9-2005

MR Spectroscopy and SWI: Neuropsyehological Outcome after Pediatric Brain Injury

Talin Babikian

LOMA LINDA UNIVERSITY
Graduate School

MR Spectroscopy and SWI: Neuropsychological Outcome after Pediatric Brain Injury

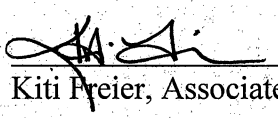
by

Talin Babikian

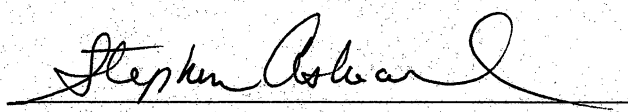
A Dissertation submitted in partial satisfaction of
the requirements for the degree of
Doctor of Philosophy in Psychology

September 2005

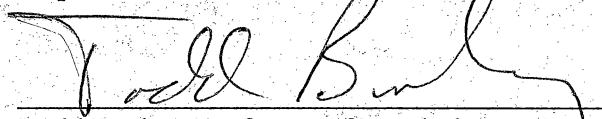
Each person whose signature appears below certifies that this dissertation in his/her opinion is adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.



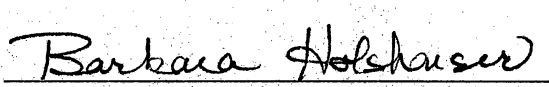
Kiti Freier, Associate Professor of Psychology and Pediatrics, Chairperson



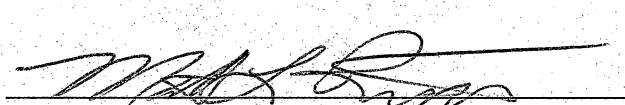
Stephen Ashwal, Professor of Pediatrics



Todd Burley, Professor of Psychology



Barbara Holshouser, Associate Professor of Radiology



Matt Riggs, Professor of Psychology

ACKNOWLEDGEMENTS

I would like to express my appreciation to the individuals who helped me complete this study. I wish to thank my dissertation committee chair, Dr. Kiti Freier, as well as my committee members, Drs. Stephen Ashwal, Todd Burley, Barbara Holshouser, and Matt Riggs, for their continued guidance and support. I am also grateful to the patients and their families for their time and willingness to participate.

DEDICATION

I would like to dedicate this work to my husband, Michael, for his continued patience and support throughout my journey.

CONTENTS

FIGURES

Figure

TABLES

Table

ABBREVIATIONS

ADHD	Attention Deficit/Hyperactivity Disorder
BASC PRS	Behavior Assessment System for Children – Parent Rating Scale
BASC SRP	Behavior Assessment System for Children – Self-Report of Personality
Cho	Choline
Cre	Creatine
CVLT-C	California Verbal Learning Test – Children's Version
CVLT-II	California Verbal Learning Test – Second Edition
DAI	Diffuse axonal injury
EEG	Electroencephalogram
FSIQ	Full Scale Intelligence Quotient
GCS	Glasgow Coma Scale
Glx	Glutamate/glutamine
GRE	Gradient-recalled echo
IQ	Intelligence Quotient
Lac	Lactate
LLUCH	Loma Linda University Children's Hospital
MAP	Mean arterial pressure
mI	Myoinositol
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MRSI	Magnetic resonance shift imaging (multi-voxel MRS)

NAA	N-acetyl aspartate
NPI	Neuropsychological Index
PIQ	Performance Intelligence Quotient
POI	Perceptual Organization Index
PRI	Perceptual Reasoning Index
PSI	Processing Speed Index
RCFT	Rey Complex Figure Test
SWI	Susceptibility weighted imaging
TBI	Traumatic brain injury
TMT	Trail Making Test
TOLDX	Tower of London – Drexel
VCI	Verbal Comprehension Index
VIQ	Verbal Intelligence Quotient
WAIS-III	Wechsler Adult Intelligence Scale – Third Edition
WIAT-II-A	Wechsler Individual Achievement Test – Edition Two – Abbreviated
WISC-IV	Wechsler Intelligence Scale for Children – Fourth Edition
WMI	Working Memory Index
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence – Third Edition

ABSTRACT OF THE DISSERTATION

MR Spectroscopy and SWI: Neuropsychological Outcome
after Pediatric Brain Injury

by

Talin Babikian

Doctor of Philosophy, Graduate Program in Psychology
Loma Linda University, September 2005
Dr. Kiti Freier, Chairperson

Traumatic brain injury (TBI) is among the most frequent pediatric neurological disorders and a significant contributor to childhood morbidity/mortality in the US. Although clinical indicators have been helpful in predicting long term outcomes, more effective prognostic tools are being sought. This study assessed the efficacies of acute single and multi-voxel Magnetic Resonance Spectroscopy (MRS) and Susceptibility Weighted Imaging (SWI) when predicting long-term neurocognitive functioning in pediatric TBI patients. Twenty children/adolescents (mean age 13.3 years, 5.8 SD) treated at Loma Linda University Children's Hospital for a head injury were administered measures of intellectual and neuropsychological functioning 1-4 years post injury. Without exception, patients scored markedly lower on all neurocognitive measures compared to age-matched norms. Clinical indicators of injury severity and age at injury were associated with outcomes. Early age at injury ($\leq$ 8 years) and severe TBI together resulted in poor neurocognitive outcome, older age and mild injury resulted in scores within the normal range, while variable outcome was noted for patients with only one of the risk factors.

Positive and strong associations were noted between both single and multi-voxel MRS NAA spectra (and associated ratios) with neurocognitive scores, with NAA/Cre alone explaining 48% or more of the variance in outcomes. Multi-voxel MRS NAA/Cre alone was a significant predictor of neurocognitive outcome, explaining 18% or more variance above and beyond a combination injury severity/age at injury variable. Furthermore, both SWI lesion number and volume were negatively and strongly associated with neurocognitive outcome. These variables explained 9% or more variance in scores, above and beyond the additive injury severity/age at injury and total days in coma variables. Exploratory analyses revealed a notable trend, with lesions in deeper brain regions (possibly linked to diffuse axonal injury) more strongly associated with poor neurocognitive outcome as compared to lesions in cortical areas. Both MRS and SWI provided a mutually exclusive contribution to the prediction of long-term outcomes, supporting their use in clinical practice. Incorporating neuroimaging technology in clinical care will improve prognostic efforts, helping clinicians and family members plan treatment and services necessary for optimal physical, cognitive, and emotional recovery following a head injury in childhood.

INTRODUCTION

Every year, one and a half million individuals in the United States sustain a traumatic brain injury (TBI), constituting eight times the breast cancer incidence rate and 34 times the HIV/AIDS incidence rate (CDC, 2003). Among pediatric populations, approximately 170,000 children survive closed head injury every year in the United States (Kraus, 1995), with vehicle accidents, bicycle or pedestrian accidents, falls, and non-accidental trauma/assault as leading etiological factors (CDC, 2002). Among children between the ages of 0 and 14, TBI results in 3000 deaths, 29,000 hospitalizations and 400,000 emergency department visits annually (CDC, 2003). In fact, head injury is among the most frequent pediatric neurological disorders and a significant contributor to childhood morbidity and mortality (Rosman, 1999), particularly in children from birth to five years of age. Survivors of pediatric head trauma may suffer from impairments in both general intellectual and specific neuropsychological functioning, including attention, memory, language, sensorimotor, visuospatial, and executive functioning deficits (Adelson & Kochanek, 1998; Kraus, 1995). The following review summarizes the literature on the clinical and neuroradiologic measures currently used to predict long-term outcomes following pediatric TBI. In addition, the literature addressing the anatomical correlates of TBI and subsequent neuropsychological sequelae is also reviewed.

Clinical Indicators

The duration of altered consciousness or posttraumatic amnesia as well as the extent of injury following a TBI have been used as clinical predictors of long-term cognitive outcome. A minimal neurologic assessment includes examination of reflexes and motor and sensory systems, ratings on the Glasgow Coma Scale (GCS), and cranial

and cranial nerve examination, including assessing papillary response to light, eye position and movement, corneal sensation, and the gag response (Adelson & Kochanek, 1998). In one study, the duration of impaired consciousness following TBI, number of intracranial lesions, as well as scores on the modified Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974) were significant predictors of both cognitive and motor outcome at three and again at 12 months following a TBI (Prasad, Ewing-Cobbs, Swank, & Kramer, 2002). The GCS is a gross but quantifiable and fairly reliable scoring system measuring a patient's level of consciousness immediately following a brain insult. The scoring system ranges from 3-15 and is composed of three separate scales measuring motor ability, verbal responses, and eye opening (Rosman, 1999). Based on the total score derived from the sum of the three GCS scales, brain injury severity has been categorized into three types: severe TBI is referred to a GCS of eight or less; moderate TBI is referred to a GCS of 9-12; and mild TBI is referred to a GCS of 13-15.

Although the use of the GCS can provide a quick and objective indication of injury severity, several patient related factors and advances in critical care management, including intubation, early use of sedatives and paralytics, can impede the accurate scoring of this measure. This limitation can in turn hinder its predictive value for long-term neurological and cognitive outcome (Rosman, 1999). In addition, the efficacy of injury severity variables, including GCS, as predictors of cognitive outcome are considered limited (Choi & Barnes, 1996; Rosman, 1999). It is therefore imperative for clinicians and researchers to investigate better outcome indicators in order to provide patients and their families more accurate prognoses and to better facilitate patient recovery.

Neuroimaging and TBI

In addition to alterations in consciousness, focal neurologic signs as detected by neuroradiologic assessments have also been used to predict the extent of injury following TBI (Bigler, 1999; Kirkpatrick, 1986; Rosman, 1999; Verger et al., 2001). The literature regarding neuroimaging as a predictor of long-term outcome following TBI is sparse at best. This is particularly true for the pediatric patient since the usefulness of various neuroimaging techniques with this population have not been explored due to variations in the maturity of the brain, etiologies of brain disorders and their subsequent presentation, and the modifications necessary to perform conventional imaging methods with younger children (Grant & Matsuda, 2003). Although a close relationship between neuroradiologic findings and long-term neuropsychological and neurobehavioral outcome would be expected, Bigler (1999) reported that this is not consistently the case. In fact, a variety of factors impede the latter expected relationship:

> "...the traumatically injured brain is in a dynamic phase of significant morphologic, hemodynamic, and biochemical change, probably for the first year post-injury and maybe longer. Thus, any view of the brain by static imaging within this time frame may not yield all of the pathological consequences that relate to neurobehavioral outcome" (pg. 418) (Bigler, 1999).

A review of neuroimaging findings following TBI revealed that no single imaging technique alone is superior over others, specifically since the neuropathological consequences following TBI vary by etiology (McAllister, Sparling, Flashman, & Saykin, 2001). Often, a combination of neuroimaging techniques will yield complimentary data, providing a clearer clinical picture of a TBI patient (Bigler, 2001). Nonetheless, the general consensus from these studies is that severity of injury as indicated by neuroimaging results will consistently be correlated with greater

neuropathological and/or structural brain damage, supporting their clinical use in the care of a TBI patient (Bigler, 1999).

The literature reviewed by Rosman (1999) indicated that a cranial MRI is an increasingly better method of evaluating the extent of injury following a pediatric TBI as compared to more traditional methods, such as the CT scan. Although the CT scan provides a quick and reliable indication of extent of injury, especially if an assessment of mental status is interfered by anesthesia or medications (Adelson & Kochanek, 1998), it has its limitations. Bony artifacts in the brain, such as the posterior fossa, hinder the CT scan, making it an ineffective neuroradiologic technique in the presence of injury in these areas (Rosman, 1999). In addition, other advantages of MR images include safety, variability of the plane in which images can be taken, excellent imaging of both normal and pathologic anatomy, and the fact that contrast injections are not needed (Rosman, 1999). However, this method is ineffective with patients who are severely ill and/or who cannot be adequately monitored during the imaging process, including very young patients who cannot remain still. According to Rosman (1999), the ease and safety by which images are obtained by an MRI allow for the visualization of small collections of blood. Nonetheless, even though MRI is superior to CT when detecting small hemorrhages, the "MR appearance of hemorrhage is quite variable and dependent on multiple intrinsic parameters such as the state of oxygenation of hemoglobin, and the integrity of red blood cells, as well as, extrinsic parameters such as field strength of the MR scanner, receiver bandwidth, type of sequence, and the degree of T1 and T2 weighting" (p. 336) (Tong et al., 2003).

Although few in number, other neuroradiologic studies attempting to predict outcome following pediatric TBI. On study reported using 18-fluorodeoxyglucose Positron Emission Tomography (PET) to predict performance on the Rancho Los Amigos Cognitive Level (RLACL) scale and on a modified version of the Glasgow Outcome Scale called the Children's Outcome Scale (COS) (Worley et al., 1995). Since glucose metabolization is directly related to rate of synaptic firing, it was assumed that PET scores would be correlated with severity and extent of brain injury and thus with clinical outcome. Conducting PET scans on 22 children who had received a non-penetrating TBI, Worley et al. (1995) were able to demonstrate a correlation between PET scores and both the RLACL and the COS. However, the authors suggested that although there was some evidence to suggest that PET was a better predictor of outcome if conducted within the first 12 weeks following injury, long-term outcome was not better explained by PET than with traditional CT or MRI scans (Worley et al., 1995).

In addition, Single Photon Emission Computed Tomography (SPECT) studies have, with limited success, also been used to predict outcome following TBI (Rosman, 1999). Goldenberg et al. (1992) compared neuropsychological outcome measures to SPECT data in a sample of 36 adult closed head injury patients as compared to an age and education matched control group. They reported that neuropsychological measures of executive function, memory, intelligence, and daily living skills did not correlate significantly with synaptic activity in the frontal, temporal, or thalamic regions. In addition, SPECT flow rates in the temporal lobe region (where the hippocampal structure and thus memory function can be localized) did not differ between the patient and control

groups, even though the former consistently scored lower on neuropsychological tests of memory than their matched controls (Goldenberg, Oder, Spatt, & Podreka, 1992).

Magnetic Resonance Spectroscopy

Brain damage could result in changes in the permeability of the blood-brain barrier, which may lead to imbalances in brain metabolites. This imbalance is associated with cellular damage above and beyond the initial brain injury. Secondary brain injury can be caused or enhanced by excitatory amino acids such as glutamate (Baker, Moulton, MacMillan, & Shedden, 1993) and aspartate (Adelson & Kochanek, 1998). The buildup of glutamate in synapses along with hypoxia can trigger a chain of intracellular events known as excitotoxicity, which result in cell damage or death (Johnston, 2004). Magnetic Resonance Spectroscopy (MRS), which is a non-invasive procedure available on most clinical MR scanners, provides quantifiable measures of neuronal and glial markers, neurotransmitters, energy metabolites, membrane markers, among other indicators of cell function or dysfunction (Hoon & Melhem, 2000). As such, it has relatively recently been suggested as a prognostic tool for TBI patients (Ashwal et al., 2000; Bigler, 1999; Brenner, Freier, Holshouser, Burley, & Ashwal, 2003; Shutter, Tong, & Holshouser, 2004; Uzan et al., 2003).

Unlike MRI, which is sensitive to signals from nuclei of water protons to construct anatomical images, MRS is sensitive to proton nuclei of molecules other than water that are present in various concentrations in the brain. MRS has also been suggested to be more sensitive at picking up brain damage than MRI. In one study, proton MRS from the thalamus indicated notable damage and was associated with severity of injury; this was true even when images from a conventional MRI indicated

normal thalami (Uzan et al., 2003). Thus, in the absence of visible structural damage, MRS can be an effective tool in identifying areas of neuronal dysfunction (McAllister et al., 2001).

In experimental animal models of traumatic brain injury, significant decreases in the metabolites around the area of contusion were noted, specifically for creatine/phosphocreatine (Cre/PCre), N-acetyl-asparatate (NAA), glutamate, inositol, and choline (Cho). These decreases were followed by notable increases over time, indicative of progressive cell recovery. In addition, a strong signal for lactate was also detected (Schuhmann et al., 2003), which is indicative of cell injury. Furthermore, several studies, with both pediatric and adult brain injury patients, have reported reductions in NAA (a neuronal marker) following a brain injury (Ariza et al., 2004; Bigler, 1999; McAllister et al., 2001).

Comparing MRS to more traditional clinical indicators, Ashwal and colleagues (2000) demonstrated a more precise efficacy in predicting long-term neurologic outcome in a pediatric sample approximately 6-12 months post head injury (accidental and nonaccidental). Patient spectra acquired to calculate metabolite ratios were taken from an 8 cm^3 volume voxel of primarily gray matter in the occipital area. The clinical predictors of neurologic outcome included GCS, glucose levels at the time of admission, occurrence of cardiac arrest, presence of nonreactive pupils, days of unconsciousness prior to MRS, and total days in coma, on ventilator and in the hospital. In this sample of 26 infants (1-18 months) and 27 children ($\geq$ 18 months), abnormal metabolite ratios (lower NAA/Cre or NAA/Cho; higher Cho/Cre) were reported in patients with poor outcome, as defined by the Pediatric Cerebral Performance Category Scale. In addition, the presence of

lactate was a significant contributor to poor outcome, correctly identifying 96% of patients in this category (Ashwal et al., 2000).

The prognostic efficacy of MRS following pediatric TBI was further confirmed by another study conducted by the above researchers (Brenner et al., 2003). MRS was used to predict the neurologic and neuropsychological outcomes 1 to 7 years post injury in 22 TBI (accidental and nonaccidental) patients (ages 1 week to 13 years at the time of injury). Clinical and neurologic variables included age at injury, presence of non-reactive pupils, occurrence of cardiac arrest, GCS score at the time of injury, number of days unconscious prior to MR studies, MRS metabolite data, EEG abnormalities (initial), as well as time passed since injury. The neuropsychological measures included tests of intellectual functioning, memory, linguistic abilities, planning, attention, visuospatial processing, and sensorimotor abilities. Consistent with the findings of Ashwal et al. (2000), the authors reported the presence of lactate to be a significant predictor of poor long-term intellectual and neuropsychological outcome. Further, both intellectual and neuropsychological functioning were negatively correlated with the presence of lactate and the Cho/Cre ratio, and positively correlated with NAA/Cho ratio. In addition to the MRS indicators, however, the clinical variables were also collectively effective as prognostic indicators for long-term cognitive outcome (Brenner et al., 2003).

Others have attempted to correlate neuropsychological indicators with spectra from specific areas of the brain that have a known association with specific neuropsychological tasks in adults. In one study, 20 adult severe TBI patients and 20 matched controls underwent neuropsychological assessments. Their performance was correlated with metabolite concentrations from voxels in the basal ganglia and temporal

regions. Decreased NAA/Cho ratios were noted in both regions as compared to controls, with concentration levels in the basal ganglia positively correlating with measures of speed, motor scanning, and attention (Ariza et al., 2004).

Furthermore, MRS studies have more recently focused on other metabolites. Occipital glutamate/glutamine (Glx) (Ashwal et al., 2004a) and myoinositol (mI) (Ashwal et al., 2004b) were significantly elevated in TBI children when compared to controls. Although Glx levels did not differ between good and poor outcome cases, higher levels of mI were associated with poorer outcome. In a sample of adult severe head injury patients, however, Glx and Cho were both sensitive indicators of neurologic outcome (poor/good) when spectroscopy was completed early (7 days) (Shutter et al., 2004).

The results from the above studies suggest that MRS is a relatively effective neuroradiologic tool when predicting neurologic and cognitive outcome following a brain injury. It remains to be determined whether spectra from regions other than those traditionally sampled for MRS or regions which are associated with specific cognitive abilities are better predictors of outcome following a TBI in childhood.

Susceptibility Weighted Imaging

Susceptibility Weighted Imaging (SWI) is a relatively recent neuroradiologic method, which uses conventional MR scanners to provide significant improvements in visualizing hemorrhages. Developed by Mark Haacke of the MRI Institute for Biomedical Imaging in St. Louis, SWI was originally referred to as High Resolution BOLD Venographic Imaging or HRBV (Reichenbach, Venkatesan, Schillinger, Kido, & Haacke, 1997). This method was used to visualize veins in the brain. Subsequently, the

HRBV acronym was replaced by a more descriptive one, AVID BOLD or Applications Venographic Imaging to Diagnose disease using the Blood Oxygen Level Dependent properties of venous blood. The latter can still be used if the purpose of the procedure is to visualize veins for vascular/anatomic purposes. However, the acronym SWI, a more general umbrella, is now used to refer to any procedure used predominantly in the brain to visualize veins to reveal anatomic and/or physiologic information about tissue using signal loss and phase data (Reichenbach et al., 1997). Using this technique within an MR scanner, differences in magnetic susceptibility or magnetic response to an applied magnetic field can be detected and quantified, revealing distinct information on quantity and location of oxygenated and deoxygenated venous products (Schewe, Stein, & Riodon, 2002; Tong et al., 2004). This technology can better detect hemorrhagic brain injury by providing sharper and clearer images of the brain, which were previously unavailable (Schewe et al., 2002). Although the SWI technology is currently used to image the brain only, promising advances will allow its use to extend to other areas of the body (Reichenbach et al., 1997).

Because the SWI technique has only recently been identified, very little information is available in regards to its clinical and prognostic utility following brain injury. In addition, although various neuroradiologic techniques have demonstrated a relatively strong efficacy to predict long-term neurologic and neuropsychological outcome, it is assumed that more of the variance in outcome, specifically following diffuse injuries (i.e., diffuse axonal injury or DAI), can be explained by more sensitive imaging techniques. This is in contrast to imaging techniques which are based on noticeable structural changes and/or abnormal metabolite activity (Tong et al., 2003). On

this basis, the team at Loma Linda University examined the potential superiority of SWI technology over more traditional methods when predicting neurologic outcome following pediatric TBI.

Using GCS as an outcome measure on seven pediatric TBI patients, the authors reported that SWI is a more effective method of quantifying brain injury and DAI than more traditional approaches (Tong et al., 2003). This was true for determining both the location and the size of brain hemorrhages as compared to the more conventional gradient-recalled echo (GRE) MR imaging technique. Specifically, the proportion of hemorrhagic lesions detected by the SWI technique was approximately 640% greater than that detected by conventional GRE, resulting in 200% more detected hemorrhagic volume (Tong et al., 2003). In addition, GCS scores were inversely related to both the number and volume of hemorrhages detected by SWI and the conventional GRE technique. Also, a higher proportion of lesions were found in the brainstem, the cerebellum, and the corpus callosum than previously reported in the literature (Tong et al., 2003). This finding is consistent with an MRI study looking at pediatric TBI cases where unexpected cerebellar atrophy was also found (Soto-Ares et al., 2001).

A similar follow-up study with a cohort of 40 children and adolescents who had incurred a brain injury revealed that the number and volume of lesions from diffuse brain injury (DAI) were significantly higher in patients with severe injury (GCS 3-8) as opposed to those with mild to moderate injury (GCS 9-15) (Tong et al., 2004). Furthermore, lesion number and volume were significantly different in patients who had experienced more than four days in a comatose state versus those with four days or less. These differences were still apparent when comparing severity groups on regional

measures of lesion number and volume. The regions studied included frontal gray and white matter, parieto-temporo-occipital gray and white matter, thalamus, basal ganglia, corpus callosum, brainstem, and the cerebellum (Tong et al., 2004).

The initial results from SWI studies suggest that it is a more superior method of detecting both hemorrhage number and volume that are associated with diffuse injuries. SWI results also appear to adequately distinguish between patients' overall neurologic outcome following a TBI. It remains to be determined whether the increased detection of hemorrhagic lesion number and volume as well as better localization of injury by using the SWI method will in turn be more predictive of long-term cognitive outcome as measured by standardized neuropsychological tests.

Anatomical and Physiological Mechanisms of TBI

Traumatic brain injuries can be categorized into open head (or penetrating) versus closed head injuries, focal versus diffuse injuries, or primary versus secondary injuries (Adelson & Kochanek, 1998). Open head injuries include instances where the scalp and/or skull are penetrated by an object, resulting in localized injury, leaving the unaffected areas intact (Farmer & Peterson, 1995). Contrarily, closed head injuries result from direct contact or inertial external forces. The former involves an inward compression of the skull at the site of the impact ("coup") with possible subsequent damage to the side of the brain opposite to the site of direct impact ("contrecoup"). This form of insult results in more localized damage while inertial force injuries result in more global or diffuse damage (Farmer & Peterson, 1995). Secondary insults, including brain swelling, increased intracranial pressure, infections, and bleeding can also follow as a result of TBI (Farmer & Peterson, 1995).

The neuropathological sequelae of a TBI are many and widely varied, ranging from changes in bone structure (i.e., fractures of the skull), tissue density, and water content, as well as blood flow, white matter integrity, pathway connectivity, and subtle biochemical changes (McAllister et al., 2001). The latter changes are currently considered critical in the gradual process that unfolds following a traumatic brain insult, which can be unlike changes that occur following structural damage only (Novack, Dillon, & Jackson, 1996).

In addition, traumatic lesions in the brain can be due to different forces of impact. Injury due to linear acceleration produce subdural hematomas and superficial contusions while lesions produced from rotational forces (deceleration and acceleration) can cause more widespread damage (Rosman, 1999). Although the latter can cause both cortical surface and brainstem/deep gray matter injury, a significant impact following such injuries is due to damage received to cerebral white matter or DAI (Rosman, 1999). Shearing injuries are often observed on neuroimaging scans following TBI and often result from differential movement of brain regions with variable tissue density (Rosman, 1999). Most damage of this kind occurs in the white matter between the frontal and temporal lobes, in the corpus callosum (particularly the posterior half of the body and splenium), and the brainstem (Rosman, 1999).

DAI occurs in approximately half of all severe head injury cases and 35% of all head injury related deaths (Graham & McIntosh, 1996). Although increasing MRI technology has significantly improved the ability to detect DAI, more recent studies suggest that DAI is harder to diagnose than previously considered and that much too often, clinical suspicions of DAI are not consistent with neuroimaging results.

Furthermore, children are more prone to experiencing diffuse injuries because of their unique unbalanced head to body ratio, weak neck musculature, lack of myelination (Adelson & Kochanek, 1998), and also because their developing skull structure does not protect them against distortions and shearing as it does in adults (Franzen & Berg, 1998).

Although DAI is considered to be a primary cause of functional deficit following pediatric TBI (Rosman, 1999), more focal structural damage has also been associated with outcome. For example, poor cognitive outcome has been associated with damage, as measured by neuroimaging tools, to the frontal and temporal regions (Berryhill et al., 1995; Levin et al., 1997; Mendelsohn et al., 1992; Soto-Ares et al., 2001; Wallesch, Curio, Galazky, Jost, & Synowitz, 2001; Wallesch, Curio, Kutz et al., 2001), as well as the corpus callosum (Verger et al., 2001), cerebellum, basal ganglia (Soto-Ares et al., 2001), and brainstem. As such, neuropsychological outcome studies have looked at both general cognitive abilities as well as specific abilities functionally associated with particular brain structures or areas.

