabilitation Institute. Inclusion criteria of the larger study were: an acute care clinical diagnosis of TBI; positive MRI or CT findings or GCS score of 12 or less (Teasdale & Jennett, 1974); ability to follow simple commands in English based on the Speech Language Pathologist's intake assessment; and, the ability to provide informed consent or the availability of a legal decision maker to provide consent.

Exclusion criteria included the following: a pre-existing disease affecting the nervous system (e.g., Parkinson's Disease, dementia of Alzheimer's Type, Multiple Sclerosis, Huntington's Disease, Lupus); a history of psychotic disorder; TBI resulting from another brain injury (e.g., a fall due to stroke); the presence of metal implants or cardiac pacemakers that precluded MRI examination.

The mechanisms of injury for participants in the present study were: (1) moving vehicle accidents (n = 13) and (2) falls (n = 5). Demographic and injury data are presented in Table 1. All but 4 participants had moderate to severe brain injury based on GCS score ($\leq$12). All four patients with a GCS of higher than 12 showed positive acute care neuroimaging findings.

Consistent with the over-representation of males in the TBI population, there were 15 males and 3 females. Sixteen participants were right handed and 2 were left handed. The symptoms of depression were assessed using the Beck Depression Inventory (BDI; Beck, 1987) at all three time points. Mean BDI scores were within the normal range during the first and second assessment indicating the absence of depression. At the third assessment BDI scores indicated presence of mild depression (mean = 10.61, SD = 9.70). The potential impact of depressive symptoms on memory performance was assessed using correlational analyses. No association was found between memory performance and BDI scores at the third assessment.

Socio-economic status was assessed using the Hollingshead Classification (Hollingshead & Redlich, 1958). Seven participants were classified in category 4 ("machine operators, semiskilled workers"), five were in category 3 ("skilled craftsmen, clerical, sales workers") five were within category 2 ("medium business, minor professional, technical") and lastly one participant was in category 1 ("major business/professional").

Pre-morbid intelligence was estimated using the Wechsler Test of Adult Reading (Wechsler, 2001). This reading test is composed of a list of 50 words that have atypical grapheme to phoneme translations. Subjects are asked to read each word aloud. Subjects' performance is not timed and the number of correctly read words is the dependent variable (Green et al., 2008). The intent in using words with irregular pronunciations is to minimize the current ability of the patient to apply standard pronunciation rules and assess previous learning of the word. Unlike many intellectual and memory abilities, reading recognition is relatively stable in the presence of cognitive declines associated with normal aging or brain injury (Wechsler, 2001).

Table 1. Demographic data of the 18 study participants.

	Mean ± SD	Range
Age	34 ± 11.69	19 - 56
GCS*	7.5 ± 4.13	3 - 13
Years of education	12 ± 3.5	8 - 21
Socio-economic status	Machine operators, semi-skilled workers**	N/A
Beck Depression Inventory (Time 1) score (classification)	6.61 ± 5.56 (normal range)	0 – 20
Estimated pre-morbid IQ (Time 1)	97.12 ± 15.88	73 – 123

*GCS score was not available for two subjects.
** Descriptor of the socio-economic status that is the most frequent in the sample. It represents mode and not average.

3.2 General Study Design

The study employed a within-subjects, repeated measures design. All participants underwent NP testing at three time points and MRI imaging on one occasion (see Figure 1). The independent variables for the study were hippocampal volume and VBR. The dependent variables were memory performances at each of the three time points, and memory change scores across assessments (see Statistical Analysis section for derivation of change scores).

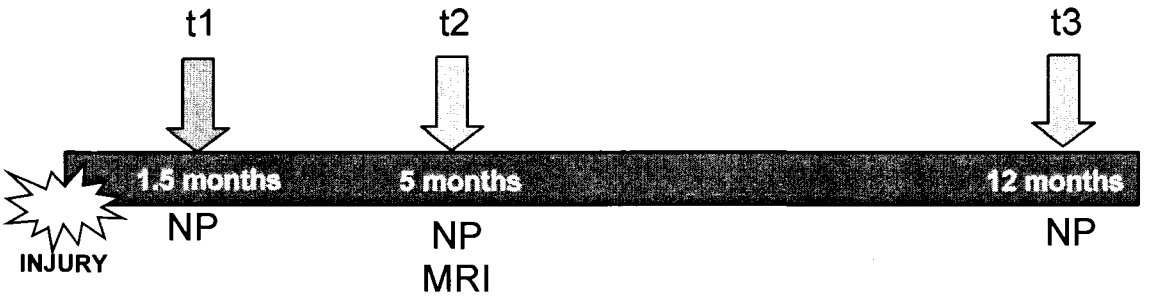


Figure 1. Study design.
Memory performance was measured at three times post injury: 1.5 months (t1), 5 months (t2) and 12 months (t3). All participants underwent structural MRI at t2.

3.3 Procedures

All participants were recruited by a member of the clinical team from the In-Patient Neurorehabilitation Program of Toronto Rehabilitation Institute according to the ethical requirements of Toronto Rehabilitation Institute's Research Ethics Board. All patients who gave their informed consent (or assent, for those patients for whom consent was provided by a legal decision maker) were administered a battery of NP tests including a range of memory tests as indicated in Figure 1. The first NP assessment took place at 1.5 months (-/+ two weeks) post-injury in order to assess cognitive impairment as early as possible. Previous studies have generally demonstrated that cognitive deficits following TBI improve most during first 6 to 12 months (Schretlen & Shapiro, 2003). Some studies have observed plateau around 6 months post-injury (Choi et al., 1994), while others estimate such plateau to occur around one year post-injury (Novack et al., 2000). Therefore, the second NP assessment took place at 5 months (-/+ two weeks) to examine initial recovery and the last NP assessment was conducted at one-year mark (-/+ 1 month). All neuropsychological testing was carried out by a trained psychometrist at Toronto Rehabilitation Institute. NP data were collected for a larger study and a subset of this was provided to us for the present project.

All participants underwent structural MRI at t2, after brain changes caused by acute injury, such as edema, would have sufficiently resolved. Furthermore, previous studies have indicated that MRI acquired at more than 3 months post-injury but not earlier, demonstrates more consistent brain-behaviour relationships in TBI patients (Bigler et al., 1996, 1997; Blatter et al., 1997; Garnett et al., 2001). In addition, a sub-set of participants (n = 7) underwent MRI at 24 months post-injury. The MRI was completed at the University Health Network, Toronto General

Division and the image processing and image data analysis was carried out at the Sunnybrook Health Sciences Centre.

3.4 Neuropsychological Assessment Protocol

All participants were administered a comprehensive neuropsychological assessment as part of the larger TBI Recovery study. The test battery for the current study was a sub-component of this larger study. The same battery was administered at all three time-points and in the same order. NP test order was counterbalanced between subjects in the larger study in order to control for order effects. For the sub-set of participants who met the inclusion and exclusion criteria for the current study, test order was, therefore, only approximately counter-balanced. The test battery for the current study included three domains, (1) estimate of pre-morbid intelligence, using the Wechsler Test of Adult Reading (Wechsler, 2001), (2) verbal learning and memory, using the RAVLT (Lezak, 2004) and the WMS – III LM (Wechsler, 1997), and (3) visuo-spatial learning and memory using the RVDLT (Lezak, 2004). The selected tests were chosen due to their high validity and reliability in assessing memory deficits in TBI population (Lezak 2004; Spreen & Strauss 1991). All memory tests had alternate forms. For psychometric properties of tests, see Lezak (2004) and Spreen and Strauss (1991).

RAVLT

Participants were administered the five repetitions of the same list of 15 unrelated. After each presentation, they were asked to recite as many items from the list as they could, in any order. The total number of correct items from the five presentations of the list represented the "total learning" score. After the fifth presentation of the first list, a different list was presented, which participants were asked to recite. Then, participants were asked to free-recall as many items as they could from the first list. The total number of items correctly recalled was the short delay "SD" score. After a delay of 20 minutes (filled with non-verbal tests in order to avert interference), participants were asked to free-recall as many items as they could from the first list. The total number of items correctly recalled was the long delay "LD" outcome measure. The range of possible raw scores for each recall trial was 1 to 15 and the maximum total score for the learning phase was 75. The maximum score of the SD trial was 15 as was the maximum LD score.

LM

Participants were read two short stories and immediately after each presentation, they were asked to free-recall aloud as much of the story as they could remember, using words as similar

to the original words as possible. The total number of units recalled was the immediate recall "IR" score. After a delay of 30 minutes, participants were asked to free-recall both stories again, one at a time. The total number of units recalled was the delayed-recall "DR" outcome measure. The range of possible scores for each recall trial was 0 to 25.

RVDLT

The RVDLT is a non-verbal, visuo-spatial analogue to the RAVLT test. The stimuli comprise 15 visual, geometric, unfamiliar designs (simple figures constructed from lines, rectangles, triangles, circles, and dots). The 15 stimuli were presented to participants one at a time. After the first presentation, participants were asked to draw as many test items as they could remember. This procedure was repeated another four times, with the same items presented in the same order, and participants drawing as many items as they could remember. The range of possible scores for each trial was 1-15 and maximum total learning score was 75.

3.5 MR Image Acquisition Protocol

MR scans were acquired on a GE Signa-Echospeed 1.5 Tesla scanner, located at Toronto General Hospital, using the standard quadrature head coil. The high-resolution 1mm isotropic T1 weighted, three-dimensional radio-frequency spoiled-gradient recalled-echo (SPGR) images were acquired in the axial plane (TR = 11.74 ms, TE = 5.14 ms, and flip angle = 20°, 160 slices). All participants underwent MRI scans of the whole head. The scanning session lasted approximately 45 minutes with T1 weighted images acquired approximately within 10 minutes.

3.5.1 Image Processing And Analysis

The MR images were transferred to a workstation for image processing. The scans were received in the DICOM (Digital Imaging and Communications in Medicine) file format, which is the most universal standard for storing MRI data. Since all of our analysis tools use MINC (Medical Imaging NetCDF, where NetCDF stands for Network Common Data Form) file format, the images were first converted into minc format, using a standard dicom-to-minc converter. MINC is a versatile file format that was created at McConnell Brain Imaging Centre of the Montreal Neurological Institute commonly used for storage of medical imaging data (http://www.bic.mni.mcgill.ca/software/). Following this procedure, the participants' names were replaced with subject numbers in order to protect their identities. This annonymization process also removed subject's name from the file header.

The pre-processed data is in native space also known as scanner space, meaning that images are displayed exactly as they were acquired in the scanner. In native space, the images are in different orientations depending upon the placement of the head and the brains display different sizes owing to the variability seen across population. To compare brain differences that are independent of brain variability, the images must be registered in a common stereotaxic space prior to the analysis. The steps in Figure 2 represent the image processing procedure described below.

The first step in image processing was the intensity non-uniformity correction (Sled, Zijdenbos, & Evans, 1998). Such non-uniformities are due to radiofrequency pulse which projects unevenly within a head coil, the head coil's uneven sensitivity in picking up signals, and the anatomy of the brain. The result is that the images end up being relatively brighter in the anterior portion of the brain compared to the posterior aspect. MR signal non-uniformity needs to be corrected as it may negatively influence the prospective analysis in which homogeneity of intensity is assumed (Sled et al., 1998).

The non-uniformity corrected images were then linearly registered (aligned) into stereotaxic coordinates (Collins, Neelin, Peters, & Evans, 1994) based on the Talairach atlas (Talairach & Tournoux, 1988). According to the Talairach co-ordinate system, the brain is defined based on the two anatomical landmarks: anterior commissure (AC) and posterior commissure (PC). The line drawn from the superior edge of the AC to the inferior aspect of the PC (also called AC-PC line) defines horizontal plane or z-axis running from superior to inferior. The second line, drawn vertically through the posterior edge of the AC, identifies the coronal plane or y-axis, running in posterior-anterior direction. Finally, the sagittal plane or x-axis is defined by the line extended laterally through the posterior edge of the AC and perpendicular to the AC-PC line. The x-axis runs in left to right direction. The standard space is then defined by the smallest box entirely enclosing the cortex where distance of various points of interest within the brain from the three planes is measured in millimeters (Collins et al., 1994). The linear registration to Talairach coordinates was accomplished through 3D cross-correlation between a given volume and an average MR brain image previously converted into the Talairach coordinate system (Collins et al., 1994). This average model brain was previously created at McConnell Brain Imaging Centre of the Montreal Neurological Institute based on 305 MR images of normal subjects, which were manually registered to stereotaxic space and averaged to create a mean brain (Collins et al., 1994). The given volume was transformed to fit the model brain using nine parameter transformation consisting of three translations, three rotations and three scales (Collins et al., 1994). After the registration the images had the same size and orientation, allowing for direct

anatomical comparisons between subjects. A second non-uniformity correction was performed after the registration which helped to remove any residual non-uniformity artifacts.

Every voxel in a non-uniformity corrected and registered image was then classified into one of the three classes: CSF, grey matter (GM) and white matter (WM) using an automated tissue classification algorithm (Zijdenbos, Forghani, & Evans, 1998). Subsequently, cortical surface extraction from the tissue-classified images was performed, resulting in a 3D reconstruction of the cortical surface. Next, the skull and scalp were removed in the tissue-classified images using the 3D surface extraction as a mask in order to obtain the tissue volumes of the whole brain. Thus, the volumes of CSF, GM, and WM reported in this study were calculated using the tissue-classified images, which excluded the skull, scalp, cerebellum and brainstem. The combination of the GM and WM was used as the whole brain volume in the VBR analysis.

3.5.2 Quality Control

Quality control (QC) of the processed images was performed for all subjects to ensure that the data was appropriate for further analysis. These images included: registered, tissue classified, cortical surface extracted and skull/scalp removed images (Figure 1). QC was not performed for non-uniformity corrected images since changes following the non-uniformity correction are subtle and not easily observable to the human eye.

The images were viewed using two interactive volume display and image analysis software: DISPLAY and REGISTER, which were developed at the Brain Imaging Centre of the Montreal Neurological Institute (MacDonald, 1996). These tools allow for viewing images simultaneously in 3 planes: sagittal, coronal and horizontal. DISPLAY can also be used to view and manipulate 3D objects of the cortical surface and was also used for manual segmentation of specific regions of interest in this study. REGISTER is utilized for simultaneous viewing of any two brain images as well as the superimposed view of the two images.

Five quality ratings were employed in the QC process of each of the images: excellent, good, fair, poor, and bad, which is a standardized protocol in Dr. Kabani's laboratory. A detailed account of QC rating is explained in Appendix 1. General interpretations associated with the ratings were as follows: (1) excellent: processing was excellent and images were usable; (2) good: processing was not ideal, however the existing problems would not affect results and the images were usable; (3) fair: some problems that may affect results of some of the prospective processing as well as data analysis. Such images were noted down for potentially affecting the findings, (4) poor: problems that would likely greatly affect the results and must be flagged for caution; and (5) bad: problems that will cause results to be unusable. Depending upon the stage

of processing and the type of problem, some manual intervention could be applied to improve the quality of images, as discussed below.

In order to assess quality of the registration, the registered T1 image was compared to the average 305 model brain and any misalignments were noted. Misalignment of the registered image could potentially result in inadequate direct anatomical comparisons between subjects. Poor quality of the registration can be improved by manually aligning T1 weighted image with the average 305 model brain by the experimenter. In order to assess quality of the tissue classification, tissue classified image was compared to the registered image. Grey and white matter delineation in the tissue classified image was compared with the registered image, and any tissue misclassifications were noted. If the registered image did not have good grey-white matter delineation, then that would be reflected in the tissue classified image. There is no manual way to correct the tissue classification. 3D cortical surface extracted and skull/scalp removed images were assessed for presence of skull, scalp and dura mater. These images were compared to the registered T1 weighted images. Extensive amounts of dura mater and skull/scalp can potentially influence volumes of GM, WM and CSF. These tissues were automatically and manually removed to improve quality of each scan.

