8-27-2009

Longitudinal changes in ventricle volume following pediatric traumatic brain injury : predictors of cognitive function one year later

Lauren Parks

Lauren Parks
Candidate

Psychology
Department

This dissertation is approved, and it is acceptable in quality and form for publication:

Approved by the Dissertation Committee:

_____, Chairperson

_____

_____

_____

_____

_____

_____

_____

LONGITUDINAL CHANGES IN VENTRICLE VOLUME FOLLOWING PEDIATRIC TRAUMATIC BRAIN INJURY: PREDICTORS OF COGNITIVE FUNCTION ONE YEAR LATER

BY

LAUREN KATHLEEN PARKS

B.S., Biopsychology, University of California, Santa Barbara, 2001
M.S., Psychology, University of New Mexico, 2006

DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of

Doctor of Philosophy
Psychology

The University of New Mexico
Albuquerque, New Mexico

August, 2009

ACKNOWLEDGMENTS

This study would not have been possible were it not for the original efforts of the following individuals:

Ronald A. Yeo, PhD

Richard Campbell, PhD

Rex Jung, PhD

John Phillips, MD

April Lightsey, MS

Members of the MIND Research Network

I would like to thank the members of my dissertation committee for their guidance, suggestions, and support.

Ronald A. Yeo, PhD

Richard Campbell, PhD

Sarah Erickson, PhD

Steve Verney, PhD

Finally, I would like to thank my family and friends for the endless amount of support they provided over the last few years.

LONGITUDINAL CHANGES IN VENTRICLE VOLUME FOLLOWING PEDIATRIC TRAUMATIC BRAIN INJURY: PREDICTORS OF COGNITIVE FUNCTION ONE YEAR LATER

BY

LAUREN KATHLEEN PARKS

ABSTRACT OF DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of

Doctor of Philosophy
Psychology

The University of New Mexico
Albuquerque, New Mexico

August, 2009

LONGITUDINAL CHANGES IN VENTRICLE VOLUME FOLLOWING PEDIATRIC TRAUMATIC BRAIN INJURY: PREDICTORS OF COGNITIVE FUNCTION ON YEAR LATER

by

Lauren Kathleen Parks

B.S., Biopsychology, University of California, Santa Barbara, 2001

M.S., Psychology, University of New Mexico, 2006

Ph.D., Psychology, University of New Mexico, 2009

ABSTRACT

Ventricular enlargement in pediatric TBI is a common observation in clinical practice, yet volumetric studies of ventricle volume are sparse. In this study, MRIs and neuropsychological testing were performed on children who had sustained a traumatic brain injury (n=38) and control children (n=34) between the ages of six and eighteen years. Children with traumatic brain injury (mean GCS=9.0) were evaluated at two time points (time one: mean=55 days post injury, n=38; time two: mean=324 days post injury, n=21). Results revealed that ventricular enlargement and deficits in cognitive function were present in the TBI group during both the semi-acute (<6 months post injury) and chronic (>6 months post injury) phases of injury (as compared to typically developing controls). Furthermore, ventricular enlargement and cognitive function during the semi-acute phase of injury were correlated with initial injury severity (as measured by the

Glasgow Coma Scale). Additionally, lateral ventricle volume and third ventricle volume were correlated with the executive composite during the semi-acute phase of injury. During the chronic phase of injury, only third ventricle volume (not lateral ventricle volume) was significantly correlated with the executive and memory composites. Examination of the longitudinal data revealed that third ventricle volume significantly decreased between times one and two, while cognitive function significantly improved. Finally, results of regression analyses revealed that third ventricle enlargement at time one was the best predictor of cognitive function at time two. Our results reiterate the importance of longitudinal designs in pediatric TBI and indicate the utility of third ventricle volume in the semi-acute phase of injury as a predictor of neuropsychological function.

TABLE OF CONTENTS

LIST OF FIGURES ..... **x**

LIST OF TABLES ..... **xi**

INTRODUCTION **1**

Overview and Epidemiology 1

Etiology and Pathophysiology of Pediatric TBI 2

Factors Mediating Outcome 5

Impact of TBI on Functioning 5

Cognitive Outcome 6

Memory 7

Neuroanatomic Correlates of Memory 8

Executive Function 8

Neuroanatomic Correlates of Executive Function 9

Attention 9

Neural Correlates of Attention 11

Language 12

Neural Correlates of Language 12

Neuroanatomic Outcome 13

Longitudinal Neuroimaging Studies 18

METHODS **21**

Participants 21

Procedures 22

Cognitive Measures 22

Wide Range Achievement Test, Third Edition (WRAT-3; Wilkinson, 1993): Reading subtest 23
Controlled Oral Word Association (COWA; Benton & Hamsher, 1994) 24
Grooved Pegboard Test (Klove, 1963) 24
Grip Strength Test 24
Digit Span (Wechsler, 1991) 24
Spatial Span (Wechsler, 1987) 25
Trail Making Test, Parts A and B (TMT) 25
Tests of Memory and Learning (TOMAL): Memory for Stories and Facial Memory subtests (Reynolds and Bigler, 1994) 25
Hopkins Verbal Learning Test (HVLT-R; Brandt and Benedict, 2001) 26
Beery-Buktenika Developmental Test of Visual Motor Integration (VMI) 26
Neuropsychological Composites 26
Image Acquisition 27
Image Analysis 27
Statistics 33
Demographics 33
Group Differences at Times One and Two 33
Time Two Analyses (TBI Group Only) 34
TBI Group Analyses 34
Longitudinal Analyses 34
Predictors of Function at Time Two 34
RESULTS 36

Demographics 36

Reliablity 41

Group Differences (Controls versus TBI) at Time 1 41

TBI group analyses 51

Group Differences (Control vs TBI) at Time 2 52

Time 2 Analyses (TBI group only) 53

Longitudinal Analyses 55

Predictors of Function at Time 2 58

DISCUSSION 67

Group Differences at Time 1 and Time 2 68

Clinical Features and Demographics 70

TBI Group Findings 73

Longitudinal Data 74

Predictors of Neuropsychological Function at Time 2 76

Limitations 78

Conclusions 81

Directions for Future Research 82

REFERENCES 84

LIST OF FIGURES

Figure 1: Axial view of the anterior commissure. 29

Figure 2: Representative brain showing all 21 axial slices included in the analyses. 30

Figure 3: Axial view of the lateral ventricles..... 32

Figure 4: Axial view of the third ventricle..... 32

Figure 5: Relationship between lateral ventricle volume and executive composite at time one in TBI group. 45

Figure 6: Relationship between lateral ventricle volume and memory composite at time one in TBI group. 46

Figure 7: Relationship between lateral ventricle volume and motor composite at time one in TBI group..... 47

Figure 8: Relationship between third ventricle volume and executive composite at time one in TBI group. 48

Figure 9: Relationship between third ventricle volume and memory composite at time one in TBI group..... 49

Figure 10: Relationship between third ventricle volume and motor composite at time one in TBI group..... 50

Figure 11: Relationship between third ventricle volume at time one and executive composite at time two in TBI group. 64

Figure 12: Relationship between third ventricle volume at time one and the executive composite at time two (controlling for executive composite at time one) in TBI group. 66

LIST OF TABLES

Table 1: Demographics and clinical features of TBI group. 37

Table 2: Age distribution of participants in the TBI group. 38

Table 3: Demographics of typically developing control and TBI groups. 39

Table 4: Correlations of age, sex, days post injury, and GCS with time 1 ventricle measures. 40

Table 5: Correlations of age, sex, and days post injury with time 1 neuropsychological composites. 40

Table 6: Composite scores for neuropsychological data in control and TBI groups at time one. 42

Table 7: Ventricles measures (mm3) for control and TBI groups. 42

Table 8: Correlation of neuropsychological composites with GCS and ventricle measures (mm3) at time 1. 44

Table 9: TBI group comparison at time 1 based on GCS score (mild/moderate=8-15, severe=3-7). 52

Table 10: Differences between TBI participants at time 2 and controls. 53

Table 11: Correlation of longitudinal ventricle measures with neuropsychological composites at time 2 in TBI group. 54

Table 12: Demographics of TBI participants with one data point compared to participants with two data points (at time 1). 56

Table 13: Longitudinal analyses: Time 1 measures compared to time 2 measures for the TBI group. 58

Table 14: Predictors of neuropsychological function at time two in TBI group. 59

Table 15: Summary of multiple regression analysis for variables predicting executive composite at time two in TBI group. 61

Table 16: Summary of multiple regression analysis for variables predicting memory composite at time two in TBI group. 62

Table 17: Summary of multiple regression analysis for variables predicting motor composite at time two in TBI group. 63

INTRODUCTION

Overview and Epidemiology

Affecting nearly half a million children each year, traumatic brain injury (TBI) is a major public health concern (Kraus et al., 1995). Labeled the silent epidemic by the Centers for Disease Control (CDC), TBI is the primary cause of death and disability among children under the age of 15 years (Langlois, Rutland-Brown, & Thomas, 2005). Pediatric TBI often leads to deficits that can disrupt key developmental processes such as learning, language, behavioral adjustment, and social functioning (Taylor, 2004). Furthermore, research has shown that moderate to severe injuries can impact brain structure and function resulting in lifelong impairment (Levin, 2003; Tasker, 2006). Despite the prevalence of TBI and its long-term effects on cognitive, emotional, and social functioning, there remains a paucity of longitudinal research on the effects of TBI on the developing brain and factors that moderate these effects.

Given the impact of TBI on the pediatric population, it is puzzling that the majority of research to date has focused on acquired brain injury in adults. One factor is certainly the greater pragmatic difficulties of conducting clinical research in children. But, the most central reason for this neglect stems from the long-accepted plasticity hypothesis that asserts that the immature brain is more likely to reorganize following injury and is therefore less vulnerable to insult (Stiles, 2000). However, while this may be true for focal injuries sustained in early childhood, this same principle does not apply to non-penetrating, diffuse injuries (Levin, 2003). In fact, results indicate that, not only is the developing brain more vulnerable to insult than the adult brain, outcome following pediatric TBI is extremely variable (Giza, Mink, & Madikians, 2007). This variability,

coupled with factors intrinsic to the developmental process, has created challenges specific to research on pediatric TBI.

It has been suggested that brain injury occurring in childhood or adolescence may alter subsequent brain maturation (Wilde et al., 2005). As a result, skills that are developing or emerging at the time of injury may be compromised and may not develop at a normal rate post-injury (Catroppa & Anderson, 2004). Similarly, cognitive skills that rely on an intact central nervous system in order to develop efficiently may be negatively impacted when injury occurs prior to their development. Evaluating outcome after TBI is further complicated by the fact that brain injury that occurs in the midst of development may not produce immediate cognitive and behavioral consequences (Oddy, 1993). Rather, deficits may become apparent as the child ages and demands become greater.

Etiology and Pathophysiology of Pediatric TBI

While pediatric and adult TBI share similar features in the acute phase of injury, it is important to note that attempting to equate adult results with those of children can be misleading. Rather, it has been suggested that, due to differing physiological properties, pediatric TBI affects the brain much differently than adult TBI. Specifically, it has been suggested that injuries sustained in childhood may be distinct from adult injuries in terms of injury response, physiological measures, markers of injury, medication effects, efficacy of therapies, and recovery of function (Giza, Mink, & Madikians, 2007). Unlike adults, the mechanism of injury, injury pathology, and outcome following traumatic brain injury in childhood are often age-dependent. Falls, sports injuries, and motor vehicle accidents are the most common causes of TBI in children between the ages of 4 and 12 years whereas motor vehicle accidents at high speeds and gunshot wounds are the most

common causes of TBI in adolescents (Fletcher, 1995). Both animal research and patient outcome studies have confirmed the hypothesis that the developing brain is particularly susceptible to diffuse injury (Kochanek, 2006; Pullela et al., 2006).

Brain injuries are divided into two categories: primary injury, which occurs at the moment of trauma, and secondary injury, which occurs immediately after trauma and produces potentially long-lasting effects. According to Wallesch and colleagues (2001), the effects of traumatic brain injury can be attributed to three mechanisms: (1) focal injuries (hemorrhagic and non-hemorrhagic) resulting from local impact, (2) diffuse axonal injury (DAI) resulting from head acceleration/deceleration and (3) secondary damage resulting from edema or hemorrhage. Both focal and diffuse mechanisms are considered primary injuries and can occur alone or in combination. Focal injuries are more likely to occur in adults whereas diffuse injuries are more likely to occur in children (Levin, 2003).

Focal injury is thought to result from the impact of the brain on the rigid inner table of the skull and produces macroscopic lesions such as contusions, intracerebral hematomas, and extra-axial hematomas. The distribution of these lesions varies with age such that in older children, lesions are most commonly observed in frontal regions (i.e., dorsolateral frontal, orbitofrontal, and frontal lobe white matter), while in infants and preschoolers common injuries include often intraparenchymal hemorrhage, subarachnoid hemorrhage, and infarct/edema (Ewing-Cobbs et al., 1998). Focal injuries often lead to behavioral deficits related to direct tissue damage as well as to remote mass effects such as midline shift, herniation, and compression of brainstem structures (Ewing-Cobbs, Barnes, & Fletcher, 2003).

Diffuse injuries result from acceleration/deceleration motion and may produce extensive disruption of neurologic function (Geddes, Hackshaw, Vowles, Nickols, & Whitwell, 2001). This acceleration/deceleration motion causes shearing forces that in turn affect interfaces of the brain such as gray matter (GM)-white matter (WM) boundaries. As a result, neuronal axons crossing multiple brain regions are particularly vulnerable to this type of injury. Common locations of injury include the corpus callosum, internal capsule, and fornix (de la Plata et al., 2007; Tasker, 2006). Diffuse injuries commonly lead to widespread microscopic lesions in the cerebral white matter; however, injury can vary from small foci of axonal injury to more widespread injury throughout the brain. As such, the consequences of these white matter injuries vary from mild concussion to prolonged coma (Levin, 2003).

Secondary injuries may develop over a period of hours or days following the initial trauma and are attributable to further cellular damage from effects of the primary injury. More specifically, secondary injuries occur when local or systemic stresses such as cerebral edema (in one or both hemispheres), increased intracranial pressure, excitotoxicity, or hypoxic-ischemic injury cause damage to healthy cells (Bruce, 1995). Recent research has shown that genetic vulnerability may mediate neuronal injury. For example, it has been suggested that carriers of the apolipoprotein E epsilon 4 allele are more likely to have a worse outcome six months post-injury than people who do not carry the allele (Samatovicz, 2000). Finally, TBI sustained in childhood can result in subsequent neurological sequelae including paresis and peripheral neuropathy, movement disorder, residua of associated musculoskeletal injuries, endocrine disturbances, and seizures (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2005).

Factors Mediating Outcome

To date, the majority of studies on pediatric TBI have focused on injury severity as a predictor of outcome. Results have indicated that severity of injury, which is most commonly measured using the Glasgow Coma Scale (GCS), plays a significant role in outcome. The GCS evaluates three components of consciousness: eye opening, motor responses, and verbal responses. Possible scores range from 3 to 15 points with a score of 3-8 indicative of severe injury, 9-12 indicative of a moderate injury, and 13-15 indicative of a mild injury. While the GCS is a useful indicator of acute injury, acute clinical condition is thought to be a less reliable predictor of outcome in children than adults (Donders & Nesbit-Greene, 2004). As a result, additional factors that play a role in recovery have recently been investigated. Though studies addressing these other factors are limited, it has been suggested that factors such as type of injury (i.e., focal or diffuse), age at injury, time since injury, social and family factors, and diversity issues (including socioeconomic status, race, and gender) also play a role in recovery and outcome (Taylor, 2004; Yeates et al., 2005).

Impact of TBI on Functioning

The impact of TBI on brain function and structure can best be conceptualized when factors such as injury severity, age at injury, time since injury, and family and social factors are taken into account. Unfortunately, the majority of studies to date rely primarily on acute injury severity as a predictor of outcome. Additionally, methodological differences among current studies not only make it difficult to compare results between studies but also lead to questions about the external validity of reported results. For example, while premorbid psychiatric disorders are thought to occur in

approximately 33-67% of children with TBI and novel post-injury psychiatric disorders are estimated to affect approximately 54-63% of children with TBI (Max, 2005), children with psychiatric disorders (both premorbid and post-injury) are often excluded from studies. While this leads to less potential confounds, it neglects a significant portion of the TBI population and possibly limits the generalizability of results. Additional methodological concerns are often related to sample characteristics and include differing age ranges, control groups, time since injury, definitions of injury severity, assessments of premorbid functioning, and cognitive measures, as well as differential attrition and the complete lack of a control group.

Cognitive Outcome

While it is well established that moderate to severe TBI often leads to deficits in a range of cognitive functions, the impact of mild TBI on cognitive function remains an area of debate (Satz, Zaucha, McCleary, Light, Asarnow, & Becker, 1997). The most commonly reported deficits following moderate and severe pediatric TBI are impaired attention and memory and slowed processing speed (Yeates et al., 2002). Additional areas of impairment include intellectual function (Catroppa & Anderson, 2003), executive function (Ewing-Cobbs et al., 2004; Levin & Hanten, 2005; Slomine et al., 2002), attention (Donders & Hoffman, 2002), academic achievement (Ewing-Cobbs et al., 2004), motor skills, and language (Catroppa & Anderson, 2004; Levin, Song, Ewing-Cobbs, Chapman, & Mendelsohn, 2001). Longitudinal studies of intellectual (Catroppa & Anderson, 2003) and neuropsychological functions in pediatric TBI (Anderson et al., 2003; Ewing-Cobbs et al., 1998, 2004; Taylor, Yeates, Wade, Drotar, Stancin, & Minich, 2002; Yeates et al., 2002) indicate that recovery occurs rapidly during the first year

following injury but the rate of recovery slows substantially after this, and significant impairments persist. Currently, there is a large degree of heterogeneity in the literature regarding specific neuropsychological deficits related to pediatric TBI. This is likely reflective of variability in factors such as mechanism of injury, age at injury, and time since injury.

With regard to mild TBI, the results of cognitive outcome studies are mixed. A review of the existing studies of mild TBI in childhood and adolescence by Satz and colleagues (1997) indicated that cognitive deficits following mild TBI were generally minimal and did not persist. According to a recent study by Hooper and colleagues (2004), the majority of caregivers report no symptoms in their children ten months post-injury. Given that the majority of children that participated in this study sustained mild injuries, these results appear to be consistent with the claim that mild injuries do not result in persistent cognitive or behavioral deficits. However, the fact that approximately 13% of the mild TBI subjects and 47% of the moderate to severe TBI subjects exhibited cognitive and social deficits that persisted at least ten months post-injury suggests that, in a small proportion of mild injuries, cognitive and behavioral deficits do in fact persist. This is consistent with research on TBI in adults indicating that a small proportion of adults with mild TBI continue to display cognitive and social deficits one year post injury (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005).

Memory

While memory has been shown to improve dramatically in the first year post-TBI, deficits persist one year, three years, and four to five years post-injury (Yeates et al., 2002). The California Verbal Learning Test, Children's Version (CVLT-C) is often used

to assess verbal learning and memory post-injury. Results indicate that brain injury affects memory and learning in a dose-dependent fashion, with severely injured children performing significantly worse than children with mild injuries. Additional predictors of poor outcome include length of coma and neurological findings (Donders & Hoffman, 2002).

