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Cerebral Metabolic and Neuropsychological Outcomes Following Mild Traumatic Brain Injury

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Cerebral Metabolic and Neuropsychological Outcomes Following Mild Traumatic Brain Injury

by

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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 Doctor of Philosophy.

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ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ANOVA	Analysis of Variance
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory, Second Edition
BG	Basal Ganglia
BYI-II	Beck Youth Inventories, Second Edition
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CC	Corpus callosum
Cho	Choline containing compounds
CPT-II	Conners' Continuous Performance Task – II, computer version
Cr	Creatine + phosphocreatine
DKEF-S	Delis-Kaplan Executive Function System
DS	Digit Span
DSC-PWI	Dynamic susceptibility contrast perfusion weighted MRI
FG	Frontal grey matter
FW	Frontal white matter
FSIQ	Full Scale Intelligence Quotient
Glx	Glutamate + Glutamine
LLU	Loma Linda University
LMI	Logical Memory I
LMII	Logical Memory I

MRI	Magnetic Resonance Imaging
MRSI	Magnetic resonance spectroscopic imaging
mTBI	Mild Traumatic Brain Injury
Ins	Myo-inositol
NAA	N-acetylaspartate
POG	Parietal and occipital grey matter
PIQ	Performance Intelligence Quotient
PW	Parietal white matter
QOL	Quality of Life
RAVLT	Rey Auditory Verbal Learning Test
RCFT	Rey Complex Figure Test
TBI	Traumatic Brain Injury
TH	Thalami
TMSE	Transactional Model of Stress and Emotion
VIQ	Verbal Intelligence Quotient
WAIS-IV	Wechsler Adult Intelligence Scale, Fourth Edition
WAYS	Ways of Coping Questionnaire
WCST	Wisconsin Card Sort Test
WCST-64	Wisconsin Card Sort Test – 64 card version
WHO	World Health Organization
WHOQOL-100	World Health Organization Quality of Life Measure
WISC-IV	Wechsler Intelligence Scale for Children, Fourth Edition
WMS-III	Wechsler Memory Scale, Third Edition

WTAR	Wechsler Test of Adult Reading

ABSTRACT OF THE DISSERTATION

Cerebral Metabolic and Neuropsychological Outcomes Following
Mild Traumatic Brain Injury

by

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Dr. Susan A. Ropacki, Chairperson

Traumatic brain injury (TBI) in adolescents and adults can result in cognitive, emotional, behavioral and neurological deficits that can persist more than a year after an injury. The current preliminary study used 3D magnetic resonance spectroscopic imaging (MRSI) and comprehensive neuropsychological assessment to determine if prolonged cerebral metabolic and cognitive alterations occur in individuals with persistent neurocognitive deficits following a mild TBI (mTBI). The current study evaluated the potential interactions between cerebral metabolism and neuropsychological performance, coping style, mood, and perceived quality of life in mTBI subjects with chronic post-concussive symptoms. The mTBI subjects performed worse than controls on neuropsychological measures, endorsed poorer mood and reported significantly poorer perceived quality of life than healthy controls. Additionally, cerebral metabolic differences were found between groups as well as significant interactions between neuropsychological performance and cerebral metabolism. The current findings may potentially guide future research to more eagerly strive to understand possible ways to alter cerebral metabolism, possibly through medication, diet, or other behavioural changes.

CHAPTER 1

INTRODUCTION/ LITERATURE REVIEW

Introduction

Traumatic brain injury (TBI) represents a significant public health and fiscal challenge, as approximately 1.5 million brain injuries occur each year in the United States and approximately 5 million Americans are living with disabilities related to those injuries (Xiong, Mahmood, Chopp, 2010). The annual cost of TBI in the United States exceeds $56 billion (Xiong, et. al., 2010). The majority of these brain injury cases (70-80%) are mild in both initial severity and outcome and many experience a complete resolution of symptoms (Arciniegas et. al., 2005). The cognitive sequelae following mild TBI (mTBI) is commonly more subtle and less often recognized than in the moderate or severe TBI population (Arciniegas et. al., 2005).

The mTBI patient may be overlooked by health care providers, educators and researchers due to the mild nature of the injury and symptomatology when compared to the more complex impairments following a moderate or severe brain injury. Up to 20% of mTBI individuals are left with chronic post-concussive syndrome, with related cognitive, emotional, behavioral and neurological deficits that will persist more than a year following the injury (Arciniegas et. al., 2005). Post-concussive syndrome describes a set of symptoms including cognitive, physical, and emotional/ behavioral dysfunction that result from TBI (Arciniegas et. al., 2005). As noted by Arciniegas (2005), typical acute and/or chronic post-concussive symptoms include cognitive problems such as attention, memory and executive dysfunction. Additionally,

emotional and behavioral problems are noted including increased irritability, anxiety, depression, affective lability, apathy and impulsivity (Arciniegas et. al., 2005). There is a body of literature devoted to understanding the cognitive changes following mild to severe TBI and the resultant deficits. However, there is a lack of research correlating neuroimaging findings to neuropsychological deficits and clinical outcomes in the post-concussive mTBI population. Moreover, psychological dysfunction and its correlation to cognition following TBI it is not clearly understood and the question of why individuals with similar injuries experience different neuropsychological deficits remains unanswered. Therefore, research is needed to better understand if alterations in cerebral metabolism as detected by neuroimaging can be found in individuals with persistent neurocognitive deficits following a mild TBI. This study intends to assess whether chronic metabolic changes mediate cognitive and psychological outcomes in mTBI patients with chronic post-concussive symptoms.

Traumatic Brain Injury: Description and Classifications

Approximately 1.4 million individuals sustain a TBI each year in the US (Tsushima et. al., 2009). Within this patient population, males are about twice as likely as females to suffer from a TBI, although it has been reported that female mortality rates are 1.28 times greater than males (Tsushima et. al., 2009). The incidence of TBI occurs most often in young adulthood and in old age; there is significant evidence that age negatively correlates with poorer prognostic outcomes (Stapert et. al., 2006). Falls are the primary cause of TBI in children and elderly, and it is estimated that 64% of

TBIs suffered by infants are a direct result of child abuse (Williamson et. al., 1996). Elderly patients are more likely than young TBI patients to develop traumatic mass lesions, including subdural hematomas and intra-cerebral hemorrhage from mild to moderate TBI (Stapert et. al., 2006).

A formal definition of mild TBI is given by the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (Kwok et. al., 2008). According to this definition, mild TBI implies that a patient has a traumatically induced physiological disruption of brain function which is marked by at least one of the following: (1) loss of consciousness of approximately 30 minutes or less; (2) after 30 minutes, an initial Glasgow Coma Scale (GCS) of 13-15; and (3) post-traumatic amnesia (PTA) not longer than 24 hours (Kwok, 2008). The GCS assesses neurological domains including verbal response, eye opening, and motor response following injury and is useful for predicting neurobehavioral outcome (Lucas et. al., 2006). PTA is the period following the TBI that is characterized by disorientation, confusion, and retrograde and anterograde amnesia (McGhee et. al., 2006). Anterograde amnesia and disorientation are typically assessed over a period of several days following the injury and may consist of evaluations of orientation and memory. The Wastmead Post-Traumatic Amnesia Scale (WPTA) is a measure of anterograde amnesia and disorientation that is frequently used to assess PTA.

TBI may result in focal, multifocal, or diffuse cerebral dysfunction and typically involves structures and systems beyond the initial site of impact (Lucas et. al., 2006). Brain damage that is the result of closed head injury typically occurs in two

stages, a primary injury followed by a secondary injury. Primary injuries result from initial damage whereas secondary injuries typically occur in response to the cascade of events that follow a primary injury. The primary injury in mild TBI is most typically diffuse axonal injury (DAI), in which axons are damaged or destroyed by acceleration and deceleration forces acting on axonal bundles and blood vessels, resulting in damage to the white matter (Kwok, 2008). The disruption of consciousness following TBI seems to be related to the extent of DAI (Williamson et. al., 1996).

In addition to DAI, brain contusions, lacerations, and disruption of vasculature can occur as primary injuries (Lucas et. al., 2006). Bruising is often seen at the original site of damage and is often referred to as a coup lesion. The pressure experienced at impact often causes the brain to rebound and hit the skull opposite the initial blow, causing an even larger lesion, known as the contre-coup lesion (Lucas et. al., 2006). Secondary injuries include ischemia, edema, hypoxia, epilepsy, increased intracranial pressure, and neurotransmitter and metabolic changes associated with damage to neurons (Lucas et. al., 2006).

Neurological Functioning Following Mild Traumatic Brain Injury

Following TBI, neuroanatomical changes, cerebral metabolic dysfunction, cerebral blood volume (CBV) and cerebral blood flow (CBF) changes have been observed.

Botteri, Bandera, Minelli, & Latronico (2008) explain that TBI involves a "primary" mechanical impact that abruptly disrupts the brain parenchyma with shearing and tearing of blood vessels and brain tissue. The primary injury then triggers a cascade

of events characterized by activation of molecular and cellular responses that lead to "secondary" ischemic injury. Cerebral metabolism is often reduced after TBI, as a result of the trauma itself or the associated use of sedatives (Botteri, Bandera, Minelli, & Latronico, 2008). Conversely, excitotoxicity may lead to an increase in cerebral metabolism (Botteri, Bandera, Minelli, & Latronico, 2008). Botteri et. al. (2008) explain that both situations will alter the cerebral blood flow (CBF) threshold for tissue survival. One study examining moderate TBI subjects revealed TBI subjects had significantly lower volumes of white matter and total brain volume than healthy controls (Vannorsdall, Rao, & Schretlen, 2007). This group revealed TBI subjects' white matter volume was reduced by an average of 0.83 standard deviations. Additionally, Vannorsdall et. al. (2007) found the TBI and control groups did not differ significantly in grey matter, CSF, total intracranial, or the ratio of brain to total intracranial volume. Another study of moderate to severe TBI patients revealed a mean frontal lobe atrophy of 12 +/- 11% and global brain atrophy of 8.5 +/- 4.5% at 6 months after the TBI (Marcoux, McArthur, Miller, Glenn, Villablanca, Martin, Hovda, Alger, & Vespa, 2008).

Metabolic dysfunction has also been observed following TBI. Animal studies have suggested that metabolic changes can be related to behavioral deficits, as the timing of recovery from metabolic depression is associated with the recovery of behavior deficits (Hovda et al., 1996). Determining the metabolic characteristics of a TBI may not only facilitate the prediction of the resulting neurological deficits, but could also direct the types of therapeutic treatments attempted. One interesting study investigated thalamic glucose metabolism in severe and closed traumatic brain injury subjects (Lull, Noe, Lull, A-Panach, Chirivella, Ferri, Pez-Aznar, Sopena, & Robles, 2010). This study

revealed thalamic hypometabolism in TBI subjects, with differences in metabolism most pronounced in the internal regions of the thalamus. Thalamic hypometabolism was positively correlated with TBI severity, as measured by decreased consciousness. Other studies have examined the cerebral metabolic dysfunction following TBI. Using F fluorodeoxyglucose positron emission tomography (FDG-PET), a significant reduction in the resting cerebral metabolic rate of glucose (CMRglc) has been found that lasts for days, weeks or months following TBI (Bergsneider et al 2000, 2001; Langfitt et al 1986; Yamaki et al 1996). Another study utilized functional near infrared spectroscopy (fNIRS) to examine possible changes in cerebral oxygenation patterns following moderate to severe TBI (Russell, Scanlon, Arenth, Schultheis, Zafonte, & Ricker, 2007). Results of this study demonstrated that oxygenation patterns for control participants suggested tightly coupled right and left hemispheric responses, while patterns among TBI subjects appeared to be "uncoupled". The study authors suggest that these findings may be a function of inter-hemispheric disconnection thought to be associated with significant white matter tract and diffuse axonal injuries known to occur with TBI. Marcoux and colleagues (2008) showed that at 6 months after a moderate to severe TBI, subjects demonstrated persistent metabolic crises, as reflected by an elevated lactate/pyruvate ratio in normal appearing posttraumatic frontal lobes.

In addition to the metabolic dysfunction, a number of studies have reported decreased cerebral blood volume (CBV) and cerebral blood flow (CBF) in areas of normal-appearing brain following a mild TBI (mTBI) using both SPECT and MRI methods (Garnett et. al, 2001; Lewine et al., 2007, Bonne et al., 2003). In a study by Bonne et al. (2003) twenty-eight clinically symptomatic male subjects with mTBI and

twenty matched controls underwent brain SPECT imaging. The study revealed that mTBI subjects demonstrated regions of hypoperfusion in frontal, pre-frontal and temporal cortices, and sub-cortical structures. Additionally, the group found that the regional cerebral blood flow (rCBF) was reduced in symptomatic subjects with longstanding mTBI and unremarkable structural brain imaging. Schroder, Muielaar, Fatouros, Kuta, and Choi (1998) carried out cerebral blood flow (CBF) studies on severe head injury patients. The group found CBF ipsilateral to the ischemic area was lower than CBF in the side contralateral to the ischemic area. Additionally, CBF in the ipsilateral side was significantly reduced compared to the contralateral side. The results of these studies suggest that cerebral hypoperfusion occurs as a result of TBI, (Garnett et. al, 2001), however, there is a lack of research correlating neuroimaging findings to neuropsychological deficits and clinical outcomes in the post-concussive mTBI population.

Magnetic resonance spectroscopy (MRS) has emerged as a non-invasive tool to measure several key brain metabolites present in the human brain. Specifically, N-acetylaspartate (NAA) represents both neuronal integrity and neuronal mitochondrial function, creatine + phosphocreatine (Cr) represents cellular energy status, total choline containing compounds (Cho) represents cellular membrane integrity and turnover, myo-inositol (Ins) represents astrocyte proliferation and brain osmotic balance, with glutamate + glutamine (Glx) representing neurotransmitter function. MRS has been successfully used to identify metabolic changes in normal appearing grey matter and white matter of the corpus callosum, frontal, occipital and parietal lobes of moderate and severely injured TBI subjects (Cecil et. al., 1998; Garnett et. al., 2000; Brooks et. al, 2001). Garnett and

colleagues (2001) reported that following mild to moderate TBI, subjects demonstrated a reduced brain NAA/Cr ratio and an increased Cho/Cr ratio when compared with controls. Garnett and colleagues (2001) conclude that there is an early reduction in N-acetylaspartate and an increase in choline compounds in normal-appearing white matter, which correlates with head injury severity. The group suggests that this may provide a pathological basis for the long-term neurological disability following TBI. Additionally, MRS has been shown to predict neurological outcome in both pediatric (Ashwal et al., 2000; Babikian et. al., 2006) and adult (Holshouser et. al., 2006; Shutter et. al., 2006) acute trauma subjects. Positive correlations have been found between MRS and neurobehavioral outcomes in children (Walz et. al., 2008). Specifically, when compared to children who had experienced an orthopedic injury, TBI children demonstrated differences on parent reports of externalizing behaviors, executive functions, and social competence (Walz et. al., 2008). Schonberger, Ponsford, Reutens, Beare, Clarke, and O'Sullivan (2011) studied the relationship between mood disorders and MRI findings following mild to severe TBI. However, the majority of subjects had moderate to severe injuries. Authors found that the presence of lesions in the frontal, temporal, parietal and the sublobar regions was not related to depression. However, an imbalance of left vs right frontal and parietal viable brain volumes was related to the development of depression (Schonberger, et. al., 2011).