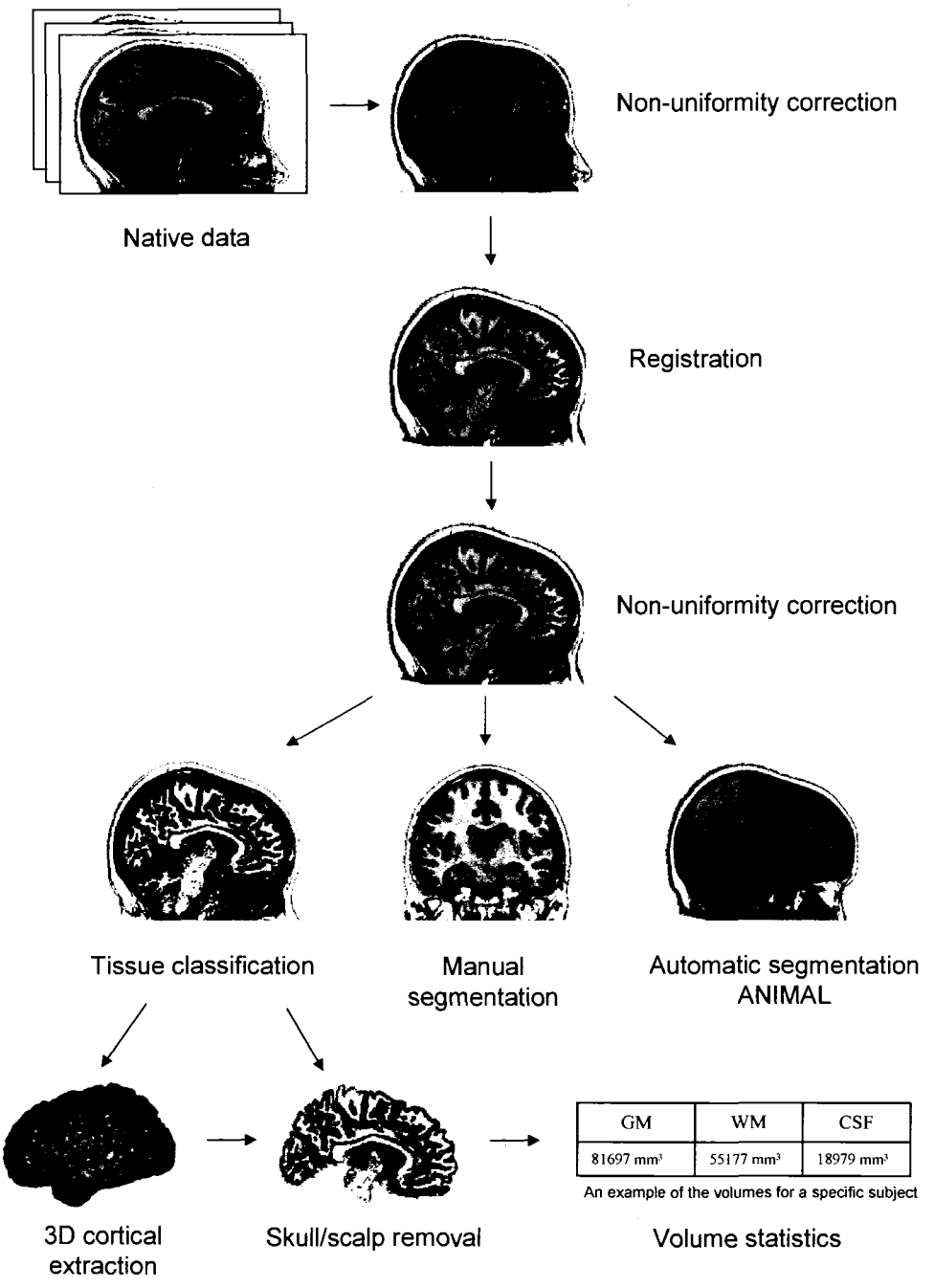


Figure 2. Image processing and analysis steps.
The native (raw) data were corrected for field inhomogeneities and subsequently registered linearly to the stereotaxic coordinates based on Talairach atlas, in order to account for differences in head sizes. A second non-uniformity correction was performed to remove any residual non-uniformity artifacts. The images were then classified into cerebrospinal fluid, grey or white matter using an automated intensity-based algorithm. Cortical surface extraction on the tissue-classified images was performed to produce a three dimensional cortical surface. This 3D surface was used as a mask to remove the skull and scalp from the tissue-classified images and calculate the volumes of the three tissue types. Manual and automatic segmentation of regions of interest was performed using the registered image.

3.5.3 Automatic Segmentation

In order to obtain the ventricular volume, the images were processed using an automatic segmentation technique. This analysis was performed using an automated non-linear image matching and anatomic labeling (ANIMAL) algorithm (Collins, Holmes, Peters & Evans, 1995; Collins, Zijdenbos, Barre, & Evans, 1999). ANIMAL utilizes the tissue classified image in conjunction with non-linear registration to automatically segment brain structures using a pre-existing template atlas. In order to accurately identify and delineate brain regions, large lesions, which were presented on MRI as visibly darkened areas, were filled with either GM or WM depending on their location within the brain.

Volumes of the lateral ventricle and third ventricle (Figure 3) obtained by this method were used for the VBR analysis.

3.5.4 Global Brain Atrophy

Global brain atrophy was measured by calculating the VBR using the following formula:

$$\text{VBR} = \frac{\text{Total ventricular volume (lateral + third ventricle)}}{\text{Total brain volume (GM + WM)}} \times 100$$

The brain volume was extracted using the combination of tissue classified volume and the 3D cortical surface. Essentially the 3D cortical surface was used as a mask to remove the scalp, skull and the dura matter from the tissue classified image as shown in Figure 2. This procedure also removed the brainstem and the cerebellum along with the fourth ventricle. The volume of the lateral and third ventricle was extracted from the automatic segmentation described earlier. The volume of the lesions that may have been misclassified as CSF was removed from the ventricular volume by manually painting any visible lesions, as described later in this section. The analysis of VBR thus included the GM and WM of the cerebrum and the CSF, primarily from the lateral and the third ventricles.

In most of 3D cortical surface extracted and skull/scalp removed images, medium to large amounts of dura mater and skull/scalp were observed. Since, extensive amounts of dura mater and skull/scalp could potentially influence volumes of GM, WM and CSF, those tissues were automatically and manually removed. Those new corrected images were used for calculation of GM, WM and CSF.

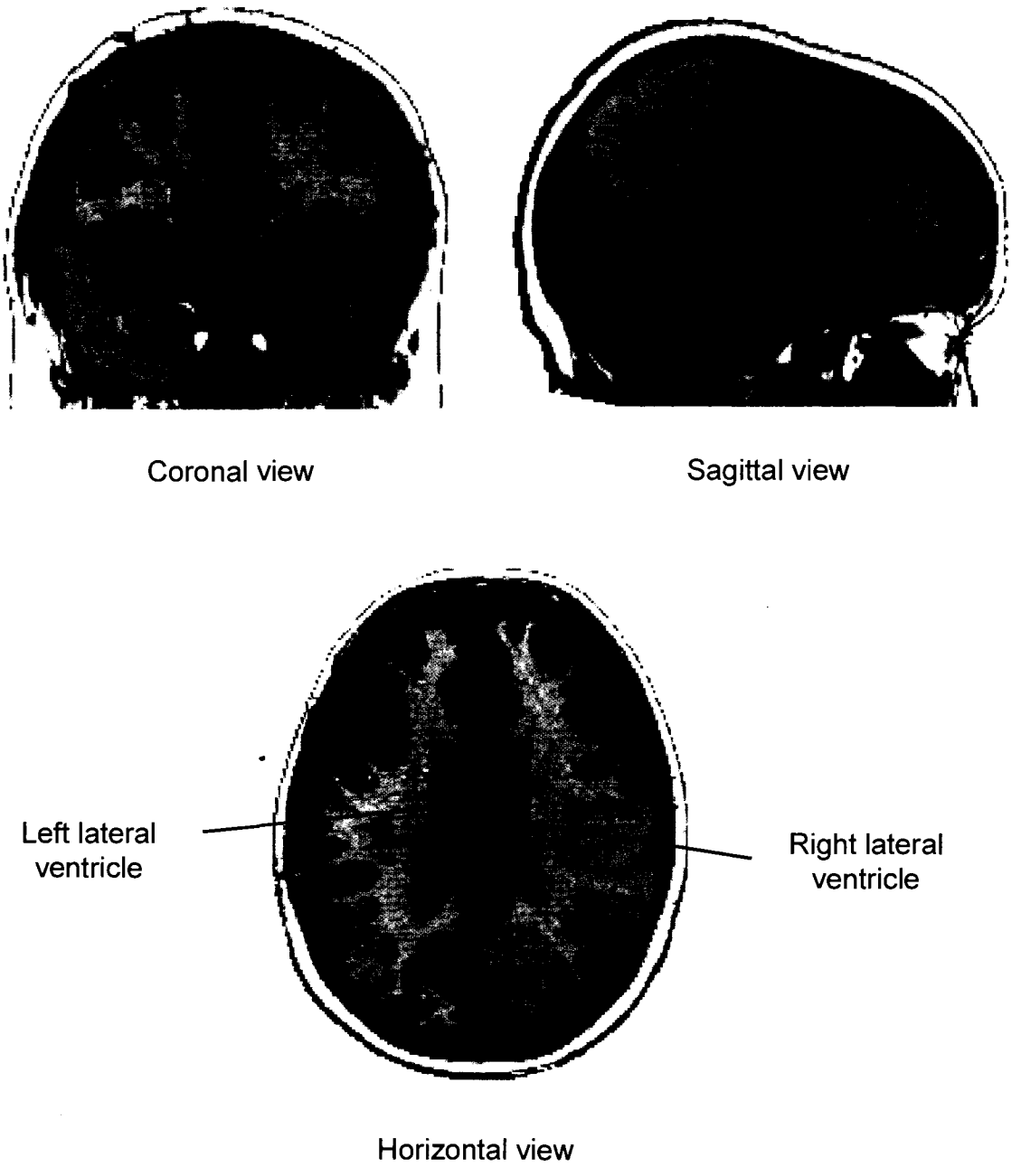


Figure 3. MR image of the brain with delineated lateral ventricles.
Automatic segmentation was performed to obtain volumes of the lateral ventricles and the third ventricle which represented the total ventricular volume in our study for the calculation of VBR.

3.5.5 Manual Segmentation

Regions of interest were segmented manually using DISPLAY software. This included the hippocampus (HC) (Figure 5, 6, 7, 8, 10), and the lesions (Figure 9, 10, 11). The HC, both left and right, was segmented in all subjects, however, lesions were labeled only in those where they were visible (14 subjects). The details of manual segmentation for each structure are described below. The structures were labeled on each slice of an image using coronal, sagittal and horizontal views and their individual volumes were calculated.

Partial Volume Effect

A major factor which affects the determination of boundaries for manually painted structures is the transitional areas from one tissue type to the other. On T1-weighted scans the CSF, WM and GM are displayed as voxels of varying intensities (Figure 4). The CSF is displayed as very dark voxels, WM as bright voxels and the GM as voxels of medium intensity. However, in areas where the tissue type changes for example from CSF to WM or from WM to GM, a single voxel may represent intensities belonging to multiple tissue types. Therefore, such voxel could appear as grey in absence of GM in a given transitional area. Such phenomenon is called the partial volume effect (Zijdenbos & Dawant, 1995). The partial volume effect blurs edges between different types of tissue, hence making them difficult to distinguish the transitional zones and thereby affecting the sharp delineation of structural boundaries from the surrounding regions. In order to avoid labeling of unwanted matter and to develop a consistent approach in segmenting, one layer of voxels with the partial volume effect was always excluded around the outer edge of the structure.

Hippocampus

Hippocampus is a brain structure located symmetrically in the medial portion of the temporal lobes of both hemispheres. It can be divided into three parts (Figure 5): (1) anterior, also called a head of hippocampus (HH); (2) medial part, frequently called a body (HB), and (3) a posterior part, also referred to as tail (HT). Anatomical boundaries for all parts will be described separately, as they differ depending on the location within the temporal lobe. Segmentation was carried out using the protocol previously developed by Pruessner et al. (2000) designed specifically for high-resolution T1 weighted, 1 mm images, which were non-uniformity corrected and registered into a standard stereotaxic space. The majority of the HC was segmented using the coronal view, however, references to the sagittal and horizontal planes

were also made for accurate delineation of the structure boundaries. In particular, the sagittal plane was used for defining the most anterior portion of the HH.

HC is manually segmented starting from the posterior extreme of the HT, moving through HB and ending at the very anterior part of HH. The most posterior portion of the HT is considered to be a protuberance of grey matter appearing in the inferior-medial portion of the trigone of the lateral ventricle (TLV). One row of grey matter voxels is consistently left unlabeled laterally, as it is considered to be the TLV. Moving anteriorly, the HT is adjacent to andreas-retzius gyrus and the fasciolar gyrus found medially and superiorly, as well as the crus of the fornix located superior-medial to the HT. Since a clear division between these structures and the HT is difficult, two arbitrary borders are employed in order to distinguish between these structures: (1) vertical line extending from medial end of the TLV to the parahippocampal gyrus; (2) horizontal line extending from the superior edge of the quadrigeminal cistern to the TLV. Following the borders, any grey matter located medial to the vertical line and superior to the horizontal line is not labeled as HT. It was found, however, that in most of our images the first border is not necessary, as due to large size of the ventricles the HT does not extend beyond the medial edge of the TLV. Laterally, HT is adjacent to the inferior horn of the lateral ventricle (IHLV) and the caudate nucleus. The IHLV is usually visible for most of the extent of the hippocampus, however, in cases when it not visible, one row of voxels is always excluded lateral to the grey matter of the hippocampus. The inferior border of the HT is the white matter separating the parahippocampal cortex and the HT. This border remains the same throughout the length of the hippocampus. One row of grey matter voxels of the hippocampus is consistently left unlabeled inferiorly, in order to avoid including the parahippocampal cortex and white matter while segmenting the hippocampus.

Moving further anteriorly, in the region near the posterior-extreme of the thalamus, HC is seen descending inferiorly in the coronal plane, becoming the HB. The superior-medial border of the HB is fimbria of fornix, and white matter of the thalamus. The fimbria of fornix, which appears on MRI as white matter, is partly embedded in the HB, therefore the embedded portion is included in labeling. Laterally, the IHLV and the caudate neighbour the HB. The inferior-medial part of the HB, called subiculum, is adjacent to the entorhinal cortex. In order to differentiate between these two structures, the HB was consistently painted by extending a 45 degree line from the superior tip of the underlying white matter to the quadrigeminal cistern. Medially, the hippocampal border is the CSF filled quadrigeminal cistern.

Moving further anteriorly, the HH begins to appear starting with a bulge of grey matter located on the superior-medial aspect of the hippocampus called the gyrus intralimbicus of the

hippocampus. The medial and inferior borders of the HH are demarcated in the same way as in the HB (Figure 6). The superior border of the HC is the quadrigeminal cistern for the posterior portion of the HH, and further anteriorly, the superior border is the amygdala. Moving anteriorly, the amygdala enlarges while the HH becomes smaller. Both of these structures appear as grey matter on MR images, and therefore, are difficult to differentiate; however, there exists a line of white matter called the alveus separating the HH from the amygdala (Figure 5). The alveus is best viewed in the sagittal plane and, as a result, demarcation of the most anterior portion of the HH was primarily accomplished in the sagittal plane. The alveus is the most anterior portion of the HH and is included in segmentation of the HH. In cases when the alveus is not clearly observed, the IHLV is used in delineating the anterior border of the HH (Figure 5). The IHLV forms the space between the superior portion of the HH and the amygdala, which is positioned at about 45 degree angle when viewed in sagittal plane. To define the anterior border of the HH using the IHLV, a line from the IHLV is extended in the inferior-anterior direction to connect it with the alveus, if visible, or, in lieu of the alveus, the white matter located inferior to the hippocampus. The lateral border of the HC is the IHLV along the posterior portion of the HH and the amygdala along the very anterior portion of the HH.

Lesions

Lesions were identified as missing brain tissue that was visually detectable on an image. A lesion was classified as an area that covered at least ten voxels and was observed continuously in at least two slices in coronal view. Lesions were either internal, which were located within grey or white matter or external appearing as large subarachnoid space with a brain pushed inside. Normally such subarachnoid enlargements were continuous with the internal lesions.

Lesions were found in 14 of the 18 scans (Figure 9, 10, 11). The remaining four scans did not show any lesions. Figure 12 displays a scan with no visible lesion. Segmentation was performed interchangeably in coronal, sagittal and horizontal planes to best identify lesion boundaries. The type of plane that was predominantly used was determined based on the lesion location. For example for lesions located near the surface of the brain, coronal plane was employed most often. Frequently, parts of brain tissue were observed to be present within the CSF filled lesion area. When such tissue fragments were connected to the remaining part of the brain, they were excluded in segmentation. However, when these parts were not connected, they were labeled as lesions.