Neuroanatomic Correlates of Memory

Memory impairment is most commonly associated with lesions in the frontal and temporal lobes. This is consistent with the role of the frontal and temporal lobes in aspects of memory such as retrieval, recognition, and organization. Additionally, it has been suggested that diffuse injury could disrupt circuits mediating the various components of memory thus leading to impairment (Salorio, Slomine, Grados, Vasa, Christensen, & Gerring, 2005). Studies of the neuroanatomic correlates of memory performance in pediatric TBI have demonstrated that frontal lobe lesion volume is predictive of memory performance (Di Stefano, Bachevalier, Levin, Song, Scheibel, & Fletcher, 2000; Salorio et al., 2005). More recently, Salorio and colleagues (2005) demonstrated that, while frontal and temporal lesion volume predicted memory performance on several measures of memory, extra-frontotemporal lesions were most predictive of memory performance in children with moderate and severe TBI. The authors related this finding to possible diffuse axonal injury, suggesting that this type of widespread injury may result in the disconnection of brain circuits that mediate memory.

Executive Function

The term executive function describes a variety of higher-order processes encompassing cognitive (planning and problem solving), self-regulative, metacognitive,

and social cognitive domains (Levin & Hanten, 2005). Like other neuropsychological functions that continue to develop throughout childhood, executive functions are rather complicated to evaluate in children and adolescents with TBI. The challenges inherent to evaluating children with TBI (i.e., heterogeneous nature of pediatric samples and the diverse developmental trajectories observed in this group) are further complicated by the fact that executive functions continue to develop into late adolescence. Generally, results indicate persistent deficits in multiple areas of executive function including working memory (Levin et al., 2002), inhibition (Leblanc et al., 2005), shifting, decision making, social cognition, and behavioral self-regulation in children with moderate to severe injuries (Levin & Hanten, 2005). Predictors of poorer performance on executive function tasks include younger age at injury, more severe injury, greater extrafrontal lesion volume, and more lesions (Slomine et al., 2002)

Neuroanatomic Correlates of Executive Function

Results of studies of the neuroanatomic correlates of executive function in pediatric TBI are mixed. Frontal lobe lesion volume has been related to some measures of executive function whereas extrafrontal lesion volume has been related to others (Levin et al., 2001). In an alternate study of executive function in children with TBI, results indicated that the volume of extrafrontal lesions and total number of lesions measured at three months post-injury were related to some measures of executive function at one year post-injury (Slomine et al., 2002). Limitations of this study included no control group, limited exploration of predictors of outcome, and a disconnect between the time of testing (one year post-injury) and the time of MRI (three months post-injury).

Attention

While attention and processing deficits are fairly well documented in adult TBI, this is not the case for pediatric TBI. To date, research has primarily focused on the relationship between injury severity and attention skills and has failed to consider developmental factors. Like other neuropsychological functions, attention skills continue to develop throughout childhood. As such, deficits or delays in certain attentional skills may not be evident until the skill is expected to emerge at a certain age, leading to cumulative deficits over time (Dennis, Guger, Roncadin, Barnes, & Schacher, 2001). Results of studies of attention following pediatric TBI have demonstrated deficits in vigilance and selective attention (Dennis et al., 2001), sustained attention (Catroppa & Anderson, 2005), and shifting attention (Catroppa & Anderson, 2005). In a longitudinal study of attentional skills, Catroppa and colleagues (2006) demonstrated that deficits in attention and processing speed persisted up to five years post-injury. Predictors of attention skills post-injury varied for different types of attention and included age at acute assessment (all attention domains), localization of lesion (sustained attention), injury severity (shifting attention), and pre-injury attention skills (divided attention). Selective attention did not vary between groups indicating that this skill was more mature at the time of injury and therefore less vulnerable to detriment. The frequency of attention deficits after a brain injury sustained in childhood or adolescence has led to increased interest in psychiatric sequelae such as Secondary Attention Deficit Hyperactivity Disorder.

Secondary Attention Deficit Hyperactivity Disorder (SADHD) is the term used to describe ADHD that develops after a brain injury. Thus, when evaluating attention skills following TBI in childhood, it is important to differentiate between children with

premorbid developmental ADHD and those children whose symptoms were a direct consequence of their injury. SADHD has been estimated to occur in approximately 19-44% of children who have sustained a brain injury. Studies investigating the development of SADHD following TBI are sparse but suggest that SADHD is more likely to occur following a severe injury (Schacher, Levin, Max, & Purvis, 2004; Wassenberg, Max, Lindgren, & Schatz, 2004). Other predictors of SADHD include high pre-injury psychosocial adversity, low pre-injury adaptive functioning, and a high number of omission errors on tests of attention administered during the acute phase of injury (Wassenberg et al., 2004). Additionally, Schacher and colleagues (2004) demonstrated a relationship between inhibition deficits and SADHD. More specifically, only children with a severe brain injury who subsequently developed SADHD demonstrated a deficit in inhibition. Conversely, children with a severe brain injury that did not develop SADHD as well as children with a mild to moderate injury who developed SADHD did not exhibit this deficit. This suggests that while less severe injury can create a behavioral phenocopy of ADHD, only severe injury results in a true cognitive phenocopy. Results highlight the importance of including a developmental ADHD control group in studies of SADHD (which has not been done to date) as well as the importance of considering pre-injury child and family psychosocial characteristics when predicting outcome of TBI in children.

Neural Correlates of Attention

Studies of the anatomic correlates of attention in children with TBI are limited. Results indicate a relationship between injury in either the thalamus or basal ganglia and the development of SADHD (Gerring et al., 2000). An alternate study of attention

indicated that the amount of injury, irrespective of location, was predictive of poor performance on measures of attention. More specifically, generalized and extrafrontal lesion severity, not frontal lesion severity, were predictive of poor performance (Power, Catroppa, Coleman, Ditchfield, & Anderson, 2007). Results highlight the need for future research in this area as well as the specific need for an investigation into the relationship between diffuse injury and measures of attention.

Language

While basic language skills often remain intact following TBI, difficulties in more complex language processes are often noted (Catroppa et al., 2004; Levin et al., 2001). This has been attributed to the fact that higher-order language skills are dependent on the efficiency of the whole brain and are thereby more vulnerable to insult. Language impairments at the level of discourse are common following TBI and are often related to injury severity. More specifically, research has shown that injury severity is related to impairments in the amount of language produced, amount of information related, organization of information, and global semantic interpretation in children injured between the ages of 5 and 10 years (Chapman, McKinnon, Levin, Song, Meier, & Chiu, 2001). Other predictors of language and literacy skills include pre-injury communication skills, vocabulary skills, SES, and age at injury (Levin et al., 2001).

Neural Correlates of Language

In a longitudinal study of the relationship between word fluency, severity of injury, frontal brain lesions, and age at injury in children with closed head injury, Levin and colleagues (2001) demonstrated that severe head injury was related to poorer word fluency. Growth curve analysis of longitudinal data revealed an interaction between age,

follow-up interval, and severity. In other words, word fluency recovery was the slowest for young children (mean age of 7 years) with severe injury as compared to older children (mean age of 12 years) with severe injury or young children with mild injury. Left frontal lesions were associated with adverse outcome in older children suggesting more established functional commitment of this region in older children. Given the variable and missing follow-up assessments for head injured children and the lack of longitudinal data for controls (cross-sectional data was used), the results of the longitudinal section of this study should be interpreted with caution. However, results demonstrate that outcome on some measures of attention is age dependent, thus highlighting the importance of comparing results within a TBI group (i.e., older children to younger children) and narrowing the age range of participants.

Neuroanatomic Outcome

To date, volumetric studies in pediatric TBI are sparse. Existing studies have revealed enlarged ventricles (Verger et al., 2001; Wilde et al., 2005), generalized atrophy, reduced prefrontal cortical volume (Wilde et al., 2007), reduced hippocampal volume (Di Stefano et al., 2000; Tasker et al., 2002; Wilde et al., 2007), reduced amygdala volume, reduced globus pallidus volume (Wilde et al., 2007), cerebellar atrophy (Spanos et al., 2007), reduced frontal and temporal white matter (Wilde et al., 2007), reduced anterior commissure volume (Wilde et al., 2007), reduced corpus callosum size (Benavidez et al., 1999; Verger et al., 2001), and reduced growth of the corpus callosum over time (Levin et al., 2000).

With the advent of magnetic resonance imaging (MRI), it has become possible to more accurately characterize diffuse axonal injury in pediatric TBI. Volumetric measures

of white matter structures as well as more novel MRI techniques such as DTI, FLAIR, and susceptibility-weighted imaging (SWI) have increased our understanding of how TBI affects WM in the developing brain (Ashwal et al., 2006; de la Plata et al., 2007; Wilde et al., 2006). Additionally, magnetic resonance spectroscopy (MRS) studies have demonstrated differences in brain metabolite ratios/concentrations (despite normal white matter appearance) when children with TBI were compared to controls (Garnett et al., 2000). Volumetric studies of WM have primarily focused on large structures, such as the corpus callosum, that are known to be particularly vulnerable to injury (Levin et al., 2000). While reduced size of the corpus callosum following moderate to severe injury has been reported consistently in the literature, the mechanism for this reduction has yet to be elucidated. Hypotheses for this reduction include increased neuronal loss, thinning of the corpus callosum, and impeded development of the corpus callosum (Benavidez et al., 1999; Wilde et al., 2005). Because the corpus callosum continues to grow into adulthood, it has been hypothesized that injury to this structure at any point during childhood or adolescence may have adverse developmental implications.

Verger and colleagues (2001) examined the relationship between ventricular size, corpus callosum area, and neuropsychological function in children at least six years post-TBI (range: 6-12 years post-injury). Results demonstrated a high correlation between speed of processing (i.e., Trail Making A, reaction time, Benton's Judgment of Line Orientation test, etc) and corpus callosum area. These results are consistent with alternate studies of intelligence that have demonstrated that, unlike other measures of performance ability that improve over time, impairments in processing speed persist (Catroppa & Anderson, 2003). However, it should be noted that the age at the time of injury was quite

variable between subjects (age at injury range: 3-15 years). This variability could have potentially masked the correlation of corpus callosum area with other measures of neuropsychological function (i.e., injury at specific developmental levels could lead to additional neuropsychological sequelae).

Given the traumatic axonal injury and post-traumatic degenerative white matter changes that have been observed in larger white matter pathways, such as the corpus callosum, Wilde and colleagues (2006) investigated anterior commissure and temporal white-matter volumes using MRI in children with moderate to severe TBI. Results revealed decreased anterior commissure and temporal white-matter volumes in children with TBI when compared to typically developing children. These volumes were positive related to each other and positively related to injury severity as measured by the Glasgow Coma Scale. Using this same sample of children with moderate to severe TBI, Spanos and colleagues (2007) demonstrated reduced cerebellar GM and WM volumes in the TBI group when compared to typically developing controls. Furthermore, when children with focal cerebellar lesions were excluded, the WM finding remained. This finding is consistent with animal studies that indicate that the cerebellum is vulnerable to fiber degeneration following traumatic insult. Finally, an additional study utilizing the same sample revealed decreased GM and WM in the superior medial and ventromedial prefrontal regions, decreased WM in the lateral frontal region, and decreased GM and WM in the temporal region when children with moderate to severe injuries were compared to typically developing controls (Wilde et al., 2005).

While studies of WM have focused on specific structures, volumetric studies of cortical GM have primarily focused on more global measures. This is likely related to the

use of region of interest methods in volumetric studies. This method relies on specific a priori hypotheses and, thus, restricts analyses to regions hypothesized to be affected. Histopathological studies have demonstrated that the corpus callosum is particularly vulnerable to diffuse axonal injury, even in the absence of focal injury (Levin et al., 2000). As a result, studies utilizing region of interest techniques in WM have primarily focused on the corpus callosum. In contrast, findings in GM have historically been related to focal lesions and thus provide less information about the specific effects of diffuse injury. Thus, volumetric studies have consistently focused on more global measures of GM integrity such as total GM volume and frontal GM volume.

Recently, findings from adult studies of TBI-related injury have begun to inform volumetric studies in pediatric TBI. Adult studies have demonstrated that deep cortical structures such as the hippocampus, amygdala, and basal ganglia are vulnerable to TBI-related injury. Volume loss in the amygdala, globus pallidus, and hippocampus (Wilde et al., 2007) as well as hippocampal abnormalities have been demonstrated in children with moderate to severe TBI (Di Stefano et al., 2000; Tasker et al., 2005; Wilde et al., 2007). Di Stefano and colleagues (2000) demonstrated a trend toward smaller hippocampal volume when children with moderate to severe TBI were compared to typically developing controls. Recently, Tasker and colleagues (2005) extended this finding, demonstrating that hippocampal abnormality in the right hemisphere was related to factors that reflected the severity of the initial injury and changes in white matter.

Finally, the global findings discussed above (i.e., reduced GM and WM volumes) have led to the investigation of alternate markers of atrophy such as ventricular enlargement and reduced head circumference. Increased total ventricular volume, total

CSF volume, and ventricle-to-brain ratio in children with moderate to severe TBI have been consistently reported in children (Bowen et al., 1997; Wilde et al., 2005) and adults (Bigler, Kurth, & Blatter, 1992, 1993; Bigler, Burr, and Gales, 1994; Bigler, Johnson, and Blatter, 1999; Cullum & Bigler, 1986; Henry-Feugeas et al., 2000; Himanen et al., 2005; Levin, Meyers, Grossman, & Sarwar, 1981). Two studies to date have examined ventricular dilation in children in relation to neuropsychological functioning (Bowen et al., 1997; Verger et al., 2001). Neither study found a significant relationship between ventricular enlargement and cognitive function, though correlations were in the expected direction. However, sample sizes were small (n=5 and n=19, respectively) and ventricle to brain ratios were used. In adults, research has shown that third ventricle volume is the best predictor of functional outcome and diffuse injury (Henry-Fuegas et al., 2000; Ryser, Bigler, & Blatter, 1996). However, to our knowledge, no studies have examined third ventricle volume and lateral ventricle volume separately in children.

While the mechanism of ventricular dilation remains unclear, it has been hypothesized that ventricular enlargement following TBI may be related to atrophy resulting from diffuse injury, to a secondary CSF absorptive deficit, or a combination of the two (Poca et al., 2005). According to Bigler (1999), ventricular enlargement represents a manifestation of hydrocephalus ex vacuo, an indirect measure of cerebral atrophy. Research on children and adults with TBI has indicated that ventricular dilation results from a loss of both gray and white matter, occurs within several weeks following injury, and persists over time (Bigler, 1999; Bowen et al., 1997; Verger et al., 2001; Wilde et al., 2005). It has been hypothesized that nonspecific ventricular change (i.e.,

ventricle to brain ratio) is a reflection of white matter change whereas third ventricle changes may suggest damage to subcortical pathways (Bigler, Johnson, & Blatter, 1999).

In a study that evaluated children with TBI with and without intracranial pressure during the acute stage of injury (ICP) five years post-TBI, decreased head circumference was reported in the TBI with ICP group. Furthermore, head circumference in that group was approximately one standard deviation below typical head circumference and equivalent to children approximately five years younger. The authors concluded that it was likely that brain growth in children with TBI with ICP had been limited or nonexistent since the time of injury five years earlier (Tasker et al., 2005).

The neuroanatomic correlates of cognitive function following TBI have primarily been investigated using lesion volume and location as predictors. Results have shown that the volume and number of extrafrontal lesions is related to impairments in various neuropsychological functions including memory (Di Stefano et al., 2000; Salorio et al., 2005), executive function (Levin et al., 2001; Slomine et al., 2002), and attention (Power et al., 2007).

Longitudinal Neuroimaging Studies

Given that volumetric studies of pediatric TBI are sparse, it is not surprising that even fewer longitudinal studies exist. As discussed above, several neuroimaging studies have evaluated brain morphometry late after injury (i.e., 1-10 years). However, these studies utilized a cross-sectional design such that these same measures of brain morphometry were not obtained in the acute phase of injury. While these long-term follow-up studies are urgently needed, their cross-sectional design does not allow one to predict the degree of change (from the acute phase to more extended follow up) or how

these changes occur (i.e., gradually or rapidly). Furthermore, it has been suggested that since cerebral changes are time-dependent, longitudinal analyses of neuroanatomy are required in order to accurately characterize specific GM and WM changes (Gale, Baxter, Roundy, & Johnson, 2005). The utility of longitudinal designs has been demonstrated in studies of neuropsychological, academic, and behavioral outcome. Specifically, the results of these studies have allowed researchers to describe the general recovery process from the acute phase of injury up to five years post-injury as well as factors that mediate outcome. Therefore, longitudinal studies are needed in order to better characterize the morphometric changes that result from pediatric TBI.

One longitudinal study to date examined the corpus callosum in children with mild to moderate (n=28) and severe (n=25) head injury at three months and three years post-injury (age range: 5-15 years). Results revealed a reduction in the area of the corpus callosum in children with severe TBI between three and 36 months post-injury and an increase for the mild to moderate group during this same time period. The rate of growth for the mild to moderate group was consistent with the findings reported for healthy children. Corpus callosum area was significantly correlated with severity of injury and functional outcome at three years post-injury (Levin et al., 2000). While this study highlights the importance of longitudinal neuroimaging studies, limitations included a wide age range (5-15 years) and the lack of a control group.

Given the lack of both volumetric studies and longitudinal studies, the purpose of the current study is to: 1) examine anatomic differences between children with TBI and controls in the semi-acute phase of injury; 2) determine how TBI affects the brain over time (between Time 1 and Time 2); and 3) determine how brain structure is related to

cognitive function in pediatric TBI. Based on results from prior neuroimaging studies, the following hypotheses were generated: 1) children with TBI will demonstrate enlarged ventricles when compared to controls in both the semi-acute (time one) and chronic (time two) phases of injury; 2) children with TBI will demonstrate significantly larger lateral ventricle volume and third ventricle volume at time two as compared to time one; 3) ventricular enlargement will predict cognitive function at time two.

METHODS

Participants

Pediatric patients admitted to local hospitals for a head injury (n=38) were recruited from Carrie Tingley Hospital (CTH) and UNM Health Sciences Center Children's Hospital. All patients had a GCS score at admission of <13, or a GCS of 13-15 and some proven radiological abnormality related to the recent TBI event. Participants in the TBI group ranged in age from 6.22 years to 18.84 years (mean age: 13.69 years). Exclusion criteria included penetrating TBI, pre-existing neurological disease, schizophrenia, hypertensive encephalopathy, CNS infection, chronic metabolic disturbance, hepatic failure, uremia, kidney transplant, uncontrolled diabetes, and neuroleptic drug use. Additionally, subjects who were unable to safely undergo an MR examination (due to factors such as pregnancy or metal or electronic implants) were excluded. Children in the brain injured group were enrolled as soon as possible after their initial trauma.

The participants were 50% Hispanic, 45% White, 2.5% Black, and 2.5% Native American, reflecting local demographics. Participants were both male and female; however, given the epidemiology of brain injury, males dominated the TBI group (31 males, 7 females). All participants were native English speakers (i.e., spoke English as their first language). Information about previous episodes of TBI, concomitant illness, neuroleptic drug use, hepatic and renal disease, acute metabolic disturbance, family support, family finances, depression, anxiety, concomitant musculoskeletal injury, and pain were collected from family members (generally, the parent), the patient, the medical record, physical examination, and/or drug screen (as appropriate).

Control children (n=34) were recruited from the University of New Mexico subject pool, local private schools, recruitment flyers posted at UNM Hospital, and children and relatives of children treated at Carrie Tingley Hospital. Control children ranged in age from 6.88 years to 18.96 years (mean age: 14.05 years) and their ethnicity reflected the local demographic as described above. Given the overrepresentation of males in TBI samples, slightly more boys were recruited than girls resulting in 20 boys and 14 girls in the control group. In addition to the exclusion criteria listed above, control children with a history of head trauma were excluded. Informed consent was obtained from the parents or guardians of the participating children in accordance with the guidelines set forth by the Human Research Review Committee at the University of New Mexico. An assent form was provided for children seven years and older.

Procedures

All children in the brain injured group were assessed within 4.2 months of injury (mean time to initial assessment: 54.6 days). Additionally, 21 of the 38 (55%) children in the brain injured group were assessed a second time (mean time to second assessment: 324 days). Assessment at each time point included a battery of cognitive tests and an MR exam.