While not extensive, and mostly related to concussion, there is a body of literature describing MRS findings in the mTBI population. Specifically, Govind and colleagues (2010) found decreases in NAA and the NAA/Cr ratio, and increases in Cho and the Cho/NAA ratio, within all lobes of the mTBI subject group, with the largest differences

seen in white matter. This study did not find any significant correlations between MRSI outcomes or neuropsychological performance and Glascow Coma Scale scores. Govindaraju et al. (2004) reported reduced NAA/Cr, increased Cho/Cr, and reduced NAA/Cho in mTBI subjects as measured by MRSI. In another study comparing concussed athletes to non-concussed athletes, concussed athletes showed significant decreases in glutamate in the primary motor cortex and NAA in the prefrontal and primary motor cortices, with no group differences found for neuropsychological performance (Henry, Tremblay, Boulanger, Ellemberg, & Lassonde, 2010). Yeo et al. (2011) found elevated white matter concentrations of Cr and Glx in the mTBI group and decreased gray matter concentrations of Glx in individuals with sub-acute mTBI when compared to controls. Lin and colleagues also reported significantly increased Cho and Glx in mTBI subjects, as compared to controls (Lin, Liao, Merugumala, Prabhu, Meehan, & Ross, 2012). Additionally, significant reductions in NAA/Cho and NAA/Cr ratios have been reported in the genu of the corpus callosum for mTBI subjects (Johnson, Gay, Neuberger, Horovitz, Hallett, Sebastianelli, & Slobounov, 2012). Johnson et al. (2012) also found that an increased number of mTBIs correlated with the length of time for symptom resolution. In another study comparing mTBI subjects to healthy controls, significantly lower levels of gray matter Glx and higher levels of white matter Cr was found in mTBI subjects (Gasparovic, Yeo, Mannell, Ling, Elgie, Phillips, Doezema, & Mayer, 2009). Additionally, this group found Cr levels to be predictive of executive function and emotional distress in the both groups. Another study compared brain metabolism in 40 post-concussive athletes to 30 healthy control subjects; subjects were evaluated at 3, 15, 22 and 30 days post-injury using MRSI (Vagnozzi, Signoretti,

Cristofori, Alessandrini, Floris, Isgro, Ria, Marziale, Zoccatelli, Tavazzi, Del Bolgia, Sorge, Broglio, McIntosh, & Lazzarino, 2010). Interestingly, at 30 days post-injury, all post-concussive athletes showed complete recovery of cerebral metabolism, with metabolite ratios comparable to controls. Of note, this experimental group reported symptoms clearance between 3 and 15 days following concussion. In another study, researchers evaluated limbic abnormalities in remote mild to severe TBI and its correlation with psychiatric functioning and social functioning (Capizzano, Jorge, and Robinson, 2010). Capizzano and colleagues (2010) found that remote TBI subjects demonstrated MRS abnormalities in the limbic system with reduced NAA/Cr ratio in the left hippocampus. These abnormalities correlated significantly with psychosocial adjustment. Additionally, authors found that the left ACC NAA/Cr ratio was reduced in TBI patients with a clinical diagnosis of mood disorder. While these studies have provided important findings regarding cerebral metabolism following TBI, more research is needed to evaluate the relationship between these cerebral metabolic findings and functional outcomes. These studies highlight a gap in the literature, which has not adequately examined the relationships between neuroimaging, neuropsychological, and psychological outcomes in the mTBI patient. To our knowledge there are no studies describing the long-term metabolic changes as they relate to neuropsychological, mood, and quality of life outcomes in mTBI individuals with chronic post-concussive syndrome.

Neuropsychological Functioning Following Mild Traumatic Brain Injury

Long-term neuropsychological outcomes following mTBI are reasonably

understood and are important to consider. Specifically, reduced capacity for learning, slowed information processing, and disruption in complex integrative functions have been found to be resultant of mTBI (Millis et. al., 2001). One meta-analytic study reviewed 28 publications that summarized injury severity and time post injury as they related to neurocognitive domains in the pediatric population (Babikian & Asornow, 2009). This meta analysis revealed that longitudinal studies of neurocognitive outcomes following mTBI in pediatric populations do not show changes in verbal skills as measured by the Verbal Intelligence Quotient (VIQ), Full Scale Intelligence Quotient (FSIQ), attention, working memory, or visual perceptual functioning over time (Babikian & Asornow, 2009). However, within this meta-analytic study, there are no studies that assessed fluency, memory, or inhibition across time. Another interesting finding within this study by Babikian and Asarnow (2009) is that the mTBI group appeared to make significant gains in nonverbal/performance-based skills as measured by the Performance Intelligence Quotient (PIQ) and processing speed, which was unexpected as these domains are not typically improved with practice (Babikian & Asornow, 2009). Specifically, it was found that small to moderate effects were found for VIQ, PIQ, processing speed, and visual perceptual functioning when subjects were assessed at three time points: 0-5 months post injury, 6-23 months post injury, and 24+ months post injury (Babikian & Asornow, 2009). Of note, significant improvements in immediate visual memory were only observed 0-5 months post injury.

It is reported in the literature that the basic components of attention, including vigilance and sustained attention, as well as the superordinate components of attention control, including selective attention, inhibition, shifting, and divided attention are

impaired following severe TBI (Galbiati et. al., 2009). According to various studies, attentional impairments observed following mild to severe TBI may be the result of reduced rate or capacity of controlled processing, or dysfunctional higher- level processes (Ziino et. al., 2006). Research utilizing tests measuring focused attention, mental speed and control, and forced choice reaction time tasks revealed that severe TBI patients are generally able to cope with interference caused by distracting stimuli, although they tend to require more time (Bate et. al., 2001). Another study found slowed processing speed associated with mild TBI as well as greater variability in processing performance, suggesting impairment and insufficient capacity to complete speed-related tasks (Meyerson et. al., 2009). This literature suggests that impairments in divided and focused attention may result from decreased speed of processing rather than insufficient cognitive capacity. However, it is important to note that pre-injury ADHD and behavioral problems are seen at higher rates in children who experience TBI; these problems are seen at the highest rates in children with severe TBI (Babikian & Asarnow, 2009). Thus post-injury testing in this population may reflect a pre-existing attentional problem. Kwok, Lee, Leung, and Poon (2008) report that in mTBI patients, divided attention was significantly poorer than healthy controls immediately post-injury but recovered in one month and returned to normal within 3 months post- injury. However, this same group found that sustained attention remained impaired for the extent of the study, which was 3 months post-injury. Additionally, Chan (2005) confirmed that patients with mTBI performed significantly worse on measures of sustained attention when tested at an average of 25 months post-injury. It is currently thought that the extent of attentional deficits a patient experiences post-TBI is correlated to the patient's age as well as severity

of the injury. The frontal and temporal regions in the child and adolescent brain are immature, and continue to develop anatomically and functionally beyond adolescence and may be more vulnerable to trauma. A focal lesion in these areas can cause structural and functional changes, thus interfering with the development of these important attentional processing areas (Galbiati et. al., 2009). Further research outlining the implications of mTBI on the developing adolescent brain as it relates to attention and processing deficits is necessary to understand cognitive outcomes following mTBI.

There is evidence that suggests that language capacity, including semantic and phonemic fluency and confrontation naming abilities, may be impaired following mTBI. King, Hough, Vos, Walker, and Givens (2006) assessed the word-finding and word-retrieval capacity of mTBI patients when compared to non-injured control subjects. It was revealed that mTBI patients were significantly slower and less accurate than controls when naming nouns (King et. al., 2006). Additionally, mTBI patients were significantly faster at completing sentences with nouns than with verbs. King and colleagues (2006) suggest that this performance discrepancy may be explained by the fact that noun naming in sentence tasks is easier than verbal naming tasks. Kwok, Lee, Leung, and Poon (2008) reported that immediately post-injury, mTBI patients' verbal fluency, specifically semantic fluency, was significantly poorer than that of healthy controls. At 1-month post-injury mTBI patients' verbal fluency ability was significantly improved, but was still significantly different than the performance of healthy controls. This further highlights the potential short and long-term complications of mTBI and the importance of researching language impairments following brain injuries. It is an aim of the current study to investigate the possible link between psychological factors, including mood,

perceived quality of life and coping style, and neuropsychological performance, including potential language deficits, following mTBI.

Additional cognitive impairments have been revealed in empirical studies with mTBI patients. Visuospatial functioning and visuoconstructional capacity, for example, is shown to decrease following mTBI. Specifically, it is reported that symptomatic mTBI patients show deficits in complex visual information processing as assessed by Event-Related Potentials (ERPs) (Lachapelle, Bolduc-Teasdale, Ptito, & McKerral, 2008). Memory and executive functioning decline have also been found following mTBI. For example, Belanger, Spiegel, and Vanderploeg (2010) revealed that patients who presented with multiple occurrences of mTBI performed poorer on measures of delayed memory and executive functioning than patients who presented with only one occurrence of mTBI. Moreover, significant effects based on injury severity have been found to inversely correlate with executive functioning in children, including planning, goal setting and problem solving (Anderson & Catroppa, 2005). Additionally, children with severe TBI demonstrated slowed and significantly less accurate performance on cognitive flexibility tasks that were mentally demanding (Anderson & Catroppa, 2005).

Mood Functioning Following Mild Traumatic Brain Injury

Psychological outcomes, including depression and anxiety, following TBI can significantly impact an individual's well-being and are important to consider. Jorge and Robinson (2002) explain the reported frequency of depressive disorders following TBI varies from 6-77%. Additionally, these authors stated that within two years of a severe TBI, 33% were characterized as depressed and 26% were characterized as anxious.

Another study found 39% of individuals demonstrated depressive symptoms following mTBI (Schoenhuber and Gentilini, 1988). Another study evaluated the long-term effect of depression following TBI (Holsinger, Steffens, Phillips, Helms, Havlik, Breitner, Guralnik, and Plassman, 2002). Specifically, Holsinger et al. followed 1718 male World War II veterans who were hospitalized between the years 1944 and 1945. From 51–53 years after the initial injury, the rate of depression was 18.5% within the group that had suffered a head injury compared with 13.5% in those who had not. In another study, Mooney and Speed (2001) reported that 24% of their participants with mild TBIs were classified as having developed an acquired anxiety disorder. Moore and colleagues (2002) state that the most common post-TBI anxiety symptoms include free-floating anxiety, fearfulness, intense worry, generalized uneasiness, social withdrawal, inter-personal sensitivity and anxiety dreams. Sigurdardottir, Andelic, Roe, Jerstad, and Schanke (2008) reported that subjective symptoms including headache, fatigue, dizziness, depression and anxiety have been reported by 24–40% mild TBI patients within 3 months post-injury. According to a meta-analytic study by Moore and colleagues (2002), there is no study to that has investigated the prevalence of Generalized Anxiety Disorder using a strictly mild TBI sample. This demonstrates a clear gap in the literature investigating the mood outcomes in a strictly mild TBI population. The majority of the current TBI literature addressing mood outcomes combine severity groups and often pay more attention to the more impairing symptoms seen in the moderate and severe TBI population. Unfortunately, this lack of focus on the chronic post-concussive patient underestimates the residual emotional symptoms experienced by the mTBI population.

Quality of Life Following Mild Traumatic Brain Injury

Quality of life changes have been observed following TBI. Anderson, Brown, Newitt, and Hoile (2011) studied the long-term quality of life outcomes from childhood TBI. The group reported significantly reduced QOL in the severe TBI group when compared to the mild and moderate groups. Unfortunately, this group did not compare the mTBI group's reported QOL with healthy controls. Therefore, the relative decline of this group's QOL was likely underestimated as they were only compared to more severe TBI subjects. Moran and colleagues (2010) evaluated quality of life in pediatric mTBI patients. Contrary to previously discussed findings, this group found that when compared to children who had suffered an orthopedic injury, mTBI children did not demonstrate significantly reduced QOL. This group concluded that brain injury in and of itself was not predictive of QOL. However, another group found that following mTBI, veterans scored lower than did healthy controls on a measure of QOL at three months and one year post- injury (Daggett, Bakas, & Habermann, 2009). Additionally, Kalpakjian et. al. (2004) reported that mild to severe TBI patients had significantly lower QOL and social support, and higher negative affect than nondisabled individuals. Current TBI literature is inconsistent with regards to QOL outcomes. Additionally, with the majority of studies comparing QOL in mTBI patients to QOL in moderate to severe TBI patients, there are very few studies that compare QOL in mTBI patients to healthy controls. This may underestimate the true decline of QOL in the mTBI patient. Overall, there is more research needed to better understand QOL as an outcome measure specifically in the chronic post-concussive mTBI population.

While a significant amount of research has contributed to our current understanding of TBI, there is clearly a lack of research on factors that may act as possible mediators to cognitive outcome following mTBI. There is currently a dearth of research exploring the possible relationship between psychological factors, such as coping style and perceived quality of life, and cognition following mTBI. Additionally, more research is needed to better understand neuropsychological outcomes following mTBI, including language abilities, verbal and nonverbal memory, and executive functioning. A significant amount of current literature compares mTBI patients to moderate and severe TBI patients, which oftentimes underestimates the neuropsychological deficits and overestimates the cognitive capacity of mTBI patients. It is thus essential to examine psychological mediating factors and to compare mild TBI patients with healthy controls in order to add depth to the current body of research on the nature and outcome of cognitive functioning after mTBI and the possible impact of psychological factors on these outcomes.

Predictive/ Mediating Factors of Outcome

Prognostic outcome following TBI can be described as the ability to predict a patient's function both psychologically and cognitively on a time continuum. This prognosis is valuable and can be utilized to develop expectations and treatment strategies post-TBI. The ability to statistically correlate psychological factors with cognitive benchmarks may offer the patient and caregiver a better understanding of cognitive potential or deficits based on neuropsychological evaluation.

TBI Severity

As previously discussed, TBI severity is predictive of resultant deficits in cognitive sequelae, including attention, processing speed, and executive functioning. Injury severity is highly predictive of neuropsychological outcomes and is an important predictor of the extent of cognitive deficits following TBI. Babikian and Asarnow (2009) report longitudinal studies of mild, moderate, and severe TBI patients that were assessed at 3 time points: 0-5 months post-injury, 6- 23 months post-injury, and 24+ months post-injury. Specifically, it is found that in the pediatric population, mild TBI patients generally demonstrate few impairments in general intelligence, attention and executive skills, and memory, and tend to show some recovery in these domains two years post injury (Babikian & Asarnow, 2009). Within the pediatric moderate TBI population, it is found that post-injury neurocognitive impairments involve several domains, including general intellectual functioning, executive skills, processing speed, attention, verbal fluency, inhibition, and problem solving (Babikian & Asarnow, 2009). In contrast, the authors reported that in the moderate TBI group, working memory, memory and visual perceptual skills were not statistically different from non-injured controls. Additionally, Babikian and Asarnow (2009) reported statistically significant improvements in FSIQ, PIQ, processing speed, attention, problems solving, and visual perceptual functioning within the first 2 years following moderate TBI (Babikian & Asarnow, 2009). No cognitive changes were observable after two years post injury in the pediatric moderate TBI group (Babikian & Asarnow, 2009). The severe TBI pediatric patients showed significant impairments in nearly all neurocognitive domains at two years post-injury. When severe TBI patients were

compared to non-injured controls, as well as mild and moderate TBI patients, the severe TBI patients demonstrated significantly more cognitive deficits across time points. Specifically, deficits were noted within general intellectual functioning, verbal memory, visual perceptual skills, executive functioning, verbal fluency, processing speed, attention, problem solving, and working memory domains (Babikian & Asarnow, 2009). At 6-23 months post-injury, it was found that moderate to large improvements were observed in general intellectual functioning (FSIQ), performance IQ (PIQ), processing speed, and visual perceptual functioning. Interestingly, no neurocognitive changes were observed after 23 months.

Demographic Factors

Demographic factors including, age, gender, education, and ethnicity have also been implicated as important predictors of long-term neurocognitive outcomes. Another longitudinal study found that five years after injury, a substantial portion of individuals with moderate to severe TBI continue to show impairments in learning, memory, complex attention, and processing speed (Millis et. al., 2001). Age was the only significant predictor of these cognitive changes following injury. Specifically, for every increase of 10 years of age at the time of injury, the risk of subsequent neuropsychological decline went up 4.97 times (Millis et. al., 2001). The predictive role of gender was identified in a study by Brewster and colleagues (2009). These researchers found that women performed significantly better on the Short Category Test, which measures executive functions, and the Trail Making Test, which assesses processing speed, following mTBI. At fifteen months following injury, the women showed better

executive processing than the men. Shames et. al (2007) found that higher education levels were positively correlated with an individual's likelihood of returning to work following mild to severe TBI. In a meta-analytic study by Gary and colleagues (2009) it was found that prior to mild to severe TBI, African Americans and Hispanics were generally younger, male, more likely to be unemployed and unmarried, earned less money and were less likely to have health insurance than Caucasians. This same study found that African Americans and Hispanics were 3-4 times more likely than Caucasians to acquire TBIs through acts of violence. Additionally, patients who were less acculturated, espousing more traditional cultural values and beliefs, scored lower than Caucasians on a composite measure of overall neuropsychological test performance (Gary et. al., 2009). Specifically, poorer neuropsychological functioning was observed on tests of attention, orientation, language, visuomotor/processing speed, visuospatial/constructional skills and memory. Of note this group of less acculturated individuals performed poorer than Caucasians even after controlling for injury severity, time since injury, age, sex, years of formal education, and socioeconomic status (Gary et. al., 2009). Overall, Gary and colleagues (2009) indicated ethnicity may be related to differences in functional outcomes, community integration and quality of life following TBI. In contrast, Proctor and Zhang (2008) researched the performance of European Americans, African Americans, and Latino/a Americans on tests of executive function following TBI and found no statistically significant impact of ethnicity on the Wisconsin Card Sort Test (WCST), a measure of cognitive flexibility and novel problem solving. In consideration of ethnicity as it relates to TBI, while there is research on ethnicity and some aspects of outcome, there is little research on ethnicity as a predictor of

neuropsychological outcomes following mTBI. The current study considered age, gender, education, and ethnicity as possible predictors of neuropsychological outcomes. It was a goal of the study to add important information about individual factors that may contribute to prognostic outcomes to the current TBI literature.