While the volume of the hippocampus was used to address both hypotheses, the manually segmented lesions were used for two purposes. One was to obtain a quantitative measure of

brain lesions for descriptive analysis and secondly, to obtain the actual tissue volume by subtracting the volume of lesions from the total brain volume, which is not done by the automated tissue classification method. The reason being that the tissue classifier does not regard lesion as a seperate category but rather identifies it as one of the three tissue types.

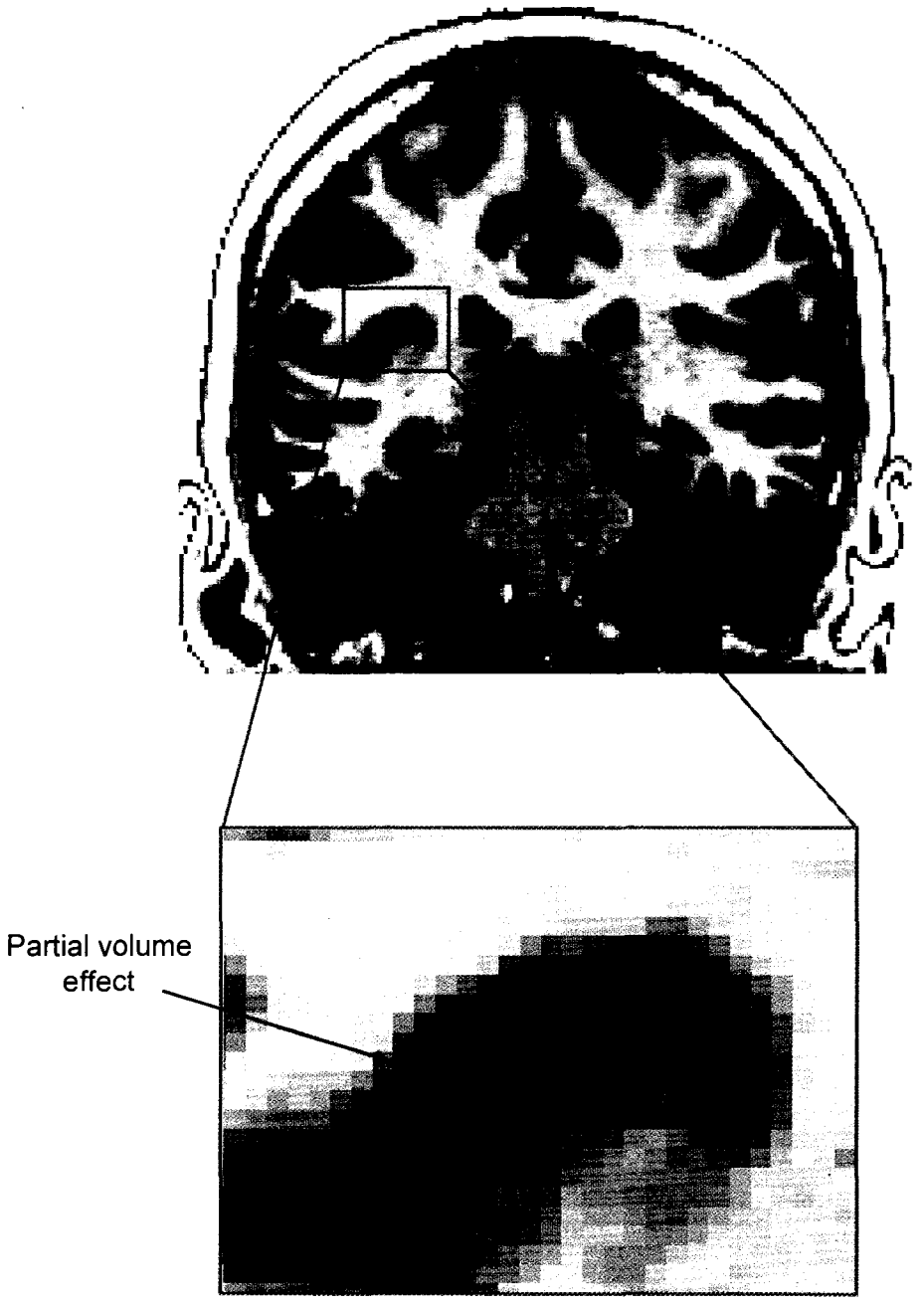


Figure 4. MR image showing partial volume effect.
In areas of the brain where the tissue type changes, for example from WM to GM, a single voxel may represent intensities belonging to multiple tissue types. Therefore, such voxel could appear as grey in absence of GM in a given transitional area (as shown by the pointing arrow). This phenomenon known as partial volume effect blurs edges between different types of tissue, affecting the sharp delineation of structural boundaries from the surrounding regions. In order to avoid labeling of unwanted matter, one layer of voxels with the partial volume effect was always excluded around the outer edge of the structure.

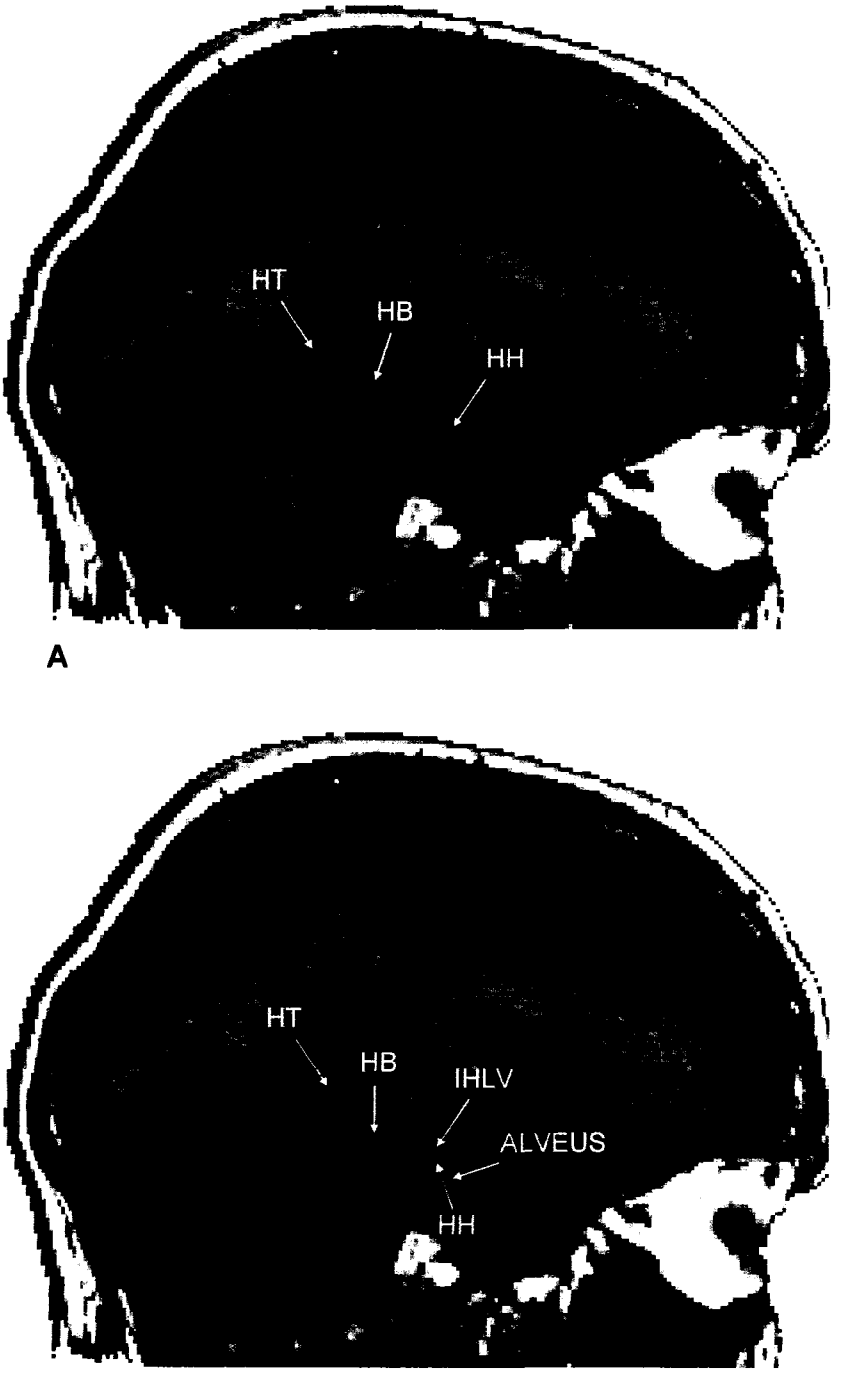


Figure 5. Guidelines for manual segmentation of the hippocampal formation.
Sagittal section of an image showing segmentation procedure for the hippocampus. The segmented hippocampus included the head (HH), body (HB), tail (HT) and the alveus, which were all identified using a single label. The IHLV was used in delineating the anterior border of the HH. The top figure shows (a) the image with label whereas the bottom figure (b) shows the same slice with the label removed.

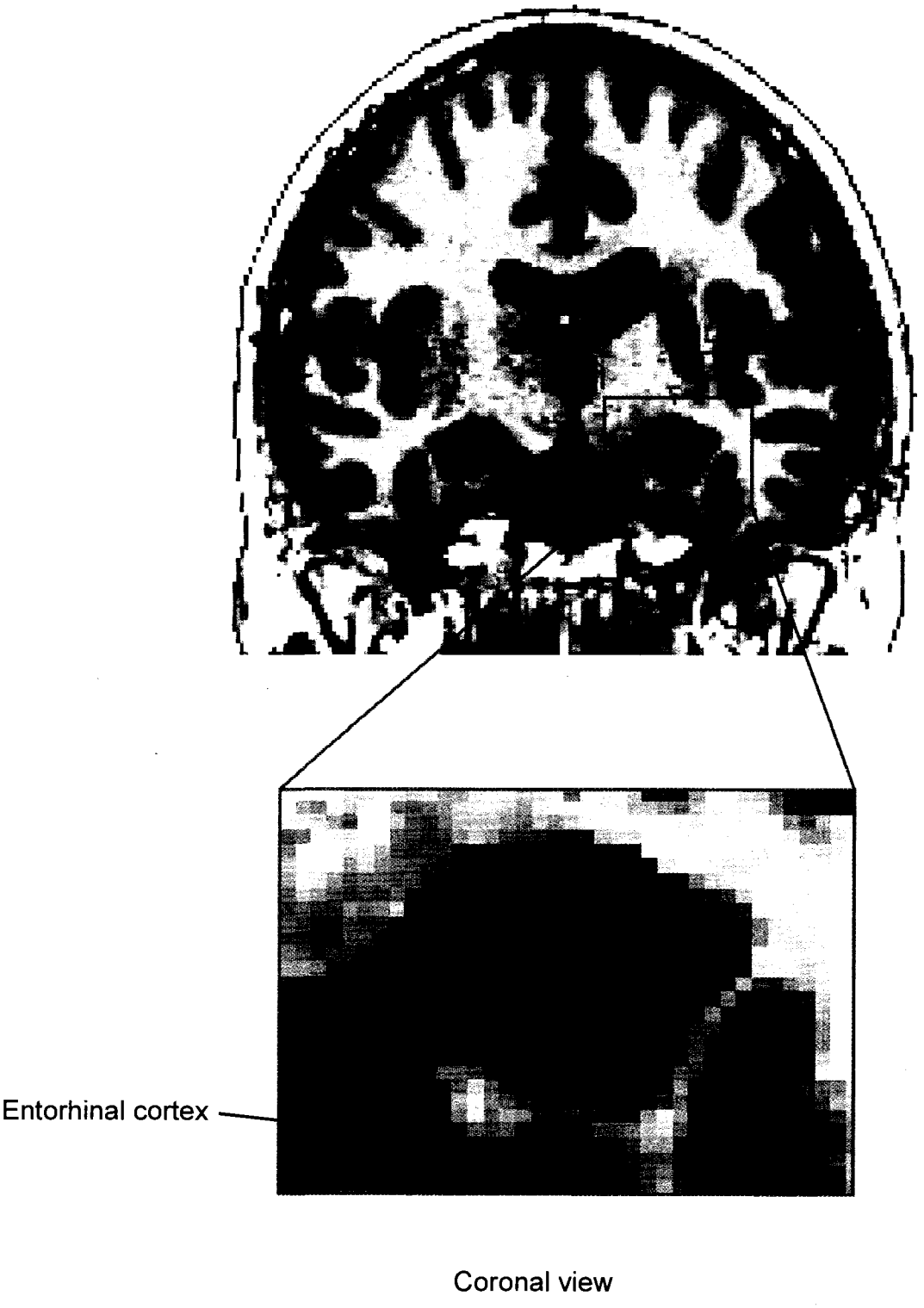
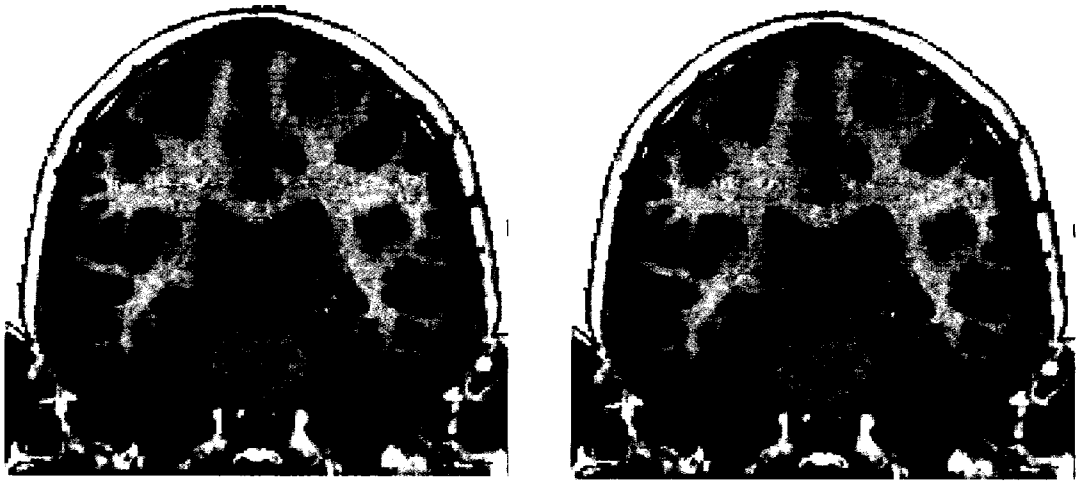
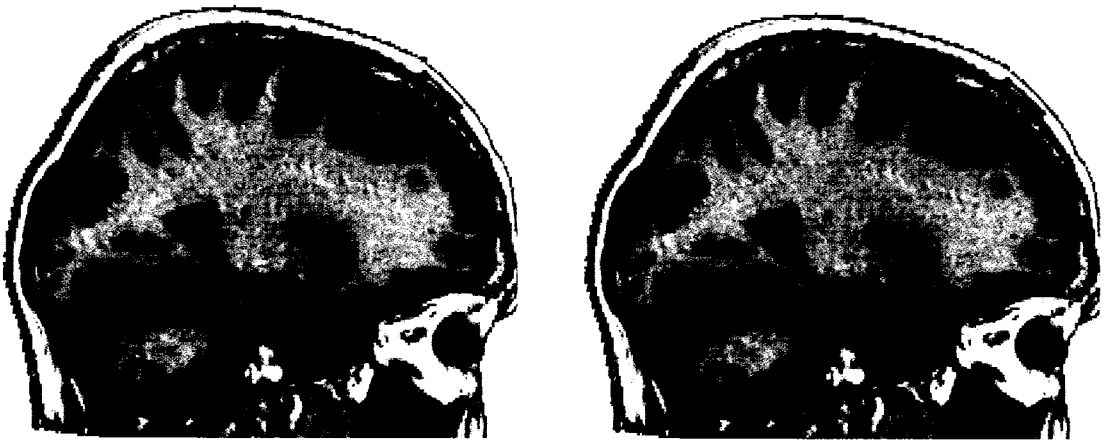


Figure 6. MR image slice with manually segmented left (blue) and right (green) hippocampus. Enlarged view of the manually segmented most anterior portion of the right hippocampus (green) – HH.