Cognitive Measures

The cognitive battery included measures of general cognitive ability (Wechsler Abbreviated Scale of Intelligence: Vocabulary, Similarities, Block Design, and Matrix Reasoning subtests), selective and sustained attention (Conners' Continuous Performance Test), verbal learning and memory ([CVLT-C]; Test of Memory and Learning [TOMAL]: Story Memory subtest), visual memory (TOMAL Facial Memory, Visual

Selective Reminding) verbal and nonverbal working memory (Spatial Span and Wechsler Intelligence Scale for Children, Third Edition [WISC-III]: Digit Span and Arithmetic subtests), rapid information processing (WISC-III: Coding and Symbol Search subtest; Trail Making Test, Parts A and B), verbal and nonverbal fluency (Controlled Oral Word Association Test [COWAT]; Design Fluency Test), executive functioning (Wisconsin Card Sorting Test [WCST]; Stroop Test), graphomotor skills (Beery-Buktenica Test of Visual-Motor Integration [VMI]), visuospatial processing (Judgment of Line Orientation; Facial Recognition Test) and motor skills (Grip Strength; Grooved Pegboard; Finger Tapping). The Wide Range Achievement Test, Third Edition—Reading subtest (WRAT3-R) was used to provide an estimate of premorbid intellectual ability. Cognitive tests were selected in order to provide a comprehensive view of neuropsychological function. Additionally, either the Galveston Orientation and Amnesia Test (GOAT; Levin, O'Donnell, & Grossman, 1979) or the Children's Orientation and Amnesia Test (COAT; Ewing-Cobbs, Levin, Fletcher, Miner, & Eisenberg, 1990) was administered to TBI subjects prior to the initial cognitive evaluation to assess each child's readiness for testing. Unfortunately, not all subjects were able to complete all of the above mentioned tests. As a result, many of these tests were excluded from analyses due to small sample sizes. The tests discussed below were administered to a large number of participants and were included in analyses of neuropsychological function.

Wide Range Achievement Test, Third Edition (WRAT-3; Wilkinson, 1993): Reading subtest

The reading subtest of the WRAT is a test of single-word reading normed by age and grade. The WRAT has well-established reliability and validity and is considered a useful measure of premorbid intellectual function in brain injured individuals.

Controlled Oral Word Association (COWA; Benton & Hamsher, 1994)

The COWA is a measure of verbal fluency normed by age in which a child is asked to generate as many words as possible in one minute that begin with a specific letter and then generate as many words as possible that belong to a certain category (i.e., animals). Verbal fluency is correlated with measures of vocabulary, auditory attention, and long-term verbal memory (Ruff, Light, Parker, & Levin, 1997).

Grooved Pegboard Test (Klove, 1963)

The Grooved Pegboard Test is a measure of hand-eye coordination normed by age. It requires the subject to place 25 pegs (or 10 for children under 9 years) in a pegboard as fast as they can with both their dominant and non-dominant hands.

Grip Strength Test

The Grip Strength Test is normed by age and identifies differences in hand strength by measuring the force exerted for each hand over two trials. Both Grooved Pegboard and Grip Strength are sensitive to lateralized injury (Lezak, 1995)

Digit Span (Wechsler, 1991)

Digit Span is a subtest of both the Wechsler Intelligence Test for Children (WISC-III) and is the most commonly administered test of auditory working memory. It consists of two different tests: Digits Forwards and Digits Backwards. Digits Forwards and Digits Backwards each consist of seven pairs of random numbers sequences that the examiner reads aloud to the subject. In digits forward, the subject is asked to repeat the

digits in the same order whereas in digits backwards, the subject is asked to repeat them in reverse order. Digit span tests are normed by age and are sensitive to a wide variety of neurological impairments (Lezak, 1995).

Spatial Span (Wechsler, 1987)

Spatial span is a measure of spatial working memory in which ten cubes are attached to a board in an irregular pattern. The subject is required to touch blocks in the same order that the experimenter touched them (both forwards and backwards). Research has shown that spatial span tests are sensitive to a wide variety of neurological impairments (Lezak, 1995). Unfortunately, no normative data is available for children. As such, we used the raw scores obtained by the control group to calculate the mean and standard deviation for spatial span forward (mean: 8; SD: 1.80) and spatial span backward (mean: 8; SD: 1.97). These means and standard deviations were used to calculate T-scores for participants in the control and TBI groups.

Trail Making Test, Parts A and B (TMT)

The Trail Making Test (TMT) is a test of processing speed (Part A) and executive function (Part B) normed by age. In Part A, the subject must first connect circled numbers in sequential order. In Part B, the subject must connect circled numbers and letters by alternating between the two (1-A-2-B-3-C). Given the involvement of motor speed in the TMT, it has been shown to be vulnerable to brain injury.

Tests of Memory and Learning (TOMAL): Memory for Stories and Facial Memory subtests (Reynolds and Bigler, 1994)

The TOMAL is an age-normed comprehensive test of memory assessing both verbal and nonverbal memory. Two subtests, each with a delayed memory component,

were included in this battery. In memory for stories, participants are read a story and then asked to retell the story to the examiner (immediate recall). After a delay, they are again asked to retell the same story to the examiner. The facial memory subtest requires participants to recognize previously seen faces from a set of distracters. The TOMAL is appropriate for children between the ages of 5 years and 19 years.

Hopkins Verbal Learning Test (HVLT-R; Brandt and Benedict, 2001)

The HVLT is a brief verbal test of learning and memory. The HVLT-R tasks include three learning trials, a delayed recall trial (20-25 minute delay), and a yes/no delayed recognition trial. The HVLT-R has high test-retest reliability, and its construct, concurrent, and discriminant validity have been well established. Unfortunately, normative data is not available for children under the age of 16 years. As such, we used the raw scores obtained by the control group to calculate the mean and standard deviation for immediate recall (mean: 24, SD: 5.08), delayed recall (mean: 9, SD: 5.02), percent retention (mean: 89, SD: 16.66) and recognition (mean: 11; SD: 1.26). These means and standard deviations were used to calculate T-scores for participants in the control and TBI groups.

Beery-Buktenika Developmental Test of Visual Motor Integration (VMI)

The VMI is an age-normed test of visual-motor integration (VMI), visual perception (VMIV-P), and visual motor (VMIM-C) skills. On the VMI, the subject is asked to draw increasingly complex figures. These same figures are then used in visual perception and motor tests to help determine how visual and fine motor problems separately contribute to the overall score.

Neuropsychological Composites

Given both the wide age range (6-18 years) and variable cognitive abilities due to injury severity in our sample, most participants were missing at least one data point. As such, three different composites were computed in order to account for this missing data. The executive composite was comprised of measures of working memory (Digit Span; Spatial Span Forward; Spatial Span Backward), executive function (Trail Making Test, Parts A & B), verbal fluency (COWA), and visual perception (VMIV-P). Despite the fact that the VMIV-P is commonly included in batteries assessing visual-motor skills, we chose to include it in the executive composite because it can also be logically construed as a test of visual perception and/or attention as it does not include a motor component. The motor composite was comprised of tests of motor function (Grooved Pegboard; Grip Strength). Finally, the memory composite was comprised of tests of verbal and nonverbal immediate and delayed memory recall (HVLT; TOMAL: Memory for Stories & Facial Memory).

Image Acquisition

All participants were scanned on a 1.5 Tesla MR scanner at the MIND Imaging Center. The protocol was a T_1-weighted volume axial series (fast-SPGR, TE=6.9ms, TR=17.7ms, flip=25, 3mm slice) and a T_2-weighted axial series (TE=30/100, TR=2800ms, 3mm slices). Participants were scanned on either a GE machine or a Siemens machine. Twenty-eight slices were acquired per participant; as such, scans did not always encompass the whole brain.

Image Analysis

Magnetic resonance imaging (MRI) data was analyzed using ANALYZE version 6.0 and Statistical Parametric Mapping Version 2 (SPM2, Wellcome Department of

Cognitive Neurology, Institute of Neurology, London) running MATLAB version 6.5. Images were converted into a three-dimensional volume (ANALYZE 7.5 format) using ANALYZE version 6.0. Given the fact that whole brain data was not acquired, it was necessary to ensure that each participant's scan encompassed the same brain areas. In order to accomplish this, the anterior commissure was identified in each scan in the axial view and the slice number where the anterior commissure was located was recorded (Figure 1). Given the differences in scans, the lowest slice where the anterior commissure was located was slice six and the highest slice was slice fifteen. Thus, since each participant had 28 slices, it was determined that the scans should encompass six slices below the anterior commissure and fifteen slices above the anterior commissure (in order to ensure uniformity across subjects). Slices located more than six slices below or fifteen slices above the anterior commissure were deleted. This resulted in a total of 21 slices per participant. The lateral ventricles and third ventricles were entirely visible in these 21 slices (Figure 2).

Figure 1: Axial view of the anterior commissure.

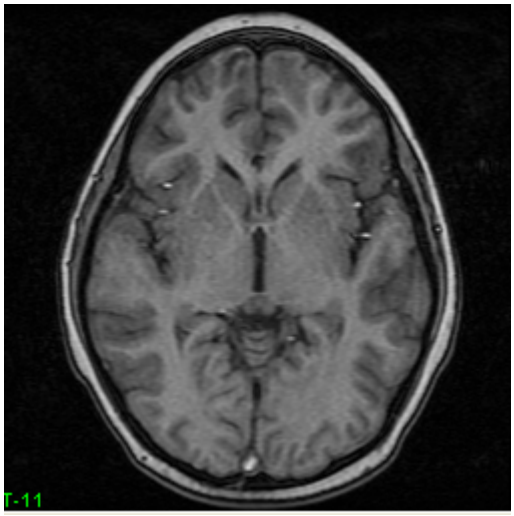
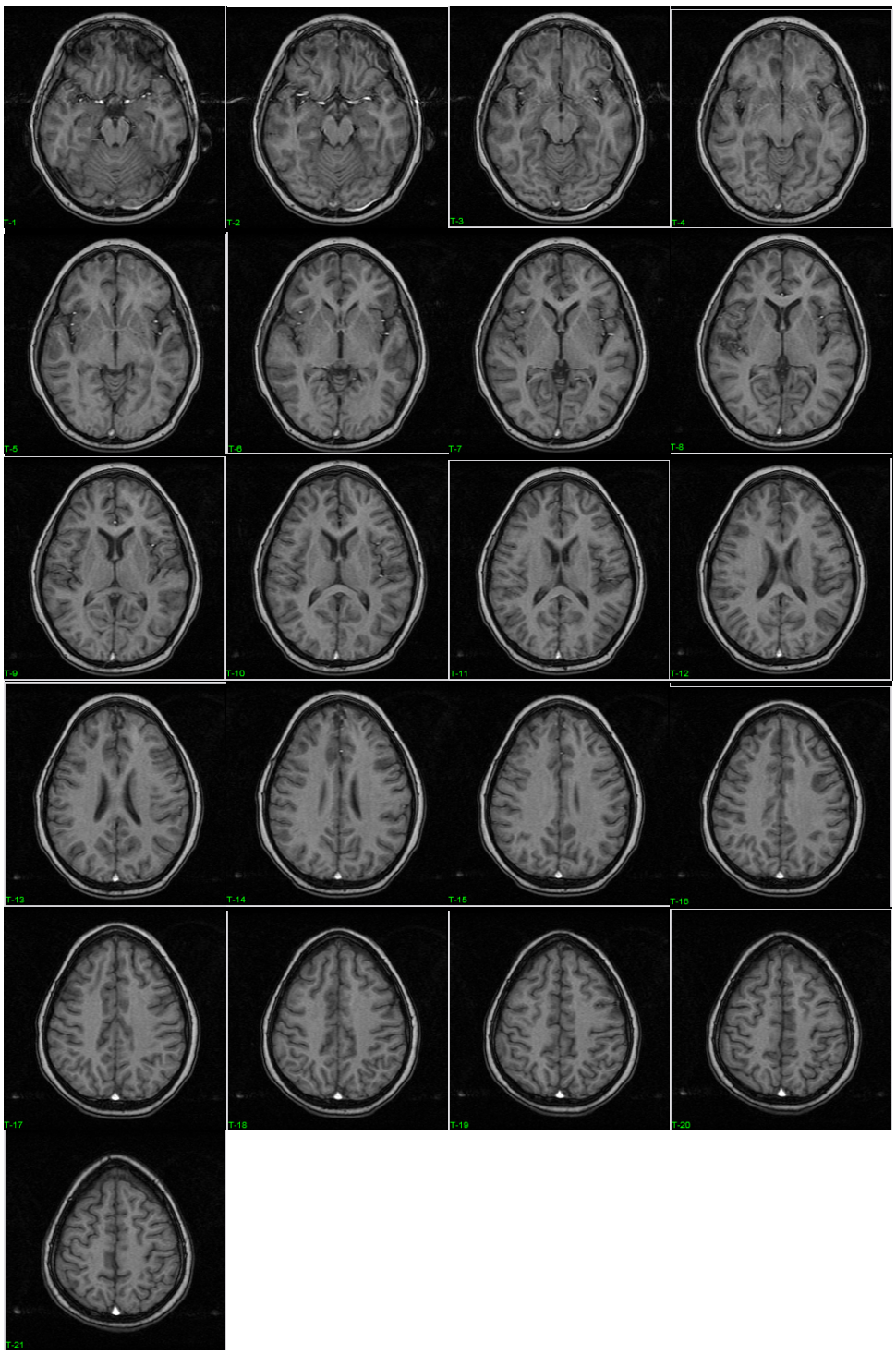


Figure 2: Representative brain showing all 21 axial slices included in the analyses.



Images were then loaded into SPM in order to use voxel-based morphometry (VBM) to perform tissue segmentation. In VBM, tissue segmentation is achieved through a combination of the use of Bayesian Priors (the use of probability images to define starting estimates to partially classify each voxel) and a discrimination analysis that operates on the basis of voxel intensities (Lagopoulos, 2007). This segmentation process results in the creation of a separate structural image for each tissue class (i.e., gray matter (GM), white matter (WM), and cerebral spinal fluid (CSF)). Using these separate structural images, total GM and WM volumes were calculated for each participant. The resulting total GM and WM volumes were summed to obtain total brain volume for each participant. It is important to note that total brain volume for this study represents partial brain volume (approximately 80% of total brain volume).

In order to obtain ventricle volumes, the CSF structural image was loaded into ANALYZE 6.0. Manual tracings of the lateral ventricles and third ventricles were performed using ANALYZE trace and editing tools (Figures 3 and 4). Finally, once manual traces were complete, pixels were summed for each measurement in order to obtain total lateral ventricle volume and total third ventricle volume (mm^3).

Figure 3: Axial view of the lateral ventricles.

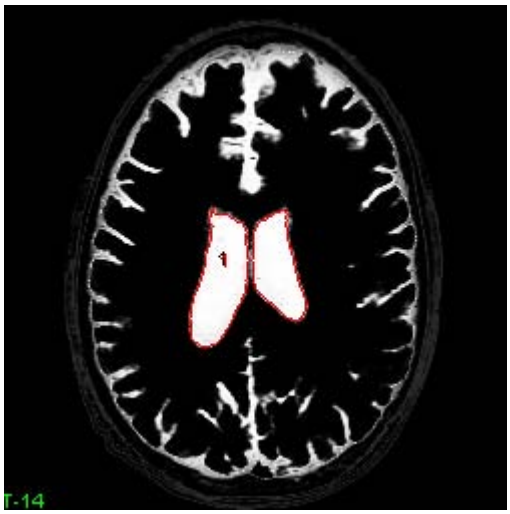
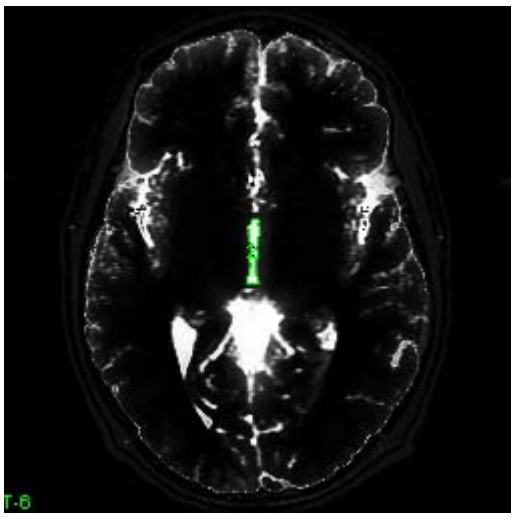


Figure 4: Axial view of the third ventricle.



Statistics

Demographics

Independent samples t-tests were performed to determine if group differences existed between the control group and the TBI group for demographic (age and sex) and clinical variables (total GM volume, total WM volume, and WRAT Reading Score). In order to determine if differences in age, sex, or days post injury were related to ventricular volume or neuropsychological function in the TBI group, simple correlations were performed. Additionally, in order to determine if there was a significant effect of age on ventricle volume or neuropsychological function, the TBI group was broken down into two small groups based on age. Given the size of our sample and the distribution of ages, participants between the ages of six years and twelve years were assigned to the young group (n=12), participants between the ages of sixteen years and eighteen years were assigned to the old group (n=11), and participants between the ages of thirteen years and fifteen years were eliminated for the purposes of this specific analysis.

Group Differences at Times One and Two

In order to determine if significant differences existed between the control group and the TBI group in the semi-acute (Time 1) and chronic (Time 2) phases of injury, independent samples t-tests were performed on clinical variables at each time point. Clinical variables included executive composite, memory composite, motor composite, lateral ventricle volume, and third ventricle volume. To examine the relationship between neuropsychological composites and clinical features, neuropsychological composites were correlated with ventricle volumes and GCS in each group. Additionally, the

neuropsychological composites were broken down into individual tests to determine how each test correlated with clinical features.

Time Two Analyses (TBI Group Only)

Similarly, we were interested in the relationship between measures of injury severity and neuroanatomical integrity and measures of neuropsychological function in the chronic phase. As such, simple correlations between GCS, ventricular volume, and neuropsychological composites were calculated.

TBI Group Analyses

The TBI group was divided into two groups based on GCS score (mild/moderate: GCS=8-15; severe: GCS=<8). Independent samples t-tests were conducted to determine if significant differences existed between the mild/moderate group and the severe group in terms of neuropsychological function or ventricular volume at each time point.

Longitudinal Analyses

Independent samples t-tests were conducted within the TBI group to determine if there was a difference between participants with only one data point and those that participated in the longitudinal part of the study. Variables examined included age, sex, GCS, days post injury, lateral ventricle volume, third ventricle volume, executive composite, memory composite, and motor composite. Paired t-tests were conducted to quantify changes in ventricle volumes and neuropsychological composites over time.

Predictors of Function at Time Two

Simple correlations between GCS, lateral ventricle volume at time one, and third ventricle volume at time one, and neuropsychological composites at time two were conducted to determine predictors of neuropsychological function approximately eleven

months post injury. Additionally, multiple regression analyses were conducted to evaluate how well clinical features at time one predicted neuropsychological function at time two. Similarly, partial correlations between lateral ventricle volume at time one, third ventricle volume at time one, and GCS with executive composite at time two (controlling for executive composite at time one) were performed in order to look at predicted improvement.