Cognitive Factors

Cognitive factors, such as premorbid intelligence and memory following the injury may also play a critical role in predicting functional outcome following TBI, including return to work. O'Connell (2000) conducted a study involving 43 adult TBI patients in which the outcome variable was return to work and predictor variables included demographic, intellectual, and memory data. Specifically, independent variables included age, gender, race, education, occupation, Performance IQ, Verbal IQ, verbal and nonverbal memory. O'Connell (2000) found that age was negatively correlated with returning to work, whereas higher scores on measures of Performance IQ and verbal memory measures (indicating a higher level of cognitive capacity) were predictive of a greater likelihood of returning to work.

Psychological Factors

It is clearly established through research studies that an important relationship exists between psychological and cognitive functions. The literature in this area provides evidence that psychological factors can meaningfully impact cognitive functioning. For example, a study by Goodman, Knoll, Isakov, and Silver (2005) found a relationship between negative attitudes towards medication and decreased cognitive outcome,

specifically with working memory capacity, in schizophrenic patients. Yen, Cheng, Huang, Ko, Yen, and Chan (2009) studied the relationship between psychosocial adjustment and executive functioning in patients with bipolar disorder and schizophrenia in remission. The results indicated that poor psychosocial adjustment, as evidenced by unemployment, lacking reliable friends and leisure activities is associated with decreased quality of life (Yen et. al., 2009). The authors report that significant correlations exist between executive function, insight, and psychosocial adjustment among schizophrenic and bipolar patients (Yen et. al., 2009). Yen and colleagues (2009) also report a positive association between verbal memory and psychosocial function in bipolar patients. This study demonstrates the relationship between psychosocial function and executive function and verbal memory, which are both important neuro-cognitive tasks. The current literature supports the correlation between various psychological factors, including negative attitudes and psychosocial functioning, and cognitive factors, including working memory, verbal memory and executive functioning, in various mental health populations. However, there is currently a dearth of research investigating the possible correlation between psychological factors, including coping process and perceived quality of life, in the mTBI population.

Psychological factors may mediate the relationship between well-being and cognition and predict long-term prognosis (outcome) following TBI. Studies have found that psychological factors, including perceived quality of life and an individual's coping process, impact functional outcomes, including return to pre-injury independent activities of daily living and cognitively dependent tasks such as work. Quality of life has been defined by Awad and Voruganti (2000) as "feelings of well-being and

satisfaction to issues related to standards of living such as housing, finances, and employment." Quality of life has also been described as the gap between a patient's expectations and achievements (Calman, 1984). The World Health Organization (WHO) defines quality of life as an individual's perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns (World Health Organization, 1997). Coping has been identified as another psychological factor that may impact functional outcomes following TBI. Fontana and McLaughlin (1998) define coping as "the thoughts and acts that people use to manage the internal and external demands posed by a stressful encounter." Folkman and Lazarus (1984) have proposed the transactional model of stress and emotion (TMSE; Lazarus and Folkman, 1984) as a framework to better understand the process by which an individual copes with stressful external stimuli. Folkman and Lazarus (1988) explain that individuals make primary appraisals when initially faced with a stressor; the individual may appraise the stimuli as stressful, positive, controllable, challenging, or irrelevant. The individual will then assert a second appraisal of the situation; this appraisal typically evaluates the individual's own coping resources and options available (Lazarus and Folkman, 1988). This secondary appraisal involves the individual's ability to manage and ameliorate the problem. Keiffer and MacDonald (2011) state that within the TMSE model, coping is considered to be a "process of changing cognitive and behavioral efforts to manage either internal or external demands placed on an individual."

Functional Outcomes

Functional outcomes following TBI are critical to the patient's social, psychological, and economic welfare. Functional outcomes following injury may be defined as the level of an individual's ability to return to premorbid levels of daily functioning. Functional outcome following TBI may be measured as return to work (O'Connell, 2000), as well as self-care, locomotion, communication, and social cognition (Cullen, Park, & Bayley, 2008).

Tsaousides et. al. (2009) found that employment-related and general self-efficacy were strongly related to perceived quality of life. Specifically, TBI patients who reported greater confidence in their ability to meet the demands within the workplace and generally within their lives also reported higher levels of life satisfaction and perceived quality of life. A study by Brewster and colleagues (2009) found that following TBI, only psychological well-being predicted whether or not the patient returned to work, a high level cognitive activity. In another study which examined return to work as a functional outcome, it was found that greater injury severity was associated with decreased life satisfaction (Wood, 2006) and patients with more severe brain injury were the least likely to return to work (Fraser et. al., 2006). Another study found several important factors that were predictive of a mild TBI patient's eventual return to work (Guerin, Kennepohl, Leveille, Dominique, McKerral, 2006). This group found that the number of subjective complaints was significantly associated with the individual's eventual return to work following TBI. Fraser et. al., 2006 reported that the group of TBI patients that was the most able to maintain complex professional work was more likely to have been female, had fewer alcohol

problems, was less severely injured and demonstrated better neuropsychological functioning. Additionally, Shames et. al (2007) reported that patients with more social interaction and pre-injury occupations that included more decision-making capacity were more likely to return to work.

The research is varied with regard to the psychological deficits that follow TBI. Goldstein and Levin (2001) found that within a sample of individuals over the age of 50 who had experienced uncomplicated mild head injury, there were no persistent cognitive deficits. However, these researchers found that although the sample demonstrated normal cognitive functioning, mild TBI patients reported significantly more depressive complaints, somatic concerns, and anxiety than non-injured control subjects. These psychological factors may seriously impact an individual's ability to return to pre-morbid levels of cognitive functioning in terms of critical thinking and ability to work. Another study, conducted in Quebec, Canada, found several important factors that were predictive of a mild TBI patient's eventual return to work (Guerin, Kennepohl, Leveille, Dominique, and McKerral, 2006). The group found that increased age, number of subjective complaints and the presence of public insurance significantly correlated with the individual's eventual return to work following TBI. Public insurance in Canada reportedly provides patients salary replacement and access to special medical services following an injury (Guerin et. al., 2006). Additionally, the group found there was no correlation between a post-TBI diagnosis of a mood or anxiety disorder and likelihood of returning to work. However, it should be noted that the individuals enrolled in this study were actively engaged in an intervention program, which provided psychological support. Therefore, it is unclear whether or not psychological factors, including depression and

anxiety, can be used to mediate the relationship between cognitive deficits following TBI and return to functionality, as measured by return to work.

Objective

This inter-departmental study aimed to use 3D magnetic resonance spectroscopic imaging (MRSI) and comprehensive neuropsychological assessment to determine if prolonged cerebral metabolic and cognitive alterations occur in individuals with persistent neurocognitive deficits following a mild TBI. The current study utilized neuropsychological and psychological assessment tools to determine the differences in cognitive functioning, coping style, mood, and perceived quality of life between groups. Additionally, this study evaluated the potential interactions between cerebral metabolism and neuropsychological performance, coping style, mood, and perceived quality of life in mTBI subjects with chronic post-concussive symptoms. Understanding the possible relationship between chronic metabolic changes and cognitive and psychological status may provide a better understanding of why some individuals experience chronic post-concussive symptoms following mTBI and others do not. In many cases, people with the same severity of injury have different outcomes; some will have a significant number of cognitive problems, some will have few. As a further mystery, MRI in mTBI is often unremarkable or shows a similar level of pathology between mTBI subjects with and without post-concussive symptoms. There is growing evidence for the use of MRS in the mTBI population, as decreases in NAA-based metabolite ratios have been identified in the mTBI population. Therefore, this study aimed to see if potential metabolic changes might

explain differences in cognitive, mood, and psychosocial functioning between mTBI subjects with similar injuries. This knowledge may potentially guide future research to more eagerly strive to understand possible ways to alter cerebral metabolism, possibly through medication, diet, or other behavioural changes.

Hypotheses

The hypothesis of this study was that following mTBI, prolonged alterations to cerebral metabolism would occur. Additionally, it was hypothesized that the mTBI group would demonstrate significantly poorer performance on neuropsychological, mood, and quality of life measures than healthy controls. It was hypothesized that mTBI subjects with chronic post-concussive symptoms would show reductions in NAA-based ratios, compared to healthy control subjects and that significant interactions would be found between cerebral NAA/Cr, NAA/Cho and Cho/Cr metabolite ratios and neuropsychological performance, coping style, mood, and perceived quality of life in mTBI subjects with chronic post-concussive symptoms.

CHAPTER 2

MATERIALS AND METHODS

Subject Enrollment

Subjects were identified either through the LLU Behavioral Health Institute Intake Department or through the LLU department of Neurology. Once a potential candidate was identified, the potential candidate and/or family members were interviewed, screened for inclusion/exclusion criteria, and enrolled by obtaining the properly signed informed written consent. If the patient's injury occurred within three months prior to testing the injury was considered recent; if the TBI occurred more than three months prior to testing, the injury was considered remote. If the patient was a minor, written consent was obtained from the parent or legal guardian and verbal assent was obtained from the patient. If a patient failed to meet necessary criteria for inclusion into the MRI portion of the study, the patient was still eligible to receive neuropsychological testing, providing that necessary inclusion criteria for neuropsychological assessment were met. This study identified 13 mTBI subjects and 6 control subjects that met the inclusion and exclusion criteria for both the MRSI and neuropsychological testing portions of the study.

Inclusion/ Exclusion Criteria

The inclusion criteria for TBI subjects were:

- Subjects were at least 10 years of age without gender or ethnic restrictions. There was an upper age limit of 65.

- Diagnosis of post-concussive syndrome or mild traumatic brain injury, and suspected cognitive change following head injury as determined by the referring physician or supervising neuropsychologist.
- Eligibility for MRI per routine screening checklist in order to confirm that the patient was physically able to undergo an MRI, as determined by the referring neurologist or radiologist.

The MRSI exclusion criteria were:

- History of a known neurological disorder prior to qualifying injury.
- Renal insufficiency or known history of kidney disease.
- Previous allergic reaction to gadolinium MR contrast.

The neuropsychological assessment exclusion criteria were:

- History of psychiatric disorder, including any individuals who received medication to treat a mental health condition. .

Age-matched normal volunteers were targeted for recruitment as control subjects. Control subjects were recruited from Loma Linda University and/or Medical Center staff, student or Resident populations as well as from family members of recruited TBI subjects.

Control Subject Inclusion Criteria:

- At least 10 years of age without gender or ethnic restrictions. There was an upper age limit of 65.
- Eligibility for MRI per routine screening checklist.

Control Subject Exclusion Criteria:

- MRI Department staff or subordinate of project Investigator.

- History of neurosurgical intervention, excluding the placement of ventriculostomy shunt.
- History of a prior known brain injury with associated loss of consciousness.
- History of a known neurological disorder.
- History of psychiatric disorder.
- Renal insufficiency or known history of kidney disease.
- Previous allergic reaction to gadolinium MR contrast.
- History of known claustrophobia.

Review of the medical record was performed to obtain patient characteristics such as age, gender, date of birth, medical history, date of injury, Glasgow coma score (GCS; initial, admission, and lowest post-resuscitation), Abbreviated Injury Score (AIS), pupillary reaction at admission, presence of associated injuries, length of patient's unconsciousness, length of post- traumatic amnesia (PTA), evidence of hypoxia, duration of ventilatory support, time to follow commands, medication regimen, and duration of stay in the ICU. In addition, the results of any outpatient neurological or neuropsychological tests were noted. Relevant demographic information was collected from the control subjects through the administration of a medical history form at the time the patient was consented. All TBI and control subjects were administered a neuropsychological assessment by a trained member of the research team.

MRI/ MRS Analysis

Alterations to cerebral metabolism can be successfully measured using MRS, where reductions in NAA (and NAA/Cr and NAA/Cho) represent neuronal cell loss or

dysfunction, increases in Cho (and Cho/Cr) and Ins (and Ins/Cr) representing axonal injury and glial reactivity, and increases or decreases in Glx representing changes in neurotransmitter function.

MRSI data were acquired using a 3T whole body imaging system (Siemens Tim Trio, Siemens Medical Solutions, Erlangen, Germany) equipped with a 12 channel receive-only head coil. Conventional 3D T1 (MPRAGE, repetition time (TR) and echo time (TE) = 1950 msec and 2.26 msec, 1 mm slice thickness, field of view (FOV; 230 x 256 mm^2) and 3D T2 (SPACE, TR/TE = 3200/415 msec, 1 mm slice thickness, FOV = 256 x 256 mm^2) weighted MR images were used for segmentation and MRSI voxel positioning, respectively. 3D ^1H MRSI of an approximately 9 x 8 x 6 cm volume covering from the level of the corpus callosum inferiorly through the mid-brain was acquired using a PRESS sequence (TR/TE = 1700/144 ms, 10 mm slab thickness, FOV = 160 x 160 x 80 mm, nominal voxel size = 1 x 1 x 1 mm, and 1 acquisition). The 3D MRSI data were post-processed off-line using LCmodel (S. Provencher, Montreal, Canada) to calculate the NAA/Cr, NAA/Cho, and Cho/Cr metabolite ratio for every voxel. Ratios with an estimated standard deviation (Cramer-Rao lower bound) greater than 10% were excluded from the analysis. Using in-house designed software incorporating routines from Matlab (version 7.0.4, Mathworks, USA) and SPM5 (Wellcome Trust Center of Neuroimaging, University College of London), the T1 weighted images were segmented into white matter (WM), gray matter (GM), and CSF masks and the position of the 3D MRSI grid was overlaid onto the segmented tissue maps and T2 images. For every voxel position, the percentage of white matter, gray matter, and CSF; NAA/Cr, NAA/Cho, and Cho/Cr metabolite ratios were recorded. The anatomical

location (hemisphere and lobe) was manually assigned to each voxel position using the T2 images. In addition, for each subject (control and mTBI), voxels were pooled to create regional mean (± SD) values for each metabolite ratio for the frontal grey (FG), frontal white (FW), corpus callosum (CC), basal ganglia (BG), thalami (TH), parieto-occipital grey (POG), parieto-occipial white (POW), temporal gray (TG) and temporal white (TW) matter. A fractional tissue volume criterion of ≥ 70% GM or WM was applied to each voxel to determine which voxels were included in the regional analysis. The spectral quality (Cramer-Rao lower bound) and tissue volume criteria excluded approximately 30% (range 18 – 42%) of brain voxels, primarily from the frontal and inferior temporal regions due to artifacts resulting from the close proximity of air (sinuses) and bone. Spectra were considered abnormal if the NAA/Cr or NAA/Cho ratio was 2 standard deviations below the control value, suggesting neuronal loss or dysfunction; or if Cho/Cr was 2 standard deviations above the mean control value, suggesting axonal injury in that region.

Materials

Subjects were administered a variety of neuropsychological and life satisfaction measures.

Neuropsychological Measures

The Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) was used to measure intelligence in adult participants (Wechsler, 2008). The Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) was used to measure intelligence in

participants ages 10-15 (Wechsler, 2003). Prorated estimates of verbal comprehension, perceptual reasoning, working memory, and processing speed were measured using select subtests. The WAIS-IV and WISC-IV subtests that were employed in this study include: Symbol Search, Digit Span subtest (forward and backward), Information, Matrix Reasoning, Similarities, Block Design, and Arithmetic. Selected subtests from the Delis-Kaplan Executive Function System (DKEF-S) were given to measure aspects of executive functioning ability (Delis, Kapan, & Kramer, 2001). Specifically, the Trails Subtest was used to assess processing speed, motor speed, and mental flexibility and the Verbal Fluency Subtest measured semantic fluency, phonemic fluency, and category switching, an aspect of mental flexibility. The Logical Memory subtest (I and II) from the Wechsler Memory Scale, Third Edition (WMS-IIII; Wechsler, 1997) was utilized to assess immediate and delayed memory for contextual information. The Wechsler Test of Adult Reading (WTAR) was employed to estimate the subject's level of intellectual functioning before the onset of injury (Wechsler, 2001). The WTAR is a test of single-word reading that has been found to be a reliable measure of pre-morbid cognitive functioning in addition to outcomes following TBI (Hanks, Millis, Ricker, Giacino, Nakese-Richardson, Frol, Novack, Kalmar, Sherer, & Gordon, 2008). Specifically, Hanks and colleagues (2008) reported the WTAR to be predictive of 1-year outcomes following TBI, including prediction of handicap, functional independence, and employability. Additionally, WTAR has been considered to be an important assessment tool in measuring cognitive reserve (Hank et. al., 2008). Cognitive reserve is an important aspect of an individual's cognitive potential and likely has important implications in predicting functional and neuropsychological outcomes following TBI. Visuoconstruction with

executive, memory, and recognition components was measured through the use of the Rey Complex Figure Test (RCFT) (Meyers & Meyers, 1995). The Conners' Continuous Performance Task – II, computer version (CPT-II) (Conners, 2000) was given to test sustained attention, distractibility, and vigilance. Verbal learning and memory was assessed using the Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996). Fine motor speed was tested by way of the Grooved Pegboard (Trites, 2002); by examining fine motor speed in both hands, inferences may be drawn regarding possible lateral brain damage. Novel problem solving was measured with the Wisconsin Card Sort Test – 64 card version (WCST-64) (Grant & Berg, 2000) Finally, the Test of Memory Malingering (TOMM) was given as a measure of effort (Tombaugh, 1996).

