Prediction of Long-Term Intellectual and Neuropsychological Effects of Closed Head Injury in Infants and Children

Tamara Sue Brenner

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LOMA LINDA UNIVERSITY
Graduate School

Prediction of Long-Term Intellectual and Neuropsychological Effects
of Closed Head Injury in Infants and Children

by

Tamara Sue Brenner

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

June 2001
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.

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DEDICATION

This dissertation is dedicated with love to my husband, John, for his love and sacrifices made to pursue this dream and to our son, Conner, for filling my heart with joy.
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ABSTRACT OF THE DISSERTATION

Prediction of Long-Term Intellectual and Neuropsychological Effects of Closed Head Injury in Infants and Children

by

Tamara Sue Brenner

Doctor of Philosophy, Graduate Program in Psychology
Loma Linda University, June 2001
Dr. Kiti Freier, Chairperson

The ability to predict long-term intellectual and neuropsychological outcome (1-7 years post-injury) in children (ages 1 week - 14 years at injury) with a history of closed head injury were investigated. Clinical indicators of injury severity including EEG reading and age at injury as well as $^1$H-MRS variables of NAA/Ch, Ch/Cr, and lactate presence accurately classified 100% of children as functioning either within or above the average range or below the average range for most outcome measures. Combined clinical and $^1$H-MRS variables accounted for approximately 50% of the variance in outcome confirming the validity of their predictive use and also the importance of further studies to examine other factors related to recovery. Exploratory analysis for predictive effects of injury etiology was partially supported. Analysis of duration of time since injury and exploratory analysis of focal effects regarding specific areas of functioning were not supported. Implications of the outcome findings as well as suggestions for future research are provided.
Prediction of Long-Term Intellectual and Neuropsychological Effects of Closed Head Injury in Infants and Children

Pediatric traumatic brain injury (TBI) is a primary cause of death and disability of children and adolescents in the United States (Annegers, 1986). For the estimated 170,000 children who survive closed head injury in the United States each year, closed head trauma can result in diffuse and widespread injury that may cause intellectual, behavioral, and functional impairment (Krause, 1995). Specific neuropsychological impairment may include intellectual and executive functions, attention and memory skills, language abilities, sensorimotor abilities, and visuospatial abilities.

However, treatment of brain injury in pediatric patients is complicated by the limited predictive power of injury severity indicators for long-term intellectual and neuropsychological outcome. Choi and Barnes (1996) offer that current indicators of injury severity have limited ability to predict outcome. In their analysis of 23 clinical variables commonly used to predict severity and outcome, it was found that most predictive clinical variables in 523 patients over a several year period included whether one-or both pupil reflexes respond appropriately at admission, the individual’s age at the time of injury, and motor responses on the Glasgow Outcome Scale. Yet clinical indicators alone may be able to predict long-term outcome in only 80% of children who experience closed head injury. Additionally, the authors report that most predictive ability occurs for children with either mild or severe injury, with limited predictive ability for children with head injuries that are more moderate. Similarly, in a comprehensive analysis of factors that contribute to the variability in outcomes following brain injury in children, Fletcher, Ewing-Cobbs, Francis, and Levin (1995) have suggested that methods
used to characterize the nature and severity of traumatic brain injury present a major source of the variability in prediction of long-term cognitive and behavioral outcome.

Some of the most predictive and often used clinical indicators of injury severity include the Glasgow Coma Scale (GCS; Jennett & Bond, 1974), duration of impaired consciousness, duration of posttraumatic amnesia, and presence of non-reactive pupils. Research has demonstrated that the GCS is a predictor of neurobehavioral outcome (Levin & Eisenberg, 1979b; Bawden, Knights, & Winogron, 1985; Ewing-Cobbs et al., 1985, 1987; Levin, Eisenberg, Wigg, & Kobayashi, 1982; Kinsella, Prior, Sawyer, Murtagh, Eisenmajer, Anderson, Bryan, & Klug, 1995). It is one of the most frequently used tools used to determine injury severity level in studies of children who have experienced brain injury. Although the GCS is moderately predictive of outcome, there remains significant variability between GCS level of severity and outcome results. Further, there is a special concern using the GCS for infants and toddlers who are preverbal. In particular, assessment using specific scores on the GCS may indicate a more severe injury for a preverbal child than a verbal child. Also a child newly admitted for TBI may obtain a higher GCS score than is achieved 24 hours later, particularly for children who demonstrate deterioration after admission or following resuscitation due to brain swelling or other problems. Children who have overall GCS scores in the moderate range (9-12) but whose motor scale score on the GCS is below 6 for 24 hours most likely have injuries that should be classified as severe (Fletcher et al., 1995).

Duration of impaired consciousness and duration of posttraumatic amnesia are also utilized as indicators of severity. Duration of impaired consciousness is usually classified as the number of days that pass before the child is able to follow commands.
A similar indicator involves number of days until the child achieves a score of 5 on the motor scale of the GCS. An injury is considered to be severe if the duration of impaired consciousness exceeds 24 hours (Fletcher et al., 1995). Duration of posttraumatic amnesia is the amount of time necessary for the child to move from recovery of consciousness (i.e., following commands) to complete temporal and spatial orientation, with return of episodic memory. As with the GCS, both of these predictors vary in their relationship to outcome (Fletcher et al., 1995).

Presence of non-reactive pupils has demonstrated correlation with outcome, yet is most predictive for severe outcomes (Levin, Aldrich, Saydjari, Eisenberg, Foulkes, Bellefleur, Luerssen, Jane, Marmarou, Marshall, & Young, 1992). In a study that assessed outcome in 103 children admitted to the hospital for severe closed head injury, Levin et al. (1992) examined the predictive power of the GCS and presence of non-reactive pupils. Outcome severity was categorized as good, moderate, severe, in a persistently vegetative state, or deceased as defined on the Glasgow Outcome Scale. Both the GCS and the presence of non-reactive pupils were predictive for children with good outcome or with severe outcome, but were not predictive for children with mild to moderate injuries.

Brain imaging techniques are also used to assess injury severity. Although studies have demonstrated that imaging techniques are predictive of long-term outcome for children who experience severe head injuries, relatively few studies have assessed the predictive utility of imaging techniques for children who sustain mild-to moderate closed head injuries (van der Naalt, Hew, Zomeren, Sluiter, & Minderhoud, 1999).
One such study to examine the predictive power of imaging techniques for children who experienced mild to moderate closed head injuries was conducted by van der Naalt et al. (1999). These researchers assessed 67 patients were considered to have mild to moderate head injuries as indicated with GCS scores ranging from 9 to 14 points and posttraumatic amnesia of at least 1 hour but less than 29 days. The patients ranged in age between 15 and 65 years (\(\bar{x} = 33.2\) years; \(SD = 14.7\) years). For 55 of the patients a computed tomography (CT) scan was conducted following admission. Magnetic Resonance Imaging (MRI) was conducted for 63 of the patients, 1 to 3 months following injury. Both CT and MRI cans were assessed for the depth and size of intracranial lesions as well as focal atrophy. Outcome was assessed 1 year after injury with an extended Glasgow Outcome Scale with global outcome categories of good recovery, mild complaints, and moderate disability and also a Differential Outcome Scale that assessed outcome in social, behavioral, cognitive, and physical areas of functioning. It was found that for patients for whom lesions were found on either the CT or MRI, there was a tendency to experience poorer outcome (\(p < .10\)). However, after controlling for duration of posttraumatic amnesia in a stepwise regression (accounting for 21-30% of the variance), presence of imaging abnormalities did not independently contribute to outcome prediction. Thus the ability to provide recommendations regarding long-term outcome for children who have experienced mild to moderate closed head injuries may be limited by the use of either of these methods alone. This point becomes particularly relevant as epidemiological reports indicate that approximately 90% of children admitted to hospitals for brain injury have mild injury (Kraus, Fife, & Conroy, 1987).
Due to the limited sensitivity of traditional indicators of injury severity in predicting long-term outcome for children who have experienced closed head injuries, some investigators are researching more sensitive indicators of long-term behavioral and cognitive functioning. One promising area of study is in the ability to more directly assess the severity of CNS insult by examining metabolite ratios that appear to change in response to brain injury.

**1H-MR Spectroscopy to Predict Outcome**

Metabolite ratios can be assessed through the utilization of proton magnetic resonance spectroscopy (1H-MRS), a non-invasive technique that provides information about the biochemical functioning of the brain. Metabolites measured with 1H-MRS include N-acetyl aspartate (NAA), an amino acid that is stored primarily in the intact neuron; creatine (Cr), comprised of phosphocreatine and its precursor creatine which are bioenergetic metabolites; choline-containing compounds (Ch) that are released during membrane disruption; lactate, which accumulates in response to tissue damage; glutamate and immediately formed glutamine (Glx) and myo-inositol (ml) (Auld, Ashwal, Holshouser, Tomasi, Perkin, Ross, & Hinshaw, 1995). When children experienced a closed head injury, metabolite ratios involving N-acetyl aspartate, creatine and choline levels change. The ratios of N-acetylaspartate to creatine (NAA/Cr) and also choline (NAA/Ch) decrease whereas the ratio of choline to creatine (Ch/Cr) increases in response to injury.

The other major change occurs when a child experiences a closed head injury is the formation of lactate. “Severe injuries cause both irreversible neuronal and glial loss,
as well as significant alterations in neuronal and glial metabolic function that increase brain lactate formation. Alternatively, brain metabolic injury or altered flow-metabolic relationships may lead to increased lactate formation, which then causes additional neuronal damage. Overall, it is likely that cerebral lactate is both a marker of and a contributor to continued injury “(Ashwal, Holshouser, Hinshaw, Schell, & Bailey, 1996, p. 410).

Seminal work conducted by Ashwal, Holshouser and colleagues indicates that \(^1\text{H}-\text{MRS}\) variables can predict neurological outcome for children who have experienced severe CNS insult from many different forms of trauma. In one of the earlier studies, Auld, Ashwal, Holshouser, Tomasi, Perkin, Ross, and Hinshaw (1995) examined metabolite ratios in thirty infants and children (\(x = 37\) months, range 34 weeks-180 months) who had experienced acute central nervous system injury. CNS Injuries resulted from acute hypoxic ischemic injury, infection, trauma, or encephalopathy. \(^1\text{H}-\text{MRS}\) spectra were obtained from each of the brain injured children between 1 and 70 days following injury (\(x = 8.7\) days). Because studies have demonstrated that metabolite peaks undergo significant changes in the first 2 years of life (Kreis, Ernst, & Ross, 1993; Kimura, Fujii, Itoh, Matsuda, Iwasaki, Maeda, Konishi, & Ishii, 1995; van der Knapp, van der Grond, van Rijen, Faber, Valk, & Willemse, 1990), patients’ spectra ratios were compared with age-matched spectra of non-head-injured children to control for age effects on metabolite ratios.

Follow-up neurological exams utilizing the Glasgow Outcome Scale (GOS) score were conducted at 3, 6, and 12 months following the injury. Due to limited sample size, the range of outcomes was dichotomized to increase predictive power. The good, mild,
and moderate outcome groups were combined into one group (good/moderate outcome) and the children who were severe, in a persistently vegetative state, or had died were combined to form a second group (bad outcome).

It was found that the children with bad outcome demonstrated significantly lower ratios of NAA/Cr and NAA/Ch. Additionally, lactate was present in 80% of the children with poor outcome and was not found for any of the children who had been classified with good to moderate outcome. In a linear discriminant analysis a combination of three clinical variables (i.e., GCS, initial pH, glucose) classified 83% of patients into the correct outcome group. Of the 18 patients in this group there was 1 false-positive result (bad predicted, G/M occurred) and 2 false-negative results (G/M outcome predicted but bad occurred). By adding number of days unconscious at the time of $^1$H-MRS as a fourth clinical variable, 94% of outcomes were correctly classified with no false-positive and 1 false-negative. Use of the spectroscopy variables (NAA/Cr, NAA/Ch, Ch/Cr, presence of lactate) alone classified 81% of patients ($n = 27$) with 2 false-positives and 3 false-negatives. Combining clinical and $^1$H-MRS variables increased the number of outcomes correctly classified to 100% of patients with no false-positives or false-negatives.

Another study conducted by Ashwal, Holshouser, Hinshaw, Schell, and Bailey (1996) examined the outcome of acute central nervous system injury resulting from congenital heart disease. The study included nine children who experienced severe CNS insults as the result of cardiovascular deficits prior to or following surgery. The children ranged in age from approximately 1 week old to 42 months old (median age of 1.25 months). GCS scores were obtained prior to surgery. These scores ranged from 3 to 15 (2 children with score of 3 indicating severe injury, 3 children with score of 12 indicating
moderate injury, and 4 children with score of 15 indicating mild injury). Patient data collected included preoperative and postoperative neurological examination findings, postoperative magnetic resonance imaging (MRI) scans, and $^1$H-MRS scans.

Neurological outcome was assessed with the Glasgow Outcome Scale (GOS) score at discharge from hospital and at follow-up between 6 and 12 months following surgery. The GOS included the following: (1) good outcome (resume all activities); (2) mild disability (minor, almost undetectable alteration in function, no assistance required); (3) moderate disability (neurological deficit, requiring assistance but remaining independent); (4) severe disability (incapable of resuming most activities, limited communication skills and partial or total dependence on others); (5) persistent vegetative state; and (6) death. As in the above cited study, the researchers noted that metabolite peaks undergo significant changes in the first 2 to 3 years after birth making it necessary to compare a patient’s spectrum with the spectrum of a normal age matched control participant.

Of the nine children in the study, six children demonstrated either a vegetative state or severe impairment at discharge. Two of those six children had detectable cerebral lactate and marked reductions in NAA/Cr ratios and demonstrated little or no recovery six to twelve months later. The four other children of those six had no lactate and demonstrated milder changes in metabolite ratios. Of the four children, one child improved to a normal condition at follow-up and the other three children demonstrated mild disability.

Two of the nine children in the study demonstrated moderate impairment at discharge and improved to a mild condition at follow-up. Neither of these children
demonstrated noticeable lactate. One of the two children demonstrated a 30% reduction in NAA/Cr ratio.

Lastly, one of the nine children in the study demonstrated mild impairment at discharge and improved to a good outcome at follow-up. This child had no detectable lactate and a normal NAA/Cr ratio assessed in the occipital area. The researchers concluded that the presence of lactate coupled with reduced NAA/Cr ratio is suggestive of poor neurological outcome.

A third study examined $^1$H-MRS spectra in children considered to be at risk for long-term neurodevelopmental impairment (Ashwal, Holshouser, Tomasi, Shu, Perkin, Nystrom, & Hinshaw, 1997). In this study children suffered acute CNS injury resulting from metabolic or infectious disorders. $^1$H-MRS and long-term follow-up data in 36 patients with cerebral lactate were compared with data in 61 children with similar disorders, but in whom an identifiable lactate signal was not detected. In addition, the spectroscopy data for head injured children with and without lactate presence were compared with those in 24 age-matched control patients (Holshouser, Ashwal, Luh, et al., 1997). All of the children were followed for a minimum of 6-12 months after insult.

At the time of admission for treatment patients were assessed for injury severity using either Sarnat criteria for infants (Sarnat, 1976) or the GCS (see above) for children. Additionally other clinical predictors including glucose level, whether the child had suffered a cardiac arrest, and number of days unconscious were considered to assess severity.

Neurological outcome assessment was conducted at 6-12 months following injury according to the Pediatric Cerebral Performance Category Scale (PCPCS) score. This
six-point outcome scoring system was adapted from the Glasgow Outcome Scale (GOS) score for use in infants and children and previously had been validated in 1,469 pediatric patients suffering acute CNS injuries (Fiser, 1992). In the study, outcomes were categorized by putting the six PCPCS scores into the following two groups: (1) good/moderate outcome = normal, mild, or moderate disability, and, (2) poor outcome = severe disability, PVS, and death.

The percentage of patients in each of the 6 PCPCS outcome categories in the Lac+ and Lac- groups were compared to determine whether patients with lactate were more likely to suffer more serious neurological sequelae or death, and conversely whether absence of detectable lactate was associated with either a good outcome or less serious degree of disability. As in previous studies interpretation of the H-MRS spectra was done immediately following processing by comparison with normal age-matched control spectra. To control for developmental changes in metabolite ratios, patients were stratified into three age groups: (1) neonates, ≤ 1 month; (2) infants, 1-18 months; and (3) children, > 18 months (Auld et al., 1995; Holshouser et al., 1997).

When the entire group of patients was analyzed, those with lactate were more often hyperglycemic, had suffered a cardiac arrest, and had lower GCS scores. The number of days that the patients were unconscious at the time of MRS study as well as the number of days spent in the hospital were similar in children with and without detectable lactate. The patients with elevated lactate had lower H-MRS NAA/Cr and NAA/Ch ratios and increased Ch/Cr ratios when compared to control children. Results were consistent for all three age groups. In each of the three age categories, patients with lactate were more likely to have poor outcomes as measured by either the PCPCS or the
GOS than the patients without detectable lactate. Further, the patients without elevated lactate were more likely to experience normal or mild-to-moderate neurological abnormalities than the patients with increased lactate. Patients with hypoxic-ischemic insults were more likely to have a poor outcome compared with those with non-hypoxic-ischemic insults; but even in the hypoxic-ischemic patients, those with increased lactate had a higher incidence of poorer outcomes.

Further outcome analyses using all patients stratified by the six PCPCS Outcome Scale scores showed that “patients with an elevated lactate were much more likely to have a severe disability (39% vs. 10%), be in a persistently vegetative state (13% vs. 2%), or have died (39% vs. 7%). In contrast, patients without detectable lactate were more likely to be normal (23% vs. 3%) or recovered to a mild (38% vs. 6%) or moderate (20% vs. 0%) disability” (p. 476). The researchers conclude, as above, that a strong association between presence of cerebral lactate and risk for poor neurological outcome exists, noting that, “ Ninety-one percent of patients with lactate had a poor neurological outcome (severe disability, PVS, or death) compared with only nine-percent of patients without lactate” (p. 478).

A further study conducted by Holshouser, Ashwal, Luh, Shu, Kahlon, Auld, Tomasi, Perkin, and Hinshaw (1997) examined the predictive power of $^1$H-MRS following acute central nervous system injury in children. In this study, children suffered several forms of CNS insult that required hospitalization including meningitis and encephalitis, hypoxic-ischemic encephalopathy, accidental and non-accidental trauma, cardiac arrest, near-drowning, metabolic disorders, and secondary insults including vasculitis, sepsis, hypoglycemia, seizures, and Rh incompatibility. The researchers
assessed 82 children in three age groups: neonates (n = 23, ≤ 1 month, \( \bar{x} = 2 \) weeks), infants (n = 31, 1-18 months, \( \bar{x} = 7 \) months), and children (n = 28, > 18 months, \( \bar{x} = 8 \) years).

Clinical indicators of injury and/or predictors of outcome included the child’s age at the time of injury, cause of brain injury, occurrence of cardiac arrest, admission GCS score, presence of fixed pupils at admission, admission arterial blood gas and blood glucose levels, the number of days after the insult and the number of days the patient was unconscious at time when \( ^{1} \)H-MRS was performed, duration of ventilatory support and hospitalization. In neonates, the 5-minute Apgar score and Sarnat score (see above, Auld et al., 1995) and the electroencephalographic score were recorded instead of the GCS score to assess injury severity. Neurological outcome at 6-12 months after injury was assigned on the basis of the Pediatric Cerebral Performance Category Scale, a version of the Glasgow Outcome Scale modified for use with children (see above, Auld et al., 1995; Fiser, 1994). Because of limited sample size and findings from prior studies, the six Glasgow Outcome Scale groups were stratified into two groups: (a) good-moderate outcome (good outcome, or mild or moderate disability), and (b) poor outcome (severe disability, PVS, and death).

\( ^{1} \)H-MRS data included metabolite ratio of NAA/Cr, NAA/Ch, Ch/Cr and lactate obtained from the occipital lobe region. In order to provide a comparison with age-matched control subjects necessary to adjust for age influences on metabolite ratios, additional spectra (n = 8) were acquired in patients without brain injury who were undergoing clinically indicated MR imaging. The control metabolite ratios were combined with ratios obtained in 16 patients with transient mild neurological symptoms
at admission who were developmentally normal at the time the $^1$H-MRS was performed and at discharge. The metabolite ratios for the 16 patients with transient neurological symptoms were within 1 standard deviation of published normal levels (Kreis, Ernst, & Ross, 1993). The combined data were used to calculate normal mean metabolite ratios for each age group. Data obtained in the eight control subjects were used to calculate only the normal metabolite ratios, but the data were not included in the t tests or linear discriminant analyses. Normal metabolite ratios from the occipital regions were plotted against age. The authors of the study noted that the number of days post-injury when children's metabolite ratios are evaluated might affect metabolite ratios. Specifically, lactate may dissipate after approximately two weeks. In the study, the time of spectroscopy examination for neonates ranged from 2 to 42 days ($x = 10$ days, $SD = 9$ days), for infants ranged from 1 to 31 days ($x = 6$ days, $SD = 6$ days) and for children ranged from 1 to 31 days ($x = 7$ days, $SD = 6$ days).

Linear discriminant analysis was used to statistically analyze the clinical and metabolite variables predictive of outcome (poor vs. good-moderate). Only clinical variables that significantly increased the percent of variance in 6-12 month outcome were considered. For neonates, clinical variables included the 5-minute Apgar score, Sarnat score, EEG score and admission blood glucose level. For infants and children clinical variables included occurrence of cardiac arrest, presence of fixed pupils at admission, admission GCS score, admission blood glucose level, and number of days unconscious at time of $^1$H-MRS. For all ages, the $^1$H-MRS variables included NAA/Cr, NAA/Ch, and Ch/Cr and the presence of lactate in the occipital region.
The investigators found that the level of lactate in patients with poor outcome was significantly higher than the level in patients with good-moderate outcome in all 3 age groups (neonate, 38% vs. 5%; infants, 87% vs. 5%, children 64% vs. 10%). The presence of lactate in children with hypoxic-ischemic brain injury and TBI was an ominous finding. In children with CNS infections, such as meningitis, the presence of lactate did not appear to correlate with poor outcome. With regard to the metabolite ratio data, for patients with poor outcomes, the NAA/Cr ratios of infants and children and the NAA/Ch ratios of infants and neonates were significantly lower. The Ch/Cr ratios were not significantly different for patients with poor vs. good-moderate outcome in any age group. In summary, the presence of lactate in any age group, the NAA/Cr ratio in infants and children, and the NAA/Ch ratio in neonates were sensitive indicators of the severity of injury for all causes of brain injury studied except CNS infections.

In infants and children, the percentage of patients with NAA/Cr ratios that fell (a) within 1 standard deviation of the mean ratios of normal, (b) below 1 standard deviation, and, (c) below 2 standard deviations were calculated. In neonates those same ratios were calculated for the NAA/Ch ratios. Also determined was the percentage of patients with lactate regardless of metabolite changes. These percentages were plotted against the Pediatric Cerebral Performance Category Scale score for neonates, infants, and children.