Coronal view

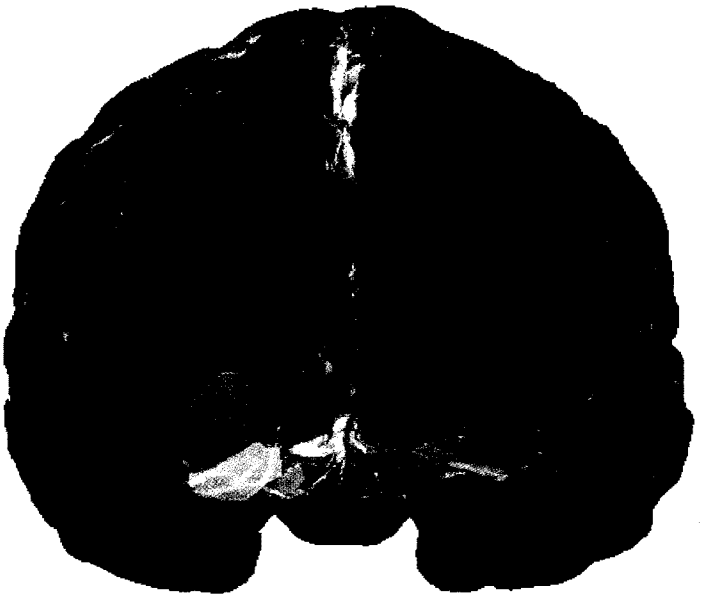


Sagittal view

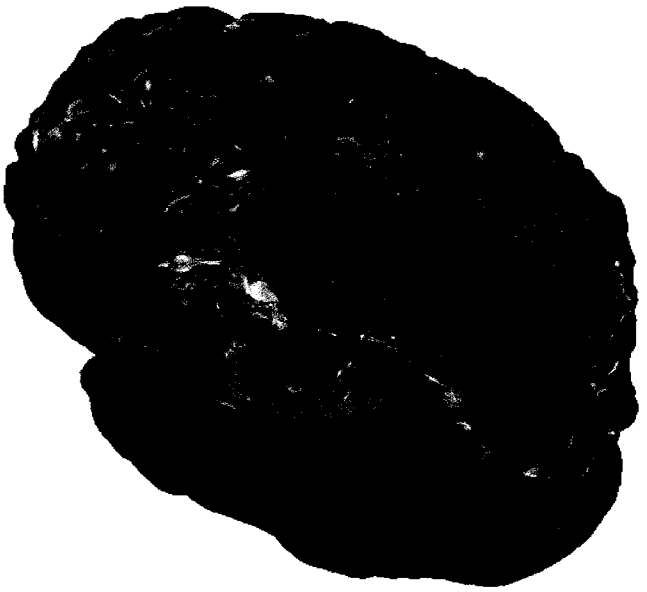
Posterior view

Left view

Figure 7. MR image slices with manually segmented left (blue) and right (green) hippocampus and their 3D reconstruction.

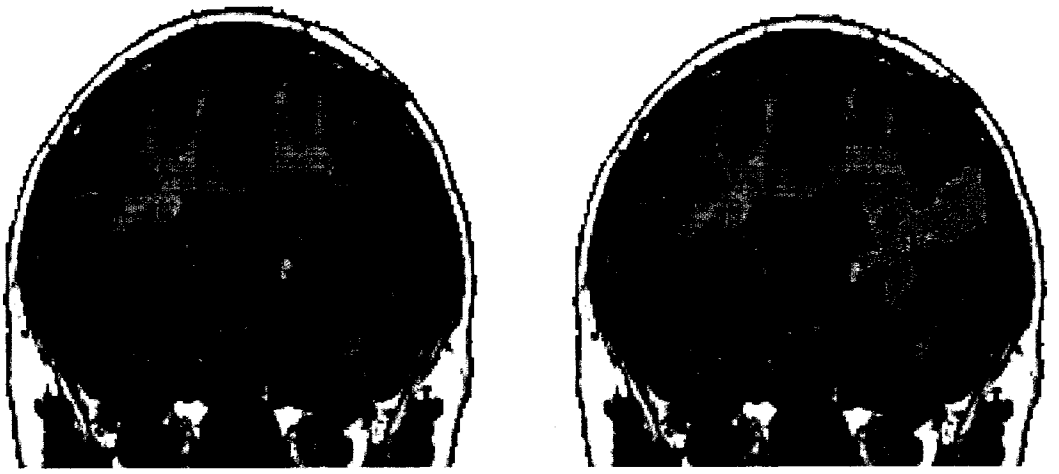


Posterior view

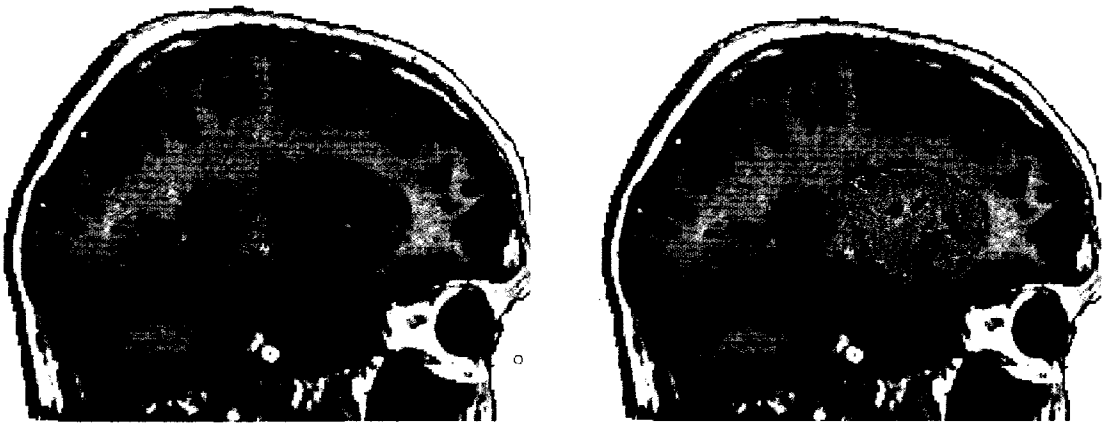


Lateral view

Figure 8. 3D view of the brain constructed from MRI volumes with 3D reconstruction of the manually segmented left (blue) and right (green) hippocampus.
Note that 3D reconstruction of the brain includes all the GM and WM of the cerebrum that were used in calculating VBR. Brain stem and cerebellum were excluded from the VBR analysis.



Coronal view



Sagittal view

Posterior view

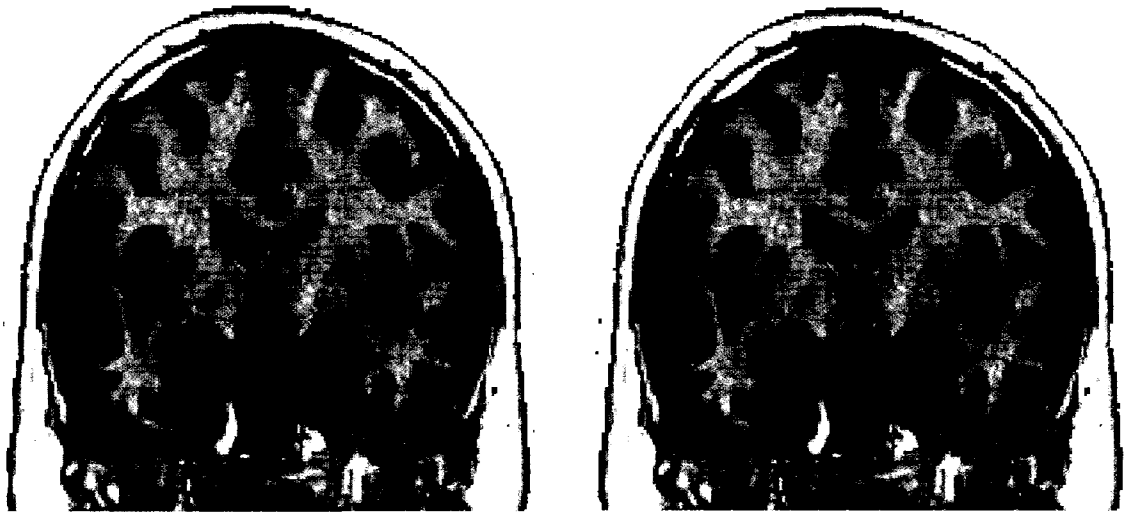
Right view

Figure 9. MR image slices with manually segmented lesion and its 3D reconstruction.
Lesions were identified as missing brain tissue that was visually detectable on an image and that covered an area of at least ten voxels. Lesions were found in 14 out of 18 scans. Four of the subjects had only one lesion, while 10 had between 2 and 6 lesions. This figure displays image with a single lesion

Posterior view

Left view

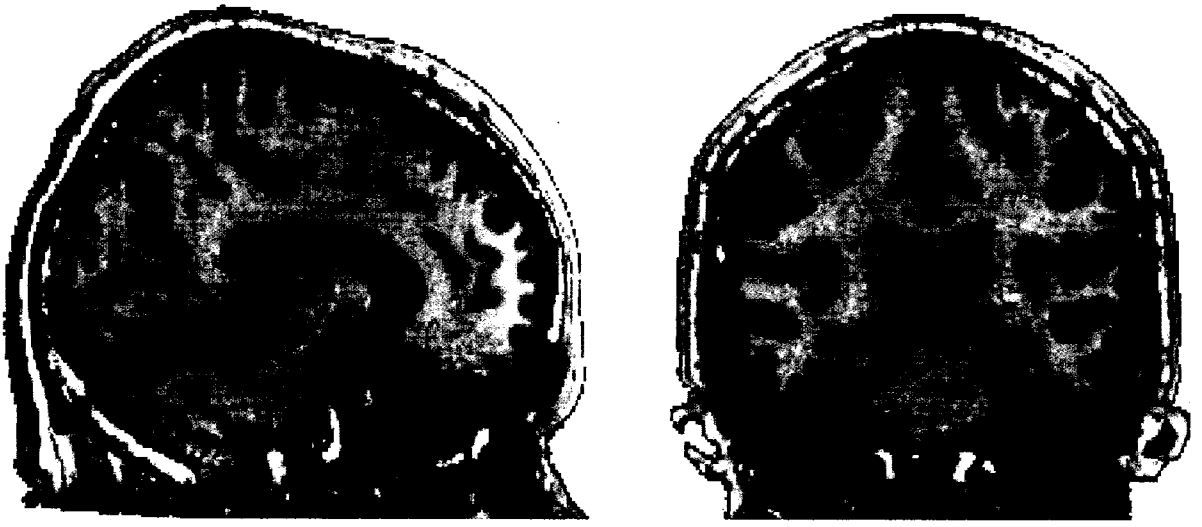
Figure 10. 3D reconstruction of all manually segmented regions of interests: left (blue) and right (green) hippocampus and lesion (yellow).



Coronal view

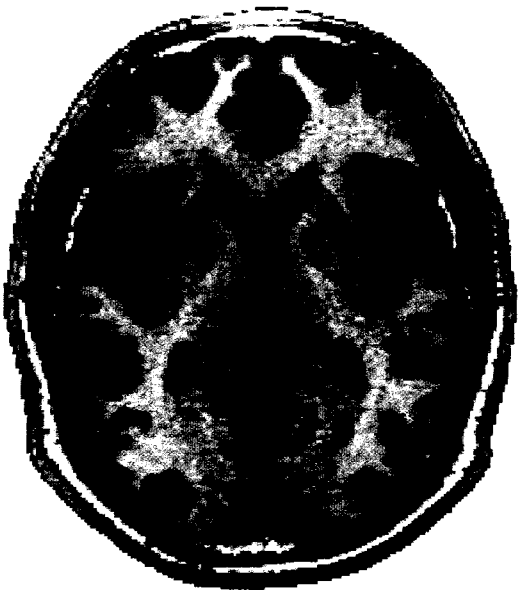
Posterior view

Figure 11. MR image coronal slices with manually segmented lesions and their 3D reconstruction. There are multiple (six) lesions in this image. Each lesion is represented in a different colour. All lesions are located in the frontal, temporal and parietal lobes of the left hemisphere.



Sagittal view

Coronal view



Horizontal view

Figure 12. MR image of the brain without any visible lesions.
Visible lesions were not detected in 4 out of 18 scans.

3.5.6 Rater Reliability Assessment

The inter- and intra-rater reliability was assessed using the intra-class correlation coefficient (Shrout & Fleiss, 1979). To assess the inter-rater reliability of the hippocampus, five scans that were not included in the study were selected. The HC on these scans had been previously manually segmented by an experienced rater and were used as the gold standard. For reliability assessment, the HC was manually segmented five times with two week intervals in these same scans by the experimenter. The intra-class inter-rater coefficient was calculated after the segmentation of the HC for each scan was completed. Rater reliability assessment for the lesions was not performed because, in contrast to the hippocampus, which is a well defined structure, lesions are extremely random and depend upon injury. Hence, there were no specific boundaries to follow.

3.6 Statistical Analysis

All data were analyzed using Version 13 of the Statistical Package for the Social Sciences (SPSS) for Windows.

Normative data. Prior to analysis, all NP test scores at all three time points were converted to age-scaled normative z-scores (except for *LM* scores which were normed using scaled score). All scores were thus converted into a common metric and corrected for age differences. Normative data were obtained for the *RAVLT* from (Geffen G, Moar, & O'Hanlon, 1990); for the *RVDLT* data from (Spreen & Strauss, 1991); and for the *LM* test from (Wechsler, 1997).

Computation of change (recovery) scores: Change scores were calculated for all memory scores to be used in Hypothesis 2. This was carried out by performing linear regression analysis from t1 to t2, t2 to t3 and t1 to t3. Each t2 memory score was regressed on each t1 memory score; each t3 memory score was regressed on each t2 memory score and each t3 score was regressed on each t1 score. The change (or recovery) scores were the unstandardized residual scores for each regression.

Overview of data: Descriptive statistics were used for memory and neuroanatomical measures to provide an overview of the data. Shapiro-Wilk tests were applied to examine distributions of memory and neuroanatomical variables in order to identify any potential departures from normality. In cases where data was not normally distributed, appropriate transformations were applied.

Memory recovery: In order to confirm that memory was indeed recovering across time, repeated measures one-way analysis of variance (ANOVA) was performed for each memory test across t1, t2 and t3. Post-hoc analyses (Newman-Keuls) were performed in order to examine differences between memory performance at different time points.

Hypotheses 1 and 2: To compare the relationship between (1) memory severity outcome measures at t1, t2 and t3 with MRI outcome measures at the same time points, and (2) memory *change* scores with MRI outcome measures, Pearson correlation coefficients were used. (Note that there was no correction for age in these analyses as memory scores had already been age corrected).

Multiple comparisons: Testing of the hypothesis required several analyses, raising the question of multiple comparisons correction. However, since the comparisons were all hypothesis driven, correction factors were not applied (Rothman, 1990). Nonetheless, without a correction, it should be noted that the risk of Type I error was greater.

4.0 Results

Normality testing revealed normal distributions of all variables except for the *RAVLT SD* change score t1 to t2 and *RAVLT LD* change score t1 to t3, which deviated significantly from normality (Shapiro-Wilk statistic = .865, df = 17, $p < .05$; Shapiro-Wilk statistic = .877, df = 15, $p < .05$ respectively). Logarithmic and square root transformations were applied to improve distribution of the *RAVLT SD* and *RAVLT LD* data respectively and the transformed values were used in all analyses.

4.1 Memory Measures

Repeated measures ANOVA revealed a significant main effect of memory recovery for all tests: *RAVLT total*, $F(2, 28) = 3.90$, $p < .05$; *RAVLT SD*, $F(2, 28) = 4.02$, $p < .05$; *RAVLT LD*, $F(2, 28) = 7.13$, $p < .01$; *RVDLT*, $F(2, 26) = 15.86$, $p < .001$; *LM IR*, $F(2, 32) = 9.93$, $p < .001$ and *LM DR*, $F(2, 30) = 8.91$, $p < .01$ (for details please see Table 2). Post-hoc analysis (Newman-Keuls) revealed significant improvements from t1 to t2 on most tests. Figure 13 illustrates significant recovery that was observed across this early epoch for *RAVLT total* ($p < .05$), and *RAVLT LD* ($p < .05$). Figures 14 and 15 show significant improvements for *RVDLT* ($p < .01$) and *LM IR* ($p < .01$) together with and *LM DR* ($p < .01$) respectively. Memory improvement was not significant for *RAVLT SD*.