Psychological and Life Satisfaction Measures

Perceived quality of life was measured with the use of the World Health Organization Quality of Life Measure (WHOQOL-100) (World Health Organization, 1997). The WHO, in collaboration with 15 centers around the world, has developed the World Health Organization Quality of Life Instrument (WHOQOL-100), a standardized measure of quality of life. The instrument assesses an individual's subjective overall QOL, physical health, psychological state, level of independence, social relationships, personal beliefs, and their relationship to their environment. The WHOQOL-100 Overall QOL Domain assesses a person's overall QOL, health and well-being. The WHOQOL-100 Physical Domain assesses an individual's perceived pain and discomfort, energy and fatigue, and sleep and rest. The WHOQOL-100 Psychological Domain measures positive feelings, thinking, learning, memory, and concentration, self-esteem, body-image and

appearance, and negative feelings. The WHOQOL-100 Level of Independence Domain examines a person's mobility, activities of daily living, dependence on medication or treatments, and working capacity. The WHOQOL-100 Social Relationships Domain includes an assessment of personal relationships, social support, and sexual activity. The WHOQOL-100 Environment Domain includes questions about physical safety and security, home environment, financial resources, health and social care availability and quality, opportunities for acquiring new information and skills, participation in and opportunities for recreation and leisure, physical environment, and transport. Finally, the WHOQOL-100 Spirituality/Religion/Personal Beliefs Domain examines the person's personal beliefs are how they affect quality of life.

The Ways of Coping Questionnaire (WAYS) is a process measure containing a range of thoughts and acts employed by people when dealing with internally or externally stressful situations (Keiffer and MacDonald, 2011). The WAYS (Folkman & Lazarus, 2003) was given to understand the subject's coping style, including the thoughts and actions he or she uses to handle stressful encounters. The WAYS measures 8 different coping factors. Measured coping factors include "confrontive coping," which describes aggressive efforts to alter the situation, "distancing," involving cognitive efforts to detach oneself and to minimize the significance of the situation, and "self-controlling," which describes efforts employed to regulate one's feelings and actions (Folkman & Lazarus, 2003). Additional factors include "seeking social support," which describes one's efforts to seek informational, tangible, and emotional support, "accepting responsibility," whereby one acknowledges one's own role in the problem and efforts to make it right, and "escape avoidance," which describes wishful thinking and behavioral efforts to

escape or avoid the problem. Final coping factors include "planful problem solving," describing the deliberate problem-focused efforts used to alter the situation, coupled with an analytic approach to problem-solving, and "positive reappraisal," or efforts employed to create positive meaning by focusing on personal growth (Folkman & Lazarus, 2003). Finally, psychological factors, including anxiety and depression in adult participants were assessed by way of the Beck Anxiety Inventory (BAI) (Beck, 1993) and Beck Depression Inventory, Second Edition (BDI-II) (Beck, 1996), respectively. Participants under the age of 16 were given the Beck Youth Inventories, Second Edition (BYI-II) (Beck, Beck, and Jolly, 2005) as a subjective measure of depression and anxiety.

Security

The study investigator kept all information obtained from the medical record review in a locked filling cabinet and password protected database. A study number replaced subject names and all PHI was removed.

Statistical Analysis

An a priori power analysis was completed using G*Power 3.1 in order to assess the sufficiency of the proposed sample size (Faul, Erdfelder, Buchner, & Lang, 2009). In order to obtain a moderate to large effect size (f^2= .30) a total of 19 participants were needed to demonstrate significant differences. The data analysis emphasizes description and graphical statistics. Descriptive statistics include the mean, minimum/maximum values and associated 95% confidence intervals. Data are reported as mean (SD or range). For all tests, an alpha level of $P < 0.05$ was taken to indicate significance. Differences in

the nature and extent of cognitive and cerebral metabolic deficits among TBI and control groups were analyzed using univariate regressions. Univariate regressions were also used to assess potential differences in mood (anxiety and depression), perceived quality of life, and coping style.

Potential interactions between neuropsychological performance, cerebral metabolism, coping style, mood, and perceived quality of life between mTBI and control subjects were analyzed using the estimation of simple slopes interaction analysis. Given the preliminary nature of the current data, this analysis was utilized to demonstrate potential interactions. This approach analyzed the data across three stages. The first stage evaluates the subject's group status and specific dependent variable in order to determine main effects. The second stage shows the dummy coded interaction between the two variables. The third stage demonstrates potential interactions through the estimation of simple slopes interaction analysis.

CHAPTER THREE

RESULTS

Demographics

Description of Sample

The cause of injury was reported as a sports related injury (46%), fall (23%), and motor vehicle accident (31%). Of note, there were no patients within the mTBI group who reported a blast injury as the mechanism of their head injury. The time between MRI/MRS and the injury ranged from 0.5 – 36.5 months. None of the mTBI subjects had imaging (CT or MRI) at the time of the injury, which in all cases, were reported as normal.

The mTBI and control groups did not significantly differ in premorbid intelligence or education (Table 1). The mTBI and control groups did differ significantly in age, with the mTBI group (mTBI Age *M*= 19.69) being significantly younger than the control group (Control Age *M=39.33;* p< .05;F=18.82*).* The final sample included thirteen mTBI subjects and six control subjects, eight male and five female mTBI subjects and four male and two female control subjects; no difference was noted in distribution of gender between groups χ^2 (1) = .05, *p* = n.s. One subject in the mTBI group is missing data for the WTAR VIQ as the result of discontinuing the test due to significant frustration. With regard to checks for statistical assumptions, descriptive statistics were analyzed for each measure, including distribution, skewness, kurtosis, and assessment of outliers. All variables in the current analysis had normal distributions with normal skewness and kurtosis. Pairwise deletion was used in the current analyses due to the fact the current data was preliminary and the maximum amount of power was needed

Table 1

Demographic Characteristics of the Sample

	N	Mean (SD)	F
Age			18.82*
mTBI	13	19.69 (8.31)	
Control	6	39.33 (19.46)	
Gender			
mTBI			
Male	8		
Female	5		
Control			
Male	4		
Female	2		
WTAR VIQ			1.16
mTBI	12	97.58 (25.64)	
Control	6	112.17 (10.87)	
Education			.263
mTBI	13	11.54 (3.31)	
Control	6	15.67 (2.94)	

* significant at <.05
** significant at <.01

for all analyses. Thus, subtle differences will be noted in number of subjects within each analysis.

Confirmation of Cognitive, Mood, Quality of Life, Coping Style, and Cerebral Metabolic Differences Between mTBI and Controls

Cognitive Outcomes Following mTBI

The mTBI group performed significantly worse than healthy controls on a number of neuropsychological measures (Table 2). Specifically, the mTBI group (WAIS-IV/WISC-IV DS Forward M=6.46, SD=1.33; CPT-II Hit Rate ISI Change *M*=47.23,

SD=6.56) performed worse than controls (WAIS-IV/WISC-IV DS Forward M=8.00, SD=0.63; CPT-II Hit Rate ISI Change *M*=59.16, SD=11.17) on measures of attention (WAIS-IV/WISC-IV DS Forward, t(17)= -1.42, p< .05, *d*=-0.69, *r*= 0.33; CPT-II Hit Rate ISI Change, t(12)= -2.44, p< .05, *d*= -1.41, *r*= 0.58). It is important to note that three of the mTBI subjects were not administered the CPT-II; two of these subjects were not tested at LLU and therefore did not have access to the computer containing the CPT-II, and one of the mTBI subjects had a history of having a seizure and therefore was not given the CPT-II. Additionally, two of the control subjects were not given the CPT-II due to the fact that they were tested off the LLU campus and therefore did not have access to the computer.

The mTBI group (RCFT 3 minute delay *M*=34.69, SD=12.63; RCFT 30 minute delay *M*=35.23, SD=11.24) performed significantly worse than controls (RCFT 3 minute delay *M*=52.17, SD=3.97; RCFT 30 minute delay *M*=54.17, SD=3.06) on measures of immediate and delayed non-verbal memory (RCFT 3 minute delay, t(17)= -3.27, p<.01, *d*=-1.59, *r*=0.62; RCFT 30 minute delay, t(17)= -4.00, p<.01, *d*=-1.94, *r*=0.70).

With regards to verbal learning and memory, the mTBI group (RAVLT Learning Trials 1-5 *M*= 47.23, SD= 12.39; RAVLT Interference Trial *M*= 46.00, SD=12.39) performed significantly worse than healthy controls (RAVLT Learning Trials 1-5 *M*= 66.50, SD=1.87; RAVLT Interference Trial *M*= 60.83, SD= 11.48) on measures of verbal learning across trials and learning of an interference word list (RAVLT Learning Trials 1-5, t(17)= -3.68, p< .01, *d*=-1.79, *r*=0.67; RAVLT Interference Trial, t(17)= -2.48, p< .05, *d*=-1.20, *r*=0.52). Additionally, the mTBI group (RAVLT Short Delay Recall *M*= 51.15, SD= 12.74; RAVLT Long Delay Recall *M*= 50.15, SD=11.59) performed

significantly worse than healthy controls (RAVLT Short Delay Recall *M*= 63.83, SD= 4.31; RAVLT Long Delay Recall *M*= 61.33, SD= 6.12) on immediate and delayed memory for unstructured information (RAVLT Short Delay Recall t(17)= -2.34, p< .05, *d*=-1.14, *r*=0.49; RAVLT Long Delay Recall t(17)= -2.20, p< .05, *d*=-1.07, *r*=0.47). Finally, the mTBI group (WMS-III LM I *M*= 7.62, SD= 4.23; WMS-III LM II *M*= 8.23, SD= 4.34) performed significantly worse than healthy controls (WMS-III LM I *M*= 12.00, SD= 1.67; WMS-III LM II *M*= 13.17, SD= 1.72) on immediate and delayed verbal memory for contextually related information (WMS-III LM I, t(17)= -2.42, p< .05, *d*= -1.17, *r*=0.51; WMS-III LM II, t(17)= -2.66, p< .05, *d*=-1.29, *r*=0.54).

Table 2

Neuropsychological Performances between groups

	N	Mean (SD)	t (df)	*d*	*r*
WAIS-IV/ WISC-IV DS Total			-1.42(17)	-0.69	0.33
mTBI	13	9.15(3.02)			
Control	6	11.33(3.33)			
WAIS-IV/ WISC-IV DS Forward			-2.67(17)*	-1.30	0.54
mTBI	13	6.46(1.33)			
Control	6	8.00(0.63)			
WAIS-IV/ WISC-IV DS Backward			0.89(17)	0.43	0.21
mTBI	13	5.23(1.88)			
Control	6	6.00(1.41)			
WAIS-IV/ WISC-IV Coding			-1.71(17)	-0.83	0.38
mTBI	13	9.15(4.38)			
Control	6	12.33(1.51)			
WAIS-IV/ WISC-IV Information			-1.09(17)	-0.53	0.26
mTBI	13	10.46(3.60)			
Control	6	12.17(1.72)			

WAIS-IV/ WISC-IV Matrix Reasoning			-1.68(17)	-0.81	0.38
	mTBI	13	9.92(2.64)		
	Control	6	12.00(2.10)		
WAIS-IV/ WISC-IV Similarities			-1.82(17)	-0.88	0.40
	mTBI	13	11.15(3.00)		
	Control	6	14.17(4.07)		
WAIS-IV/ WISC-IV Block Design			-1.11(16)	-0.56	0.27
	mTBI	13	9.83(3.33)		
	Control	6	11.50(2.17)		
WAIS-IV/ WISC-IV Arithmetic			-1.04(16)	-0.52	0.25
	mTBI	13	10.83(3.30)		
	Control	6	12.50(3.02)		
WAIS-IV/ WISC-IV Symbol Search			-1.65(17)	-0.80	0.37
	mTBI	13	9.00(4.10)		
	Control	6	12.33(4.03)		
CPT-II Omissions			0.17(12)	0.10	0.05
	mTBI	11	47.41(5.92)		
	Control	3	46.68(9.26)		
CPT-II Commissions			0.15(12)	0.09	0.04
	mTBI	11	54.96(8.52)		
	Control	3	54.11(10.58)		
CPT-II Hit Rate			1.44(12)	0.83	0.38
	mTBI	11	41.38(8.14)		
	Control	3	33.23(10.93)		
CPT-II Hit Rate ISI Change			-2.44(12)*	-1.41	0.58
	mTBI	11	47.22(6.56)		
	Control	3	59.16(11.17)		
DKEFS Letter Fluency			-1.67(17)	-0.81	0.38
	mTBI	13	8.77(5.10)		
	Control	6	12.67(3.67)		
DKEFS Category Fluency			-1.80(17)	-0.87	0.40
	mTBI	13	10.31(4.88)		
	Control	6	14.33(3.61)		
DKEFS Category Switching			-1.77(17)	-0.86	0.39
	mTBI	13	10.31(4.29)		
	Control	6	13.83(3.37)		
RCFT 3 minute delay			-3.27(17)**	-1.59	0.62
	mTBI	13	34.69(12.63)		

Control	6	52.17(3.97)			
RCFT 30 minute delay			-4.00(17)**	-1.94	0.70
mTBI	13	35.23(11.24)			
Control	6	54.17(3.06)			
RAVLT Learning Trials 1-5			-3.68(17)**	-1.79	0.67
mTBI	13	47.23(12.58)			
Control	6	66.50(1.87)			
RAVLT Interference Trial			-2.48(17)*	-1.20	0.52
mTBI	13	46.00(12.39)			
Control	6	60.83(11.48)			
RAVLT Short Delay Recall			-2.34(17)*	-1.14	0.49
mTBI	13	51.15(12.74)			
Control	6	63.83(4.31)			
RAVLT Long Delay Recall			-2.20(17)*	-1.07	0.47
mTBI	13	50.15(11.59)			
Control	6	61.33(6.12)			
WMS-III LM 1			-2.42(17)*	-1.17	0.51
mTBI	13	7.62(4.23)			
Control	6	12.00(1.67)			
WMS-III LM II			-2.66(17)*	-1.29	0.54
mTBI	13	8.23(4.34)			
Control	6	13.17(1.72)			

* significant at <.05
** significant at <.01

mTBI Related to Differences in Mood and Quality of Life

The mTBI group performed significantly worse than healthy controls on mood measures (Table 3). Specifically, the mTBI group (BAI *M*=15.56, SD=9.77; BDI-II *M*=16.89, SD=7.46; Depression Total *M*=63.00, SD=12.26), when compared to controls (BAI M=4.00, SD=3.79; BDI-II= 3.83, SD=4.58; Depression Total *M*=43.33, SD=7.53), endorsed more symptoms of anxiety and depression (BAI, t(13)= 2.73, p<.05, *d*=1.51,

r=0.60; BDI-II, t(13)= 3.81, p<.01, *d*=2.11, *r*=0.73; Depression Total t(16)= 3.58, p<.01, *d*=1.79 , *r*=0.67). The "Depression Total" scores include inverted T scores from both BDI-II and BYI performance; therefore including adult and pediatric subject scores. The mTBI group's average BAI and BDI-II scores were in the mildly anxious and depressed ranges, respectively, whereas the normal control group's average BAI and BDI-II scores were in the minimally anxious and depressed ranges.