The metabolite findings were presented by age category for neonates, infants, and children. Neither of the neonates who died showed presence of lactate. This was in contrast to infants or children who did not survive, in whom lactate presence was detected. Another neonate who showed mild disability also showed lactate. With regard to these two neonates, the parents of one refused treatment, and the neonate may not have
demonstrated lactate because the spectroscopy was performed later than 2 weeks after injury. Lactate has been reported to resolve within 2 weeks of ischemic brain injury (Fenstermacher & Narayana, 1990). None of the neonates had NAA/Ch ratios reduced below 2 standard deviations. A higher percentage of neonates in the poor outcome groups showed a 1 standard deviation reduction in NAA/Ch ratio than seen in neonates of the good outcome groups (good, mild, or moderate). Presence of lactate and lower than normal metabolite ratios were indicative of poor outcomes in neonates with traumatic brain injury or hypoxic-ischemic injuries.

Infants who evolved to a vegetative state or who died had a NAA/Cr ratio below 2 standard deviations and had lactate present. Infants with severe disability did have lactate present although distinguishing between NAA/Cr ratios was difficult. In the infants with moderate disability only one of 3 children showed lactate, which was believed to be the result of localized infarction rather than global injury. None of the infants in the group with good to mild outcome showed lactate. The percentage of infants with normal NAA/Cr ratios increased as the Pediatric Cerebral Performance Category Scale score progressed from severe to good. For children who evolved to a vegetative state or who died had a NAA/Cr ratio below 2 standard deviations and had lactate. For children with severe or moderate disability there were reductions in NAA/Cr ratios below 2 standard deviations (severe 100%; moderate, 67%) and neither group had lactate. There was difficulty distinguishing between severe and moderate disability. All children with no lactate and normal or 1 standard deviation reduction in NAA/Cr ratio had good outcomes. Lactate was not detected in spectra obtained in children with good, mild, moderate or severe Pediatric Cerebral Performance Category Scale scores.
Clinical variables were also predictive of outcome. Children and infants with poor outcomes were significantly more likely to have lower admission GCS scores, be hypoglycemic, have experienced cardiac arrest, and have non-reactive pupils. In neonates, the Sarnat score was the sole clinical variable predictive of outcome.

Utilizing discriminant function analysis of $^1$H-MRS variables (NAA/Cr, NAA/Ch, Ch/Cr, and presence of lactate) in the occipital area, the authors were able to predict the 6-12 month outcome by age in 87% of neonates, 100% of infants, and 93% of children. With combined $^1$H-MRS variables and clinical variables the prediction decreased to 83% in neonates (2 false positives), remained at 100% for infants, and increased to 100% in children. With the addition of MRI the percentage of neonates increased to 91% (1 false positive and 1 false negative) and other 2 groups remained at 100%. With clinical variables alone the percentage predicted decreased to 78% in neonates, 81% in infants, and 86% in children and resulted in the greatest number of false positives in all age groups. The combination of MRI and clinical variables did not reach the 100% correct predictions achieved with combination of clinical variables and $^1$H-MRS metabolite ratios. Results of the discriminant analyses demonstrated that metabolite ratios including markedly reduced NAA/Cr and the presence of lactate usually indicated poor outcome in infants and children with CNS injury. For neonates the NAA/Cr ratio alone had the highest discriminant power. Importantly, using metabolite ratios alone resulted in four false-negatives. For two of the children and two neonates, good outcome was predicted but poor outcome occurred. This occurred because although there were decreased NAA/Cr ratios below 2 standard deviations indicating that neuronal injury has occurred, there was also an absence of lactate suggesting a potential for recovery.
The authors concluded by reporting that “One of the main benefits of using proton MR spectroscopy to help predict outcome was a reduction in the number of false-positive cases to zero in infants and children. . . . In general, the addition of proton MR spectroscopy data to the analysis not only increased the percentage of cases classified correctly but also helped reduce the number of false-positive cases in each age group to less than the number determined with clinical or MR imaging data alone” (p. 493).

In a more recent study, Ashwal, Holshouser, Shu, Simmons, Perkin, Tomasi, Knierim, Sheridan, Craig, Andrews, and Hinshaw (2000) considered the predictiveness of $^1$H-MRS for children who had sustained a severe brain injury through closed head trauma. Twenty-six infants and 27 children were assessed at 6-12 months following the time of injury. As in previous studies, good outcome included those children who demonstrated an ability to engage in at least most age-appropriate activities, although possibly with significant cognitive impairment. Children who were dependent on others for daily support, were in a persistently vegetative state, or who had died comprised the group for poor outcome.

As in their earlier studies, both clinical and $^1$H-MRS variables were considered for their predictive ability with neurological impairment. Clinical variables that were predictive of poorer outcome included EEG abnormalities, lower GCS scores, number of days in coma, and number of ventilator-dependent days. Presence of cardiac arrest, non-reactive pupils, and duration of unconsciousness to $^1$H-MRS were not statistically predictive. In discriminant analysis, EEG reading singularly predicted outcome in 73% of infants and children combined. Of the MRI variables, presence of hypoxic-ischemic
injury and diffuse cerebral edema was predictive of poorer outcome in infants only. Other MRI indicators of injury were not predictive of outcome when examined individually. $^1$H-MRS indicators predictive of neurological impairment were reductions in NAA/Cr and NAA/Ch, increase in Ch/Cr, and presence of lactate. Of the $^1$H-MRS variables, presence of lactate alone predicted outcome in 96% of infants and children. Notably, lactate was not detected in any of the infants who recovered with a good/moderate outcome. Conversely, 91% of infants and 80% of children with poor outcomes had elevated lactate at the time of injury.

When all of the studies that examine the predictive power of $^1$H-MRS are considered together there is suggestion that a combination of metabolite ratios (most specifically NAA/Cr NAA/Ch in neonates and NAA/Cr and NAA/Ch coupled with the presence of lactate in infants and children) in conjunction with clinical variables (EEG reading, the Sarnat score for neonates and the Glasgow Coma Score for infants and children, presence of non-reactive pupils, number of days unconscious, and sustaining cardiac arrest) are predictive of outcome when outcome is measured by the Glasgow Outcome score. The current study is designed to determine whether these same variables are predictive of more sensitive measures of neuropsychological functions that have been shown to become impaired as the result of brain injury, including intellectual functioning and memory, linguistic abilities, planning and attention, visuospatial skills and sensorimotor abilities.

One study was found in the literature that correlated $^1$H-MRS variables in children with non-verbal intellectual functioning. The study assessed 14 children ranging in age between 4 years and 13 years old, who suffered from adrenoleukodystrophy (ALD).
ALD is a cerebral degenerative disease that causes demyelination of neurons. The children with ALD tended to have lower NAA/Ch and NAA/Cr ratios and higher Ch/Cr ratios than the 5 control children. Metabolite ratios for children with ALD were predictive of intellectual functioning on the age appropriate Wechsler non-verbal (performance) intellectual functioning scale (WISC-III, Wechsler, 1991; WPPSI-R, Wechsler, 1989). Metabolite ratios from affected regions were not predictive of functioning on the TOVA, an assessment of attention.

In the studies cited above, $^1$H-MRS ratios were typically obtained from the occipital gray matter, or with some of the children, from the parietal white matter. Use of a single location to determine metabolite ratio is based on the assumption that what is being assessed are global changes in the brain as a result of injuries that are considered global in their effect (i.e., near-drowning, asphyxia) or that may be localized (i.e., trauma, stroke) but produce a global effect with widespread changes in metabolite ratios and accumulation of lactate. The authors chose the occipital gray matter as the standardized region of interest because findings in previous studies in near-drowning victims showed that this region reflects early changes in brain chemistry (Kreis, Arcinue, Ernst, Shonk, Flores, & Ross, 1996). Yet it was indicated that utilizing findings from one brain location could become problematic if a localized injury occurred very near or in the standardized area, since evaluation would then reflect local, rather than global, injury.

Also, the presence of lactate may depend on the type of injury. Specifically, lactate may not occur in areas of diffuse axonal injury (e.g., when axon is injured or separated from the cell body but the cell body remains intact and living), as compared to injury that results in cell death. Findings suggest that spectra obtained from these
locations adequately reflects diffuse injuries that are located in diverse areas of the brain as is commonly found for children who experience closed head injuries (not solely limited to occipital and/or parietal insult). It has been suggested that MRI may be necessary for determining the effects of long term, focal cerebral injury (Ashwal et al., 1996).

Intellectual and Neuropsychological Outcome Findings in the Literature

Closed head injury in children has been found to correlate with long-term impairment in the areas of intellectual functioning, memory abilities, receptive and expressive language abilities, attention and planning abilities, sensorimotor skills, and visuospatial abilities.

Intellectual functioning and memory

Intellectual functioning has been found to be adversely affected in children who sustain closed head injuries. Fay, Jaffe, Polissar, Liao, Rivara, and Martin (1994) conducted a study that examined memory abilities, academic performance, and intellectual functioning in 103 children who experienced closed head injury between the ages of 6 and 15 years. These participants were compared with healthy control subjects who were matched with regard to age (within 12 months), gender, school grade, and the classroom teacher’s assessment of level of academic performance in reading and arithmetic (Jaffe, Fay, Polissar, Martin, Shurtleff, Rivara, & Winn, 1992). There were 72 eligible pairs of children in the current study, of whom 40 children had mild injury, 17 demonstrated moderate injury, and 15 evidenced severe injury as indicated with GCS scores. Neurobehavioral assessment included assessment of intellectual functioning,
adaptive problem solving, memory, and academic functioning. It was found that moderately and severely injured children performed more poorly than matched controls on measures of intellectual functioning as measured with the WISC-R/WAIS-R). Significant differences were found for verbal and non-verbal intellectual functioning as well as on the similarities, digit span, picture completion, picture arrangement, object assembly, and coding subtests. Academic performance, measured with the WRAT-R, was significantly affected by severity of injury for reading, writing, and arithmetic. Adaptive problem solving, as measured by the Category test and Trails B, was also correlated with severity of injury. Additionally, memory deficits, as measured by the California verbal Learning Test, were associated with injury in all areas assessed including short term free recall, short term cued, long term free recall, long term cued and long term recognition.

A study conducted by Kinsella, Prior, Sawyer, Murtagh, Eisenmajer, Anderson, Bryan, and Klug (1995) examined intellectual functioning and academic achievement in 51 children who were between the ages of 9 and 15 years at the time of injury. Children were grouped according to injury severity as indicated on the GCS. Measures of intellectual and academic abilities were assessed at three months and 1 year post-injury.

It was found that severity of brain injury significantly predicted deficits on indicators of verbal and non-verbal intellectual achievement, auditory verbal learning and auditory verbal short and long-term memory, but not academic achievement. All three age groups performed within the average range on measures of academic achievement. The authors of the study suggested that the absence of differences in academic achievement may suggest that skills acquired prior to injury are less vulnerable to injury
effects than other cognitive abilities (Donders, 1994; Perrot et al., 1991). Results were not significantly different between 3 months and 1 year post-injury.

Ewing-Cobbs, Miner, Fletcher, and Levin (1989) examined intellectual, motor, and language functioning in preschoolers who sustained closed head injuries. The children ranged in age between 4 months and 5 years at the time of injury. Assessment was conducted at least 6 months following the time of injury with a mean injury-test interval of 8.3 months. The mean age at the time of assessment was 32.7 months. Injury severity was assessed using the GCS score, duration of impaired consciousness, and the results of computed tomography. Since the GCS was designed for use with adults it was modified for use with children in the current study. Specifically goal-directed movement (e.g. reaching for an object) was regarded as an age-appropriate substitute for obeying one-stage commands. For the verbal scale, inappropriate responding was considered to have occurred when the infant cried and appeared confused or cried to indicate needs. Appropriate responding was determined to have occurred if the infant babbled or attempted to communicate through gesture or verbal means. Severity of injury was grouped into mild-moderate and severe categories. Children in the mild-moderate group served as the comparison group. The mild-moderate group was composed of 8 children exhibiting impaired consciousness for less than 24 hours and with GCS scores ranging from 9 to 15. The severely injured group was composed of 13 children who exhibited impaired consciousness for at least 1 day. GCS scores ranged from 3 to 8 for 11 of the severely injured children. Two severely injured children had GCS scores between 9 and 12 but demonstrated deterioration after hospital admission.
Intellectual abilities were assessed with the Bayley Scales of Infant Development Mental Scale and the Stanford-Binet Intelligence Scale for children between the ages of 4 and 42 months. The McCarthy Scales of Children’s Abilities were used for children between the ages of 42 and 72 months. Children with severe injuries performed significantly below children with mild-moderate injuries at baseline and during the follow-up evaluation with an average of 21-point difference between the 2 groups at the 8-month follow-up. When comparing children less than 31 months and children between 31 and 64 months (separation occurred based on a median split) it was found that there were no age differences with regard to intellectual functioning for either mild-moderately injured or the severely injured children. The language and motor findings are presented below.

Recovery of memory in children with acute head injury was assessed by Ewing-Cobbs, Levin, Fletcher, Miner, and Eisenberg (1990). The participants in the study were 37 children and adolescents between the ages of 4 and 15 years. Verbal and nonverbal memory functions were evaluated after resolution of posttraumatic amnesia as well as 6 and 12 months after injury. Verbal memory was assessed with the Selective Reminding Test and nonverbal memory was assessed using the Nonverbal Selective Reminding Test. Selective Reminding results were found to increase from the time at which posttraumatic amnesia had resolved and 1 year later. Children with left hemispheric injuries had relatively lower scores in verbal selective reminding than children with lesions to other areas or global injury. In general, children with shorter duration of posttraumatic amnesia demonstrated fewer verbal and non-verbal memory difficulties. It was found
that duration of posttraumatic amnesia was more predictive of verbal and non-verbal selective reminding at 6 months and 1 year than was the Glasgow Coma Score.

Levin, Fletcher, Kusnerik, Kufera, Duffy, Chapman, Mendelsohn, and Bruce (1996) examined semantic and episodic memory following closed head injury in 77 children between the ages of 5 and 16 years at the time of injury. The children’s lowest post resuscitation GCS score determined injury severity. The children were assessed at 3 and 12 months post-injury. Results of functional ability for participants in the study were compared with age matched controls. Semantic memory was assessed by evaluating category fluency, word fluency, semantic clustering on the California Verbal Learning Test, semantic verification accuracy and latency, and the Vocabulary subtest on the WISC-R. Episodic memory was assessed by examining the total recall, short delay recall, and long delay recall of the Monday list on the California Verbal Learning Test. Children who had sustained a serious head injury demonstrated significantly impaired performance on the semantic verification task only. These deficits were present at 3 and 12 months. Additionally, there was a significant effect of age at time of injury on all of the memory measures for children who sustained a severe head injury, with younger children performing more poorly on all tasks. There was no evidence of semantic or episodic memory deficits in children who sustained a mild closed head injury when compared to normal control children.

In a study of intellectual functioning and memory outcome designed to examine age effects, Levin, Eisenberg, Wigg, and Kobayashi (1982) studied groups of children and adolescents with sustained head-injury. The children and adolescents sustained similar levels of injury severity and type of injury (e.g. focal brain injury). In the study
there were 30 children (age range 5-12 years) and 30 adolescents (age range 14-19 years). For each group there were 15 children who suffered mild injury and 15 who sustained severe injury as indicated by the GCS (> 8 = mild, < 9 = severe) and duration of impaired consciousness. On all measures, duration of impaired consciousness was found to be predictive of outcome whereas the GCS score was not predictive.

It was found that the number of severely injured children and adolescents whose scores were significantly discrepant from normative controls of similar age was proportionally greater with regard to deficits in measures of verbal memory and visual recognition memory than mildly injured participants. Children, but not adolescents, with severe head injury exhibited long-term residual effects in recognition memory. Intellectual abilities assessed with the age appropriate Wechsler Intelligence Scale revealed that injury severity correlated with verbal intellectual abilities and that this correlation was stronger for children than for adolescents. Whereas 5 out of 15 severely injured children demonstrated long-term verbal intellectual deficits with standard scores below 80, all of the severely injured adolescents recovered to a higher level with standard scores of 80 or above. The authors suggested that children may be more affected by severe brain injury than adolescents because visual recognition and several aspects of intellectual ability develop during childhood and diffuse cerebral insult may impair newly developing skills.

Levin, High, Ewing-Cobbs, Fletcher, Eisenberg, Miner, and Goldstein (1988) further studied age effects on memory by following three groups of children who had suffered a closed head injury (6-8 years, 9-12 years, and 13-15 years). The children in these age ranges with mild/moderate injury as measured with the GCS were compared to
children with severe injury both at the time of injury and 1 year later. It was found that severity of injury was related to level of continuous visual recognition memory at baseline and follow-up in both children and adolescents. No age-related differences were found for continuous visual recognition memory. Impairment of verbal memory was also correlated with injury severity for children and adolescents. Lower verbal memory scores were found for adolescents at baseline than for children although this difference was not significant at the 1-year follow-up. Lag in word recognition, however, was demonstrated for severely injured adolescents and was not present for children, leading to the hypothesis that “the late maturation of semantic organization as a mnemonic strategy contributed to the vulnerability of the adolescents and mitigated the impairment exhibited by children. According to this interpretation, it is anticipated that the severely injured children will have difficulty developing semantic organizational skills as they enter adolescence.”

A study conducted by Ewing-Cobbs, Thomson, Miner, and Fletcher (1994) examined the effects of age at time of injury for 13 children and adolescents who sustained gunshot wounds. Children were placed into age categories with a younger group of 7 children aged 1.5 to 4 years and an older group of 6 children aged 5 to 14 years. At a 3-year follow-up it was found that 85% of the children and adolescents had moderate disabilities and 8% had severe injuries. Results of the neuropsychological tests revealed that significant and persistent deficits varied with the child’s developmental level at the time of injury. Intellectual functioning was more impaired in children under 5 years of age than in older children and adolescents. Additionally, younger children experienced greater deficiencies on measures of expressive language and gross motor
functioning. Disability in older children and adolescents, however, was primarily associated with impaired attention, adaptive behavior deficits, and behavioral disturbance rather than impaired intellectual function or expressive difficulties.

Korkman, Kirk, and Kemp (1998) examined neuropsychological functioning in head injured children using the NEPSY Developmental Neuropsychological Assessment. The NEPSY was administered to a sample of 8 children with closed head injury. Performance was compared to a group of control children matched for gender, age, parent education, and race/ethnicity. Brain injured children with a GCS score of 9-12 at admission or 13-15 at admission coupled with the presence of CT or MRI scan abnormality, a skull fracture, or a duration of impaired consciousness lasting more than 24 hours were classified as moderately injured. Brain injured children with a GCS score equal to or less than 8 at admission, or duration of impaired consciousness lasting more than 24 hours were classified as severe. Children were assessed between 5 and 28 months following the injury \( (x = 13 \text{ months}) \). For both moderately and severely brain injured children, NEPSY scores in four of the five domains (attention/executive, language, sensorimotor, memory and learning) were significantly impaired with performance more than two standard deviations below the mean for the standardized sample. The visuospatial domain demonstrated a trend toward significance (Korkman, Kirk, & Kemp, 1998).

To summarize intellectual and memory findings, research indicates that intellectual and memory functions in children are impaired as a result of sustaining a closed head injury. Specifically, intellectual full-scale, verbal, and non-verbal intellectual abilities, short-and long-term memory functioning, academic performance, and adaptive problem
solving become impaired, particularly for children with severe injury. For most areas of intellectual and memory abilities, younger children appear to be at greater risk of experiencing long-term sequelae.

*Linguistic deficits*

Ewing-Cobbs, Miner, Fletcher, and Levin (1989) studied 21 infants and preschoolers, 13 of who had severe injuries and 8 with mild to moderate injuries. It was found that intellectual level improved over time and was higher for mild/moderate children than for severe children at follow-up. With regard to language functioning, in the same study Ewing-Cobbs and colleagues found that severely injured children demonstrated impaired expressive and receptive language skills, relative to the mild to moderate head injury group on both the initial and follow-up exams. For head injured children, expressive language scores were below receptive language scores at baseline. At the 6-month follow-up expressive language skills had improved, so that expressive and receptive language skills were no longer discrepant. Ewing-Cobbs and coworkers interpreted this initial disparity in receptive and expressive skills as consistent with the vulnerability of more rapidly developing skills (i.e., expressive language, as compared to the firmly established receptive abilities). This pattern of language recovery in infants and preschoolers parallels the findings in school-aged children, which reflects greater vulnerability of expressive than receptive language (Ewing-Cobbs et al., 1987). To examine the effects of age at injury, the brain-injured children were divided into two groups: those older than 31 months and those younger. It was revealed that expressive language was lower in the younger group than in the older children at baseline and
follow-up. Although receptive skills were also lower in the younger group at baseline, there was no age effect at follow-up.

To examine the effects of linguistic disturbances (i.e. dyscalculia, dysgraphia, and difficulty spelling) in older children, Ewing-Cobbs, Levin, Eisenberg, and Fletcher (1987; cited in Levin, Ewing-Cobbs, & Eisenberg, 1995) administered the Neurosensory Center Comprehensive Examination for Aphasia (NCCEA, Spreen & Benton, 1969) to 23 children (age 5-10 years) and 33 adolescents (age 11 to 15 years) who had sustained closed head injuries. It was found that a direct relationship existed between severity of injury and impaired performance on the NCCEA measures. Expressive functions (i.e., visual naming, sentence repetition, word fluency, and writing to dictation) were more affected by level of injury severity than were receptive functions. There was no relationship between injury severity and receptive language functions. When the performance of head injured children was compared to the performance of head injured adolescents, it was found that the expressive skill of writing to dictation was significantly more affected in children than in adolescents. Whereas expressive skills of visual naming, sentence repetition and word fluency are fairly established by the age of 5 years, the skill of writing develops most rapidly between the ages of 6 and 8 years. Thus, the increased impairment of writing fluency for children between the ages of 5-10 years as compared to adolescents was interpreted as indicating that emerging linguistic skills are more vulnerable to the effects of head injury than abilities that are more firmly established at the time of the injury.