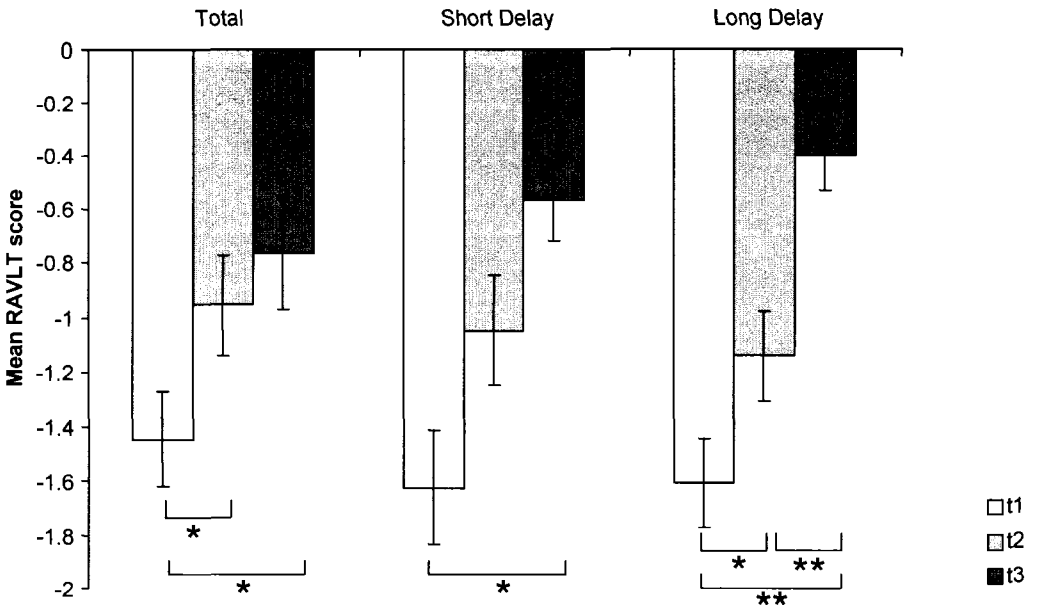
Across the second epoch (t2 to t3), significant improvements in memory function were observed for *RAVLT LD* ($p < .01$) and *RVDLT* ($p < .05$). The remaining tests did not show significant improvements, counter to expectation, although change did move in the expected direction, with scores increasing from t2 to t3 as can be seen in Figures 13, 14, and 15.

In addition, significant increase between all t1 and t3 scores, indicating improved memory function, was observed. Figure 13 illustrates significant recovery that was observed across this time period for *RAVLT total* ($p < .05$), *RAVLT SD* ($p < .05$), and *RAVLT LD* ($p < .01$) tests. Figures 14 and 15 show significant improvements for *RVDLT* ($p < .01$) and *LM IR* ($p < .01$) together with and *LM DR* ($p < .01$) respectively.

Table 2. The mean and standard deviation (in z-scores and scaled scores) of memory scores at t1, t2 and t3.

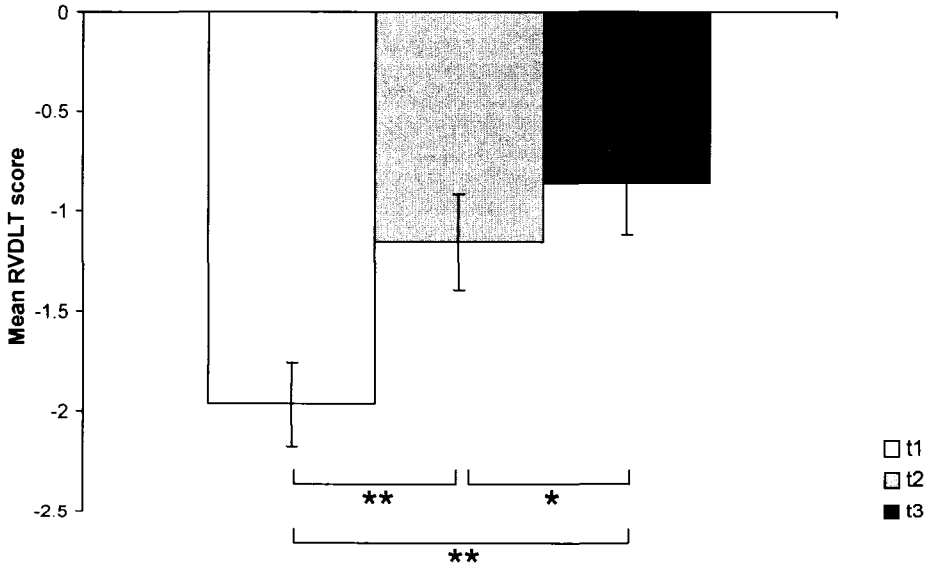
NP measure	RM ANOVA	t1 n	t1 Mean ± SD	t2 n	t2 Mean ± SD	t3 n	t3 Mean ± SD
RAVLT							
Total	$F(2, 28) = 3.90^{\dagger}$	17	-1.45 ± 1.43	17	-0.96 ± 1.51*	15	-0.77 ± 1.59 *
SD	$F(2, 28) = 4.02^{\dagger}$	17	-1.62 ± 1.74	17	-1.05 ± 1.68	15	-0.57 ± 1.14 *
LD	$F(2, 28) = 7.13^{\dagger\dagger}$	17	-1.61 ± 1.36	17	-1.14 ± 1.37*	15	-0.40 ± 0.97 **§§
RVDLT	$F(2, 26) = 15.86^{\dagger\dagger\dagger}$	16	-1.97 ± 1.69	17	-1.15 ± 1.97**	15	-0.86 ± 1.94 **§
LM							
IR	$F(2, 32) = 9.93^{\dagger\dagger\dagger}$	18	9.07 ± 2.78	18	10.49 ± 2.71**	17	11.31 ± 2.05 **
DR	$F(2, 30) = 8.91^{\dagger\dagger}$	17	8.67 ± 3.06	17	11.03 ± 3.21**	16	11.59 ± 2.36 **

RM ANOVA = repeated measures analysis of variance.
$^{\dagger}p < .05$, $^{\dagger\dagger}p < .01$, $^{\dagger\dagger\dagger}p < .001$
* Significantly different from t1: $*p < .05$; $**p < .01$
§ Significantly different from t2: $^{\S}p < .05$; $^{\S\S}p < .01$



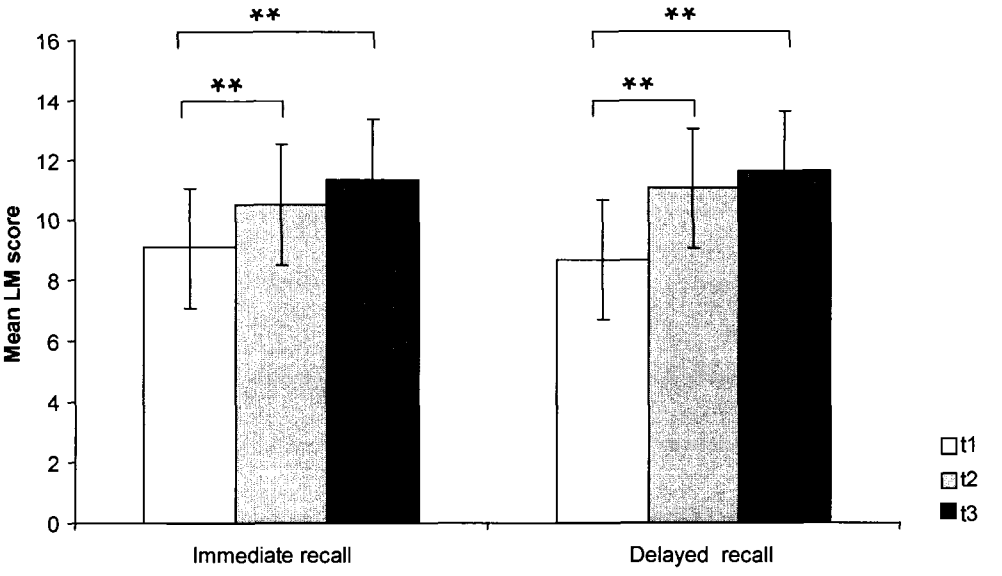
*p < .05, **p < .01.

Figure 13. The mean z-score of *RAVLT total*, *RAVLT SD* and *RAVLT LD* at t1, t2 and t3.
There was a significant difference in means between t1 and t2 for *RAVLT total* and *RAVLT LD*, but not for *RAVLT SD*. Significant improvement from t2 to t3 was observed only for *RAVLT LD*. Error bars represent standard error.



*p < .05, **p < .01

Figure 14. The mean z-score of *RVDLT* at t1, t2 and t3.
Significant improvement in visuo-spatial memory performance was observed from t1 to t2, t2 to t3 and between t1 and t3. Error bars represent standard error.



**p < .01.

Figure 15. The mean scaled score of *LM IR* and *LM DR* at t1, t2 and t3.
Significant improvement in verbal memory performance was observed from t1 to t2 and t1 to t3. Although memory improved from t2 to t3, such improvement was not statistically significant. Error bars represent standard error.

4.2 Neuroanatomical Measures

4.2.1 Quality Control Of Images.

Table 3 displays quality control ratings assigned to all MR images. All scans were determined to be suitable for analysis.

Table 3. Quality control rating.

Images	Quality control ratings				
	Excellent	Good	Fair	Poor	Bad
Registration	1	16	1	-	-
Tissue classification	-	16	2	-	-
3D surface extraction	-	-	4	14*	-
Skull/scalp removal	-	-	4	14*	-

n = 18
*3D surface extracted and skull/scalp removed images were manually corrected which improved the QC ratings for all the subjects to "good".

4.2.2 Rater Reliability Assessment

The intraclass inter-rater and intra-rater coefficients for the hippocampus were r = .92 and r = .91 respectively.

4.2.3 Neuroanatomical Measures

Means and standard deviations for hippocampal volumes and VBR are summarized in Table 4. Volumes of the left and right hippocampus were highly correlated (r = 0.834, p < .001) and did not differ significantly. Similar findings were previously reported (Bigler et al., 1997).

Table 4. The mean and standard deviation of neuroanatomical measures.

Measure	Mean ± SD n = 18	Range
Left hippocampus	3281 ± 423	2459 - 4119
Right hippocampus	3330 ± 400	2701 - 4159
VBR	2.69 ± 0.90	1.34 - 4.76
Total brain volume*[ab]	364453 ± 62264	1249980 - 1463299
Total ventricular volume*[c]	36351 ± 11296	19497 - 59464

Hippocampal, total brain and total ventricular volumes are expressed in mm^3.
* Volumes not used in the analysis but used in calculation of VBR.
[a] Total brain volume consists of total GM and WM and excludes lesions. On average, the volume of lesions did not exceed 0.70% of the total brain volume.
[b] The volume of the hippocampi is very small compared to the total brain volume, hence it is not excluded from the total brain volume in the VBR analysis. On average volume of the hippocampi did not exceed 0.49% of the total brain volume.
[c] The volume included the lateral and the third ventricles.

4.3 Hippocampal Volume And Memory Impairment - Hypothesis 1.

The first hypothesis was that the severity of memory impairment would be more strongly correlated with the degree of hippocampal volume than with VBR at each time point.

The results of correlational analyses between memory impairment scores with hippocampal and VBR volumes are presented in Tables 5, 6, and 7 respectively. As predicted, significant correlations were observed at all three time points between behavioural and volumetric measures. At t1, *RAVLT total*, *RAVLT LD* and *RVDLT* showed significant correlations with the left hippocampus volume, r = 0.527, p < .05 (Figure 16A), r = 0.524, p < .05 (Figure 16B), and r = 0.509, p < .05 (Figure 16C) respectively. At t2, *RAVLT total*, *RAVLT* SD and *RVDLT* correlated with the left hippocampal volume, r = 0.535, p < .05 (Figure 17A), r = 0.526, p < .05 (Figure 17B), and r = 0.557, p < .05 (Figure 17C) respectively. At t3, *RAVLT SD*, *RAVLT LD* and *RVDLT* showed significant correlations with the left hippocampal volume, r = 0.671, p < .01 (Figure 18A), r = 0.617, p < .05 (Figure 18B), and r = 0.602, p < .05 (Figure 18C) respectively.

Consistent with the hypothesis, there were no significant correlations at any of the three time points with any of the behavioural measures with VBR. Counter to prediction, *LM* test performances did not show significant correlation with the hippocampal volume.

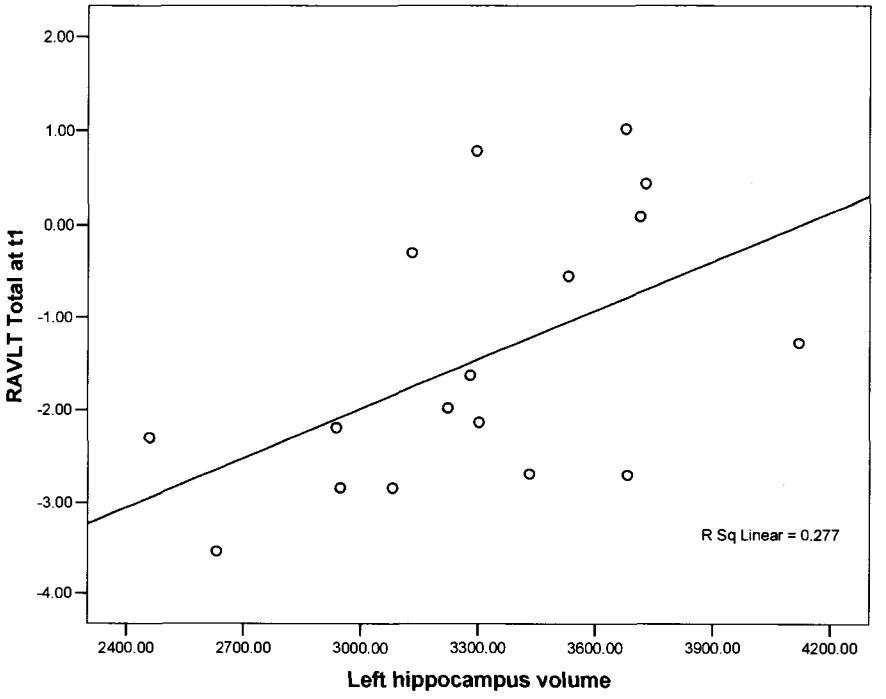
Overall, hypothesis 1 was supported. Performances on the *RAVLT* verbal and *RVDLT* tests positively correlated with the left hippocampus volume and VBR did not correlate with any of the learning or memory scores at any of the three time points.

Table 5. Correlations between t1 memory impairment scores and neuroanatomical measures.