RESULTS

Demographics

The traumatic brain injury group consisted of 38 children who had sustained mild to severe traumatic brain injury (Glasgow Coma Scale score = 3-15; mean=9.00, SD=4.92; Tables 1 & 2). The control group was made up of 34 children matched for age. No significant between group differences were found for age (Control: 14.1 years; TBI: 13.7 years; t(70) = .457, p=.649) or WRAT Reading T-Score (Control: 51; TBI: 47; t(39) = 1.24, p=.222); however, a significant difference was found for sex (Control: 59% males; TBI: 82% males; t(70) = 2.160, p=.034; Table 3). The sex difference observed in this study is consistent with the results of other studies which report an overrepresentation of males in traumatic brain injury samples. A significant group difference was found for partial GM volume (Control: 539.4; TBI: 501.2; t(70)=2.825, p=.006). No significant group difference was found for partial WM volume (Control: 312.99; TBI: 296.89; t(70)=1.719, p=.090). Further analyses were conducted to determine if differences in age, sex, or days post injury were related to ventricular volume or neuropsychological composites in the TBI group (Tables 4 and 5). Results revealed no significant correlations between ventricular volume and age, sex, or days post injury. A statistically significant correlation was found between age and executive composite in the TBI group (r=-.382). Similarly, in the control group, the correlation between age and executive composite was in the same direction (r=-.362). However, when age was controlled in future analyses, the results were unchanged. As such, age, sex, and days post injury were ignored in subsequent analyses. Additionally, when the TBI group was broken down into two small groups based on age (young verses old),

results revealed no significant differences in ventricle volume or neuropsychological function at time one or time two.

Table 1: Demographics and clinical features of TBI group.

Variable	TBI	
	n=38	
	Mean	SD
Time to first assessment (days)	54.61	36.80
Time to second assessment (days)	323.90	174.24
GCS[a]	9.00	4.92

[a]GCS=Glasgow Coma Scale Score

Table 2: Age distribution of participants in the TBI group.

Age (in years)	# of TBI Subjects
6	2
7	1
8	0
9	2
10	3
11	1
12	3
13	6
14	5
15	4
16	7
17	3
18	1

Table 3: Demographics of typically developing control and TBI groups.

Demographic	Control		TBI		Statistics		
	n=34		n=38				
	Mean	SD	Mean	SD	t	df	p
Age (years)	14.05	3.48	13.69	3.19	.457	70	.649
Sex					2.160	70	.034
Female (%)	41		18				
Male (%)	59		82				
GM Volume (mm^3)	539.40	52.62	501.20	61.14	2.825	70	.006
WM Volume (mm^3)	312.99	40.79	296.89	38.68	1.719	70	.090
WRAT-R[a] (T-Score)	51.17	11.77	47.00	9.09	1.24	39	.222

[a]Wide Range Achievement Test, Third Edition, Reading Subtest

Table 4: Correlations of age, sex, days post injury, and GCS with time 1 ventricle measures.

Variable	Control		TBI	
	n=34		n=38	
	LV1[b] (mm^3)	TV1[c] (mm^3)	LV1[b] (mm^3)	TV1[c] (mm^3)
Age (years)	.182	.263	.261	.058
Sex	-.200	-.068	-.260	-.356
Days Post Injury	-	-	-.082	-.048
GCS[a]	-	-	-.341*	-.361*

[a]GCS=Glasgow Coma Scale Score
[b]LV1=Lateral Ventricle Volume, Time 1
[c]TV1=Third Ventricle Volume, Time 1
*=p<.05
**=p<.01

Table 5: Correlations of age, sex, and days post injury with time 1 neuropsychological composites.

Demographic	Control			TBI		
	n=34			n=38		
	Cog[a]	Mem[b]	Mot[c]	Cog[a]	Mem[b]	Mot[c]
Age (years)	-.362*	.188	-.343*	-.382*	.168	.042
Sex	.038	.348*	.341*	.283	.204	.149
Days Post Injury	-	-	-	.042	.149	-.432*

[a]Cog=Executive composite, Time 1
[b]Mem=Memory Composite, Time 1
[c]Mot=Motor Composite, Time 1
*=p<.05
**=p<.01

Reliablity

The extremely high correlation between lateral and third ventricle measures at time one and lateral and third ventricle measures at time two (0.982** and 0.833**, respectively) supports the reliability of these measurements.

Group Differences (Controls versus TBI) at Time 1

As predicted, when the control group was compared to the TBI group , significant differences were found for lateral ventricle volume ($t(70) = -4.397$, $p<.001$), third ventricle volume ($t(70) = -6.777$, $p<.001$), executive composite ($t(68) = 5.293$, $p<.001$), memory composite ($t(64) = 4.224$, $p<.001$), and motor composite ($t(65) = 4.519$, $p<.001$). Specifically, ventricle volumes were significantly greater and neuropsychological composites were significantly lower for the TBI group as compared to controls (Tables 6 and 7). Although we were unable to compute total brain volume for each participant, we did compute partial brain volume. The correlation between the ratio of lateral ventricle volume to total brain volume and raw lateral ventricle volume was very high ($r=0.98$). Similarly, the correlation between the ratio of third ventricle volume to total brain volume and raw third ventricle volume was also very high ($r=0.98$).

Table 6: Composite scores for neuropsychological data in control and TBI groups at time one.

Clinical Feature	Control		TBI		Statistics		
	n=34		n=38				
	Mean	SD	Mean	SD	t	df	p
Executive composite	51.11	5.15	38.42	13.05	5.293	68	.000
Memory Composite	55.69	7.18	45.91	11.18	4.224	64	.000
Motor Composite	51.76	6.25	43.39	8.73	4.519	65	.000

Table 7: Ventricles measures (mm3) for control and TBI groups.

Clinical Feature	Control		TBI		Statistics		
	n=34		n=38				
	Mean	SD	Mean	SD	t	df	p
LV[a] (mm^3)							
Time 1	12506.42	4151.20	21657.27	11474.42	-4.397	70	.000
Time 2			20325.98	11197.79			
TV[b] (mm^3)							
Time 1	469.04	126.57	1012.58	451.75	-6.777	70	.000
Time 2			900.70	327.74			

[a]LV=Lateral Ventricle Volume
[b]TV=Third Ventricle Volume

To examine the relationship between neuropsychological composites and clinical features, neuropsychological composites were correlated with ventricle volumes and GCS in each group (Table 8; Figures 5-10). Results were considered significant at $p<.05$. The results of the correlational analyses presented in Table 7 show no statistically significant correlations in the control group. However, in the TBI group, the executive composite was significantly correlated with GCS, lateral ventricle volume, and third ventricle volume. When the executive composite was broken down by individual test, results indicated that verbal fluency, Trails A, and Trails B were significantly correlated with GCS, lateral ventricle volume, and third ventricle volume. Digit span total was significantly correlated with lateral and third ventricle volumes, while spatial span forward and backward were significantly correlated with GCS. The test of visual spatial perception (i.e., VMI: visual perceptual) was the only test included in the executive composite that did not correlate with GCS, lateral ventricle volume, or third ventricle volume. Additionally, the motor composite was significantly correlated with third ventricle volume. When the motor composite was broken down into individual tests, results revealed a statistically significant correlation between third ventricle volume and VMI Motor Performance. Pegboard and grip strength scores were not correlated with ventricle volumes or GCS.

Table 8: Correlation of neuropsychological composites with GCS and ventricle measures (mm3) at time 1.

Demographic	Control			TBI		
	n=34			n=38		
	Cog[d]	Mem[e]	Mot[f]	Cog[d]	Mem[e]	Mot[f]
GCS[a]	-	-	-	.542**	.207	.186
LV1[b]	.099	-.217	-.161	-.641**	-.287	.216
TV1[c]	-.048	.012	-.13	-.533**	-2.92	-.359*

[a]GCS=Glasgow Coma Scale Score
[b]LV1=Lateral Ventricle Volume, Time 1
[c]TV1=Third Ventricle Volume, Time 1
[d]Cog=Executive composite, Time 1
[e]Mem=Memory Composite, Time 1
[f]Mot=Motor Composite, Time 1
*=p<.05
**=p<.01

Figure 5: Relationship between lateral ventricle volume and executive composite at time one in TBI group.

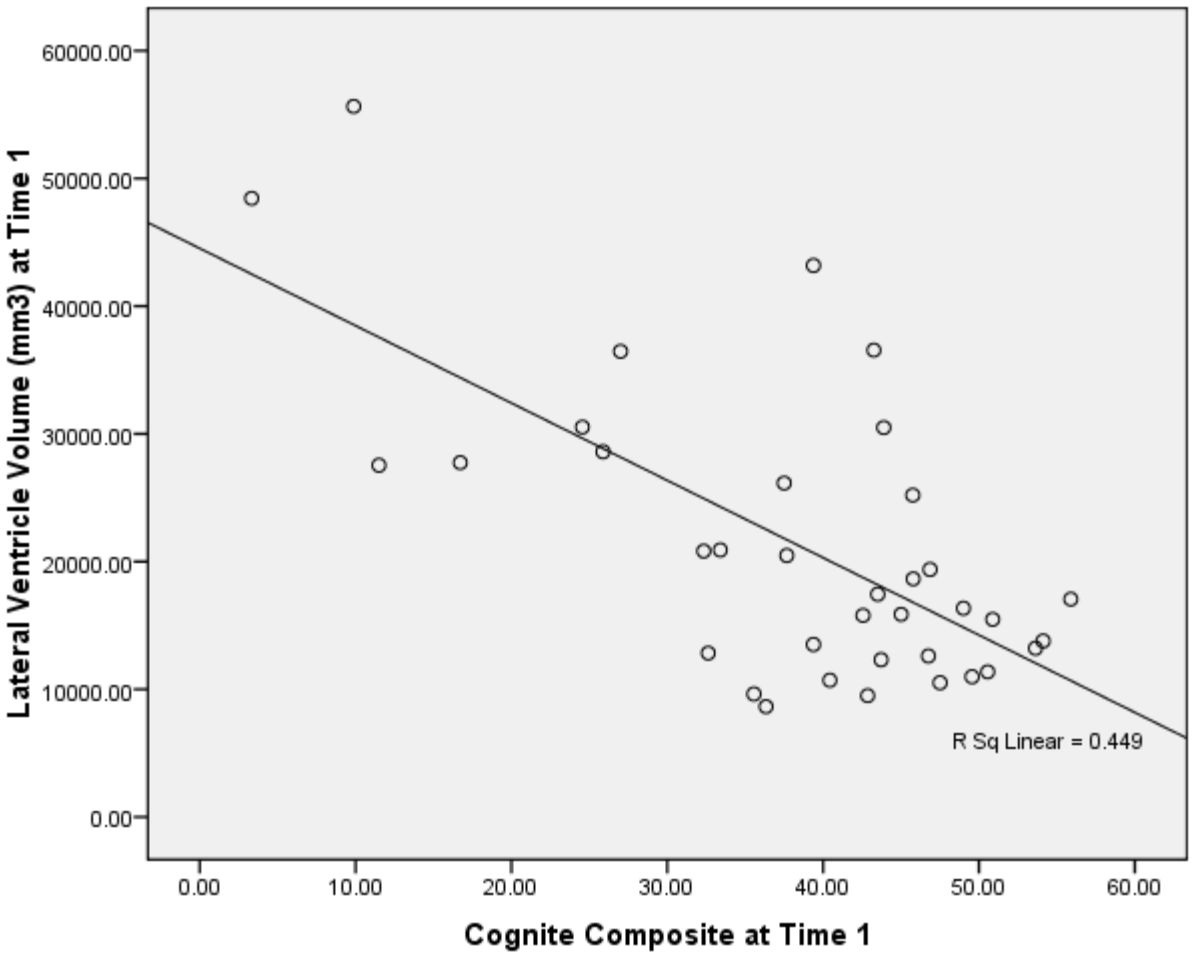


Figure 6: Relationship between lateral ventricle volume and memory composite at time one in TBI group.

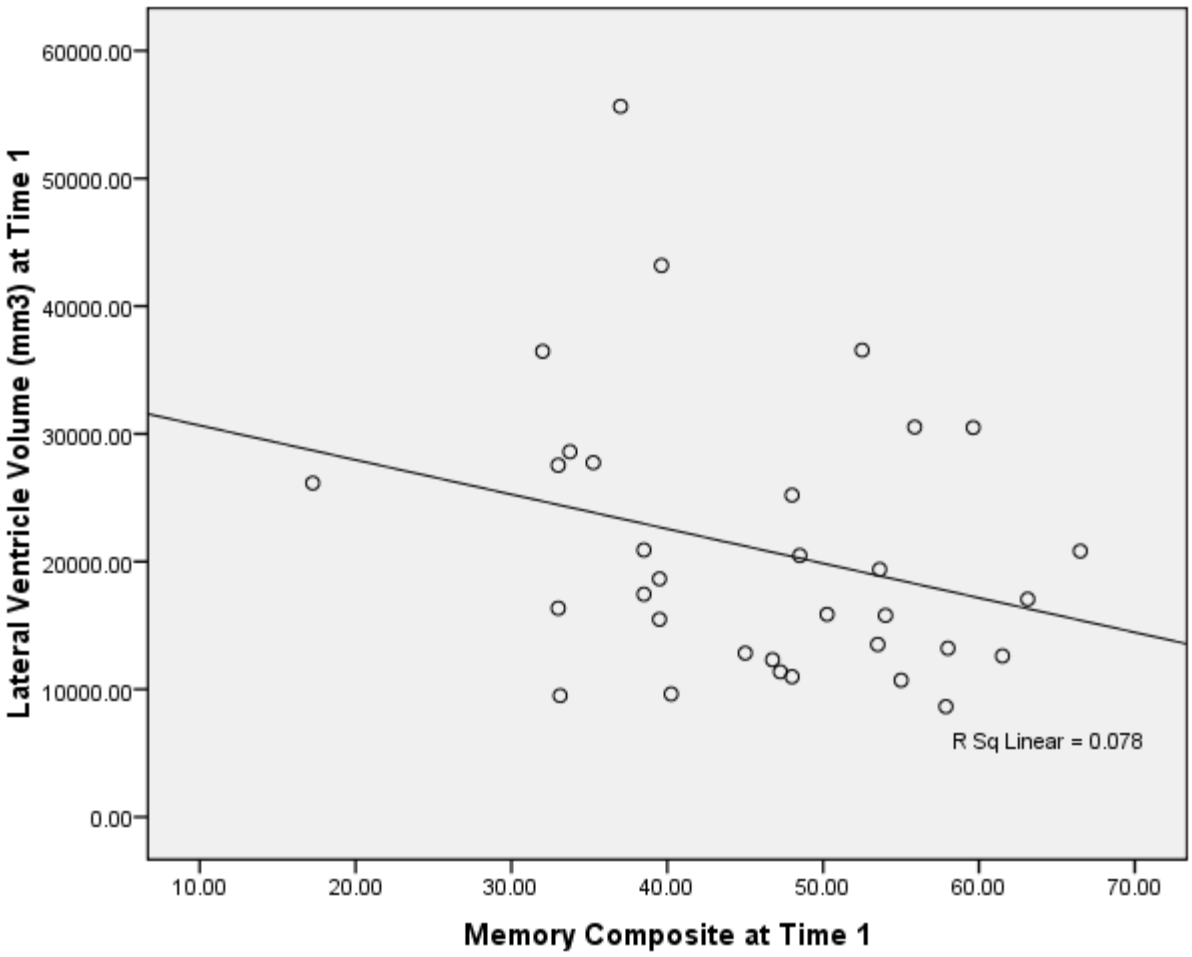


Figure 7: Relationship between lateral ventricle volume and motor composite at time one in TBI group.

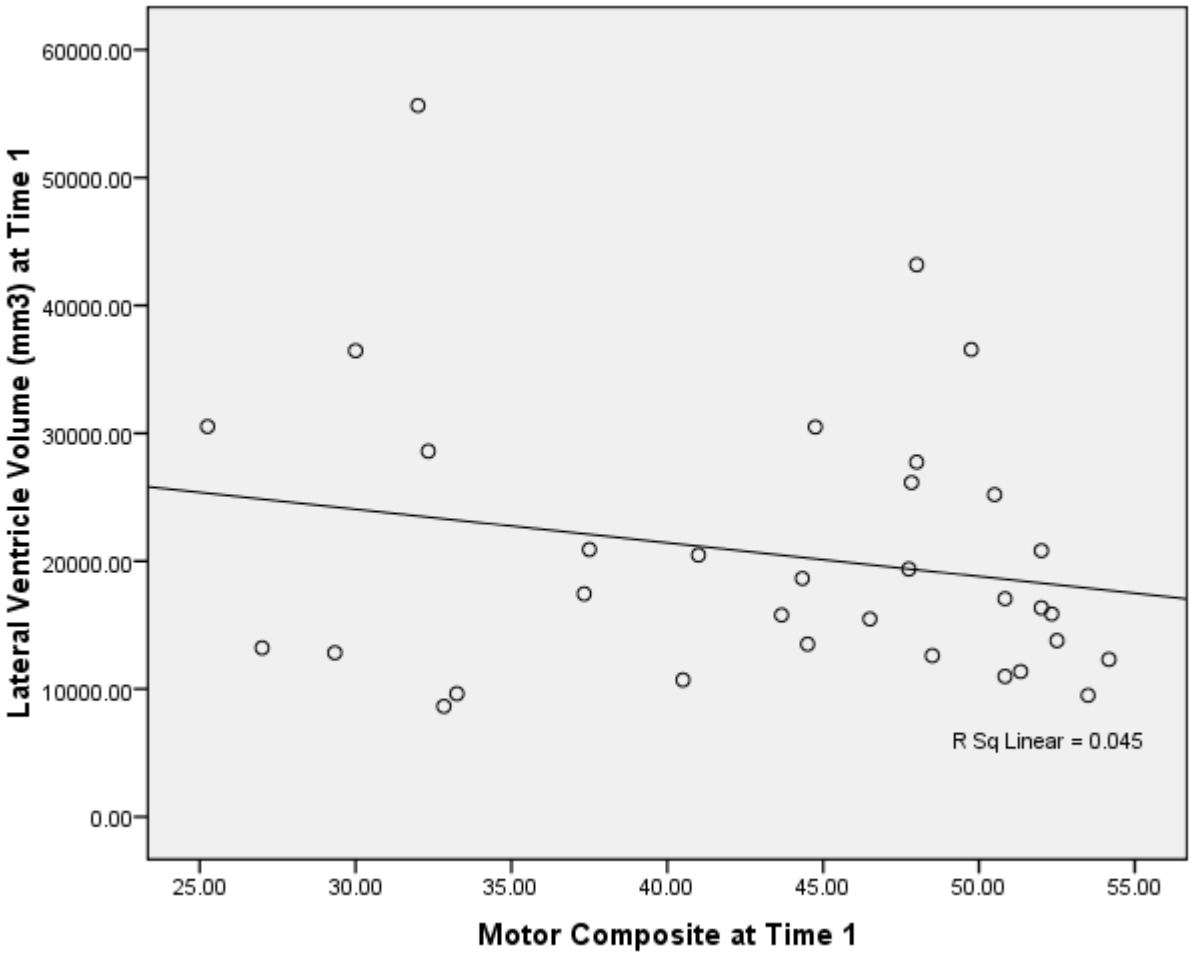


Figure 8: Relationship between third ventricle volume and executive composite at time one in TBI group.