The mTBI group reported significantly poorer perceived quality of life than healthy controls. Specifically, the mTBI group (WHO Psychological M=60.77, SD=14.19; WHO Independence *M*=59.46, SD=23.31; WHO Physical *M*=52.11, SD=15.95; WHO Social *M*=68.75, SD=15.31; WHO Environmental *M*=68.81, SD=16.41; WHO Spirituality *M*=72.12, SD=19.20) when compared to controls (WHO Psychological M= 82.14, SD=13.96; WHO Independence *M*=90.63, SD=10.78; WHO Physical *M*= 84.45, SD=11.28; WHO Social *M*= 84.37, SD=13.87; WHO Environmental *M*= 90.75, SD=13.45; WHO Spirituality *M*=90.63, SD=14.66) endorsed significantly worse psychological, independence, physical, social, environmental, and spiritual quality of life (WHO Psychological, t(17)=-3.06, p< .01, *d*=-1.48 , *r*=0.60; WHO Independence, t(17)=-3.09, p< .01, *d*=-1.50 , *r*=0.60; WHO Physical, t(17)=-4.45, p< .01, *d*=-2.16 , *r*=0.73; WHO Social, t(17)=-2.13, p< .05, *d*=-1.03 , *r*=0.46; WHO Environmental, t(17)=-2.85, p< .01, *d*= -1.38, *r*=0.57; WHO Spirituality, t(17)=-2.09, p<.05, *d*=-1.01, *r*=0.45).

Table 3

Mood and Quality of Life between groups

	N	Mean (SD)	t (df)	*d*	*r*
BAI			2.73(13)*	1.51	0.60
mTBI	9	15.56 (9.77)			
Control	6	4.00 (3.79)			
BDI-II			3.81(13)**	2.11	0.73
mTBI	9	16.89 (7.46)			
Control	6	3.83 (4.58)			
Depression Total			3.58(16)**	1.79	0.67
mTBI	12	63.00 (12.26)			
Control	6	43.33 (7.53)			
WHO Psychological			-3.06(17)**	-1.48	0.60
mTBI	13	60.77 (14.19)			
Control	6	82.14 (13.96)			
WHO Independence			-3.09(17)**	-1.50	0.60
mTBI	13	59.46 (23.31)			
Control	6	90.63 (10.78)			
WHO Physical			-4.45(17)**	-2.16	0.73
mTBI	13	52.11 (15.95)			
Control	6	84.45 (11.28)			
WHO Social			-2.13(17)*	-1.03	0.46
mTBI	13	68.75 (15.31)			
Control	6	84.37 (13.87)			
WHO Environmental			-2.85(17)**	-1.38	0.57
mTBI	13	68.81 (16.41)			
Control	6	90.75 (13.45)			
WHO Spirituality			-2.09(17)*	-1.01	0.45
mTBI	13	72.12 (19.20)			
Control	6	90.63 (14.66)			

* significant at <.05
** significant at <.01

MTBI Related to Differences in Coping

Significant differences were found within coping style between the mTBI and control groups (Table 4). Specifically, the mTBI group (WAYS Confrontive *M*=7.42, SD= 4.26; WAYS Distancing *M*=12.45, SD= 7.47), when compared to controls (WAYS Confrontive *M*=13.68; WAYS Distancing *M*=5.17), endorsed significantly less confrontive coping and more distancing (WAYS Confrontive, t(16)=-2.26, p<.05, , *d*= -1.13, *r*=0.49; WAYS Distancing, t(16) = 3.70, p<.01, *d*=1.69, *r*=0.64). Other coping styles assessed, including self-controlling, seeking social support, accepting responsibility, escape avoidance, planful problem solving, and positive reappraisal, did not statistically differ between groups.

Table 4

Coping style between groups

	N	Mean (SD)	t (df)	*d*	*r*
WAYS Confrontive			-2.26(16)*	-1.13	0.49
mTBI	13	7.42 (4.26)			
Control	5	13.68 (7.47)			
WAYS Distancing			3.37(16)**	1.69	0.64
mTBI	13	12.45 (4.27)			
Control	5	5.17 (3.57)			
WAYS Self-Controlling			0.80(16)	0.40	0.20
mTBI	13	16.49 (6.31)			
Control	5	14.03 (4.07)			
WAYS Seeking Social Support			0.12(16)	0.06	0.03
mTBI	13	14.12 (6.31)			
Control	5	13.69 (7.31)			
WAYS Accepting Responsibility			0.26(16)	0.13	0.06
mTBI	13	12.55 (5.28)			
Control	5	11.79 (6.73)			
WAYS Escape Avoidance			1.42(16)	0.71	0.33
mTBI	13	10.63 (4.48)			
Control	5	6.32 (8.53)			
WAYS Planful Problem Solving			-1.55(16)	-0.78	0.36
mTBI	13	14.59 (4.88)			
Control	5	19.13 (7.21)			
WAYS Positive Reappraisal			-1.46(16)	-0.73	0.34
mTBI	13	12.23 (5.01)			
Control	5	16.19 (5.66)			

* significant at <.05
** significant at <.01

MTBI Related to Differences in Cerebral Metabolite Ratios

MRSI analyses obtained metabolite data from brain areas important for cognition, including the frontal, parietal and occipital grey matter, frontal and parietal white matter, thalami, basal ganglia, and the corpus callosum. The frontal matter is involved in executive functioning including, planning, organizing, and problem solving, attention, executing behavior, and personality. The parietal lobe processes visual, auditory, and touch information, while the occipital lobe primarily processes visual information. Grey matter in the brain is made up of neuronal cell bodies while white matter primarily consists of glial cells and myelinated axons. The thalami processes and relays sensory information, the basal ganglia are associated with motor control and procedural learning, the corpus callosum connects and allows for communication between the left and right hemispheres. Measurements of the following metabolites were recorded from the MRS report: NAA/Cr, NAA/Cho, and Cho/Cr, where NAA represents both neuronal integrity and neuronal mitochondrial function, Cr represents cellular energy status, and Cho represents cellular membrane integrity and turnover.

Significant differences were found in cerebral metabolite ratios between the mTBI and control groups (Table 5). Specifically, the mTBI group (Cho/Cr M=1.09, SD=0.10), when compared to controls (Cho/Cr M=1.25, SD=0.10), demonstrated a decreased Cho/Cr ratio in the corpus callosum, with a large effect size (Cho/Cr, $t(17)=-3.11$, $p<.01$, $d=-1.51$, $r=0.60$), implying elevated creatine.

Other cerebral metabolic ratios examined did not statistically differ between groups (Table 5). However, small to medium effects sizes between groups were found in the NAA/Cr ratio in the corpus callosum, the NAA/Cr and Cho/Cr ratios in the frontal grey

matter, the NAA/Cr and Cho/Cr ratios in the frontal white matter, NAA/Cho ratio in the parieto-occipital white matter, and the Cho/Cr ratio in the thalami (CC NAA/Cr, t(17)=-0.73, p>.05, *d*=-0.36, *r*=0.18; FG NAA/Cr, t(17)=-0.87, p>.05, *d*= -0.42, *r*=0.21; FG Cho/Cr, t(17)=-0.69, p>.05, *d*=-0.33, *r*=0.17; FW NAA/Cr, t(17)=-0.71, p>.05, *d*=-0.34, *r*=0.17; FW Cho/Cr, t(17)=0.69, p>.05, *d*=0.33, *r*=0.17; POW NAA/Cho, t(17)=-0.65, p>.05, *d*=-0.32, *r*=0.16; TH Cho/Cr, t(17)=-0.73, p>.05, *d*=-0.35, *r*=0.17). Specifically, NAA/Cr and NAA/Cho were decreased in the corpus callosum, frontal grey and white matter, and parieto-occipital white matter, implying NAA/neuronal loss. Medium to large effect sizes were noted, between groups, for the NAA/Cho and Cho/Cr ratios in the basal ganglia, the NAA/Cho ratio in the frontal white matter, and the NAA/Cr ratio in the parieto-occipital grey matter (BG NAA/Cho, t(17)=1.89, p>.05, *d*=0.92, *r*=0.42; BG Cho/Cr, t(17)=-1.92, p>.05, *d*=-0.93, *r*=0.42; FW NAA/Cho, t(17)=-1.15, p>.05, *d*=-0.56, *r*=0.27; POG NAA/Cr, t(17)=-0.94, p>.05, *d*=-0.46, *r*=0.22). Additionally, medium to large effect sizes were found for the NAA/Cr ratio in the parieto-occipital white matter, the NAA/Cr and NAA/Cho ratios in the thalami, and NAA/Cho and Cho/Cr ratios in the temporal white matter (POW NAA/Cr, t(17)=-1.37, p>.05, *d*=-0.66, *r*=0.32; TH NAA/Cr, t(17)=1.65, p>.05, *d*=0.80, *r*=0.37; TH NAA/Cho, t(17)=1.12, p>.05, *d*=0.54, *r*=0.26; TW NAA/Cho, t(17)=1.22, p>.05, *d*=0.59, *r*=0.28; TW Cho/Cr, t(17)=-1.02, p>.05, *d*=-0.49, *r*=0.24). These effect sizes demonstrate that NAA/Cr and NAA/Cho were decreased in the frontal white matter and parieto-occipital grey and white matter, implying NAA/neuronal loss. Additionally, NAA/Cr and NAA/Cho were increased in the basal ganglia, thalami, and temporal white matter, implying reduced creatine or choline. While these cerebral metabolic ratios were not found to significantly differ

between mTBI and control groups, given the small to large effect sizes, it is likely that there are significant differences that this underpowered study is unable to effectively capture.

Table 5

Cerebral metabolite ratios between groups

	N	Mean (SD)	t (df)	*d*	*r*
BG NAA/Cr			0.46(17)	0.22	0.11
mTBI	13	2.05(0.24)			
Control	6	2.01(0.11)			
BG NAA/Cho			1.89(17)	0.92	0.42
mTBI	13	2.04(0.36)			
Control	6	1.75(0.12)			
BG Cho/Cr			-1.92(17)	-0.93	0.42
mTBI	13	1.04(0.13)			
Control	6	1.16(0.10)			
CC NAA/Cr			-0.74(17)	-0.36	0.18
mTBI	13	2.69(0.38)			
Control	6	2.85(0.50)			
CC NAA/Cho			0.25(17)	0.12	0.06
mTBI	13	2.45(0.43)			
Control	6	2.40(0.51)			
CC Cho/Cr			-3.11(17)**	-1.51	0.60
mTBI	13	1.09(0.10)			
Control	6	1.25(0.10)			
FG NAA/Cr			-0.87(17)	-0.42	0.21
mTBI	13	2.33(0.38)			
Control	6	2.49(0.37)			
FG_NAA_Cho			-0.41(17)	-0.20	0.10
mTBI	13	2.26(0.39)			
Control	6	2.35(0.43)			
FG Cho/Cr			-0.69(17)	-0.33	0.17
mTBI	13	1.06(0.11)			
Control	6	1.09(0.09)			

FW NAA/Cr			-0.71(17)	-0.34	0.17
mTBI	13	2.53(0.54)			
Control	6	2.70(0.32)			
FW NAA/Cho			-1.15(17)	-0.56	0.27
mTBI	13	2.29(0.36)			
Control	6	2.51(0.40)			
FW Cho/Cr			0.69(17)	0.33	0.17
mTBI	13	1.20(0.32)			
Control	6	1.11(0.13)			
POG NAA/Cr			-0.94(17)	-0.46	0.22
mTBI	13	2.46(0.40)			
Control	6	2.63(0.26)			
POG NAA/Cho			-0.42(17)	-0.20	-0.10
mTBI	13	2.84(0.39)			
Control	6	2.92(0.40)			
POG Cho/Cr			-0.57(17)	-0.28	0.14
mTBI	13	0.88(0.76)			
Control	6	0.90(0.09)			
POW NAA/Cr			-1.37(17)	-0.66	0.32
mTBI	13	2.79(0.26)			
Control	6	2.98(0.31)			
POW NAA/Cho			-0.65(17)	-0.32	0.16
mTBI	13	2.80(0.34)			
Control	6	2.90(0.30)			
POW Cho/Cr			-0.45(17)	-0.22	0.11
mTBI	13	1.01(0.11)			
Control	6	1.04(0.10)			
TG NAA/Cr			0.20(17)	0.10	0.05
mTBI	13	1.95(0.27)			
Control	6	1.93(0.18)			
TG NAA/Cho			0.42(17)	0.20	0.10
mTBI	13	1.84(0.31)			
Control	6	1.79(0.14)			
TG Cho/Cr			-0.60(17)	-0.29	0.14
mTBI	13	1.10(0.09)			
Control	6	1.13(0.12)			
TH NAA/Cr			1.65(17)	0.80	0.37
mTBI	13	2.17(0.24)			

Control	6	1.99(0.16)			
TH NAA/Cho			1.12(17)	0.54	0.26
mTBI	13	1.90(0.25)			
Control	6	1.77(0.19)			
TH Cho/Cr			-0.73(17)	-0.35	0.17
mTBI	13	1.16(0.11)			
Control	6	1.22(0.28)			
TW NAA/Cr			0.37(17)	0.18	0.89
mTBI	13	2.18(0.31)			
Control	6	2.12(0.33)			
TW NAA/Cho			1.22(17)	0.59	0.28
mTBI	13	2.10(0.39)			
Control	6	1.89(0.28)			
TW Cho/Cr			-1.02(17)	-0.49	0.24
mTBI	13	1.08(0.11)			
Control	6	1.13(0.07)			

* significant at <.05
** significant at <.01

Interaction between MRS Outcomes and Neuropsychological Performance, Coping Style, Mood and Perceived Quality of Life

The Relationship Between Neuropsychological Performance and MRS Outcomes in MTBI and Control Groups

Interaction data between MRS outcomes and neuropsychological performance between mTBI and control subjects is presented in three stages in the following tables (see Table 6-14). The small to large effect sizes between mTBI and control groups, where NAA/Cr or NAA/Cho is lower than seen in controls, suggests that neuronal loss in that region may be related to non-verbal abstraction, visuoconstruction, processing speed, phonemic and semantic fluency, mental flexibility, and delayed non-verbal memory. The

small to large effect sizes between mTBI and control groups, where Cho/Cr was greater than in controls, suggests axonal injury in that region may be related to attention. The first stage presents the subject's group status and neurocognitive test to determine main effects. The second stage shows the dummy coded interaction. Given that this data are preliminary with low subject numbers, to show potential interactions an estimation of simple slopes interaction analysis was used and is shown in the third stage.

In examination of the relationship between non-verbal abstraction and the NAA/Cr ratio within the frontal white matter (see Table 6 & Figure 1), stage one shows a significant relationship between non-verbal abstract reasoning and NAA/Cr ratio in the frontal white matter ($R2=.389$; $F(2,15)= 4.766$; $p<.01$). Stage two shows a significant interaction between group membership and abstract reasoning for NAA/Cr ratio ($\beta= 1.91$; $p<.05$). To further clarify this interaction an estimation of simple slopes interaction analysis was used, which shows a significant slope for the controls ($\beta= 0.165$; $p<.01$), but not the mTBI group ($\beta=-.027$; $p>.05$).

Through an analysis of the interaction between visuoconstruction and the NAA/Cr ratio within the frontal white matter (see Table 7 & Figure 2), stage one shows a significant relationship between visuoconstruction and NAA/Cr ratio in the frontal white matter ($R2= .493$; $F(2,15)= 7.307$; $p<.01$). Stage two shows a non-significant interaction between group membership and visuoconstruction for NAA/Cr ratio ($\beta=.101$; $p>.05$). The estimation of simple slopes interaction analysis shows a significant slope for the controls ($\beta=.130$; $p<.01$) and a non-significant slope for the mTBI group ($\beta=.029$; $p>.05$).

An analysis of the relationship between processing speed and the NAA/Cr ratio within the thalami was carried out (see Table 8 & Figure 3); stage one shows a significant

relationship between processing speed and NAA/Cr ratio in the thalami (R2=.370; F(2,16)= 4.690; p<.05). Stage two shows a non-significant interaction between group membership and processing speed for NAA/Cr ratio (β=-.021; p>.05). To show a potential interaction an estimation of simple slopes interaction analysis was used, which shows a significant slope for the controls (β=-.034; p<.05) and a non-significant slope for the mTBI group (β=-.013; p>.05).

In examining the relationship between delayed non-verbal memory and the NAA/Cho ratio within the basal ganglia (see Table 9 & Figure 4), stage one shows a significant relationship between delayed non-verbal memory and NAA/Cho ratio in the basal ganglia (R2=.433; F(2,16)=6.110; p<.01). Stage two shows a non-significant interaction between group membership and delayed non-verbal memory for NAA/Cho (β=-.010; p>.05). The estimation of simple slopes interaction analysis shows a significant slope for the controls (β=-.019; p<.05) and a non-significant slope for the mTBI group (β=-.008; p>.05).

An analysis of the interaction between phonemic fluency and the NAA/Cr ratio within the thalami was completed (see Table 10 & Figure 5); stage one shows a significant relationship between phonemic fluency and NAA/Cr ratio in the thalami (R2=.345; F(2,16)=4.208; p<.05). Stage two shows a non-significant interaction between group membership and phonemic fluency for NAA/Cr ratio (β=-.031; p>.05). An estimation of simple slopes interaction analysis shows a significant slope for the controls (β=-.028; p<.05) and a non-significant slope for the mTBI group (β=.002; p>.05).