Structural Abnormality and Neuropsychological Outcome

Several studies have suggested neuropsychological impairment following pediatric TBI. The literature reviewed by Rosman (1999) indicated that the most common neuropsychological sequelae following pediatric head injury is memory impairment, followed by attention problems. Although, as discussed below, numerous studies have reported on neuropsychological deficits following pediatric TBI, studies specifically examining differences in neuropathology following various etiologies of injury (i.e., more general injury such as DAI versus focal injury) in children are limited.

Therefore, the literature for adult and pediatric TBI is reviewed next, specifically with regard to cognitive outcome following DAI.

Wallesch et al. (2001) assessed the neuropsychological skills of 60 mild to moderate TBI patients between the ages of 16 and 70 years at 8-31 days and again 18-45 weeks post injury in order to differentiate cognitive outcomes following focal injuries as compared to DAI. The neuropsychological measures were designed to assess attention and psychomotor speed, memory function, executive functions, as well as visuoconstructional abilities. The clinical measures addressed included the GCS at the site of injury and the Injury Severity Score (ISS) at admission (with higher scores indicative of more severe trauma). Neuroradiologic measures included a CT scan at admission, which was used to assess the presence and extent of DAI. In this study, the extent of DAI was associated with notable neuropsychological deficits, particularly in the weeks immediately following injury. The deficits observed from both DAI and focal contusions were mainly related to injuries in the frontal and temporal lobes. As such, resulting impairments were limited to tests of executive skills (response selection and suppression), semantic fluency, as well as behavioral deficits (Wallesch, Curio, Galazky et al., 2001).

In a separate but related paper, this same group of researchers reported that initial GCS was correlated with DAI (measured by a CT scan) but not with focal pathology (Wallesch, Curio, Kutz et al., 2001). On tests of neuropsychological ability, extent of DAI was in turn strongly associated with tasks generally associated with the frontal lobes, including deficits in semantic fluency and interference tasks. Local lesions, however, were also associated with frontal lobe dysfunction, including problems with concept

formation, fluency tasks, and behavioral concerns. Frontal contusions, on the other hand, were associated with visuomotor planning and performance deficits. Based on these results, the authors concluded that both DAI and focal lesions can result in deficits associated with the frontal lobes (Wallesch, Curio, Kutz et al., 2001).

In addition to frontal and temporal regions, other studies on TBI outcome have reported structural damage to the corpus callosum with subsequent neuropsychological impairments (Johnson, Pinkston, Bigler, & Blatter, 1996; Verger et al., 2001). In a study with a TBI sample of 97 adults, Johnson and colleagues (1996) compared the estimated area of the corpus callosum (from MRI scans) to that of 166 normal controls. Neuropsychological tests, including the Wechsler Adult Intelligence Scale – Revised (WAIS-R) and the Wechsler Memory Scale – Revised (WMS-R), were administered only to the TBI patients. The authors reported a significant yet selective atrophy in specific areas of the corpus callosum, namely, the genu (anterior bend) and isthmus (posterior bend). The authors attributed the decrease in corpus callosum volume to either cortical degeneration or DAI at sites other than the corpus callosum. Neuropsychological findings suggested an association between splenium area and the Digit Symbol task (a measure of rapid graphomotor skills), specifically for female TBI patients. This finding is in the context of apparent gender differences with regard to corpus callosum volume, with women having a larger corpus callosum volume than men relative to their overall cranial volume (Johnson et al., 1996).

Similarly, Verger et al. (2001) studied 19 children and adolescents at least six years post TBI and compared their performance on measures of neuropsychological abilities to matched controls. MRI scans were also used to estimate ventricular volume

as well as corpus callosum area. The authors reported that the TBI patients performed significantly poorer than their matched controls on measures of general intelligence, visual memory, visuospatial abilities, and frontal lobe functioning. In addition, they reported that unlike ventricular volume, corpus callosum area was significantly associated with both processing speed and visuospatial abilities (Verger et al., 2001). Finally, one study suggested that the presence of petechial hemorrhage on neuroimaging studies following TBI was associated with lower scores, specifically in the areas of cognitive, motor, and academic functioning (Bowen, 1995).

Neuropsychological Findings Following Pediatric TBI

Although severity of injury is negatively associated with neuropsychological outcome, it has been suggested that even mild TBI has subsequent neurobehavioral sequelae (Bigler, 2003), despite negative neuroimaging results. This may suggest that some structural, or metabolic/physiologic damage may exist below thresholds necessary for detection by neuroimaging (Bigler & Snyder, 1995).

In a longitudinal study of neuropsychological outcome following TBI in early life, Ewing-Cobbs and colleagues (1997) assessed 35 mild/moderate and 44 severe TBI patients who were between four months and seven years of age at the time of injury. A neuropsychological battery, comprised of age appropriate IQ composites, motor tests, and receptive/expressive language abilities was administered at baseline (immediately following injury), and again at 6, 12, and 24 months following TBI (Ewing-Cobbs et al., 1997). Severe TBI patients demonstrated deficits in all of the above neuropsychological areas as compared to the mild/moderate TBI group. Consecutive assessments revealed improvement of performance in all neuropsychological domains over time (Ewing-Cobbs

et al., 1997). Time past since injury was reported to be important when predicting functional outcome. Although severity of and time since injury were found to be significantly associated with neuropsychological functioning, age of injury was not related to outcome. In fact, cognitive deficits following TBI between the ages of 4-41 months and 42-72 months were not different (Ewing-Cobbs et al., 1997). It is important to note, however, that both groups of patients were relatively young (i.e., ≤6 years of age), which may account for the lack of differences noted.

Reporting on a comparably older sample of pediatric TBI patients, a team of researchers from the University of Washington published a series of cohort prospective studies to address neurobehavioral outcome (Jaffe et al., 1992). The original report included neuropsychological outcomes on 98 TBI patients out of the 129 children eligible patients on consecutive admissions to two regional hospitals. Enrollment eligibility included age (6 to 15 years at the time of injury) and admission to the hospital due to a closed head injury (mild, moderate, or severe, as defined by the GCS). In addition, 98 controls matched for age, gender, school grade, and academic performance (as provided by teacher assessments), were also enrolled in the study. A comprehensive neuropsychological battery was administered to all study participants. The TBI patient group was administered the battery approximately three weeks following full orientation after injury. The battery included measures of intelligence (Wechsler Intelligence Scale for Children-Revised); adaptive problem solving (Category Test, Progressive Figures, Color Form), Trails B (9 to 14 year old battery); memory (California Verbal Learning Test); academic (Wide Range Achievement Test – Revised); motor (Coding, name

writing, tapping, grip strength); and psychomotor (Tactual Performance Test) functioning (Jaffe et al., 1992).

The results suggested a marked decline in performance across all neuropsychological domains, including intelligence, memory, adaptive problem solving, motor performance, and academic functioning, with poorer performance noted with increasing injury severity (Jaffe et al., 1992). In addition, although the moderate and severe injury groups performed at normal levels on the intelligence measure as compared to published normative data, they revealed significantly lower scores than their demographically matched controls (Jaffe et al., 1992), reiterating the importance of using a healthy comparison group when identifying deficits in performance.

Although the above study indicated significant impairments in neuropsychological functioning immediately following TBI, Jaffe and colleagues performed longitudinal assessments approximately one year following the initial evaluations in order to determine the chronicity of the deficits (Jaffe et al., 1993). Subsequently, 94 of the original TBI sample and their matched controls were retested across all six neuropsychological domains. Similar to their original results, performance in all six domains was significantly correlated with injury severity. This was especially true for tests of intelligence, academic functioning, and motor performance (Jaffe et al., 1993). In addition, severity of injury was related to recovery, determined by a rank-sum measure of change for each domain (specifically for the moderate and severe injury groups). Again, deficits were observed only when the patients' scores were compared to their matched controls and not when they were compared to published norms (Jaffe et al., 1993).

Three years following their TBI, 72 of the original patients and their matched controls were reassessed. Moderate and severe TBI patients consistently demonstrated deficits compared to their control counterparts across all neuropsychological domains (Fay et al., 1994). It was concluded that the consistent deficits experienced by this patient population, at least up to three years post injury, are not transient. Again, the association between injury severity and neurobehavioral outcome three years post injury was noted (Fay et al., 1994). In a different publication on this same sample, Massagli et al. (1996) performed several more in depth analyses examining the relationship between injury severity and outcome. They reported that significant impairments were found specifically in patients who took at least one month to reach a GCS of 15 or who had an initial GCS in the 3-5 range (Massagli et al., 1996).

Although studies, which provide information on a wide array of neuropsychological/neurobehavioral domains, such as the cohort study reviewed above, are rare, there are numerous studies describing the sequelae of specific cognitive and neuropsychological domains following pediatric TBI. These studies will be reviewed next.

Learning/Memory

The literature in the cognitive sciences has indicated that there are indeed two main types of memory, each with its own associated neurocircuitry (Nelson, 1997). These two distinct systems have been given various titles: memory vs. habit (Bachevalier & Mishkin, 1992); explicit vs. implicit memory; declarative vs. procedural memory (Nelson, 1997). Reviewing the neuroanatomical research on these two mechanisms of retention, namely "memory" and "habit," Bachevalier and Mishkin (1992) outline the

following neurocircuitry for each. Stated simply, "memories" are dependent on medial temporal structures while the formation of "habits," although less distinct, are likely to involve the striatum (caudate and putamen) but not the temporal medial region (including the hippocampus), cerebellum, or frontal lobes (Bachevalier & Mishkin, 1992; Nelson, 1997). Because of the distinction in neurocircuitry in the two forms of memory function, it is believed that damage to different parts of the brain can result in varying memory deficits.

In order to investigate this possibility, Ward et al. (2002) separately assessed procedural and explicit memory in a group of 15 children who had sustained a moderate or severe TBI and compared their performance to 15 matched control subjects. The procedural memory tasks involved a motor-perceptual task (i.e., rotary pursuit) and a cognitive task (i.e., mirror reading). The explicit memory tasks involved the recall or recognition of items on the previous two tasks (Ward, Shum, Wallace, & Boon, 2002). The results from this study suggested that the TBI group performed significantly poorer than the control group on the explicit memory tasks; there were no differences in performance on the procedural memory tests, suggesting that it is explicit and not implicit memory skills which are negatively affected by a brain insult (Ward et al., 2002).

Roman et al. (1998) evaluated verbal memory skills in a pediatric sample of TBI patients. Participants in this study included 44 TBI patients and 18 non-TBI trauma patients who were admitted to San Diego area inpatient trauma units and who were between 6 and 16 years 11 months of age. Exclusion criteria included left-handedness, non-monolingual English speakers, or children with any prior history of neurological, psychiatric or medical disorders. Both groups of patients were assessed at approximately

one month post injury and again in three months using the California Verbal Learning Test – Children's Version (CVLT-C) (Roman et al., 1998). The CVLT-C provides a detailed analysis of an examinee's verbal memory and learning strategy skills, including general learning ability (i.e., number of words recalled following a series of presentations, including time delayed recall tasks); type and number of response errors; learning characteristics (including learning slope and recall consistency); and learning strategy (i.e., semantic or serial clustering vs. none). The results from this study indicated that compared to controls, the severe TBI participants demonstrated a mild encoding deficit, consistent with lower scores on immediate recall, delayed recall, and recognition accuracy. The mild/moderate TBI participants, however, did not perform differently than the non-TBI controls (Roman et al., 1998), suggesting that severity of injury is related to the extent of verbal memory deficits experienced.

Finally, gender differences in regards to memory and learning ability in pediatric TBI were explored by one group of researchers based on the broader assumption that females experience a notably better outcome following an insult to the brain (i.e., brain infections or other insults during infancy) (Donders & Hoffman, 2002). The CVLT-C was administered to 30 male and 30 female patients who were between 6 and 16 years of age, experienced a loss of consciousness following TBI, who had no prior histories of psychiatric/neurologic problems, or other variables which would potentially interfere with study findings (i.e., non-monolingual English speaker). No differences in demographic variables, which could potentially confound test results, were found. A hierarchical multiple regression analysis was performed to predict the CVLT-C composite T score. Although length of coma, presence of an intracranial lesion, and age

at the time of assessment were significant predictors (explaining 36% of the variance in composite scores), gender added a statistically significant proportion of explained variance (5%) (Donders & Hoffman, 2002). These study results indicate that females may have a slight but remarkable advantage in verbal learning and memory abilities following a TBI. Reviewing the literature in this area, Donders and Hoffman (2002) suggested that boys may be more vulnerable than girls to language and/or learning disorders, perhaps due to the more asymmetrical development of the male brain (allowing lateralized damage to have a significant impact on related neuropsychological functions) or due to hormonal influences during cerebral development (Donders & Hoffman, 2002).

Attention/Information Processing

Catroppa and Anderson (1999) evaluated the attentional abilities in the acute phase following injury of children who had sustained a TBI. Of the 167 children who were consecutively admitted to the hospital for sustaining a TBI of various severities, 76 met the inclusion criteria and volunteered to participate in this study (27 mild, 33 moderate, and 16 severe TBI cases). The inclusion criteria were: 1) between 8 and 13 years of age at time of injury; 2) documented head injury; and 3) medical records which clearly delineated injury severity. The exclusion criteria were: 1) prior history of a neurological, psychiatric, or learning disorder, or previous head injury (Catroppa & Anderson, 1999). Intellectual and attentional abilities were measured. Intelligence was assessed by the Wechsler Intelligence Scale for Children – This Edition (WISC-III) while sustained attention and processing speed were assessed by the Continuous Performance Task (Catroppa & Anderson, 1999).

Analysis of variance statistics suggested significant group differences among the severe, moderate, and mild head injury groups on measures of intellectual functioning, including verbal, performance (nonverbal), and full scale (combined verbal and performance) intelligence quotients, as well as the various indices (i.e., verbal comprehension, processing speed, freedom from distractibility, and perceptual organization) (Catroppa & Anderson, 1999). Post-hoc analyses indicated that, in general, the severe TBI group performed more poorly on these measures than the moderate and/or mild injury groups. In addition, during the acute phase following a brain injury, the severe TBI group demonstrated poorer sustained attention scores in comparison to the mild and moderate TBI patients (Catroppa & Anderson, 1999). There were no statistically significant differences among the severity groups on measures of processing speed; however, a decreasing trend in reaction times was found for the severe TBI as compared to the mild and moderate groups. This was attributed to more impulsive errors made by the severe TBI group (Catroppa & Anderson, 1999).

Kaufmann and colleagues (1993) investigated the attentional abilities of mild, moderate, and severe pediatric closed head injury patients approximately six months following injury. Thirty-six children between the ages of 7 and 16 years were included. Measures of attention included the Digit Span subtest of the Wechsler Intelligence Scale for Children – Revised (WISC-R) and The Continuous Performance Test (Kaufmann, Fletcher, Levin, Miner, & Ewing-Cobbs, 1993). Results suggested that severe TBI patients performed more poorly on the Continuous Performance measure than either the mild or moderate TBI patients. This relationship between performance and injury severity was not present for the Digit Span subtest. In addition, age of the child had a

significant impact on performance; namely, younger patients exhibited poorer scores on the continuous performance task. The authors concluded that brain injury, specifically when it occurs early in life, can have a significant impact on attentional and information processing abilities (Kaufmann et al., 1993).

A later study conducted by Ewing-Cobbs and colleagues (1998) prospectively evaluated the long-term consequences of pediatric TBI on attentional abilities. The participants in this study included 91 children who were evaluated five to eight years after injury and ranged between 4 months and 15 years of age at the time of TBI. Exclusion criteria were 1) history of a neurologic, neuropsychological, or developmental disorder, 2) non-English speaking, 3) suspicion of abuse or neglect, and 4) penetrating brain injury (Ewing-Cobbs, Prasad et al., 1998). Using a theoretical framework of attention with four components, Ewing-Cobbs and colleagues (1998) measured 1) focus/executive skills (Coding and Digit Symbol subtests of the WISC; Trail Making Test, The Underlining Test, and the false alarm scores from the Continuous Recognition Memory Test); 2) shifting in attention (Wisconsin Card Sorting Test – number of categories completed and number of perseverative errors); 3) attentional encoding (Arithmetic and Digit Span subtests of the WISC); and 4) sustained attention (adaptive rate of the Continuous Performance Test) (Ewing-Cobbs, Prasad et al., 1998).

Consistent with the findings of Kauffman et al. (1993), the results from this study indicated that severity of injury was associated with performance on tests of attention; specifically, participants who had experienced a severe TBI had significantly lower scores on the focus/executive and shift construct tasks than those with mild-moderate injuries (Ewing-Cobbs, Prasad et al., 1998). In addition, notable age effects were also

found, with younger participants, regardless of injury severity, consistently scoring lower on the basic attention test (i.e., Digit Span) and on the adaptive rate on the Continuous Performance Test (Ewing-Cobbs, Prasad et al., 1998). Finally, an interaction effect between age and injury severity was reported for timed tests of perceptual-motor skills; specifically, lower scores were noted in both the severe and the mild-moderate younger TBI patients and also in the older severe TBI group (Ewing-Cobbs, Prasad et al., 1998). The authors attributed these findings to differences in developmental status. Namely, skills, which were in the process of development, specifically rapid development (Ewing-Cobbs, Levin, Eisenberg, & Fletcher, 1987), were at greater risk for disruption than were more well established abilities (Ewing-Cobbs, Prasad et al., 1998).

Finally, Vriezen and Pigott (2000) evaluated aspects of attentional abilities and the efficacy of commonly used measures to determine deficits in pediatric TBI patients. They administered the Continuous Performance Test, the Digit Span subtest of the Wechsler Intelligence Scales, the Trailmaking Test, as well as the Attention Problems scale from the Achenbach Child Behavior Checklist in order to evaluate aspects of attention. These measures were administered to two groups of pediatric patients between four and nine months post-injury (14 mild TBI and 13 moderate and severe TBI patients) (Vriezen & Pigott, 2000). The authors reported that no impairments were noted for either of the groups on the Digit Span subtest, the Trail Making Test, or the Achenbach Attention Scales. However, moderate/severe brain injury patients demonstrated poorer scores on the Continuous Performance Test (Vriezen & Pigott, 2000). The authors iterated the importance of measuring sustained attentional abilities in addition to basic attention when evaluating deficits in this population (Vriezen & Pigott, 2000).

Executive Functions

Executive skills are defined as a "…collection of related yet distinct abilities that provide for intentional, goal-directed, problem solving action" and "…an umbrella construct defined as the control, supervisory, or self-regulatory functions that organize and direct all cognitive activity, emotional response, and overt behavior" (p. 138) (Gioia & Isquith, 2004). Because the executive circuits are believed to be associated with the frontal lobes, specifically the prefrontal cortex, it is assumed that damage to this area of the brain, which is relatively common following TBI, will disrupt the associated cognitive processes. Further, a review of the available literature by Brookshire et al. (2004) indicated that while most neuropsychological deficits recover over time, deficits in executive functioning are persistent (Brookshire, Levin, Song, & Zhang, 2004).

Considered a significant aspect of executive abilities, Hanten et al. (2000) studied the construct of metacognition following pediatric TBI in nine patients and nine matched controls. Although no differences in recall abilities were noted between the patient and control groups, the TBI patients demonstrated significant deficits in their ability to identify the ease by which an item could be learned or to predict recall of a test item following a long delay (Hanten, Bartha, & Levin, 2000). In a similar study, Hanten et al. (2002) studied selective learning, or one's ability to choose items to learn among many others, which is a specific component of metacognition. Performance on a selective learning task in a sample of 14 TBI children (ages 8-15) was compared to that of healthy age-matched controls. Again, although no differences in ability to encode and recall a series of words were apparent between the TBI and control groups, the former

demonstrated significant deficits on the selective learning task (Hanten, Zhang, & Levin, 2002).

Word fluency, as measured by the number of words generated for three given letters within 60-second intervals each, is also a commonly used measure of frontal lobe function. Levin et al. (2001) studied performance on a word fluency test in a longitudinal sample of 122 closed head TBI patients (78 severe and 44 mild injuries). In addition, they compared the performance of 112 closed head injury children (68 severe and 44 mild injury) on the word fluency test to 104 normal matched controls in a cross-sectional study (Levin, Song, Ewing-Cobbs, Chapman, & Mendelsohn, 2001). In the cross sectional analyses, the severe TBI group performed significantly worse on the word fluency measure than the mild and the control groups. Similar results were obtained in the longitudinal analyses with a slower recovery in world fluency ability associated with severe injury, specifically in the younger patient group. This finding was not true for the older severe TBI group or the younger mild TBI group (Levin et al., 2001). Poorer performance on this measure was also associated with damage to the left frontal lobe only (Levin et al., 2001), perhaps because the left hemisphere of the brain is primarily associated with verbal abilities in most individuals. In addition to the measures of executive function reviewed above, deficits in working memory have also been identified in pediatric TBI populations, with severity of injury being associated with extent of deficit (Levin et al., 2002). Working memory refers "…to the computational ability to relate old information to new, incoming information" (pg. 21) (Roncadin, Guger, Archibald, Barnes, & Dennis, 2004).

Further, Slomine et al. (2002) evaluated 68 TBI patients (ages 7-15) with moderate or severe TBI approximately one year post injury in order to assess the nature and extent of executive deficits. In addition to using a word generation test (described above), these researchers used a measure of problem solving ability (Tower of Hanoi) as a measure of categorization and ability to shift rules and strategies when problem solving (Wisconsin Card Sorting Test) (Slomine et al., 2002). Controlling for premorbid intellectual deficits and behavioral problems, the authors were able to demonstrate a positive relationship between age at injury and performance on measures of executive functioning. Using available MRI data, Slomine and colleagues (2002) found no association between frontal lobe lesion volume and performance; however, a significant association was found between extrafrontal lesion volume as well as total number of lesions and poor performance on the word fluency test. These authors concluded that younger age at injury is a significant risk factor for cognitive deficits, specifically for executive functions. In addition, they suggested that damage to areas of the brain other than the frontal region alone may have a role in cognitive deficits (Slomine et al., 2002), even if these deficits are traditionally considered part of the frontal lobe circuitry.

Using the Wisconsin Card Sorting Test on a sample of 80 TBI children (9-16 years of age) on average two months following injury, Kizilbash and colleagues (1999) examined the factor structure of the test as well as associations between each factor and clinical variables. Consistent with similar studies in adult samples, the authors reported a three factor solution for the test variables, including 1) a response accuracy dimension (i.e., erroneous and/or perseverative tendencies, inefficiency in determining the first conceptual rule as well as the conceptual principles of the task); 2) difficulty in consistent

self-monitoring; and 3) improvement in efficiency with strategies used to solve problems over the span of the test (Kizilbash & Donders, 1999). Significant associations were found between the response accuracy factor and both age and length of coma, with older age and shorter period of coma being associated with better scores. No such associations were found between the latter and the second two factors (Kizilbash & Donders, 1999). The results from this study are consistent with others (Levin et al., 2002; Levin et al., 2001; Slomine et al., 2002), which have indicated that age at injury is associated with poorer executive functioning abilities.

Although test-based measures are relatively common methods of assessing executive functioning, it has been suggested that such formal measures tap into the "molecular level" since they address only specific components of executive functioning such as working memory and planning, among others (Gioia & Isquith, 2004). A molar level or "real-world" assessment of a child's executive functioning is encouraged, which takes into account how aspects of executive abilities play out in the child's everyday physical and social environment.

Language

Chapman and colleagues (1992) assessed the narrative discourse abilities of 20 children and adolescents approximately one year post TBI. Children were asked to verbally produce a narrative for shown pictures. These narratives were rated in terms of language structure, information structure, as well as flow of information (Chapman et al., 1992). Similar to other domains of neuropsychological functioning following TBI, severity of injury, measured by impairment in consciousness, was associated with deficits in language and information structure, confirming original hypotheses that severity of

injury is associated with "disorganized discourse" (Chapman et al., 1992). The authors associated this finding to the role of frontal lobe circuitry, which is a common area of lesion following TBI, in language production, with particular emphasis on vocabulary and memory functions (Chapman et al., 1992).

Similarly, Chapman and colleagues (2001) longitudinally assessed the language abilities of 22 severe and 21 mild/moderate TBI patients between the ages of 5 and 10 over the course of three years post injury. Much like the study described above, these researchers presented a sequence of pictures for which patients were asked to produce a narrative discourse. Again, severity of injury was associated with performance, with the severe TBI group performing more poorly than the mild/moderate TBI group (Chapman et al., 2001). The authors concluded that severe TBI can result in significant impairments in language abilities specifically related to narrative discourse (Chapman et al., 2001).

Finally, in a review of the effects of pediatric TBI on measures of language abilities, Ewin-Cobbs and Barnes (2002) reported that a child's developmental status is a significant predictor of outcome in language abilities following TBI and that differential outcome in language abilities are apparent for different age groups. Specifically, it appears that younger children (with severe TBI) have difficulty with both lexical (word knowledge) and narrative/discourse abilities. Contrarily, children who are older at the time of TBI demonstrate difficulties only in "higher-order discourse functions" (Ewing-Cobbs & Barnes, 2002). This may in part be due to the reality that TBI affects the extent and nature of deficits in cognitive skills which are in the process of or which have not been acquired, but not skills that have been learned or over-learned (such as lexical knowledge). In addition, Ewing-Cobbs and colleagues (1997) suggested that persistent

deficits in neuropsychological functioning in general, including language abilities, may be due to lack of acquisition of skills following severe TBI.

Academic Achievement

Few studies have specifically addressed academic problems following pediatric TBI. Ewing-Cobbs and colleagues (1998) conducted a two-year longitudinal study of the academic achievement and placement of 38 children (5-10 years of age) and 23 adolescents (11-15 years of age) with either severe or mild/moderate head injury. The inclusion criteria for the study were 1) TBI requiring hospitalization, 2) no prior history of TBI, other learning disabilities, or developmental delay, 3) resolution of posttraumatic amnesia by at least the third month following injury, 4) no suspicion of neglect or physical abuse, and 5) English as a primary language (Ewing-Cobbs, Fletcher, Levin, Iovino, & Miner, 1998). The Wide Range Achievement Test, including measures of reading, spelling, and mathematics, was used to screen for age appropriate academic achievement. This measure was administered at baseline (upon resolution of posttraumatic amnesia) and again at 6, 12, and 24 months post injury. Academic placement was assessed by reviewing school records approximately two years following the injury; variables of interest included the child's classroom level (i.e., accelerated, regular, or modified curriculum), any changes in level since prior to injury, and whether the child failed a grade (Ewing-Cobbs, Fletcher et al., 1998).