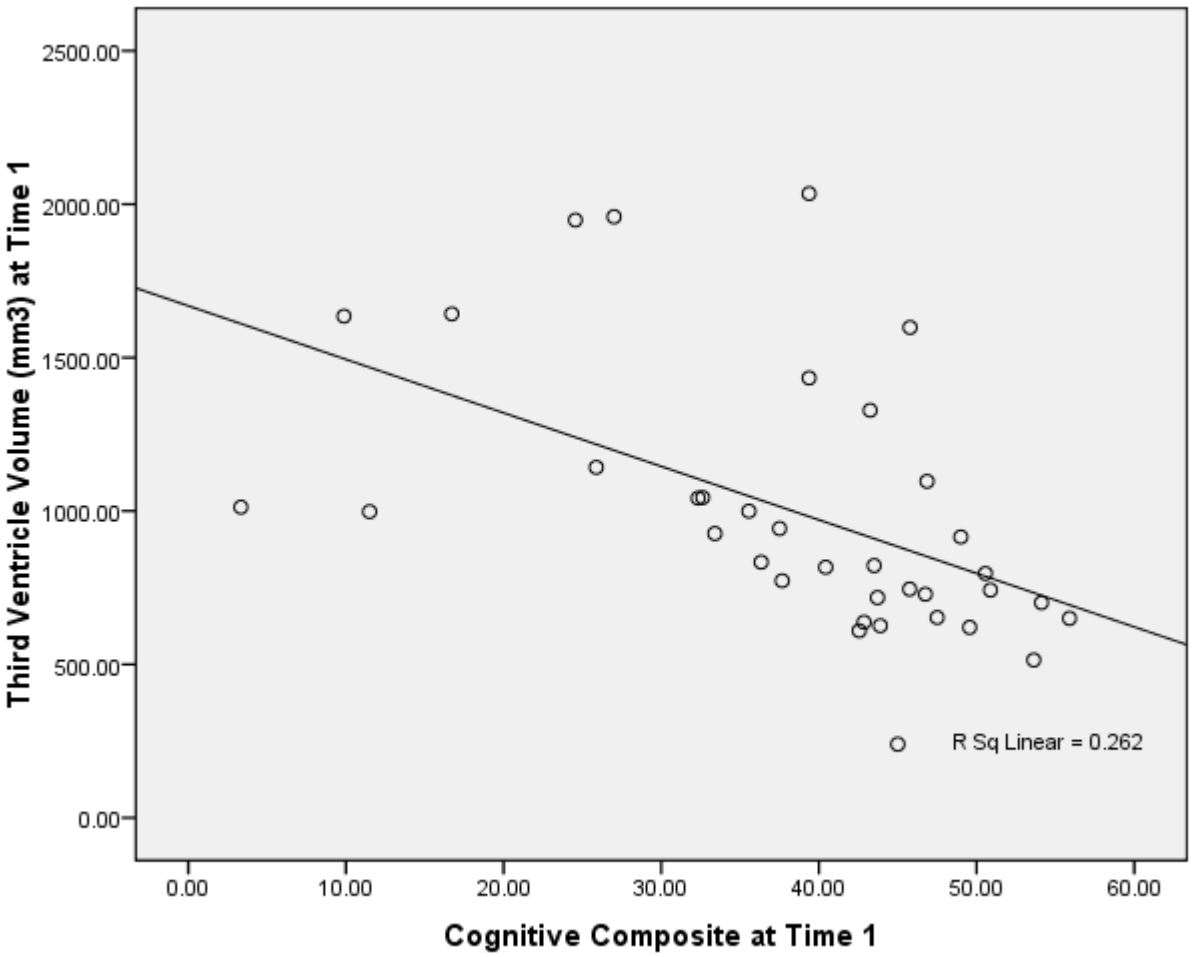


Figure 9: Relationship between third ventricle volume and memory composite at time one in TBI group.

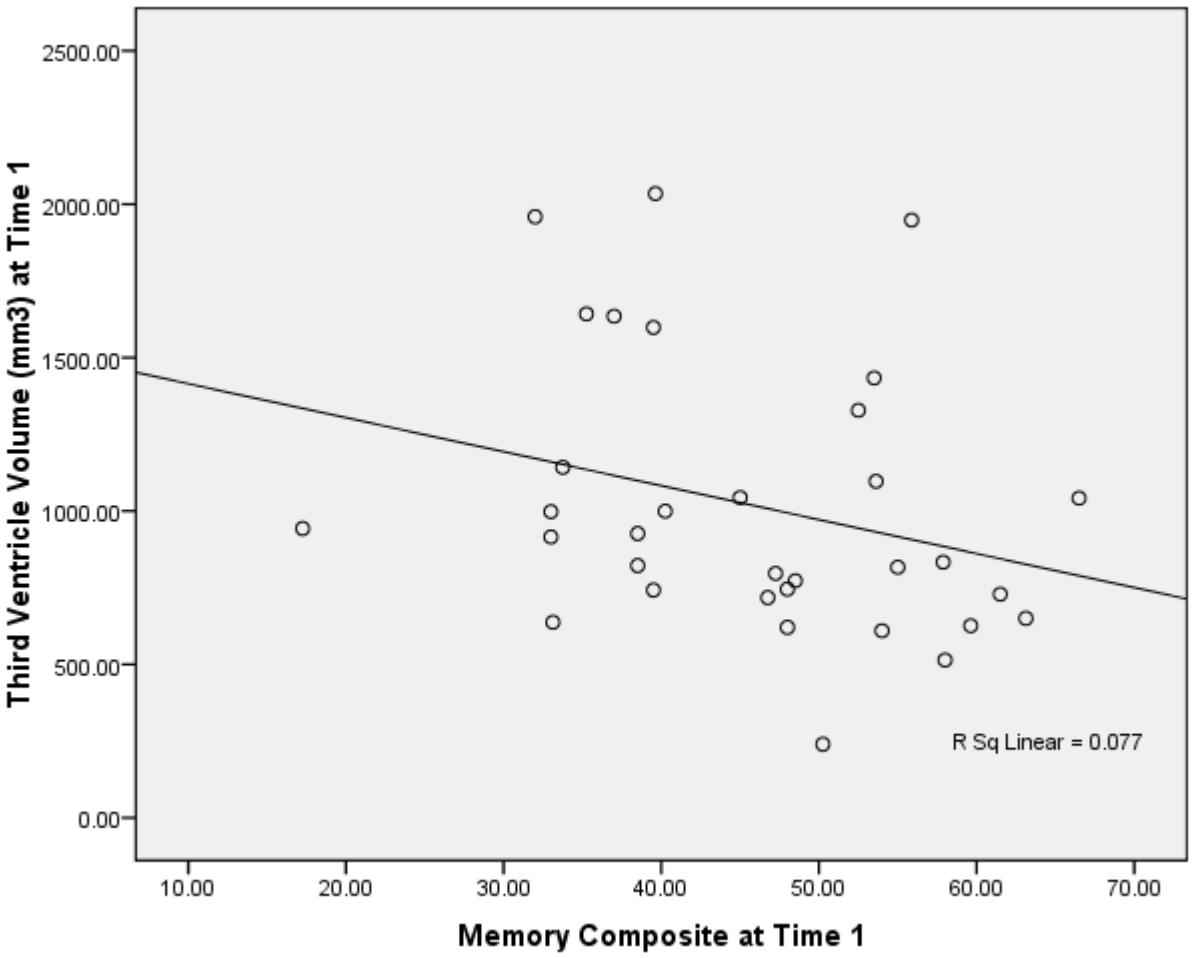
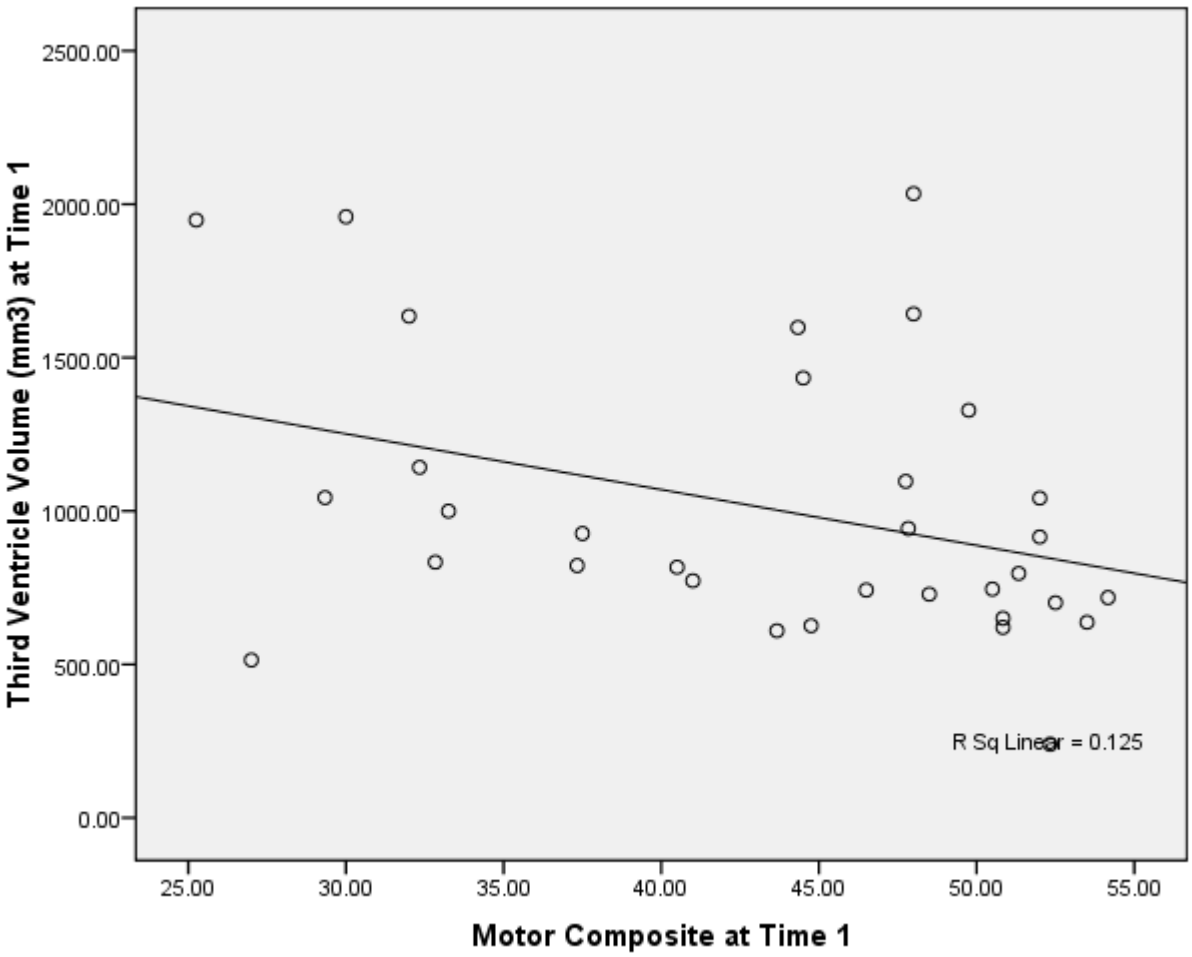


Figure 10: Relationship between third ventricle volume and motor composite at time one in TBI group.



TBI group analyses

Given the statistically significant correlations between GCS and measures of ventricular volume and neuropsychological function, the TBI group was divided into two groups based on GCS score. For the purposes of this analysis, the mild/moderate group included participants with a GCS score ranging from 8-15 (n=21) while the severe group included participants with a GCS score ranging from 3-7 (n=17). Independent samples t-tests were conducted at each time point (time 1 and time 2) to determine the relationship between GCS group and measures of ventricular volume and neuropsychological function. Results at time one indicated that the severe TBI group demonstrated significantly lower scores on tests of cognitive function ($t(34) = -3.550$, $p=.001$) than the mild/moderate group (Table 9). Additionally, the severe TBI group showed significantly greater lateral ventricle volume ($t(36) = 2.279$, $p=.029$) and third ventricle volume ($t(36) = 2.401$, $p=.022$) when compared to the mild/moderate group. Similarly, results at time two indicated that the severe TBI group continued to demonstrate significantly lower scores on tests of cognitive function ($t(18) = -2.266$, $p=.036$) and significantly greater third ventricle volume ($t(19) = 2.718$, $p=.014$) when compared to the mild/moderate group. No significant difference was found for lateral ventricle volume at time two between the mild/moderate and severe groups.

Table 9: TBI group comparison at time 1 based on GCS score (mild/moderate=8-15, severe=3-7).

Variable	TBI (mild/mod)		TBI (severe)		Statistics		
	n=17		n=21				
	Mean	SD	Mean	SD	t	df	p
Cog[a]	44.07	8.19	30.51	14.66	-3.550	34	.001
Mem[b]	48.03	10.03	43.04	12.38	-1.277	31	.211
Mot[c]	44.33	9.41	41.94	7.72	-.763	31	.451
LV1[d]	18089.85	9759.71	26161.78	12.083.64	2.279	36	.029
TV1[e]	869.58	434.81	1199.23	402.77	2.401	36	.022

[a]Cog=Executive composite, Time 1
[b]Mem=Memory Composite, Time 1
[c]Mot=Motor Composite, Time 1
[d]LV1=Lateral Ventricle Volume, Time 1
[e]TV1=Third Ventricle Volume, Time 1

Group Differences (Control vs TBI) at Time 2

Independent samples t-tests were conducted to evaluate the hypothesis that children in the TBI group would continue to show impaired neuropsychological function and enlarged ventricles one year post injury when compared to the control group (Table 10). Consistent with predictions, results indicated that the TBI group continued to demonstrate significantly lower scores on tests of cognitive ($t(52) = 3.756$, $p<.001$), memory ($t(48) = 2.920$, $p<.005$), and motor function ($t(50) = 2.929$, $p<.005$). Similarly, the TBI group continued to show enlarged lateral ventricles ($t(53) = -3.346$, $p<.005$) and third ventricles ($t(53) = -6.848$, $p<.001$) approximately one year post-injury, as compared to controls.

Table 10: Differences between TBI participants at time 2 and controls.

Variable	Control		TBI		Statistics		
	n=34		n=21				
	Mean	SD	Mean	SD	t	df	p
Cog[a]	51.11	5.15	43.69	3.19	3.756	52.000	.000
Mem[b]	55.69	7.18	47.74	12.10	2.920	48.000	.005
Mot[c]	51.76	6.25	44.27	12.27	2.929	50.000	.005
LV[d] (mm^3)	12506.42	4151.20	19704.03	11435.26	-3.346	53.000	.002
TV[e] (mm^3)	469.04	126.57	880.82	313.01	-6.848	53.000	.000

[a]Cog=Executive composite
[b]Mem=Memory Composite
[c]Mot=Motor Composite
[d]LV=Lateral Ventricle Volume
[e]TV=Third Ventricle Volume

Time 2 Analyses (TBI group only)

Additionally, simple correlations were computed to determine if the relationships between GCS, ventricle volumes, and neuropsychological composites at time two were consistent with those obtained at time one (Table 11). Results were considered significant at $p<.05$. Consistent with correlations obtained at time one, third ventricle volume at time two was significantly correlated with GCS ($r=-.447$, $p=.042$); however, lateral ventricle volume at time two was no longer correlated with GCS ($r=-.198$, $p=.389$). Also consistent with correlations obtained at time one, results indicated that third ventricle volume was significantly correlated with the executive composite at time two. Additionally, results indicated that third ventricle volume was significantly correlated with the memory composite at time two (this correlation was not significant at time 1; $r=-.292$, $p=.099$).

However, correlations between the executive composite and GCS (r=.393, p=.129), the executive composite and lateral ventricle volume (r=-.351, p=.087), and the motor composite and third ventricle volume (r=-.025, p=.923), correlations that were statistically significant at time one, were no longer significant at time two. While the memory composite as a whole was not significantly correlated with GCS at time two, two measures of complex verbal memory (i.e., TOMAL-Story Memory: Immediate Recall and Delayed Recall) were positively correlated (p=.05 and p=.03) with GCS at time two; however, the HVLT and the facial memory subtest of the TOMAL did not correlate with GCS at time two.

Table 11: Correlation of longitudinal ventricle measures with neuropsychological composites at time 2 in TBI group.

Variable	TBI		
	n=21		
	Cog2[d]	Mem2[e]	Mot2[f]
GCS[a]	.393	.439	.275
LV2[b] (mm^3)	-.351	-.360	.354
TV2[c] (mm^3)	-.480*	-.666**	-.025

[a]GCS=Glasgow Coma Scale Score
[b]LV2=Lateral Ventricle Volume, Time 2
[c]TV2=Third Ventricle Volume, Time 2
[d]Cog=Executive composite, Time 2
[e]Mem=Memory Composite, Time 2
[f]Mot=Motor Composite, Time 2
*=p<.05
**=p<.01

Longitudinal Analyses

Longitudinal data was successfully collected for 21 out of the 38 of the children in the TBI group. The mean time of first assessment (n=38) was 54.6 days (SD=36.8) while the mean time of second assessment (n=21) was 323.9 days (SD=174.24). No significant differences were found for age ($t(36) = -.497$, $p=.622$), sex ($t(36) = -.108$, $p=.915$), GCS ($t(36) = .591$, $p=.558$), or days post injury ($t(36) = .155$, $p=.878$) between participants in the longitudinal study (i.e., those with two data points) and participants with only one time point (Table 12).

Table 12: Demographics of TBI participants with one data point compared to participants with two data points (at time 1).

Demographic at Time 1	TBI (initial only)		TBI (longitudinal)		Statistics		
	n=17		n=21				
	Mean	SD	Mean	SD	t	df	p
Age (years)	13.40	3.61	13.93	2.87	-.497	36	.622
Gender					-.108	36	.915
Female (%)	18		19				
Male (%)	82		81				
GCS[a]	9.53	4.99	8.57	4.95	.591	36	.558
Days Post Injury	55.65	33.97	53.76	39.74	.155	36	.878
LV1[b] (mm^3)	23255.74	10700.13	20363.27	12167.63	.768	36	.447
TV1[c] (mm^3)	982.44	470.89	1036.97	445.83	-.366	36	.717
Cog[d]	38.58	15.54	38.30	11.35	.062	34	.951
Mem[e]	43.79	12.57	47.29	10.28	-.877	31	.387
Mot[f]	44.00	10.04	43.00	12.57	.318	31	.753

[a]GCS=Glasgow Coma Scale Score
[b]LV1=Lateral Ventricle Volume, Time 1
[c]TV1=Third Ventricle Volume, Time 1
[d]Cog=Executive composite, Time 1
[e]Mem=Memory Composite, Time 1
[f]Mot=Motor Composite, Time 1

Paired t-tests were conducted to quantify changes in ventricle volumes and neuropsychological composites over time (Table 13). Contrary to prediction, no significant differences were found for lateral ventricle volume (p=.221) from time one to time two. However, a significant difference was noted for third ventricle volume between times one and two (p=.009). More specifically, third ventricle volume decreased between time one (M=1036.97, SD=445.83) and time two (M=880.82, SD=313.31). Consistent with prediction, a significant difference was found for the executive composite from time one to time two (p=.02) indicating that performance on measures of cognitive function was significantly better at time two as compared to time one. No statistically significant differences were found for motor or memory composites between times one and two.

Table 13: Longitudinal analyses: Time 1 measures compared to time 2 measures for the TBI group.

Pair	Time 1		Time 2		Correlation	Statistics		
	n=21		n=21					
	Mean	SD	Mean	SD		t	df	p
LV[a] (mm^3)	20363.27	12167.63	19704.03	11435.26	.981**	1.264	20	.221
TV[b] (mm^3)	1036.97	445.83	880.82	313.31	.843**	2.887	20	.009
Cog[c]	38.25	11.65	44.00	8.78	.578**	-2.620	19	.017
Mem[d]	47.36	9.78	47.13	12.23	.866**	.430	16	.673
Mot[e]	42.81	7.52	43.62	12.32	.202	.034	17	.973

[a]LV1=Lateral Ventricle Volume
[b]TV1=Third Ventricle Volume
[c]Cog=Executive composite
[d]Mem=Memory Composite
[e]Mot=Motor Composite
*=p<.05
**=p<.01

Predictors of Function at Time 2

Simple correlations were conducted to determine predictors of neuropsychological function one year post injury (Table 14). Results were considered significant at p<.05. Results indicated statistically significant correlations between third ventricle volume at time one and cognitive and memory composites at time two. No significant difference was found between the third ventricle volume and cognition correlation and the lateral ventricle volume and cognition correlation (this was determined by testing the statistical significance of the difference between correlation coefficients).

Table 14: Predictors of neuropsychological function at time two in TBI group.