The relationship between semantic fluency and the NAA/Cr ratio within the thalami was evaluated (see Table 11 & Figure 6). Stage one shows a significant

relationship between semantic fluency and NAA/Cr ratio in the thalami (R2=.403; F(2,16)=5.396; p<.05). Stage two shows a non-significant interaction between group membership and semantic fluency for NAA/Cr ratio (β=-.013; p>.05). The estimation of simple slopes interaction analysis shows a significant slope for the controls (β=-.029; p<.05) and a non-significant slope for the mTBI group (β=-.016; p>.05).

When examining the interaction between mental flexibility and the NAA/Cr ratio within the thalami (see Table 12 & Figure 7), stage one shows a significant relationship between semantic fluency and NAA/Cr ratio in the thalami (R2=.300; F(2,16)=3.421; p<.05). Stage two shows a non-significant interaction between group membership and mental flexibility for NAA/Cr ratio (β=-.049; p>.05). The estimation of simple slopes interaction analysis shows a significant slope for the controls (β=-.034; p<.05) and a non-significant slope for the mTBI group (β=-.015; p>.05).

Table 13 and Figure 8 demonstrate the significant interaction between attention and the Cho/Cr ratio within the corpus callosum; stage one shows a significant relationship between attention and Cho/Cr ratio in the corpus callosum (R2=.750; F(2,11)=16.540; p<.01). Stage two shows a non-significant interaction between group membership and attention for Cho/Cr ratio (β=.007; p>.05). The estimation of simple slopes interaction analysis shows a significant slope for the controls (β=.011; p<.01) and a non-significant slope for the mTBI group (β=.004; p>.05).

The relationship between attention and the Cho/Cr ratio within the parieto-occipital white matter is examined in Table 14 and Figure 9. Stage one shows a significant relationship between attention and Cho/Cr ratio in the parieto-occipital white matter (R2=.568; F(2,11)=7.227; p<.01). Stage two shows a non-significant interaction

between group membership and attention for Cho/Cr ratio (β=.004; p>.05). The estimation of simple slopes interaction analysis shows both a significant slope for the controls (β=.012; p<.01) and a non-significant slope for the mTBI group (β=.008; p>.05).

Table 6

The relationship between non-verbal abstraction and the NAA/Cr ratio within the frontal white matter

	F(df)	T(df)	R2	β
Main Effects	4.766(2,15) **		.389	
(Constant)		14.305 (2,15)		2.531**
Group		.359 (2,15)		.080
WAIS_MR		2.967 (2,15)		.122**
Dummy Coded	5.491 (3,14) **		.541	
(Constant)		14.752 (3,14)		2.738**
Group		-.452 (3,14)		-.098
WAIS_MR		-.338 (3,14)		-.027
Group*WAIS_MR		2.152 (3,14)		1.91*
Estimation of Simple Slopes	5.491 (3, 14) **		.541	
(Constant)		14.752 (3,14)		2.738**
Group		-.452 (3,14)		-.098
Control*WAIS_MR (simple slope)		3.931 (3,14)		.165**
TBI*WAIS_MR (simple slope)		-.338 (3,14)		-.027

* significant at <.05
** significant at <.01

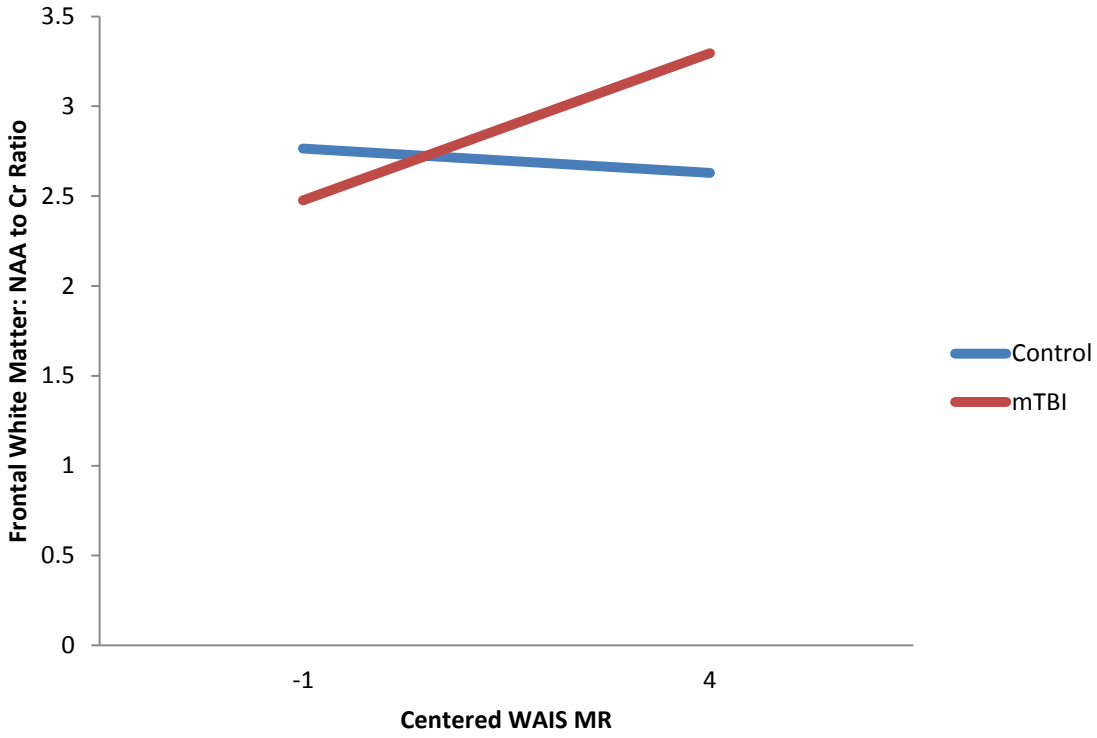

Figure 1. The relationship between non-verbal abstraction and the NAA/Cr ratio within the frontal white matter

Table 7

The relationship between visuoconstruction and the NAA/Cr ratio within the frontal white matter

	F(df)	T(df)	R2	β
Main Effects	7.307(2, 15) **		0.493	
(Constant)		16.882 (2, 15)		2.575**
Group		.262 (2, 15)		.050
WAIS_BD		3.746 (2, 15)		.113**
Dummy Coded	5.579 (3,14) **		0.545	
(Constant)		15.939 (3,14)		
2.669**				
Group		-.178(3,14)		-.035
WAIS_BD		.389 (3,14)		.029
Group*WAIS_BD		1.252 (3,14)		.101
Estimation of Simple Slopes	5.579 (3,14) **		0.545	
(Constant)		15.939 (3,14)		
2.669**				
Group		-.178(3,14)		-.035
Control*WAIS_BD (simple slope)		3.997 (3,14)		.130**
TBI*WAIS_BD (simple slope)		.389 (3,14)		.029

* significant at <.05
** significant at <.01

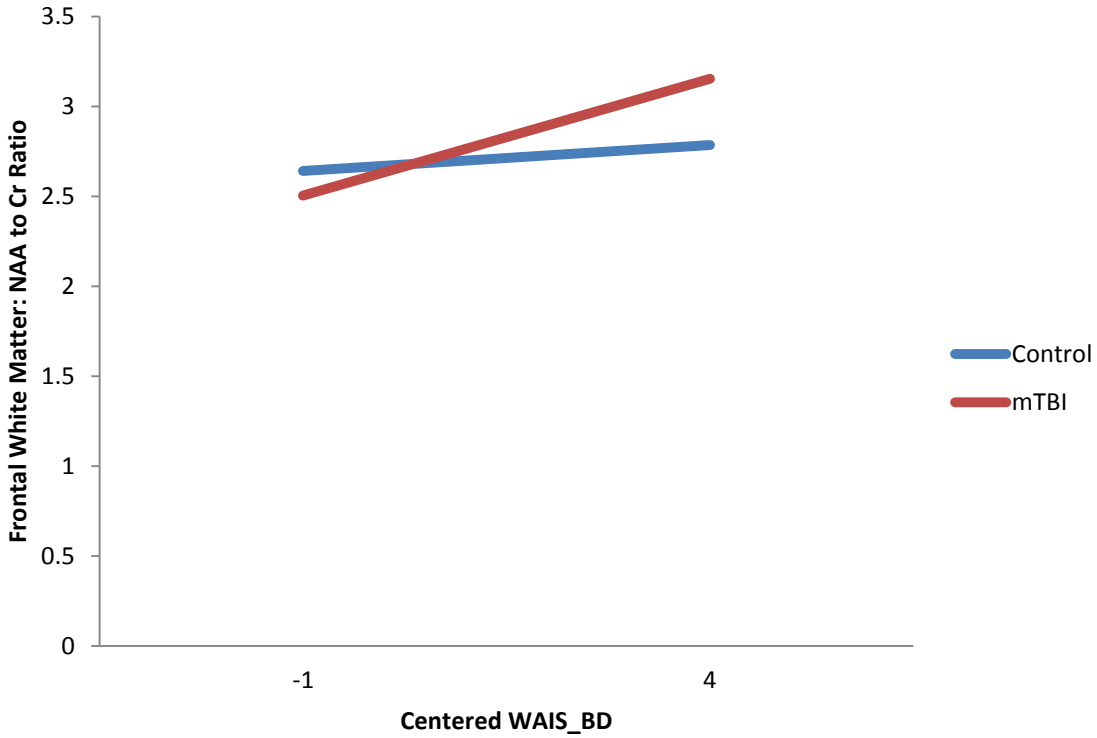

Figure 2. The relationship between visuoconstruction and the NAA/Cr ratio within the frontal white matter

Table 8

The relationship between processing speed and the NAA/Cr ratio within the thalami

	F(df)	T(df)	R2	β
Main Effects	4.690 (2,16) *		.370	
(Constant)		24.601 (2,16)		2.056**
Group		.831 (2,16)		.086
WAIS_SS		-2.426 (2,16)		-.028*
Dummy Coded	3.297 (3,15) *		.397	
(Constant)		21.448 (3,15)		2.022**
Group		1.041(3,15)		.114
WAIS_SS		-.585 (3,15)		-.013
Group*WAIS_SS		-.832 (3,15)		-.021
Estimation of Simple Slopes	3.297 (3,15) *		.397	
(Constant)		21.448 (3,15)		2.022**
Group		1.041(3,15)		.114
Control*WAIS_SS (simple slope)		-2.474 (3,15)		-.034*
TBI*WAIS_SS (simple slope)		-.585 (3,15)		-.013

* significant at <.05
** significant at <.01

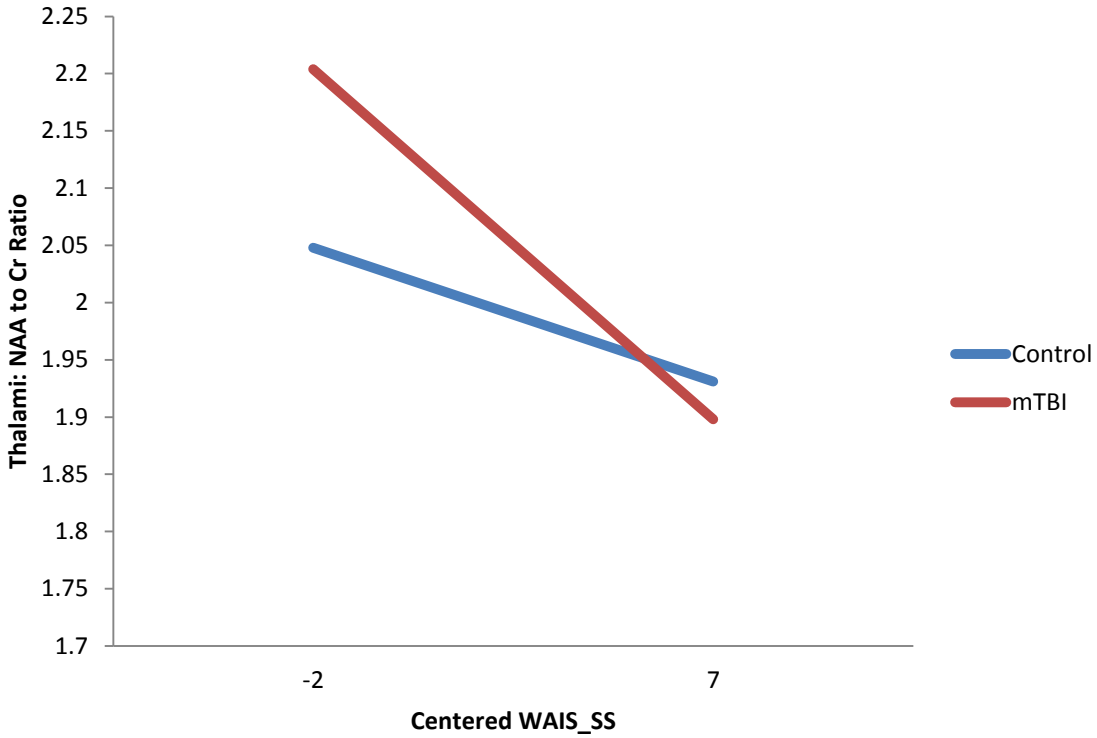

Figure 3. The relationship between processing speed and the NAA/Cr ratio within the thalami

Table 9

The relationship between delayed non-verbal memory and the NAA/Cho ratio within the basal ganglia

	F(df)	T(df)	R2	β
Main Effects	6.110 (2,16) **		.433	
(Constant)		14.251 (2,16)		1.986**
Group		-.298 (2,16)		-.055
RCFT_ 30 Delay		-2.707 (2,16)		-.018*
Dummy Coded	3.857 (3,15) *		.435	
(Constant)		3.491 (3,15)		1.854**
Group		.139 (3,15)		.075
RCFT_ 30 Delay		-.202 (3,15)		-.008
Group*RCFT_ 30 Delay		-.257 (3,15)		-.010
Estimation of Simple Slopes	3.857 (3, 15) *		.435	
(Constant)		3.491 (3,15)		1.854**
Group		.139 (3,15)		.075
Control*RCFT_ 30 Delay(simple slope)		-2.631 (3,15)		-.019*
TBI*RCFT_ 30 Delay (simple slope)		-.202 (3,15)		-.008

* significant at <.05
** significant at <.01

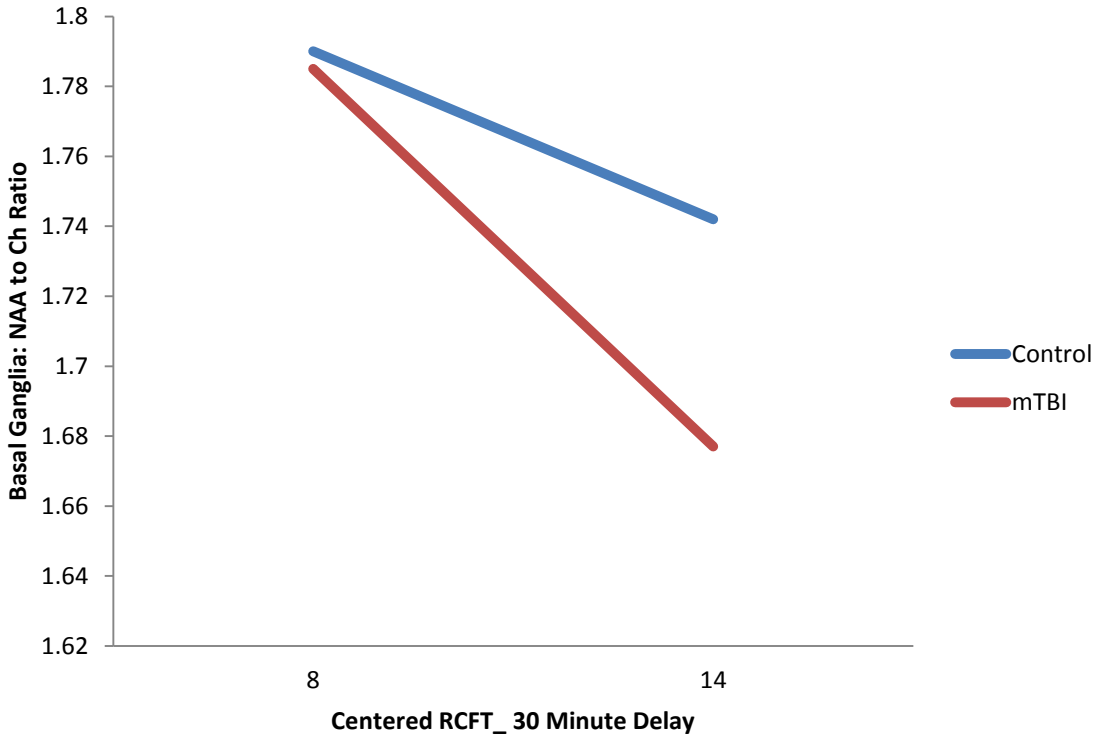

Figure 4. The relationship between delayed non-verbal memory and the NAA/Cho ratio within the basal ganglia