The results indicated that severe TBI patients obtained lower scores in all three of the achievement areas (i.e., reading, spelling, and mathematics) than those in the mild/moderate TBI group. Factoring out severity of injury, however, adolescents were more likely to score lower on the mathematics and reading tests than the younger

children. In addition, overall scores increased between the baseline and six month assessments; however, no changes in scores were evident after six months (Ewing-Cobbs, Fletcher et al., 1998). The authors suggested that although both groups of TBI patients achieved average scores on the achievement tests by two years post injury, a significant proportion (79%) of the severe TBI cases were either in special education classes or had failed a grade in school. They recommended that traditional measures of academic performance may not be sensitive to the specific deficits experienced by pediatric TBI patients (Ewing-Cobbs, Fletcher et al., 1998).

Finally, using growth curve analyses, longitudinal models of academic performance after pediatric TBI were explored by Ewing-Cobbs et al. (2004). Changes in academic performance across at least three consecutive assessments of academic performance were noted. Specifically, older children experienced greater increases in their academic achievement scores over time than their younger counterparts. This was true for both the severe TBI and mild/moderate TBI groups, although the severe injury group scored considerably and consistently lower on the academic measures than their age matched mild/moderate TBI peers (Ewing-Cobbs et al., 2004).

Psychiatric/Behavioral Functioning

Relatively few studies have assessed the behavioral and/or psychiatric outcome following pediatric TBI. A brief review of the studies in this area suggest temperament changes, increased irritability, aggressive and hyperactive behaviors, impulsivity, temper outbursts, and difficulties with social and interpersonal relationships are relatively common, and particularly chronic in severe versus mild/moderate head injury in children (Adelson & Kochanek, 1998).

In one study, the incidence of elevated behavioral problems four years post injury were higher in the severe TBI group (36%) than the moderate TBI (22%) and orthopedic (no head injury) (10%) groups (Schwartz et al., 2003). Behavioral problems were typically noted within the first year post injury with significant predictors including severe head injury, socioeconomic disadvantage, and pre-injury behavioral concerns. Furthermore, current behavioral problems were associated with poor working memory and adaptive behavior skills, adverse family outcomes, and poor school and behavior competency (Schwartz et al., 2003).

Fletcher et al. (1996) reported on the behavioral outcomes and adaptive functioning following pediatric closed head injuries. Their sample consisted of 138 mild, moderate, and severe TBI patients between the ages of 6 and 16. All of these patients were assessed using the Personality Inventory for Children – Revised. In addition, 77 of these participants were also administered the Vineland Adaptive Behavior Scales (Fletcher et al., 1996). Although severity of injury was not related to any of the subscales on the personality inventory that related to psychopathology per se, significant group differences were found on scales measuring various aspects of cognition, with the severe TBI group revealing more difficulties in this area than the mild or moderate head injury groups (Fletcher et al., 1996). In addition, the Communication and the Socialization subscales of the Vineland Adaptive Behavior Scales were considered notable areas of difficulty for the severe but not the moderate or mild TBI groups (Fletcher et al., 1996). Although severity of injury was a distinguishing factor for performance on some of the behavior scales, as summarized above, other clinical factors such as size and location of

frontal lobe lesions (as determined by MRI results) were not (Fletcher et al., 1996). This, again, highlights the importance of injury severity on behavioral outcome.

In addition, Bloom and colleagues (2001) reported on both lifetime and novel psychiatric disorders in a sample of pediatric TBI patients who were between 6 and 15 years of age at the time of injury. Forty-six patients were evaluated approximately one year post injury using both standardized measures (self and parent reports) as well as semistructured interviews of both patients and parents (Bloom et al., 2001). Although both novel and lifetime (premorbid) psychiatric problems were identified, a significant proportion reported novel disorders. The most common psychiatric disorders were Attention-Deficit/Hyperactivity Disorder (ADHD) and a range of depressive disorders, which were present in approximately half of the sample (Bloom et al., 2001). Furthermore, although both internalizing (i.e., anxiety, depression) and externalizing (i.e., behavioral disorders, ADHD) problems were apparent, the former were more likely to resolve than the latter. Based on their findings, the authors concluded that novel psychiatric disorders are relatively common in pediatric TBI patients (Bloom et al., 2001), and should be screened and treated accordingly.

With regard to ADHD specifically, Max et al. (2004) reported that among a relatively large sample of pediatric head injury patients (severe TBI n = 37, mild/moderate TBI n = 57, orthopedic non-head injury n = 24), severity of injury was associated with acquired or "secondary" ADHD. Also related to the diagnosis were deficits in intellectual and adaptive functioning, as well as personality changes. Lesion location, as determined by CT scans, were not associated with secondary ADHD (Max et al., 2004), perhaps because CT scans are not sensitive to diffuse injuries which are

commonly associated with the outcome studied. The authors claimed that although severe TBI status is markedly associated with post injury attentional problems, it remains unclear whether moderate TBI can result in such symptoms in the absence of premorbid difficulties (Max et al., 2004). Furthermore, Schachar and colleagues (2004) reported that secondary ADHD was not related to age at the time of injury or time since injury but rather with premorbid behavioral problems. After individuals with premorbid diagnoses were excluded, an ADHD diagnosis was three times more common in head injury children as compared to controls (Schachar, Levin, Max, Purvis, & Chen, 2004).

Summary of Neuropsychological Outcome Literature

Although a significant proportion of pediatric TBI patients regain ambulatory and self-care skills, a substantial number demonstrate difficulties with lingering neuropsychological and behavioral deficits. Specifically, when compared to age matched non-brain injured trauma patients or healthy normative groups, pediatric TBI patients perform more poorly on several measures of neuropsychological functioning. As noted in the literature review above, specific deficits have been documented on measures of intellectual abilities (both verbal and nonverbal), academic performance, adaptive problem solving/executive skills, attention/information processing speed, learning and memory, speeded motor tasks, language, and perceptual-motor skills. In addition to neuropsychological measures of various cognitive abilities, some studies have indicated novel and premorbid psychiatric and/or behavioral problems, most common of which have included ADHD and depressive disorders.

Moreover, severity of injury has consistently been associated with poorer outcome on measures of neuropsychological functioning, both during the acute phase

following injury and long-term functioning. Finally, in addition to severity of injury, the above review of the literature has revealed age at the time of injury to be a significant predictor of neuropsychological outcome, with younger children demonstrating poorer performance on several outcome measures as compared to their older counterparts. These findings are not surprising because the predictors of outcome following brain injury in children are diverse and include an interplay between the specific pathophysiology of brain injury, developmental stage of the child at the time of injury, and the length of time passed since injury, as well as the psychosocial resources available to the child (i.e., premorbid abilities, course of newly acquired skills, family, school, and peer support, and rehabilitation) (Chapman & McKinnon, 2000).

Study Objectives

Neuroradiologic findings are important prognostic indicators following a brain injury. However, their long-term clinical utility, specifically with regard to functional outcome, are yet to be better understood and documented. Predicting functional outcome following TBI in children is extremely important because it can provide much needed information to the patient, his or her family, caregiver(s), and teachers with regard to ability, expectations, and optimal methods of treatment. The following study is designed to assess the long-term relative predictive efficacies of the SWI and MRS techniques during the acute phase following TBI in a sample of pediatric patients. In addition, clinical variables, including severity of injury (as determined by the GCS), age at time of injury, and time since injury will be used as covariates in the results, since based on the literature review above, these variables are important indicators of outcome following pediatric brain injury.

Hypotheses

Based on the literature review above, the following hypotheses are proposed:

1. On average, TBI patients will perform more poorly (i.e., there will be statistically significant differences in group means) on all measures of intellectual and neuropsychological functioning than age matched healthy individuals, based on the standardized age appropriate published norms for each instrument.
2. Consistent with the available literature, it is hypothesized that:
    a) Time passed since injury (in years) will be positively associated with intellectual and neuropsychological outcome 1 to 4 years post injury;
    b) Age at the time of injury (in years) will be positively associated with intellectual and neuropsychological outcome 1 to 4 years post injury;
    c) Injury severity (as defined by the GCS) will be negatively associated with intellectual and neuropsychological outcome 1 to 4 years post injury.

Neuropsychological outcome is defined as the combined (averaged) standardized scores in the following domains: memory (verbal and nonverbal), attention/information processing speed, problem solving/executive skills, visual-perceptual abilities, language skills, motor skills, and academic achievement.

3. Based on the MRS neuroimaging results:
    a) On both the single voxel and multi-voxel spectra, the N-acetyl-aspartate and choline ratio (NAA/Cho) will be positively correlated with intellectual and neuropsychological outcome indices;

b) On both the single voxel and multi-voxel spectra, choline (Cho) and creatine (Cre) will be negatively correlated with itellectual and neuropsychological outcome indices;

c) Additional metabolites from the single-voxel analyses, including glutamate/glutamine (Glx), myoinositol (mI), and lactate (Lac) will be negatively correlated with intellectual and neuropsychological outcome;

d) Exploratory analyses will be conducted to investigate whether regional MRS results from the multi-voxel imaging will vary in association with specific neuropsychological outcome indices.

4. Based on the SWI neuroimaging results:

a) Both total hemorrhage volume and lesion number will be significant predictors of intellectual and neuropsychological outcome;

b) Total lesion number as determined by SWI will be a better predictor of intellectual and neuropsychological outcome compared to lesion number determined from conventional MR images (GRE);

c) Exploratory analyses will be conducted to investigate whether regional hemorrhage volume and lesion number will vary in association with specific neuropsychological outcome indices.

5. Exploratory analyses will be conducted to investigate the relative predictive efficacy of MRS and SWI results on intellectual and neuropsychological outcome.

METHODS

Participants

Forty children and adolescents (between the ages of 1 and 18) who presented at the Loma Linda University Children's Hospital (LLUCH) for sustaining a TBI between January, 2000 and April, 2003 were eligible to participate. Inclusion criteria were patients who 1) received MRS and SWI as part of their routine clinical care following medical stabilization after brain injury, 2) were at least one year post injury at the time of the neuropsychological evaluation, and 3) provided appropriate consent (parental consent if under the age of 18) to participate in the study (see Procedure section below). Exclusion criteria included patients 1) who were living in a comatose or a vegetative state or 2) for whom English was not a primary language.

Procedure

Once Loma Linda University Institutional Review Board (IRB) approval for the study protocol was granted (Appendix A), eligible patients meeting inclusion criteria were contacted by telephone with a brief description of the study. If patients were currently minors (under 18 years of age), their parents were contacted first. Interested patients/parents were scheduled for a neuropsychological evaluation.

All neuropsychological assessments were conducted at the Kids FARE laboratory of the Loma Linda University Graduate School. On the day of the appointment, patients (and their parents if minors) were provided further detail regarding the study protocol and the informed consent documents. Appropriate signatures were collected on the informed consent (Appendix B and C), assent (for minors) (Appendix D), and Personal Health Information (PHI) (Appendix E) forms. Patients and/or their parents were advised that

the assessments would be paper and pencil in nature with minimal risk (i.e., fatigue). They were also reminded that their participation was voluntary and that withdrawing from the study at any time would not interfere with their medical care at LLUCH.

Enrolled patients under the age of 18 were asked to be accompanied by a parent during the entire testing session. While their children were being tested, parents were asked to complete a measure of their child's behavioral and emotional functioning (BASC-PRS). On average, assessments took between two to three hours, depending on the age of the participant and his or her ability level. In return for their participation, a summary report outlining the results of the neuropsychological assessment, as well as a list of relevant recommendations and referrals were provided for all participants. In addition to the neuropsychological evaluation, patients were offered a neurologic evaluation conducted by an LLUCH pediatric neurologist.

Data Analysis and Storage

Accommodations have been made to keep all patient related data in individually labeled charts in a locked filing cabinet. Per Loma Linda University IRB protocol, the data will be saved for three years at the Kids FARE laboratory following the completion of the study. Computerized databases were de-identified and stored in a password protected file.

Data were entered into an SPSS database. Data analysis was done using SPSS 10.0 and Minitab 14 (for group comparisons using summary statistics only). Prior to analyses, databases were screened for missing data and entry error and all other discrepancies were identified and corrected.

Instruments

Injury Severity

The Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974) administered at the time of injury was used as a measure of injury severity. The GCS is a quick scoring system measuring severity following a brain injury with impairment in consciousness. The scale has been used in several studies with TBI patients as a reliable measure of injury severity and as considered to be a fairly reliable predictor of neuropsychological and cognitive outcome post injury (Ewing-Cobbs et al., 1997; Fay et al., 1994; Jaffe et al., 1992; Massagli et al., 1996; Roman et al., 1998; Wallesch, Curio, Galazky et al., 2001; Wallesch, Curio, Kutz et al., 2001). The GCS ranges from 3-15 and is composed of three separate scales measuring motor ability, verbal responses, and eye opening (Rosman, 1999). Based on the total score yielded from the sum of the three scales, brain injury severity has been categorized into three types: severe TBI referring to a GCS of $\leq$ 8; moderate TBI referring to a GCS of 9-12; and mild TBI referring to a GCS of 13-15.

Neuroimaging Evaluations

Upon medical stabilization following TBI, participants were imaged by an MR scanner, using a circularly polarized head coil in a conventional 1.5T whole body imaging system (Magnetom Vision; Siemens Medical Solutions, Iselin, New Jersey).

Magnetic Resonance Spectroscopy (MRS)

Proton MRS (^{1}H-MRS) was used as a non-invasive measure of various brain metabolites following injury. Upon medical stabilization following TBI, participants were imaged using a circularly polarized head coil in a conventional 1.5T whole body MR scanner (Magnetom Vision, Siemens Medical Solutions, Iselin, New Jersey). MRI

sequences included sagittal T1 weighted scans (TR/TE=500/14 msec, 5 mm thick, 20% gap), axial and coronal fast T2 weighted scans (TR/TE = 3500/90 msec, 5 mm thick, 40% gap), and axial 2D gradient echo susceptibility weighted scans (TR/TE = 500/25 msec, flip angle = 20°, 4 mm thick).

Single voxel spectra.

Two single voxel proton spectra were acquired with 8 cc^3 volumes in normal-appearing brain; one in the occipital gray matter (OGM) located in a paramedian position across the interhemispheric fissure and a second in the parieto-occipital white matter (PWM) placed in the right or left hemisphere to avoid obvious areas of injury. A water-suppressed stimulated echo acquisition mode (STEAM) sequence was used with TR/TE/TM = 3000/20/13 msec and 128 NEX, following manual localized shimming to achieve water line widths less than 8 Hz. A reference spectrum was acquired with identical acquisition parameters and 8 acquisitions to use for eddy current correction. Metabolite levels for NAA, Cre, Cho, mI, and Glx for each patient was quantitatively measured using a Linear Combination Model of in-vitro spectra, (LCModel), an automatic (user independent) frequency-domain fitting routine (Provencher, 1993). Metabolite ratios, NAA/Cre, NAA/Cho, and Cho/Cre were also calculated.

Multi voxel spectra or MRSI.

In addition, 2D-MRSI (multi-voxel MR Shift Imaging) was acquired using a water-suppressed point resolved spectroscopy sequence (PRESS) with TR/TE=3000/144 msec. The multi-voxel acquisition was acquired with a 10-mm thick axial slab through the level of the corpus callosum which covered portions of the frontal white and gray matter, and parieto-occipital white and gray matter (2-3 cc/voxel) and included visibly

injured and normal appearing brain. MRSI spectra were post-processed to include zero-filling to 32k, 1-Hz exponential multiplication, Fourier transformation, zero-order phase correction, and baseline correction (Luise, Numaris VB33D, Siemens Medical Solutions) to obtain peak areas for NAA, Cre, Cho, and Lac, if present. Peak areas were transferred to an automatic processing program to calculate metabolite ratios and transfer those values to a statistical spreadsheet for further analysis. Each spectrum was visually inspected by a medical physicist (BAH) for adequate spectral quality and metabolite ratios from accepted voxels (up to 64) within a slab were averaged to obtain a pooled mean metabolite ratio (or total) for each patient. For comparison, mean total ratios were obtained for five different regions as follows: frontal white matter, frontal gray matter, corpus callosum, parieto-occipital white matter, and parieto-occipital gray matter.

Susceptibility Weighted Imaging

As previously described (Tong et al., 2004), susceptibility weighted images consisted of a strongly susceptibility-weighted, low-bandwidth (78 Hz/pixel) three-dimensional fast low angle shot (3D-FLASH) sequence (TR/TE = 57/40 milliseconds, flip angle = 20 degrees) with first-order flow compensation in three orthogonal directions. Using a rectangular field-of-view (5/8 of 256 mm) and a matrix of 160 x 512, 64 partitions of 2 mm each were acquired, resulting in a voxel size of 1 x 0.5 x 2 mm. The 64 partitions were collapsed, resulting in 32 slices with effective thickness of 4 mm. Susceptibility weighted imaging included most of the cerebral areas and the posterior fossa with an acquisition time of 9.5 minutes.

Susceptibility weighted images were reviewed on a clinical workstation (DS3000, Impax, Agfa Inc.) to determine study quality and then downloaded for off-line analysis of

hemorrhagic lesions. Because lesions were variable in shape, a computer software program (Image Pro Plus, Media Cybernetics Inc.) was used to semi-automatically trace the outline of lesions using selected minimum intensity threshold levels refined by the user. After pre-defined observer-dependent adjustments, the program automatically counted and calculated the pixel area of lesions in each image. After correcting for pixel size, the area of each lesion was multiplied by the effective slice thickness to determine the volume of each lesion. Lesions for each image were counted and summed. The volumes of each lesion were also summed. These summed values provided a global number and volume load of hemorrhagic diffuse axonal injury lesions for each patient. In addition, MR images were used to locate shearing lesions (i.e., diffuse axonal injury); subsequently, regional susceptibility weighted imaging data was collected for frontal gray (FGM) and white (FWM) matter, parieto-temporo-occipital gray (PTOG) and white (PTOW) matter, corpus callosum (CC), basal ganglia (BG), thalamus (TH), brainstem (BS), and cerebellum (CB).

Neuropsychological Measures

The neuropsychological measures used in this study assessed nine areas of functioning; namely, intelligence, memory (verbal and nonverbal), attention/information processing speed, problem solving/executive skills, visual-perceptual abilities, language skills, academic achievement, motor skills, and behavioral/psychiatric functioning (Table 1). Brief descriptions for the specific measure(s) for each domain are provided below.

Intelligence

Intelligence was assessed by the age appropriate Wechsler Scales and their subsequent derived indices. Participants between the ages of 16 and 22 were

administered the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) (Wechsler, 1997). The WAIS-III was normed on a sample of 16 to 90 year olds (based on current US census data). It is composed of 11 subtests and takes between 60 to 90 minutes to administer.

Participants between the ages of 6 and 15 years and 11 months were administered the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV) (Wechsler, 2003). This is a recently published fourth generation instrument assessing various aspects of intelligence, cognitive ability, and information processing in children. Like the WAIS-III, the WISC-IV takes between 60 and 90 minutes to administer. The WISC-IV was normed on a representative sample (based on current US census data) of individuals between the ages of 6 and 16.

Finally, participants between the ages of 3 and 6 were administered the Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III) (Wechsler, 2000). This measure was normed on a sample of participants (based on US census data) between the ages of 2 years and 6 months and 7 years and 3 months. The administration of the WPPSI-III takes between 45 to 60 minutes.

All three of the above measures of intelligence yield a Full Scale Intelligence Quotient (FSIQ) and a Processing Speed Index (PSI). The WAIS-III and WPPSI-III also include a Verbal Intelligence Quotient (VIQ) and a Performance (nonverbal) Intelligence Quotient (PIQ), which are composed of scales included in the FSIQ. The WISC-IV and WAIS-III include a Verbal Comprehension Index (VCI) and Working Memory Index (WMI). The WAIS-III includes a Perceptual Organization Index (POI) and the WISC-IV includes a Perceptual Reasoning Index (PRI). All indices are based on a mean of 100 and

a standard deviation of 15 IQ points. The individual subtests, which comprise the indices described above, have a mean of 10 and a standard deviation of 3 scaled points.

Verbal Memory

Verbal learning and memory was evaluated by one of two versions of the California Verbal Learning Test. Participants between the ages 16 years and 22 years were administered the California Verbal Learning Test – Second Edition (CVLT-II) (Delis, Kramer, Kaplan, & Ober, 2000). The test requires examinees to learn a series of words across multiple trials and has both immediate and delayed free recall trials as well as a recognition trial. The CVLT-II provides several scores representing participants' performance, including indicators of not only general memory ability but also encoding strategies, types of errors made, learning rates, and other processing data. This test is appropriately normed for individuals between 16 and 89 years of age and takes approximately 30 minutes to administer (in addition to an approximate 30 minute delay interval during which other tests can be administered).

The California Verbal Learning Test – Children's Version (CVLT-C) (Delis, Kramer, Kaplan, & Ober, 1994) is normed for individuals between the ages of 5 years and 16 years and 11 months and was administered to participants between 5 and 15 years of age. The CVLT-C provides data on a child's performance on a word memory task (recall and recognition trials), their learning strategy, type of errors made, learning rates, and other processing data. The administration time for this test is between 15 and 20 minutes (in addition to a 20 minute delay interval during which time other tests can be administered).

In order to create a single combined index of verbal memory abilities for analyses, standardized scores (based on z transformations) were averaged for 1) List A Total Trials 1-5 Scaled Score and 2) the List A Long-Delay Free Recall Scaled Score. The CVLT-C was not normed for children under the age of five years and thus was not administered to children less than five. These two scores were significantly correlated and loaded on the same factor in a factor analysis. Reliability analyses indicated high inter-item correlations (alpha = .91), supporting their combination into a single index.

Nonverbal Memory

Nonverbal (visual) memory was assessed by the Rey Complex Figure Test (RCFT) and Recognition Trial (Meyers & Meyers, 1995). This test requires the respondent to first copy a complex figure design, after which the respondent is asked to reproduce the drawing from memory in an immediate and delayed recall trial. Following the free recall trials, the respondent is asked to choose among a group of smaller figures, which they identify to be part of the original complex figure. In addition to providing a measure of visual memory, this test reflects on an individual's planning and organizational skills, as well as perceptual and motor functions (Spreen & Strauss, 1998). The test was normed for individuals between the ages of 6 and 89 (N=601 for the 18-89 age range; N=505 for the 6-17 age range) (Meyers & Meyers, 1995) and takes approximately 10-15 minutes to administer.

In order to create a single combined index of nonverbal memory abilities for analyses, standardized scores (based on z transformations) were averaged for 1) RCFT Immediate Recall and 2) RCFT Delayed Recall scores. The RCFT was not normed for children under the age of six years and thus was not administered to children less than

six. These two scores were significantly correlated and loaded on the same factor in a factor analysis. Reliability analyses indicated high inter-item correlations (alpha = .97), supporting their combination into a single index.

Attention and Information Processing Speed

Basic attentional abilities were estimated by the Digit Span subtest of the age appropriate Wechsler Scales of Intelligence (described previously) (WISC-IV and WAIS-III only). The Digit Span subtest includes increasingly longer strings of numbers, which respondents are asked to repeat back immediately after presentation. The subtest yields an overall standard score (based on age appropriate norms) and is based on a mean of 10 and a standard deviation of 3 scaled points (Wechsler, 1997, 2003).

Divided attention was estimated by the Letter-Number Sequencing subtest of the age appropriate Wechsler Scales of Intelligence (described previously) (WISC-IV and WAIS-III only). The Letter-Number Sequencing subtest includes increasingly longer strings of numbers and letters, which respondents are asked to reorganize (based on increasing order) and repeat back immediately after presentation. The subtest yields an overall standard score (based on age appropriate norms) and is based on a mean of 10 and a standard deviation of 3 scaled points (Wechsler, 1997, 2003).

Information Processing Speed was estimated by the Digit Symbol Coding and Symbol Search subtests of the age appropriate Wechsler Scales of Intelligence (described previously) (WPPSI-III, WISC-IV, and WAIS-III). On the Digit Symbol Coding subtest, respondents are asked to fill in empty squares with the corresponding symbol based on a symbol key provided at the top of the page. On the Symbol Search subtest, respondents are asked to scan two groups of symbols and indicate whether the target symbol is in the

second set of symbols (Spreen & Strauss, 1998). Their performance (accuracy and time) is used to calculate a standard score, with a mean of 10 and a standard deviation of 3 scaled points (Wechsler, 1991, 1997, 2000, 2003).

In addition, Trails A, from the Trail Making Test (TMT), was administered as a measure of attention and processing speed. The TMT was originally constructed in 1938 as part of the Army Individual Test Battery and was later included in the Halstead Neuropsychological Battery (Spreen & Strauss, 1998). Trails A of the TMT is composed of a series of circles with consecutive numbers on a page. Respondents are asked to connect circles with sequential numbers as fast as they can. In the standard version, participants ages 15 and above are asked to connect 25 circles in sequential order. Participants between 6 and 14 years of age are administered the intermediate version of the test and are asked to connect 15 circles in sequential order (Spreen & Strauss, 1998). Age appropriate norms (means and standard deviations), published in Spreen and Strauss (1998) (Table 12-14 for Standard and Table 12-16 for Intermediate versions), were used to calculate z scores.

In order to create a single combined index of attention and processing abilities for analyses, standardized scores (based on z transformations) were averaged for the 1) Digit Span, 2) Letter-Number Sequencing, 3) Symbol Search, and 4) Coding subtests of the Wechsler Scales of Intelligence, and the 5) Trails A test. The Digit Span and Letter-Number Sequencing subtests as well as the Trails A test were not normed for children under 6 years of age and thus were not administered to this age group. In this case, the average of the other two tests administered was used to compute this index. These scores were significantly correlated and loaded on the same factor in a factor analysis.

Reliability analyses indicated high inter-item correlations (alpha = .89), supporting their combination into a single index.

Problem Solving and Executive Skills

Also part of the TMT, Trails B was used as a measure of executive skills. On this measure, respondents are asked to connect a series of numbers and letters in sequential and alternate (letter-number) order. As such, Trails B is appropriately considered a measure of mental flexibility (Spreen & Strauss, 1998). Like Trails A, two forms of the test are available: 1) the standard form with 25 encircled numbers and letters used with individuals 15 years of age and older, and 2) the intermediate form with 15 encircled numbers and letters used with individuals between the ages of 6 and 14. Age appropriate norms (means and standard deviations), published in Spreen and Strauss (1998) (Table 12-14 for Standard and Table 12-16 for Intermediate versions), were used to calculate z scores. The administration time for both Trails Tests together is between 5 and 10 minutes (Spreen & Strauss, 1998).

Problem solving skills were also measured by the Tower of London – Drexel (TOLDX) (Culbertson & Zilmer, 2000) test. This measure is designed for children 7 years and older and involves assessment of both the time and accuracy of completing individual items. Respondents are asked to move the stimulus pegs one at a time in a recommended number of maximum moves to match the examiner's design. Administration takes between 10-15 minutes. Performance on similar Tower tests have been associated with frontal lobe function (Levin et al., 1994), overall executive functioning (Culbertson & Zillmer, 1998a), and sensitive and specific to ADHD (Culbertson & Zillmer, 1998b).