A study by Dennis and Barnes (1990) found that pragmatic communication (discourse) becomes impaired as the result of closed head injury that occurred in children
between the ages of 2 and 19 years (x = 9.2, SD = 5.14). The children were assessed approximately 3 years following the injury (SD = 1.99, range = 0.91 to 9.25). Both pragmatic and social communicative language skills were assessed by examining the ability to recognize and interpret two distinct meanings from a single sentence, the ability to interpret metaphors within a situation, the ability to make an inference when given two causally connected events, and the ability to produce a sentence given two or three words and a picture conveying context. It was found that 79% of the participants demonstrated impairment on at least one of the four discourse tasks. Notably, word naming ability was not impaired in the children who demonstrated discourse deficits. However, impairment in the ability to find multiple meanings to one word was correlated with discourse difficulty. Similarly, Jordan, Murdoch, and Buttsworth (1991) studied the ability for children with a history of closed head injury to communicate narrative stories. The children in the study ranged from 5 years to 13 years at the time of injury and were evaluated for communication difficulties 3 years after the injury. This age range was selected because 5 year olds are thought to have acquired the majority of language structures used for mature oral communication. The upper limit of 13 years was selected because after the age of 13 years, many new metalinguistic skills are utilized which advance pragmatic language functions, which could confound results of examining narrative language structure. Scores achieved on the GCS determined severity of injury. Interestingly, the authors did not find differences between mildly and severely head injured children. They attributed the difference between their findings and the findings in other studies to the fact that their procedure allowed the children to generate their own stories that allowed the children to demonstrate typical performance. The authors
suggested that other studies evaluate optimum performance by providing more structured assignments that may require the child to demonstrate a goal-based sequence of events. It appears that the difference may stem from other studies examining metacognitive abilities associated with narrative discourse.

Dennis, Barnes, Donnelly, Wilkinson, and Humphreys (1996) conducted a study examining the ability to analyze and use metacognitive abilities to repair semantic-pragmatic anomalies. The participants in the study were 111 children and adolescents who had sustained a closed head injury and age matched controls. The age at the time of injury ranged from 1.33 years to 15.67 years ($x = 7.98$, SD = 3.33). Children were stratified into five groups according to age at time of testing: 6-7 years, 8-9 years, 10-11 years, 12-13 years, and 14-15 years. Time of testing was at least 6 months following injury. It was found that younger children (age 6-7 years) were less able than older children (age 8-15 years) to evaluate unambiguous directions in both head injured and non-head injured groups. Additionally, the ability to appraise sentences structure correlated with increasing age in both head injured and non-head injured groups. Age effects with regard to these abilities were deemed to be developmentally appropriate and not related to injury. Also, head injured children were as accurate as non head injured children in recognizing well-formed and unambiguous instructions, suggesting that difficulties did not stem from problems with language comprehension or possession of the necessary knowledge base. However, head injured children demonstrated poorer performance in the ability to engage in sustained cognitive appraisal where they actively repair a semantic-pragmatic anomaly. This suggested that metacognitive abilities were impaired. Mild to moderate injury as assessed with the GCS was associated with
relatively good preservation of metacognitive abilities. Head injury involving frontal lobe injury, bilateral damage, or coup-contra coup contusions were associated with poor metacognitive performance. Also, left-sided contusion was associated with poorer metacognitive abilities.

To summarize language findings, studies indicate that children who sustain closed head injuries suffer expressive and receptive language impairment, with greater impairment evidenced for expressive language abilities. Expressive impairment may include difficulties in social communication and the ability to evaluate metaphors and multiple meanings of speech.

**Planning and attention**

Kaufman, Fletcher, Levin, Miner, and Ewing-Cobbs (1993) examined whether age would influence the extent of attention deficits in children (age 7-21 years) who had sustained closed head injury 6 months prior. To assess attention a computer-based adaptive-rate continuous performance test was administered. This assessment required that the child press a response key as quickly as possible to the onset of a particular target while withholding a response to non-target stimuli. The assessment was designed to modify the rate of presentations of targets and distracters based on the rate and accuracy of responding. It was found that severity of injury predicted the extent of attention deficits. Additionally, after standardizing results according to age-norms, it was found that younger children were significantly more likely to sustain attention deficits than older children. These researches also examined the effects of injury on the Wechsler
Digit Span subscale, a subtest thought to assess attention, and did not find a significant correlation.

Planning, problem solving, response modulation skills, and conceptual productivity were assessed in 81 children who sustained a closed head injury (Levin, Fletcher, Kufera, Harward, Lilly, Mendelsohn, Bruce, & Eisenberg, 1996). The children in the study ranged in age from 5 to 16 years (\(x = 10.5\) years). The scores for brain-injured children were compared with age matched normal control children. Severity of injury was measured using the lowest post resuscitation GCS and children were categorized as having mild, moderate, or severe brain injury. Several cognitive tasks were administered to assess cognitive functioning. These tasks were factor analyzed and resulted in five factors that significantly accounted for the variance in injury severity. The factor with the greatest contribution was that of conceptual productivity which accounted for 40.8% of the variance. Tasks that loaded on this factor included the Wisconsin Card Sorting Test, verbal fluency, and design fluency. The second factor represented planning-execution functions, which accounted for 11.5% of the variance. Tasks that loaded on the factor included Tower of London variables of percentage of problems solved within three trials, and number of broken rules. Factor 3 accounted for 10% of the variance and was termed ‘schema’. This factor appeared to represent the ability to create a mental representation of the task and store that representation in working memory. This factor included the percentage of Tower of London problems solved on Trial 1 and the percentage of constraint-seeking questions asked (i.e., questions that eliminated more than one alternative) on the Twenty Questions Test. Factor 4, termed ‘cluster’ consisted of the ability to strategically organize semantically related
words during recall on the California Verbal Learning Test. The fifth factor appeared to represent inhibitory processes and consisted of the initial planning time on the Tower of London and the number of false alarm errors on the Go/No-Go task. Factor 5 accounted for 7.1% of the variance. This five-factor solution accounted for 79% of the variance in test scores. While there was shared variability, the factor analysis appeared to identify separable dimensions. Severity of Injury significantly predicted deficits for Factor 1 (conceptual productivity), Factor 2 (planning), Factor 4 (cluster), and Factor 5 (inhibition). Age at testing significantly predicted deficits for Factor 1, Factor 2, and Factor 5. There were no significant age by severity effects.

To summarize executive functioning findings, research indicates that attention difficulties result from sustaining a closed head injury, with younger children sustaining greater impairment than older children. Additionally, the ability to plan, problem solve, modulate responses, and conceptualize alternative solutions may become impaired as a result of injury.

**Visuospatial and sensorimotor abilities**

Visuospatial and sensorimotor functioning have been found to be negatively affected in children who sustain closed head injuries. Klonoff, Low, and Clark (1977) studied a group of 131 children (younger than 9 years, \( \bar{x} = 5.87 \) years) and 100 adolescents (9 years and older, \( \bar{x} = 11.53 \) years) recovering from a sustained head injury. At the time of injury the children ranged between 2.7 years old and 15.9 years old. Severity of head injury was determined according to length of loss of consciousness and evidence of concussion. The first assessment of brain injured participants occurred at the
time of injury. Participants were then assessed at one-year intervals for a period of 5 years. The scores of head injured children were compared with standardized norms and with age/gender-matched controls. Neuropsychological functioning was assessed with the Reitan-Indiana Neuropsychological Test Battery for Children, two of Benton’s tests, a lateral dominance test, the Stanford Binet Form L-M for children (under 5 years), or the Wechsler Intelligence Scale for Children (5 years and older), and the Klove Motor Steadiness Battery for children older than 9 years. When comparing findings across all years, children and adolescents with head injuries demonstrated significantly impaired performance on most measures when compared to matched controls. At the time of injury children demonstrated significant impairment in 29 of the 32 tasks attempted including finger tapping, trail making, marching, TPT, right-left orientation, lateral dominance, and full-scale intellectual achievement. Similarly, at the time of injury, adolescents demonstrated significant impairment in 43 of the 48 tasks they completed including finger tapping, trail making, marching, TPT, right left orientation, maze coordination, grooved steadiness, steadiness, grooved pegboard, foot tapping, and full-scale intellectual achievement. Both children and adolescents demonstrated significant recovery over time. For children, psychomotor and sensorimotor deficits were largely resolved by approximately 3 years following the injury. For adolescents, most psychomotor and sensorimotor deficits resolved by two years following the injury. However deficits in lateral dominance, grooved steadiness, and foot tapping were evidenced at the five-year assessment. There were no significant differences between children and adolescents with regard to extent of impairment or improvement over time.
Bawden, Knights, and Winogron (1985) examined motor functioning in 51 head-injured children. At the time of injury children ranged in age from 2.5 years to 17.3 years with mean ages of 9.4 for mildly injured children, 9.5 for moderately injured children and 9.6 for severely injured children. Level and duration of consciousness as rated with the GCS determined injury severity. Children with a GCS score of 7 or less were classified as severely injured. Children with a GCS score between 8 and 14 were classified as either moderately injured or mildly injured depending on duration of unconsciousness 'neurological indices of the severity of brain damage'. Ages at the time of testing ranged from 4.7 to 17.6 years with a duration of time between injury and testing ranging from 1 year for mildly injured children, 0.9 years for moderately injured children, and 1.1 years for severely injured children. Twenty-five measures of motor and visual-spatial skills were administered. Tasks were divided into groupings according to whether successful performance required a high, moderate, or low degree of response speed. Highly speeded tasks included the Finger-Tapping Test, Foot-Tapping Test, Pegboard Test-Time, and the WISC-R Coding subtest. These measures assessed fine motor control, psychomotor speed, and/or visual-motor coordination. Moderately speeded tests included the WISC-R Block Design subtest, WISC-R Object Assembly subtest, WISC-R Picture Arrangement subtest, Maze Test-Timer, and the Maze Test-Counter. These measures assessed analysis and synthesis of visual-spatial information, visual-motor coordination, visual memory, nonverbal reasoning and planning, visual memory, and gross motor steadiness and control. Low speeded tests included the Target Test, Developmental Drawings, Dynamometer, Holes Test-Timer, and the Pegboard Test-Errors. These
measures assessed visual-spatial ability, visual memory, grip strength, fine motor steadiness and control, and visual-motor coordination.

Researchers found that severely injured children had significantly lower performance intellectual functioning scores on the WISC-R than the mildly and moderately head injured children. There were no significant differences between mildly, moderately, and severely injured children on verbal intellectual functioning performance scores of the WISC-R. The severely head injured group had particular difficulty with the Coding subtest of the WISC-R. Based on composite scores for performance across different motor tests in each of these areas, severely injured children were more impaired on highly speeded tasks. Other tasks requiring manual dexterity were also affected (i.e., moderately speeded tasks of Picture Completion and Block Design subtests on the WISC-R, and all Maze Tests). Injury severity was not predictive of performance on low speed tasks. Task requirements for motor speed did not seem to influence the performance of children with mild and moderate injuries. Similarly, Chadwick, Rutter, Shaffer, and Shrout (1981) examined motor functioning tasks that required rapid responding and found that finger tapping and manual dexterity deficits were evidenced at the time of injury, at one-year and two-years.

In the study summarized above conducted by Fay et al. (1994) that examined intellectual functioning in 103 children who experienced closed head injury between the ages of 6 and 15 years, motor and sensorimotor abilities were also evaluated. Motor functioning was evaluated by subtests of coding on the WISC-R/WAIS-R, name writing, finger tapping speed, grip strength, and the Woodcock Johnson Scale of Independent Behavior gross and fine motor subtests. These measures are designed to evaluate
speeded motor responses and strength. Sensorimotor abilities were assessed with the Tactual Performance Test that evaluates tactile-kinesthetic problem solving ability involving visual memory, location determination, and speed of responding. Significant delays were evidenced on the coding subtests, tapping speed, and the Woodcock-Johnson gross and fine motor scales. On the Tactual Performance Test only the speed aspect was significantly affected.

Another study cited above by Kinsella et al. (1995) examined visuospatial learning and speed of visuomotor information processing in addition to examining intellectual and academic functioning. As indicated, the study included 51 children who were between the ages of 9 and 15 years at the time of injury. The GCS was used to assess injury severity. Measures of visuospatial and visuomotor functioning were assessed at 3 months and again at 1 year post-injury. There was a significant injury effect for both visuospatial and visuomotor functioning with greater injury severity resulting in greater impairment. Results were not significantly different between the 3-month assessment and the 1-year follow-up.

In one other study cited above, Ewing-Cobbs et al. (1989) assessed neurobehavioral sequelae following brain injury in 21 infants and preschoolers between the ages of 4 months and 5 years at the time of injury. Part of the study included an assessment of motor functioning at the time of injury and at a follow-up period that occurred at least 6 months ($\mu = 8.3$ months) following the injury. Of the 21 children, 13 were classified as having a severe injury and 8 were classified with mild to moderate injury. Motor abilities were assessed with the Bayley Scales of Infant Development Motor Scale for children between the ages of 4 and 42 months and with the McCarthy
Motor Scale for children between the ages of 42 and 72 months. It was found that severely injured children demonstrated greater impairment in motor functioning at the baseline assessment and at the follow-up when compared with mild-moderately injured children. Notably, performance for the entire group of head injured children improved substantially over time although the severely injured children remained significantly impaired relative to mild-moderately injured children.

To summarize visuospatial and sensorimotor findings, studies indicate that children who sustain a closed head injury may have visuospatial orientation and information processing impairment. Additionally, sensorimotor functioning, particularly on highly speeded tasks and tasks requiring manual dexterity may become impaired as a result of injury.

In most of the studies outline above that demonstrate intellectual and neuropsychological functioning impairment resulting from closed head injury in children, injury severity was assessed utilizing the GCS. Typically, children were usually divided into two groups for outcome assessment, children with severe injury, and children with mild/moderate injury. Additionally, outcome assessment was typically conducted between 6 months and 1 year. In summary, studies indicate significant impairment to intellectual, memory, linguistic abilities, planning and attention abilities, visuospatial skills, and sensorimotor abilities when a child sustains a closed head injury, particularly if that injury is severe.
Potential Covariate Main Effects: Duration of Time since Injury and Age at Injury

Younger children have been found to be at greater risk than older children who suffer a head injury on several tasks including those requiring memory, attention, response modulation, planning, rule-governed behavior and language (Fletcher et al., 1987; Kaufmann et al., 1993; Levin, et al., 1993; and Levin et al., 1994). The hypothesis generated for the findings that younger children demonstrate greater deficits than older children is that brain injury is most likely to cause an interruption in newly developing skills and impairs the development of later skills while leaving previously developed skills relatively intact (Donders, 1994; Perrot et al., 1991).

Bijur, Haslum, and Golding (1990) found that age at the time of injury was predictive of mathematics achievement as measured by the Friendly Math Test. The children in their study were assessed at the age of 5 years and again at the age of 10 years. It was found that children who were between the ages of 5 and 8 years of age at the time of injury had significantly lower math scores than children who were injured between the ages of 8 years and 10 years. It is possible that experiencing injury between the ages of 5 and 8 years results in greater deficit because math skills assessed by the Friendly Math Test (i.e., knowledge, concepts, and applications in arithmetic, geometry, algebra, and statistics) are developing during these years. Intelligence as measured by the Word Definitions, Recall of Digits, Similarities, and Matrices subtests of the British Abilities Scale did not show age-related deficits. Also, reading skills, as measured by the Einburgh Reading Test, and vocabulary, measured by the Child Health and Education Study Language Pictorial Comprehension Test, did not show age related deficits.
Few studies were found in the literature that followed children and adolescents with head injury over time. The studies located indicated that deficits related to sustaining a traumatic brain injury are most apparent within the first one- to two years following injury.

A series of longitudinal studies conducted by Fay, Jaffe and colleagues (Jaffe et al., 1992; Jaffe, Fay, Polissar, Martin, Shurtleff, Rivara, & Winn, 1993; Fay et al., 1994; Jaffe et al., 1995) examined children with sustained closed head injury at 3 weeks, 1 year, and 3 years following resolution of post-traumatic amnesia. The 72 children in the studies ranged in age between 6 and 15 years at the time of injury. Assessment consisted of examining intellectual functioning (WISC-R/WAIS-R), adaptive problem solving (Trails B), memory (Category Test, California Verbal Learning Test), academic performance (Wide Range Achievement Test-Revised), Motor performance (Coding, Name-writing, Tapping, Grip strength, Woodcock-Johnson Scale of Independent Behaviors fine and gross motor subscales), psychomotor problem solving (Tactual Performance Test), independent living skills (Woodcock-Johnson Scale of Independent Behaviors), parent’s rating of social, educational, and behavioral status (Child Behavior Checklist), and teacher’s ratings of social, educational, and behavioral status (Child Behavior Checklist, Teacher Report Form). For analysis of change over time, scores within each of the 10 domains were transformed into z-scores and then combined. Trend analysis was used to examine case-controlled paired differences over time.

Three patterns emerged with regard to improvement over time. For performance intellectual functioning, adaptive problem solving, memory, and motor performance, the moderately and severely injured demonstrated greater impairment than mildly injured
children but performance for moderately and severely injured groups did increase significantly over one year. However, significant improvement was not indicated between 1 and 3 years. A second pattern was evidenced for verbal intellectual abilities and academic performance deficits. These were significantly lower for moderately and severely injured children and remained stable at 3 weeks, 1 year, and 3 years with little improvement. The third pattern was evidenced for psychomotor performance and independent living skills where initial differences were demonstrated only for the severely injured children and differences disappeared by the 3-year follow-up.

Klonoff et al. (1977) assessed neuropsychological improvement over a 5-year period. As indicated above, these researchers studied a group of 131 children (younger than 9 years, \( \bar{x} = 5.87 \) years) and 100 adolescents (9 years and older, \( \bar{x} = 11.53 \) years) recovering from a sustained head injury. At the time of injury the children ranged between 2.7 years old and 15.9 years old. Severity of head injury was determined according to length of loss of consciousness and evidence of concussion. The first assessment of brain injured participants occurred at the time of injury. Participants were then assessed at one-year intervals for a period of 5 years. The scores of head injured children were compared with standardized norms and with age/gender-matched controls. Neuropsychological functioning was assessed with the Reitan-Indiana Neuropsychological Test Battery for Children, two of Benton’s tests, a lateral dominance test, the Stanford Binet, form L-M for children under 5 years of age, or the Wechsler Intelligence Scale for Children for children older than 5 years, and the Klove Motor Steadiness Battery for children older than 9 years.
Additionally, in the study cited above (Bijur et al., 1990) it was found that mathematic skills improve as the duration of time since injury lengthens.

When comparing findings across all years, children and adolescents with head injuries demonstrated significantly impaired performance on most measures when compared to matched controls. At the time of injury, children demonstrated significant impairment in 29 of the 32 tasks attempted including the psychomotor and sensorimotor tasks outlined above, intellectual ability, the injury, 13 tasks at two years following injury, 5 tasks at three years, 4 tasks at four years, and on one measure, intellectual achievement, at five years following injury. When examining improvement over time for adolescents, significantly impaired performance was demonstrated on 31 tasks one year following injury, 15 tasks at two years following injury, 12 tasks at three years, 8 tasks at four years, and 6 tasks, including measures of grooved steadiness, maze coordination, foot tapping, and intellectual achievement, at five years following injury. Statistical analyses were not conducted to determine whether improvement demonstrated an observable trend. Visual inspection of the data appears to suggest that most recovery was evidenced by two years for children and adolescents. However, recovery was still apparent at the fourth and fifth year of testing with only intellectual ability level being substantially impaired by the fifth year following injury for both children and adolescents.

Taken together, it appears that age of the child at the time of injury may significantly affect degree of impairment, with younger children demonstrating greater deficits as a result of sustaining a head injury. It also appears that deficits improve over time. Thus, duration of time since the injury may moderate the findings of
neuropsychological assessment, with greatest resolution of deficits occurring between 1 and 2 years following the injury.

**Exploratory Variables**

**Focal effects**

Several studies have examined the extent to which focal brain injury results in specific neurocognitive deficits. Although the brain may be functionally divided into many areas (e.g., left frontal, right frontal, left parietal, right parietal, left temporal, right temporal, occipital, basal ganglia, limbic system), most research examining focal injury in children has presented findings according to injury in three broad functional domains including frontal injury, left hemispheric injury, and right hemispheric injury.

A study cited above by Levin et al. (1996) examined the effects of focal injury on visual recognition and episodic semantic memory in 12 children between the ages of 6 and 15 years. Children in the study who sustained a severe head injury, as indicated by the score on the GCS, were assessed with an MRI scan using both sagittal and coronal images. Left hemisphere injury was found to correlate with semantic memory performance deficits. Left frontal lesion predicted category fluency at 3 months, whereas left, non-frontal lesion predicted category fluency at 12 months. Left, non-frontal injury was predictive of difficulty with semantic memory word clustering at 3 and 12 month and difficulties with semantic verification at 12 months. Vocabulary deficits were associated with right, non-frontal injury. These findings remained after controlling for age at injury and severity of impaired consciousness.

Another study by Chapman, Culhane, Levin, Harward, Mendelsohn, Ewing-Cobbs, Fletcher, and Bruce (1992) examined focal findings in expressive language. In
the study, 20 head-injured children between the ages of 9 and 18 years were assessed. The children were assessed between 1 and 5 years post injury. Eighteen of the children underwent magnetic resonance imaging that was performed within 1 month following the injury and 9 of those children demonstrated focal injury. Of the children with focal injury, four children with frontal lobe involvement were assessed. Children with frontal lobe injury generally sustained more severe acute injury compared to children who sustained extra-frontal lobe injury. Expressive language was assessed by measuring abilities in the domains of language structure, information structure, and flow of information.

Two children with left frontal lobe injury demonstrated a marked reduction in the amount of language comprehension, decreased sentence length and complexity, and a diminished ability to provide the gist of the story and essential story components. Verbal fluency was relatively intact, however. One child with left and right frontal lobe injury demonstrated no reduction in the amount or complexity of language. However, the amount of story information was reduced and the story contained inaccurate information, a diminished ability to provide the gist of the story, and temporal sequencing deficits. As in the two other children, verbal fluency was intact. A fourth child demonstrated a reduction in the amount of language compared to controls although sentence complexity and length were preserved.

A study cited above by Levin, et al. (1996) examined the effects of planning, problem solving, response modulation skills, and conceptual productivity in a subset of children with focal injury. As indicated, children in the study ranged in age from 5 to 16 years (x = 10.5 years). Focal injury that occurred in the frontal or extrafrontal regions
was assessed to determine if location of injury increased outcome prediction. Outcome was assessed according to factors scores along five dimensions (i.e., verbal fluency and design fluency, planning and executive functions, schema, or, mental representation of problem, cluster, or, ability to semantically organize related words, and, inhibition). More information regarding selection of factors is described above. The presence of frontal lobe injury, either left or right, was correlated with factor 2 (planning). The presence of left (but not right) frontal and extrafrontal lobe lesion was correlated with factor 3 (schema). The findings suggest that left hemisphere abnormality is predictive of deficits in cognitive variables. Frontal lesions in either hemisphere predicted semantic clustering.