Variable	TBI		
	n=21		
	Cog2[d]	Mem2[e]	Mot2[f]
GCS[a]	.377	.308	.377
LV1[b] (mm^3)	-.399	-.342	.240
TV1[c] (mm^3)	-.669**	-.530*	-.009

[a]GCS=Glasgow Coma Scale Score
[b]LV1=Lateral Ventricle Volume, Time 1
[c]TV1=Third Ventricle Volume, Time 1
[d]Cog2=Executive composite, Time 2
[e]Mem2=Memory Composite, Time 2
[f]Mot2=Motor Composite, Time 2
*=p<.05
**=p<.01

Three separate multiple regression analyses were conducted to evaluate how well clinical features at time one predicted neuropsychological function at time two (Tables 15, 16, & 17). The predictors were GCS, lateral ventricle volume (time one), and third ventricle volume (time one), while the criterion variables were neuropsychological composites at time two (executive, memory, and motor). The linear combination of clinical features at time one was significantly related to the executive composite at time two, $F(4,12) = 6.761$, $p=.004$ (Table 15; Figure 11). The sample multiple correlation coefficient was .674, indicating that approximately 45% of the variance (36% of adjusted variance) of the executive composite at time two could be accounted for by the linear combination of clinical features at time one. Multiple regression analyses for memory (Table 16) and motor composites (Table 17) at time two were not significant.

Table 15: Summary of multiple regression analysis for variables predicting executive composite at time two in TBI group.

Model	R	R^2	Adj R^2	Std Error of the Estimate
Clinical Features: GCS, lateral ventricle volume, third ventricle volume	0.674	0.454	0.357	6.8586

Variable	Executive composite (Time 2)		
	B	SE B	β
Step 1			
(Constant)	60.896	7.859	-
GCS[a]	-.164	.402	-.096
LV1[b](mm^3)	.000	.000	.040
TV1[c](mm^3)	-.017	.006	-.757*

[a]GCS=Glasgow Coma Scale Score
[b]LV1=Lateral Ventricle Volume, Time 1
[c]TV1=Third Ventricle Volume, Time 1
*=p<.05
**=p<.01

Table 16: Summary of multiple regression analysis for variables predicting memory composite at time two in TBI group.

Model	R	R^2	Adj R^2	Std Error of the Estimate
Clinical Features: GCS, lateral ventricle volume, third ventricle volume	0.535	0.287	0.134	10.995

Variable	Memory Composite (Time 2)		
	B	SE B	β
Step 1			
(Constant)	59.391	12.845	-
GCS[a]	.210	.669	.089
LV1[b](mm^3)	.000	.000	-.027
TV1[c](mm^3)	-.014	.010	-.460

[a]GCS=Glasgow Coma Scale Score
[b]LV1=Lateral Ventricle Volume, Time 1
[c]TV1=Third Ventricle Volume, Time 1
*=p<.05
**=p<.01

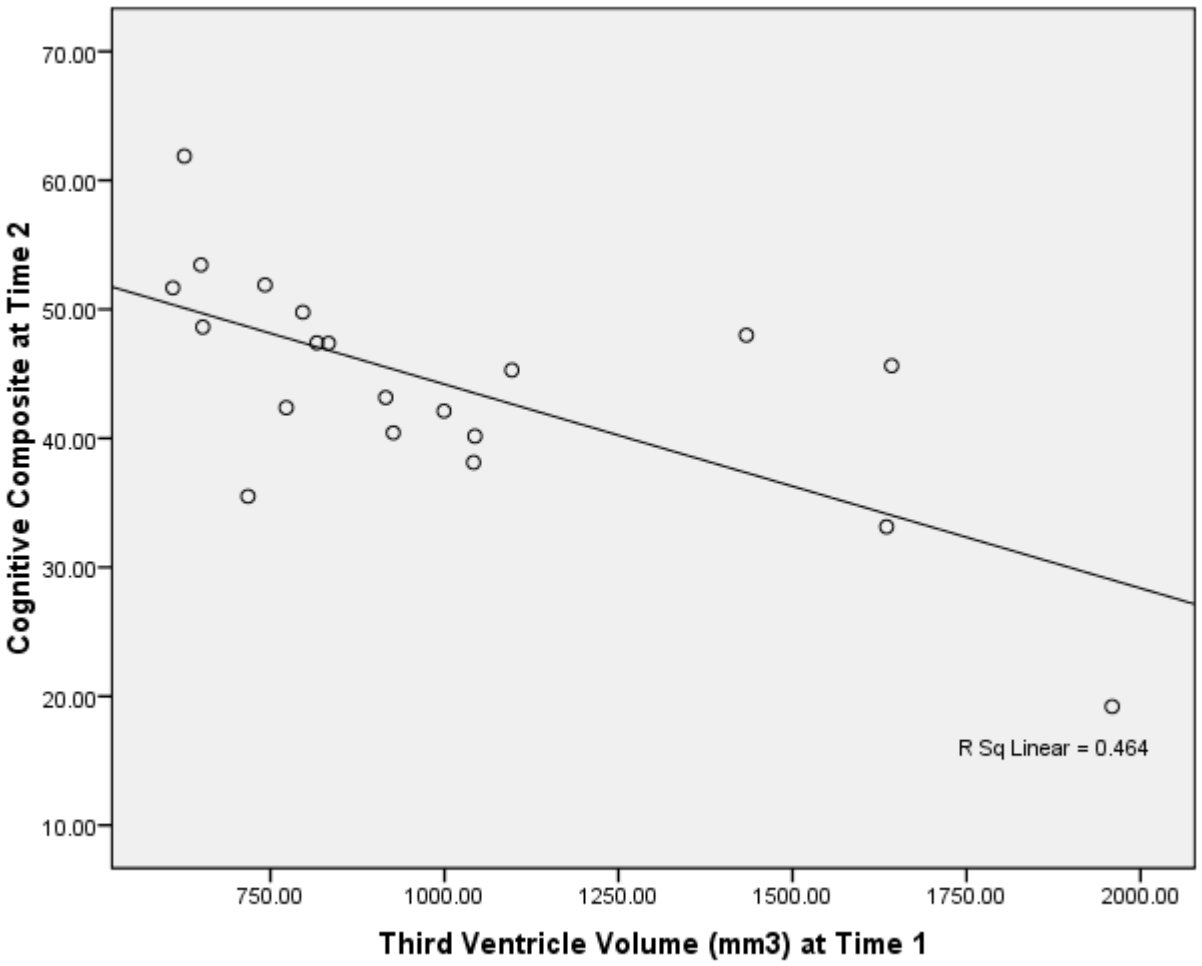
Table 17: Summary of multiple regression analysis for variables predicting motor composite at time two in TBI group.

Model	R	R^2	Adj R^2	Std Error of the Estimate
Clinical Features: GCS, lateral ventricle volume, third ventricle volume	.505	.255	.106	11.420

Variable	Motor Composite (Time 2)		
	B	SE B	β
Step 1			
(Constant)	19.969	15.486	-
GCS[a]	1.360	.738	.561
LV1[b](mm^3)	.000	.000	.350
TV1[c](mm^3)	.007	.012	.180

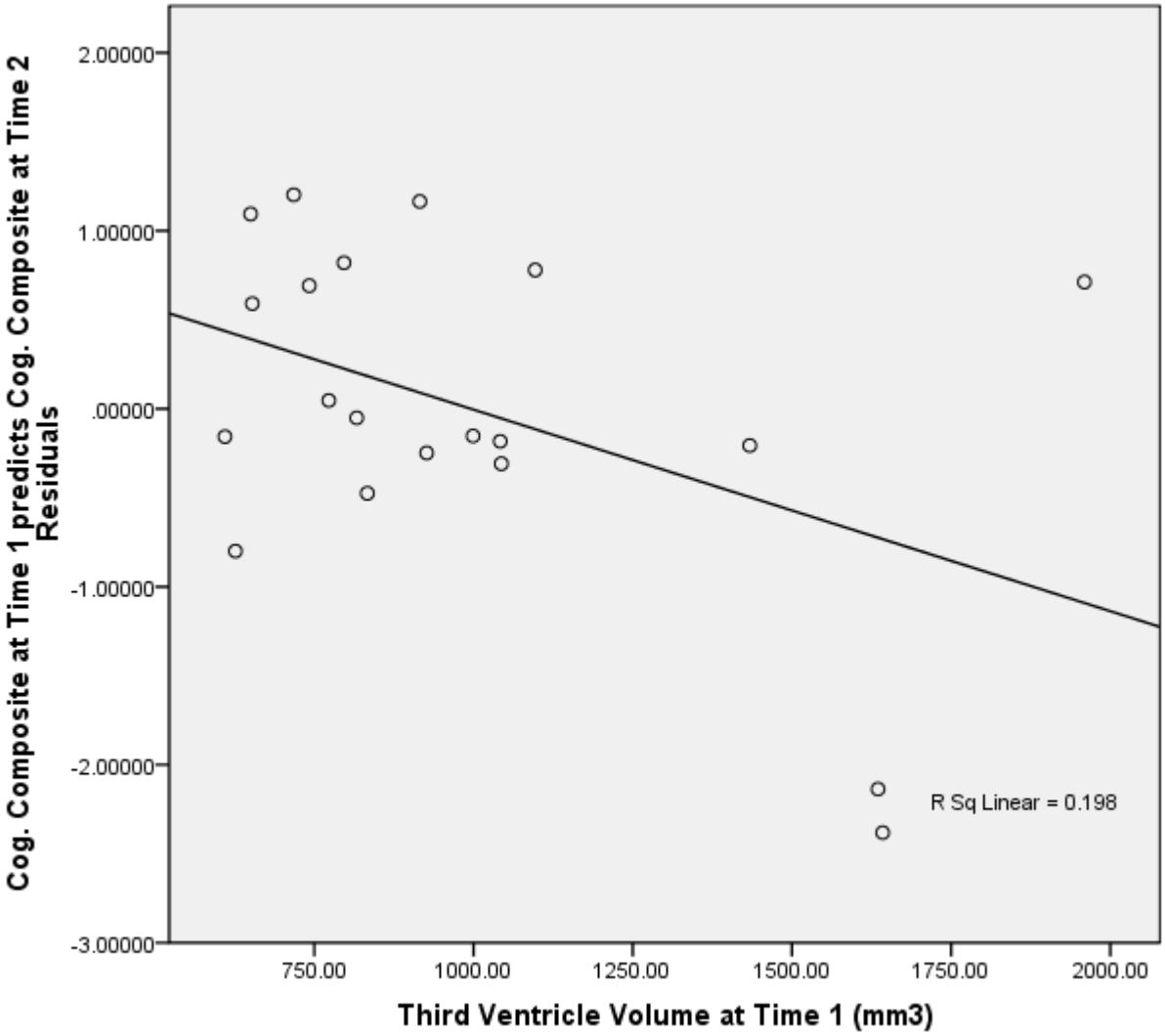
[a]GCS=Glasgow Coma Scale Score
[b]LV1=Lateral Ventricle Volume, Time 1
[c]TV1=Third Ventricle Volume, Time 1
*=p<.05
**=p<.01

Figure 11: Relationship between third ventricle volume at time one and executive composite at time two in TBI group.



In order to further examine the variables at time one that predict change in cognitive function from time one to time two, partial correlations were performed between lateral ventricle volume at time one, third ventricle volume at time one, and GCS (controlling for executive composite at time one) with the executive composite at time two. Results indicated that even when controlling for executive composite at time one, third ventricle volume at time one still predicted executive composite at time two ($r=-.47$, $p=.04$). When controlling for executive composite at time one, lateral ventricle volume was not significant. Figure 12 demonstrates the relationship between third ventricle volume at time one and the executive composite at time two (controlling for executive composite at time one).

Figure 12: Relationship between third ventricle volume at time one and the executive composite at time two (controlling for executive composite at time one) in TBI group.



DISCUSSION

Increased ventricle size following traumatic brain injury is a frequent observation in clinical practice (Levin et al., 1981). Research on children and adults with TBI has indicated that ventricular dilation results from a loss of both gray and white matter, occurs within several weeks following injury, and persists over time (Bigler, 1999; Bowen et al., 1997; Verger et al., 2001; Wilde et al., 2005). However, the mechanism of ventricular dilation remains unclear and the majority of volumetric studies of children with TBI have not included a typically developing control group. To our knowledge, only one study to date has demonstrated quantitative differences in ventricle volume in children with TBI compared to age-matched, typically developing controls; however, this study was cross sectional in nature (Wilde et al., 2005). Furthermore, while ventricular dilation is a common clinical observation following pediatric TBI, the difference between lateral ventricles and third ventricle with regard to clinical outcome has yet to be elucidated.

Enlargement of the ventricles has been described in both organic and nonorganic brain disorders including dementia, multiple sclerosis, depression, schizophrenia, autism, bipolar disorder, and TBI (Fannon et al., 2000; Hardan, Minshew, Harenski, & Keshavan, 2001; Staal et al., 2000; Strasser et al., 2005). In many cases, studies have found significant correlations between the degree of ventricular dilation and various aspects of cognitive function including attention, executive functioning, and motor function (Crespo-Facorro, Barbadillo, Pelayo-Teran, & Rodriguez-Sanchez, 2007). Additionally, when lateral ventricles and third ventricle are examined independently, the relationship

between ventricle volumes and neuropsychological variables can be quite different. Studies of ventricular enlargement in adults following TBI have demonstrated that third ventricle dilation is the best indicator of severity of injury (Reider-Groswasser, Cohen, Costeff, & Groswasser, 1993), diffuse brain injury (Henry-Feugeas et al., 2000), and functional outcome (Ryser et al., 1996). More specifically, third ventricle dilation shows stronger correlations with severity of injury (Henry Fuegas et al., 2000) and global clinical outcome (Henry-Feugeas et al., 2000; Redier-Groswasser et al., 1993; Ryser et al., 1996) than other ventricular and corpus callosal measures. Our findings appear consistent with these observations. To our knowledge, volumetric studies of third ventricle in pediatric TBI are absent from the literature. As such, third ventricle findings in this study are of considerable importance.

Group Differences at Time 1 and Time 2

As predicted, when the control group was compared to the TBI group at time one (mean=55 days post injury) and time two (mean=324 days post injury), significant differences were found for both lateral ventricle volume and third ventricle volume. More specifically, ventricular volumes were significantly larger in the TBI group when compared to the control group indicating that ventricular enlargement is present at least two months post injury and persists at least eleven months post-injury. This is consistent with previous research showing that ventricular enlargement following TBI in children (Bowen et al., 1997; Wilde et al., 2005) and adults (Bigler et al., 1992, 1993; Bigler et al., 1994; Bigler et al., 1999; Cullum & Bigler, 1986; Henry-Feugeas et al., 2000; Himanen et al., 2005; Levin et al., 1981) is present within four weeks post injury and persists at least one year post-injury. Research on ventricular volume in children is sparse. While

several studies have demonstrated ventricular enlargement following TBI in children, ventricular measures are often not directly correlated with other measures of neural integrity making it difficult to draw conclusions about the impact of ventricular dilation on the rest of the brain. However, studies reporting ventricular dilation in children have also reported reduced whole brain volume, reduced total GM volume (Wilde et al., 2005), and corpus callosum atrophy (Verger et al., 2000). Similarly, in adults with TBI, research has indicated that third ventricle width is highly correlated with corpus callosum atrophy, suggesting involvement of deep white matter structures (Henry-Fuegas et al., 2000). Additionally, increased lateral ventricle volume has been associated with decreased total brain volume (Blatter et al., 1997). As such, it appears that ventricular enlargement is related to a loss of both GM and WM structures in children and adults.

Despite the previous reports of ventricular enlargement discussed above, the mechanism of this dilation remains unclear. It has been hypothesized that ventricular enlargement following TBI may be related to atrophy resulting from diffuse injury, to a secondary CSF absorptive deficit, or to a combination of the two (Poca et al., 2005). According to Bigler (1999), ventricular enlargement represents a manifestation of hydrocephalus ex vacuo, an indirect measure of cerebral atrophy in which damage to brain tissue causes cerebral volume loss and subsequent expansion of the ventricles due to the CSF pressure gradient.

With regard to neuropsychological measures, consistent with predictions, children in the TBI group performed significantly worse on tests of executive, memory, and motor skills as compared to the control group at times one (mean=55 days post injury) and two (mean=324 days post injury). This is consistent with previous research on children with

TBI showing impairment on various measures of neuropsychological function that persist well into the recovery period (Yeates et al., 2002). Results of previous studies of neuropsychological outcome following pediatric TBI are mixed; however, areas of impairment that are commonly reported include attention, memory, processing speed (Yeates et al., 2002), intellectual function (Catroppa & Anderson, 2003; Donders & Hoffman, 2002), executive function (Ewing-Cobbs et al., 2004; Levin & Hanten, 2005; Slomine et al., 2002), academic achievement (Ewing-Cobbs et al., 2004), motor skills, and language skills (Catroppa & Anderson, 2004; Levin et al., 2001). In this study, tests of working memory (digit span), verbal fluency (COWA), executive function (Trails B), processing speed (Trails A), and motor skills (VMIM-C) were correlated with ventricular volume. This is partially consistent with previous research showing that nonspecific ventricular dilation is associated with tests of verbal memory, executive function (i.e., Wisconsin Card Sorting Test), and visual reaction time approximately nine years post injury, though these results did not reach statistical significance (Verger et al,. 2001). While the tests mentioned above all tap a slightly different aspect of cognitive function, the majority of these tests include an attentional component.

Clinical Features and Demographics

In our sample, Glasgow Coma Scale (GCS) score, a measure of initial injury severity (i.e., lower GCS = larger ventricles), appeared to be the most important clinical demographic in ventricular enlargement and neuropsychological functioning. Consistent with previous research, GCS was negatively correlated with lateral ventricle volume and third ventricle volume and positively correlated with the executive composite. In studies of adults with TBI, a significant correlation between injury severity and ventricular

enlargement has been frequently reported (i.e., lower GCS score correlates with greater degree of ventricular enlargement) (Levin, Williams, & Valastro, 1990; Henry-Feugeas et al., 2000). The relationship between injury severity and ventricular dilation in children has not been as well documented; however, injury severity has been shown to be related to changes in brain structure and neuropsychological outcome (Levin et al., 2000; Wilde et al., 2005; Yeates et al., 2002). Previous research has shown that injury severity is the most consistent predictor of neuropsychological outcome following TBI in childhood (Yeates, 2002). In this study, injury severity (as measured by GCS) was positively correlated with the executive composite in the semi-acute phase of injury, but not the motor or memory composites. While the reason for this is unclear, the lack of correlation between GCS and the motor composite could be related to location of injury. Our sample was comprised primarily of children who sustained diffuse injuries. As a result, it was not possible to include focal injury as a covariate in any analyses making it impossible to comment further on this finding. The lack of correlation between GCS and the memory composite is slightly more puzzling but could reflect the sensitivity of memory to insult. Support for this comes from a recent review indicating that even mild TBI can lead to impairment in memory function (Hooper et al., 2004). It is possible that injury to the brain, regardless of severity, causes some disruption to memory function. Interestingly, while the memory composite as a whole was not significantly correlated with GCS at time two, two measures of complex verbal memory (i.e., TOMAL-Story Memory: Immediate Recall and Delayed Recall) were positively correlated with GCS at time two; however, the HVLT and the facial memory subtest of the TOMAL did not correlate with GCS at time two. This suggests that while memory impairment in the semi-acute phase of

injury does not appear to be dependent on injury severity, injury severity does play a part in continued impairment in complex verbal memory approximately one year post-injury. In other words, children with more severe injuries continue to perform poorly on tests of complex verbal memory approximately one year post-injury while children with more mild injuries show some recovery of function.