In order to create a single combined index of problem solving and executive skills for analyses, standardized scores (based on z transformations) were averaged for the TOLDX 1) Total Rule Violation, 2) Total Correct, 3) Total Move, 4) Total Initiation Time, and 5) Total Problem-Solving Time Standard Scores, as well as the 6) Trails B test. Because the TOLDX and the Trails B were not normed for children under seven years and six years of age, respectively, they were not administered to this age group. These scores were significantly correlated and loaded on the same factor in a factor analysis. Reliability analyses indicated high inter-item correlations (alpha = .82), supporting their combination into a single index.

Visual-Perceptual Abilities

Visual-perceptual abilities were measured by the Block Design and Picture Completion subtests of the age appropriate Wechsler Intelligence Scales (described previously). The Block Design subtest includes increasingly more complex models displayed either by the examiner or in a picture, which the respondent is then asked to replicate using red and white blocks. For the Picture Completion subtest, respondents are asked to identify an important missing part for stimulus pictures (Spreen & Strauss, 1998). The subtests yield an overall standard score (based on age appropriate norms) with a mean of 10 and a standard deviation of 3 scaled points. In addition, the Rey Complex Figure Test (RCFT) copy trial was used as a measure of visual-perceptual abilities (see tests of memory section above).

In order to create a single combined index of visual perceptual abilities for analyses, standardized scores (based on z transformations) were averaged for the 1) Block Design and 2) Picture Completion subtests of the Wechsler Scales of Intelligence

and 3) RCFT copy trial. The RCFT is normed for individuals ages 6 years and older and thus was not administered to children younger than 6 years. In this case, the average of the other two tests administered was used to compute this index. These scores were significantly correlated and loaded on the same factor in a factor analysis. Reliability analyses indicated high inter-item correlations (alpha = .79), supporting their combination into a single index.

Language Performance

A brief screening of language ability was conducted by the Vocabulary and Similarities subtest of the age appropriate Wechsler Intelligence Scales (described previously). The Vocabulary subtest presents respondents with increasingly difficult vocabulary words which they are asked to define. The Similarities subtest measures a respondent's ability to demonstrate verbal abstraction skills by explaining how two given words are alike. The subtests yield an age based standard score with a mean of 10 and a standard deviation of 3 scaled points. In addition, the Reading subtest of the WIAT-II-A, described below) was used as a measure of language functioning and tests a respondent's word reading ability.

In order to create a single combined index of language abilities for analyses, standardized scores (based on z transformations) were averaged for the 1) Vocabulary and 2) Similarities subtests of the Wechsler Scales of Intelligence and 3) WIAT-II-A Reading subtest. The WIAT-II-A is normed for individual 6 years and older and thus was not administered to children less than 6 years of age. In this case, the average of the other two tests administered was used to compute this index. These scores were significantly correlated and loaded on the same factor in a factor analysis. Reliability

analyses indicated high inter-item correlations (alpha = .84), supporting their combination into a single index.

Motor Skills

The Purdue Pegboard was used as a measure of motor skills, specifically with regard to finger and hand dexterity. The Purdue Pegboard consists of a board with two parallel columns of 25 holes each. Respondents are asked to place pegs into the holes one at a time using their dominant hand only, nondominant hand only and both hands simultaneously within 30 second trials each. This instrument is normed for individuals five years and older and takes approximately five minutes to administer. Age and gender appropriate norms (means and standard deviations), published in Spreen and Strauss (1998) (Table 14-15 for ages 5 to 15 years and 14-7 for ages 15 and up), were used to calculate z scores.

In order to create a single combined index of motor skills for analyses, standardized scores (based on z transformations) were averaged for the 1) dominant hand, 2) nondominant hand, and 3) simultaneous both hand trials. These scores were significantly correlated and loaded on the same factor in a factor analysis. Reliability analyses indicated high inter-item correlations (alpha = .89), supporting their combination into a single index.

Academic Skills

Academic achievement was measured by the Wechsler Individual Achievement Test – Edition Two – Abbreviated (WIAT-II-A) (Wechsler, 2001). This abbreviated instrument is a widely used measure of the following three academic areas: spelling, reading, and numerical operations. It is normed for a wide range of respondents,

including from kindergarteners to adults, and has high test-retest reliability and validity. The WIAT-II-A can be administered in approximately 10 to 20 minutes.

In order to create a single combined index of academic abilities for analyses, standardized scores (based on z transformations) were averaged for the 1) Reading, 2) Spelling, and 3) Mathematics subtests of the WIAT-II-A. This instrument is normed for individuals six years and older and thus was not administered to children less than six years of age. These scores were significantly correlated and loaded on the same factor in a factor analysis. Reliability analyses indicated high inter-item correlations (alpha = .94), supporting their combination into a single index.

Combined Neuropsychological Index (NPI)

In order to create an overall neuropsychological functioning index, the above indices were averaged for each participant. The indices included all areas of cognitive functioning assessed except for intellectual functioning, including memory (verbal and nonverbal), attention/information processing speed, problem solving/executive skills, visual-perception, language, motor skills, and academic achievement. In the few instances where patients (i.e., younger patients for whom appropriate norms were not available) were not administered all of the tests for a given index, their average for all administered indices was used to represent their combined neuropsychological index. All of the individual index scores were significantly correlated and loaded on the same factor in a factor analysis. Reliability analyses indicated high inter-item correlations (alpha = .92), supporting their combination into a single index.

Behavioral/Psychiatric Functioning

The Behavior Assessment System for Children (BASC) was used to assess possible behavior and/or psychiatric concerns (Reynolds & Kamphaus, 1992). This paper and pencil set of scales provides a multimethod and multidimensional evaluation of behavioral and emotional functioning. Although self, parent, and teacher forms are available, only the former two were used in this study, namely the Self-Report of Personality (SRP) and the Parent Rating Scale (PRS) versions. The scales are normed for individuals between 2 years and 6 months to 18 years and 11 months of age and provide both positive (adaptive scales) and negative (clinical scales) dimensions of personality and behavior. Norms are based on T-scores and percentiles and can be based on general, gender-specific, or clinical populations (Reynolds & Kamphaus, 1992).

The SRP has two forms: child (ages 8 to 11) and adolescent (ages 12-18). The clinical scales on the SRP include Anxiety, Atypicality, Locus of Control, Social Stress, Somatization, Attitude to School, Attitude to Teachers, Sensation Seeking, Depression, and Sense of Inadequacy. In addition, adaptive scales include Relations with Parents, Interpersonal Relations, Self-Esteem, and Self-Reliance. These scales are combined to provide the following composite scores: Clinical Maladjustment, School Maladjustment, Personal Adjustment, and Emotional Symptoms Index. The SRP takes approximately 30 minutes to complete (Reynolds & Kamphaus, 1992).

The PRS has three forms: preschool (ages 2½ to 5); child (ages 6 to 11); and adolescent (ages 12 to 18). The clinical scales on the PRS include Aggression, Hyperactivity, Conduct Problems, Anxiety, Depression, Somatization, Attention Problems, Learning Problems, Atypicality, and Withdrawal. In addition, adaptive scales

include Adaptability, Leadership, Social Skills, as well as Study Skills. These scales are combined to provide the following composite scores: Externalizing Problems, Internalizing Problems, School Problems, Adaptive Skills, and an overall Behavioral Symptoms Index. The PRS takes approximately 10 to 20 minutes to complete (Reynolds & Kamphaus, 1992).

Table 1

Tests of Neuropsychological Functioning by Domain Area

Domain		**Measure**	**Admin Time**
Intelligence		WAIS-III (16 and up)	60-90 minutes
	or	WISC-IV (6-15)	60-90 minutes
	or	WPPSI-III (3-5)	45-60 minutes
Memory			
Verbal		CVLT-II (16 and up)	30 minutes
	or	CVLT-C (5-15)	15-20 minutes
Nonverbal		RCFT	10-15 minutes
Attention/Processing Speed		Digit Span	from Wechsler Scales
		Digit Symbol Coding	from Wechsler Scales
		Letter-Number Sequencing	from Wechsler Scales
		Symbol Search	from Wechsler Scales
		Trails A	5 minutes
Problem Solving/Executive skills		Trails B	5 minutes
		Tower of London	10-15 minutes
Visual-Perceptual Abilities		Block Design	from Wechsler Scales
		Picture Completion	from Wechsler Scales
		RCFT Copy Trial	from RCFT
Language		Vocabulary	from Wechsler Scales
		Similarities	from Wechsler Scales
		Reading	from WIAT-II-A
Motor Skill		Purdue Pegboard	5 minutes
Academic Achievement		WIAT-II-A	10-20 minutes
Behavioral/Psychiatric Functioning		BASC SRP (Self-Report)	30 minutes
		BASC PRS (Parent-Report)	30 minutes
		Approximate Total Time	**2.5-3.5 hours**

RESULTS

Participants

Forty patients were eligible for participation. Fourteen patients were unreachable due to disconnected or incorrect phone numbers. Three patients refused to participate due to scheduling problems and three patients expressed interest but failed to follow-up with scheduled appointments. Twenty patients, therefore, agreed and participated in the study (n = 20). There were no significant differences in any of the demographic, clinical, or primary imaging variables with the exception that the study participants had higher mean choline levels. Furthermore, based on previous reports on the magnitude of association between cognitive and neuropsychological outcome and MRS metabolite ratios (report magnitude), 80% power was approximated using an alpha of .05.

All participants had accidental TBIs; seventeen involved motor vehicle accidents, two involved pedestrian/auto collisions, and one involved a motorcycle accident. Sixty-five percent of the participants were male. At the time of injury, participants' average age was 11.2 years (5.9 SD). Neuropsychological assessments were administered between November 2003 and May 2004. At the time of assessment, participants were on average 2.1 years post injury (0.7 SD). Average age at assessment was 13.3 years (5.8 SD).

Clinical Variables

Several clinical variables were recorded for the patients at or around the time of injury. These included initial GCS, mean arterial blood pressure, heart rate, sodium and glucose levels, hematocrit (%), initial pH, presence of nonreactive pupils, occurrence of cardiac arrest or seizures, and abnormalities in EEG readings or intracranial pressure. In

addition, days from injury to imaging studies, as well as total days in coma, on ventilator, and in the hospital were recorded. Table 2 displays summary data for patient demographic and clinical variables.

Table 2

Summary of Patient Demographic and Clinical Variables

	Summary Statistic Mean (SD) and Range		
Demographic Variables			
Gender	65% Male		35% Female
Age at Injury (years)	11.2	(5.9)	1.1 – 18.4
Time Since Injury (years)	2.1	(0.7)	1.0 – 4.1
Age at Assessment (years)	13.3	(5.8)	4.2 – 21.6
Clinical Variables			
GCS[a]	6.0	(3.7)	3 – 15
MAP	103.0	(27.2)	54 – 160
Heart Rate	122.2	(33.3)	60 – 172
Initial pH	7.4	(0.1)	7.0 – 7.6
Glucose (mg/dL)	170.6	(55.5)	82.0 – 279.0
Sodium (mg/dL)	138.7	(4.7)	27.0 – 148.0
Hematocrit (%)	34.1	(6.3)	24.5 – 48.0
Days in Coma[a]	6.6	(8.5)	0 – 31
Days on Ventilator[a]	8.7	(7.9)	0 – 27
Days in Hospital[a]	32.8	(27.5)	4 – 93
Days to MRI/MRS[a]	6.3	(3.9)	1 – 16
Days Unc. before MRI/MRS[a,c]	4.0	(4.4)	0 – 14
Cardiac Arrest		0%	
Fixed Dilated Pupils		15%	
Increased Intracranial Pressure		18%	
Seizures		10%	
EEG[b]			
Normal		7%	
Mild Abnormal		13%	
Moderate Abnormal		27%	
Severe Abnormal		53%	

[a] Negatively correlated with Full Scale IQ and Neuropsychological Index at $p < .05$ (Pearson coefficient).
[b] Negatively correlated with Full Scale IQ and Neuropsychological Index at $p < .05$ (Spearman coefficient).
[c] Days unconscious before MRI/MRS.

Results of Cognitive Measures

Intelligence

Two patients were administered the WPPSI-III, eight the WISC-IV, and eight the WAIS-III as appropriate based on their age. An additional two patients could not complete the test because of severe functional disability and thus were assigned basal scores. Table 3a displays the medians, means, standard deviations, and ranges for relevant composites.

Table 3a

Summary Statistics for Measures of Intelligence

	N	Median	Mean (SD)	Range
Full Scale IQ[a]	20	74.5	73.2 (17.7)	40-100
Verbal IQ	10	82.5	79.5 (10.1)	64-93
Performance IQ	10	85.0	86.0 (19.5)	55-110
Processing Speed Index	20	84.5	78.5 (17.7)	50-106
Verbal Comprehension Index	18	79.5	75.1 (14.9)	45-96
Working Memory Index	18	75.0	75.0 (15.7)	50-107
Perceptual Reasoning Index	10	78.5	75.3 (20.5)	45-98
Perceptual Organization Index	8	101.0	95.0 (17.2)	70-116

[a] Norms based on a mean standard score of 100 and a standard deviation of 15.

Verbal and Nonverbal Memory

Eight patients were administered the CLVT-C and seven the CVLT-II. Two additional patients could not complete the test because of severe functional disability and were assigned basal scores. One patient was not administered either verbal memory test due to lack of norms for his age group and one patient did not complete the neuropsychological battery and had missing data. With regard to nonverbal memory, 15 patients were administered the RCFT. Two additional patients could not complete the test due to severe functional disability and were assigned basal scores. Two patients were not administered the RCFT due to lack of norms for

their age group and one patient had missing data. Table 3b displays the medians, means, standard deviations, and ranges for relevant summary statistics.

Table 3b

Summary Statistics for Measures of Verbal and Nonverbal Memory

	N	Median	Mean (SD)	Range
CVLT-C/CVLT-II				
Total Trials 1-5 T Score[a]	18	32.5	33.7 (13.1)	20.0-62.0
List A Short-Delay Free Recall[b]	18	-1.5	-1.6 (1.2)	-4.5-0.5
List A Long-Delay Free Recall	18	-1.5	-1.8 (1.5)	-4.5-0.5
Correct Recognition Hits	18	-0.8	-1.3 (1.9)	-5.0-0.5
RCFT				
Immediate Recall T Score[a]	17	25	30.7 (13.5)	20-57
Delayed Recall T Score	17	30	31.9 (13.3)	20-61
Recognition T Score	17	44	37.8 (16.2)	18-69

[a] T Scores are based on a mean of 50 and a standard deviation of 10.
[b] z scores are based on a mean of 0 and a standard deviation of 1.

Attention and Processing Speed

Eighteen patients were administered the Symbol Search and Coding subtests of the Wechsler Scales of Intelligence. Two patients could not complete the test because of severe functional disability and were assigned basal scores. Further, 16 patients were administered the Digit Span and Letter-Number Sequencing subtests of the Wechsler Scales of Intelligence. Two patients could not complete the test because of severe functional disability and thus were assigned basal scores and another two were not administered these subtests because they were not available on their age appropriate Wechsler measure. Finally, 15 patients were administered Trails A of the Trail Making Test. An additional two patients could not complete the test because of severe functional disability and thus were assigned scores one standard deviation below the lowest z score

attained by any given study participant. Two patients were not administered this measure due to lack of norms for their age group and one patient had missing data. Table 3c displays the medians, means, standard deviations, and ranges for relevant summary statistics.

Table 3c

Summary Statistics for Measures of Attention and Processing Speed

	N	Median	Mean (SD)	Range
Symbol Search[a]	20	7.0	6.0 (3.4)	1-10
Coding	20	7.5	6.3 (3.4)	1-12
Digit Span	18	6.0	5.9 (3.3)	1-12
Letter-Number Sequencing	18	5.5	5.5 (2.9)	1-11
TMT, Trails A[b]	17	-0.9	-1.8 (2.7)	-7.0-1.1

[a] Scaled Scores based on a mean of 10 and a standard deviation of 3.
[b] z scores are based on a mean of 0 and a standard deviation of 1.

Problem Solving and Executive Abilities

Thirteen patients were administered the TOLDX. Two patients could not complete the test because of severe functional disability and thus were assigned basal scores. Four patients were not administered the measure due to lack of norms for their age group and one patient did not finish testing. The Trails B was also administered to 15 patients; two additional patients could not complete the test because of severe functional disability and were assigned scores one standard deviation lower than the lowest score attained by any given study participant. Two patients were not administered this measure due to lack of norms for their age group and one patient had missing data. Table 3d displays the medians, means, standard deviations, and ranges for relevant summary statistics.

Table 3d

Summary Statistics for Measures of Problem Solving/Executive Abilities

	N	Median	Mean (SD)	Range
TOLDX[a]				
Total Move	15	82	82.4 (17.7)	60-116
Total Correct	15	88	85.3 (11.4)	60-100
Total Rule Violation	15	84	83.5 (21.3)	60-106
Total Time Violation	15	94	86.0 (21.6)	60-108
Total Initiation Time	15	92	92.3 (6.1)	80-102
Total Execution Time	15	76	78.1 (16.0)	60-104
Total Problem-Solving Time	15	82	81.5 (17.3)	60-106
TMT, Trails B[b]	17	-1.4	-4.0 (4.7)	-12.0-0.6

[a] Standard Scores are based on a mean of 100 and a standard deviation of 15.
[b] z scores are based on a mean of 0 and a standard deviation of 1.

Visual-Perceptual Abilities

Eighteen patients were administered the Block Design and Picture Completion subtests of the Wechsler Scales of Intelligence. Two patients were assigned basal scores due to severe functional disability. In addition, 15 patients were administered the RCFT Copy Trial. Two additional patients were assigned basal scores due to severe functional disability, two patients were not administered the test due to lack of norms for their age group, and one patient had missing data. Table 3e displays the medians, means, standard deviations, and ranges for relevant summary statistics.

Table 3e

Summary Statistics for Measures of Visual-Perceptual Abilities

	N	Median	Mean (SD)	Range
Block Design[a]	20	7	7.1 (3.7)	1-13
Picture Completion	20	5	6.4 (3.9)	1-12
RCFT Copy Trial	17	Within Normal Range 29.4%		
		Within Impaired Range 70.6%		

[a] Scaled Scores are based on a mean of 10 and a standard deviation of 3.

Language Abilities

Eighteen patients were administered the Vocabulary and Similarities subtests of the Wechsler Scales of Intelligence. Two patients could not complete the test because of severe functional disability and were assigned basal scores. In addition, 16 patients were administered the WIAT-II-A Reading subtest and two additional patients assigned basal scores due to severe functional disability. An additional two patients were not administered the test due to lack of norms for their age group. Table 3f displays the medians, means, standard deviations, and ranges for relevant summary statistics.

Table 3f

Summary Statistics for Measures of Language Functioning

	N	Median	Mean (SD)	Range
Vocabulary[a]	20	6	5.2 (2.4)	1-8
Similarities	20	6	5.6 (3.0)	1-10
Reading Subtest[b]	18	85	80.0 (21.9)	40-108

[a] Scaled Scores are based on a mean of 10 and a standard deviation of 3.
[b] Standard Scores are based on a mean of 100 and a standard deviation of 15.

Motor Functioning

The Purdue Pegboard (dominant, nondominant, and simultaneous both hand trials) was administered to 16 patients. Two additional patients could not complete the test because of severe functional disability and were assigned scores one standard deviation lower than the lowest score attained by any given study participant. Further, one patient was not administered this measure due to lack of norms for her age group and one patient had missing data. Table 3g displays the medians, means, standard deviations, and ranges for relevant summary statistics.

Table 3g

Summary Statistics for Measures of Motor Functioning

	N	Median	Mean (SD)	Range
Dominant Hand[a]	18	-2.3	-3.0 (1.8)	-6.0--0.8
Nondominant Hand	18	-2.4	-2.8 (2.0)	-6.0-0.6
Both Hands	18	-2.5	-2.7 (1.9)	-6.0-0.2

[a] z scores are based on a mean of 0 and a standard deviation of 1.

Academic Achievement

Sixteen patients were administered the Reading, Spelling, and Numerical Operations subtests of the WIAT-II-A. Two additional patients were assigned basal scores because of severe functional disability and another two patients were not administered the measure due to lack of norms for their age group. Table 3h displays the medians, means, standard deviations, and ranges for relevant summary statistics.

Table 3h

Summary Statistics for Measures of Academic Achievement

	N	Median	Mean (SD)	Range
Reading[a]	18	85	80.0 (21.9)	40-108
Spelling	18	81	79.3 (21.4)	40-109
Numerical Operations	18	88	77.0 (22.4)	40-111
Total Composite	18	83	78.4 (17.7)	46-110

[a] Standard Scores are based on a mean of 100 and a standard deviation of 15.

Behavioral/Psychiatric Functioning

Five patients were administered the age appropriate BASC Self-Report measure and nine parents were administered the age appropriate BASC Parent-Report measure. Missing values were due to lack of age appropriate forms, non English-speaking parents,

and patient's inability to complete the measure due to severe disability. Table 3i displays the medians, means, standard deviations, and ranges for relevant summary statistics.

Table 3i

Summary Statistics for Measures of Behavioral/Psychiatric Functioning

	N	Median	Mean (SD)	Range
Self-Report				
School Maladjustment[a,b]	5	57	55.8 (14.7)	41-77
Clinical Maladjustment[b]	5	45	46.2 (5.5)	40-55
Personal Adjustment[c]	5	46	41.8 (15.4)	16-55
Emotional Symptoms Index[b]	5	47	50.2 (10.2)	43-68
Parent-Report				
Externalizing Problems[b]	9	52	55.1 (12.5)	37-74
Internalizing Problems[b]	9	56	54.6 (11.9)	37-72
Behavioral Symptoms Index[b]	9	54	56.8 (11.9)	36-72
Adaptive Skills[c]	9	36	38.2 (14.3)	20-56

[a] T Scores are based on a mean of 50 and a standard deviation of 10.
[b] Higher T Scores represent poorer functioning.
[c] Higher T Scores represent better functioning.

Tests of Hypotheses

Hypothesis 1

Comparison of Cognitive Outcomes with Normative Samples

It was hypothesized that on average, TBI patients would perform more poorly (i.e., there would be statistically significant differences in group means) on all measures of intellectual and neuropsychological functioning as compared to age matched nonclinical individuals based on the standardized age appropriate published norms for each instrument. A z-test was used to identify statistically significant differences in mean scores of the study sample as compared to published norms. Because raw data was not available for the normative sample in most instances, summary statistics, including means and standard deviations, were used to test for significant differences using Minitab

14. Table 4 lists the sample size for each group with respective z statistics, p values, and 95% confidence intervals for the mean. Consistent with hypothesis 1, the results in Table 4 demonstrate that all of the test scores were statistically significantly lower in the study sample as compared to published norms (all $p < .02$).

Table 4

Comparison of Cognitive Test Results with Normative Samples

	N (study/norm)	**z-value**	***P***	**95% CI for mean**
FSIQ	20/200	-6.77	<.001	65.4 – 81.0
Symbol Search		-5.26	<.001	4.5 – 7.5
Coding		-4.87	<.001	4.8 – 7.8
Digit Span		-5.27	<.001	4.4 – 7.4
Letter-Number Sequencing		-6.58	<.001	4.2 – 6.8
Block Design		-3.51	<.001	5.5 – 8.7
Picture Completion		-4.13	<.001	4.7 – 8.1
Vocabulary		-8.94	<.001	4.1 – 6.3
Similarities		-6.56	<.001	4.3 – 6.9
CVLT Total Trials 1-5 T	18/70	-5.28	<.001	27.6 – 39.8
List A Short-Delay Free Recall		-5.66	<.001	-2.2 – -1.0
List A Long-Delay Free Recall		-5.09	<.001	-2.5 – -1.1
RCFT Immediate Recall	17/30	-5.89	<.001	24.3 – 37.1
RCFT Delayed Recall		-5.61	<.001	25.6 – 38.2
TMT A	17/30	-2.75	.006	-3.1 – -0.5
TMT B		-3.51	<.001	-6.2 – -1.8
TOLDX Move	15/100	-3.85	<.001	73.4 – 91.4
TOLDX Correct		-4.99	<.001	79.5 – 91.1
TOLDX Rule Violation		-3.00	.003	72.7 – 94.3
TOLDX Time Violation		-2.51	.012	75.1 – 96.9
TOLDX Initiation Time		-4.81	<.001	89.2 – 95.4
TOLDX Execution Time		-5.30	<.001	70.0 – 86.2
TOLDX Problem-Solving Time		-4.14	<.001	72.7 – 90.3
Purdue Dominant Hand	18/30	-7.07	<.001	-3.8 – -2.2
Purdue Nondominant Hand		-5.94	<.001	-3.7 – -1.9
Purdue Both Hands		-6.03	<.001	-3.6 – -1.8
WIAT-II-A Reading	18/100	-3.87	<.001	69.9 – 90.1
WIAT-II-A Spelling		-4.10	<.001	69.4 – 89.2
WIAT-II-A Num. Operations		-4.36	<.001	66.7 – 87.3
WIAT-II-A Total Composite		-5.18	<.001	70.2 – 86.6

Hypothesis 2a

Time Passed Since Injury and Cognitive Outcome

It was hypothesized that time passed since injury (in years) would be positively associated with intellectual and neuropsychological outcome one to four years post injury. Because the variables of interest approximated the normal distribution, a Pearson correlation coefficient was run to evaluate the association between the time variable and outcome scores. Contrary to what was expected, time passed since injury yielded only a mild (not statistically significant) association with Full Scale IQ ($r = .14$, $p = .56$) and the combined Neuropsychological Index (NPI) ($r = .13$, $p = .60$) (Figures 1 and 2). This held true even when the sample was divided into two groups by age at injury (i.e., 8 years or younger and older than 8 years). The 8-year cut-off was chosen based on available literature suggesting this to be a critical period of higher order cognitive development (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2000; Duval, Dumont, Braun, & Montour-Proulx, 2002; Hanten et al., 2004).