In the study conducted by Levin and his colleagues (1996), seventy-six head-injured children and adolescents were assessed for neuropsychological deficits following closed head injury. The children in the study ranged from 6 to 16 years at the time of testing and were assessed 3 or more months following the date of injury. Injury severity was assessed with the GCS. Children with a GCS score equal to or lower than 8 were given a severity level of ‘severe’ and children with a score of more than 8 were given a severity level of ‘mild’. Of the seventy-six children, 57 patients had focal areas of abnormal signal on MRI images. Twenty children had areas of abnormal signal confined to the frontal region (seven unilateral left, six unilateral right, seven bilateral). Eleven patients had predominantly frontal abnormalities (four left hemisphere, two right hemisphere, five bilateral) which extended to an extrafrontal region. Together these 31 children with frontal injury comprised 40% of the total sample. Another group of 11 children had predominantly extrafrontal (two left hemisphere, nine bilateral)
abnormalities (five temporal, five parietal, and one basal ganglia) lesions that moved toward or into frontal areas. Fifteen patients had areas of abnormal signal confined to an extrafrontal region (six left hemisphere, nine right hemisphere) that involved the temporal lobe (n=5), parietal lobe (n=6), and occipital lobe (n=4).

It was found that the presence of a frontal lesion improved prediction of verbal fluency scores after controlling for GCS scores. A trend for significance was demonstrated for memory and response modulation. Further analysis revealed that left frontal lesion was associated with concept formation-problem solving skills on the WCST and response modulation (trials to reach criterion on the Go-No Go Task). Left frontal lesion was also associated with verbal fluency and response modulation. Right frontal lesion size was correlated with verbal fluency, semantic clustering on the CVLT, and response modulation on the Go-No Go Task. The presence of extrafrontal lesions was not correlated with increased prediction on any of the cognitive tasks. With regard to specific frontal regions, an orbital lesion (i.e., rectal, orbital, and/or inferior frontal gyri) increased the predictive power over the GCS on measures of verbal fluency. A trend toward significance was evidenced with planning as measured by the Tower of London.

Importantly, area of injury may result in different deficits for children as compared to adults, particularly for linguistic deficits. Stiles and colleagues followed a group of children who has sustained focal brain injury before or around the time of birth and the long-term effects on linguistic and spatial cognitive development (Stiles, 1998). The children were assessed on or before their first birthday and followed longitudinally. It was found that early deficits occurred in the areas of both language and spatial cognition. During early stages of language acquisition (between 10 and 17 months),
comprehension deficits were more common with right-hemisphere injury than left-hemisphere injury. Children with left posterior temporal injury were delayed in word production but not comprehension. The delays were present into the 4th year but resolved by the age of 5 years. This finding contrasted to the profile of deficits demonstrated in adults where damage to the left posterior temporal area leads to impaired comprehension rather than production. Stiles suggested that the data indicate that language acquisition may depend on different neural structures than the structures used by proficient language users. Regardless of the lesion site, however, children developed normal or near-normal levels of linguistic proficiency.

With regard to spatial cognition, as measured by the ability to engage in part-whole processing, injury to the left posterior region of the brain was associated with difficulty of segmenting a pattern into a set of constituent parts. Injury to the right posterior area of the brain resulted in difficulty integrating the parts into wholes. Findings with children were shown to be similar to those evidenced by adults with regard to lesion location suggesting that similar structures may be used throughout development.

**Non-accidental trauma compared with accidental closed head injury**

In a review of epidemiological studies of head injury in children conducted during the last 15 years Krause (1995) found that between 2 and 10 percent of head injury cases reportedly resulted from inflicted injury through assault or abuse. Often non-accidental trauma occurs when an infant or child has been repeatedly shaken forcefully and has suffered from blunt forces being inflicted to the head. The resulting injury may include
retinal, subdural, and/or subarachnoid hemorrhage and is commonly referred to as “shaken baby syndrome” (Caffey, 1972; Hadley, Sonntag, Rekate, & Murphy, 1989).

Researchers and clinicians have hypothesized that children who suffer from a non-accidental head trauma may experience more serious neurological impairment (Bruce, 1995; Goldstein, Kelly, Bruton, & Cox, 1993; Ewing-Cobbs, Duhaime, & Fletcher, 1995). There is a greater incidence of non-accidental trauma occurring with infants and younger children than for older children and adolescents (Hahn, Raimondi, McLone, & Yamanouchi, 1983; Duhaime, Alario, Kraus, Rock, & Hemyari, 1990). The infant brain is more vulnerable to repeated acceleration and deceleration forces that commonly occur when a non-accidental trauma is inflicted on a child (Hadley, Sonntag, Rekate, & Murphy, 1989). Additionally, there is often a delay in seeking medical care. When the child of suspected abuse is brought in for medical treatment, injury may not be obvious and the nature and extent of injury may be minimized (Ward, 1999). These findings lead Ewing-Cobbs, Duhaime, & Fletcher (1995) to hypothesize that “the less favorable neurobehavioral outcome frequently identified in infants and preschoolers in relation to that in other pediatric age groups is likely due to the high rate of inflicted injury in young children” (p.22).

One study located in the literature examined the extent of neuropsychological injury and neurological outcome in children who had experienced accidental and non-accidental head injury (Goldstein, Kelly, Bruton, & Cox, 1993). Thirty-five percent of the 40 children in the study suffered from non-accidental injuries. All of the children were assessed for extent of injury and outcome at the time of hospital discharge. It was found that children with inflicted head injuries were younger than children of accidental
traumas. Mortality rates were greater in children with inflicted injuries as compared to children who suffered from accidental injuries (36% vs. 12% respectively). Additionally, children who suffered from non-accidental injuries experienced more severe injuries and greater neuropsychological impairment than children who suffered from accidental trauma (57% vs. 38% respectively).

Yet, studies comparing the long-term effects of accidental and non accidental trauma are significantly limited, leading Ewing-Cobbs, Duhaime, and Flecher (1995) to suggest that “long-term follow-up of children with inflicted and noninflicted injuries is particularly important” so that appropriate intervention can be developed (p. 22).

Hypotheses

Prediction of intellectual and neuropsychological deficit

1) As indicated in previous research, it was hypothesized that clinical data including EEG reading, the GCS score, presence of non-reactive pupils on admission, number of days unconscious at the time of imaging, and cardiac arrest correlates with deficits in intellectual and neuropsychological functioning 1-7 years later. Specific areas of neuropsychological impairment hypothesized to correlate with these clinical indicators of childhood brain injury included memory, linguistic, planning and attention, visuospatial and sensorimotor abilities.

2) It was hypothesized that a decrease in $^1$H-MRS metabolite ratios (NAA/Ch, NAA/Cr) in injured neonates, infants, and children as well as the presence of lactate in infants and children correlates with deficits in intellectual and neuropsychological functioning 1-7
years later. Specific areas of neuropsychological impairment hypothesized to correlate with these $^1$H-MRS indicators of closed head injury include memory, linguistic, planning and attention, visuospatial and sensorimotor abilities. Testing measures utilized to assess outcome are listed below in Table 1.

Table 1

List of Clinical, Intellectual, and Neuropsychological Measures

<table>
<thead>
<tr>
<th>Injury Severity Assessment</th>
<th>Intellectual and Neuropsychological Outcome Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical severity indicators:</td>
</tr>
<tr>
<td></td>
<td>- EEG reading</td>
</tr>
<tr>
<td></td>
<td>- GCS (infants and children)</td>
</tr>
<tr>
<td></td>
<td>- Non-reactive pupils</td>
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<tr>
<td></td>
<td>- Number of days unconscious</td>
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<tr>
<td></td>
<td>- Cardiac arrest</td>
</tr>
<tr>
<td>Spectroscopy severity indicators:</td>
<td>- Luria-Nebraska Neuropsychological Battery (ages 13-19 years)</td>
</tr>
<tr>
<td>- NAA/Ch metabolite ratio</td>
<td></td>
</tr>
<tr>
<td>- NAA/Cr metabolite ratio</td>
<td></td>
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<tr>
<td>- Ch/Cr metabolite ratio</td>
<td></td>
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<tr>
<td>- Lactate presence</td>
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</table>

3) It was hypothesized that combining clinical data with $^1$H-MRS variables provides the greatest predictive power with regard to intellectual and neuropsychological functioning outcome 1-7 years following closed head injury. As was characteristic in previous research, children were divided into two groups based on severity of outcome impairment (i.e., children with functioning in the average range of functioning and children with scores below the average range of functioning) to test this hypothesis. Further regression analysis was conducted with children as a single group to determine whether more sensitive prediction estimates of outcome scores could be developed.
Covariate main effects of age at injury and improvement over time

1) Based on previous research, it was hypothesized that age of the child at the time of injury correlates with the effects of closed head injury. Specifically, younger child age will negatively correlate with greater deficits in intellectual functioning and all areas of neuropsychological functioning.

2) Based on previous research, it was hypothesized that the length of time since the injury negatively correlates with intellectual and neuropsychological functioning over time.

Covariate main effect variables and outcome measures are listed below in Table 2.

Table 2
List of Covariate Main Effects, Intellectual, and Neuropsychological Measures

<table>
<thead>
<tr>
<th>Covariate Main Effects</th>
<th>Intellectual and Neuropsychological Outcome Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at injury</td>
<td>Intellectual assessment:</td>
</tr>
<tr>
<td>Duration of time since injury</td>
<td>- Wechsler Preschool and Primary</td>
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<tr>
<td></td>
<td>Scale of Intelligence-R</td>
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<tr>
<td></td>
<td>(ages 3-6 years)</td>
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<tr>
<td></td>
<td>- Wechsler Intelligence Scale for Children-Third Edition</td>
</tr>
<tr>
<td></td>
<td>(ages 7-16 years)</td>
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<tr>
<td></td>
<td>- Wechsler Adult Intelligence Scale- Third Edition</td>
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<tr>
<td></td>
<td>(ages 17-19 years)</td>
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<tr>
<td></td>
<td>Neuropsychological assessment:</td>
</tr>
<tr>
<td></td>
<td>- NEPSY Developmental</td>
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<tr>
<td></td>
<td>Neuropsychological Assessment</td>
</tr>
<tr>
<td></td>
<td>(ages 3-12 years)</td>
</tr>
<tr>
<td></td>
<td>- Luria-Nebraska</td>
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<tr>
<td></td>
<td>Neuropsychological Battery</td>
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<td></td>
<td>(ages 13-19 years)</td>
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</table>

Exploratory moderator effects of focal injury and non-accidental injury

1) It was hypothesized that focal injury as indicated by MRI scans will correlate with specific intellectual and neuropsychological deficits. Specifically, frontal injury will correlate with impaired ability to relay the gist and temporal sequencing of a story, and
engage in appropriate planning and response modulation to tasks. Left hemispheric injury will correlate with difficulty in tasks measuring semantic memory, the ability to maintain a visual mental representation in memory and in general language abilities. Right hemispheric injury will correlate with vocabulary deficiencies and visuospatial integration deficits. Outcome measures used to assess focal findings are listed in Table 3.

### Table 3

**Outcome Measures Used to Assess Focal Findings**

<table>
<thead>
<tr>
<th>Exploratory Moderator MRI Focal Injury Location</th>
<th>Intellectual and Neuropsychological Outcome Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frontal lobe injury</strong></td>
<td><strong>Planning and Response Modulation:</strong></td>
</tr>
<tr>
<td></td>
<td>- NEPSY Attention/Executive Functions Domain</td>
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<tr>
<td></td>
<td>- Luria-Nebraska L1 Left and L5 Right Frontal Localization Scales</td>
</tr>
<tr>
<td></td>
<td><strong>Semantic Memory:</strong></td>
</tr>
<tr>
<td></td>
<td>- NEPSY Narrative Memory Subtest</td>
</tr>
<tr>
<td></td>
<td>- Luria-Nebraska C10 Verbal Memory Items (Factor ME1)</td>
</tr>
<tr>
<td><strong>Left hemisphere injury</strong></td>
<td><strong>Visual Representation Memory:</strong></td>
</tr>
<tr>
<td></td>
<td>- NEPSY Memory for Faces Subtest</td>
</tr>
<tr>
<td></td>
<td>- Luria-Nebraska C10 Visual Memory items (Factor ME2)</td>
</tr>
<tr>
<td></td>
<td><strong>General Language Abilities:</strong></td>
</tr>
<tr>
<td></td>
<td>- NEPSY Language Domain</td>
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<tr>
<td></td>
<td>- Luria-Nebraska C5 Receptive and C6 Expressive Speech Scales</td>
</tr>
<tr>
<td><strong>Right hemisphere injury</strong></td>
<td><strong>Vocabulary:</strong></td>
</tr>
<tr>
<td></td>
<td>- Wechsler Vocabulary Subtest</td>
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<tr>
<td></td>
<td><strong>Visuospatial Integration:</strong></td>
</tr>
<tr>
<td></td>
<td>- NEPSY Visuospatial Processing Domain</td>
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<tr>
<td></td>
<td>- Luria-Nebraska Visuospatial Factor Scale</td>
</tr>
</tbody>
</table>

2) It was hypothesized that suffering from non-accidental head injury will correlate with greater intellectual and neuropsychological deficits than suffering from accidental head injury.
Method

Participants

Twenty-two children between the ages of 3 years and 19 years ($x = 9.41$ years, SD = 5.55 years) who were treated for closed head injury at Loma Linda University Children’s Hospital between August 1993 and January 2000 participated in the study. The duration of time that had passed since date of injury ranged from 12 ½ months to 86 months ($x = 54.76$ months, SD = 19.03 months). Each of the children had received $^1$H-MRS and MR Imaging to assess injury severity at the time of injury. All of the children in the study sustained a closed head injury through either non-accidental trauma (9) or accidental injury (13). Children who meet criteria for the study were English speaking and living in a non-comatose state.

Procedure

Children from the list of those who were treated at the Loma Linda University Children’s Hospital for head injury between August 1993 and January 2000 were contacted to participate in the study. Of the 31 individuals who could be contacted by phone, 22 of the children (with parental consent) participated in the study. There were no significant differences between the children who participated and those who declined to participate with regard to the clinical or $^1$H-MRS with the exception of $^1$H-MRS Ch/Cr (children in the study had a higher mean Ch/Cr ratio). With regard to children who were unable to be contacted, one variable, presence of non-reactive pupils was significantly discrepant between the two groups (uncontacted children had a higher prevalence of non-reactive pupils).
Participation was voluntary and participants were given a gift certificate ($10) to participate in the study. Parents were provided with an assessment report and recommendations given assessment results. After being informed of the nature of the study, a consent form was signed by parents, or by the individuals themselves for those participants who were 18 or 19 years old. Participants’ clinical findings (i.e. EEG, GCS, presence non-reactive pupils, number of days unconscious to MR imaging, cardiac arrest), 

\(^1\)H-MRS metabolite ratios, and MRI findings from the time of injury as well as follow-up neurological examination findings were obtained from patient clinical records. Current intellectual and neuropsychological outcome assessment was conducted through the Kid’s F.A.R.E. laboratory in the Loma Linda University Department of Psychology.

Outcome assessment included a neuropsychological assessment (i.e., NEPSY Developmental Neuropsychological Assessment or Luria-Nebraska Neuropsychological Battery) and an intellectual assessment (i.e., appropriate Wechsler Intelligence scale given the participant’s age).

**Instruments**

**Assessment of injury severity and location**

**Glasgow Coma Scale** (GCS; Teasdale & Jennett, 1974). The GCS has been used to reliably assess coma and the severity of brain injury (Levin, Benton, and Grossman, 1982; Teasdale & Mendelow, 1984). It has been used extensively in research as a measure for classifying brain injury severity in children (Bawden et al., 1985; Ewing-Cobbs et al., 1985, 1987; Dennis, Barnes, Donnelly, and Wilkinson, 1996; Dikmen et al., 1990; Fay et. al., 1993; 1994). Injury severity is measured with the scale according to
functioning in 3 areas: eye opening, best verbal response, and best motor response. The scale is provided below. Scoring of severity is typically divided into one of three levels: (1) mild, when the initial score of 13-15, and, (2) moderate, initial score of 9-12, and, severe, initial score of 3-8.

**MR Imaging and \(^1\)H-MR Spectroscopy Techniques**

Prior to imaging children were sedated with chloral hydrate (dose, 40-80 mg per kilogram of body weight) or midazolam hydrochloride (dose, 0.1 mg/kg) was provided as needed. Examinations were performed using a circularly polarized head coil in a conventional 1.5-T whole-body imaging system (Magnetom SP4000, Numaris 2.3; Simens Medical Systems, Erlangen, Germany).

\(^1\)H-MR Spectroscopy (\(^1\)H-MRS) was utilized for evaluation of metabolite ratios. The metabolite ratios NAA/Ch, NAA/Cr, and Ch/Cr as well as the presence of lactate were assessed by conducting \(^1\)H-MRS in the occipital lobe region of brain injured children. This assessment was conducted at the time of injury. For the one neonate in the study the \(^1\)H-MRS was conducted at 7 days. In infants, spectra were acquired at a mean of 3.6 days (SD = 1.17, range 0-22 days; median 3.0 days). In children, spectra were acquired at a mean of 9.45 days (SD = 5.75, range 2-6 days, median 8.5 days).

MR images were used to define optimal placement of the region of interest in the \(^1\)H-MRS examination. Localized water-suppressed proton spectra were obtained with use of a stimulated echo acquisition mode, or STEAM, sequence (3,000/20, middle interval time of 30 msec, 1,024 data points, and 128 signals acquired). Proton spectra were acquired in an 8-cm\(^3\) region of interest placed in the occipital region of the brain,
which consists primarily of gray matter, and in a parietal region, which consists primarily of white matter. For this study only proton spectra obtained from the occipital region were used. The occipital voxel location was fixed independently of the MR imaging information. An additional eight acquisition spectra without water suppression were obtained and used to correct eddy current-induced phase shifts. Localized shimming and optimization of the Gaussian pulse amplitude for maximum water suppression was adjusted prior to acquisition of the spectra. Total study time averaged 60-70 minutes.

Spectral post-processing of N-acetyl compounds (NAA), creatine and phosphocreatine (Cr), and choline-containing compounds (Ch) included eddy current correction, zero filling to 4096 points, multiplication of corrected time-domain signal by a Gaussian function, Fourier transformation to the frequency domain, and manual zero-order phase correction. Peak area metabolite ratios (NAA/Cr, NAA/Ch, Ch/Cr) were calculated for each absorption spectrum. The presence of lactate was determined by identifying a characteristic peak doublet with 7-Hz splitting at 1.3 ppm relative to NAA on the proton spectra.

Studies indicate that the presence of lactate is most likely to be detected at about 4 days post injury and resolves approximately two weeks following injury (Kreis, Arcinue, Ernst, Shonk, Flores, and Ross, 1996; Fenstermacher & Narayana, 1990).

**Magnetic Resonance Imaging (MRI)** was utilized for evaluation of focal injury. The presence of focal injury was assessed by conducting MR imaging at the time of injury. As above, examinations were performed using a circularly polarized head coil in a conventional 1.5-T whole-body imaging system (Magnetom SP4000, Numaris 2.3;
Simens Medical Systems, Erlangen, Germany). Routine MR imaging examination included axial dual spin-echo imaging (repetition time msec/echo time msec = 2,500/22, 90; one signal acquired; 5 mm-thick sections), sagital spin-echo imaging (550/22, four signals acquired, 5-mm thick sections), and coronal spin-echo imaging (1,800/22, 90; half-Fourier acquisition; 5 mm-thick sections).

Assessment of intellectual functioning

Assessment tool selection to examine intellectual functioning was determined by administering the appropriate Wechsler Intelligence Scale given the participant's age. The Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R; Wechsler, 1989) was used for children between the ages of 3 years through 6 years 11 months. The Wechsler Intelligence Scale for Children-Third Edition (WISC-III; Wechsler, 1991) was used for children between the ages of 7 years and 16 years 11 months. The Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 1987) was used for children between the ages of 17 years and 19 years 11 months.

Wechsler Preschool and Primary Scale of Intelligence-Revised; (WPPSI-R; Wechsler, 1989). This instrument assesses intellectual functioning in children ages 3 years through 7 years 3 months. The instrument provides three composite intellectual functioning scores including a verbal intellectual functioning score, a performance (non-verbal) intellectual functioning score, and a combined score of verbal and performance functioning to create an overall full-scale intellectual functioning. Each of the intellectual functioning scores has a mean of 100 and a standard deviation of 15-scaled points. Subtest scores that comprise intellectual functioning scores have a mean of 10
and a standard deviation of 3-scaled points. The means for subtest scores and intellectual functioning scores were determined according to age referenced groups.

The WPPSI-R was standardized on a sample of over 2100 children that included 100 boys and 100 girls in each of eight age groups (50 boys and 50 girls in the eldest age group of 7 years, 0 months through 7 years, 3 months). The standardized sample for each age group was selected to proportionally represent age, race/ethnicity, parental education, and geographic region according to Census Bureau reports to provide a representative sample of children living in the United States. Children were selected from one of four major geographic areas in the United States.

Test reliability refers to the accuracy, consistency, and stability of the test scores across situations (Anastasi, 1988). Average test-retest reliability coefficients of most WPPSI-R subtests range from .53 to .81 when the assessment was given at a 3 to 7 week interval (mean = 4 weeks). Average test-retest reliability for the intellectual functioning scores range between .87 and .91.

Construct validity refers to the extent to which the assessment reveals the function being measured. It is not based on statistics or empirical testing, but is based on the items and whether the items measure the intended construct. Factor analytic studies have shown a general factor corresponding to verbal intellectual functioning, non-verbal (performance) intellectual functioning, and to full-scale intellectual functioning.

The WPPSI-R has demonstrated criterion validity through correlation with other measures designed to assess cognitive ability including the WISC-R (r ranging from .80 to .82; Wechsler, 1974), the Stanford-Binet Intelligence Scale, Fourth Edition (r = .32-63
for subtests, .56-.75 for verbal, performance and full-scale intellectual functioning; 
Thorndike, Hage, & Sattler, 1986), and the McCarthy Scales of Children's Abilities 
(r ranging from .59 to .75 for performance, verbal and full-scale scores; McCarthy, 1972).

Wechsler Intelligence Scale for Children-Third Edition (WISC-III; Wechsler, 1991). This instrument assesses intellectual functioning in individuals ages 6 years 
through 16 years 11 months. The instrument provides three composite intellectual 
functioning scores including a verbal intellectual functioning score, a performance (non-
verbal) intellectual functioning score, and a combined score of verbal and performance 
functioning to create an overall full-scale IQ (intelligence quotient). There are also four 
additional scores that may be assessed including a verbal comprehension index, 
perceptual organization index, freedom from distractibility index, and a processing speed 
index. Each of the intellectual functioning scores as well as the additional index scores 
have a mean of 100 and a standard deviation of 15 scaled points. Subtest scores that 
comprise the index and intellectual functioning scores have a mean of 10 and a standard 
development of 3-scaled points. The means for subtest scores, index scores, and intellectual 
functioning scores were determined according age referenced groups.