Finally, at time two, injury severity was not correlated with any of the neuropsychological composites, although there was a trend towards statistical significance for the executive composite ($p=.07$). This suggests that while injury severity is an important factor in semi-acute cognitive function, injury severity has a more profound impact on ventricle size approximately one year post injury than on cognitive function. While the reason for this remains unclear, it is possible that it could reflect reorganization of function.

Interestingly, while others have reported a relationship between age at injury and measures of structural integrity in children (Kriel, Krach, & Panser, 1989), we did not find a relationship between age and ventricle volume in the TBI group or the control group in this study. While the reason for this remains unclear, it is possible that, unlike other structures in the brain, brain injury affects ventricle volume equally across age groups. This is supported by the fact that studies of adults have also failed to find a significant relationship between ventricle volume and age (Poca et al., 2005). Alternately, the lack of relationship between age and ventricle volume could also be related to the normal course of ventricle maturation. Studies of developmental changes in ventricle volume in typically developing children have shown that ventricle size increases by a factor of 1.5 during childhood and follows a nonlinear segmental pattern. Ventricular

growth is much more rapid during the first three years of life after which it stabilizes to a steady rate of growth with age (Xenos et al., 2002). Given that the majority of ventricle growth occurs during the first three years of life, it is possible that, because our sample included only children older than the age of six years, the small changes in ventricle volume that occur in middle to late childhood were too small to detect in a sample of this size (n=38).

TBI Group Findings

Consistent with predictions, both lateral and third ventricle volumes were significantly correlated with the executive composite at time one (i.e., more enlarged ventricles = worse performance on tests of cognitive function). This is consistent with previous research on adults indicating that ventricular dilation is significantly correlated with neuropsychological deficits. Two studies to date have examined ventricular dilation in relation to neuropsychological functioning in children (Bowen et al., 1997; Verger et al., 2001). Neither study found a significant relationship between ventricular enlargement and cognitive function, though correlations were in the expected direction. However, sample sizes were small (n=5 and n=19, respectively), ventricle to brain ratios were used, and third ventricle volume and lateral ventricle volume were not examined independently. In our sample, the motor composite was correlated only with third ventricle volume while the memory composite was unrelated to ventricular dilation at time one. As mentioned above, it is possible that memory function is extremely sensitive to brain injury and is thus unrelated to conventional measures of neural integrity in the semi-acute phase of injury.

Approximately one year post-injury (time two), the cognitive and memory composites were significantly correlated with third ventricle volume. This suggests that while both lateral and third ventricle volumes are good indicators of neuropsychological function during the semi-acute phase, third ventricle volume is a more reliable indicator of cognitive and memory function later in the recovery process. It is possible that there is less plasticity in the structures surrounding the third ventricle than those surrounding the lateral ventricles. Research from animal and lesion studies suggests that the dorsomedial nucleus, which surrounds the third ventricle, plays an important role in memory (Isaac et al., 1998; Peinado-Manzano & Pozo-Garcia, 1996). Evidence for this comes from animal and lesion studies which indicate that damage to the dorsomedial nucleus results in amnesia in humans and animals. Thus, it is not surprising that third ventricle enlargement adjacent to the dorsomedial nucleus has an impact on memory function in children with TBI.

Longitudinal Data

No significant differences were found for lateral ventricle volume from time one to time two. This is consistent with previous research indicating that ventricular expansion appears to stabilize around 9-12 weeks following injury in adults with TBI (Johnson, Bigler, Burr, & Blatter, 1994). However, a significant difference was noted for third ventricle volume. More specifically, while third ventricle volume was still enlarged in the TBI group as compared to the control group, third ventricle volume decreased between times one and two. While the reason for this remains unclear, it could be related to several mechanisms such as swelling in adjacent tissue, remyelination of adjacent tissue, or blockage in between the third and fourth ventricle that was relieved.

Consistent with predictions, cognitive function significantly improved between times one and two indicating partial recovery of cognitive function during the first year post-injury. This is consistent with previous research indicating that recovery of neuropsychological function is most rapid during the first year post-injury but that impairments remain evident when children with TBI are compared to typically developing controls (Anderson et al., 2003; Ewing-Cobbs et al., 1998, 2004; Taylor et al., 2002; Yeates et al., 2002). In this study, areas of significant improvement in the first year post-injury included measures of verbal fluency (COWA: FAS and Animals) and processing speed (Trails A). No significant differences were found for motor or memory composites between times one and two. This suggests that memory and motor impairments present in the semi-acute phase of injury are less likely to significantly improve during the first year post-injury than are other areas of neuropsychological function. This lends support to the idea that impairment in motor function is often more dependent on location of injury than injury severity.

One longitudinal study to date examined the corpus callosum in children with mild to moderate (n=28) and severe (n=25) head injury at three months and three years post-injury (age range: 5-15 years). Results revealed a reduction in the area of the corpus callosum in children with severe TBI between three and 36 months post-injury and an increase for the mild to moderate group during this same time period. The rate of growth for the mild to moderate group was consistent with the findings reported for healthy children. Corpus callosum area was significantly correlated with severity of injury and functional outcome at three years post-injury (Levin et al., 2000). When the TBI group in this study was divided into two based on injury severity, our results indicated that the

severe group demonstrated significantly greater ventricular enlargement and significantly lower scores on tests of cognitive function than the mild/moderate group. While the results for the severe group (corpus callosum thinning) appear consistent with our results (ventricular enlargement), the results for the mild-moderate group (increased corpus callosum size) are not entirely consistent with our results. Based on the results of Levin and colleagues (2000), one would predict that ventricular enlargement would not be present in the mild-moderate during the chronic phase of injury. However, the above described study was limited by the lack of a control group. Furthermore, while the size of the corpus callosum is known to increase significantly during childhood, changes in ventricle volume during the same time period are more moderate. This suggests that, unlike the corpus callosum, increases in ventricle size in typically developing controls in middle to late childhood would be difficult to detect in a small sample.

Predictors of Neuropsychological Function at Time 2

Given the relative paucity of longitudinal neuroimaging studies in pediatric TBI, the clinical and neuroanatomic factors at time one that predict neuropsychological function at time two are of considerable importance. In our sample, third ventricle volume at time one was significantly correlated with executive and memory composites at time two. Similarly, when executive function at time one was controlled, third ventricle volume at time one remained a significant predictor of executive function at time two. This indicates that third ventricle volume is a more specific indicator of neuropsychological outcome than lateral ventricle volume. Furthermore, multiple regression analyses indicated that the linear combination of GCS, lateral ventricle volume, and third ventricle volume were predictive of executive function at time two.

However, third ventricle volume was the only variable of the three that was significant (p=.01) when examined independently. Additionally, when the executive composite at time one was controlled for, third ventricle volume was still predictive of executive function at time two. While no studies to date have examined the relationship between third ventricle volume and neuropsychological outcome in TBI, our results appear consistent with previous research on adults suggesting that third ventricle volume is the best indicator of functional outcome following TBI (Ryser et al., 1996). Despite previous research demonstrating the usefulness of examining the third ventricle, most studies of TBI use global evaluations of ventricles, such as ventricle to brain ratio, and very few examine lateral ventricle volume and third ventricle volume separately. To our knowledge, there have been no longitudinal studies of third ventricle volume in TBI in children or adults to date.

While the reason for the predictive value of third ventricle volume remains unclear, it is thought to be related to its position in the brain. Bigler (1999) asserted that the position of the third ventricle makes it sensitive to any generalized change in brain volume. More specifically, its position between the thalami makes it a more sensitive indicator of morphological change in the entire brain. In addition, it has been hypothesized that nonspecific ventricular change (i.e., ventricle to brain ratio) is a reflection of white matter change whereas third ventricle changes may suggest damage to subcortical pathways (Bigler, Johnson, & Blatter, 1999). These hypotheses are consistent with research indicating that third ventricle enlargement is the most reliable MRI index of the severity of diffuse axonal injury after TBI in adults (Henry-Feugeas et al., 2000). Furthermore, when third ventricle measurements in adults with TBI are broken down into

parts (i.e., interthalamic, subthalamic, and anterior), all parts are correlated with clinical status (Henry-Fuegas et al., 2000). This suggests that third ventricular enlargement (based on linear ventricular measurements) results both from thalamic atrophy and white matter atrophy of adjacent deep structures (i.e., internal capsules and mesencephalic area). Thus, third ventricle enlargement is thought to reflect trauma of adjacent brain structures.

Limitations

A potential confound of this study may be that it is not possible to determine from our data whether ventricular enlargement in the TBI group was the result of an innate predisposition to ventricular dilation rather than a direct consequence of insult to the brain. It would be ideal to acquire preinjury MRI scans in order to control for this potential variable. However, because it is virtually impossible to predict who will sustain a traumatic brain injury, it is not possible to attain premorbid imaging data. However, if ventricular dilation was solely related to an innate predisposition, one would predict that measures of neuronal integrity, such as N-Acetylaspartate (NAA) concentration, would not relate to ventricular enlargement. As such, this potential confound could be addressed in the future by examining measures of neuronal integrity in relation to ventricular dilation. Spectroscopy data was collected in this sample and will be reported in future publications in order to address this issue.

While important conclusions can be drawn from absolute ventricle volumes, numerous studies report ventricle to whole brain volume ratios (VBR). Unfortunately, the neuroimaging parameters used in this study prevented the acquisition of complete brain images thereby making it impossible to obtain whole brain volume. Thus, VBR ratios were not calculated. As such, it is difficult to directly compare our results to results of

studies reporting VBR as the only measure of ventricular enlargement. However, one would predict that ventricle-to-brain ratios would be significantly larger in children showing absolute ventricular enlargement. Additionally, our available brain volume measures account for approximately 75-80% of total brain volume. As such, this percentage is likely to correlate very highly with measures of total brain volume suggesting that our results are likely comparable to studies reporting total brain volume. However, the lack of whole brain images also prevented us from attaining total GM and WM volumes in our sample. As such, it was not possible to investigate the relationship between ventricular enlargement and GM and WM loss. Given that this is a gap in the pediatric TBI literature, future studies should address the relationship between GM volume, WM volume, and ventricular enlargement.

As in most studies of pediatric TBI, sample demographics were a significant limitation in our study. Limitations include heterogeneity in gender, age at injury, and post-injury interval. Approximately 82% of our sample was male. While males are overrepresented in pediatric TBI, the paucity of females in our sample requires that caution be taken when extrapolating our findings to females. Furthermore, the post-injury interval in our sample was extremely variable, particularly at time two. At time two, the mean follow up interval was 324 days; however, post-injury intervals ranged from 101 days to 697 days. While one can draw general conclusions about the long-term consequences of pediatric TBI, it is unclear how these differ between one and two years post injury. Finally, age at injury was quite variable in this sample, with participants ranging in age from six years to eighteen years. As such, it was impossible to draw conclusions about how injury at a specific age affects neuropsychological function and

brain structure. However, when our sample was divided into two groups based on age (i.e., young, old), no significant differences were found indicating that findings were consistent across age groups. Thus, it would seem that our findings do not lend support to the theory of brain plasticity in children which asserts that young children often fare better following brain insult. However, preschool age children, who are often the topic of discussion with regard to brain plasticity, were not included in our sample.

Proponents of the brain plasticity model argue that the consequences of brain injury for young children are far less severe, both functionally and structurally, than for older children and adults (Anderson et al., 2005). Reports of remarkable recovery after focal cerebral injury in young children have been cited as evidence for the theory that brain physiologic features and structures are more modifiable early in life (Levin, 2003). It has been proposed that when injury occurs in young children, healthy tissue assumes the function of damaged tissue, thereby leading to minimal impairment. However, it is unclear whether the same recovery occurs when injury is more generalized and tissue damage is more extensive. Unfortunately, focal injuries are less likely in pediatric TBI than more generalized and diffuse injury. This has been attributed to physiologic properties such as the flexibility of children's cranial bones, the fact that children have a larger head supported by a smaller neck, and immature frontal regions and myelinating fibers in the pediatric brain that are particularly vulnerable to insult (Tasker, 2006).

In contrast to the plasticity hypothesis, others have proposed that brain injury that occurs in childhood has the potential to disrupt brain development. Evidence for this comes from studies of cognitive, social, emotional, and adaptive outcome following TBI indicating that deficits can be severe and lifelong (Yeates et al., 2002, 2005). Recent

neuroimaging studies have revealed abnormalities in WM and GM regions that persist for at least five years following moderate to severe injury in childhood (Wilde et al., 2005; Tasker et al., 2005). Taken together, results suggest that the immature brain is particularly vulnerable to insult, with outcomes being the worst for children who sustain a severe injury at a young age (Anderson et al., 2005).

Again, as in most longitudinal studies of pediatric populations, our study was plagued by attrition and missing data. Of the 38 original participants in the TBI group, only 21 (55%) returned for the extended follow up. Analyses revealed no significant differences in age at injury, severity of injury, or days post injury between children who participated in the longitudinal part of the study and those with only one time point. However, there is no way to know for certain why individual children withdrew from the study or predict their level of functioning at the extended follow-up time (time two). In addition, given the heterogeneity in injury severity in our sample, multiple participants were missing data points for various neuropsychological tests. This was the result of participant's inability to complete testing due to injury severity or fatigue. To control for missing data, composites were calculated for each participant in three different domains (cognitive, memory, and motor). While this is a logical solution to this problem, complete neuropsychological data for each participant is preferable.

Conclusions

To our knowledge, this is the first study to longitudinally examine ventricular volume in pediatric TBI. Additionally, this is the first neuroimaging study to examine the difference between lateral ventricle volume and third ventricle volume with regard to clinical outcome in children with TBI. Longitudinal studies in pediatric TBI are

extremely rare. This paucity is likely related to the fact that longitudinal studies are difficult to conduct due to their time consuming nature as well their high rates of attrition. To our knowledge, only one other longitudinal neuroimaging study to date has been conducted on children with TBI. Longitudinal studies of TBI are especially important in pediatric samples given the extensive neuroanatomic and neuropsychological changes that occur during childhood. Unlike injuries sustained in adulthood, brain injuries sustained during childhood may not have immediate cognitive or behavioral consequences. Rather, deficits may become apparent as a child ages and particular functions come on line. As such, longitudinal studies of pediatric TBI have the potential to inform our understanding of how TBI affects the developing brain in ways that are not possible from cross-sectional studies. In conclusion, our results reiterate the importance of longitudinal designs in pediatric TBI and indicate the utility of third ventricle volume in the semi-acute phase of injury as a predictor of neuropsychological function.

Directions for Future Research

Based on the results described above, there are several directions that future studies should take. First, this study should be replicated using MRI images that include the whole brain. This would allow for the calculation of ventricle-to-brain ratios thus making results easier to directly compare to other studies of ventricular enlargement in TBI. Additionally, the acquisition of whole brain images would allow for computation of total GM and total WM volumes. Thus, it would be possible to examine ventricular enlargement and cerebral atrophy simultaneously. Additionally, the acquisition of whole brain images would allow for the use of techniques such as voxel-based morphometry (VBM). VBM techniques could be applied in order to determine areas of the brain that

differ between children with TBI and controls. As such, it is possible that regions of the brain that have yet to be investigated using region of interest measurements could be identified as areas that differ between children with TBI and controls. Second, given that third ventricle volume was the best predictor of cognitive outcome one year post-injury in our sample, future studies should examine the third ventricle in relation to neuropsychological outcome several years or more post-injury. Third, as discussed above, future studies should examine alternate measures of neural integrity such as spectroscopy. Finally, to our knowledge, this is only the second study to date to examine longitudinal neuroimaging data in pediatric TBI. Our results reiterate the utility of studying TBI in a longitudinal design. Future longitudinal neuroimaging studies have the potential to identify other brain areas that are predictive of long-term cognitive outcome. As such, it may be possible to predict children that are at risk for poor outcome during the semi-acute phase based on MRI or CT results and subsequently provide intensive intervention.

REFERENCES

Anderson, V.A., Catroppa, C., Haritou, F., Morse, S., & Rosenfeld, J.V. (2003). Identifying factors contributing to child and family outcome 30 months after traumatic brain injury in children. *Journal of Neurology, Neurosurgery, and Psychiatry, 76,* 401-408.

Anderson, V.A., Catroppa, C., Morse, S., Haritou, F., & Rosenfeld, J. (2005). Functional plasticity or vulnerability after early brain injury? *Pediatrics, 116,* 1374-1382.

Ashwal, S., Babikian, T., Gardner-Nichols, J., Freier, M.C., Tong, K.A., & Holshouser, B.A. (2006). Susceptibility-weighted imaging and proton magnetic resonance spectroscopy in assessment of outcome after pediatric traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 87*(S12), S50-S58.

Belanger, H.G., Curtiss, G., Demery, J.A., Lebowitz, B.K., & Vanderploeg, R.D. (2005). Factors moderating neuropsychological outcomes following mild traumatic brain injury: A meta-analysis. *Journal of the International Neuropsychological Society, 11*, 215-227.

Benavidez, D.A., Fletcher, J.M., Hannay, H.J., Bland, S.T., Caudle, S.E.,& Mendelsohn, et. al. (1999). Corpus callosum damage and interhemispheric transfer of information following closed head injury in children. *Cortex, 35*(3), 315-336.

Benton A.L. & Hamsher, K.D.S. (1994). *Multilingual aphasia examination.* Iowa City, IA: AJA Associates Inc.

Benz, B., Ritz, A., & Kiesow, S. (1999). Influence of age-related factors on long-term outcome after traumatic brain injury (TBI) in children: A review of recent literature and some preliminary findings. *Restorative Neurology and Neuroscience, 14,* 135-141.

Bigler E.D., Kurth, S., Blatter., D., & Abildskov, T (1992). Degenerative changes in traumatic brain injury: post-injury magnetic resonance identified ventricular expansion compared to pre-injury levels. *Brain Research Bulletin, 28*(4), 651-653.

Bigler E.D., Kurth, S., Blatter., D., & Abildskov, T (1993). Day-of-injury CT as an index to pre-injury brain morphology: degree of post-injury degenerative changes identified by CT and MR neuroimaging. *Brain Injury, 7*(2): 125-134.

Bigler, E.D., Burr, R., Gale, S., Norman, M., Kurth, S., Blatter, D., & Abildskov, T. (1994). Day of injury CT scan as an index to pre-injury brain morphology. *Brain Injury, 8*(3), 231-238.

Bigler, E.D., Johnson, S.C., & Blatter, D.D. (1999). Head trauma and intellectual status: relation to quantitative magnetic resonance imaging findings. *Applied Neuropsychology, 6*(4), 217-225.

Bigler, E.D. (1999). Neuroimaging in pediatric traumatic head injury: Diagnostic considerations and relationships to neurobehavioral outcome. *Journal of Head Trauma Rehabilitation, 14*(4), 406-423.

Blatter, D.D., Bigler, E.D., Gale, S.D., Johnson, S.C., Anderson, C.V., Burnett, B.M., et al. (1997). MR-based brain and cerebrospinal fluid measurement after traumatic brain injury: Correlation with neuropsychological outcome. *American Journal of Neuroradiology, 18*, 1–10.

Bowen, J.M., Clark, E., Bigler, E.D., Gardner, M., Nilsson, D., Gooch, J., & Pompa, J. (1997). Childhood traumatic brain injury: Neuropsychological status at the time of hospital discharge. *Developmental Medicine and Child Neurology, 39*(1), 17-25.

Brandt, J. & Benedict, R.H.B. (2001). *Hopkins Verbal Learning Test – Revised.* Psychological Assessment Resources, Inc.

Catroppa, C., & Anderson, V. (2003). Recovery and predictors of intellectual ability two years following paediatric traumatic brain injury. *Neuropsychological Rehabilitation, 5*, 517-536.

Catroppa, C. & Anderson, V. (2004). Recovery and predictors of language skills two years following pediatric traumatic brain injury. *Brain and Language, 88*, 68-78.