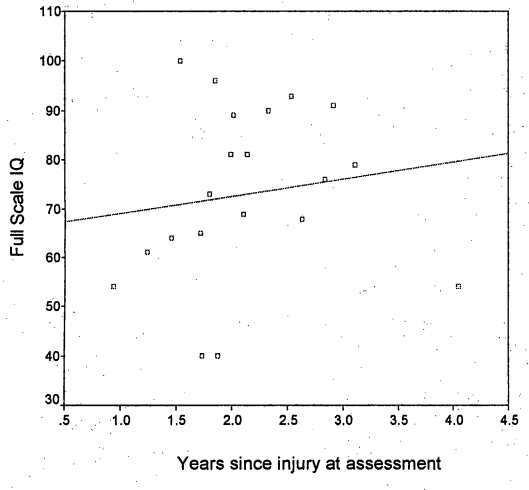


Figure 1. Time since injury and FSIQ

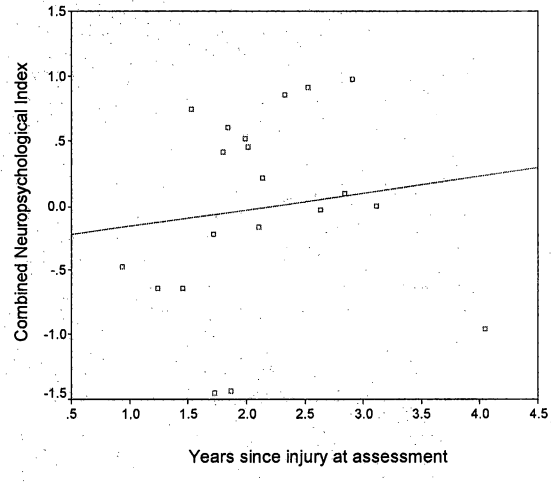


Figure 2. Time since injury and NPI

Hypothesis 2b

Age at Injury and Cognitive Outcome

It was hypothesized that age at the time of injury (in years) would be positively associated with intellectual and neuropsychological outcome one to four years post injury. Pearson correlation coefficients were run to evaluate the association between age at injury and the outcome scores. Moderate associations were noted in the positive and expected direction between age at injury and both Full Scale IQ ($r = .39$, $p = .09$) and NPI ($r = .27$, $p = .25$). Lack of statistical significance was likely due to the small sample size.

When coefficients were recalculated for the younger (≤ 8 years) and older (> 8 years) age at injury groups, no notable correlations were noted for the younger group. In fact, scores were consistently low regardless of age at injury with a mild trend in the positive direction (Figure 3). In the older group, however, age at injury was strongly associated not only with Full Scale IQ ($r = .72$, $p = .01$) (Figure 4), but also a number of neuropsychological indices, including attention, problem solving/executive skills, language, verbal memory, and motor skills (r's between .58 and .71 and all $p < .05$).

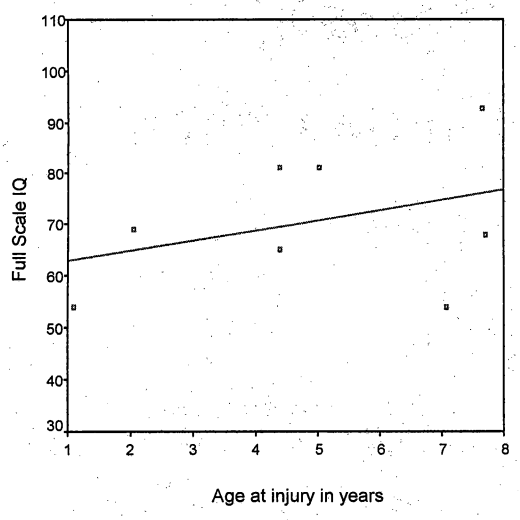


Figure 3. Injury age and FSIQ (≤ 8 years)

Figure 4. Injury age and FSIQ (> 8 years)

Hypothesis 2c

Injury Severity and Cognitive Outcome

It was hypothesized that injury severity (GCS) would be negatively associated with intellectual and neuropsychological outcome one to four years post injury. Spearman correlation coefficients (based on the non-normal configuration of the GCS variable) were run to evaluate the association between injury severity and the outcome scores. As expected, GCS was positively associated with the combined NPI ($r = .52$, $p = .02$), yielding a large effect size. GCS was also positively and moderately associated with Full Scale IQ ($r = .33$, $p = .16$). This association was especially strong in the ≤ 8 years at time of injury group; NPI: $r = .72$, $p = .04$ and FSIQ: $r = .57$, $p = .14$ (Figure 5).

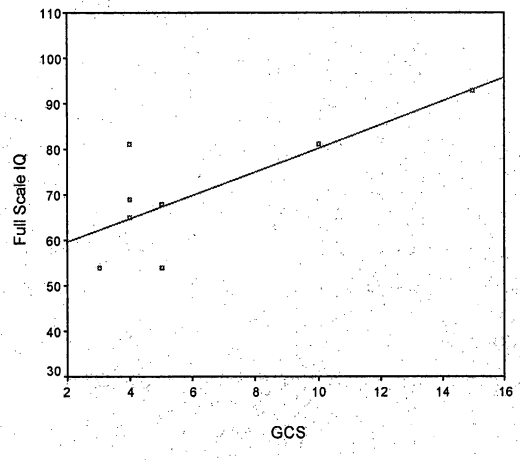


Figure 5. GCS and FSIQ (≤8 years)

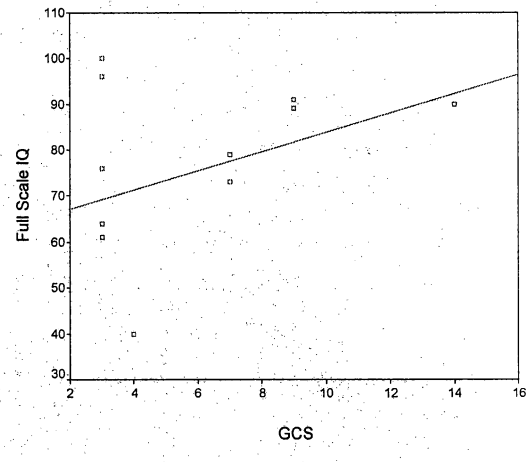
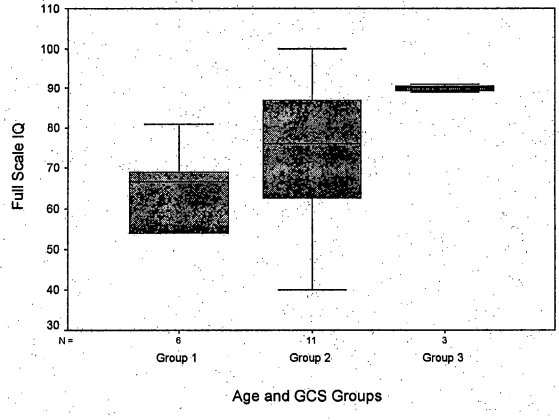


Figure 6. GCS and FSIQ (>8 years)

In fact, many of the individual neuropsychological domains, including attention, problem solving/executive skills, visual-perception, language, verbal memory, and academic achievement were also notably associated with GCS (r's between .53 to .79) in the ≤ 8 years at time of injury group. However, the association between GCS and either Full Scale IQ or NPI, although exhibiting a positive trend, was not as strong in the older group; NPI: $r = .38$, $p = .22$ and FSIQ: $r = .14$, $p = .66$ (Figure 6). These results suggest

that at older age at time of injury (>8 years), cognitive functioning outcome is variable, even in severe head injury cases. This, however, does not appear to hold true for children experiencing a head injury at age 8 or younger.

The relationship between age at time of injury and injury severity was explored further by assessing whether an interaction (additive or multiplicative) exists. Two combined variables were created by 1) summing and 2) multiplying the standardized GCS and age at injury variables. Pearson correlation coefficients indicated that the combined score using the product term was mild to moderately correlated with either FSIQ ($r = -.22$, $p = .36$) or the combined NPI ($r = -.16$, $p = .49$). However, a strong correlation was noted between the additive coefficient and both FSIQ and NPI (both r's = .60, $p = .01$). Further, in a regression model predicting FSIQ, the additive coefficient explained 13% more variance above and beyond what both age and severity variables explained collectively ($F = 3.44$, $p = .04$). These results support the additive combined score, where the presence of *both* risk factors (younger age at injury and severe injury) resulted in poor outcome and the absence of both resulted in good outcome. Those with only one of the risk factors had variable outcome (Figure 7).



Group 1: Age < 8 at injury *AND* GCS < 9
Group 2: Age < 8 at injury *OR* GCS < 9
Group 3: Neither Age < 8 Nor GCS < 9

Figure 7. FSIQ by Age at Injury and GCS Grouping

Hypothesis 3a

Role of N-acetylasparatate (NAA) in Cognitive Outcome

Single Voxel Spectra

It was hypothesized that NAA ratios from the single voxel spectra would be positively correlated with cognitive outcome. Pearson's correlation coefficients were used to correlate NAA spectra and the metabolite ratios NAA/Cho and NAA/Cre from the occipital and parietal regions with FSIQ and NPI. As hypothesized, FSIQ was positively and strongly associated with parietal NAA, occipital/parietal NAA/Cre, and parietal NAA/Cho (r's ranging from .57 - .63; all $p < .01$). Also, NPI was positively and strongly associated with occipital/parietal NAA, NAA/Cre, and NAA/Cho (r's ranging from .48 - .64; all $p < .04$).

MRSI or Multi-Voxel Spectra

It was hypothesized that MRSI NAA ratios would be positively correlated with cognitive outcome. NAA spectra metabolite ratios (with Cre and Cho) were calculated and correlated with both FSIQ and NPI using Pearson's correlation coefficients. Spectra were sampled from the: 1) anterior/middle/posterior corpus callosum; 2) right/middle/left frontal gray matter; 3) right/left frontal white matter; 4) right/middle/left parieto-occipital gray matter; and 5) right/left parietal white matter. Except for NAA/Cho in the parieto-occipital gray matter, FSIQ was strongly associated with NAA/Cre and NAA/Cho from all five sampled regions separately and when combined into a total score (r's ranging from .45 to .70; all $p < .05$). Similarly, NPI was strongly correlated with all the regional metabolite ratios individually as well as the combined total from all five regions (r's ranging from .48 to .71; all $p < .04$).

Hypothesis 3b

Role of Choline (Cho) and Creatine (Cre) in Cognitive Outcome

Single Voxel Spectra

It was hypothesized that Cho and Cre would be negatively correlated with cognitive functioning. Single voxel metabolite ratios for Cho/Cre from the occipital and parietal regions were correlated with both FSIQ and NPI using Pearson's correlation coefficients. Contrary to the proposed hypothesis, the correlations between occipital or parietal Cho/Cre and FSIQ or NPI were not statistically significant (r's ranging from -.09 to .18, all $p > .46$). Furthermore, no statistically significant correlations were noted between the individual Cho and Cre measurements in the occipital or the parietal regions with FSIQ or NPI.

MRSI or Multi-Voxel Spectra

As part of the same hypothesis, it was expected that Cho and Cre would be negatively associated with cognitive outcome. MRSI Cho/Cre metabolite ratios were calculated and correlated with both FSIQ and NPI using Pearson's correlation coefficients. Spectra were sampled from the: 1) anterior/middle/posterior corpus callosum; 2) right/middle/left frontal gray matter; 3) right/left frontal white matter; 4) right/middle/left parieto-occipital gray matter; and 5) right/left parietal white matter. Again, neither FSIQ nor NPI were strongly correlated with Cho/Cre regional metabolite ratios or the combined total from all five regions (r's ranging from -.29 to .12, all $p > .28$).

Hypothesis 3c

Role of Other Metabolites in Cognitive Outcome

Single Voxel Spectra

It was hypothesized that other metabolites, including Glx, mI, and Lac would be negatively correlated with cognitive outcome. Single voxel metabolite ratios for Glx and mI from both the occipital and parietal regions were correlated with both FSIQ and NPI using Pearson's correlation coefficients. Glx was mild to moderately correlated with FSIQ and NPI in the negative direction, as expected (r's ranging from -.22 to -.35). In addition, both occipital and parietal mI were moderate to strongly correlated with FSIQ (both r's -.45, $p < .05$) and NPI (occipital: $r = -.44$, $p = .05$; parietal $r = -.38$, $p = .10$).

Since only one patient had a detectable lactate peak in the occipital region spectra and none had a lactate peak in the parietal region spectra, correlational analyses were not possible for this variable. This was not expected since previous studies have associated lactate levels to presence and degree of cognitive deficits.

Multivariable Modeling of Cognitive Outcome Using MRS

Predicting FSIQ and NPI Using Linear Regression Modeling

Using a multiple linear regression equation, FSIQ was modeled using single voxel MRS variables which were strongly correlated with the outcome but which did not contribute redundantly (i.e., no significant multicollinearity) to FSIQ. Thus, the NAA/Cre ratios from both the parietal and occipital regions were included in the model. The overall model was significant, $F(2, 17) = 6.517$, $p = .008$, with the predictor variables explaining 43.4% of the variance in FSIQ. Next, the total combined (from the five regions of interest) MRSI NAA/Cre ratio was included in the second step of a subsequent

regression model. The overall model was significant, $F(3, 16) = 5.038$, $p = .012$, with MRSI contributing an additional 5.2% to the total variance explained in FSIQ (although not statistically significant, $p = .223$) (Table 5a, Model 1).

Similar results were noted when predicting NPI. Occipital and parietal NAA/Cre ratios significantly predicted NPI, $F(2, 17) = 6.761$, $p = .007$, accounting for 44.3% of the variance in NPI. The addition of the MRSI total NAA/Cre ratio resulted in a statistically significant overall model, $F(3, 16) = 6.059$, $p = .006$, with an additional 9% of the variance in NPI accounted for. The change in F was not statistically significant ($p = .101$) (Table 5b, Model 1). Further, the MRSI total NAA/Cre alone explained a significant portion of the variance in both FSIQ (40%) and NPI (51%) (Tables 5a and 5b, Model 2).

In addition, two models were run which took into account important clinical covariates. The covariates included the continuous additive combined score of age and injury severity (i.e., GCS scores) and number of days in a coma, both of which were strongly correlated with the outcome but did not provide redundant information. The regional NAA/Cre explained variance above and beyond the additive combined age at injury and injury severity variable, explaining 18% ($p = .02$) more in FSIQ and 26% ($p = .003$) more in NPI (Tables 5a and 5b, Model 3). However, when both the combined additive variable and total days in coma were included as covariates, the clinical covariates explained 65% of the variance in FSIQ. The change in variance after adding the MRSI total NAA/Cre variable was not statistically significant, adding 2% to the overall variance explained in FSIQ (Table 5a, Model 4). Similar results were noted when predicting NPI. The covariate variables alone significantly predicted NPI, $F(2, 17) =$

26.989, $p < .001$, accounting for 76.0% of the variance. Contributing another 3% to the total explained variance, the NAA/Cre combined ratio did not contribute significantly to the overall variance explained ($p = .138$) (Table 5b, Model 4).

Table 5a

Summary of Linear Regression Models Using MRS to Predict FSIQ

		R^2	Adj. R^2	R Change	Sig. of F Change	F (p-value)	Std. Beta
Model 1							
Step 1	1 - NAA/Cre Occipital	.434	.367	--	--	6.517	.267
	2 - NAA/Cre Parietal					(.008)	.445
Step 2	1 - NAA/Cre Occipital	.486	.389	.052	.223	5.038	-.017
	2 - NAA/Cre Parietal					(.012)	.382
	3 - Regional[a] NAA/Cre						.402
Model 2							
	1 - Regional NAA/Cre	.403	.370	--	--	12.153	.635*
						(.003)	
Model 3							
Step 1	1 - GCS/Age at Inj.[b]	.355	.319	--	--	9.910	.596*
						(.006)	
Step 2	1 - GCS/Age at Inj.	.539	.485	.184	.018	9.944	.404*
	2 - Regional NAA/Cre					(.001)	.470*
Model 4							
Step 1	1 - GCS/Age at Inj.	.650	.609	--	--	15.799	.402*
	2 - Days in Coma					(.000)	-.577*
Step 2	1 - GCS/Age at Inj.	.670	.608	.019	.348	10.804	.361*
	2 - Days in Coma					(.000)	-.471*
	3 - Regional NAA/Cre						.187

[a] NAA/Cre metabolite ratio from MRSI (multi-voxel) combined regional spectra.

[b] Additive combined score for GCS and age at injury.

* Standardized beta coefficient significant at the $p < .05$ level.

Table 5b

Summary of Linear Regression Models Using MRS to Predict NPI

		R^2	Adj. R^2	R Change	Sig. of F Change	F (p-value)	Std. Beta
Model 1							
Step 1	1 - NAA/Cre Occipital	.443	.378	--	--	6.761	.473
	2 - NAA/Cre Parietal					(.007)	.245
Step 2	1 - NAA/Cre Occipital	.532	.444	.089	.101	6.059	.100
	2 - NAA/Cre Parietal					(.006)	.161
	3 - Regional NAA/Cre[a]						.527
Model 2							
	1 - Regional NAA/Cre	.508	.481	--	--	18.597	.713*
						(.000)	
Model 3							
Step 1	1 - GCS/Age at Inj.[b]	.363	.328	--	--	10.277	.603*
						(.005)	
Step 2	1 - GCS/Age at Inj.	.625	.581	.261	.003	14.162	.374*
	2 - Regional NAA/Cre					(.000)	.560*
Model 4							
Step 1	1 - GCS/Age at Inj.	.760	.732	--	--	26.989	.378*
	2 - Days in Coma					(.000)	-.669*
Step 2	1 - GCS/Age at Inj.	.792	.753	.032	.138	20.332	.326*
	2 - Days in Coma					(.000)	-.534*
	3 - Regional NAA/Cre						.240

[a] NAA/Cre metabolite ratio from MRSI (multi-voxel) combined regional spectra.
[b] Additive combined score for GCS and age at injury.
*Standardized beta coefficient significant at the $p < .05$ level.

Hypothesis 3d

Regional MRS Data and Cognitive Outcome

Compared to single voxel spectra, MRSI (multi-voxel) is unique in that metabolites from various regions of the brain can be sampled for comparison. Exploratory analyses were conducted to investigate whether notable differences in regional MRSI results were associated with below average performance on FSIQ or the various neuropsychological domains. To this end, independent sample t-tests were

conducted to test differences in average metabolite ratios for groups identified by < or ≥ one standard deviation below the normative mean on FSIQ and other neuropsychological domains. This cutoff was based on the available literature assessing the efficacy of MRS variables in predicting neuropsychological outcome (Brenner et al., 2003). Only NAA metabolite ratios were included since the correlation and regression analyses above indicated them to be a robust and strong predictor of cognitive outcome.

Consistent and statistically significant group differences were noted for metabolite ratios across the various regions sampled for FSIQ, nonverbal memory, and visual-perceptual functioning, perhaps suggesting that the integrity of these functions is sensitive to changes in NAA (and its metabolites) across the brain regions sampled. Further, a notable but consistent trend in lower scores was observed for metabolite ratios of the frontal gray matter. Again, this finding may suggest that the frontal regions, specifically frontal gray matter, play a significant role in various neuropsychological functions and that significant changes in brain metabolites (i.e., NAA and its ratio combinations) in this region are associated with poor functioning across several cognitive domains (Table 6). Larger sample sizes are necessary to confirm these findings.

Hypothesis 4a

SWI Lesion Number and Volume and Cognitive Outcome

Predicting FSIQ and NPI Using Linear Regression Modeling

It was hypothesized that hemorrhage volume and lesion number would be significant predictors of intellectual and neuropsychological outcome. Although the total SWI lesion number and lesion volume variables slightly deviated from normality (based on a visual inspection of histogram and the Kolmogorov-Smirnov test statistic), these

Table 6

Means and Standard Deviations (±) of Regional MRS Results by Function

Domain	Group	CC	FGM	FWM	POGM	PWM	Comb.
FSIQ	< 1 SD	1.4 ± .4[a]	**1.3 ± .3***	1.4 ± .2	**1.4 ± .3***	**1.6 ± .3***	**1.4 ± .2***
		1.1 ± .3[b]	**1.2 ± .3***	1.3 ± .2	1.7 ± .5	**1.4 ± .3***	**1.3 ± .2***
	≥ 1 SD	1.7 ± .4	1.8 ± .4	1.7 ± .2	1.7 ± .2	2.0 ± .2	1.8 ± .1
		1.4 ± .4	1.7 ± .2	1.7 ± .4	2.0 ± .5	2.0 ± .4	1.8 ± .3
Verbal	< 1 SD	1.4 ± .4	1.4 ± .5	1.5 ± .3	1.4 ± .3	1.6 ± .3	1.5 ± .3
Memory		1.1 ± .3	1.3 ± .4	1.4 ± .3	1.8 ± .6	1.6 ± .3	1.4 ± .3
	≥ 1 SD	1.6 ± .4	1.5 ± .4	1.6 ± .3	1.7 ± .3	1.8 ± .4	1.7 ± .3
		1.3 ± .4	1.4 ± .4	1.5 ± .4	2.0 ± .5	1.7 ± .6	1.6 ± .4
Nonverbal	< 1 SD	1.4 ± .4	**1.3 ± .3***	**1.5 ± .2***	1.5 ± .3	1.6 ± .3	**1.5 ± .2***
Memory		1.2 ± .2	**1.3 ± .3***	**1.4 ± .2***	1.8 ± .4	**1.5 ± .2***	**1.4 ± .2***
	≥ 1 SD	1.6 ± .5	2.1 ± .5	1.9 ± .0	1.8 ± .2	2.0 ± .2	1.9 ± .2
		1.4 ± .5	2.0 ± .3	1.9 ± .4	2.3 ± .9	2.2 ± .5	2.0 ± .4
Attention	< 1 SD	1.3 ± .4	1.2 ± .3	1.4 ± .3	1.3 ± .3	1.6 ± .3	1.4 ± .3
		1.1 ± .2	**1.1 ± .2***	1.4 ± .3	1.7 ± .6	1.5 ± .3	1.4 ± .3
	≥ 1 SD	1.6 ± .3	1.6 ± .2	1.6 ± .2	1.6 ± .3	1.8 ± .3	1.7 ± .2
		1.3 ± .3	1.5 ± .4	1.5 ± .3	1.9 ± .5	1.7 ± .4	1.6 ± .3
Executive	< 1 SD	1.3 ± .4	1.3 ± .3	1.5 ± .3	1.5 ± .3	1.6 ± .3	1.5 ± .2
		1.1 ± .2	1.2 ± .3	1.4 ± .2	1.9 ± .5	1.5 ± .2	1.4 ± .2
	≥ 1 SD	1.6 ± .4	1.7 ± .6	1.7 ± .3	1.7 ± .3	1.9 ± .3	1.7 ± .3
		1.4 ± .4	1.6 ± .4	1.5 ± .4	2.0 ± .5	1.8 ± .5	1.7 ± .4
Visual-	< 1 SD	**1.3 ± .3***	**1.3 ± .3***	**1.4 ± .2***	**1.3 ± .3***	**1.5 ± .2***	**1.4 ± .2***
Perceptual		**1.1 ± .2***	**1.2 ± .3***	**1.3 ± .2***	**1.6 ± .4***	**1.4 ± .2***	**1.3 ± .2***
	≥ 1 SD	1.8 ± .3	1.7 ± .4	1.7 ± .2	1.8 ± .2	2.0 ± .1	1.8 ± .1
		1.5 ± .3	1.6 ± .3	1.8 ± .3	2.2 ± .6	2.0 ± .3	1.8 ± .3
Language	< 1 SD	1.4 ± .4	1.3 ± .3	1.5 ± .3	1.4 ± .4	1.7 ± .3	1.5 ± .3
		1.2 ± .4	**1.2 ± .3***	1.4 ± .4	1.8 ± .7	1.6 ± .5	1.4 ± .4
	≥ 1 SD	1.6 ± .2	1.6 ± .5	1.6 ± .2	1.6 ± .2	1.7 ± .3	1.6 ± .2
		1.3 ± .2	1.6 ± .4	1.5 ± .2	1.9 ± .2	1.6 ± .3	1.5 ± .2
Motor	< 1 SD	1.4 ± .4	1.4 ± .5	1.5 ± .3	1.4 ± .3	1.7 ± .3	1.5 ± .3
		1.1 ± .3	**1.3 ± .4***	1.4 ± .2	1.7 ± .5	1.5 ± .3	1.4 ± .2
	≥ 1 SD	1.8 ± .2	1.7 ± .2	1.7 ± .3	1.7 ± .2	1.8 ± .3	1.8 ± .2
		1.5 ± .4	1.8 ± .0	1.6 ± .5	2.4 ± .6	1.9 ± .6	1.8 ± .4
Achievement	< 1 SD	1.4 ± .5	1.2 ± .4	1.5 ± .4	1.4 ± .3	1.7 ± .4	1.5 ± .4
		1.2 ± .4	1.2 ± .4	1.5 ± .4	1.8 ± .7	1.7 ± .5	1.5 ± .4
	≥ 1 SD	1.6 ± .3	1.6 ± .4	1.6 ± .2	1.6 ± .2	1.8 ± .3	1.6 ± .2
		1.3 ± .2	1.5 ± .4	1.5 ± .3	2.0 ± .4	1.6 ± .3	1.6 ± .2

[a] First row of results for each group representative of regional MRS NAA/Cre ratios.
[b] Second row of results for each group representative of regional MRS NAA/Cho ratios.
* Significant ($p<.05$) group differences in MRS results for scores < or ≥ 1 standard deviation below mean.
CC = corpus callosum; FGM = frontal gray matter; FWM = frontal white matter; PGM = parieto-occipital gray matter; PWM = parietal white matter; Comb = combined regional MRS data.

distributions were not extreme, warranting parametric test statistics were used. SWI lesion number and volume were correlated with FSIQ and NPI using the Pearson correlation coefficient. As hypothesized, NPI yielded a large magnitude association with total SWI lesion number ($r = -.490$, $p = .039$) and a very large magnitude association with total SWI lesion volume ($r = -.666$, $p = .003$) (negative direction). Similar associations were noted between FSIQ and both lesion volume ($r = -.573$, $p = .013$) and number ($r = -.377$, $p = .123$). These coefficients reflected large effect sizes in the negative direction.

Using multiple regression, FSIQ was modeled using SWI lesion volume and number. The overall model was significant, $F(2, 15) = 4.314$, $p = .033$, with these two variables together explaining 36.5% of the variance in FSIQ. The majority of the contribution to the explained variance in FSIQ was from lesion volume (standardized beta = -.868, $p = .037$), with lesion number having a relatively smaller contribution to the overall model (standardized beta = .351, $p = .368$). Similarly, SWI lesion number and volume together were significant predictors of NPI, $F(2, 15) = 6.361$, $p = .010$, accounting for 45.9% of the variance. Only lesion volume variable had a statistically significant contribution to the overall model (standardized beta = -.861, $p = .026$) with lesion number contributing relatively less (standardized beta = .233, $p = .515$) (Table 7).

Finally, a set of regression models including important clinical variables were investigated. The clinical covariates modeled were the continuous additive combined score of age at injury and injury severity (i.e., GCS scores) and number of days in a coma, both of which were strongly correlated with the outcome but did not provide redundant information. When predicting FSIQ, the clinical variables alone explained 70.7% of the variance. The addition of the SWI total lesion number and volume

variables in the second step added an additional 12% to the proportion of variance explained ($p = .040$). Similarly, when predicting NPI, the covariates alone accounted for 78.5% of the variance. The addition of the SWI variables resulted in an additional 9% of the variance being explained ($p = .030$) (Table 7). In both models, SWI lesion volume and number had a unique and statistically significant contribution to the prediction of the outcome variables ($p < .05$) and were, therefore, retained in the final models.