	Hippocampus		
t1 memory measure	Left	Right	VBR
RAVLT Total	0.527*	0.315	0.105
RAVLT SD	0.282	-0.008	-0.249
RAVLT LD	0.524*	0.241	-0.311
RVDLT	0.509*	0.285	-0.092
LM IR	0.338	0.227	0.027
LM DR	0.330	0.372	0.119

* $p < .05$

A



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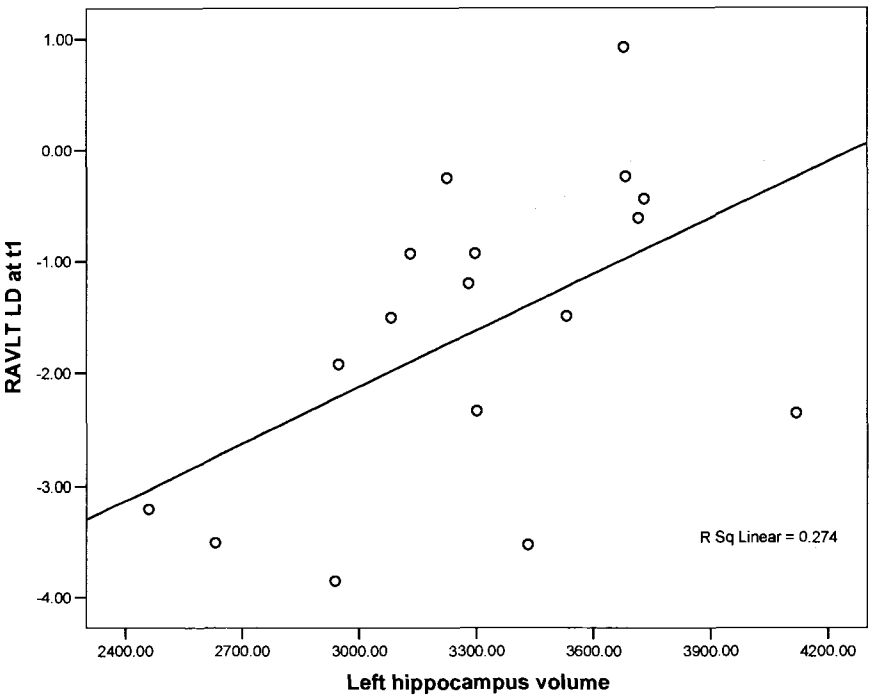

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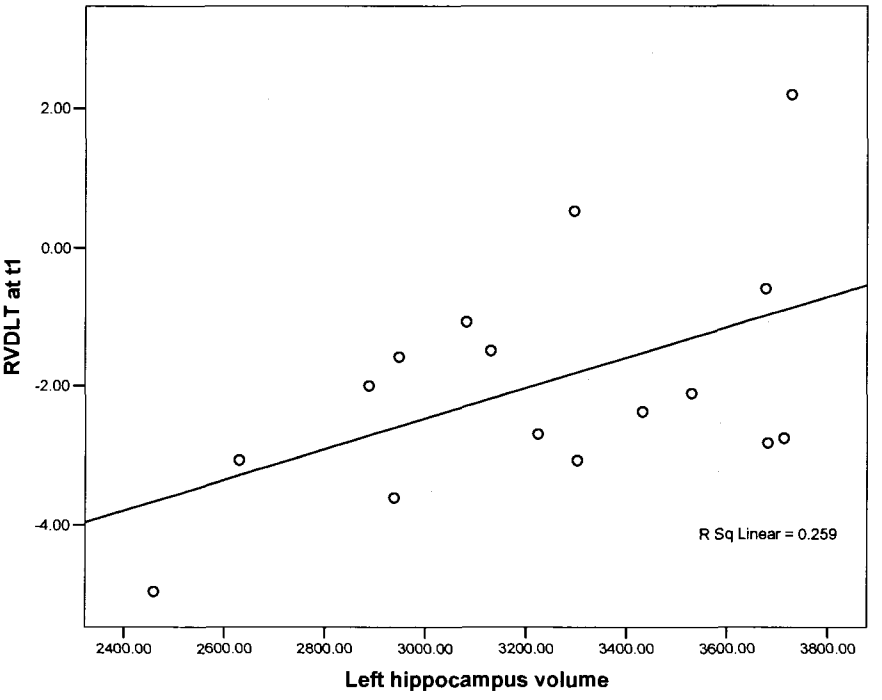


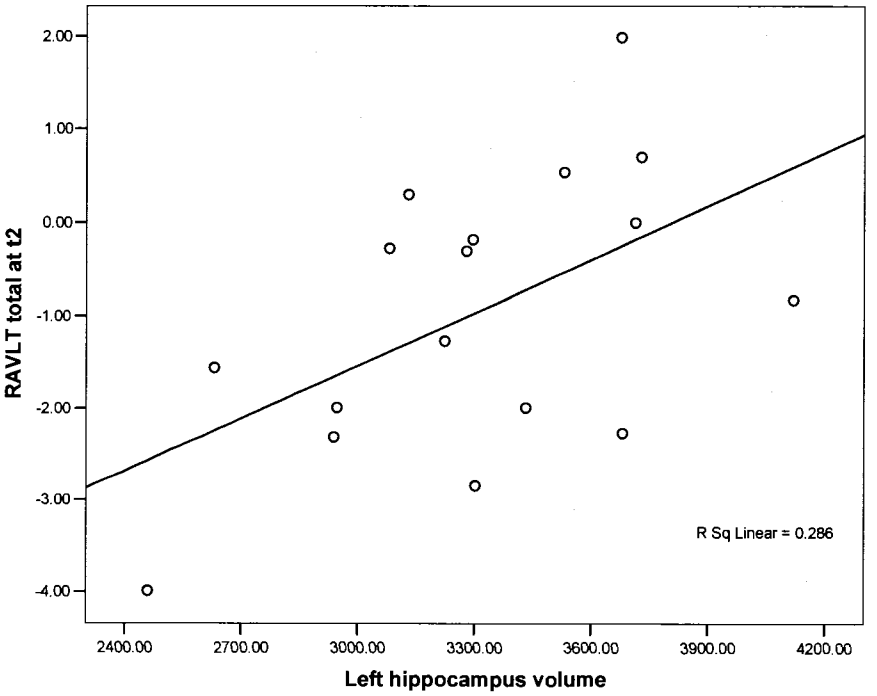
Figure 16. Scatterplots displaying the relationship between degree of hippocampal volume and memory performance at t1.
Greater left hippocampal volume is associated with the higher verbal memory performance measured by (A) *RAVLT total* ($r = 0.527$, $p < .05$), (B) *RAVLT LD* ($r = 0.524$, $p < .05$) and visuo-spatial memory measured by (C) *RVDLT* ($r = 0.509$, $p < .05$).

Table 6. Correlations between t2 memory impairment scores and neuroanatomical measures.

	Hippocampus		
t2 memory measure	Left	Right	VBR
RAVLT Total	0.535*	0.279	-0.055
RAVLT SD	0.526*	0.209	-0.141
RAVLT LD	0.431	0.164	-0.457
RVDLT	0.557*	0.361	0.037
LM IR	0.158	0.047	-0.287
LM DR	0.109	-0.093	-0.407

* $p < .05$

A



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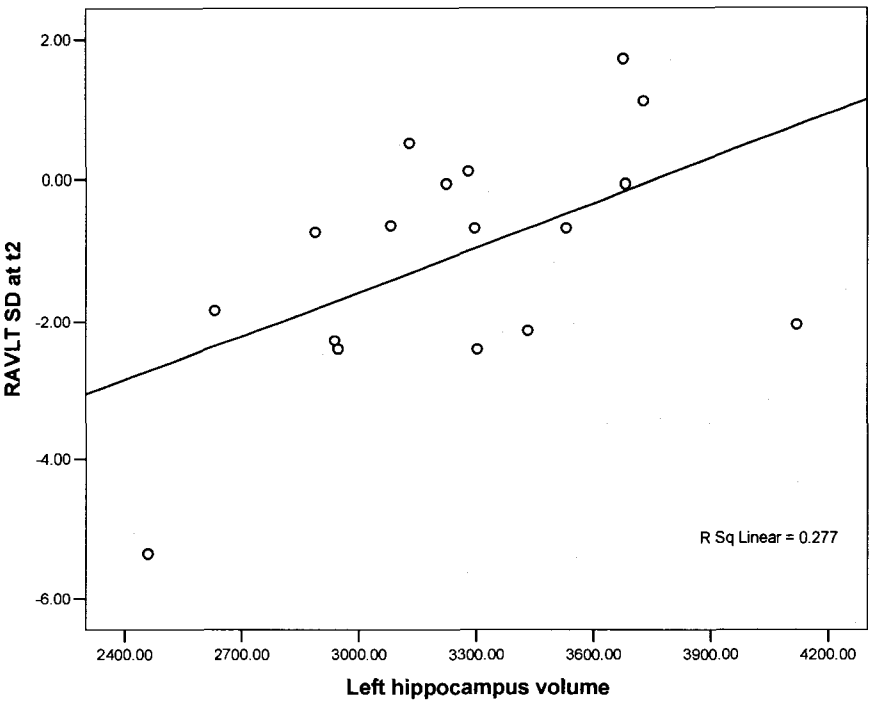

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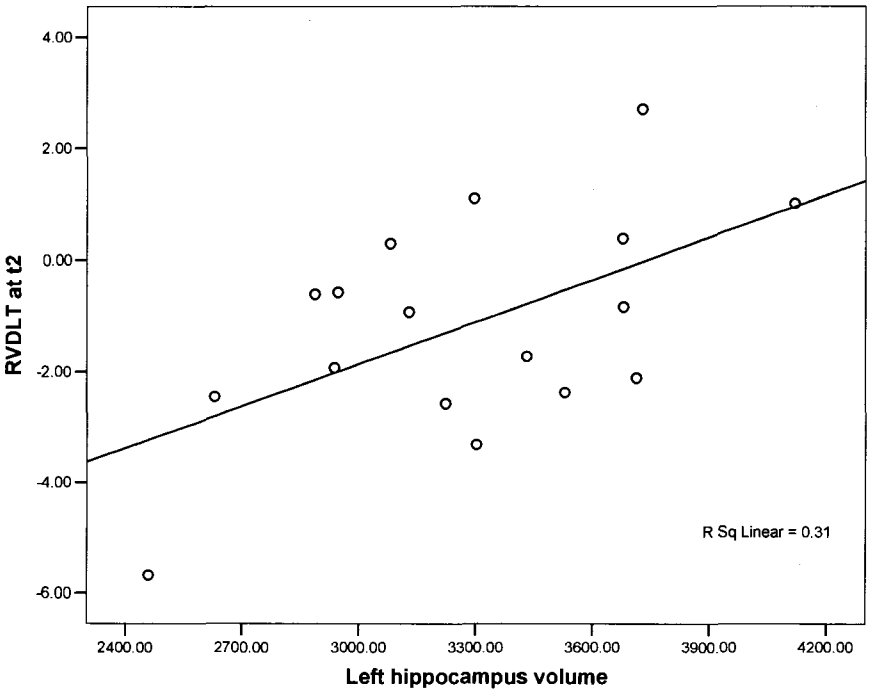


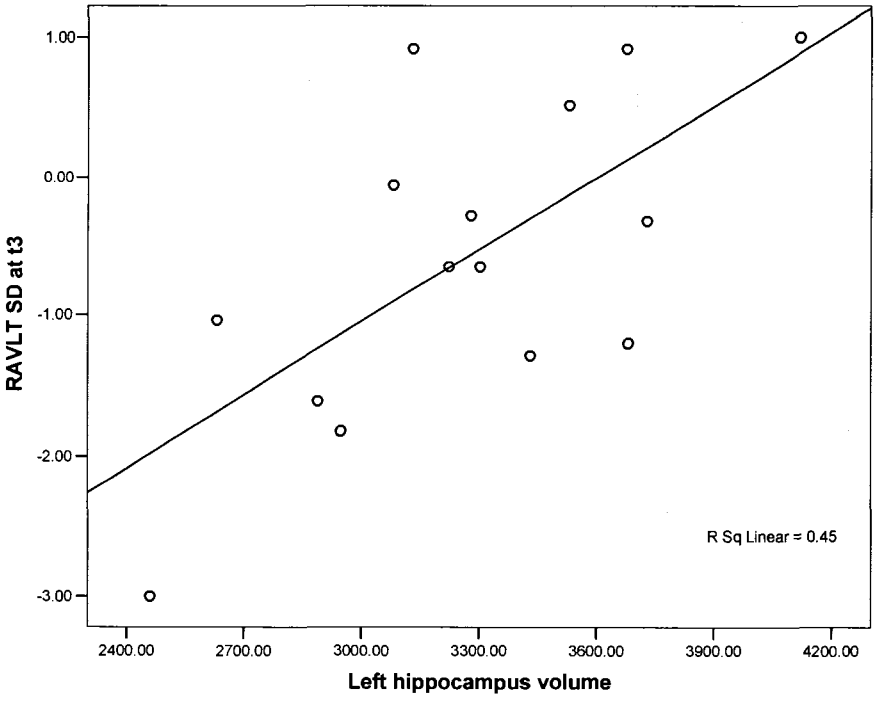
Figure 17. Scatterplots displaying the relationship between degree of hippocampal volume and memory performance at t2.
Greater left hippocampal volume is associated with the higher verbal memory performance measured by (A) *RAVLT total* ($r = 0.535$, $p < .05$), (B) *RAVLT SD* ($r = 0.526$, $p < .05$) and visuo-spatial memory measured by (C) *RVDLT* ($r = 0.557$, $p < .05$).

Table 7. Correlations between t3 memory impairment scores and neuroanatomical measures.

	Hippocampus		
t3 memory measure	Left	Right	VBR
RAVLT Total	0.449	0.274	0.286
RAVLT SD	0.671**	0.358	0.086
RAVLT LD	0.617*	0.355	0.204
RVDLT	0.602*	0.409	-0.002
LM IR	0.451	0.257	0.172
LM DR	0.243	0.075	0.002

* $p < .05$; ** $p < .01$

A



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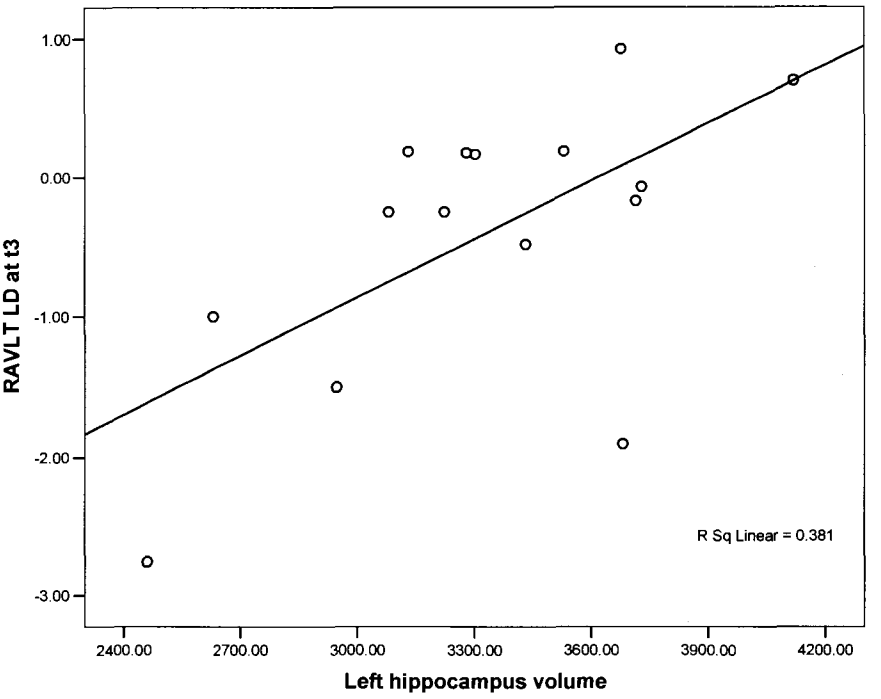

C

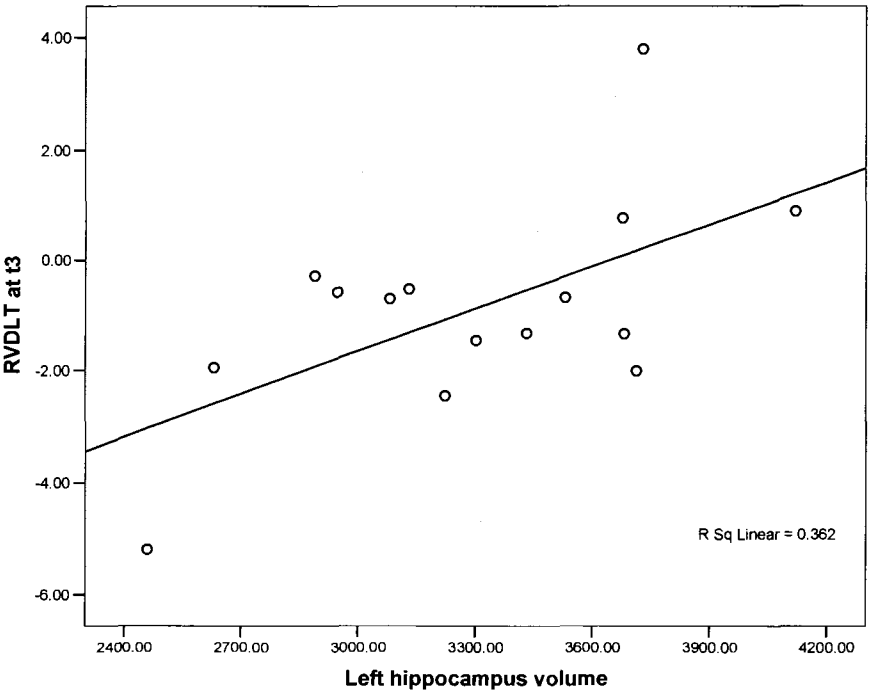

Figure 18. Scatterplots displaying the relationship between degree of hippocampal volume and memory performance at t3.
Greater left hippocampal volume is associated with the higher verbal memory performance measured by (A) *RAVLT SD* ($r = 0.671$, $p < .01$), (B) *RAVLT LD* ($r = 0.617$, $p < .05$) and visuo-spatial memory measured by (C) *RVDLT* ($r = 0.602$, $p < .05$).