Table 10

The relationship between phonemic fluency and the NAA/Cr ratio within the thalami

	F(df)	T(df)	R2	β
Main Effects	4.208 (2,16) *		.345	
(Constant)		24.074 (2,16)		2.053**
Group		.854 (2,16)		.090
DKEFS_FAS		-2.249 (2,16)		-.023*
Dummy Coded	3.315 (3,15) *		.399	
(Constant)		19.423 (3,15)		1.986**
Group		1.291 (3,15)		.150
DKEFS_FAS		.095 (3,15)		.002
Group*DKEFS_FAS		-1.160 (3,15)		-.031
Estimation of Simple Slopes	3.315 (3,15) *		.399	
(Constant)		19.423 (3,15)		1.986**
Group		1.291 (3,15)		.150
Control*DKEFS_FAS (simple slope)		-2.550 (3,15)		-.028*
TBI*DKEFS_FAS (simple slope)		.095 (3, 15)		.002

* significant at <.05
** significant at <.01

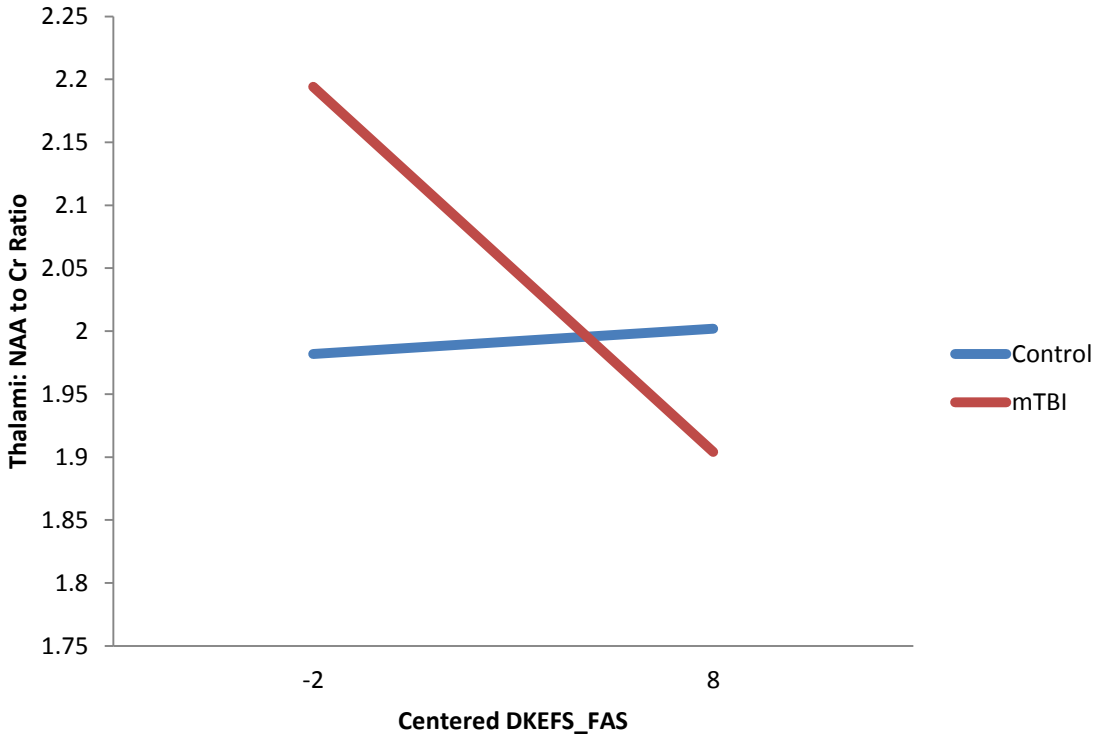

Figure 5. The relationship between phonemic fluency and the NAA/Cr ratio within the thalami

Table 11

The relationship between semantic fluency and the NAA/Cr ratio within the thalami

	F(df)	T(df)	R2	β
Main Effects	5.396 (2,16) *		.403	
(Constant)		25.187 (2,16)		2.066**
Group		.699 (2,16)		.071
DKEFS_ Animals		-2.665 (2,16)		-.027*
Dummy Coded	3.513 (3,15) *		.413	
(Constant)		19.774 (3,15)		2.036**
Group		.836 (3,15)		.098
DKEFS_ Animals		-0.668 (3,15)		-.016
Group*DKEFS_ Animals		-0.502 (3, 15)		-.013
Estimation of Simple Slopes	3.513 (3,15) *		.413	
(Constant)		19.774 (3,15)		2.036**
Group		.836 (3,15)		.098
Control*DKEFS_ Animals (simple slope)		-2.565 (3,15)		-.029*
TBI*DKEFS_ Animals (simple slope)		-.668 (3,15)		-.016

* significant at <.05
** significant at <.01

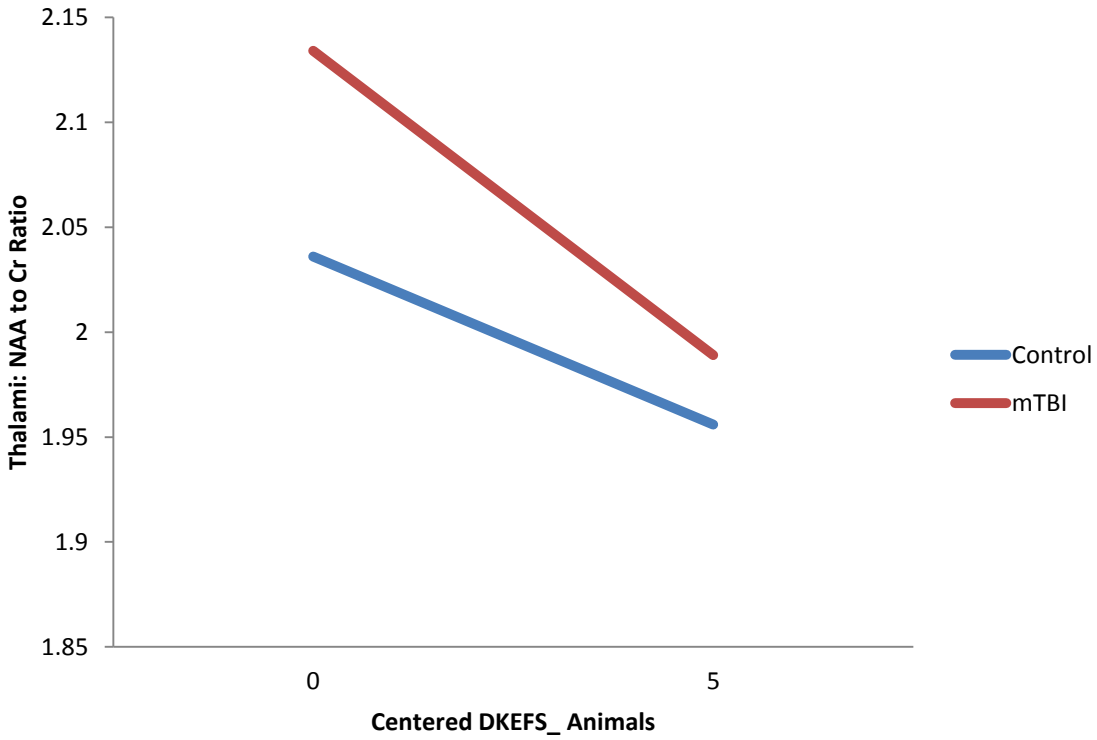

Figure 6. The relationship between semantic fluency and the NAA/Cr ratio within the thalami

Table 12

The relationship between mental flexibility and the NAA/Cr ratio within the thalami

	F(df)	T(df)	R2	β
Main Effects	3.421 (2,16) *		.300	
(Constant)		23.101 (2, 16)		2.049**
Group		.872 (2, 16)		.096
DKEFS_ Category Switching		-1.923 (2, 16)		-.024
Dummy Coded	3.498 (3,15) *		.412	
(Constant)		19.447 (3, 15)		1.956**
Group		1.551 (3, 15)		.178
DKEFS_ Category Switching		.588 (3, 15)		.015
Group*DKEFS_ Category Switching		-1.690 (3, 15)		-.049
Estimation of Simple Slopes	3.498 (3,15) *		.412	
(Constant)		19.447 (3,15)		1.956**
Group		1.551 (3,15)		.178
Control*DKEFS_Category Switching(simple slope)		-2.576 (3,15)		-.034*
TBI*DKEFS_ Category Switching (simple slope)		.588 (3,15)		-.015

* significant at <.05
** significant at <.01

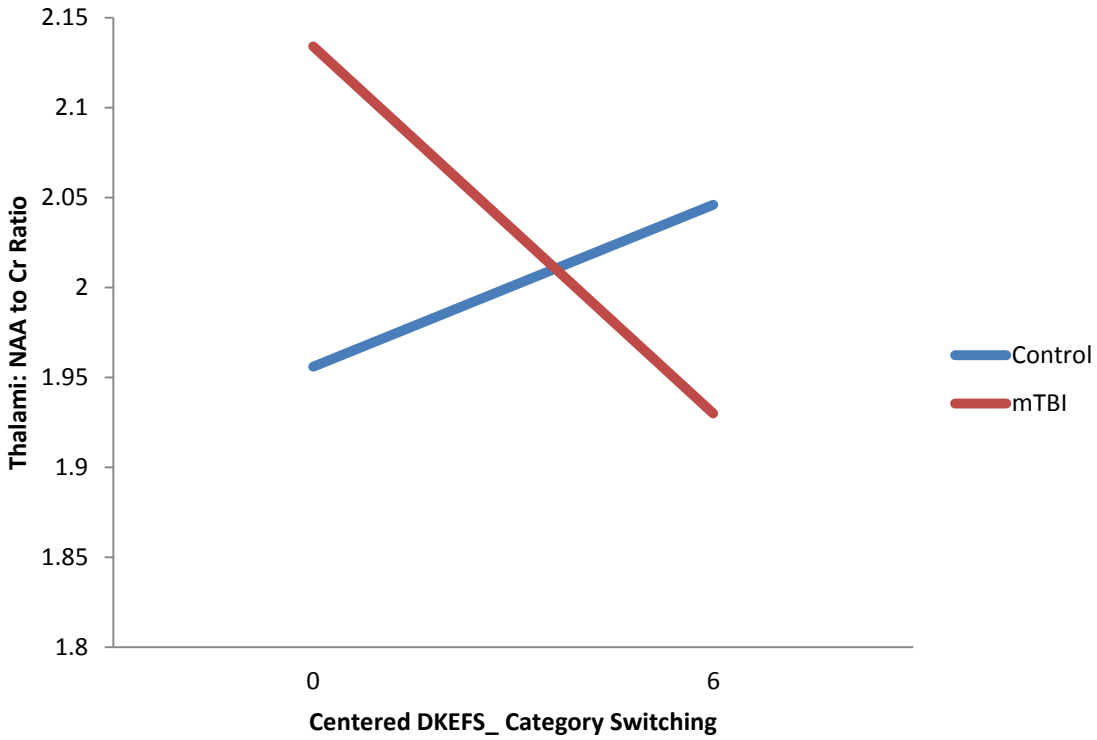

Figure 7. The relationship between mental flexibility and the NAA/Cr ratio within the thalami

Table 13

The relationship between attention and the Cho/Cr ratio within the corpus callosum

	F(df)	T(df)	R2	β
Main Effects	16.540(2,11) **		.750	
(Constant)		32.823 (2,11)		1.309**
Group		-4.463 (2,11)		-.201**
CPT_D		3.340 (2,11)		.009**
Dummy Coded	11.973 (3,10) **		.782	
(Constant)		33.486 (3,10)		1.313**
Group		-4.624 (3,10)		-.204**
CPT_D		.895 (3,10)		.004
Group*CPT_D		1.208 (3,10)		.007
Estimation of Simple Slopes	11.973 (3,10) **		.782	
(Constant)		33.486 (3,10)		1.313**
Group		-4.624 (3,10)		-.204**
Control*CPT_D(simple slope)		3.504 (3,10)		.011**
TBI*CPT_D (simple slope)		.895 (3,10)		.004

* significant at <.05
** significant at <.01

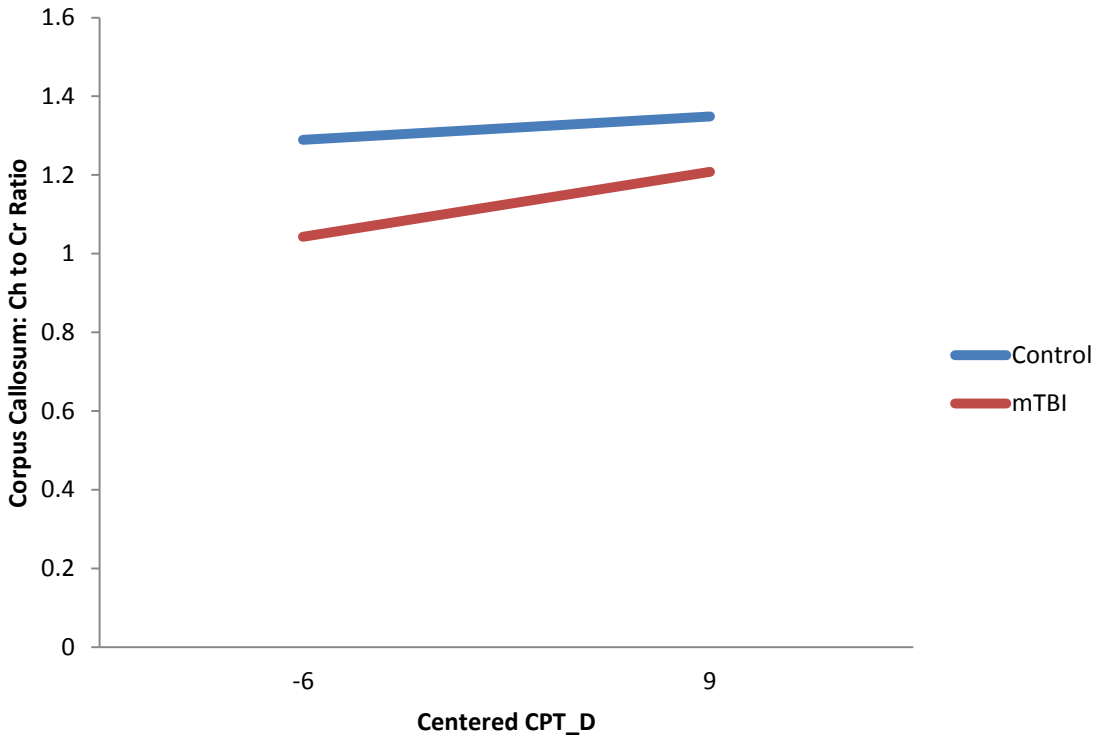

Figure 8. The relationship between attention and the Cho/Cr ratio within the corpus callosum

Table 14

The relationship between attention and the Cho/Cr ratio within the parieto-occipital white matter

	F(df)	T(df)	R2	β
Main Effects	7.227 (2,11) **		.568	
(Constant)		23.254 (2,11)		1.094**
Group		-1.472 (2,11)		-.078
CPT_D		3.406 (2,11)		.011**
Dummy Coded	4.683 (3,10) *		0.584	
(Constant)		22.576 (3,10)		1.096**
Group		-1.468 (3,10)		-.080
CPT_D		1.323 (3,10)		.008
Group*CPT_D		.626 (3,10)		.004
Estimation of Simple Slopes	4.683 (3, 10) *		0.584	
(Constant)		22.576 (3,10)		1.096**
Group		-1.468 (3,10)		-.080
Control*CPT_D(simple slope)		3.099 (3,10)		.012**
TBI*CPT_D (simple slope)		1.323 (3,10)		.008