The WISC-III was standardized on a sample of 2,200 children that included 200 
children in 11 age groups. The mean age in each of the age groups was the sixth month. 
The standardized sample for each age group was selected to proportionally represent age, 
gender, race/ethnicity, parent education, and geographic region according to Census 
Bureau reports to provide a representative sample of children living in the United States.
Children were selected from one of five major geographic areas in the United States.
Average test-retest reliability coefficients of most WISC-III subtests range from .60 to .89 when the assessment was given at a 12 to 63 day interval \((x = 23\) days). Test-retest reliability coefficients typically increase for older subgroups of children and are typically higher on the verbal subtests. Average test-retest reliability for the index scores and intellectual functioning scores are between .74 and .93.

With regard to construct validity, the WISC-III was developed to measure an ‘aggregate of cognitive abilities’ that contribute to a construct termed ‘intelligence’. Several studies are cited that offer evidence that the WISC-III provides an adequate measure of global ability \((g)\) as well as underlying scales to global ability that include both verbal and a non-verbal performance factors. Internal validity was demonstrated through factor analysis, suggestive of a four-factor solution for index scales.

The WISC-III has demonstrated criterion validity through correlation with other measures designed to assess cognitive ability including the WPPSI-R \((r = .85;\) Wechsler, 1989), Differential Ability Scales \((r = 84-91;\) Elliott, 1990), the Stanford-Binet Intelligence Scale, Fourth Edition \((r = .82-83;\) Thorndike, Hage, & Sattler, 1986), the Kaufman Assessment Battery for Children \((r = .70;\) Kaufman & Kaufman, 1983), and the Woodcock-Johnson Psycho-Educational Battery-Revised \((r = .65;\) Woodcock & Johnson, 1989).

**Wechsler Adult Intelligence Scale-Third Edition** (WAIS-III; Wechsler, 1997). This instrument assesses intellectual functioning in individuals ages 16 years through 89 years. The instrument provides three composite intellectual functioning scores including a verbal intellectual functioning score, a performance (non-verbal) intellectual
functioning score, and a combined score of verbal and performance functioning to create an overall full-scale intellectual functioning. There are also four additional scores that may be assessed including a verbal comprehension index, perceptual organization index, working memory index (similar to freedom from distractibility on the WISC-III), and a processing speed index. Each of the intellectual functioning scores as well as the additional index scores have a mean of 100 and a standard deviation of 15 scaled points.

Subtest scores that comprise the index and intellectual functioning scores have a mean of 10 and a standard deviation of 3-scaled points. The means for subtest scores, index scores, and intellectual functioning scores were determined according age referenced groups. For this study the age-referenced groups were comprised of one of two ages groups: 16 to 17 years or 18 to 19 years.

The WAIS-III was standardized on a sample of 2,450 adults that included 200 adults in 11 of 13 age groups (150 adults and 100 adults respectively in the two eldest age groups) with persons ranging in age from 16 to 89 years of age. The standardized sample for each age group was selected to proportionally represent age, race/ethnicity, education, and geographic region according to Census Bureau reports to provide a representative sample of adults living in the United States. Adults were selected from one of five major geographic areas in the United States.

Average test-retest reliability coefficients of most WAIS-III subtests range from .82 to .93 when the assessment was given at a 2 to 12 week interval ($x = 34.6$ days). Two of the subtests, Picture Arrangement and Object Assembly have slightly lower test-retest reliabilities ($r = .74$ and .70 respectively). Average test-retest reliability for the index scores and intellectual functioning scores are between .88 and .97.
Content validity refers to the extent to which the assessment reveals the function being measured. It is not based on statistics or empirical testing, but is based on the items and whether the items measure the intended construct. For the WAIS-III the goal was to ‘adequately sample domains of behavior delineated by the constructs the tests are intended to measure’ (The Psychological Corporation, 1997).

Construct validity is the extent to which the instrument measures the theoretical it was designed to measure. Several studies have demonstrated that a general intelligence factor ‘g’ is present throughout the subtests provided in the WAIS-III. Additionally, an assumption that verbal intellectual functioning more closely correlates with ‘g’ than non-verbal intellectual functioning. This has been shown to be the case with verbal subtests correlating more highly than non-verbal subtests to overall full-scale functioning. Additionally, evidence supports a four factor model within the WAIS-III, breaking down aspects of intellectual functioning into distinct areas: verbal comprehension, perceptual organization, working memory, and processing speed. Subtests within these factors load more heavily with other subtests in the factors than with subtests in other factors (The Psychological Corporation, 1997).

The WAIS-III has demonstrated criterion validity through correlation with other measures designed to assess cognitive ability including the WISC-III (r = .88; Wechsler, 1989), Stanford Progressive Matrices (r = .49-.79; Raven, 1976), the Stanford-Binet Intelligence Scale, Fourth Edition (r = .36-83 for factor, verbal intellectual functioning, non-verbal intellectual functioning, and full-scale scores; Thorndike, Hage, & Sattler, 1986), and the Wechsler Individual Achievement Test (r = .18 –82; The Psychological Corporation, 1992).
Assessment of neuropsychological functioning

Assessment tool selection to examine neuropsychological functioning was determined by the participant's age. The NEPSY Developmental Neuropsychological Assessment was used to assess neuropsychological functioning in children between the ages of 3 through 12 years. The Luria-Nebraska Neuropsychological Battery: Form I was used to assess neuropsychological functioning in children 13 through 19 years 11 months.

NEPSY Developmental Neuropsychological Assessment (Korkman, Kirk, & Kemp, 1998). This instrument assesses neuropsychological functioning for children ages 3 through 12 years. Neuropsychological functioning is assessed along five cognitive function domains that were determined by developmental and neuropsychological theory. The domains include memory and learning, language, attention and executive functions, visuospatial processing, and sensorimotor functions. Within each of these functional domains there are several age-determined subtests that are multifactorial with a total of 37-40 subtests that may be given. The NEPSY Domain Area scores have a mean of 100 and a standard deviation of 15.

The NEPSY was standardized on a sample of 1,000 children that included 100 children in each of 10 age groups ranging from 3 to 12 years of age. The median age for each age group was the fifth month. There were 50 males and 50 females in each group. Children were selected to proportionally represent race/ethnicity, parent education, and geographic region according to Census Bureau reports to provide a representative sample of children living in the United States. Children were selected within one of four major geographic regions.
With regard to content validation, the NEPSY was designed to provide a comprehensive assessment of neuropsychological function in the five cognitive domains outlined above. The test was originally designed to reflect the neuropsychological practices and theory of A. R. Luria. Several revisions have occurred based on the performance of children with and without known neurodevelopmental disabilities. Content revisions were based on a review of the literature regarding the development of executive functions, attention and concentration, memory and learning, visuospatial abilities, and sensorimotor functions and the impact of neurological disease including traumatic brain injury (Korkman, Kirk, & Kemp, 1998).

With regard to construct validity, there are moderate positive relationships among core domain scores for children aged 3-4 years and low to moderate correlations for children aged 5-12 years. The authors suggest that a moderate correlation is expected for children without specific neurocognitive deficit. Subtests within domains are more highly correlated than subtests across domains. The NEPSY has been correlated with other widely used scales assessing intellectual abilities, academic performance and neuropsychological functioning for children with and without specific deficits in these areas. The NEPSY has demonstrated a consistent low moderate relationship across WISC-III (Wechsler, 1991) IQ and index scores ($r = .19$ to $.62$; with $r = .25$ to $.49$ across the five NEPSY domain scores and full-scale intellectual functioning). Intercorrelations between the NEPSY domains and WPPSI-R (Wechsler, 1989) full-scale intellectual functioning score correlations range between $.26$ and $.57$. Intercorrelations between the NEPSY subtests and similar Benton Neuropsychological subtests (Benton, Hamsher, Varney & Spreen, 1983) range from relatively low ($r = -.03$ Benton facial recognition,
NEPSY immediate memory for faces) to high (r = .77 Benton judgment of line orientation, NEPSY arrows) with other subtests demonstrating correlations in the moderate range. Most domains assessed with the Multilingual Aphasia Examination (Benton & Hamsher, 1989) demonstrate a high correlation with NEPSY subtests (r = .44 to .76) with one low correlation in the area of sentence repetition (r = .01). The Children’s Memory Scale (Cohen, 1997) subtests have demonstrated moderate to high correlation with similar subtests on the NEPSY ranging from .36 to .60. Correlations between miscellaneous attention tests and the NEPSY range from relatively low to moderate correlations. With the Conners’ Continuous Performance Test (Conners, 1994), the NEPSY domains with the highest correlations are the sensorimotor domains (r = -.28 to .36) and the visuospatial domains (r = -.43 to .31).

Luria-Nebraska Neuropsychological Battery: Form I (Golden, Purisch, & Hammeke, 1985). This instrument assesses neuropsychological functioning for adolescents and adults. Although originally designed for children aged 15 years and older, it has been used successfully for children as young as 13 years (Golden, Purisch, & Hammeke, 1985, pg. 2). Neuropsychological functioning is assessed along eleven cognitive function domains that were determined by developmental and neuropsychological theory. The eleven domains are: motor functions (primarily sensorimotor with some visuomotor items), rhythm (perception and replication), tactile functions (sensitivity to touch), visual functions (visual perception and visuospatial perception), receptive speech, expressive speech, writing (spelling and motor writing), reading, arithmetic, memory (immediate), and intellectual processes. In addition to the
11 clinical scales, the Luria Nebraska provides five summary scales reflecting level of impairment, eight localization of injury scales, and 28 factor scales that assess more homogeneous abilities as compared to the clinical scales.

The Luria Nebraska Form I was normed with a sample of 50 adults that included 26 females and 24 males who were in the hospital for various, non-neuropsychologically based injuries. None of the participants were known to have cerebral dysfunction based on medical history, symptoms, laboratory data, and the opinion of the attending physician. The average age of those in the sample was 42.0 years with a standard deviation of 14.8 years. The average years of education for those in the sample was 12.2 years with a standard deviation of 2.9 years. All of the clinical, localization, and factor scores are provided as T-scores with a mean of 50 and a standard deviation of 10 scaled points.

Average test-retest reliability coefficients of most WAIS-III subtests range from .82 to .93 when the assessment was given at a 2 to 12 week interval ($x = 34.6$ days). Two of the subtests, Picture Arrangement and Object Assembly have slightly lower test-retest reliabilities ($r = .74$ and .70 respectively). Average test-retest reliability for the index scores and intellectual functioning scores are between .88 and .97.

With regard to content validity, the items selected for the Luria Nebraska Neuropsychological battery were selected for their qualitative importance in diagnosis so that each item was selected to represent a specific aspect of a particular skill. No two items are thought to measure exactly the same skill. Thus, internal consistency is suggested to be high enough for meaningful interpretation of the clinical scales, yet heterogeneous enough to assess the varied unique skills of the individual.
Construct validity for the Luria Nebraska was assessed through factor analysis of the test items in several studies. It is reported that across studies, obtained factor solutions were consistent for different patient populations and with theoretical expectations. One scale, the C5 receptive speech clinical scale, does not factor into more specific aspects of receptive functioning. It appears that the C5 scale may represent a single factor of phonemic discrimination (similar to the functional ability that is assessed with the NEPSY receptive language subtest).

Discriminant validity has been demonstrated in which the Luria Nebraska accurately discriminates between individuals who do and do not have brain injury. Findings of several studies have revealed discriminant validity at the .05 level for most items on the test (252 of 269 items) as well as for all of the clinical scales. Studies reveal that the Luria Nebraska is able to correctly classify between approximately 70 to 90 percent of individuals with and without brain injury. The findings remained consistent when differences in education level, age, and gender were controlled.

For the current study clinical and localization scales that appeared to most closely represent functional areas of study interest were selected for analysis. Attention and executive functions were assessed with the left (L1) and right (L5) frontal lobe localization scales. These scales were chosen because they appeared to most closely capture the ability to attend and utilize planning and problem-solving abilities as is consistent with research regarding frontal lobe functioning (Damasio & Anderson, 1993). Receptive and expressive language abilities were assessed with the receptive (C5) and expressive (C6) speech clinical scales. Sensorimotor abilities were assessed with the motor (C1) scale. Visuospatial abilities were assessed using the visual-spatial
organization factor scale. Memory and learning abilities were assessed with the memory (C10) clinical scale.
Results

Data Screening and Participant Characteristics

The data were first examined for missing data, univariate outliers, and normality. With regard to missing data, EEG reading was not conducted for two of the children and the GCS score was missing for one child. Because relatively few cases had missing data and missing data appeared to be randomly distributed, the cases were deleted from analysis when these variables were utilized. Additionally, three of the children were unable to complete parts of the assessment because of limited functioning and were given basal scores determined by minimum standard scores indicated for those outcome measures. Characteristics of the children who participated in the study are listed in Table 4.

Table 4

Characteristics of Participants in the Study

<table>
<thead>
<tr>
<th>Participant No.</th>
<th>Age at injury (mos.)</th>
<th>Current age (yrs)</th>
<th>Etiology</th>
<th>EEG abnormality</th>
<th>Lactate</th>
<th>Neurological outcome</th>
<th>Full-Scale intellectual functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.5</td>
<td>7</td>
<td>NAT</td>
<td>Mild</td>
<td>No</td>
<td>Mild</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>1.25</td>
<td>6</td>
<td>NAT</td>
<td>Severe</td>
<td>Yes</td>
<td>Severe</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>1.75</td>
<td>5</td>
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<td>Normal</td>
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<td>Mild</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>1.25</td>
<td>5</td>
<td>NAT</td>
<td>Moderate</td>
<td>No</td>
<td>Moderate</td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td>142.0</td>
<td>17</td>
<td>TBI</td>
<td>Mild</td>
<td>No</td>
<td>Moderate</td>
<td>102</td>
</tr>
<tr>
<td>6</td>
<td>8.0</td>
<td>5</td>
<td>TBI</td>
<td>Mild</td>
<td>No</td>
<td>Good</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>165.0</td>
<td>19</td>
<td>TBI</td>
<td>--</td>
<td>No</td>
<td>Mild</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>0.27</td>
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<td>Mild</td>
<td>75</td>
</tr>
<tr>
<td>9</td>
<td>168.0</td>
<td>19</td>
<td>TBI</td>
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<td>No</td>
<td>Mild</td>
<td>84</td>
</tr>
<tr>
<td>10</td>
<td>173.0</td>
<td>19</td>
<td>TBI</td>
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<td>No</td>
<td>Moderate</td>
<td>98</td>
</tr>
<tr>
<td>11</td>
<td>15.0</td>
<td>5</td>
<td>NAT</td>
<td>Moderate</td>
<td>Yes</td>
<td>Severe</td>
<td>41</td>
</tr>
<tr>
<td>12</td>
<td>14.0</td>
<td>5</td>
<td>NAT</td>
<td>Mild</td>
<td>No</td>
<td>Good</td>
<td>96</td>
</tr>
<tr>
<td>13</td>
<td>113.0</td>
<td>14</td>
<td>TBI</td>
<td>Mild</td>
<td>No</td>
<td>Mild</td>
<td>89</td>
</tr>
<tr>
<td>14</td>
<td>5.0</td>
<td>4</td>
<td>NAT</td>
<td>Mild</td>
<td>Yes</td>
<td>Moderate</td>
<td>45</td>
</tr>
<tr>
<td>15</td>
<td>30.0</td>
<td>10</td>
<td>TBI</td>
<td>Moderate</td>
<td>No</td>
<td>Good</td>
<td>96</td>
</tr>
<tr>
<td>16</td>
<td>24.0</td>
<td>6</td>
<td>TBI</td>
<td>--</td>
<td>No</td>
<td>Good</td>
<td>102</td>
</tr>
<tr>
<td>17</td>
<td>8.0</td>
<td>5</td>
<td>NAT</td>
<td>Mild</td>
<td>No</td>
<td>Moderate</td>
<td>95</td>
</tr>
<tr>
<td>18</td>
<td>6.25</td>
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<td>Severe</td>
<td>57</td>
</tr>
<tr>
<td>19</td>
<td>147.25</td>
<td>15</td>
<td>TBI</td>
<td>Mild</td>
<td>No</td>
<td>Mild</td>
<td>93</td>
</tr>
<tr>
<td>20</td>
<td>96.2</td>
<td>10</td>
<td>TBI</td>
<td>Mild</td>
<td>No</td>
<td>Severe</td>
<td>55</td>
</tr>
<tr>
<td>21</td>
<td>127.0</td>
<td>11</td>
<td>TBI</td>
<td>Moderate</td>
<td>Yes</td>
<td>Severe</td>
<td>49</td>
</tr>
<tr>
<td>22</td>
<td>144.0</td>
<td>13</td>
<td>TBI</td>
<td>Severe</td>
<td>Yes</td>
<td>Severe</td>
<td>55</td>
</tr>
</tbody>
</table>
All the continuous variables were assessed for normality. Of the clinical variables, GCS and number of days in a coma had a mild positive skew. Cardiac arrest had a mild negative skew. Of the \(^1\)HMRS variables NAA/Ch demonstrated mild kurtosis. With the moderator variables, one, age in months at injury, demonstrated moderate kurtosis. Of the outcome variables, verbal intellectual functioning, memory, and sensorimotor abilities demonstrated moderate kurtosis. Language abilities demonstrated a mild skew. The exploratory variables were also assessed for normality. Of these variables NEPSY narrative memory, NEPSY attention and executive functions, NEPSY language and Luria Nebraska attention and executive functions, Luria Nebraska visual memory, and visual clinical scale were mildly positively skewed. NEPSY attention and executive functions and Luria Nebraska attention and executive functions were mildly kurtotic. Luria Nebraska was moderately kurtotic. Because the data are most meaningful in their original numbers, they were not transformed. However, because of skewness and kurtosis effect sizes may be deflated.

Assessment battery was selected based on the participant’s age. Univariate analysis of variance was conducted to determine whether outcome scores differed according to the test battery given. Age effects were controlled when examining for variance in outcome measures. There were no significant differences between the WPPSI-R, the WISC-III, or the WAIS-R on measures of full-scale ($F_{3,21} = .189$, $p = .830$), verbal ($F_{3,21} = .125$, $p = .884$), or non-verbal performance ($F_{3,21} = .193$, $p = .826$) intellectual functioning.

Luria Nebraska scores appeared somewhat inflated, compared to the NEPSY. However, differences were not significantly discrepant between the NEPSY
Developmental Neuropsychological Assessment and the Luria Nebraska Neuropsychological Battery in any of the domains assessed including attention and executive functions ($F_{2, 21} = .996, p = .338$), language ($F_{2, 21} = 1.658, p = .213$), sensorimotor abilities ($F_{2, 21} = 1.898, p = .184$), visuospatial abilities ($F_{2, 21} = .020, p = .890$), or memory skills ($F_{2, 21} = .143, p = .710$). Means, standard deviations, and score ranges for the outcome measures are listed in Table 5.

Table 5

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Mean (x)</th>
<th>Standard Deviation</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-scale intellectual functioning (FS-IQ)</td>
<td>73.95</td>
<td>22.94</td>
<td>41-102</td>
</tr>
<tr>
<td>Verbal intellectual functioning (V-IQ)</td>
<td>77.23</td>
<td>20.84</td>
<td>46-107</td>
</tr>
<tr>
<td>Non-verbal intellectual functioning (P-IQ)</td>
<td>74.59</td>
<td>22.69</td>
<td>45-106</td>
</tr>
<tr>
<td>Attention/Executive</td>
<td>84.49</td>
<td>24.95</td>
<td>50-121</td>
</tr>
<tr>
<td>Language</td>
<td>85.14</td>
<td>28.54</td>
<td>50-138</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>75.98</td>
<td>27.16</td>
<td>50-122</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>77.55</td>
<td>22.60</td>
<td>50-122</td>
</tr>
<tr>
<td>Memory</td>
<td>83.50</td>
<td>25.45</td>
<td>50-118</td>
</tr>
</tbody>
</table>

All indicators of injury severity including EEG reading, the GCS score, presence of non-reactive pupils, number of days unconscious and metabolite ratios were provided in either dichotomous or interval format and were assessed through correlational statistical analysis. All measures of outcome for intellectual functioning and areas of neuropsychological functioning in the areas of memory, linguistic abilities, planning and attention, visuospatial, and sensorimotor abilities scores were also in interval format and assessed through correlational analysis. Therefore, correlational statistical analysis was used to determine independent and moderator variables that correlate significantly with the outcome variables. Based on previous research indicated above, a $p$ level of .05
determined statistical significance in the current study. The $p$ level of .05 selected for the current study indicates a 5% chance that significance may be achieved through random sampling error.

Hypothesis One-Predictiveness of Clinical Variables

The first hypothesis was that clinical data including EEG reading, presence of fixed dilated pupils at the time of admission, GCS score, number of days unconscious, and experiencing cardiac arrest are predictive of intellectual and neuropsychological functioning 1-6 years later. These five variables have been predictive of outcome for children who have experienced closed head injury in previous studies. They were analyzed for correlations with outcome in areas of full-scale, verbal, and non-verbal intellectual functioning, and neuropsychological functioning in areas of memory, linguistic, planning and attention abilities, and visuospatial and sensorimotor skills.

Severity of the EEG rating was significantly correlated with full-scale intellectual functioning ($r = -.449, p = .024$), verbal intellectual functioning ($r = -.446, p = .032$), non-verbal intellectual functioning ($r = -.435, p = .028$) and with neuropsychological areas of attention and executive functions ($r = -.436, p = .027$), and memory functions ($r = -.470, p = .018$). Number of days unconscious was correlated with the neuropsychological functioning area of visuospatial processing ($r = -.379, p = .041$). Presence of non-reactive pupils, the GCS, and presence of cardiac arrest tended to have very low $r$ values and were not significantly correlated with any of the outcome variables. The hypothesis that clinical variables are predictive of outcome was partially supported. More specifically, EEG correlated significantly with five of the eight outcome variables and
number of days unconscious correlated with one outcome variable. The other clinical variables, presence of non-reactive pupils, GCS score and cardiac arrest did not correlate with outcome measures. Clinical variable correlations with outcome measures are listed below in Table 6.