4.4. VBR And Memory Recovery - Hypothesis 2.

The second hypothesis was that *recovery* of memory function (i.e., change scores from t1 to t2, t2 to t3, and from t1 to t3) would be more strongly associated with VBR than with hippocampal volume (N.B., A negative correlation between VBR and memory recovery would provide support for the hypothesis because the greater the VBR, the greater the atrophy). Tables 8, 9 and 10 provide the correlations between memory recovery scores (t1 to 2, t2 to 3 and t1 to 3) with VBR and hippocampal volumes. Correlational analyses were performed using those memory tests for which significant improvements were observed. Hence, data for the following change scores and their correlations are not presented: *RAVLT SD* (t1 to t2) and *RAVLT total*, *RAVLT SD*, *LM IR* and *LM DR* (t2 to t3).

As predicted, VBR was negatively correlated with recovery of *LM DR* ($r = -0.570$, $p < .05$) (Figure 19) from t1 to t2, indicating that higher VBR was associated with poorer verbal memory recovery. Otherwise, there were no other significant correlations for this period in recovery. In addition, as hypothesized there were no significant correlations between memory recovery and hippocampal volume. Counter to prediction, there were no significant correlations between VBR and memory recovery from t2 to t3. It should also be noted that no significant correlations between memory recovery and hippocampal volumes were observed for this period in recovery. Furthermore, contrary to prediction, recovery of verbal memory from t1 to t3 measured by *RAVLT SD* was significantly correlated with the left hippocampal volume ($r = 0.625$, $p < .05$) (Figure 20). No other significant correlations were found for this period of time post-injury. Thus, there was albeit, a weak support for hypothesis 2 for the period between t1 to t2, but not from t2 to t3 or t1 to t3.

Taken together, there was partial support for both hypotheses. VBR was not correlated with memory function at any of the three time points. VBR only showed correlation with recovery of memory (t1 to t2). On the other hand, hippocampal volume was strongly correlated with memory function at each of the three time points and with recovery of memory function from t1 to t3.

Table 8. Correlations between t1-t2 memory recovery scores and neuroanatomical measures.

		Hippocampus	
t1-t2 memory measure	VBR	Left	Right
RAVLT Total	-0.204	0.210	0.063
RAVLT LD	-0.356	-0.007	-0.064
RVDLT	0.063	0.073	-0.009
LM IR	-0.431	-0.113	-0.161
LM DR	-0.570*	-0.090	-0.362

* $p < .05$

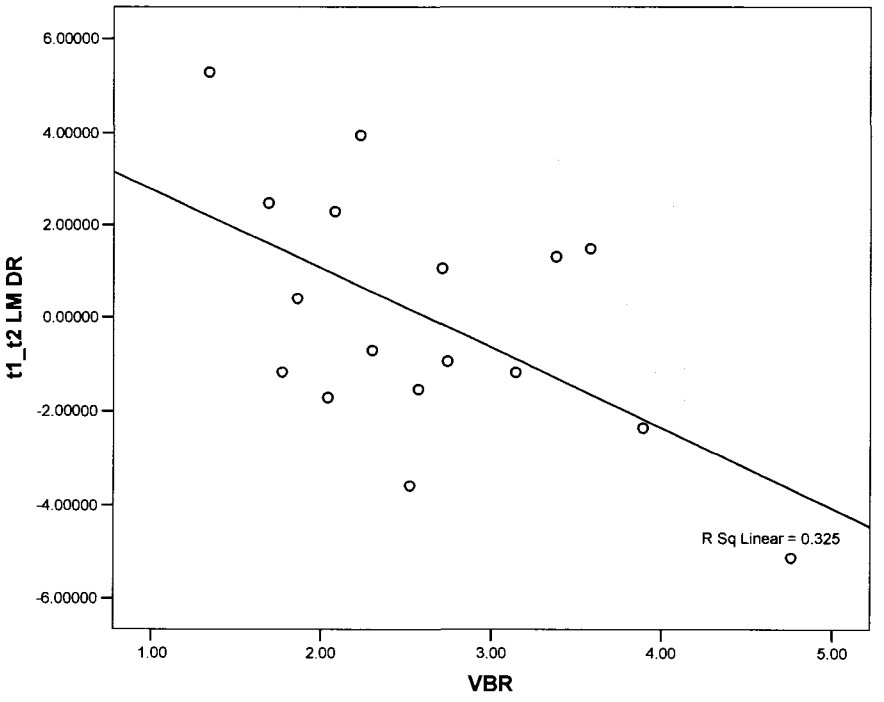

Figure 19. Scatterplot displaying the relationship between VBR and recovery of verbal memory function from t1 to t2.
Higher VBR (indicating greater brain atrophy) is associated with the poorer recovery of verbal memory as measured by *LM DR* ($r = -0.570$, $p < .05$).

Table 9. Correlations between t2-t3 memory recovery scores and neuroanatomical measures.

		Hippocampus	
t2-t3 memory measure	VBR	Left	Right
RAVLT LD	0.448	0.496	0.369
RVDLT	0.071	0.178	0.184

Table 10. Correlations between t1-t3 memory recovery scores and neuroanatomical measures.

		Hippocampus	
t1-t3 memory measure	VBR	Left	Right
RAVLT Total	0.364	0.102	0.078
RAVLT SD	0.213	0.625*	0.426
RAVLT LD	-0.383	-0.497	-0.353
RVDLT	0.261	0.278	0.368
LM IR	0.173	0.328	0.169
LM DR	-0.121	0.098	-0.127

* $p < .05$

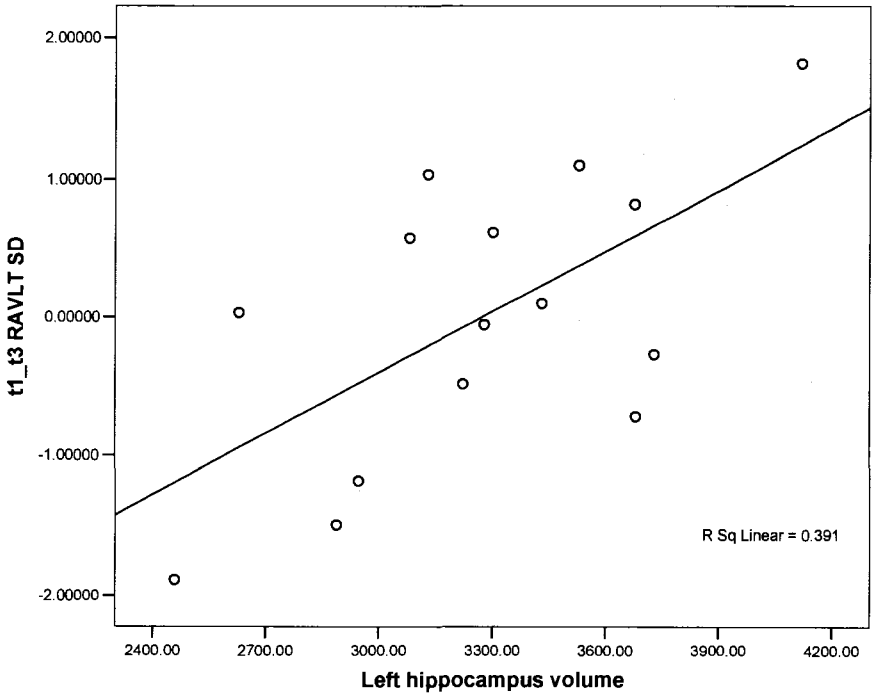

Figure 20. Scatterplot displaying the relationship between degree of hippocampal volume and recovery of verbal memory function from t1 to t3.
Greater left hippocampal volume is associated with the greater recovery of verbal memory as measured by *RAVLT SD* ($r = 0.625$, $p < .05$).

4.5. Exploratory Analysis

During the course of this thesis, some of the subjects underwent a second scan at 24 months post-injury. The statistical analysis of memory performance revealed no consistent improvements form t2 to t3. To better understand possible mechanisms associated with the lack of memory improvement, which may involve progressing hippocampal atrophy, further analysis was performed in which 5 and 24-month hippocampal volumes were compared. These analyses are considered exploratory due to small sample size (n = 7) and because they were not part of the original set of hypotheses. Due to time limitations, VBR and neuropsychological data were not studied. Detailed analysis of this data will be part of a future study and is beyond the scope of this thesis.

Table 11 presents the means and standard deviations for the 5 and 24-month hippocampal volumes. Statistically significant declines in hippocampal volumes were found for the left ($t = 2.95, 6, p < .05$, cohen's $d = 0.36$) and right ($t = 2.77, 6, p < .05$, cohen's $d = 0.26$) hippocampus. The average percentage decrease in volumes over 19 months (5-24 months) was 4.31% and 4.76% for the left and right hippocampus respectively. Such change in volume translates into the annual volume decrease by 2.72% and 3.01% in the left and right hippocampus respectively.

Table 11. The mean and standard deviation of 5 and 24-month hippocampal volumes.

Hippocampus	5 months Mean ± SD	24 months Mean ± SD	Total percent change	Annual percent change
Left	3533 ± 380	3387 ± 442*	4.3%	2.7%
Right	3423 ± 533	3273 ± 623*	4.8%	3.0%

n=7
*p < .05

5.0 Discussion

This study is the first to examine the neuroanatomical correlates of memory recovery in TBI patients. While past studies have focused primarily on cross-sectional data, we have developed an added approach in looking at the effects of focal and global neuropathological alterations in the context of longitudinal outcome of memory functions. The novelty of this study also lies in the use of high resolution, 1 mm isotropic, MR images as well as meticulous measurement of hippocampal volumes and VBR using standardized protocols to allow for a reliable method for comparison with other studies in future.

5.1 Summary Of Findings And Interpretations

We measured the hippocampus volume as an indicator of focal injury. While the study did not include normal control data, comparison with existing norms published in the literature (Pruessner et al., 2000) indicated that the hippocampus in our patient group was atrophic compared to normal population. The normal control data were reported in the study by Pruessner et al. (2000) using the same segmentation protocol with the same MR image resolution as in this study, allowing for comparison of the hippocampal volumes (image quality in both studies can be different though due to different scanners used to acquire the images). The mean volumes (n = 40) that were reported by Pruessner and colleagues (2000) were $4244mm^3 \pm 438$ (mean ± SD) and $4395mm^3 \pm 468$ for the left and right hippocampus respectively. In our study we have reported mean volumes of $3281mm^3 \pm 423$ and $3330mm^3 \pm 400$ for the left and right hippocampus respectively.

The global atrophy was measured by VBR. Although in this study data for age-matched normal control subjects was not available, based on the previously published normative data, we have confirmed that on average our TBI group exhibited generalized cerebral atrophy. As indicated in the study by Blatter et al. (1995), normal VBR (n = 164) is approximately 1.32 (uncorrected for head size) for the ages 16 to 54 (Blatter et al., 1995). In our sample the average VBR was 2.69, indicating generalized brain atrophy. These results are consistent with those previously reported, where VBR in TBI patients (n = 54) scanned more than 90 days post-injury was 2.43 (Bigler et al., 1996).

In addition, since our sample included 14 patients with visible lesions we also evaluated the relationship between the laterality of the lesion volume and the ipsilateral hippocampal atrophy. For instance, the right sided trauma may be associated with greater right hippocampal atrophy (Ariza et al., 2006; Bramlett & Dietrich 2002; Bramlett et al., 1997). However, no relationship was found between hippocampal volumes and the corresponding lesion volumes.

5.1.1 Neural Correlates Of Memory Impairment – Hypothesis 1.

We expected that the severity of memory impairment would be more strongly correlated with the degree of hippocampal volume than with VBR. As hypothesized, we found that hippocampal volume was in general more strongly correlated with memory impairment compared to VBR. However, the significance of correlations between the hippocampus and memory scores varied depending upon the laterality as well as the time point measure.

Volume of the left hippocampus showed significant correlations with verbal memory and learning scores measured by *RAVLT* tests. The relationship found between hippocampus and

RAVLT measures are in agreement with previous studies that have shown similar positive association between verbal memory performance and the left hippocampal volume in the TBI population (Bigler et al., 1996, 1997; Hopkins et al., 2005; Serra-Grabulosa et al., 2005). Hence, the association between degree of left hippocampal volume and verbal memory provides further evidence of the predominant involvement of the left hippocampus in verbal learning and memory. Furthermore, it has been previously shown that, in addition to more specific verbal learning and memory performance (Callahan & Johnston, 1994), *RAVLT* is a sensitive measure of global brain dysfunction. Thus, the relationship between the left hippocampal volume and the *RAVLT* performance in the current study indicates that the left hippocampal volume post injury may be a potential good predictor of memory and learning outcomes as well as more global cognitive function.

In contrast to our hypothesis, verbal memory measured by *LM IR* and *LM DR* did not correlate with the left hippocampal volume at any of the three time points. At t3 however, *LM DR* showed a trend toward significant correlation with the left hippocampus volume ($r = 0.451$, $p = .069$). These findings are in contrast with some reports (Bigler et al., 1996, 1997; Petersen et al., 2000) but consistent with others (Hopkins et al., 2005; Tate & Bigler, 2002; Tomaiuolo et al., 2004). One possible explanation for the lack of correlations may be that in addition to the left hippocampus, *LM* performance is mediated by other regions within the brain (Lezak, 2004; Squire & Morgan-Zola, 1991). For instance, human and animal studies have found that memory impairment may be more evident in cases when damage is more extensive and involving other regions of the medial temporal lobe such as subiculum and entorhinal cortex (Mishkin, 1978; Squire & Zola-Morgan, 1991; Squire 1992). Therefore, volumetric analyses of these regions could reveal positive associations with memory performance measured by *LM*. In addition, discrepancies in memory-hippocampus association presented in various studies may emerge from differences in methods used in measurement of *LM* performance. For instance, Bigler et al. (1996) used *LM* savings scores, calculated as a ratio of delayed recall to immediate recall, as opposed to separate *LM* IM and *DR* scores. These ratio scores have been suggested to be a better indicator of retention of information implicated in memory and were indeed correlated with the left hippocampus volume (uncorrected for head size) (Bigler et al., 1996).

While left hippocampus has primarily been associated with verbal memory, the right hippocampus has been proposed to be related to visuo-spatial memory in various previous animal and human studies (Lezak, 2004; Squire & Butters, 1992). Contrary to this belief, we found no significant correlations between the right hippocampus and the visuo-spatial memory scores, measured by *RVDLT*, at any of the three time points. Instead, it was the left hippocampus

that was found to be significantly correlated with this memory measure. In recent years some researchers have reported findings similar to ours where a relationship between visuo-spatial memory and either the left or the bilateral hippocampal volume was found (Bigler et al., 1996; Hopkins et al., 2005; Kilpatrick et al., 1997). For example, Bigler et al. (1996) have found a correlation between the left and right hippocampus volume and visual memory scores in TBI patients scanned more than 90 days post-injury, but not in patients scanned less than 90 days post-injury. Whereas, similar to our findings, Kilpatrick et al. (1997) found correlation between left hippocampal atrophy and measures of verbal and non-verbal memory function in temporal lobe epilepsy patients and no correlation between the right hippocampus and any of the memory measures. A potential explanation for relationship between visuo-spatial memory and the left hippocampus may be associated with the nature of the NP tests used. For example, the visual designs presented in tests of visuo-spatial memory may elicit verbal associations or verbal labeling since the stimuli may be encoded in a verbal manner (i.e., square or circle) (Lezak, 2004). Therefore, to some extent these tests could be verbally mediated and hence may be better correlated with the left hippocampus volume.

In summary the differences in the hippocampus-memory association may stem from different NP tests used and differences in sample sizes, recruitment criteria and time of post-injury evaluation as well as from differences in methods of volume measurement and reporting (such as head size correction, absolute volume or ratio etc.) and MR resolution (Kilpatrick et al., 1997).