Catroppa, C. & Anderson, V. (2005). A prospective study of the recovery of attention from acute to 2 years following pediatric traumatic brain injury. *Journal of the International Neuropsychological Society, 11*(1), 84-98.

Chapman, S. B., McKinnon, L., Levin, H. S., Song, J. X., Meier, M. C., & Chiu, S. (2001). Longitudinal outcome of verbal discourse in children with traumatic brain injury: Three-year follow-up. *Journal of Head Trauma Rehabilitation, 15*(5), 441-455.

Crespo-Facorro, B., Barbadillo, L., Pelayo-Terán, J.M., & Rodríguez-Sánchez, J.M. (2007). Neuropsychological functioning and brain structure in schizophrenia. *International Review of Psychiatry, 19*(4), 325-336.

Cullum, C.M. & Bigler, E.D. (1986). Ventricle size, cortical atrophy and the relationship with neuropsychological status in closed head injury: a quantitative analysis. *Journal of Clinical and Experimental Neuropsychology*, *8*(4): 437-452

de la Plata, C.M., Ardelean, A., Koovakkattu, D., Srinivasan, P., Miller, A., Phuong, V., et al. (2007). Magnetic resonance imaging of diffuse axonal injury: Quantitative assessment of white matter lesion volume. *Journal of Neurotrauma, 24*(4), 591-598.

Dennis, M., Guger, S., Roncadin, C., Barnes, M., & Schacher, R. (2001). Attentional-inhibitory control and social-behavioral regulation after childhood closed head injury: Do biological, developmental, and recovery variables predict outcome? *Journal of the International Neuropsychological Society, 7,* 683-692.

Di Stefano, G., Bachevalier, J., Levin, H.S., Song, J.X., Scheibel, R.S., & Fletcher, J.M. (2000). Volume of frontal brain lesions and hippocampal formation in relation to memory function after closed head injury in children. *Journal of Neurology, Neurosurgery, and Psychiatry, 69*, 210-216.

Donders, J., & Hoffman, N. M. (2002). Gender differences in learning and memory after pediatric traumatic brain injury. *Neuropsychology, 16*(4), 491-499.

Donders, J. & Woodward, H.R. (2003). Gender as a moderator of memory after traumatic brain injury in children. *Journal of Head Trauma Rehabilitation, 18*(2), 106-115.

Donders, J. & Nesbit-Greene, K. (2004). Predictors of neuropsychological test performance after pediatric traumatic brain injury. *Assessment, 11*(4), 275-284.

Ewing-Cobbs, L., Levin, H.S., Fletcher, J., Miner, M.E., & Eisenberg, H. (1990). The Children's Orientation and Amnesia Test: Relationship to severity of acute head injury and to recovery of memory. *Neurosurgery, 27,* 683-691.

Ewing-Cobbs, L., Kramer, L., Prasad, M., Canales, D.N., Louis, P.T., Fletcher, J.M., et al. (1998). Neuroimaging, physical, and developmental findings after inflicted and noninflicted traumatic brain injury in young children. *Pediatrics, 102*(2), 300-307.

Ewing-Cobbs, L., Barnes, M.A., & Fletcher, J.M. (2003). Early brain injury in children: Development and reorganization of cognitive function. *Developmental Neuropsychology, 24*(2-3), 669-704.

Ewing-Cobbs, L., Barnes, M., Fletcher, J.M., Levin, H.S., Swank, P.R., & Song, J. (2004). Modeling of longitudinal academic achievement scores after pediatric traumatic brain injury.

Ewing-Cobbs, L., Prasad, M.R., Kramer, L., Cox, C.S., Baumgartner, J., Fletcher, S., et al. (2006). Late intellectual and academic outcomes following traumatic brain injury sustained in early childhood. *Journal of Neurosurgery, 105,* 287-296.

Fannon, D., Tennakoon, L., Sumich, A., O'Ceallaigh, S., Doku, V., Chitnis, X., et al. (2000). Third ventricle enlargement and developmental delay in first-episode psychosis: Preliminary findings. *British Journal of Psychiatry, 177*, 354-359.

Gale, S.D., Baxter, L., Roundy, N., & Johnson, S.C. (2005). Traumatic brain injury and grey matter concentration: A preliminary voxel based morphometry study. *Journal of Neurology, Neurosurgery, and Psychiatry, 76,* 984-988.

Geddes, J. F., Hackshaw, A. K., Vowles, G. H., Nickols, C. D., & Whitwell, H. L. (2001). Neuropathology of inflicted head injury in children: I. Patterns of brain damage. *Brain, 124,* 1290-1298.

Gerring, J., Brady, K., Chen, A., Quinn, C., Herskovits, E., Bandeen-Roches, K., et al. (2000). Neuroimaging variables related to development of Secondary Attention Deficit Hyperactivity Disorder after closed head injury in children and adolescents. *Brain Injury, 14*(3), 205-218.

Giza, C.C., Mink, R.B., & Madikians, A. (2007). Pediatric traumatic brain injury: Not just little adults. *Current Opinion in Critical Care, 13,* 143-152.

Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., Vaituzis, A.D., et al. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America, 101*(21), 8174-8179.

Hanten, G., Scheibel, R.S., Li, X., Oomer, I., Stallings-Roberson, G., Hunter, J.V., et al. (2006). Decision-making after traumatic brain injury in children: A preliminary study. *Neurocase, 12,* 247-251.

Hardan, A.Y., Minshew, N.J., Harenski, K., & Keshavan, M.S. (2001). Posterior fossa magnetic resonance imaging in autism. *Journal of the American Academy of Child & Adolescent Psychiatry*, *40*(6), 666-672.

Henry-Feugeas, M.C., Azouvi, P., Fontaine, A., Denys, P., Bussel, B., Maaz, F. et al. (2000). MRI analysis of brain atrophy after severe closed-head injury: relation to clinical status. *Brain injury, 14*(7): 597-604

Himanen, L., Portin, R., Isoniemi, H., Helenius, H., Kurki, T., & Tenovuo, O. (2005). Cognitive functions in relation to MRI findings 30 years after traumatic brain injury. *Brain Injury, 19*(2), 93–100.

Hooper, S. R., Alexander, J., Moore, D., Sasser, H. C., Laurent, S., King, J., et al. (2004). Caregiver reports of common symptoms in children following a traumatic brain injury. *NeuroRehabilitation, 19,* 175–189.

Isaac, C.L., Holdstock, J.S., Cezayirli, E., Roberts, J.N., Holmes, C.J., & Mayes, A.R. (1998). Amnesia in a patient with lesions limited to the dorsomedial thalamic nucleus. *Neurocase, 4*, 497-508.

Johnson, S.C., Bigler, E.D., Burr, R.B., & Blatter, D.D. (1994). White matter atrophy, ventricular dilation, and intellectual functioning following traumatic brain injury. *Neuropsychology, 8*(3), 307-315.

Klove, H. Clinical neuropsychology (1963). In F.M. Forster (Ed.). *The medical clinics of North America.* New York: Saunders, 1647-1658.

Kochanek, P.M. (2006). Pediatric traumatic brain injury: Quo vadis? *Developmental Neuroscience, 28*, 244-255.

Kriel, R.L., Krach, L.E., & Panser, L.A. (1989). Closed head injury: Comparison of children younger and older than 6 years of age. *Pediatric Neurology, 5*, 296-300.

Kurca, E., Sivak, S., & Kucera, P. (2006). Impaired cognitive functions in mild traumatic brain injury patients with normal and pathologic magnetic resonance imaging. *Neuroradiology, 48*(9), 661-669.

Lagopoulos, J. (2007). Voxel-based morphometry made simple. *Acta Neuropsychiatrica, 19*, 213–214.

Langlois, J.A., Rutland-Brown, W., & Thomas, K.E. (2005). The incidence of traumatic brain injury among children in the United States: Differences by race. *Journal of Head Trauma Rehabilitation, 20*(3), 229-238.

Leblanc, N., Chen, S., Swank, P.R., Ewing-Cobbs, L., Barnes, M., & Dennis, M., et al. (2005). Response inhibition after traumatic brain injury (TBI) in children: Impairment and recovery. *Developmental Neuropsychology, 28*(3), 829-848.

Levin, H.S., O'Donnell, V.M., & Grossman, R.G. (1979). The Galveston Orientation and Amnesia Test. A practical scale to assess cognition after head injury. *The Journal of Nervous and Mental Disease, 167*, 675-684.

Levin**,** H.S., Grossman**,** R.G., Sarwar, M., & Meyers, C.A. (1981). Linguistic recovery after closed head injury. *Brain and Language, 12*(2), 360-374.

Levin, H.S., Meyers, C.A., Grossman, R.G., & Sarwar, M. (1981). Ventricular enlargement after closed head injury. *Archives of Neurology, 38*(10), 623-629.

Levin, S.H., Williams, D.H., & Valastro, M. (1990). Corpus callosal atrophy following head injury: Detection with magnetic resonance imaging. *Journal of Neurosurgery, 73*, 77-81.

Levin, H.S., Benavidez, D.A., Verger-Maestre, K., Perachio, N., Mendelsohn, D.B., & Fletcher, J.M. (2000). Reduction of corpus callosum growth after severe traumatic brain injury in children. *Neurology, 54*(3), 647-653.

Levin, H.S., Song, J., Ewing-Cobbs, L., Chapman, S.B., & Mendelsohn, D. (2001). Word fluency in relation to severity of closed head injury, associated frontal brain lesions, and age at injury in children. *Neuropsychologia, 39*, 122-131.

Levin, H. S., Hanten, G., Chang, C., Zhang, L., Schachar, R., Ewing-Cobbs, L., et al. (2002). Working memory after traumatic brain injury in children. *Annals of Neurology, 52*(1), 82-88.

Levin, H.S. (2003). Neuroplasticity following non-penetrating traumatic brain injury. *Brain Injury, 17*(8), 665-674.

Levin, H.S., Zhang, L., Dennis, M., Ewing-Cobbs, L., Schachar, R., Max, J., et al. (2004). Psychosocial outcome of TBI in children with unilateral frontal lesions. *Journal of the International Neuropsychological Society, 10*, 305-316.

Levin, H.S. & Hanten, G. (2005). Executive functions after traumatic brain injury in children. *Pediatric Neurology, 33*(2), 79-93.

Lezak, M. D. (1995). *Neuropsychological assessment* (Third ed.). New York: Oxford University Press.

Max, J.E. (2005). Children and Adolescents. In *Textbook of Traumatic Brain Injury.* Washington, DC: American Psychiatric Publishing, Inc.

McCarthy, M.L., Serpi, T., Kufera, J.A., Demeter, L.A., & Paidas, C. (2002).Factors influencing admission among children with a traumatic brain injury. *Academic Emergency Medicine, 9*(7), 684-693.

Mendelsohn, D., Levin, H.S., Bruce, D., Lilly, M., Harward, H., Culhane, K.A. (1992). Late MRI after head injury in children: relationship to clinical features and outcome. *Child's Nervous System, 8,* 445-452.

Oddy, M. (1993). Head injury during childhood. *Neuropsychological Rehabilitation, 3*(4), 301-320.

Peinado-Manzano, M.A. & Pozo-Garcia, R. (1996). Retrograde amnesia in rats with dorsomedial thalamic damage. *Behavioral Brain Research, 80*, 177-184.

Poca, M.A., Sahuquillo, J., Mataro, M., Benejam, B., Arikan, F., & Baguena, M. (2005). Ventricular enlargement after moderate or severe head injury: a frequent and neglected problem. *Journal of Neurotrauma, 22*(11): 1303-10.

Power, T., Catroppa, C., Coleman, L., Ditchfield, M., & Anderson, V. (2007). ; Do lesion site and severity predict deficits in attentional control after preschool traumatic brain injury (TBI)? *Brain Injury, 21*(3), 279-292.

Prins, M. L., & Hovda, D. A. (2003). Developing experimental models to assess traumatic brain injury in children. *Journal of Neurotrauma, 20*(2), 123-137.

Pullela, R., Raber, J., Pfankuch, T., Ferriero, D.M., Claus, C.P., Koh, S., et al. (2006). Traumatic injury to the immature brain results in progressive neuronal loss, hyperactivity and delayed cognitive impairments. *Developmental Neuroscience, 28*, 396-409.

Raz, S., Lauterbach, M.D., Hopkins, T.L., Glogowski, B.K., Porter, C.L., Riggs, W.W., et al. (1995). A female advantage in cognitive recovery from early cerebral insult. *Developmental Psychology, 31*(6), 958-966.

Reider-Groswasser, I., Cohen, M., Costeff, H., & Groswasser, Z. (1993). Late CT findings in brain trauma: relationship to cognitive and behavioral sequelae and to vocational outcome. *American Journal of Roentgenology, 160*(1), 147-152.

Reynolds, C.R. & Bigler, E.D. (1994). *Test of Memory and Learning.* Austin, Tx: Pro-Ed.

Ruff, R. M., Light, R. H., Parker, S. B., & Levin, H. S. (1997). The psychological construct of word fluency. *Brain and Language, 57*, 394-405.

Ryser, D., Bigler, E.D., & Blatter, D.D. (1996). Clinical and neuroimaging predictors of post TBI outcome. In: Ponsford, J., Snow, Anderson, V., eds. *International Perspectives in Traumatic Brain Injury*. Bowen Hills QLD: Australian Academic Press; 1996: 79-83.

Salorio, C.F., Slomine, B.S., Grados, M.A., Vasa, R.A., Christensen, J.R., & Gerring, J.P. (2005). Neuroanatomic correlates of CVLT-C performance following pediatric traumatic brain injury. *Journal of the International Neuropsychological Society, 11*, 686-696.

Samatovicz, R.A. (2000). Genetics and brain injury: Apolipoprotein E. *Journal of Head Trauma and Rehabilitation, 15*(3), 869-874.

Satz, P., Zaucha, K, McCleary, C., Light, R., Asarnow, R., & Becker, D. (1997). Mild head injury in children and adolescents: A review of studies (1970-1995).

Schacher, R., Levin, H.S., Max, J.E., & Purvis, K. (2004). Attention deficit hyperactivity disorder symptoms and response inhibition after closed head injury in children: Do preinjury behavior and injury severity predict outcome. *Developmental Neuropsychology, 25*(1&2), 179-198.

Slomine, B. S., Gerring, J. P., Grados, M. A., Vasa, R., Brady, K. D., Christensen, J. R., et al. (2002). Performance on measures of `executive function' following pediatric traumatic brain injury. *Brain Injury, 16*(9), 759-772.

Sowell, E.R., Thompson, P.M., Tessner, K.D., & Toga, A.W. (2001). Mapping continued gray matter density reduction in dorsal frontal cortex: Inverse relationships during postadolescent brain maturation. *The Journal of Neuroscience, 21*(22), 8819-8829.

Spanos, G.K., Wilde, E.A., Bigler, E.D., Cleavinger, H.B., Fearing, M.A., Levin, H.S., et al. (2007). Cerebellar atrophy after moderate-to-severe pediatric traumatic brain injury. *American Journal of Neuroradiology, 28,* 537-542.

Staal**,** W.G., Hulshoff Pol, H.E., Schnack, H.G., Hoogendoorn, M. L. C., Jellema, K., & Kahn, R. (2000). Structural brain abnormalities in patients with schizophrenia and their healthy siblings. *American Journal of Psychiatry, 157*(3), 416-421.

Strasser, H.C., Lilyestrom, J., Ashby, E.R., Honeycutt, N.A., Schretlen, D.J., Pulver, A.E., et al. (2005). Hippocampal and ventricular volumes in psychotic and nonpsychotic bipolar patients compared with schizophrenia patients and community control subjects: A pilot study. *Biological Psychiatry, 57*(6), 633-639.

Stiles, J. (2000). Neural plasticity and cognitive development. *Developmental Neuropsychology, 18*(2), 237-272.

Tasker, R.C., Salmond, C.H., Westland, A.G., Pena, A., Gillard, J.H., Sahakian, B.J., et al. (2005). Head circumference and brain and hippocampal volume after severe traumatic brain injury in childhood. *Pediatric Research, 58*(2), 302-308.

Tasker, R.C. (2006). Changes in white matter late after severe traumatic brain injury in childhood. *Developmental Neuroscience, 28,* 302-308.

Taylor, H.G., Yeates, K.O., Wade, S.L., Drotar, D., Stancin, T., & Minich, N. (2002). A prospective study of short- and long-term outcomes after traumatic brain injury in children: Behavior and achievement. *Neuropsychology, 16*(1), 15-27

Taylor, H.G. (2004). Research on outcomes of pediatric traumatic brain injury: Current advances and future directions. *Developmental Neuropsychology, 25*(1&2), 199-225.

Verger, K., Junqué, C., Jurado, M. A., Tresserras, P., Bartumeus, F., Nogués, P., et al. (2000). Age effects on long-term neuropsychological outcome in paediatric traumatic brain injury. *Brain Injury, 14*(6), 495-503.

Verger, K., Junque, C., Levin, H.S., Jurado, M.A., Perez-Gomez, M., Bartres-Faz, D., et al. (2001). Correlation of atrophy measures on MRI with neuropsychological

sequelae in children and adolescents with traumatic brain injury. *Brain Injury, 15*(3), 211-221.

Wallesch, C. W., Curio, N., Galazky, I., Jost, S., & Synowitz, H. (2001). Neuropsychology of blunt head injury in the early postacute stage: Effects of focal lesions and diffuse axonal injury. *Journal of Neurotrauma, 18*(1), 11-20.

Wassenberg, R., Max, J.E., Lindgren, S.D., & Schatz, A. (2004). Sustained attention in children and adolescents after traumatic brain injury: relation to severity of injury, adaptive functioning, ADHD and social background. *Brain Injury, 18*(8), 751-764.

Wechsler D. (1987). *Wechsler Memory Scale–Revised.* New York, NY: Psychological Corporation.

Wechsler D. (1991). *Wechsler Intelligence Scale for Children—Third Edition.* San Antonio, TX: Psychological Corporation.

Wilde, E.A., Hunter, J.V., Newsome, M.R., Scheibel, R.S., Bigler, E.D., Johnson, J.L., et al. (2005). Frontal and temporal morphometric findings on MRI in children after moderate to severe brain injury. *Journal of Neurotrauma, 22*(3), 333-344.

Wilde, E.A., Bigler, E.D., Haider, J.M., Chu, Z., Levin, H.S., Li, X., et al. (2006). Vulnerability of the anterior commissure in moderate to severe pediatric traumatic brain injury. *Journal of Child Neurology, 21*, 769-776.

Wilde, E.A., Chu, Z., Bigler, E.D., Hunter, J.V., Fearing, M.A., Hanten, G., et al. (2006). Diffusion tensor imaging in the corpus callosum in children after moderate to severe brain injury. *Journal of Neurotrauma, 23*(10), 1412-1426.

Wilde, E.A., Bigler, E.D., Hunter, J.V., Fearing, M.A., Scheibel, R.S., Newsome, M.R., et al. (2007). Hippocampus, amygdala, and basal ganglia morphometrics in children after moderate-to-severe traumatic brain injury. *Developmental Medicine and Child Neurology, 49,* 294-299.

Wilkinson G. (1993). *Wide Range Achievement Test–Third Edition*. Wilmington, Del: Wide Range Inc.

Xenos, C., Sgouros, S., & Natarajan, K. (2002). Ventricular volume change in childhood. *Journal of Neurosurgery, 97*(3), 584-590.

Yeates, K.O., Wade, S.L., Stancin, T., Taylor, H.G., Drotar, D., & Minch, N. (2002). A prospective study of short- and long-term neuropsychological outcomes after traumatic brain injury in children. *Neuropsychology, 16*(4), 514-523.

Yeates, K. O., Swift, E., Taylor, G., Wade, S. L., Drotar, D., Stacin, T., et al. (2005). Short- and long-term social outcomes following pediatric traumatic brain injury. *Journal of the International Neuropsychological Society, 10*, 412-426.