Table 6
Clinical Variables Correlations and Significance Levels with Intellectual and Neuropsychological Outcome

<table>
<thead>
<tr>
<th></th>
<th>FS-IQ</th>
<th>V-IQ</th>
<th>P-IQ</th>
<th>Attention/Executive</th>
<th>Language</th>
<th>Sensorimotor</th>
<th>Visuospatial</th>
<th>Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG</td>
<td>-.449*</td>
<td>-.441*</td>
<td>-.435*</td>
<td>-.436*</td>
<td>-.353</td>
<td>-.370</td>
<td>-.366</td>
<td>-.470*</td>
</tr>
<tr>
<td></td>
<td>.024</td>
<td>.026</td>
<td>.028</td>
<td>.027</td>
<td>.063</td>
<td>.054</td>
<td>.113</td>
<td>.018</td>
</tr>
<tr>
<td>Non-reactive</td>
<td>-.086</td>
<td>-.228</td>
<td>-.080</td>
<td>-.134</td>
<td>-.220</td>
<td>-.253</td>
<td>.083</td>
<td>-.209</td>
</tr>
<tr>
<td>pupils</td>
<td>.362</td>
<td>.154</td>
<td>.362</td>
<td>.276</td>
<td>.163</td>
<td>.128</td>
<td>.714</td>
<td>.175</td>
</tr>
<tr>
<td>Glasgow Coma</td>
<td>-.065</td>
<td>-.060</td>
<td>-.246</td>
<td>-.089</td>
<td>-.043</td>
<td>-.037</td>
<td>-.049</td>
<td>.832</td>
</tr>
<tr>
<td>Scale</td>
<td>.390</td>
<td>.399</td>
<td>.135</td>
<td>.347</td>
<td>.424</td>
<td>.436</td>
<td>.832</td>
<td>.376</td>
</tr>
<tr>
<td>Days unconscious</td>
<td>.105</td>
<td>.242</td>
<td>-.056</td>
<td>-.136</td>
<td>-.199</td>
<td>.233</td>
<td>.001</td>
<td>.140</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>.642</td>
<td>.278</td>
<td>.806</td>
<td>.546</td>
<td>.376</td>
<td>.297</td>
<td>.998</td>
<td>.533</td>
</tr>
<tr>
<td></td>
<td>.302</td>
<td>.947</td>
<td>.154</td>
<td>.445</td>
<td>.412</td>
<td>.187</td>
<td>.898</td>
<td>.478</td>
</tr>
</tbody>
</table>

*significant at the .05 level

Hypothesis Two-Predictiveness of $^1$H-MRS Variables

The second hypothesis was that a decrease in the $^1$H-MRS metabolite ratios NAA/Cr and NAA/Ch correlates with deficits in intellectual and neuropsychological functioning 1-6 years later. Additionally, presence of cerebral lactate was hypothesized to correlated with long-term intellectual and neuropsychological outcome in the areas of functioning listed above.

The $^1$H-MRS variables that significantly correlated with outcome were presence of lactate, and NAA/Ch. NAA/Cr did not correlate with any of the intellectual or
neuropsychological variables. Presence of lactate correlated with all of the intellectual and neuropsychological outcome areas with correlations ranging from $r = -0.606$ to $-0.780$ and significance levels ranging from $p = 0.000$ to $0.005$. NAA/Ch correlated with sensorimotor ($r = 0.434, p = 0.028$), visuospatial abilities ($r = 0.425, p = 0.027$) and short-term memory skills ($r = 0.3987, p = 0.041$) with a trend towards significance for language abilities ($r = 0.366, p = 0.056$), and planning and attention skills ($r = 0.354, p = 0.063$). The hypothesis that NAA/Ch, NAA/Cr, and presence of lactate correlate with intellectual and neuropsychological outcome was partially supported. Lactate correlated with all eight of the outcome measures, and NAA/Ch correlated with three of the eight outcome measures. NAA/Cr was not significantly correlated with outcome measures.

Although a decrease in Ch/Cr was not hypothesized to be predictive of outcome, post-hoc analysis revealed that Ch/Cr correlated with all of the intellectual and neuropsychological outcome variables with correlations ranging from $r = 0.403$ to $0.581$ and significance levels ranging from $p = 0.005$ to $0.035$. Thus, it was considered important to add as a predictor in the current study. $^1$H-MRS variable correlations with outcome measures are listed below in Table 7.
Table 7

\(^1\)H-MR Spectroscopy Variables Correlations and Significance Levels with Intellectual and Neuropsychological Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>FS-IQ</th>
<th>V-IQ</th>
<th>P-IQ</th>
<th>Attention/Executive</th>
<th>Language</th>
<th>Sensorimotor</th>
<th>Visuospatial</th>
<th>Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate</td>
<td>-.769*</td>
<td>-.702*</td>
<td>-.780*</td>
<td>-.678*</td>
<td>-.647*</td>
<td>-.606*</td>
<td>-.720*</td>
<td>-.701*</td>
</tr>
<tr>
<td>Ch/Cr</td>
<td>-.464*</td>
<td>-.484*</td>
<td>-.410*</td>
<td>-.511*</td>
<td>-.510*</td>
<td>-.532*</td>
<td>-.410*</td>
<td>-.589*</td>
</tr>
<tr>
<td>NAA/Ch</td>
<td>.248</td>
<td>.279</td>
<td>.194</td>
<td>.351</td>
<td>.366</td>
<td>.421*</td>
<td>.425*</td>
<td>.398*</td>
</tr>
<tr>
<td>NAA/Cr</td>
<td>-.145</td>
<td>-.090</td>
<td>-.196</td>
<td>.056</td>
<td>.050</td>
<td>.054</td>
<td>-.201</td>
<td>.021</td>
</tr>
</tbody>
</table>

*significant at the .05 level

Analysis of Covariate Variables

Prior to conducting the regression analysis it was necessary to examine whether there existed a need to control for two potential covariates including age at the time of injury and ‘duration of time since the injury occurred’. As indicated above, younger children are at greater risk for long-term sequelae from closed head injury than older children. Additionally, the \(^1\)HMRS ratios change as children develop. Specifically, NAA and Cr increase with increasing age whereas Ch decreases with age, thus adding age related variability within the ratios. Regarding duration of time since the injury occurred, research has shown the there is a positive correlation between time elapsed since injury and improvement in intellectual and neuropsychological functioning.

Using correlational analysis, it was shown that age in months at the time of injury significantly correlated with two of the four \(^1\)HMRS variables and five of the eight outcome variables. Specific correlations between the age at the time of injury and \(^1\)HMRS variables included NAA/Ch (\(r = .742, p = .000\)), and Ch/Cr (\(r = -.638, p = .001\)) with a trend toward significance for NAA/Cr (\(r = .320, p = .073\)). Age at the time of
injury was not correlated with presence of lactate. Specific intellectual and neuropsychological outcome variables that correlated with age at injury were verbal intellectual functioning ($r = .383, p = .039$), attention/executive functions ($r = .432, p = .025$), language ($r = .518, p = .008$), sensorimotor abilities ($r = .663, p = .001$), and memory skills ($r = .5369, p = .006$). Duration of time since injury did not correlate with any of the outcome variables. Covariate main effect variable correlations with outcome measures are listed below in Table 8.

Table 8

Covariate Variables Correlations and Significance Levels with $^1$HMRS and Outcome Variables

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age In Months at Time of Injury</th>
<th>Age in Months since Time of Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r$ and $p$ level</td>
<td>$r$ and $p$ level</td>
</tr>
<tr>
<td>Full-scale intellectual</td>
<td>.312</td>
<td>.256</td>
</tr>
<tr>
<td>functioning</td>
<td>.078</td>
<td>.125</td>
</tr>
<tr>
<td>Verbal intellectual functioning</td>
<td>.383*</td>
<td>.238</td>
</tr>
<tr>
<td>Performance intellectual</td>
<td>.199</td>
<td>.249</td>
</tr>
<tr>
<td>functioning</td>
<td>.188</td>
<td>.132</td>
</tr>
<tr>
<td>Attention/Executive</td>
<td>.443*</td>
<td>.196</td>
</tr>
<tr>
<td></td>
<td>.025</td>
<td>.198</td>
</tr>
<tr>
<td>Language</td>
<td>.518*</td>
<td>.143</td>
</tr>
<tr>
<td></td>
<td>.008</td>
<td>.268</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>.663*</td>
<td>.201</td>
</tr>
<tr>
<td></td>
<td>.001</td>
<td>.191</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>.040</td>
<td>.087</td>
</tr>
<tr>
<td></td>
<td>.430</td>
<td>.354</td>
</tr>
<tr>
<td>Memory</td>
<td>.537*</td>
<td>.154</td>
</tr>
<tr>
<td></td>
<td>.006</td>
<td>.253</td>
</tr>
<tr>
<td>$^1$HMRS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAA/Cr</td>
<td>.320</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>.073</td>
<td>--</td>
</tr>
<tr>
<td>NAA/Ch</td>
<td>.742*</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>.000</td>
<td>--</td>
</tr>
<tr>
<td>Ch/Cr</td>
<td>-.638*</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>.001</td>
<td>--</td>
</tr>
<tr>
<td>Lactate</td>
<td>-.208</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>.177</td>
<td>--</td>
</tr>
</tbody>
</table>

*significant at the .05 level
The hypothesis that age at the time of injury and duration of time since injury would correlate with intellectual and neuropsychological outcome was partially supported. Age at injury was correlated with both predictor and outcome variables demonstrating itself an important variable in further analysis. Duration of time was not correlated with any outcome variable, and thus not considered to have a significant effect in this analysis.

**Hypothesis Three-Predictiveness of Combined Clinical and $^1$H-MRS Variables**

It was hypothesized that a combination of clinical and $^1$H-MRS variables would provide the greatest predictive power regarding outcome. Of the clinical variables, only one, an abnormal EEG reading correlated significantly with more than one outcome variable. Additionally, a covariate main effect of age at the time of injury was predictive of outcome. The three $^1$H-MRS variables that correlated with outcome were NAA/Ch, Ch/Cr, and the presence of lactate. Thus, age at the time of injury, EEG reading, and the three $^1$H-MRS variables were utilized in the discriminant function analysis. Missing data were excluded in pair-wise fashion (2 missing cases on EEG reading).

**Intellectual Outcome Findings-Discriminant Analysis**

Discriminant function analysis was conducted to determine the extent to which outcome could be accurately classified by clinical variables, $^1$H-MRS variables, and combining clinical and $^1$H-MRS variables. As has been characteristic in previous research, children were divided into two outcome groups according to severity of impairment. In previous studies outcome was assessed using neurological outcome,
placing children in one of two outcome categories: (good outcome; able to engage in most or all age-appropriate independent activities) or (poor outcome; dependent on others for daily support because of impaired brain function).

Clinical and \(^1\)H-MRS indicators of injury severity were more predictive of poor outcome than for good outcome in both infants and children. For infants, EEG reading, number of days unconscious to MR imaging, presence of lactate and NAA/Ch ratio were correlated with poor outcome. However, none of the clinical or \(^1\)H-MRS variables were significantly predictive of good outcome. Similarly, for children, presence of Ch/Cr was predictive of poor outcome. Yet, clinical and \(^1\)H-MRS variables were not significantly correlated with good outcome. Clinical and \(^1\)H-MRS variable means are presented in Table 9 below for infants and children with good and poor neurological outcome.

Table 9

Clinical and \(^1\)H-MRS Variable Correlations of Infants and Children with Good or Poor Neurological Outcome

<table>
<thead>
<tr>
<th>Clinical and (^1)H-MRS</th>
<th>Infants Good N = 8</th>
<th>Infants Poor N = 3</th>
<th>Children Good N = 8</th>
<th>Children Poor N = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG reading</td>
<td>1.13</td>
<td>2.33*</td>
<td>1.17</td>
<td>2.00</td>
</tr>
<tr>
<td>Age at injury</td>
<td>5.35</td>
<td>7.50</td>
<td>120.28</td>
<td>122.40</td>
</tr>
<tr>
<td>Non-reactive pupils</td>
<td>.88</td>
<td>.67</td>
<td>.50</td>
<td>.33</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>8.50</td>
<td>4.00</td>
<td>6.00</td>
<td>3.33</td>
</tr>
<tr>
<td>Days unconscious</td>
<td>1.50</td>
<td>4.00*</td>
<td>4.12</td>
<td>5.33</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>.75</td>
<td>.67</td>
<td>.88</td>
<td>.33</td>
</tr>
<tr>
<td>(^1)H-MRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate</td>
<td>.25</td>
<td>1.00*</td>
<td>.00</td>
<td>.67</td>
</tr>
<tr>
<td>Ch/Cr</td>
<td>1.262</td>
<td>1.294</td>
<td>.582</td>
<td>.481*</td>
</tr>
<tr>
<td>NAA/Ch</td>
<td>.963</td>
<td>.622*</td>
<td>2.129</td>
<td>2.734</td>
</tr>
<tr>
<td>NAA/Cr</td>
<td>1.12</td>
<td>.795</td>
<td>1.169</td>
<td>1.316</td>
</tr>
</tbody>
</table>

*significant at the .05 level with independent sample t test
To avoid overfitting the discriminant function analysis, a maximum of four predictor variables should be entered in the analysis for a sample size of 22 children. For neurological function in infants the most predictive clinical variables included EEG reading and the GCS score. The most predictive $^1$H-MRS variables were presence of lactate and NAA/Ch.

In infants, using clinical variables alone correctly predicted outcome in 82% of the cases (with two false positives). When $^1$H-MRS variables were considered alone outcome correctly predicted 82% of infants (with two false positives). Combining clinical variables with the $^1$H-MRS variables increased the ability to predict neurological functioning for 100% of infants. Discriminant function predictions of clinical and $^1$H-MRS findings for neurological outcome in infants are presented in Table 10.

Table 10

Prediction of Neurological Outcome Group for Infants

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>Infants</th>
<th># of False Positives</th>
<th># of False Negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical EEG reading GCS</td>
<td>82%</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>MRS Lactate NAA/Ch</td>
<td>82%</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Clinical and MRS</td>
<td>100%</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

For neurological function in children the most predictive clinical variables included EEG reading and sustaining a cardiac arrest. The most predictive $^1$H-MRS variables were presence of lactate and Ch/Cr. In children, using clinical variables alone
correctly predicted outcome in 78% of the cases (with one false positive and one false negative). When $^1$H-MRS variables were considered alone outcome correctly predicted 91% of children (with one false negative). Combining clinical variables with the $^1$H-MRS variables decreased the ability to predict neurological functioning outcome to 89% of children (with one false negative). Discriminant function predictions of clinical and $^1$H-MRS findings for neurological outcome in children are presented in Table 11.

Table 11

Prediction of Neurological Outcome Group for Children

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>Percent Predicted Correctly</th>
<th># of False Positives</th>
<th># of False Negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical EEG reading** Cardiac arrest</td>
<td>78%</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MRS Lactate Ch/Cr</td>
<td>91%</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Clinical and MRS</td>
<td>89%</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**missing two cases on EEG for children, N=9

In the current study, outcome was also assessed according to measures of intellectual and neuropsychological functioning. On these measures, one group was comprised of children functioning in the average range of skills on outcome measures and the other group was formed based on level of functioning below the average range of skills. For full-scale intellectual functioning and verbal intellectual functioning this dichotomy was reflected in the scaled scores where a natural break occurred between standard scores between 70 and 80. A natural break that did not correspond with dichotomy of severity of impairment occurred for attention and executive functions at 90
and in language functions at 100, possibly resulting in a tendency for analysis of outcome to underestimate predictiveness.

To avoid overfitting the discriminant function analysis it is important to have four- to five times as many participants as independent variables. Based on the sample size of 22 participants in this study, a maximum of five variables should be utilized. Only those clinical and $^1$H-MRS variables that significantly correlated with intellectual and neuropsychological outcome were entered into the analysis. The clinical variable that correlated with most outcome measures was EEG. Additionally, age at the time of injury was demonstrated to be a significant covariate for intellectual and neuropsychological functioning. Thus, these two clinical variables were considered in the discriminant function analysis. The three $^1$H-MRS variables that correlated with intellectual and neuropsychological outcome were presence of lactate, Ch/Cr and NAA/Ch. Thus these three $^1$H-MRS variables were considered in the discriminant function.

For predictive analysis of full-scale intellectual functioning, using clinical variables alone correctly predicted outcome in 91% of the cases for infants (one false negative; good outcome predicted yet poor outcome evidenced) and 78% of children (one false positive, one false negative). When $^1$H-MRS variables were considered alone outcome was predicted for 100% of infants and 91% of children (one false negative). Combining clinical variables with the $^1$H-MRS variables maintained or increased the ability to predict full-scale intellectual functioning outcome to 100% of infants and 100% of children.
For predictive analysis of verbal intellectual functioning, clinical variables alone correctly predicted outcome for 73% of infants (three false negatives) and 78% of children (one false positive, one false negative). When \(^1\)H-MRS variables were considered alone outcome was correctly predicted in 82% of infants (two false negatives) and 91% of children (one false negative). Combining clinical variables with the \(^1\)H-MRS variables increased the ability to predict verbal intellectual functioning outcome to 100% of infants and children.

For predictive analysis of non-verbal intellectual functioning, using clinical variables alone correctly predicted outcome in 64% of infants (one false positive and three false negatives) and 78% of children (two false negatives). When \(^1\)H-MRS variables were considered alone, outcome was correctly predicted in 82% of infants (two false negatives) and 82% of children (with two false negatives). Combining clinical variables with the \(^1\)H-MRS variables increased the ability to predict non-verbal intellectual functioning to 91% of infants (one false negative). Combining clinical and \(^1\)H-MRS variables in children decreased prediction to 68% (one false positive, two false negatives). For all indicators of intellectual functioning, poor outcome was predicted more accurately than good outcome. Likely this findings stems from the high predictive power of lactate presence that was indicative of poor outcome for every child with lactate presence. Discriminant function predictions of clinical and \(^1\)H-MRS findings with intellectual outcome are presented in Table 12 for infants Table 13 for children.
Table 12

Prediction of Intellectual Outcome Group for Infants

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>FS-IQ</th>
<th>V-IQ</th>
<th>P-IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Predicted Correctly</td>
<td># of False Positives</td>
<td># of False Negatives</td>
</tr>
<tr>
<td>Clinical -EEG</td>
<td>91%</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>-Age at injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-EEG only</td>
<td>73%</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>MRS -NAA/Ch</td>
<td>100%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>-Ch/Cr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Lactate</td>
<td>73%</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Clinical and MRS</td>
<td>100%</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 13

Prediction of Intellectual Outcome Group for Children

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>FS-IQ</th>
<th>V-IQ</th>
<th>P-IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Predicted Correctly</td>
<td># of False Positives</td>
<td># of False Negatives</td>
</tr>
<tr>
<td>Clinical -EEG**</td>
<td>78%</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>-Age at injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-EEG only**</td>
<td>78%</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MRS -NAA/Ch</td>
<td>91%</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>-Ch/Cr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Lactate</td>
<td>91%</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Clinical and MRS</td>
<td>100%</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**missing two cases on EEG variable for children, N=9**
Neuropsychological Outcome Findings-Discriminant Analysis

For predictive analysis of attention/executive neuropsychological functioning, using clinical variables alone correctly predicted outcome in 91% of infants (one false negative) and 68% of children (two false positives, one false negative). $^1$H-MRS variables alone correctly predicted outcome in 100% of infants and 91% of children (one false negative). Combining clinical variables with the $^1$H-MRS variables maintained the ability to predict attention and executive functioning outcome in 100% of infants and increased the ability to predict attention and executive functioning outcome to 100% of children.

For predictive analysis of language neuropsychological functioning, using clinical variables alone correctly predicted outcome in 91% of infants (one false negative) and 67% of children (two false positives, one false negative). When $^1$H-MRS variables were considered alone outcome was correctly predicted in 100% of infants and 73% of children (two false positives and one false negative). Combining clinical variables with the $^1$H-MRS variables maintained the ability to predict language functioning outcome to 100% in infants and increased the ability to predict language outcome to 100% in children.

For predictive analysis of sensorimotor neuropsychological functioning, analysis of infants was not possible because all 11 infants had sensorimotor outcome scores below the average range of functioning. Using clinical variables alone correctly predicted outcome in 78% of children (one false positive, one false negative). When $^1$H-MRS variables were considered alone outcome was correctly predicted in 91% of children (one
false negative). Combining clinical variables with the $^1$H-MRS variables increased the ability to predict sensorimotor functioning outcome in 100% of children.

For predictive analysis of visuospatial neuropsychological functioning, using clinical variables alone correctly predicted outcome in 64% of infants (one false positive, three false negatives) and 67% of children (two false positives, one false negative). When $^1$H-MRS variables were considered alone outcome was correctly predicted in 82% of infants (two false negatives) and 73% of children (one false positive and two false negatives). Combining clinical variables with the $^1$H-MRS variables correctly predicted outcome for 100% of infants and 89% of children (one false negative).

For predictive analysis of memory functioning, using clinical variables alone correctly predicted outcome in 73% of infants (three false negatives) and 67% of children (two false positives, one false negative). When $^1$H-MRS variables were considered alone outcome was correctly predicted in 83% of infants (two false negatives) and 91% of children (one false negative). Combining clinical variables with the $^1$H-MRS variables increased the ability to predicted memory functioning outcome to 100% in infants, yet decreased predictive ability of children to 78% (one false positive, one false negative).

As with intellectual functioning, poor outcome was predicted more accurately than good outcome again appearing to stem from the high correlated between lactate presence and poor neuropsychological outcome. Discriminant function predictions of clinical and $^1$H-MRS findings with neuropsychological outcome are presented in Table 14 for infants Table 15 for children.
### Table 14

**Prediction of Neuropsychological Outcome Group for Infants**

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>Attention/Executive</th>
<th>Language</th>
<th>Sensorimotor</th>
<th>Visuospatial</th>
<th>Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% correct predict</td>
<td># of False Pos.</td>
<td>% of False Neg.</td>
<td># of False Pos.</td>
<td>% of False Neg.</td>
</tr>
<tr>
<td>Clinical -EEG <strong>Age at injury</strong></td>
<td>91% 0 1</td>
<td>91% 0 1</td>
<td>-- - -</td>
<td>64% 1 3</td>
<td>73% 0 3</td>
</tr>
<tr>
<td>-EEG only</td>
<td>73% 0 3</td>
<td>73% 0 3</td>
<td>-- - -</td>
<td>64% 1 3</td>
<td>82% 0 2</td>
</tr>
<tr>
<td>MRS -NAA/Ch -Ch/Cr -Lactate</td>
<td>100% 0 0</td>
<td>100% 0 0</td>
<td>-- - -</td>
<td>82% 0 2</td>
<td>82% 0 2</td>
</tr>
<tr>
<td>-Lactate only</td>
<td>73% 0 3</td>
<td>73% 0 3</td>
<td>-- - -</td>
<td>82% 0 2</td>
<td>82% 0 2</td>
</tr>
<tr>
<td>Clinical and MRS</td>
<td>100% 0 0</td>
<td>100% 0 0</td>
<td>-- - -</td>
<td>100% 0 0</td>
<td>100% 0 0</td>
</tr>
</tbody>
</table>

**missing two cases on EEG variable for children, N= 9**

### Table 15

**Prediction of Neuropsychological Outcome Group for Children**

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>Attention/Executive</th>
<th>Language</th>
<th>Sensorimotor</th>
<th>Visuospatial</th>
<th>Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% correct predict</td>
<td># of False Pos.</td>
<td>% of False Neg.</td>
<td># of False Pos.</td>
<td>% of False Neg.</td>
</tr>
<tr>
<td>Clinical -EEG <strong>Age at injury</strong></td>
<td>67% 2 1</td>
<td>67% 2 1</td>
<td>78% 1 1</td>
<td>78% 1 1</td>
<td>67% 2 1</td>
</tr>
<tr>
<td>-EEG only**</td>
<td>67% 2 1</td>
<td>67% 2 1</td>
<td>78% 1 1</td>
<td>67% 1 2</td>
<td>67% 2 1</td>
</tr>
<tr>
<td>MRS -NAA/Ch -Ch/Cr -Lactate</td>
<td>91% 0 1</td>
<td>73% 1 2</td>
<td>91% 0 1</td>
<td>73% 1 2</td>
<td>91% 0 1</td>
</tr>
<tr>
<td>-Lactate only</td>
<td>82% 1 1</td>
<td>73% 1 2</td>
<td>91% 0 1</td>
<td>73% 1 2</td>
<td>82% 1 1</td>
</tr>
<tr>
<td>Clinical and MRS</td>
<td>100% 0 0</td>
<td>100% 0 0</td>
<td>100% 0 0</td>
<td>89% 0 1</td>
<td>78% 1 1</td>
</tr>
</tbody>
</table>

**missing two cases on EEG variable for children, N= 9**
The hypothesis that combining clinical and $^1$H-MRS variables would provide the greatest predictive power for long-term intellectual and neuropsychological outcome was supported for seven of the eight outcome variables including verbal, non-verbal and full-scale intellectual functioning as well as attention/executive functioning, language abilities, sensorimotor abilities, and visuospatial abilities. For one variable, memory abilities, $^1$H-MRS variables were more predictive when entered alone. Adding the clinical variables for this measure decreased prediction, adding one false positive.