In terms of the relationship between NP and VBR, no significant correlations were found between these two parameters at any of the three time points. These findings are in agreement with our hypothesis and are also corroborated by Bigler et al. (1996), where none of the memory measures, including verbal and visual memory, correlated with VBR. Thus, our findings support the notion that learning and memory impairment at least to some degree are associated with a damage to a more specific brain region as opposed to global neuropathologic changes within the brain.

5.2.2 Neural Correlates Of Memory Recovery – Hypothesis 2.

We hypothesized that VBR would be a stronger correlate of memory recovery than hippocampal volume. In our study we found significant recovery of verbal learning, verbal memory, and visuo-spatial memory from t1 to t2, and from t1 to t3, while significant improvements in these cognitive domains from t2 to t3 were limited. In fact, we found a decline in memory functioning from t2 to t3 in some of the patients. As a result, testing of the second

hypothesis for the period from t2 to t3 was limited to two tests (*RAVLT LD* and *RVDLT*). Further examination of the t2 to t3 data is discussed later.

As hypothesized we found significant correlations between VBR and recovery of memory as measured by *LM DR* from t1 to t2, and there were no significant correlations between hippocampal volumes and memory recovery. Therefore, there was some support for the hypothesis (for the period from t1 to t2). These findings converge with recent findings in the animal literature, where a complete recovery of memory function, assessed with Morris Water Maze performance, in relation to hippocampal atrophy was studied in animal model of brain injury by Pereira et al. (2007). In this study brain injured rats were stimulated by enriched environment, which resulted in complete reversal of memory impairment assessed 11 weeks post-injury. Despite such improvement in function, animals showed reduction in hippocampal volumes, suggesting that marked recovery in memory function was not associated with the loss of the hippocampal volume. As such, recovery of spatial memory deficits could have been mediated by regions different than hippocampus.

Recovery of memory function from t2 to t3, as measured by *RAVLT LD* and *RVDLT*, was not associated with VBR. In addition, there were no significant correlations between memory recovery and hippocampal volumes. However, a trend toward significance was observed between *RAVLT LD* change score and the left hippocampal volume ($r = 0.496$, $p = .06$). Thus, it is probable that recovery of memory from t2 to 3 may be associated to a greater degree with hippocampal volume rather than the VBR. Potential involvement of hippocampus is also supported by the fact that we found recovery of memory, measured by *RAVLT SD*, from t1 to t3, to be associated with the hippocampal volume, as opposed to VBR. This suggests that greater hippocampal volume at 5 months was associated with better recovery of memory function at 12 months interval. These findings suggest that while short-term (5 months post-injury) memory recovery (as measured by *LM DR*) may be driven by the extent of global damage to the brain, the long-term (12 month post-injury) memory (as measured by *RAVLT SD*) appears to be influenced by the extent of focal damage to the brain structure. Thus, it is likely that although hippocampus in TBI is atrophic (compared to the norm reported in literature), it may still contain varying degrees of healthy and functional neurons that may support the recovery of memory function. In fact, hippocampus is a structure known for cellular plasticity (Chen & Manjii, 2006) and it is one of the few areas of the adult brain that continues to produce new neurons in adulthood. The process of creation of new neurons, known as neurogenesis (Becker & Wojtowicz, 2006), appears to be one of the mechanisms underlying recovery. Significant increases in neurogenesis, have been shown following TBI, which may contribute to functional

recovery through generation of new neurons and neural networks in order to replace those lost due to injury (Sun et al., 2007; Thored et al., 2006). An amplified neurogenesis following TBI has been shown in animal models (Dash et al., 2001; Sun et al., 2005, 2007). A recent study conducted by Sun et al. (2007) showed that brain injured rats showed spontaneous cognitive recovery, assessed with Morris Water Maze, which coincided with integration of newly generated cells into the hippocampal circuitry. Compared to sham rats, TBI animals displayed significantly impaired cognitive performance when assessed at 11-25 and 26-30 days post-injury, which was no longer apparent when they were assessed 56-60 days post-injury. Newly generated neurons were shown to be integrated into the hippocampal circuitry around the same time. Thus, authors conclude that cognitive recovery of animals may be a reflection of the integration of the new neurons into existing circuitry. The result of this study also demonstrate that neurogenetic response in injured animals was 4 times greater than that observed in sham group, but compared to sham group in injured animals a smaller percentage (46% versus 65%) of these new cells survived up to 10 weeks post-injury. It is possible then, authors conclude, that the injured brain may be less conductive for long-term cell survival.

Research has also demonstrated a relationship between increases in hippocampal volumes and improvements in memory performance in various populations, such as post-traumatic stress disorder victims (Vermetten et al., 2003) and bipolar disorder patients (Yucel et al., 2007) following pharmacological treatment. For instance, study by Yucel and colleagues (2007) reported bilateral increases in volume of the hippocampi over the period of 4 years in patients with bipolar disorder who received lithium treatment. These patients underwent MRI at 2 and 4 years from the baseline scanning, and their verbal memory performance was assessed using the California Verbal Learning Test at each of these time points. The hippocampal volumes increased significantly by 4-5% when measured 4 years post-baseline. In addition, verbal memory performance significantly improved in those patients. Over time a small number of robust positive correlations between change in hippocampal volumes and California Verbal Learning Test performance was found. Authors conclude that increases in hippocampal volume may have contributed to improved performance, but the relationship between these factors remains to be clarified. Furthermore, authors hypothesize that such bilateral increases in hippocampal volumes stem from the effects of lithium treatment on hippocampal neurogenesis, however alternative causes are possible (i.e., alternations in brain water). Thus, such hypothesis should be interpreted with caution and further investigation in this area is needed.

The results from our study indicate that to some extent hippocampal volume appears to be associated with recovery of memory function (as measured by *RAVLT SD*). Perhaps the

association between hippocampus and recovery of memory may further be strengthened by intervention with pharmacological treatments. As such, it could be a future incentive for the development of alternative pharmaceutical therapies aimed specifically at hippocampal neurons that have the potential to alleviate memory deficits following TBI (Geddes et al., 2003).

Despite our expectations that memory recovery would be dependent upon the global trauma to the brain, we did not find many significant correlations between VBR and memory recovery. Since this is the first study to explore this relationship, we cannot compare our findings to the literature. However, we can speculate a few probable causes.

It is possible that assessing global pathologic changes within the whole brain in relation to recovery of memory function may have diluted results, and as such it may be necessary to focus on global changes within more specific areas of the brain. It has been suggested that recovery from brain injury may most likely result from a change in organization of local cortical circuits in regions directly or indirectly disrupted by injury rather than from global cortical reorganization (Kolb & Gibb, 1999). Since memory system is located within temporal lobe, to some degree recovery of memory function may be associated with global neuropathologic changes within this region of the brain. Bigler et al. (2002) have examined temporal lobe morphology, using MRI, in normal controls and in TBI. It was found that, compared to normal controls, TBI patients had reduced volume of temporal lobe WM, increased volume of the IHLV and reduced hippocampal volumes. In addition, it was reported that increased volume of IHLV was associated with a decrease in WM volume and not the hippocampal volume, possibly indicating that these volumes are representative of global neuropathological changes. Interestingly, the WM and IHLV volumes were not related in the healthy controls. Thus, possibly volumes of the temporal WM and IHLV could be used in studying global neuropathological changes in relation to memory recovery.

In addition to white matter volume, our measurement of global neuropathology using VBR may not have been sensitive enough to evaluate the disruptions in white matter connectivity as a result of brain trauma. This may require the use of other imaging modalities such as diffusion tensor imaging.

It could also be that recovery of memory function may be associated with changes in 'memory dominant' cortical regions adjacent to the hippocampus, such as entorhinal, perirhinal and parahippocampal cortices. Although hippocampal role in memory function is well established, these adjacent cortical regions provide input to the hippocampus and they also participate in memory function (Lezak, 2004; Squire & Zola-Morgan, 1991). It is possible then that recovery of memory function is associated with volumetric changes in these areas (i.e.,

atrophy of these regions may be associated with worse recovery of memory), thus a detailed analysis of these temporal structures will possibly shed light on recovery of memory function.

The final factor could be the insufficient sample size and the consequent increase in Type II error risk. The lack of significant findings on some comparisons may simply be a reflection of insufficient power to detect the neuroanatomical correlates of memory recovery (Cohen, 1992; Hopkins et al., 2005).

The examination of the NP data revealed significant recovery of memory function from 1.5 to 12 months post-injury with the most significant degree of recovery observed within first 5 months and deceleration of recovery from 5 to 12 months. Further inspection of this phenomenon revealed inconsistent improvements in memory performance among our subjects, with some patients showing increased performance while others showing a decrease in memory function during that period of time. These inconsistencies in memory recovery are consistent with those found by Millis et al. (2001). In their study, considerable heterogeneity of cognitive outcome was noted (22% of subjects improved, 15% declined and 62% of the subjects showed no change) in TBI patients studied from 1 to 5 years post-injury. In the Millis study, patients were assessed later than in the present study, nonetheless they show the same variability in outcome observed.

A likely explanation of the apparent decline in memory recovery between months 5 and 12 post-injury may be derived from the exploratory analysis that we conducted on the data for 7 subjects. These subjects received a second MRI at 24 months post-injury. As such we were able to compare the hippocampal volumes at 5 and 24 months post-injury and found an overall annual decrease in volume of 2.87% (left and right hippocampus combined). By comparison, normal control subjects, aged from 16 to 72 years show an annual volumetric decrease of 0.25% Bigler et al. (2002). This accelerated decline in post-injury hippocampal volume in our exploratory study suggests a potential compromise of memory recovery in TBI. Caution needs to be exercised with this interpretation however, due to the small sample size ($n = 7$). To our knowledge, decrease in hippocampal volumes measured by MRI has not yet been reported in studies that assess hippocampal volume longitudinally in a TBI population. Therefore, our work offers new insights into a possible factor associated with memory impairment and recovery. In order to fully understand association between hippocampal atrophy and memory impairment or recovery during the second year post-injury, more detailed morphological data needs to be compared with the behavioural data. Such analysis would be a future direction of the current work and is beyond the scope of this thesis.

The fluctuation in cognitive data thus indicates that there is a sudden surge of memory recovery in all patients shortly after injury. However, further improvement or the sustenance of such improvement is dependant upon currently undefined factors; though one might speculate on the likely factors being the extent and/or location of injury, the potential of the brain parenchyma to recover physically from such insult as well as post-injury clinical care and rehabilitation.

In summary, our hypothesis that global and not focal injury determines the outcome of memory recovery was only partly supported for the period from t1 to t2, but not from t2 to t3 and t1 to t3. Our results indicate that perhaps both focal and global pathologies may be associated with the recovery of memory function (as measured by *LM DR* and *RAVLT SD*) at varying time points. However, the greatest amount of memory recovery as measured by cognitive testing took place within the first 5 months post-injury and was associated with global trauma suggesting that intact connectivity of neuronal circuits may be a crucial factor for the short-term outcome. In contrast, the overall recovery of memory (as measured by *RAVLT SD*) over the first year of injury seems to be related to some degree with the hippocampal volume. Thus, it may be that the plastic changes within the hippocampus as well as other brain structures may support the recovery of memory function and there is a possibility that recovery mechanisms may operate differently at various times post-injury.

This study was the first attempt to relate focal and global injury with recovery of memory functions. It is obvious that in order to fully understand the process, a larger sample size and more sensitive measurement techniques are needed to evaluate focal and global brain injury. However, if the involvement of hippocampus in long-term outcome of memory functioning in TBI is true, it could lead to therapeutic treatments involving both behavioural therapy and pharmacological agents (Duffau, 2006; Kolb & Gibb, 1999). To date, the timing of the rehabilitation in such manner has been controversial, as it has been suggested that early treatment may exacerbate injury (DeBow, McKenna, Kolb, & Colbourne, 2004; Duffau, 2006; Humm et al., 1998). Further investigation in recovery studies is thus necessary in order to improve treatment options for TBI patients.

5.2 Future Directions

This work has provided some very preliminary evidence that the memory impairment level and recovery may be differentially associated with focal and global neuropathology of the brain following TBI. A larger follow-up study is clearly required to substantiate our preliminary results. Replication of our findings in a larger sample of TBI patients would strengthen the

power of the results obtained from our main study as well as from the exploratory analysis. In addition, it would be important to examine VBR and memory performance at 24 months post-injury in order to determine the impact of global pathology on the long term outcome of recovery.

The sample in the current study was too small to investigate statistically distinct sub-groups of patients with regard to recovery patterns (i.e., improvement, no change, decline). Given variability in memory performance from t2 to t3, it is of importance to examine patients in sub-groups based on the pattern of their recovery and associated neuroanatomical correlates.

More sensitive neuroanatomical measures need to be applied in order to alleviate any possible factors that may mask the subtle alterations in brain morphology. These, as discussed previously, would include an evaluation of global changes within more specific areas of the brain, such as the temporal lobe instead of the entire brain, a focus on memory dominant structures other than the hippocampus, such as entorhinal, perirhinal and parahippocampal cortices and finally application of more sensitive MR techniques to examine brain connectivity and integrity of fiber tracts such as diffusion tensor imaging.

5.3 Conclusions And Implications For Rehabilitation

To date, there is a very limited understanding of the neural mechanisms associated with brain injury and subsequent recovery. Given the variable nature of TBI and its devastating long-term effects, the need for improving existing and developing new clinical and rehabilitation methods as well as determining appropriate timing for intervention is critical. However, without deeper understanding of mechanisms of brain injury and recovery, clinicians are unable to design more effective patient-specific treatments that would promote recovery in the areas of cognitive deficits.

This study has made an attempt to address questions surrounding recovery of memory function following TBI in relation to neuropathological findings observed on MRI. Our findings are the first step towards the understanding of basic neuroanatomical mechanisms of memory recovery and may, in time, lead to the development of treatment plans in rehabilitation of TBI individuals thereby decreasing its debilitating effects and improving the quality of life for individuals with brain injury. Since rehabilitation interventions address deficits in specific cognitive domains, such as memory, it is imperative to conduct more research to address the course of recovery within these specific domains. The contribution made by our novel study thus specifically supports the need for deeper research into the relationship between memory recovery and brain morphology following traumatic brain injury.

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7.0 Appendices

7.1 Quality Control Rating Guide (Kabani Lab Manual, 2006).

	Registration	Tissue classification	3D surface extraction	Skull and scalp removal
Excellent	Perfect alignment of lobes; no over/under-scaling; proper rotation and translation.	Flawless cortical definition; good demarcation of internal structures; no "graininess" or over/under-classification of one tissue type as another.	Perfectly smooth surface; no bumps that might not be cortex; good sulcal definition everywhere.	No extra tissue included; no tissue missing.
Good	Best fit possible; any misalignment or over/under-scaling due to unique properties of the particular volume.	Good cortical definition; decent demarcation of internal structures; "graininess" that is consistent with the signal of the acquired image; smooth boundaries between tissue types.	Smooth surface with only a couple of rough spots; very few/small bumps which might not be cortex.	Small amounts of extra tissue such as dura mater or orbital tissue included; small amounts of tissue missing in some outer areas.
Fair	Reasonable fit; small amounts of misalignment or over/under-scaling that could have been avoided.	Decent cortical definition; so-so demarcation of internal structures; moderate amounts of mis-classified tissue; moderately jagged boundaries between tissue types.	Cortex surface is clear and relatively smooth, rough spots limited to certain areas; some bumps of dura mater, skull/ scalp.	Medium sized chunks of extra tissue, no skull/scalp; medium amounts of tissue missing, but relatively spread out, not taken from one spot.
Poor	Poor fit; general misalignment or over/under-scaling; still close to reasonable.	Poor cortical definition; large amounts of mis-classified tissue throughout the volume; jagged boundaries between tissue types.	Large sections of rough surface, indicating missing tissue; large bumps of dura mater, skull/scalp.	Large chunks of extra tissue, skull/scalp included; large amounts of tissue missing in at least one lobe.
Bad	Complete failure of alignment; brain is distorted, stretched, or rotated in really weird ways.	Failure to classify a tissue type (eg. no GM at all); complete misclassification of tissue type; unrecognizable internal structures.	Huge chunks of dura mater/skull/scalp covering almost entire volume; large sections of cortex missing; rough angled surface everywhere.	Unrecognizable; nothing like actual brain.