Table 7

Summary of Linear Regression Models Using SWI to Predict Outcome

		R^2	Adj. R^2	R Change	Sig. of F Change	F (p-value)	Std. Beta
Predicting FSIQ							
Model 1							
Step 1	1 - SWI Lesion #	.365	.281	--	--	4.314	.351
	2 - SWI Lesion V[a]					(.033)	-.868*
Model 2							
Step 1	1 - GCS/Age at Inj.[b]	.707[c]	.668	--	--	18.071	.309
	2 - Days in Coma					(.000)	-.688*
Step 2	1 - GCS/Age at Inj.	.821	.766	.115	.040	14.928	.286*
	2 - Days in Coma					(.000)	-.758*
	3 - SWI Lesion #						.634*
	4 - SWI Lesion V						-.542*
Predicting NPI							
Model 1							
Step 1	1 - SWI Lesion #	.459	.387	--	--	6.361	.233
	2 - SWI Lesion V					(.010)	-.861*
Model 2							
Step 1	1 - GCS/Age at Inj.	.785	.757	--	--	27.420	.291*
	2 - Days in Coma					(.000)	-.747*
Step 2	1 - GCS/Age at Inj.	.875	.837	.090	.030	22.748	.267*
	2 - Days in Coma					(.000)	-.729*
	3 - SWI Lesion #						.505*
	4 - SWI Lesion V						-.549*

[a] SWI total lesion volume; [b] Additive combined GCS and age at injury; [c] Differs from regression statistics presented in Table 5 due to smaller N (18 SWI vs. 20 MRS); * Standardized beta coefficient significant at the $p < .05$ level.

Hypothesis 4b

Comparison of SWI and GRE in Predicting Cognitive Outcome

It was hypothesized that lesion number from SWI would be a better predictor of cognitive outcome compared to those from conventional MR images. SWI has been demonstrated to be substantially better than conventional MRI (GRE) when detecting hemorrhagic lesion number and volume (Tong et al., 2003). However, it is not clear if improvement in detection of lesions corresponds with better prediction of long-term cognitive outcome. Thus, total SWI and GRE detected lesion numbers only from regions of the brain where MRSI data was collected were compared.

Large magnitude associations were noted between FSIQ and both SWI and GRE lesion number in the expected negative direction (GRE: $r = -.376$, $p = .125$; SWI: $r = -.443$, $p = .051$). Furthermore, both GRE and SWI lesion number strongly moderately correlated with NPI (GRE: $r = -.486$, $p = .041$; SWI: $r = -.472$, $p = .036$). In a linear multiple regression predicting FSIQ, total GRE lesion number explained 14.1% of the variance in FSIQ. When SWI lesion number was entered in the second step, the amount of explained variance approximately doubled to 29.4%. Although the p-value associated with this statistic ($p = .091$) was not statistically significant, its magnitude is relatively large and both clinically and practically meaningful. Similar results were noted when predicting NPI. Total GRE lesion number accounted for 23.6% of the variance. Adding total SWI lesion number in a second step explained an additional 10% (Table 8).

It is important to note that there are two important limitations in the data used to run these comparison analyses: 1) only GRE and SWI lesion numbers were available for analysis, which was demonstrated in the above analyses to be a weaker predictor as

compared to lesion volume, and 2) GRE lesion data only from regions of the brain sampled for MRS studies (see above) were available, allowing comparisons between GRE and SWI lesion numbers only from these limited regional areas as compared to data from the entire brain. Both of these may have significantly affected comparative analyses between GRE and SWI as predictors of long-term cognitive outcome.

Table 8

Summary of Linear Regression Models Comparing GRE and SWI

		R^2	Adj. R^2	R Change	Sig. of F Change	F (p-value)	Std. Beta
Predicting FSIQ							
Model 1							
Step 1	1 - GRE Lesion #[a]	.141	.087	--	--	2.628 (.125)	-.376
Step 2	1 - GRE Lesion #	.294	.200	.153	.091	3.128	.097
	2 - SWI Lesion #[a]					(.073)	-.613
Predicting NPI							
Model 1							
Step 1	1 - GRE Lesion #	.236	.188	--	--	4.938 (.041)	-.486*
Step 2	1 - GRE Lesion #	.339	.251	.103	.147	3.846	-.098
	2 - SWI Lesion #					(.045)	-.503

[a] Lesion number based only on regions of the brain imaged using MRS.
* Standardized beta coefficient significant at the $p < .05$ level.

Hypothesis 4c

Regional SWI Lesions and Cognitive Outcome

Exploratory analyses were conducted to investigate whether regional hemorrhage volume and lesion number varied in association with specific neuropsychological

outcome indices. Both lesion number and volume from nine brain regions were correlated with each intellectual and neuropsychological domain index using Pearson's correlation coefficients. The nine SWI regions included: 1) frontal gray matter, 2) frontal white matter, 3) parietal-temporal-occipital gray matter, 4) parietal-temporal-occipital white matter, 5) corpus callosum, 6) basal ganglia, 7) thalamus, 8) brain stem, and 9) cerebellum. The neuropsychological domains included FSIQ, executive, attention, visual-perceptual, language, achievement, verbal and nonverbal memory, and motor skills. Magnitudes of associations were reported instead of statistical significance since due to the relatively small sample size of the study, meaningful associations which can be identified using magnitudes may otherwise have been lost. Large effect sizes were attributed to correlation coefficients close to .5, medium effect sizes were attributed to correlation coefficients close to .3, and small effect sizes were attributed to correlation coefficients close to .1 (Cohen, 1992).

There were several large, medium, and small correlation coefficients noted. In general, both SWI lesion number and SWI volume in deep brain regions such as the basal ganglia, thalamus, and brain stem, were strongly associated with almost all domains of intellectual and neuropsychological functioning with primarily large effect sizes noted. The association between neuropsychological outcomes and lesions in the corpus callosum and cerebellum were primarily associated with medium to large effect sizes, while the cortical regions, including parietal-temporal-occipital gray matter and frontal gray matter, were primarily associated with small to medium effect sizes. Table 9 lists all of the correlation coefficients, with large to very large correlation effect sizes denoted in bold and medium correlation effect sizes denoted by #. Further, in a stepwise linear regression

model, basal ganglia and brainstem lesion volumes were the two most predictive variables of both the Full Scale IQ and the neuropsychological index among all of the variables representing regional lesion number and volume. Basal ganglia and brainstem SWI lesion volume together explained 64% of the variance in the FSIQ, $F(2, 15) = 13.559$, $p < .01$, and 70% of the variance in NPI, $F(2, 15) = 17.519$, $p < .01$.

Hypothesis 5

Comparison of MRS and SWI in Predicting Cognitive Outcome

Exploratory analyses were conducted to investigate the relative predictive efficacy of MRS and SWI results on cognitive outcome. Using linear multiple regression equations to predict FSIQ and NPI, MRS variables (single and multi-voxel NAA/Cre ratios) and SWI variables (total lesion volume and number) were entered in either the first or second step. When SWI variables were entered second, they demonstrated a significant contribution to the overall variance explained (an additional 21% to FSIQ and 23% to NPI) above and beyond that of the MRS variables alone. Similarly, when the MRS variables were entered second, they also demonstrated a significant contribution to the overall variance explained (an additional 31% to FSIQ and 27% to NPI) above and beyond that of the SWI variables (Table 10). Furthermore, in a stepwise linear regression model, out of all the MRS and SWI predictor variables addressed in this study, the two significant variables when predicting FSIQ or NPI were the MRSI NAA/Cre ratio and the total SWI lesion volume ($p < .01$). All of these results combined suggest that MRS and SWI have a unique and important contribution when predicting long-term intellectual or neuropsychological functioning.

Table 9

Correlation Coefficients between Regional SWI and Test Results

Region	FSIQ	Exec	Attn	VP	Lang	Achiev	VMem	NVMem	Motor
FGM									
N	-.05	-.23	-.02	-.02	.18	.23	-.09	**-.40**	.06
V	-.14	-.29#	-.10	-.14	.09	.12	-.07	**-.45**	-.01
FWM									
N	-.31#	**-.42**	-.37#	-.25#	-.29#	-.30#	**-.50**	-.13	**-.41**
V	-.17	-.34#	-.26#	-.14	-.13	-.12	**-.47**	-.08	-.23
PTOG									
N	-.15	-.37#	-.23	-.12	-.18	-.16	**-.51**	-.12	-.06
V	-.16	-.33#	-.26#	-.08	-.23	-.23	**-.51**	-.11	-.14
PTOW									
N	-.19	-.23	-.30#	-.15	-.35#	-.37#	**-.40**	-.26#	-.34#
V	-.39#	-.31#	**-.49**	-.32#	**-.50**	**-.52**	**-.46**	-.33#	**-.55**
CC									
N	**-.43**	-.30#	**-.43**	-.35#	**-.42**	-.28#	**-.45**	**-.51**	-.39#
V	-.30#	-.15	-.32#	-.23	-.31#	-.21	-.25#	**-.49**	-.29#
BG									
N	**-.63**	**-.55**	**-.67**	**-.50**	**-.63**	**-.62**	**-.56**	-.21	**-.65**
V	**-.63**	-.39#	**-.73**	**-.43**	**-.61**	**-.61**	**-.61**	-.27#	**-.72**
TH									
N	**-.63**	**-.54**	**-.64**	**-.52**	**-.60**	**-.54**	**-.52**	**-.40**	**-.60**
V	-.38#	-.17	**-.41**	-.35#	**-.55**	**-.49**	-.26#	-.36#	-.37#
BS									
N	**-.64**	-.34#	**-.73**	**-.43**	**-.77**	**-.74**	**-.52**	-.31#	**-.67**
V	**-.67**	**-.46**	**-.73**	**-.51**	**-.73**	**-.70**	**-.54**	-.31#	**-.69**
CB									
N	-.35#	-.16	-.39#	-.24	**-.52**	**-.49**	-.36#	-.06	-.19
V	-.36#	-.17	**-.41**	-.26#	**-.55**	**-.52**	-.36#	-.12	-.25#
Total									
N	-.38#	**-.46**	**-.47**	-.30#	**-.43**	**-.42**	**-.60**	-.29#	**-.45**
V	**-.57**	**-.48**	**-.69**	**-.42**	**-.60**	**-.59**	**-.70**	-.35#	**-.67**
FGM									
N	-.05	-.23	-.02	-.02	.18	.23	-.09	**-.40**	.06
V	-.14	-.29#	-.10	-.14	.09	.12	-.07	**-.45**	-.01

#: Total lesion number for given brain region; V: Total lesion volume for given brain region; Exec = executive; Attn = attention; VP = visual-perceptual; Lang = language; Achiev = academic achievement; VMem = verbal memory; NVMem = nonverbal memory; FGM = frontal gray matter; FWM = frontal white matter; PTOG = parietal-temporal-occipital gray matter; PTOW = parietal-temporal-occipital white matter; CC = corpus callosum; BG = basal ganglia; TH = thalamus; BS = brainstem; CB = cerebellum; Total = total of all of the above regions combined. Large correlations effect sizes (coefficients around .5 and above) in bold; medium (coefficients around .3) denoted by an asterisk (#); all others in regular font.

Table 10

Summary of Linear Regression Models Comparing MRS and SWI

		R^2	Adj. R^2	R Change	Sig. of F Change	F (p-value)	Std. Beta
Predicting FSIQ							
Model 1							
Step 1	1 - MRS variables[a]	.468	.354	--	--	4.111	.316
						(.028)	.142
							.304
Step 2	1 - MRS variables	.674	.538	.205	.054	4.953	.283
						(.011)	-.084
	2 - SWI variables[b]						.430
							.449
							-.801*
Model 2							
Step 1	1 - SWI variables	.365	.281	--	--	4.314	.351
						(.033)	-.868*
Step 2	1 - SWI variables	.674	.538	.308	.040	4.953	.449
	2 - MRS variables					(.011)	-.801*
							.283
							-.084
							.430
Predicting NPI							
Model 1							
Step 1	1 - MRS variables[a]	.504	.398	--	--	4.743	.491
						(.017)	.161
							.110
Step 2	1 - MRS variables	.729	.617	.225	.026	6.468	.420
						(.004)	-.051
	2 - SWI variables[b]						.235
							.318
							-.754*
Model 2							
Step 1	1 - SWI variables	.459	.387	--	--	6.361	.233
						(.010)	-.861*
Step 2	1 - SWI variables	.729	.617	.270	.035	6.468	.318
	2 - MRS variables					(.004)	-.754*
							.420
							-.051
							.235

[a] MRS variables include, in order: 1) multi-voxel combined, 2) single voxel occipital, and 3) single voxel parietal NAA/Cre.

[b] SWI variables include, in order: 1) total lesion number and 2) total lesion volume.

* Standardized beta coefficient significant at the $p < .05$ level.

DISCUSSION

Traumatic brain injury is one of the leading causes of morbidity and mortality among youth in the United States every year. Survivors of pediatric head trauma may suffer from impairments not only in neurological and intellectual functioning, but also in specific neuropsychological abilities, including attention, memory, language, sensorimotor, visuospatial, and executive abilities (Adelson & Kochanek, 1998; Kraus, 1995), as well as in behavioral and psychiatric functioning. Clinical indicators have traditionally been used to predict long-term neurologic and cognitive outcome in order to provide patients, families, and the health care team an estimate of expected recovery so that appropriate and timely treatments and services can be provided.

Although there is push to examine the relationship between brain-behavior relationships using more detailed measurements of brain status and function after a head injury, most researchers still use the GCS, which is a global estimator of injury severity (Taylor, 2004). Improvements in neuroimaging technology have allowed for better detection of the nature and extent of brain injury in order to evaluate the relationship between structural and functional status (Dennis & Levin, 2004). This study evaluated the efficacy of two relatively recent neuroimaging technologies, which are available on most clinical MR scanners, as predictors of long-term cognitive outcome following pediatric traumatic brain injury.

Correlates of Neurocognitive Functioning

As hypothesized, intellectual and neuropsychological deficits were noted without exception in all of the areas assessed when performance of the patients was compared to normative samples. The specific cognitive functions assessed included overall

intelligence, verbal and nonverbal memory, attention and processing speed, problem solving and executive skills, visual-perceptual abilities, language functioning, motor skills, as well as academic achievement. In addition, it is important to note that none of the 20 study participants achieved an overall IQ greater than 100. Deficits across multiple neuropsychological domains are consistent with reports in the literature, which suggest consistent and chronic impairments in several cognitive domains (Fay et al., 1994; Jaffe et al., 1992; Taylor, 2004).

Furthermore, previous research has indicated a notable increase in behavioral and/or psychiatric outcome following pediatric TBI, including temperament changes, increased irritability, aggressive and hyperactive behaviors, impulsivity, temper outbursts, and difficulties with social and interpersonal relationships, as well as novel and lifetime (premorbid) Attention-Deficit/Hyperactivity Disorder (ADHD) (Bloom et al., 2001; Max et al., 2004; Schachar et al., 2004). In this study sample, mean scores across all self and parent report measures of behavioral and/or psychiatric functioning were within normal limits, except for a below average mean score on a parent report index of adaptive skills. It should be noted, however, that data on this measure were available only for a small subset of the study sample (self report n = 5; parent report n = 9) who were able to complete the questionnaire and for whom appropriate norms were available. It is, therefore, important to further investigate the relationship between behavioral/psychiatric functioning and the neuroimaging indices examined in this study in larger samples.

Several variables have been consistently associated with intellectual and neuropsychological outcome following pediatric TBI. These have included time passed since injury, age at the time of injury, and injury severity (Ewing-Cobbs et al., 1997; Jaffe et al., 1992; Jaffe et al., 1993; Massagli et al., 1996; Taylor, 2004). As such, a positive association between age at injury and time passed since injury with cognitive outcome were hypothesized, as was a negative association between injury severity and cognitive outcome. The study results, however, indicated that time passed since injury was not associated with either overall intellectual or neuropsychological functioning and thus was not included as a covariate in the multivariable regression models predicting cognitive outcome. This finding may be specific to this sample since on average, patients were at least two years post injury, with no patient under one year post injury in accordance with the study's inclusion criteria. The one year cutoff was chosen because the literature suggests that a substantial amount of recovery occurs within the first 12 months after injury (Adelson & Kochanek, 1998), with negligible recovery during the second year post injury (Jaffe, Polissar, Fay, & Liao, 1995). Nonetheless, some have suggested that final cognitive assessments should be conducted years after injury in order to ensure maximum recovery (Laurent-Vannier, Brugel, & De Agostini, 2000) and that judging full recovery in a developing individual may be premature because deficits can arise at a later time when a particular milestone is being met or when new skills are being acquired (Chapman & McKinnon, 2000; Franzen & Berg, 1998). This is particularly relevant to the pediatric TBI patient because of the dynamic nature of growth and development and its interplay with a brain insult during childhood.

In addition to time since injury, age at injury was investigated as a covariate of cognitive outcome following TBI. Small to medium associations were noted between age at injury and both intellectual and neuropsychological functioning, with a generally positive trend. However, when the sample was divided into a younger ($\leq$ 8 years) and an older (> 8 years) group for age at injury, the latter was still not notably associated with intellectual functioning in the younger group; however, in the older age at injury group, higher intellectual functioning scores were strongly associated with older age. The cutoff of eight years of age was chosen because several cognitive and developmental changes occur during this point in development. The literature reviewed by Hanten et al. (2004) suggested that it is approximately around this age when important global cognitive changes occur that allow children to have metacognitive skills (the ability to become aware of one's cognitions), employ strategies for learning and retaining information, and effectively problem solve (Hanten et al., 2004). Furthermore, studies investigating age at injury effects on cognitive outcome post injury have noted significant group differences in recovery trends based on this age cutoff (Anderson et al., 2000; Duval et al., 2002). It has, therefore, been suggested that age at injury is a moderator of outcome and not a predictor since injury occurs in the context of ongoing cognitive and physical development (Dennis & Levin, 2004). In addition, outcome is affected by an interplay of several factors such as pathophysiology of injury, developmental state at the time of injury, time passed since injury, and a child's psychosocial resources, including premorbid abilities, as well as support from family, school, and peers (Chapman & McKinnon, 2000; Dennis & Levin, 2004).

Finally, injury severity, characterized by GCS at the time of injury, was investigated as an indicator of long-term cognitive outcome. Positive and moderate associations were noted between GCS and intellectual and neuropsychological functioning. This trend was very pronounced for patients who sustained a head injury at or before the age of eight, with none of the severe head injury patients achieving an IQ score over one standard deviation below the normative mean; however, for those over the age of eight at time of injury, outcome was variable, with even severe head injury patients achieving average IQ scores. Because of the above noted relationship between age at injury and injury severity, the possibility of an additive combined score effect between the two variables was explored. In fact, when the latter two variables were standardized and summed, the new variable was strongly associated with both intellectual and neuropsychological functioning, and accounted for 13% more variance above and beyond the individual variables when predicting intelligence scores. This additive combined score was therefore used in subsequent regression analyses as a covariate accounting for both age at injury and injury severity. The additive combined score finding suggests that poor outcome resulted from the presence of both risk factors (i.e., younger age at injury and severe injury) while the absence of both risk factors resulted in good cognitive outcome. Those with only one of the risk factors had variable cognitive outcome, perhaps explained by variables other than the two considered here.

Although this finding is not typically referred to as an additive interaction in the literature, several authors have documented this effect in studies with pediatric TBI patients. For example, in a series of longitudinal analyses, slower recovery in word fluency was associated with severe injury; however, this finding was specific to the

younger age at injury group who also had severe injuries, and did not apply to older severe TBI or younger mild TBI patients (Levin et al., 2001). Furthermore, in a study of 124 children divided into two age at injury groups (3-7 and 8-12), more severe injury was associated with poorer intelligence scores; however, age at injury was not associated with outcome for children with mild/moderate injuries. Severe injury and younger age at injury led to minimal recovery while recovery from later injury was similar to that of adults (Anderson et al., 2000). Therefore, although age at injury, time since injury, and injury severity are considered to be predictors of cognitive outcome, "symptom expression" is, nevertheless, variable, even in severe brain injury cases (Taylor, 2004), depending on developmental status. The variability in recovery associated with age at injury is frequently discussed in the context of the brain's plasticity or its ability to reorganize and recover from an insult (Johnston, 2004). It is, therefore, important to consider some of the principles associated with brain plasticity, especially in the context of the developing brain.

Plasticity and Recovery after Injury

Historically, the name of Margaret Kennard has been associated with the concept of developmental brain plasticity. She was an American pioneer who in the 1930s and 1940s examined the sparing of motor function after cortical damage in experimental studies with monkeys and apes. Although her work contributed to understanding the importance of developmental status after an injury and the role of neural reorganization of brain areas spared from damage (Finger, 1999; Finger & Wolf, 1988), her findings have been generalized to humans across all cognitive functions to suggest that younger age at injury is associated with better outcome. In fact, in a survey of various health

professionals, including neurosurgeons, neurologists, neuropsychologists, general practitioners, nurses, and physical, occupation, and speech therapists, respondents were asked to judge the recovery outcome of several fictitious cases. Referencing the Kennard Principle, although there were slight differences in opinion among the various professionals, all of them predicted better outcome recovery for younger patients (i.e., those under 10 years of age) than adults with similar brain injuries (Webb, Rose, Johnson, & Attree, 1996). Similarly, a survey of attorneys indicated that they were more confident in a consulting neurologist's estimate of recovery if it was consistent with this Principle. In fact, it is likely that compensation for children with brain injury is currently being underestimated in litigation, thereby prejudicing the long-term outcome of a child who has incurred a head injury (Johnson, Rose, Brooks, & Eyers, 2003).

Contrary to the Kennard Principle, however, there is a substantial body of literature suggesting that recovery is not better in children compared with adults, or in younger children compared with older ones, especially after diffuse injuries. Prognosis typically depends on the nature of the injury, remaining ability to learn new information (Laurent-Vannier et al., 2000), and a child's developmental status. Cognitive abilities which are in the process of development, specifically rapid development, at the time of injury are at greater risk for disruption than more well-established skills (Ewing-Cobbs et al., 1987; Ewing-Cobbs, Prasad et al., 1998; Johnston, 2004). Disruption can be due to a developing child's inability to retain what has been learned already, learn and process new information (Adelson & Kochanek, 1998), or lack of commitment of brain regions typically associated with a certain function (Dennis & Levin, 2004). In a longitudinal study of recovery after TBI, pediatric patients with an older age at injury demonstrated

better intellectual functioning than their younger counterparts, suggesting that the Kennard Principle is not universal (Duval et al., 2002). These results suggest the need to differentiate between recovery in skills already acquired at the time of injury and new skills that are in the process of developing (Taylor, 2004).

The mechanisms for the young brain's plasticity and its role in the recovery process after a brain injury are multifaceted. On the one hand, enhanced brain plasticity is observed due to the developing brain's ability for neurogenesis well after the postnatal period, elimination of ineffective neurons through apoptosis or programmed cell death, proliferation and pruning of synapses, and refinement of synaptic connections through new connections and reinforcements (Johnston, 2004). However, such biological plasticity does not necessary translate into developmentally appropriate recovery and can, in fact, hinder normal development (Chapman & McKinnon, 2000). Further, the same molecular mechanisms which promote brain plasticity in the developing brain contribute to its vulnerability following an injury. For example, the build-up of the brain metabolite glutamate within synapses together with hypoxia severe enough to depolarize synaptic membranes leads to opening of NMDA receptors, abundant during younger life, triggering calcium entry into neurons and a cascade of intracellular events known as excitotoxicity. This chain of events can cause cell death by apoptosis or necrosis (Johnston, 2004). Together, all of the above information as well as the study findings suggest that, along with clinical variables, developmental factors have an important role in influencing cognitive outcome after a head injury. An understanding of these variables is important in order to consider relevant covariates in the subsequent analyses evaluating the efficacy of various neuroimaging tools when predicting long-term cognitive outcome.

MRS and the Role of Metabolites in Predicting Outcome

N-acetyl Aspartate (NAA)

Associations between both single and multi-voxel MR Spectroscopy (MRSI) metabolite data and cognitive functioning were explored with the hypothesized expectation that NAA levels would be positively correlated with cognitive scores. Very consistently, NAA spectra and its associated ratios (NAA/Cho and NAA/Cre) were strongly and positively associated with both intellectual and neuropsychological functioning, with correlation coefficients ranging from .45 to .71. This was true for both the single voxel spectra (from the occipital and parietal regions of the brain) and the multi-voxel spectra (individual regional data from the corpus callosum, frontal gray and white matter, parieto-occipital gray matter, parietal white matter, as well as the combined data from all regions sampled).

The findings from the current study are consistent with the literature on single voxel spectra and suggest that the presence and level of NAA measured relatively soon after a brain injury are associated with long-term neurologic or cognitive outcome (Friedman et al., 1999; McAllister et al., 2001). NAA's association with cognitive outcome is due to its function as a marker for neuronal integrity. As such, decreases in NAA have been reported not only in traumatic brain injury (Friedman et al., 1999) but also in Alzheimer's Disease (Schuff et al., 1997; Schuff et al., 1998), HIV infection (Keller et al., 2004), multiple sclerosis (Zaffaroni, 2003), and other nervous system disorders in children (Kulak, Sobaniec, Kubas, & Walecki, 2004; Shevell, Ashwal, & Novotny, 1999), which are known to have associated cognitive deficits.

Other Metabolites

Somewhat contrary to hypotheses and the literature (Ashwal et al., 2000; Brenner et al., 2003), individual and ratio measurements of choline (Cho) and creatine (Cre) were not remarkably associated with either intellectual or neuropsychological outcome, at least not as strongly as NAA. This was true for both the single and multi-voxel MRS results. Furthermore, although no statistically significant associations were noted between single voxel Glx spectra and intellectual or neuropsychological functioning, small to medium correlations in the expected negative direction were noted. Lack of statistical significance may in part be due to the small sample size of the current study. However, moderate correlations were noted between occipital and parietal mI and both intellectual and neuropsychological functioning. Elevations in mI have been associated with poor neurologic outcome following pediatric head injury, although its reasons remain unclear (Ashwal et al., 2004b).

The absence of expected strong associations between some of the above metabolites with cognitive outcome may be related to the variability in the number of days following injury spectra were obtained. In this study, patients were imaged on average 6.3 days (3.9 SD) following injury, with some as long as 16 days after injury. In an experimental study (with rats) where spectra were obtained consecutively over several days, both Cho and mI not only recovered to baseline levels but increased by 74% and 31%, respectively, by the seventh day following injury (Schuhmann et al., 2003). This is unlike NAA where, although increases were noted, overall levels were still notably lower than baseline at seven days post injury (Schuhmann et al., 2003). Furthermore, it has been reported that Glx and Cho are sensitive predictors of long-term neurologic outcome

when MRS was conducted early (i.e., 7 days) after injury (Shutter et al., 2004). However, when Glx was measured on average seven days after injury (but with the same standard deviation and range as the current study) in a sample of pediatric head injury patients, no differences were noted between good or poor neurologic outcome based on metabolite levels (Ashwal et al., 2004a). The variability in the rate of change (increase and decrease) of metabolites as a function of time following a head injury, therefore, may have contributed to the relatively strong association between NAA and cognitive outcome, and the mild to moderate associations between mI, Glx, Cre, and Cho and cognitive outcome.