**Intellectual Outcome Findings – Regression Analysis**

Hierarchical multiple regression was conducted to determine whether accuracy of outcome could be improved through the ability to predict outcome scores. Missing data were excluded in pair-wise fashion (2 missing cases on EEG reading). Age at time of injury was entered on the first step to control for covariate age effects. Since $^1$H-MRS variables correlated more highly with outcome measures that did the clinical variable EEG, they were entered in the second step. In the analyses where EEG significantly correlated with outcome (see above) EEG was entered as a third step.

The predictor variables that correlated with full-scale intellectual functioning were presence of lactate, Ch/Cr, and EEG reading. Regression with these variables provided a good fit (R$^2$ adj = 60%) with a statistically significant relationship ($F_{4,15} = 7.99$, $p = .001$). After controlling for the shared variance associated with the child's age ($F_{1,18} = 1.95$, $p = .180$), one of the four predictor variables, lactate, contributed significantly to full-scale intellectual functioning ($F_{chg 3,15} = 9.13$, $p = .001$). Adding the clinical variable EEG to $^1$HMRS variables did not significantly increase predictive power.
Regression analysis findings for full-scale intellectual functioning are provided in Table 16.

Table 16

Regression Analysis of Full-Scale Intellectual Functioning

<table>
<thead>
<tr>
<th>Dependent Variable: Full-Scale Intellectual Functioning</th>
<th>Standardized Coefficient Beta</th>
<th>T</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at injury</td>
<td>.036</td>
<td>.178</td>
<td>.861</td>
</tr>
<tr>
<td>Presence of Lactate</td>
<td>-.587</td>
<td>-3.353</td>
<td>.004</td>
</tr>
<tr>
<td>1H-MRS Ch/Cr</td>
<td>-.250</td>
<td>-1.186</td>
<td>.254</td>
</tr>
<tr>
<td>EEG</td>
<td>-.219</td>
<td>-1.304</td>
<td>.212</td>
</tr>
</tbody>
</table>

The predictor variables that correlated with verbal intellectual functioning were presence of lactate, Ch/Cr, and EEG reading. Regression with these variables provided a good fit \( R^2 \text{ adj} = 52\% \) with a statistically significant relationship \( F_{4,15} = 6.15, p = .004 \). After controlling for the shared variance associated with the child's age \( F_{1,18} = 3.10, p = .095 \), one of the four predictor variables, lactate, contributed significantly to verbal intellectual functioning \( F_{\text{chg}3,15} = 6.26, p = .006 \). Adding the clinical variable EEG to \(^1\)HMRS variables did not significantly increase predictive power \( R^2 \text{ chg} = .018, F_{1,15} = 1.701, p = .212 \). Regression analysis findings for verbal intellectual functioning are provided in Table 17.
Table 17

Regression Analysis of Verbal Intellectual Functioning

<table>
<thead>
<tr>
<th>Dependent Variable:</th>
<th>Standardized Coefficient Beta</th>
<th>T</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Intellectual Functioning</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Independent Variables:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at injury</td>
<td>.088</td>
<td>.420</td>
<td>.681</td>
</tr>
<tr>
<td>Presence of Lactate</td>
<td>-.494</td>
<td>-2.622</td>
<td>.019</td>
</tr>
<tr>
<td>1H-MRS Ch/Cr</td>
<td>-.273</td>
<td>-1.235</td>
<td>.236</td>
</tr>
<tr>
<td>EEG</td>
<td>-.246</td>
<td>-1.369</td>
<td>.191</td>
</tr>
</tbody>
</table>

The predictor variables that correlated with non-verbal intellectual functioning were presence of lactate, Ch/Cr, and EEG reading. Regression with these variables provided a good fit ($R^2_{adj} = 59\%$) with a statistically significant relationship ($F_{4,15} = 7.67, p = .001$). After controlling for the shared variance associated with the child's age ($F_{1,18} = 0.74, p = .401$), one of the four predictor variables, lactate, contributed significantly to non-verbal intellectual functioning ($F_{chg 3,15} = 9.65, p = .001$). Adding the clinical variable EEG to 1H-MRS variables did not significantly increase predictive power ($R^2_{chg} = 0.18, F_{1,15} = 1.701, p = .212$). Regression analysis findings for non-verbal intellectual functioning are provided in Table 18.

Table 18

Regression Analysis of Non-Verbal Intellectual Functioning

<table>
<thead>
<tr>
<th>Dependent Variable:</th>
<th>Standardized Coefficient Beta</th>
<th>T</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Verbal Intellectual Functioning</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Independent Variables:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at injury</td>
<td>-.136</td>
<td>-.701</td>
<td>.494</td>
</tr>
<tr>
<td>Presence of Lactate</td>
<td>-.627</td>
<td>-3.577</td>
<td>.003</td>
</tr>
<tr>
<td>1H-MRS Ch/Cr</td>
<td>-.296</td>
<td>-1.440</td>
<td>.170</td>
</tr>
<tr>
<td>EEG</td>
<td>-.204</td>
<td>-1.223</td>
<td>.240</td>
</tr>
</tbody>
</table>
The primary predictor for each of the intellectual variables was the presence or absence of lactate. Differences in scores between children with and without lactate present are shown in Figure 1 below. Notably, no child with lactate had any intellectual scale score above 70.

![Figure 1](image)

**Presence of Lactate**

Figure 1. Full-Scale, Verbal, and Non-Verbal Intellectual Functioning for Children With and Without Lactate Present.

**Neuropsychological Outcome Findings-Regression Analysis**

The predictor variables that correlated with attention/executive neuropsychological functioning were presence of lactate, Ch/Cr, and EEG reading. Regression with these variables provided a good fit ($R^2_{adj} = 52\%$) with a statistically significant relationship ($F_{4,15} = 6.08, p = .004$). After controlling for the shared variance
associated with the child's age ($F_{1,18} = 3.76, p = .068$), one of the four-predictor variables, lactate, contributed significantly to attention/executive functioning ($F_{chg,3,15} = 5.85, p = .007$). Adding the clinical variable EEG to $^1$HMRS variables did not significantly increase predictive power ($R^2_{chg} = .018, F_{1,15} = 1.701, p = .212$). Regression analysis findings for attention/executive neuropsychological functioning are provided in Table 19.

Table 19
Regression Analysis of Attention/Executive Neuropsychological Functioning

<table>
<thead>
<tr>
<th>Dependent Variable:</th>
<th>Standardized Coefficient Beta</th>
<th>T</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention/Executive Functioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at injury</td>
<td>- .109</td>
<td>- .522</td>
<td>.609</td>
</tr>
<tr>
<td>EEG</td>
<td>- .258</td>
<td>- 1.431</td>
<td>.173</td>
</tr>
<tr>
<td>Presence of Lactate</td>
<td>- .451</td>
<td>- 2.385</td>
<td>.031</td>
</tr>
<tr>
<td>$^1$H-MRS Ch/Cr</td>
<td>- .258</td>
<td>- 1.431</td>
<td>.173</td>
</tr>
</tbody>
</table>

The predictor variables that correlated with language neuropsychological functioning were presence of lactate and Ch/Cr. Regression with these variables provided a good fit ($R^2_{adj} = 50\%$) with a statistically significant relationship ($F_{3,18} = 8.04, p = .001$). After controlling for the shared variance associated with the child's age ($F_{1,20} = 6.90, p = .016$), one of the four predictor variables, lactate, contributed significantly to language functioning ($F_{chg,2,18} = 6.66, p = .007$). EEG was not significantly correlated with language functioning and was not put into the analysis. Regression analysis findings for language neuropsychological functioning are provided in Table 20.
The predictor variables that correlated with sensorimotor neuropsychological functioning were presence of lactate, Ch/Cr, and NAA/Ch. Regression with these variables provided a good fit ($R^2$ adj = 61%) with a statistically significant relationship ($F_{4,17} = 9.10, p = .000$). After controlling for the shared variance associated with the child's age ($F_{1,20} = 14.88, p = .001$), two of the four predictor variables, age at injury and lactate, contributed significantly to sensorimotor functioning ($F_{chg3,17} = 4.54, p = .016$). EEG reading was not significantly correlated with sensorimotor functioning and was not placed into the analysis. Regression analysis findings for sensorimotor neuropsychological functioning are provided in Table 21.
The predictor variables that correlated with visuospatial neuropsychological functioning were presence of lactate, Ch/Cr, and NAA/Ch. Regression with these variables provided a good fit ($R^2_{adj} = 55\%$) with a statistically significant relationship ($F_{4,17} = 7.28$, $p = .001$). After controlling for the shared variance associated with the child's age ($F_{1,20} = .032$, $p = .859$), one of the four predictor variables, lactate, contributed significantly to visuospatial functioning ($F_{chg,1} = 9.68$, $p = .001$). EEG reading was not significantly correlated with visuospatial functioning and was not put into the analysis. Regression analysis findings for attention/executive neuropsychological functioning are provided in Table 22.

Table 22
Regression Analysis of Visuospatial Neuropsychological Functioning

<table>
<thead>
<tr>
<th>Independent Variables:</th>
<th>Standardized Coefficient Beta</th>
<th>T</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at injury</td>
<td>-.356</td>
<td>-1.591</td>
<td>.130</td>
</tr>
<tr>
<td>Presence of Lactate</td>
<td>-.652</td>
<td>-4.152</td>
<td>.001</td>
</tr>
<tr>
<td>$^{1}$H-MRS Ch/Cr</td>
<td>-.440</td>
<td>-1.875</td>
<td>.078</td>
</tr>
<tr>
<td>$^{1}$H-MRS NAA/Ch</td>
<td>-.027</td>
<td>-.103</td>
<td>.919</td>
</tr>
</tbody>
</table>

For analysis with memory functioning, five variables, EEG reading, presence of lactate, $^{1}$HMRS ratios of Ch/Cr, NAA/Ch, and age at injury were considered for hierarchical multiple regression analysis. Tabachnick and Fidell (1989) suggest that ‘a bare minimum requirement’ regarding the number of cases per independent variable is at least five cases. The current study includes 22 cases, suggesting that only four
independent variables should be used. Thus, the analysis was run twice, the second time taking out the clinical variable EEG reading to examine the effect on predictiveness.

Regression with all five variables provided a good fit ($R^2_{\text{adj}} = 67\%$) with a statistically significant relationship ($F_{5,14} = 8.60, p = .001$). After controlling for the shared variance associated with the child's age ($F_{1,18} = 7.90, p = .012$), one of the four predictor variables, lactate, contributed significantly to memory functioning ($F_{\text{chg} 4,14} = 6.40, p = .004$). Removing the fifth variable from analysis decreased adjusted $R^2$ by 5% for a new adjusted $R^2$ of 62% ($F_{4,17} = 9.44, p = .000$). Regression analysis findings for memory neuropsychological functioning are provided in Table 23.

Table 23

Regression Analysis of Memory Neuropsychological Functioning

<table>
<thead>
<tr>
<th>Dependent Variable: Memory Functioning</th>
<th>Standardized Coefficient Beta</th>
<th>T</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at injury</td>
<td>.347</td>
<td>1.646</td>
<td>.122</td>
</tr>
<tr>
<td>Presence of Lactate</td>
<td>-.430</td>
<td>-2.766</td>
<td>.015</td>
</tr>
<tr>
<td>$^1$H-MRS Ch/Cr</td>
<td>-.372</td>
<td>-1.743</td>
<td>.103</td>
</tr>
<tr>
<td>$^1$H-MRS NAA/Ch</td>
<td>-.190</td>
<td>-.800</td>
<td>.473</td>
</tr>
<tr>
<td>EEG</td>
<td>-.269</td>
<td>-1.773</td>
<td>.098</td>
</tr>
</tbody>
</table>

Similar to the findings for intellectual functioning, the primary predictor for each of the neuropsychological variables was the presence or absence of lactate. Differences in scores between children with and without lactate present are shown in Figure 2 below.

No child with lactate presence had a neuropsychological functioning score above 87.
Regression analysis with age and the $^1$H-MRS variables was significantly, moderately predictive of every outcome variable including full-scale intellectual functioning, verbal intellectual functioning, non-verbal intellectual functioning, attention/executive functions, expressive and receptive language abilities, sensorimotor and visuospatial abilities, and short-term memory skills. The findings support discriminant function findings and lend validation to the possibility that outcome scores can be predicted from clinical and $^1$H-MRS variables. Age at the time of injury demonstrated a significant predictive effect for the neuropsychological functions of language, sensorimotor abilities, and memory abilities. Thus the hypothesis that age at
the time of injury would serve as a covariate main effect in outcome was partially supported.

In regression analysis, the clinical variable EEG did not significantly increase the predictive power in any of the regression equations, suggesting that the most accurate predictors of outcome were age at the time of injury and the \(^{1}\text{H-MRS} variables.

Exploratory Analysis of MRI Findings

Based on previous research and due to limited sample size, MRI findings were divided into three broad areas of injury: frontal injury, left side injury (i.e., left parietal, temporal, cerebellar areas), and right side injury (i.e., right parietal, temporal, cerebellar areas). Any indication of potential injury including evidence of lesions, subdural or epidural hematomas, hemorrhage or edema were scored positive for injury in the broad area of the brain in which it occurred. Based on this very general categorization of injury, 19 of 22 children demonstrated frontal lobe injury, 17 of 22 children sustained left hemisphere injury, and 15 of 22 children showed evidence of right hemisphere injury. Univariate analysis of variance was utilized to examine differences in the means of intellectual and neuropsychological deficits.

It was hypothesized that children with frontal lobe injury would evidence difficulty in the areas of temporal sequencing and understanding the gist of a story. The mean scores for children with frontal lobe injury compared to children without evidence of frontal injury were not statistically discrepant on the NEPSY narrative memory task ($t = .297, F_{1,13} = 1.26, p = .283$). Mean differences on the Luria Nebraska narrative memory item could not be determined due to lack of variability (i.e., all participants
achieved the same score on the item). It was further hypothesized that children with frontal lobe injury would perform less well on tasks assessing attention and executive functions. Mean scores were not discrepant for children with and without frontal injury on the NEPSY attention/executive functions core domain (r = .223, F₁,₁₃ = .682, p = .424), or on the Luria Nebraska attention/executive functions items (r = .033, F₁,₅ = .005, p = .994).

Regarding left hemisphere injury, it was hypothesized that children who sustained injury to this area would demonstrate impairment on abilities of semantic memory. The NEPSY narrative memory task and Luria Nebraska verbal memory items were used to assess this hypothesis. Mean scores were not discrepant for children with and without left hemisphere injury on the NEPSY narrative memory subtest (r = .065, F₁,₁₃ = .055, p = .818), or on the Luria Nebraska verbal memory items (r = -.451, F₁,₅ = 1.279, p = .309). It was further hypothesized that general language abilities would be affected by left hemisphere injury. However, mean scores did not differ on either the NEPSY language core domain (r = -.127, F₁,₁₃ = .212, p = .653) or the Luria Nebraska combined language clinical scales (r = .014, F₁,₁₃ = .001, p = .976). The third hypothesis for left hemispheric injuries was that visual representation memory would be impaired as a result of injury to this area. Findings for mean differences on the NEPSY memory for faces (r = -.042, F₁,₁₃ = .023, p = .881) and the Luria Nebraska visual memory items (r = -.361, F₁,₅ = .750, p = .426) were not significantly different.

Hypothesis regarding right hemisphere injury were that vocabulary abilities and visuospatial functions would be impaired from injury to this area. Mean scores on the
vocabulary subtest of the Wechsler intellectual assessment did not differ for children with right hemisphere injury from children without right hemisphere injury ($r = -0.197, F_{1,20} = 0.810, p = 0.379$). Additionally, regarding visuospatial functioning, both the NEPSY visuospatial core domain ($r = 0.074, F_{1,13} = 0.071, p = 0.794$) and the Luria Nebraska visual clinical scale ($r = 0.506, F_{1,5} = 1.717, p = 0.247$) failed to reach significance.

The findings did not support the hypothesis that focal effects assessed with MR Imaging would predict specific neurocognitive deficits.

**Exploratory Analysis of Accidental vs. Non-Accidental Trauma**

Based on prior research, it was hypothesized that children who experienced a closed head injury through non-accidental means may evidence greater long-term deficits when compared with children who had been injured through an accidental event. A possible confound of etiology is child’s age at the time of injury. Most children who sustain closed head injury through non-accidental trauma are younger than children injured through accidental trauma. In the current study all of the children who sustained a non-accidental trauma were between the ages of one month and 15 months ($x = 6.33$ months, $SD = 5.18$ months). Children who sustained an accidental brain injury ranged in age between 0.27 months and 173 months ($x = 102.9$ months, $SD = 64.59$ months). Additionally, age is an important predictor of long-term outcome for children with head injury. Thus, univariate analysis of variance was conducted, keeping age constant as a covariate.
After controlling for age, the mean intellectual outcomes for etiology were not statistically discrepant for measures of full-scale intellectual functioning ($F_{2, 21} = 3.74$, $p = .068$), verbal intellectual functioning ($F_{2, 21} = 3.16$, $p = .091$), or non-verbal intellectual functioning ($F_{2, 21} = 3.50$, $p = .077$) although a trend toward significance was evidenced for each of these outcome measures. The variance accounted for ranged from $R^2_{adj} = .103$ to .192. Etiology findings for intellectual functioning are presented in Table 24.

Table 24

Intellectual Outcome for Children With and Without Non-Accidental Trauma With Control for Age at Injury

<table>
<thead>
<tr>
<th>Dependent Variable:</th>
<th>F</th>
<th>Sig.</th>
<th>Eta Squared</th>
<th>$R^2$</th>
<th>Adj $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-scale intellectual functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at injury (in months)</td>
<td>.063</td>
<td>.805</td>
<td>.003</td>
<td>.246</td>
<td>.166</td>
</tr>
<tr>
<td>Etiology</td>
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<td>.068</td>
<td>.164</td>
<td>.246</td>
<td>.166</td>
</tr>
<tr>
<td>Verbal intellectual functioning</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at injury</td>
<td>.017</td>
<td>.896</td>
<td>.001</td>
<td>.269</td>
<td>.192</td>
</tr>
<tr>
<td>Etiology</td>
<td>3.164</td>
<td>.091</td>
<td>.143</td>
<td>.269</td>
<td>.192</td>
</tr>
<tr>
<td>Non-verbal intellectual functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at injury</td>
<td>.405</td>
<td>.532</td>
<td>.021</td>
<td>.189</td>
<td>.103</td>
</tr>
<tr>
<td>Etiology</td>
<td>3.498</td>
<td>.077</td>
<td>.155</td>
<td>.189</td>
<td>.103</td>
</tr>
</tbody>
</table>

After controlling for age, the mean neuropsychological outcomes for etiology were not statistically discrepant for measures of attention and executive functions ($F_{2, 21} = 2.52$, $p = .129$), language ($F_{2, 21} = 3.36$, $p = .082$), sensorimotor abilities
(F_{2,21} = 1.14, p = .300), or memory skills (F_{2,21} = 2.68, p = .118), although there was a trend toward significance with language functions. Children who sustained a non-accidental trauma were significantly more likely to demonstrate visuospatial difficulties (F_{2,21} = 6.63, p = .019) with etiology explaining uniquely an additional 24-percent of the variance. Etiology findings for neuropsychological functioning are presented in Table 25.

Table 25

Neuropsychological Outcome for Children With and Without Non-Accidental Trauma

With Control for Age at Injury

<table>
<thead>
<tr>
<th>Dependent Variable: Attention/Executive functioning</th>
<th>F</th>
<th>Sig.</th>
<th>Eta Squared</th>
<th>R^2</th>
<th>Adj R^2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent Variables:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at injury (in months)</td>
<td>.149</td>
<td>.704</td>
<td>.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td>2.516</td>
<td>.129</td>
<td>.117</td>
<td>.270</td>
<td>.193</td>
</tr>
</tbody>
</table>

| Dependent Variable: Language functioning          |      |      |             |      |         |
| **Independent Variables:**                        |      |      |             |      |         |
| Age at injury                                     | .460 | .506 | .173        |      |         |
| Etiology                                          | 1.136| .082 | .150        | .368 | .302    |

| Dependent Variable: Sensorimotor functioning      |      |      |             |      |         |
| **Independent Variables:**                        |      |      |             |      |         |
| Age at injury                                     | 3.978| .061 | .001        |      |         |
| Etiology                                          | 3.164| .300 | .056        | .459 | .402    |

| Dependent Variable: Visuospatial functioning      |      |      |             |      |         |
| **Independent Variables:**                        |      |      |             |      |         |
| Age at injury                                     | 3.193| .090 | .144        |      |         |
| Etiology                                          | 7.525| .013 | .284        | .285 | .210    |

| Dependent Variable: Memory functioning             |      |      |             |      |         |
| **Independent Variables:**                        |      |      |             |      |         |
| Age at injury                                     | .771 | .391 | .039        |      |         |
| Etiology                                          | 2.682| .118 | .124        | .364 | .297    |
The hypothesis that children who suffered a brain injury from non-accidental trauma would evidence greater long-term neuropsychological impairment was partially supported. Children who sustained a non-accidental trauma were more likely than other children to have greater visuospatial and memory impairment.
Discussion

When a child has a trauma resulting in head injury, those involved in the child’s care desire to accurately estimate whether, and the extent to which injury will impair future functioning. A reliable estimate of long-term functioning can help parents and health care professionals develop a plan that will aid the child’s recovery to the greatest extent possible. An accurate understanding of how the child will progress can also help parents maintain hope and begin the process of coping with changes that their child may experience. Yet, most current clinical indicators of injury are limited in their ability to predict long-term intellectual and neuropsychological outcome, leading investigators to search for more sensitive measures of prediction.

Clinical Variables

In the current study, the only clinical variable that was predictive of intellectual and neuropsychological functioning was EEG reading. Presence of non-reactive pupils, GCS score, days unconscious at MR Imaging, and whether the child experienced cardiac arrest were not predictive of intellectual or neuropsychological functioning. With regard to neurological functioning the GCS was predictive for infants and presence of cardiac arrest was predictive for children. Lack of prediction of clinical variables may stem in part from the small sample size. For example, presence of non-reactive pupils and the number of days unconscious did show low to moderate correlations with some outcome measures, suggesting that they would correlate significantly in a larger sample. However, for most measures, these variables as well as the GCS score and presence of cardiac arrest demonstrated low correlation with outcome. In combination the
predictiveness of clinical variables increased, yet continued to account for approximately 30% of the outcome variance, a relatively small predictive value. The findings are consistent with previous research on children with closed head injury and suggest the need for more sensitive indicators of injury severity (Levin et al., 1992; Ashwal et al., 2000).

A surprising finding was the lack of correlation between the GCS score and outcome on intellectual and neuropsychological measures. Possibly, the lack of prediction stems from the relatively large number of children in the study who were preverbal at the time of injury. As indicated above, the scale may be a less sensitive indicator of injury for preverbal children (Fletcher et al., 1995). Another possibility is that the GCS is an indicator of severe injury that is more likely to be captured when the sample size is stratified into severity levels based on neurological functioning. In the current study, children were stratified based on functioning either within or below the average range on measures of intellectual and neuropsychological functioning. When compared with neurological outcome, children in this study were more likely to have poor intellectual or neuropsychological functioning and yet be considered to have good outcome when assessed for neurological functioning alone. It appears that the GCS may be most predictive for children who are very seriously impaired.

\(^1\)H-MRS Variables

The \(^1\)H-MRS variables of NAA/Ch, Ch/Cr, and presence of lactate correlated with outcome variables. Previous studies have demonstrated that clinical and \(^1\)H-MRS variables are predictive of neurological functioning. This is the first known study that
validates the predictive value of $^1$H-MRS indicators for intellectual and neuropsychological functioning. Notably throughout the analysis, the single most predictive variable of outcome was presence of lactate. In previous studies of children with closed head injury, presence of lactate was particularly indicative of poorer outcome for neurological functioning in infants and children. This study provides support indicating that lactate presence is also a significant prognostic indicator of poorer intellectual and neuropsychological functioning for infants and children who sustain a closed head injury. Of the 7 of 22 children in this study who had lactate presence following injury, none had an intellectual functioning standard score above 70 or a neuropsychological functioning score above 86.

Ch/Cr was predictive of outcome for all intellectual and neuropsychological outcome measures. Ch/Cr was also predictive of neurological outcome in children but not infants. In previous studies the predictive value of Ch/Cr has been mixed. In studies where injury was sustained through means that included non-trauma related insult, Ch/Cr was usually not predictive of outcome (Auld et al., 1995; Ashwal et al., 1997). Yet in a study that examined only children who sustained closed head injury Ch/Cr was an indicator of injury severity (Ashwal et al., 2000). Possibly an increase in Ch/Cr may be more predictive for children with closed head injury than for children who suffer for CNS insult through some other means.

NAA/Ch was predictive of three outcome areas, sensorimotor abilities, visuospatial abilities, and memory skills. NAA/Cr was not predictive of outcome. This finding contrasts with previous studies that found NAA/Cr to be correlated with neurological outcome. Both NAA and Cr decrease in response to injury severity.
Possibly in the current study the two metabolites decreased similarly, canceling out the effect of change in either metabolite independently.

Covariate Main Effects

The covariate main effect of age at the time of injury correlated with most of the outcome measures, whereas the amount of time passed since injury did not. Age at the time of injury was predictive of outcome on most measures including verbal intellectual functioning, attention and executive functions, language functions, sensorimotor functions, and memory functions, with children who were older at the time of injury performing better than children who were younger at the time of injury. One area of neuropsychological functioning, sensorimotor abilities, were particularly affected by age effects. All 11 of the infants demonstrated sensorimotor abilities below the average range of functioning, whereas 5 of 11 children demonstrated sensorimotor functioning below the average range. These findings are consistent with previous studies indicating that younger children suffer greater adverse effects of closed-head injury than older children on measures of expressive language ability, sensorimotor abilities, attention/executive functions, and memory skills (Ewing-Cobbs et al., 1989; Miner et al., 1996; Levin et al., 1982, Ewing-Cobbs et al., 1994, Ewing-Cobbs, et al., 1989, Kaufman et al., 1993).

Whereas verbal intellectual functioning was correlated with age at injury, non-verbal (performance) intellectual functioning and full-scale intellectual functioning were not. Findings from previous research regarding non-verbal and full-scale intellectual functioning are mixed. Ewing-Cobbs et al. (1989) found that although motor and language functions correlated with time of injury, full-scale intellectual functioning did
not. However, Levin et al. (1982) found that children performed more poorly with regard to non-verbal and full-scale intellectual functioning than did adolescents.

Additionally visuospatial abilities were not correlated with age at the time of injury. Of the limited number of studies found in the literature examining the effects of head injury on visuospatial skills, analysis of age effects was not provided. It appears that visuospatial skills that develop in the right hemisphere may be largely developed within the first few months of life (Chiron, Jambaque, Nabbout, Lounes, Syrota, & Dulac, 1997). If so, age effects may be mitigated by the relatively few infants younger than a few months in the study. For example, visuospatial scores were compared for children 6 months or younger at the time of injury with children older than six months. Children older than 6 months had a mean visuospatial score approximately twenty-two scaled points higher than younger children ($p = .085$).

Findings such as these have contributed to hypotheses in more recent research indicating that sustaining a head injury is more likely to impair developing skills and the development of new skills, whereas skills that have been previously developed remain intact. This hypothesis may explain why sensorimotor skills that are developing during the early years may be drastically impaired when a child suffers a head injury during the first three or four years of life. Motor skills are fairly well developed during infancy and toddler-hood and thus, may be significantly less susceptible to injury effects after that time. Additionally, age effects for visuospatial skills may go undetected in samples where the age span is large and few of the children studied sustained head injuries when very young.
Contrary to prediction, the amount of time that passed since injury showed non-significant low correlations ($r = .087$ to $.256$) with outcome. In studies cited above children’s functioning improved with the passage of time with most improvement demonstrated during the first year following injury. In the current study, children were assessed at least one year following the time of injury, with the majority of children having sustained head injury 4-6 years prior to assessment. There was a trend towards significance for when comparing children who were injured 1-3 years prior to assessment with children who were injured 4-6 years prior to assessment. Although not directly assessed, these findings likely reflect previous research indicating that most improvement occurs during the first year of recovery. Also indicated is that improvement continues, though to a limited degree, particularly during the second and third years following injury.

**Combined Clinical and $^1$H-MRS Variables**

In the current study, the most accurate prediction of how a child would recover from injury resulted from combining clinical and $^1$H-MRS variables. When children were divided into two groups, one group of children functioning in the average range of abilities, and the other group of children functioning below the average range of abilities, a combination of clinical and $^1$H-MRS variables were able to accurately predict 100% of the children’s future functioning for areas of full-scale and verbal intellectual functioning and 100% of functioning with regard to attentiveness, planning and problem solving, and language abilities. Combined clinical and $^1$H-MRS variables accurately predicted visuospatial and memory functioning for 100% of infants and sensorimotor functioning.
for 100% children. Prediction for visuospatial and memory skills was somewhat lower with 78% accurate classification of memory skills and 89% accuracy in classification of visuospatial skills. Notably, for most outcome measures $^1$H-MRS variables were more predictive of outcome than were clinical variables of age at injury and EEG reading. Additionally, combining clinical with $^1$H-MRS variables provided the most accurate predictive ability.

Discriminant analysis offers information about whether a particular person is more likely to be placed in one or another group. In this study, discriminant analysis was utilized to determined whether a child with head injury would with have long-term functional difficulties that are below the average range, and therefore may be aided through additional intervention, or in the average range or above, where normal functioning is expected. Regression analysis provides an estimate of a child’s actual functioning score on any particular outcome measure. For example, if it is estimated that a child will function in the average range of abilities or above, regression analysis will provide an estimate of where, within that range, a child’s functional abilities are likely to be. Similarly, for a child whose estimated abilities may be below the average range, regression analysis will provide a scored estimate indicating whether functional abilities will be mild, moderate, or severe.

In this study regression analysis was performed to determine the best predictive combination of variables for each outcome measure. For all outcome measures including full-scale intellectual functioning, verbal and performance intellectual functioning, as well as areas of attention and planning/problem solving, receptive and expressive language abilities, sensorimotor abilities, visuospatial abilities, and short-term memory
functions, combining the clinical variables (age at injury, and EEG reading for most measures) with $^{1}$H-MRS ratios (NAA/Ch, Ch/Cr) and presence of lactate, provided significant prediction of outcome. Prediction of outcomes ranged from explaining 50% to 67% of the variance. In the study, poorer outcomes were predicted more effectively than good outcomes, primarily because of the significant correlation of lactate presence with poorer outcomes. For example, when regression analyses were conducted without entering lactate presence as an indicator, predictive ability decreased substantially ($R^2_{\text{adj}} = .134$ to .403), indicating the importance of this predictor for poor outcome.

These findings support previous research findings indicating that $^{1}$H-MRS ratios and presence of lactate coupled with other clinical indicators provide the most effective prediction when neurological outcome is categorized as either good or poor. Additionally this study may be the first to extend previous research through assessment of several long-term outcome measures of intellectual and neuropsychological functioning. This study clearly demonstrates that combining clinical variables with $^{1}$H-MRS metabolite ratios (NAA/Ch, Ch/Cr) and presence of lactate provides strong predictive abilities for neuropsychological outcome. With the high accuracy of predictiveness for children functioning at or above the average range with regard to intellectual and neuropsychological skills as well as children with areas of functioning below the average range of skills, parents can be provided with information about the extent to which their child may engage in age appropriate activities, and also about future intellectual and neuropsychological functioning. More specifically, for children with predicted functioning scores below the average range, specific interventions are particularly warranted to provide the best possibility of appropriate interventions.
Knowledge of this information can help health professionals develop an appropriate treatment plan geared toward specific areas of impairment.

In the current study, combining clinical and $^1$H-MRS variables accounted for approximately 50% of the variance in regression analysis. Of interest is whether a child’s future functioning following closed head injury may be improved when an estimate of pre-injury intellectual functioning is considered. Based on research suggesting that previously developed skills tend to be less affected than newly developing skills, children with higher pre-injury intellectual functioning may achieve a higher level of functioning following injury. Another consideration for future research is the extent to which post-injury rehabilitation intervention aids in the improvement of intellectual and neuropsychological functioning skills. For example, most improvement occurs during the first year of functioning. A valuable finding would be the extent to which rehabilitative interventions such as speech and language therapy, physical and occupational therapy, and interventions or compensatory measures for strengthening and improving skills (e.g., memory strategies, visual or verbal learning approaches) result in functional improvement during the first year and beyond. Additionally, some of the parents in the study described their own interventions in the early post-injury phases and indicated that they continue to work diligently with their child to overcome injury-related difficulties. Consideration of these and other external influences on recovery from head injury may provide information about how to create the most effective intervention possible.
**Focal Effects**

Focal effects were not demonstrated in this group of head injured children. Likely, focal effects were not demonstrated because of the twenty-two children in the study, only one child had sustained observable injury to a circumscribed area. The remaining children sustained injury that encompassed both hemispheres or one hemisphere and the frontal lobe region. The findings support previous research that indicates a closed head injury results in diffuse trauma that affects several brain areas (Krause, 1995). The findings point out the importance of study design in testing for focal effects. Looking for focal effects may be best addressed when head injured individuals have sustained a focal injury rather than closed head trauma. The findings also point to the serious nature of injury resulting from closed head trauma. When closed head trauma occurs, the brain is assaulted with acceleration/deceleration forces and coup/contra coup injuries, leaving few areas unaffected.

**Accidental vs. Non-Accidental Trauma**

After controlling for age effects, children who suffered a non-accidental trauma were more likely to suffer long-term deficits in the areas of visuospatial and memory functions than children who sustained accidental trauma. Although, etiology of head injury was not predictive of functioning for other outcome measures, possibly the lack of significant findings stems from the disproportionate number of infants in the study who sustained non-accidental trauma.

Previous researchers have suggested that children who sustain head injury through non-accidental trauma demonstrated greater long-term impairment and have further
hypothesized that the reason age effects are seen for children with head injuries may be a result of the large number of infants who receive non-accidental injuries (Ewing-Cobbs et al., 1995). This study provides supportive evidence of the disproportionate number of infants who are injured through non-accidental means. Sadly, 41% of the children assessed sustained closed head injuries through non-accidental trauma. Of those children, all were infants at the time of injury. Graphically, it appears that infants who were injured through non-accidental means did suffer greater impairment. However, only two of the infants in the current study sustained a head injury that was not due to accidental trauma. Because of the small number of infants who were injured through accidental means, statistical analysis is not a reliable indicator of etiological effects.

The nine children who suffered a non-accidental trauma did demonstrate lower functioning than the two children who sustained an accidental injury. The findings were consistent on measures of intellectual functioning as demonstrated on Figure 3 and neuropsychological functioning as demonstrated on Figure 4.
Etiology of Head Injury

Figure 3. Intellectual Functioning in Children Who Sustained Non-Accidental and Accidental Closed Head Injuries.

Etiology of Head Injury

Figure 4. Neuropsychological Functioning in Children Who Sustained Non-Accidental and Accidental Closed Head Injuries.
An effective study design for future studies may control for age effects through assessing infants (as compared to older children) who have suffered head injury through accidental and non-accidental means. In this way, it would be possible to assess etiological effects independent of age. Clearly, more research is needed to assess the effects of non-accidental trauma. Additionally, the large number of children who suffer non-accidental closed head injuries indicates the importance of preventive intervention for families at risk for inflicting non-accidental injuries.

Study Limitations

Based on previous research indicated above, most studies examining childhood closed head injury demonstrated moderate to large effect sizes. In the current study the number of children who may be assessed depends upon the number of children who have sustained head injury and received treatment that included $^1$H-MRS. Fewer children were available to test than the suggested number of children needed to assure statistical significance and/or power of .80. The recommended number of children to be assessed was 40. Small sample sizes are not uncommon in studies examining closed head injury in children. However, findings should be interpreted with some caution as fewer participants were assessed than recommended (Tabacknick & Fidell, 1989). Based on the skew of several variables it appears most likely that predictive ability was underestimated rather than overestimated. Also, because most effect sizes in the current study were at least moderate in prediction, they lend support to their consideration as meaningful, even in analysis where statistical significance may not have been achieved (Riggs, Warka,&
Lastly, to minimize the possibility of reporting over-inflated effect sizes, predictive findings that were adjusted for small sample size were reported in this paper. A second caveat of the study was that a group of control children was not assessed so it was not possible to directly compare the prediction of clinical and $^1$H-MRS variables in terms of predictability of outcome for non-head injured children with children who were head injured. In one study located in the literature, researchers found a correlation between levels of N-acetylaspartate, creatine, and choline and intellectual functioning on measures of full-scale, verbal, and performance intellectual functioning (Jung, Brooks, Yeo, Chiulli, Weers, & Sibbitt, 1999). The findings indicate that these metabolites may be predictive of intellectual functioning in individuals without brain injury. However, reference in the current study can be made solely regarding prediction of intellectual and neuropsychological functioning for children with closed head injury. No assumptions can be made regarding the predictiveness of $^1$H-MRS variables for intellectual and neuropsychological functioning in non-head injured children.

Lastly, in previous studies, $^1$H-MRS research included neonates (children less than one month at the time of injury) in addition to infants and children. Clinical and $^1$H-MRS variables that are predictive for neonates differ from clinical and $^1$H-MRS variables that are predictive of outcome for infants and children (Holshouser et al., 1997). Only one neonate was assessed in the current study so results of the study do not generalize to include neonates who sustain a closed head injury.
Study Implications

This study draws attention to considering lactate as possibly the most significant clinical indicator available in predicting adverse intellectual and neuropsychological effects for children who sustain a closed head injury. Children with lactate presence following injury demonstrated consistently impaired performance, usually below the average range of functioning, on all eight intellectual and neuropsychological outcome measures. As indicated above by Holshouser et al., (1997) presence of lactate was an ominous finding regarding neurological impairment for children who suffered a closed head injury. This study offers evidence that presence of lactate is also an ominous finding regarding intellectual and neuropsychological impairment for those children.

Further, evidence indicates that prediction of intellectual and neuropsychological functioning is possible, particularly for children with poorer long-term functioning. This study may be the first to demonstrate the predictive value of \(^1\)H-MRS variables with long-term intellectual and neuropsychological outcome. Findings indicate 100% predictive ability on most outcome measures when a child’s functioning is considered in terms of functioning at or above the average range and below that range. Also indicated is the importance of continuing to increase the predictive ability of children with good outcome.

This study provides supportive evidence that parents can be offered a longed-for indication of the recovery that their child can achieve following a closed head injury. If indicators of outcome are suggestive of possible impairment, parents can be provided with services that may help them to understand and cope with the changes their child may experience. Also, rehabilitative services can be put into place to offer the child the best
possible chances for recovery. If indicators of outcome are suggestive of full recovery, parents can receive reassurance and an increased sense of hope. Also, services may be made available as needed, thereby minimizing the use of interventions that may be of limited help.

Further, Ashwal et al. (2000) have underscored the importance of outcome indicators erring ‘on the side of false optimism’ to avoid ‘incorrect prediction of poor outcome.’ These findings provide support that combining clinical and $^1$H-MRS variables for outcome prediction typically predicted 100% of outcome. Yet, for outcome variables that were not predicted with 100% accuracy, group misplacement was more likely to incorrectly indicate good outcome, rather than poor outcome on most measures. Thus, combining clinical and $^1$H-MRS variables to predict outcome may offer the most accurate and optimistic indication of recovery.

A concerning finding was that infants were significantly more likely to have sensorimotor and visuospatial impairment than older children who suffered a closed head injury. Similarly, younger children were more likely to suffer impairment than older children. Findings support previous hypothesis that newly developing skills and skills not yet developed may incur greater impairment than previously developed skills. Additionally, the findings point to the importance of conducting further research with infants who suffer a closed head injury. If future studies indicate similar findings, it may be clinically indicated for all infants to receive assessment of sensorimotor and visuospatial skills following injury to provide appropriate intervention.

In conclusion, the findings validate the use of a combination of clinical (EEG reading and age at injury) and $^1$H-MRS (NAA/Ch, Ch/Cr, presence of lactate) variables
for good prediction of intellectual and neuropsychological recovery in children who suffer a closed head injury. Further, age at the time of injury was predictive of outcome on most measures and age findings highlight the importance of continued research, particularly for infants with closed head injury. Additionally, injury etiology was predictive of outcome on two measures, with a trend toward significance on other long-term indicators, emphasizing the importance of intervention for families at risk of inflicting non-accidental trauma.
References


APPENDIX

Loma Linda University
Student Research in Kids F.A.R.E. Laboratory

Informed Consent Document
For
Intellectual and Neuropsychological Functioning in Children
with a History of Closed Head Injury

Purposes and Procedures

We conduct studies, such as this one, in order to further our knowledge of child behavior and development. We want you and your child to find his or her experience to be positive and informative. Therefore, we will keep you and your child fully informed of everything we will be doing.

The purpose of this research study in which your child is invited to participate is to learn more about intellectual and neuropsychological functioning in children who have experienced a closed head injury. Your child has been invited to participate in this study because he or she has experienced a closed head injury during childhood or falls into a comparison group of children who have not experienced head injury but have received a $H$-MR spectroscopy examination.

Your child will be asked to perform a number of tasks. In some tasks you child will be asked to answer questions with verbal responses. In other tasks your child will be asks to respond to visual cues by either verbally responding or pointing to the responses. In other tasks your child will be asked to use manual dexterity to complete the tasks. Participation in this study involves one or two visits to the laboratory and should take about 3 hours.

Benefits and Risks

Your child’s participation in this research study will result in the direct benefit of assessment findings and referral information if necessary. We anticipate hat your child’s participation will contribute to our understanding about the recovery of skills as well as areas that may benefit from intervention in children.

The procedures used in this study are not harmful. Therefore, the committee at Loma Linda University that reviews studies (Institutional Review Board) has determined that your child’s participation in this study exposes him or her to minimal risk.

Alternative Treatments and Costs

Because this study does not involve treatment of any medical or psychological condition, consideration of alternative treatments is not applicable.

Your child’s participation in this research study will be without cost to you or any third party.

Inducement

As our way of saying thank you to your child for his or her participation in the study, your child will receive a $10 gift certificate to Wal-Mart.

_______ Initial
_______ Date
Participant’s Rights and Confidentiality

All of the information gathered during your child’s participation in this research study is confidential. No public presentation or any publication resulting from this study will disclose your child’s identity. The information he or she provides will be grouped with that of other participants. If you or your child have any questions regarding this study we will be happy to answer them.

We prefer only to work with volunteers, and your child may terminate that experiment at any time for any reason. All you have to do is tell the experimenter that you wish to do so. Whether or not your child completes these tasks, we will be happy to discuss his or her performance with you, and your child will still receive the gift certificate. Please feel free to ask any questions that you may have about this experiment at any time.

If you have any questions at a later date, you can contact Kiti Freier, Ph.D. at the Department of Psychology, Loma Linda University, 909/478-8577. Or if you wish to contact an impartial third party not associated with this study regarding any complaint you may have about this study, you may contact the Office of Patient Representatives, Loma Linda University Medical Center, Loma Linda, CA, 92354 (telephone number: 909/824-4647) for further information and assistance.

Consent Statement

We ask you to sign below to indicate that:

1. My child is participating in this experiment on a voluntary basis.

2. I am aware that either my child or I may terminate this experiment at any time.

3. I understand this experiment does not involve risk or physical or mental harm or injury to my child and as such has been designated as “minimally risky” by the Institutional Review Board.

4. The nature of this experiment has been explained to me and to my child at the level my child can understand.

5. I understand that all information gained from my child as a result of his or her participation will remain confidential.

6. My child and I have the right to ask questions about this experiment and to have them answered to our satisfaction.

7. I have been offered a copy of this Informed Consent Document.

8. I hereby give voluntary consent for my child to participate in this study. Signing this document does not waive my rights nor does it release the investigators or institution from their responsibilities.

Parent’s Signature ______________ Date ______________

Participant’s Signature ______________ Date ______________

Experimenter’s Signature ______________ Date ______________