Also contrary to previous findings (Ashwal et al., 2000; Brenner et al., 2003; Holshouser et al., 1997), lactate was not detected in any of the patients except for one, and was therefore not analyzed in relation to cognitive outcome. Although the previous studies also evaluated the role of lactate in pediatric brain injury, their samples were notably different in that they included neonates, infants, and very young children and/or nonaccidental brain injury. In general, nonaccidental head injury patients represent a different population of traumatic brain injury that tend to be younger and have poorer prognoses (Gilles, 1999). The neuropathology and neurophysiology of nonaccidental trauma is distinct from that of accidental brain injury (Geddes et al., 2001), which may explain the differences in findings.

Multivariable MRS Models Predicting Outcome

In order to minimize the number of predictor variables in regression models with a relatively small sample (n = 20) and because none of the metabolites were as strongly correlated with cognitive outcome as NAA, NAA levels and associated ratios from the

single and multi-voxel spectra were analyzed as predictors of outcome. Furthermore, of the various NAA measures, the NAA/Cre ratio was selected because it had the strongest and most consistent correlation with the cognitive outcome measures.

In a linear regression model predicting cognitive outcome, the single voxel (parietal and occipital) NAA/Cre accounted for over 40% of the variance in both intellectual and neuropsychological functioning. The combined regional multi-voxel NAA/Cre ratio contributed an additional 5% to FSIQ and 9% to neuropsychological outcome above and beyond what was explained by the single voxel spectra alone. These results suggest that multi-voxel MR results, specifically with regard to NAA, are slightly better at predicting intellectual and neuropsychological outcome as compared to the single-voxel spectra.

The multi-voxel MR NAA/Cre ratio alone was a strong predictor of both intellectual and neuropsychological scores, explaining 37% and 48% of the variance in outcome, respectively. This finding was true even when the combined age at injury and injury severity variable was accounted for. In fact, an additional 18% of the variance in intellectual scores and 26% of the variance in neuropsychological scores was explained above and beyond the age at injury and injury severity variable alone. However, when days in coma and the combined injury severity/age at injury term were both included as covariates, the multi-voxel MRS ratio did not add significantly to the overall variance explained in the intellectual or neuropsychological outcome scores. This finding was similar to that reported in Ashwal et al. (2000) where when predicting good or poor neurologic outcome, MRS variables did not contribute significantly to the overall percent of correctly grouped patients after clinical variables and the presence of lactate were

accounted for. Similarly, although MRS variables improved prediction of both intellectual functioning and neuropsychological scores in a different study above and beyond age at the time of injury, the MRS variable that was substantially contributing to this effect was the presence of lactate, and not other metabolites (Brenner et al., 2003). Nonetheless, the days in coma variable is not always available during the acute stages of injury when images may be taken and prognosis is considered, making the multi-voxel MRS data an important contributor to long-term outcome prediction early on during the recovery process.

Regional MRS and Outcome

Finally, exploratory analyses were conducted to investigate whether regional NAA/Cre and NAA/Cho ratios differed by intellectual and individual neuropsychological functions, including verbal and nonverbal memory, attention, academic achievement, and executive, visual-perceptual, motor, and language skills. The resulting statistics indicated some general notable trends. Specifically, both NAA/Cre and NAA/Cho ratios across most if not all of the regions sampled were significantly less for patients who scored lower than one standard deviation below the normative mean on the visual-perceptual tests as compared to those who scored at or above this cutoff.

Similar findings, although somewhat less pronounced, were noted for tests of general intelligence and nonverbal memory. These results suggest that regardless of location, lower NAA (represented by its respective ratios with Cre and Cho) is associated with below average performance on measures of intelligence, neuropsychological tests of nonverbal memory, and visual-perceptual skills. Also notable was the relatively consistent and statistically significant difference in both NAA/Cre and NAA/Cho ratios

in the frontal gray matter across overall intelligence and most neuropsychological scores. Again, this finding suggests that lower metabolite ratios, specifically with regard to NAA, in the frontal gray matter may be an important marker for below average performance across several domains of cognitive functioning.

Very few studies have assessed neuropsychological correlates of regional brain metabolites following a brain injury. Only one study was identified that correlated neuropsychological outcome with regional MRS data (Ariza et al., 2004); however, this study was conducted on a group of 20 adult severe TBI patients and the voxels under study included the basal ganglia and temporal regions only. To date, therefore, the current study is the first to assess MRS data from various regions of the brain and their relationship with a wide range of both overall and specific cognitive abilities. In general, decreases in NAA in the frontal gray matter appeared to be a sensitive measure across most cognitive domains while deficits in visual-perception, intelligence, and nonverbal memory appeared to be related to NAA reduction across most if not all regions sample. Further studies with larger samples would help identify if the above findings are replicated and whether it is plausible to associate regional neuroimaging findings to specific cognitive functions.

SWI and Cognitive Outcome

Previous studies have shown that not only is SWI better at identifying a substantially higher number of hemorrhage number and volume after a TBI (Tong et al., 2003), SWI lesion number and volume are also better at predicting poor versus good neurologic outcome when compared to conventional MRI methods (Tong et al., 2004). Specifically, the authors reported that patients with normal neurologic outcome or with

mild disability had fewer lesions and smaller hemorrhagic volume than those with moderate or severe disability or in a vegetative state. Thus, it was hypothesized in the current study that better detection of lesion number and/or hemorrhage volume would improve the predictability of long-term intellectual or neuropsychological outcome.

As expected, results indicated that SWI hemorrhage volume was significantly correlated with both intelligence and neuropsychological scores. SWI lesion number, however, was significantly correlated with neuropsychological outcome (albeit slightly less so than SWI lesion volume). The weaker correlation between outcome and SWI lesion number as compared to volume may be related to the methods used to quantify them. As described more thoroughly in Tong et al. (2004), hemorrhagic lesion number may have been inflated because the computer software used to quantify them counted lesions per image, even though some lesions extended across several contiguous slices and may have been counted more than once. Therefore, hemorrhage volume may be a more accurate representation of extent of injury (Tong et al., 2004).

Multivariable SWI Models Predicting Outcome

In a linear regression model predicting cognitive outcome, SWI lesion number and volume together significantly predicted cognitive outcome, explaining 37% of the variance in intelligence scores and 46% of the variance in neuropsychological functioning. In addition, unlike the MRS results above, when important clinical variables, including days in coma and the combined injury severity/age at injury term, were added in the model first, SWI lesion number and volume contributed significantly to the overall variance explained above and beyond the clinical variables alone. Specifically, approximately 12% more in variance was explained by SWI when

predicting intelligence scores and 9% more when predicting neuropsychological functioning.

Finally, Tong et al. (2003) reported that SWI is markedly more effective at identifying lesion number and volume as compared to the conventional GRE method following a TBI. Unlike SWI, conventional GRE lesion information for the whole brain was not available for this study's sample. However, both SWI and conventional GRE lesion number were available only for regions of the brain sampled for the multi-voxel MRS spectra (i.e., 1) anterior/middle/posterior corpus callosum; 2) right/middle/left frontal gray matter; 3) right/left frontal white matter; 4) right/middle/left parieto-occipital gray matter; and 5) right/left parietal white matter).

In multiple linear regression models predicting cognitive outcome, SWI lesion number, although not statistically significant, contributed 15% to the variance explained in intelligence scores and 10% to the variance explained in neuropsychological scores above and beyond conventional GRE lesion numbers. The improvement in predictive efficacy may have been deflated, however, due to several important limitations associated with the nature of the data used for analyses. Specifically, only GRE and SWI lesion numbers (not volume) were available for analysis, which according to prior analyses, was a weaker predictor as compared to lesion volume. Further, GRE lesion data only from regions of the brain sampled for MRS studies were available, limiting the variability that may have otherwise been present. Despite these limitations, SWI appears to be a relatively stronger predictor of long-term intellectual and neuropsychological outcome as compared to conventional GRE. However, a comparison of whole brain SWI and GRE

lesion data, including number and volume, may more accurately depict the relative predictive efficacy of SWI over conventional GRE.

Regional SWI and Outcome

Further, exploratory analyses were conducted to investigate whether regional susceptibility weighted imaging lesion number and volume were associated with intellectual and each neuropsychological domain index. The findings suggested that in general, both lesion number and volume in deep brain regions such as the basal ganglia, thalamus, and brain stem, were strongly associated (with large effect sizes noted) with almost all domains of intellectual and neuropsychological functioning. Furthermore, lesions in the corpus callosum and cerebellum yielded moderate to large effects when correlated with cognitive outcomes. Relatively weaker (mild to moderate) correlations were noted between lesion number/volume and specific cognitive domains in the cortical areas (frontal, parietal, temporal, and occipital white and gray matter). These findings suggest that lesions in deeper brain structures are associated with a wide range of deficits in cognitive functioning. This pattern was not as consistently noted for lesions in the cortical regions. It remains to be seen if these results are replicated in larger samples.

The above findings may be associated with the nature of injury incurred after a TBI. Specifically, SWI is very effective in detecting hemorrhagic lesions that are associated with diffuse axonal injury (DAI) (Tong et al., 2004; Tong et al., 2003). DAIs often result from the accelerating and decelerating motion associated with motor vehicle accidents and are especially common in children because of their unique head to body ratio, lack of myelination, and weak neck muscles (Adelson & Kochanek, 1998). Most DAI occurs in the corpus callosum, subcortical structures, basal ganglia, brainstem, and

cerebellum, with more deeper structures affected by increasing injury severity (Khalatbari, Yilmaz, Ibrahim, Dardel, & Froment, 2003; Parizel et al., 1998). Further, it has been suggested that depth of lesion (DOL) classification is associated with GCS, lesion number, functional/motor outcome (Grados et al., 2001), hospital stay, and acute rehab admission (Blackman et al., 2003). Therefore, the association between a range of cognitive abilities and lesions in these regions may be related to DAI and its effect on a variety of cognitive skills. Although some studies have attempted to associate regional DAI to specific neuropsychological functioning (Wallesch, Curio, Galazky et al., 2001; Wallesch, Curio, Kutz et al., 2001), none have used SWI to quantify extent of DAI.

Comparison of MRS and SWI in Predicting Outcome

Finally, MRS variables (including single and multi-voxel NAA/Cre ratio) and SWI variables (lesion number and volume) were interchangeably included in either the first or the second step in hierarchical linear regression models. The results indicated that regardless of which set of imaging variables was entered first, the second set significantly contributed to the overall variance explained in either intelligence or neuropsychological performance. These results suggest that the two imaging techniques evaluated in this study provide a unique and significant contribution when predicting cognitive outcome and as such, should both be used for prognostic purposes. This finding is plausible since although lesion severity and location may not only be related but also contribute to changes in brain metabolites, the latter may also be a result of a dynamic cascade of neuronal events that occur in various regions of the brain that are not necessarily limited to areas of observable physical injury.

Study Implications

As expected, marked deficits across a range of intellectual and neuropsychological scores were noted, with extent of the deficit strongly predicted by clinical variables such as days in coma following injury and a combined age at injury/injury severity score. These results reiterate the importance of injury severity within the context of developmental factors, including cognitive status at the time of an insult which can significantly influence the interplay between developing brain plasticity and response to an injury. As a result, various clinical and/or developmental variables can serve as moderators when predicting cognitive outcome, with the influence of one substantially varied within the presence and extent of the other.

As such, the relative predictive power of such clinical and developmental indicators and their prognostic utility cannot be ignored, even with the advent of new and technologically advanced neuroimaging methods. Nonetheless, neuroimaging methods have a unique and notable contribution to predicting long-term cognitive outcome. The results of this study demonstrate how various relatively new neuroimaging methods help to further delineate long-term cognitive outcome following a head injury, even after clinical and developmental factors have been accounted for. Furthermore, with the advent of more sophisticated neuroimaging technology, the role of regional neuroimaging data and its predictive utility of specific cognitive functioning are promising and a tool to explore further.

Study Limitations

There were several limitations associated with this study. The relatively small study sample size may have resulted in lack of precision in the estimates for otherwise

important clinical, neuroimaging, and/or cognitive variables. Furthermore, no data on control subjects was available. Although significant associations between imaging variables and cognitive scores post TBI were noted, the nature and extent of this relationship in non-brain injured individuals is not clear (particularly for the MRS data). This is especially true since some studies have indicated that significant differences in neuropsychological performance are noted between matched control and pediatric TBI patients that are otherwise not apparent when patient scores are compared to published norms (Jaffe et al., 1992; Jaffe et al., 1993). Finally, nontraditional measures of functional status as opposed to formal tests may better represent real life and practical functional problems associated with brain injury. Recommended assessments have included measures of real life functioning, such as classroom learning and organizational behaviors and abilities (Gioia & Isquith, 2004).

Finally, preinjury factors as well as family environment variables have been associated with outcome following a head injury (Satz et al., 1997; Taylor, 2004). Although a subjective assessment of premorbid cognitive functioning, including self and/or parent report of academic skills or overall symptom characterization, was collected, there were no formal measures of premorbid functioning. Thus, associations between post TBI cognitive functioning and clinical or neuroimaging data did not account for the degree of change in functioning directly as a result of injury. For example, one of the patients was diagnosed with mental retardation prior to injury and scored within this range when assessed for this study. Because of the extent of his head injury, his cognitive scores did not affect the overall results; however, it is plausible that similar premorbid cognitive abilities partly contributed to lower test scores with respect

to other patients for whom such information was not available. Therefore, the error associated with premorbid functioning, if appropriately measured and covaried, could have reduced the overall error in the study analyses and have resulted in better prediction of functioning following injury.

Future Directions

Neuroimaging technology is a growing and effective prognostic tool when predicting long-term functioning following a traumatic brain injury. The results from this study suggest that clinical variables alone, especially age at injury and extent of injury (including days in a coma and GCS), are very strong predictors of outcome. However, neuroimaging results using MR technology make a notable and unique contribution when predicting cognitive outcome. Since MRS and SWI are relatively practical in that they do not require significant technology far beyond a basic clinical MR scanner, they can be an effective and efficient prognostic tool when determining functioning following a head injury. The use of such technology will foster better prognostic ability to help clinicians and family members plan treatment and services that are necessary for optimal physical, cognitive, and emotional recovery following a head injury in childhood.

REFERENCES

Adelson, P. D., & Kochanek, P. M. (1998). Head injury in children. *J Child Neurol, 13*(1), 2-15.

Anderson, V., Catroppa, C., Morse, S., Haritou, F., & Rosenfeld, J. (2000). Recovery of intellectual ability following traumatic brain injury in childhood: impact of injury severity and age at injury. *Pediatr Neurosurg, 32*(6), 282-290.

Ariza, M., Junque, C., Mataro, M., Poca, M. A., Bargallo, N., Olondo, M., et al. (2004). Neuropsychological correlates of basal ganglia and medial temporal lobe NAA/Cho reductions in traumatic brain injury. *Arch Neurol, 61*(4), 541-544.

Ashwal, S., Holshouser, B. A., Shu, S. K., Simmons, P. L., Perkin, R. M., Tomasi, L. G., et al. (2000). Predictive value of proton magnetic resonance spectroscopy in pediatric closed head injury. *Pediatr Neurol, 23*(2), 114-125.

Ashwal, S., Holshouser, B. A., Tong, K. A., Serna, T., Osterdock, R. J., Gross, M., et al. (2004a). Proton MR spectroscopy detected glutamate/glutamine is increased in children with traumatic brain injury. *J Neurotrauma, 21*(11), 1539-1552.

Ashwal, S., Holshouser, B. A., Tong, K. A., Serna, T., Osterdock, R. J., Gross, M., et al. (2004b). Proton spectroscopy detected myoinositol in children with traumatic brain injury. *Pediat Res, 56*(4), 630-638.

Bachevalier, J., & Mishkin, M. (1992). Ontogenetic development and decline of memory functions in nonhuman primates. In I. Kostovic, S. Knezvic, H. M. Wisniewski & G. J. Spilich (Eds.), *Neurodevelopment, Aging and Cognition*. Boston: Birkhauser.

Baker, A. J., Moulton, R. J., MacMillan, V. H., & Shedden, P. M. (1993). Excitatory amino acids in cerebrospinal fluid following traumatic brain injury in humans. *J Neurosurg, 79*(3), 369-372.

Berryhill, P., Lilly, M. A., Levin, H. S., Hillman, G. R., Mendelsohn, D., Brunder, D. G., et al. (1995). Frontal lobe changes after severe diffuse closed head injury in children: a volumetric study of magnetic resonance imaging. *Neurosurgery, 37*(3), 392-399; discussion 399-400.

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

Bigler, E. D. (2001). Quantitative magnetic resonance imaging in traumatic brain injury. *J Head Trauma Rehabil, 16*(2), 117-134.

Bigler, E. D. (2003). Neurobiology and neuropathology underlie the neuropsychological deficits associated with traumatic brain injury. *Arch Clin Neuropsychol, 18*(6), 595-621; discussion 623-597.

Bigler, E. D., & Snyder, J. L. (1995). Neuropsychological outcome and quantitative neuroimaging in mild head injury. *Arch Clin Neuropsychol, 10*(2), 159-174.

Blackman, J. A., Rice, S. A., Matsumoto, J. A., Conaway, M. R., Elgin, K. M., Patrick, P. D., et al. (2003). Brain imaging as a predictor of early functional outcome following traumatic brain injury in children, adolescents, and young adults. *J Head Trauma Rehabil, 18*(6), 493-503.

Bloom, D. R., Levin, H. S., Ewing-Cobbs, L., Saunders, A. E., Song, J., Fletcher, J. M., et al. (2001). Lifetime and novel psychiatric disorders after pediatric traumatic brain injury. *J Am Acad Child Adolesc Psychiatry, 40*(5), 572-579.

Bowen, J. M. (1995). The correlates of neuropsychological testing and clinical ratings of neuroimaging data: A study of brain-injured children. *Dissertation Abstracts International: Section B: The Sciences and Engineering, 56*(5-B), 2932.

Brenner, T., Freier, M. C., Holshouser, B. A., Burley, T., & Ashwal, S. (2003). Predicting neuropsychologic outcome after traumatic brain injury in children. *Pediatr Neurol, 28*(2), 104-114.

Brookshire, B., Levin, H. S., Song, J., & Zhang, L. (2004). Components of executive function in typically developing and head-injured children. *Dev Neuropsychol, 25*(1-2), 61-83.

Catroppa, C., & Anderson, V. (1999). Attentional skills in the acute phase following pediatric traumatic brain injury. *Neuropsychol Dev Cogn Sect C Child Neuropsychol, 5*(4), 251-264.

CDC. (2002, May 13). *Traumatic brain injury in the United States: Assessing outcomes in children*. Retrieved March 9, 2003, from http://www.cdc.gov/ncipc/tbi_report/09_Appendix_B.htm

CDC. (2003, February 28). *Traumatic Brain Injury*. Retrieved March 9, 2003, from http://www.cdc.gov/ncipc/factsheets/tbi.htm

Chapman, S. B., Culhane, K. A., Levin, H. S., Harward, H., Mendelsohn, D., Ewing-Cobbs, L., et al. (1992). Narrative discourse after closed head injury in children and adolescents. *Brain Lang, 43*(1), 42-65.

Chapman, S. B., & McKinnon, L. (2000). Discussion of developmental plasticity: factors affecting cognitive outcome after pediatric traumatic brain injury. *J Commun Disord, 33*(4), 333-344.

Chapman, S. B., McKinnon, L., Levin, H. S., Song, J., Meier, M. C., & Chiu, S. (2001). Longitudinal outcome of verbal discourse in children with traumatic brain injury: three-year follow-up. *J Head Trauma Rehabil, 16*(5), 441-455.

Choi, S. C., & Barnes, T. Y. (1996). Predicting outcome in the head-injured patient. In R. K. Narayan, J. E. Wilberger & J. T. Povlishock (Eds.), *Neurotrauma* (pp. 779-792). New York: McGraw Hill.

Cohen, J. (1992). A power primer. *Psychol Bull, 112*(1), 155-159.

Culbertson, W. C., & Zillmer, E. A. (1998a). The construct validity of the Tower of LondonDX as a measure of the executive functioning of ADHD children. *Assessment, 5*(3), 215-226.

Culbertson, W. C., & Zillmer, E. A. (1998b). The Tower of London(DX): a standardized approach to assessing executive functioning in children. *Arch Clin Neuropsychol, 13*(3), 285-301.

Culbertson, W. C., & Zilmer, E. A. (2000). Tower of London - Drexel University: MHS.

Delis, D., Kramer, J. H., Kaplan, E., & Ober, B. A. (1994). *California Verbal Learning Test - Children's Version (CVLT-C)*. San Antonio: The Psychological Corporation.

Delis, D., Kramer, J. H., Kaplan, E., & Ober, B. A. (2000). *California Verbal Learning Test - Second Edition (CVLT-II)*. San Antonio: The Psychological Corporation.

Dennis, M., & Levin, H. S. (2004). New perspectives on cognitive and behavioral outcome after childhood closed head injury. *Dev Neuropsychol, 25*(1-2), 1-3.

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

Duval, J., Dumont, M., Braun, C. M., & Montour-Proulx, I. (2002). Recovery of intellectual function after a brain injury: a comparison of longitudinal and cross-sectional approaches. *Brain Cogn, 48*(2-3), 337-342.

Ewing-Cobbs, L., & Barnes, M. (2002). Linguistic outcomes following traumatic brain injury in children. *Semin Pediatr Neurol, 9*(3), 209-217.

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. *Dev Neuropsychol, 25*(1-2), 107-133.

Ewing-Cobbs, L., Fletcher, J. M., Levin, H. S., Francis, D. J., Davidson, K., & Miner, M. E. (1997). Longitudinal neuropsychological outcome in infants and preschoolers with traumatic brain injury. *J Int Neuropsychol Soc, 3*(6), 581-591.

Ewing-Cobbs, L., Fletcher, J. M., Levin, H. S., Iovino, I., & Miner, M. E. (1998). Academic achievement and academic placement following traumatic brain injury in children and adolescents: a two-year longitudinal study. *J Clin Exp Neuropsychol, 20*(6), 769-781.

Ewing-Cobbs, L., Levin, H. S., Eisenberg, H. M., & Fletcher, J. M. (1987). Language functions following closed-head injury in children and adolescents. *Journal of Clinical and Experimental Neuropsychology, 9*, 575-592.

Ewing-Cobbs, L., Prasad, M., Fletcher, J. M., Levin, H. S., Miner, M. E., & Eisenberg, H. M. (1998). Attention after pediatric traumatic brain injury: A multidimensional assessment. *Child Neuropsychology, 4*(1), 35-48.

Farmer, J. E., & Peterson, L. (1995). Pediatric traumatic brain injury: Promoting successful school reentry. *School Psychology Review, 24*(2), 230-244.

Fay, G. C., Jaffe, K. M., Polissar, N. L., Liao, S., Rivara, J. B., & Martin, K. M. (1994). Outcome of pediatric traumatic brain injury at three years: a cohort study. *Arch Phys Med Rehabil, 75*(7), 733-741.

Finger, S. (1999). Margaret Kennard on sparing and recovery of function: a tribute on the 100th anniversary of her birth. *J Hist Neurosci, 8*(3), 269-285.

Finger, S., & Wolf, C. (1988). The 'Kennard effect' before Kennard. The early history of age and brain lesions. *Arch Neurol, 45*(10), 1136-1142.

Fletcher, J. M., Levin, H. S., Lachar, D., Kusnerik, L., Harward, H., Mendelsohn, D., et al. (1996). Behavioral outcomes after pediatric closed head injury: relationships with age, severity, and lesion size. *J Child Neurol, 11*(4), 283-290.

Franzen, M. D., & Berg, R. A. (1998). *Screening Children for Brain Impairment* (2nd ed.). New York: Springer Publishing Company.

Friedman, S. D., Brooks, W. M., Jung, R. E., Chiulli, S. J., Sloan, J. H., Montoya, B. T., et al. (1999). Quantitative proton MRS predicts outcome after traumatic brain injury. *Neurology, 52*(7), 1384-1391.

Geddes, J. F., Vowles, G. H., Hackshaw, A. K., Nickols, C. D., Scott, I. S., & Whitwell, H. L. (2001). Neuropathology of inflicted head injury in children. II. Microscopic brain injury in infants. *Brain, 124*(Pt 7), 1299-1306.

Gilles, E. E. (1999). Nonaccidental Head Injury. In K. F. Swaiman & S. Ashwal (Eds.), *Pediatric Neurology: Principles and Practice* (pp. 898-914). St. Louis: Mosby.

Gioia, G. A., & Isquith, P. K. (2004). Ecological assessment of executive function in traumatic brain injury. *Dev Neuropsychol, 25*(1-2), 135-158.

Goldenberg, G., Oder, W., Spatt, J., & Podreka, I. (1992). Cerebral correlates of disturbed executive function and memory in survivors of severe closed head injury: a SPECT study. *J Neurol Neurosurg Psychiatry, 55*(5), 362-368.

Grados, M. A., Slomine, B. S., Gerring, J. P., Vasa, R., Bryan, N., & Denckla, M. B. (2001). Depth of lesion model in children and adolescents with moderate to severe traumatic brain injury: use of SPGR MRI to predict severity and outcome. *J Neurol Neurosurg Psychiatry, 70*(3), 350-358.

Graham, D. I., & McIntosh, T. K. (1996). Neuropathology of brain injury. In R. W. Evans (Ed.), *Neurology and Trauma*. Philadelphia: WB Saunders.

Grant, P. E., & Matsuda, K. M. (2003). Application of new MR techniques in pediatric patients. *Magn Reson Imaging Clin N Am, 11*(3), 493-522.

Hanten, G., Bartha, M., & Levin, H. S. (2000). Metacognition following pediatric traumatic brain injury: a preliminary study. *Dev Neuropsychol, 18*(3), 383-398.

Hanten, G., Dennis, M., Zhang, L., Barnes, M., Roberson, G., Archibald, J., et al. (2004). Childhood head injury and metacognitive processes in language and memory. *Dev Neuropsychol, 25*(1-2), 85-106.

Hanten, G., Zhang, L., & Levin, H. (2002). Selective learning in children after traumatic brain injury: a preliminary study. *Neuropsychol Dev Cogn Sect C Child Neuropsychol, 8*(2), 107-120.

Holshouser, B. A., Ashwal, S., Luh, G. Y., Shu, S., Kahlon, S., Auld, K. L., et al. (1997). Proton MR spectroscopy after acute central nervous system injury: outcome prediction in neonates, infants, and children. *Radiology, 202*(2), 487-496.

Hoon, A. H., Jr., & Melhem, E. R. (2000). Neuroimaging: applications in disorders of early brain development. *J Dev Behav Pediatr, 21*(4), 291-302.

Jaffe, K. M., Fay, G. C., Polissar, N. L., Martin, K. M., Shurtleff, H., Rivara, J. B., et al. (1992). Severity of pediatric traumatic brain injury and early neurobehavioral outcome: a cohort study. *Arch Phys Med Rehabil, 73*(6), 540-547.

Jaffe, K. M., Fay, G. C., Polissar, N. L., Martin, K. M., Shurtleff, H. A., Rivara, J. M., et al. (1993). Severity of pediatric traumatic brain injury and neurobehavioral recovery at one year: a cohort study. *Arch Phys Med Rehabil, 74*(6), 587-595.

Jaffe, K. M., Polissar, N. L., Fay, G. C., & Liao, S. (1995). Recovery trends over three years following pediatric traumatic brain injury. *Arch Phys Med Rehabil, 76*(1), 17-26.

Johnson, D. A., Rose, F. D., Brooks, B. M., & Eyers, S. (2003). Age and recovery from brain injury: legal opinions, clinical beliefs and experimental evidence. *Pediatr Rehabil, 6*(2), 103-109.

Johnson, S. C., Pinkston, J. B., Bigler, E. D., & Blatter, D. D. (1996). Corpus callosum morphology in normal controls and traumatic brain injury: Sex differences, mechanisms of injury, and neuropsychological correlates. *Neuropsychology, 10*(3), 408-415.

Johnston, M. V. (2004). Clinical disorders of brain plasticity. *Brain Dev, 26*(2), 73-80.

Kaufmann, P. M., Fletcher, J. M., Levin, H. S., Miner, M. E., & Ewing-Cobbs, L. (1993). Attentional disturbance after pediatric closed head injury. *J Child Neurol, 8*(4), 348-353.

Keller, M. A., Venkatraman, T. N., Thomas, A., Deveikis, A., LoPresti, C., Hayes, J., et al. (2004). Altered neurometabolite development in HIV-infected children: correlation with neuropsychological tests. *Neurology, 62*(10), 1810-1817.

Khalatbari, K., Yilmaz, H., Ibrahim, A., Dardel, P., & Froment, J. C. (2003). *Diffuse axonal injury*. Retrieved May 31, 2004, from http://www.eurorad.org/case.cfm?uid=1707

Kirkpatrick, J. A., Jr. (1986). Imaging procedures in pediatrics. *Adv Pediatr, 33*, 77-93.

Kizilbash, A., & Donders, J. (1999). Latent structure of the Wisconsin Card Sorting Test after pediatric traumatic head injury. *Neuropsychol Dev Cogn Sect C Child Neuropsychol, 5*(4), 224-229.

Kraus, J. F. (1995). Epidemiological features of brain injury in children: Occurrence, children at risk, causes and manner of injury, severity, and outcomes. In S. H. Broman & M. E. Michel (Eds.), *Traumatic Brain Injury in Children* (pp. 22-39). New York: Oxford University Press.

Kulak, W., Sobaniec, W., Kubas, B., & Walecki, J. (2004). Proton magnetic resonance spectroscopy in children with spastic diplegia. *Neurosci Lett, 363*(1), 62-64.

Laurent-Vannier, A., Brugel, D. G., & De Agostini, M. (2000). Rehabilitation of brain-injured children. *Childs Nerv Syst, 16*(10-11), 760-764.

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

Levin, H. S., Mendelsohn, D., Lilly, M., Fletcher, J. M., Culhane, K. A., Chapman, S. B., et al. (1994). Tower of London performance in relation to Magnetic Resonance Imaging following closed head injury in children. *Neuropsychology, 8*(2), 171-179.

Levin, H. S., Mendelsohn, D., Lilly, M. A., Yeakley, J., Song, J., Scheibel, R. S., et al. (1997). Magnetic resonance imaging in relation to functional outcome of pediatric closed head injury: a test of the Ommaya-Gennarelli model. *Neurosurgery, 40*(3), 432-440; discussion 440-431.

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*(2), 122-131.

Massagli, T. L., Jaffe, K. M., Fay, G. C., Polissar, N. L., Liao, S., & Rivara, J. B. (1996). Neurobehavioral sequelae of severe pediatric traumatic brain injury: a cohort study. *Arch Phys Med Rehabil, 77*(3), 223-231.

Max, J. E., Lansing, A. E., Koele, S. L., Castillo, C. S., Bokura, H., Schachar, R., et al. (2004). Attention deficit hyperactivity disorder in children and adolescents following traumatic brain injury. *Dev Neuropsychol, 25*(1-2), 159-177.

McAllister, T. W., Sparling, M. B., Flashman, L. A., & Saykin, A. J. (2001). Neuroimaging findings in mild traumatic brain injury. *J Clin Exp Neuropsychol, 23*(6), 775-791.

Mendelsohn, D., Levin, H. S., Bruce, D., Lilly, M., Harward, H., Culhane, K. A., et al. (1992). Late MRI after head injury in children: relationship to clinical features and outcome. *Childs Nerv Syst, 8*(8), 445-452.

Meyers, J. E., & Meyers, K. R. (1995). *Rey Complex Figure Test and Recognition (RCFT)*. San Antonio: The Psychological Corporation.

Nelson, C. A. (1997). The neurobiological basis of early memory development. In N. Cowan (Ed.), *The Development of Memory in Children*. New York: Psychology Press.

Novack, T. A., Dillon, M. C., & Jackson, W. T. (1996). Neurochemical mechanisms in brain injury and treatment: a review. *J Clin Exp Neuropsychol, 18*(5), 685-706.

Parizel, P. M., Ozsarlak, Van Goethem, J. W., van den Hauwe, L., Dillen, C., Verlooy, J., et al. (1998). Imaging findings in diffuse axonal injury after closed head trauma. *Eur Radiol, 8*(6), 960-965.

Prasad, M. R., Ewing-Cobbs, L., Swank, P. R., & Kramer, L. (2002). Predictors of outcome following traumatic brain injury in young children. *Pediatr Neurosurg, 36*(2), 64-74.

Provencher, S. W. (1993). Estimation of metabolite concentrations from localized in vivo proton NMR spectra. *Magn Reson Med, 30*(6), 672-679.

Reichenbach, J. R., Venkatesan, R., Schillinger, D. J., Kido, D. K., & Haacke, E. M. (1997). Small vessels in the human brain: MR venography with deoxyhemoglobin as an intrinsic contrast agent. *Radiology, 204*(1), 272-277.

Reynolds, C. R., & Kamphaus, R. W. (1992). *Behavior Assessment System for Children (BASC)*. Circle Pines: AGS Publishing.

Roman, M. J., Delis, D. C., Willerman, L., Magulac, M., Demadura, T. L., de la Pena, J. L., et al. (1998). Impact of pediatric traumatic brain injury on components of verbal memory. *J Clin Exp Neuropsychol, 20*(2), 245-258.

Roncadin, C., Guger, S., Archibald, J., Barnes, M., & Dennis, M. (2004). Working memory after mild, moderate, or severe childhood closed head injury. *Dev Neuropsychol, 25*(1-2), 21-36.

Rosman, N. P. (1999). Traumatic Brain Injury in Children. In K. F. Swaiman & S. Ashwal (Eds.), *Pediatric Neurology: Principles and Practice* (pp. 873-897). St. Louis: Mosby.

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). *Psychol Bull, 122*(2), 107-131.

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

Schewe, P. F., Stein, B., & Riodon, J. (2002). *Physics News Update*. Retrieved December 9, 2002, from http://groups.google.com/groups?q=magnetic+susceptibility+imaging&hl=en&lr=&ie=UTF-8&selm=3CA1CAA5.C080CFF3%40iastate.edu&rnum=2

Schuff, N., Amend, D., Ezekiel, F., Steinman, S. K., Tanabe, J., Norman, D., et al. (1997). Changes of hippocampal N-acetyl aspartate and volume in Alzheimer's disease. A proton MR spectroscopic imaging and MRI study. *Neurology, 49*(6), 1513-1521.

Schuff, N., Amend, D. L., Meyerhoff, D. J., Tanabe, J. L., Norman, D., Fein, G., et al. (1998). Alzheimer disease: quantitative H-1 MR spectroscopic imaging of frontoparietal brain. *Radiology, 207*(1), 91-102.

Schuhmann, M. U., Stiller, D., Skardelly, M., Bernarding, J., Klinge, P. M., Samii, A., et al. (2003). Metabolic changes in the vicinity of brain contusions: a proton magnetic resonance spectroscopy and histology study. *J Neurotrauma, 20*(8), 725-743.

Schwartz, L., Taylor, H. G., Drotar, D., Yeates, K. O., Wade, S. L., & Stancin, T. (2003). Long-term behavior problems following pediatric traumatic brain injury: prevalence, predictors, and correlates. *J Pediatr Psychol, 28*(4), 251-263.

Shevell, M. I., Ashwal, S., & Novotny, E. (1999). Proton magnetic resonance spectroscopy: clinical applications in children with nervous system diseases. *Semin Pediatr Neurol, 6*(2), 68-77.

Shutter, L., Tong, K. A., & Holshouser, B. A. (2004). Proton MRS in acute traumatic brain injury: Role of glutamate/glutamine and choline for outcome prediction. *J Neurotrauma, 21*(12), 1693-1705.

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 Inj, 16*(9), 759-772.

Soto-Ares, G., Vinchon, M., Delmaire, C., Abecidan, E., Dhellemes, P., & Pruvo, J. P. (2001). Cerebellar atrophy after severe traumatic head injury in children. *Childs Nerv Syst, 17*(4-5), 263-269.

Spreen, O., & Strauss, E. (1998). *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary* (2nd ed.). New York: Oxford University Press.

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

Teasdale, G., & Jennett, B. (1974). Assessment of coma and impaired consciousness. A practical scale. *Lancet, 2*(7872), 81-84.

Tong, K. A., Ashwal, S., Holshouser, B. A., Nickerson, J. P., Wall, C. J., Shutter, L., et al. (2004). Diffuse axonal injury in children: Clinical correlation with hemorrhagic lesions. *Ann Neurol, 56*, 36-50.

Tong, K. A., Ashwal, S., Holshouser, B. A., Shutter, L. A., Herigault, G., Haacke, E. M., et al. (2003). Hemorrhagic shearing lesions in children and adolescents with posttraumatic diffuse axonal injury: improved detection and initial results. *Radiology, 227*(2), 332-339.

Uzan, M., Albayram, S., Dashti, S. G., Aydin, S., Hanci, M., & Kuday, C. (2003). Thalamic proton magnetic resonance spectroscopy in vegetative state induced by traumatic brain injury. *J Neurol Neurosurg Psychiatry, 74*(1), 33-38.

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 Inj, 15*(3), 211-221.

Vriezen, E. R., & Pigott, S. (2000). Sensitivity of measures of attention to pediatric brain injury. *Brain and Cognition, 44*, 67-82.

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

Wallesch, C. W., Curio, N., Kutz, S., Jost, S., Bartels, C., & Synowitz, H. (2001). Outcome after mild-to-moderate blunt head injury: effects of focal lesions and diffuse axonal injury. *Brain Inj, 15*(5), 401-412.

Ward, H., Shum, D., Wallace, G., & Boon, J. (2002). Pediatric traumatic brain injury and procedural memory. *J Clin Exp Neuropsychol, 24*(4), 458-470.

Webb, C., Rose, F. D., Johnson, D. A., & Attree, E. A. (1996). Age and recovery from brain injury: clinical opinions and experimental evidence. *Brain Inj, 10*(4), 303-310.

Wechsler, D. (1991). *Wechsler Intelligence Scale for Children - Third Edition (WISC-III)*. San Antonio: The Psychological Corporation.

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale - Third Edition (WAIS-III)*. San Antonio: The Psychological Corporation.

Wechsler, D. (2000). *Wechsler Preschool and Primary Scale of Intelligence - Third Edition (WPPSI-III)*. San Antonio: The Psychological Corporation.

Wechsler, D. (2001). *Wechsler Individual Achievement Test - Edition Two - Abbreviated (WIAT-II-A)*. San Antonio: The Psychological Corporation.

Wechsler, D. (2003). *Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV)*. San Antonio: The Psychological Corporation.

Worley, G., Hoffman, J. M., Paine, S. S., Kalman, S. L., Claerhout, S. J., Boyko, O. B., et al. (1995). 18-Fluorodeoxyglucose positron emission tomography in children and adolescents with traumatic brain injury. *Dev Med Child Neurol, 37*(3), 213-220.

Zaffaroni, M. (2003). Biological indicators of the neurodegenerative phase of multiple sclerosis. *Neurol Sci, 24 Suppl 5*, S279-282.

Appendix A

LLU Institutional Review Board Approval

INSTITUTIONAL REVIEW BOARD

Initial Approval Notice - Expedited Review

OSR # 53172

Kiti Freier, ext. 88725

OFFICE OF SPONSORED RESEARCH • 11188 Anderson Street • Loma Linda, CA 92350
(909) 558-4531 (voice) • (909) 558-0131 (fax)

To: **Freier, Kiti**
Department: **Psychology**
Protocol: *Head injury and cognitive outcome in children and adolescents*

This study was reviewed and approved administratively on behalf of the IRB. This decision includes the following determinations:

1. Risk to research subjects: **Minimal**
2. Approval period begins **09/30/2003** and ends **09/29/2004.**
3. Stipulations of approval are: **(None Specified)**

Consent Form

If a written consent form is required, approval will be indicated by the affixed IRB approval stamp. This now becomes your official consent form for the dates specified and should be used as a master for making the necessary copies.

Adverse Events / Protocol Changes

The IRB should be notified in writing of any modifications to the approved research protocol. All adverse effects, anticipated or not, should be reported to the IRB: serious events should be reported within seven days; all others within 15 days.

Protocol Review

To assure uninterrupted approval of this project, you are required to complete and return a status report at least two weeks prior to the approval end-date indicated above. (See http://research.llu.edu - select "IRB Tools for Investigators", then "Research Report Form.") In addition to requesting a renewal, you may also use the Research Report Form to close the study.

Records

All records relating to this project, including signed consent forms, must be kept on file for three years following completion of the study.

Please note the PI's name and the OSR number assigned your IRB application (as indicated above) on any future communications with the IRB about this project. Direct all communications to the IRB c/o the Office of Sponsored Research.

Thank you for your cooperation in LLU's shared responsibility for the ethical use of human subjects in research

Signature of IRB Chair/Designee: R L Rigsby

B Chair:
odes L. Rigsby, M.D.
partment of Medicine
)9) 558-2341, rrigsby@ahs.llumc.edu

IRB Administrator:
Linda G. Halstead, M.A., Director
Office of Sponsored Research
Ext. 43570, Fax 80131, lhalstead@univ.llu.edu

IRB Specialist:
Anuradha Job, MPH
Office of Sponsored Research
Ext 87130, Fax 80131, ajob@univ.llu.edu

Appendix B

Informed Consent (Adult Patients)

LOMA LINDA UNIVERSITY

iduate School
ls F.A.R.E.

164 West Hospitality Lane, Suite 3
San Bernardino, California 92408
Phone: (909) 558-7290
Fax: (909) 379-1517

Informed Consent

Head Injury and Cognitive Outcome in Children and Adolescents

Purpose:
You are invited to participate in a research study because you sustained a head injury and were treated at Loma Linda University Medical Center. The purpose of this project is to study possible long-term effects of a brain injury that occurred in childhood or adolescence on various mental abilities. In addition, we wish to see how well neuroradiologic tests performed immediately after brain injury are related to long-term mental functioning.

Procedures:
Participation in this study will take approximately 3 to 4 hours and will involve several age appropriate paper-and-pencil type tests that measure intelligence, memory, attention, and various other mental abilities. In addition to these test results, certain information will be used from your hospital medical chart. This will include medical information regarding the severity of your injury (for example, Glasgow Coma Scale scores, papillary reactivity following the injury) as well as your date of injury. In addition, results from neuroimaging tests performed following your brain injury will also be collected. All of this information is already in your medical chart and no new imaging studies will be conducted.

Risks:
The risks for participation in this study are minimal. Potential risks involve fatigue following the paper-and-pencil testing session. In order to minimize fatigue, you will be provided with as many breaks as needed during the 3 to 4 hour session. If you are uncomfortable at any point during the session, you can ask to either break down the testing session into two days or withdraw from participation altogether, without facing any adverse consequences.

Benefits:
You may personally benefit from participating in this study by becoming aware of your specific strengths and weaknesses. You will receive a brief summary report of the test results, which you may discuss with your physician or use to set up educational support in the school system. This report will not be included in your hospital medical chart. In addition, the results from this study will provide valuable information to health care professionals regarding the benefits of various neuroradiologic techniques administered following a brain injury. These benefits will include how well these techniques predict long-term outcome of mental abilities, including intellectual and neuropsychological skills.

Date _____

LOMA LINDA UNIVERSITY
INSTITUTIONAL REVIEW BOARD
APPROVED 9/30/03 VOID AFTER 9/25/2004
53172 CHAIR R-L Rogalyn MD

Head Injury and Cognitive Outcome in Children and Adolescents

Participants' Rights:
Your participation in this study is completely voluntary, and you may decide to withdraw from this study at any time. Your participation or withdrawal from this study will not affect your present or future medical care and will not involve penalty or loss of benefits to which you are otherwise entitled.

Confidentiality:
All of the data obtained during the course of the study, including information from your medical chart will be kept confidential. No one outside of the study will be able to access this information without your consent. The data collected will be summarized for publication and/or professional presentations and will not disclose your identity. No one will be able to identify your information.

Additional Costs:
There is no cost to you for participating in this study.

Impartial Third Party Contact:
If you wish to contact an impartial third party not associated with this project regarding any question or complaint you may have about the study, you may contact the Office of Patient Relations, Loma Linda University Medical Center, Loma Linda, CA 92354, (909) 558-4647 for information and assistance.

Informed Consent Statement:
"I have read the contents of the consent form and have listened to the verbal explanation given by the investigator. My questions concerning this study have been answered to my satisfaction. I hereby give voluntary consent to participate in this study. Signing this consent document does not waive my rights nor does it release the investigators, institution, or sponsors from their responsibility. I may call Kiti Freier, PhD, during routine office hours at (909) 558-8725 if I have additional questions or concerns. I have been given a copy of this form."

Signature of Subject	Date	Signature of Witness

Investigator's Signature:
"I have reviewed this consent form with the person signing above. I have explained potential risks and benefits of the study."

Signature of Investigator	Phone Number	Date

Appendix C

Informed Consent (Parent or Guardian)

LOMA LINDA UNIVERSITY

aduate School
ds F.A.R.E.

Informed Consent

164 West Hospitality Lane, Suite 3
San Bernardino, California 92408
Phone: (909) 558-7290
Fax: (909) 379-1517

Head Injury and Cognitive Outcome in Children and Adolescents

Purpose
You and your child are invited to participate in a research study because your child sustained a head injury and was treated at Loma Linda University Medical Center. The purpose of this project is to study possible long-term effects of a brain injury that occurred in childhood or adolescence on various mental abilities. In addition, we wish to see how well neuroradiologic tests performed immediately after brain injury are related to long-term mental functioning.

Procedures:
Your child's participation in this study will take approximately 3 to 4 hours and will involve several age appropriate paper-and-pencil type tests that measure intelligence, memory, attention, and various other mental abilities. Parents will also spend approximately 30 minutes filling out a questionnaire. In addition to these test results, certain information will be used from your child's hospital medical chart. This will include medical information regarding the severity of your child's injury (for example, Glasgow Coma Scale scores, papillary reactivity following the injury) as well as your child's date of injury. In addition, results from neuroimaging tests performed following the injury will also be collected. All of this information is already in your child's medical chart and no new imaging studies will be conducted.

Risks:
The risks for your child's participation in this study are minimal. Potential risks involve fatigue following the paper-and-pencil testing session. In order to minimize fatigue, your child will be provided with as many breaks as needed during the 3 to 4 hour testing session. If your child is uncomfortable at any point during the session, either you or your child can ask to break down the testing session into two days or withdraw from participation altogether, without adverse consequences.

Benefits:
You and your child may personally benefit from participating in this study by becoming aware of your child's specific strengths and weaknesses. You will receive a brief summary report of the test results, which you may discuss with your child's physician or use to set up educational support in the school system. This report will not be included in your child's hospital medical chart.

In addition, the results from this study will provide valuable information to health care professionals regarding the benefits of various neuroradiologic techniques administered following a brain injury. These benefits will include how well these techniques predict long-term outcome of mental abilities, including intellectual and neuropsychological skills.

LOMA LINDA UNIVERSITY
INSTITUTIONAL REVIEW BOARD
APPROVED 9/30/03 VOID AFTER 9/29/2004
3172 CHAIR R-1 Rigsby MD

Head Injury and Cognitive Outcome in Children and Adolescents

Participants' Rights:
Your and your child's participation in this study is completely voluntary, and you and your child may decide to withdraw from this study at any time. Your child's participation or withdrawal from this study will not affect his or her present or future medical care and will not involve penalty or loss of benefits to which your child is otherwise entitled.

Confidentiality:
All of the data obtained on your child during the course of the study will be kept confidential. No one outside of the study will be able to access this information without your consent. The data collected will be summarized for publications and/or professional presentations and will not disclose your child's identity. No one will be able to identify your child's information.

Additional Costs:
There is no cost to you and/or your child for participating in this study.

Impartial Third Party Contact:
If you wish to contact an impartial third party not associated with this project regarding any question or complaint you may have about the study, you may contact the Office of Patient Relations, Loma Linda University Medical Center, Loma Linda, CA 92354, (909) 558-4647 for information and assistance.

Informed Consent Statement:
"I have read the contents of the consent form and have listened to the verbal explanation given by the investigator. My questions concerning this study have been answered to my satisfaction. I hereby give voluntary consent for me and my child to participate in this study. Signing this consent document does not waive my rights nor does it release the investigators, institution, or sponsors from their responsibility. I may call Kiti Freier, PhD, during routine office hours at (909) 558-8725 if I have additional questions or concerns. I have been given a copy of this form."

_____	_____	_____
Signature of Subject	Date	Signature of Witness

"This protocol has been explained to my child at a level that he/she can comprehend and I give my consent for my child to participate in this study."

_____	_____
Signature of Parent or Guardian	Date

Investigator's Signature:

"I have reviewed this consent form with the person signing above. I have explained potential risks and benefits of the study."

_____	_____	_____
Signature of Investigator	Phone Number	Date

Appendix D

Assent (Minor Patients)

LOMA LINDA UNIVERSITY

Graduate School
Department of Psychology

11130 Anderson Street
Loma Linda, California 92350
(909) 558-8577
FAX: (909) 558-0171

Participant Assent

Head Injury and Cognitive Outcome in Children and Adolescents

You are invited to participate in a research study about your brain ability because you hurt yourself and were treated at Loma Linda University Medical Center. If it is ok with you to participate, you will be asked to complete some game-like tasks using papers and pencils. You will be here for about 3 to 4 hours.

Nothing you will be asked to do will hurt. You may get tired during the day. If you do, you may ask to get as many breaks as you need or ask to come back on a different day.

Your participation is voluntary. You may decide to quit at any time if you would like to do so without any problems. Whether or not you decide to participate will not affect your medical care at the hospital.

You and/or your parents will know how well you did on the tasks and will know your strengths and weaknesses. This can help you in school, especially if you are having problems at school or at home when completing your homework. Also, the information gathered from this study will be used by doctors to better understand what happens after a brain injury.

If you have read this form, agree to participate in the study, and have had all of your questions answered by the examiner, please sign your name at the bottom.

Thank you for your participation!

Signature of Participant _____ Date _____

LOMA LINDA UNIVERSITY
INSTITUTIONAL REVIEW BOARD
APPROVED 9/30/03 VOID AFTER 9/29/2004
5317 CHAIR R-1 Regulyms

Appendix E

Personal Health Information (PHI)

INSTITUTIONAL REVIEW BOARD
Authorization for Use of Protected Health Information (PHI)

OSR# 53172

Per 45 CFR §164.508(b)

OFFICE OF SPONSORED RESEARCH
Loma Linda University • 11188 Anderson Street • Loma Linda, CA 92350
(909) 558-4531 (voice) / (909) 558-0131 (fax)

TITLE OF STUDY: Head Injury and Cognitive Outcome in Children and Adolescents

PRINCIPAL INVESTIGATOR: Kiti Freier, PhD

Others who will use, collect, or share PHI: Talin Babikian, MA

The study named above may be performed only by using personal information relating to your health. National and international data protection regulations give you the right to control the use of your medical information. Therefore, by signing this form, you specifically authorize your medical information to be used or shared as described below.

The following personal information, considered "Protected Health Information" (PHI) is needed to conduct this study and may include, but is not limited to: your name, date of birth, medical records and charts, including results from previous neuroimaging tests, as well as and neuropsychological and intellectual testing protocols.

The individual(s) listed above will use this PHI in the course of this study or share it with the Institutional Review Board (IRB) of Loma Linda University and health care providers who provide services to you in connection with this study.

The main reason for sharing this information is to be able to conduct the study as described earlier in the consent form. In addition, it is shared to ensure that the study meets legal, institutional, and accreditation standards. Information may also be shared to report adverse events or situations that may help prevent placing other individuals at risk.

All reasonable efforts will be used to protect the confidentiality of your PHI, which may be shared with others to support this study, to carry out their responsibilities, to conduct public health reporting and to comply with the law as applicable. Those who receive the PHI may share with others if they are required by law, and they may share it with others who may not need to follow the federal privacy rule.

Subject to any legal limitations, you have the right to access any protected health information created during this study. You may request this information from the Principal Investigator named above but it will only become available after the study analyses are complete.

This authorization will continue indefinitely unless you inform the researchers that you wish to revoke it.

You may change your mind about this authorization at any time. If this happens, you must withdraw your permission in writing. Beginning on the date you withdraw your permission, no new personal health information will be used for this study. However, study personnel may continue to use the health information that was provided before you withdrew your permission. If you sign this form and enter the study, but later change your mind and withdraw your permission, you will be removed from the study at that time. To withdraw your permission, please contact the Principal Investigator or study personnel, Kiti Freier, PhD, at 909-558-8725.

You may refuse to sign this authorization. Refusing to sign will not affect the present or future care you receive at this institution and will not cause any penalty or loss of benefits to which you are entitled. However, if you do not sign this authorization form, you will not be able to take part in the study for which you are being considered.

I agree that my personal health information may be used for the study purposes described in this form.

Signature of Patient *or* Patient's Legal Representative	Date
Printed Name of Legal Representative (if any)	Representative's Authority to Act for Patient
Signature of Person Obtaining Authorization	Date

LOMA LINDA UNIVERSITY
INSTITUTIONAL REVIEW BOARD
APPROVED 9/30/03 VOID AFTER 9/29/2004
#53172 CHAIR R. Ragland