* significant at <.05
** significant at <.01

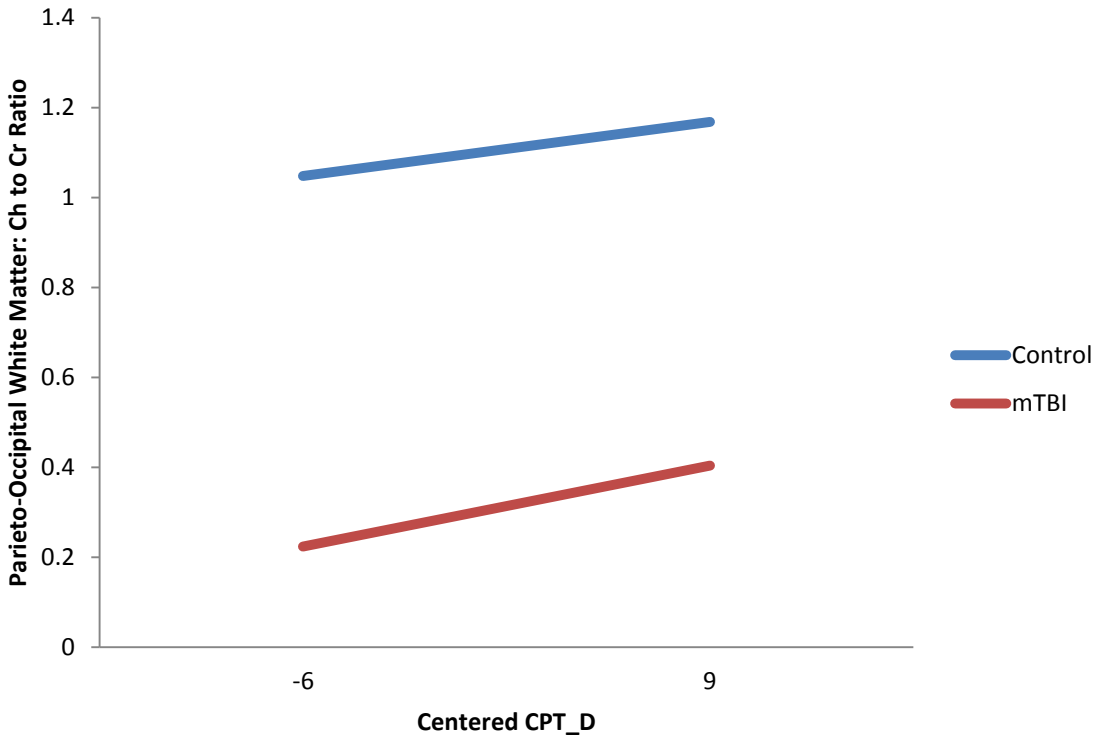

Figure 9. The relationship between attention and the Cho/Cr ratio within the parieto-occipital white matter

The Relationship Between Coping Style and MRS Outcomes in MTBI and Control Groups

The potential interaction between coping style and MRS outcomes was examined. Measured coping factors included confrontive coping, distancing, self-controlling, seeking social support, accepting responsibility, escape avoidance, planful problem solving, and positive reappraisal. The accepting responsibility coping style was the only style found to significantly interact with MRS outcomes. It was found that all other coping styles did not significantly interact with MRS outcomes.

In examining the relationship between the accepting responsibility coping style and the NAA/Cr ratio within the corpus callosum (see Table 15 & Figure 10) stage one shows a significant relationship between the accepting responsibility coping style and NAA/Cr ratio in the corpus callosum ($R2=.542$; $F(2,15)=8.878$; $p<.05$). Stage two shows a non-significant interaction between group membership and the accepting responsibility coping style and NAA/Cr ratio ($\beta=-.034$; $p>.05$). An estimation of simple slopes interaction analysis shows a significant slope for both the controls ($\beta=.043$; $p<.05$) and mTBI groups ($\beta=.077$; $p<.01$).

Table 15

The relationship between coping style (accepting responsibility) and the NAA/Cr ratio within the corpus callosum

	F(df)	T(df)	R2	β
Main Effects	8.878 (2,15)**		.542	
(Constant)		21.006 (2,15)		2.820**
Group		-.874 (2,15)		-.138
WAYS_AR		4.169 (2,15)		.055**
Dummy Coded	6.687 (3,14)**		.589	
(Constant)		21.456 (3,14)		2.833**
Group		-.953 (3,14)		-.148
WAYS_AR		3.538 (3,14)		.077**
Group*WAYS_AR		-1.264 (3,14)		-.034
Estimation of Simple Slopes	6.687 (3,14)**		.589	
(Constant)		21.456 (3,14)		2.833**
Group		-.953 (3,14)		-.148
Control*WAYS_AR(simple slope)		2.675 (3,14)		.043*
TBI*WAYS_AR(simple slope)		3.538 (3,14)		.077**

* significant at <.05
** significant at <.01

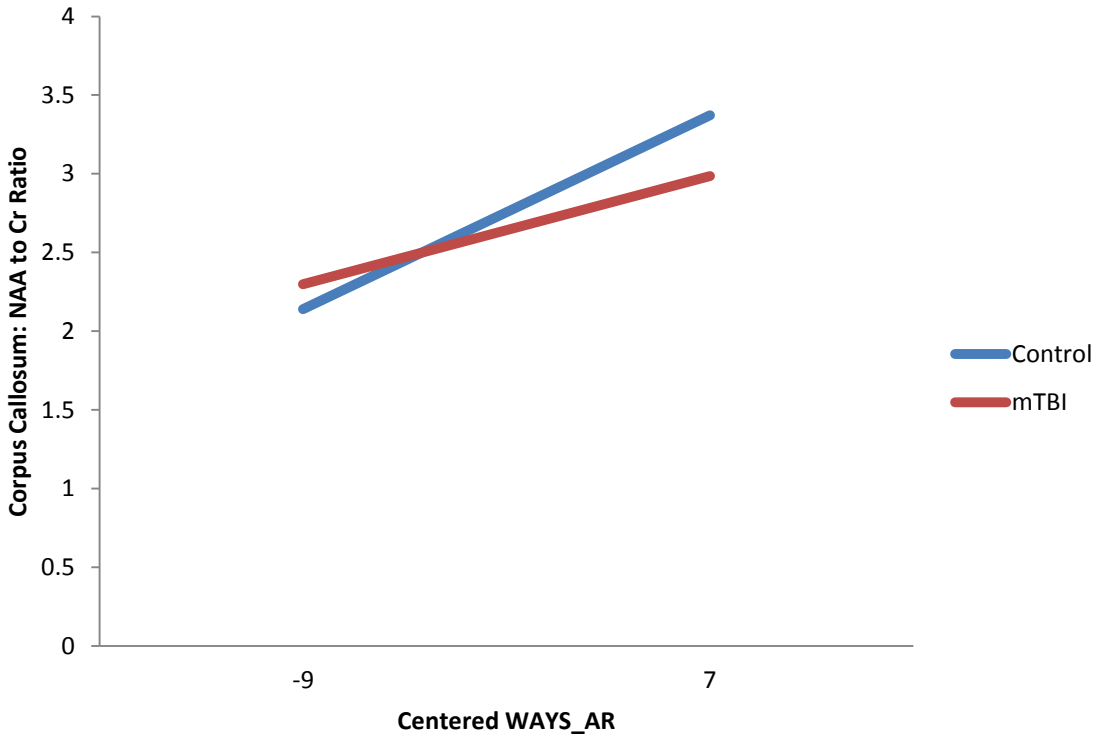

Figure 10. The relationship between coping style (accepting responsibility) and the NAA/Cr ratio within the corpus callosum

The Relationship Between of Mood and Perceived Quality of Life and MRS Outcomes

The potential relationship between mood and MRS outcomes and perceived quality of life and MRS outcomes was also examined. Measured mood factors included depression and anxiety. Perceived quality of life factors included physical health, psychological state, level of independence, social relationships, personal beliefs, and one's relationship to their environment. The hypothesis that there would be a significant relationship between mood and cerebral metabolite ratios and perceived quality of life and cerebral metabolite ratios, as measured by MRSI, was not confirmed. Mood and perceived quality of life did not significantly interact with MRS outcomes.

CHAPTER FOUR

DISCUSSION

Results from the current study demonstrate differences between cognition, mood, perceived quality of life, coping style, and cerebral metabolism between mTBI subjects and healthy controls. The mTBI group performed significantly worse than healthy controls on a number of neuropsychological measures. Specifically, the mTBI group performed worse than controls on measures of attention, immediate and delayed non-verbal memory, verbal learning, immediate and delayed memory for unstructured information, and immediate and delayed verbal memory for contextually related information. These findings confirm established research, which has shown that mTBI negatively affects cognition. Specifically, previous studies have shown reduced learning and memory, executive functioning decline, and slowed processing speed to be resultant of mTBI. Additionally, previous research has found declines in divided and sustained attention, visuospatial and visuoconstructional capacity, and language, including verbal fluency and confrontation naming in the mTBI population.

Significant differences in mood and perceived quality of life were observed between groups. With regards to mood, mTBI subjects endorsed significantly worse mood than healthy controls, reporting more depression and anxiety. Specifically, the mTBI group's average BAI and BDI-II/BYI scores were in the mildly anxious and depressed ranges, whereas the control group's average BAI and BDI-II/BYI scores were in the minimally anxious and depressed ranges. These findings confirm previously established literature, which shows that mTBI contributes to increased depression and anxiety. Regarding perceived quality of life, the mTBI group reported significantly

poorer perceived quality of life, in all domains assessed, than healthy controls. Specifically, the mTBI group when compared to controls endorsed significantly worse psychological, independence, physical, social, environmental, and spiritual quality of life. The quality of life findings were surprising, as it was not expected that all domains of quality of life assessment would indicate such significant decline in the mTBI group. Overall, these findings show that mTBI individuals with chronic post-concussive symptoms endorse significantly poorer mood and quality of life than healthy controls, which may have important implications for treatment planning with this patient population.

Results showed significant differences within coping style between the mTBI and control groups. Specifically, the mTBI group, when compared to controls, endorsed significantly less confrontive coping and more distancing. Specifically, when compared to controls, the mTBI group endorsed more coping efforts that allocated cognitive effort to detaching from and minimizing the significance of stressful situations. Moreover, the mTBI group endorsed less aggressive efforts to alter stressful situations than controls. These findings suggest that the mTBI group may possess less effective coping strategies than healthy controls. This may in turn have an impact on an individual's ability to effectually cope with cognitive and psychological changes following a head injury. Additionally, it is possible that confrontive coping may be more cognitively demanding than other coping styles, requiring proactive efforts to alter a stressful situation. Therefore, it is reasonable to posit that this coping style would be less effectively executed in a population with cognitive deficits. It is unclear whether the manifested coping differences are the direct result of the head injury or if individuals with poorer

coping styles are more prone to chronic post-concussive symptoms following mTBI. Interestingly, no other between-group differences were noted within coping style analyses. One possible explanation of why more group differences were not found within coping style analyses may be that the majority of the current subjects were from the Loma Linda area, which is a predominantly Seventh-day Adventist community. It is possible that this group of people is more religious and/or spiritual than members of other communities. This increased spirituality may in turn predict better overall ability to cope with life's stressors. An additional possible factor that may have led to minimal significant findings than was predicted may be related to a limitation of the WAYS coping style measure. Specifically, this measure evaluates the most stressful situation that has occurred for the individual over the past week. Throughout testing, numerous individuals reported that they had not experienced anything significantly stressful over the past week. As a result, the subjects "most stressful situation" may have been an event that was minimally distressing. Conversely, other individuals responded to questions with a highly stressful situation in mind. Therefore, this measure may have inaccurately evaluated the true coping style of individuals who reported not having experienced a stressful situation over the past week. Specifically, it is unlikely that a minimally stressful situation would have evoked significant coping skills, therefore diminishing the potential for true coping style to be evaluated with a measure. Additionally, a possible explanation of why coping style between groups did not yield more robust findings may be related to the fact the some of the participants may have been involved in psychotherapy, thus likely focusing on developing effective coping skills within the therapeutic context. It is known that some of the participants were actively involved in therapy or had received

therapy at some time following their head injury. Unfortunately, this information was not available for all subjects as it was not a formal variable being measured within the scope of the current study. Another potential limitation of the coping style analyses may arise from the fact that child and adult data were examined together. It is likely that children are significantly less capable of demonstrating an array of effective coping styles than adults. Unfortunately, the coping measure utilized did not provide normative data for individuals across the age spectrum, which is a limitation of this measure. However, these are important considerations for future research. Overall, while more research is needed, with larger sample sizes, the current conclusion from the population studied is that mTBI subjects did demonstrate poorer coping efforts than controls, with significantly more distancing and less confrontive coping.

Analyses of cerebral metaboltie ratios between groups revealed a decreased Cho/Cr ratio in the corpus callosum in mTBI subjects when compared to controls. These metabolites are important in maintaining cellular energy status and cellular membrane integrity and turnover. Another metabolite measured included NAA, which represents both neuronal integrity and neuronal mitochondrial function. While the current finding is noteworthy and significant in showing a difference between mTBI subjects and healthy controls, it was anticipated that there would have been more cerebral metabolic differences between groups. Specifically, a number of previous studies have shown metabolite ratio changes following mTBI (Govind et al., 2010; Govindaraju et al., 2004; Henry et al., 2010; Yeo et al., 2011; Lin et al., 2012; Johnson et al., 2012; Gasparovic et al., 2009; Vagnozzi et al., 2010; Capizzano et al., 2010). It is possible that the small sample size of the current study made it difficult to effectively observe significant

differences between groups. Of note, while only one cerebral metabolic ratio in one brain area was found to be significant between groups, the majority of other ratios assessed, across brain regions, had small to large effect sizes. Specifically, small to medium effects sizes between groups were found in the NAA/Cr ratio in the corpus callosum, the NAA/Cr and Cho/Cr ratios in the frontal grey matter, the NAA/Cr and Cho/Cr ratios in the frontal white matter, NAA/Cho ratio in the parieto-occipital white matter, and the Cho/Cr ratio in the thalami. Medium to large effect sizes were noted, between groups, for the NAA/Cho and Cho/Cr ratios in the basal ganglia, the NAA/Cho ratio in the frontal white matter, and the NAA/Cr ratio in the parieto-occipital grey matter. Additionally, medium to large effect sizes were found for the NAA/Cr ratio in the parieto-occipital white matter, the NAA/Cr and NAA/Cho ratios in the thalami, and NAA/Cho and Cho/Cr ratios in the temporal white matter. Therefore, although these cerebral metabolic ratios did not significantly differ between mTBI and control groups, given the small to large effect sizes, it is likely that there are significant differences that this underpowered study was unable to effectively capture. Another possible explanation of why more significant differences were not found between groups may be due to the fact that pediatric and adult subjects with both recent and remote injuries were studied as one group, with the majority of mTBI subjects being adults with remote injuries. It is possible that more differences may have been captured if these groups were compared to one another in addition to healthy controls. It would have been expected that there would have been more variability in neuropsychological outcomes of pediatric mTBI subjects. Specifically, it would have been expected that following mTBI, when compared to an adult, a child would demonstrate more frontal dysfunction due to the fact that this

specific brain region has not yet reached it's developmental potential. Additionally, it would have been hypothesized that children would fare worse over time than adults. Specifically, it is presumed that a child would experience more cognitive difficulty than an adult when faced with cognitively demanding tasks over time. This may be due to the fact that an mTBI interrupts key developmental neurological processes and thus may be more devastating to a developing brain than to an adult brain. Additionally, it is feasible that individuals with more recent injuries may show more alterations in cerebral metabolism when compared to individuals with more remote injuries and healthy controls. Therefore, it is hopeful that future research, with larger sample sizes, will be able to identify additional cerebral metabolic differences in the mTBI population when compared to controls.

Significant interactions were found between cerebral metabolism and both neuropsychological performance and coping style, indicating that these variables may be related differently in the mTBI population than in healthy controls. Neuropsychological performance was found to have a significant relationship with cerebral metabolism in various brain regions in the mTBI population. Specifically, significant interactions were found between non-verbal abstraction and the NAA/Cr ratio within the frontal white matter, visuoconstruction and the NAA/Cr ratio within the frontal white matter, and processing speed and the NAA/Cr ratio within the thalami. Additionally, delayed non-verbal memory and the NAA to Ch ratio within the basal ganglia, phonemic fluency and the NAA/Cr ratio within the thalami, semantic fluency and the NAA/Cr ratio within the thalami, mental flexibility and the NAA/Cr ratio within the thalami, attention and the Cho/Cr ratio within the corpus callosum and parieto-occipital white matter were found to

significantly interact. With regards to the relationship between coping style and MRS outcomes, the accepting responsibility coping style was the only style found to significantly interact with MRS outcomes. It was found that all other coping styles, including confrontive coping, distancing, self-controlling, seeking social support, escape avoidance, planful problem solving, and positive reappraisal did not significantly interact with MRS outcomes. The relationship between mood and perceived quality of life and MRS outcomes in mTBI and control groups was also analyzed. It was found that although mood and perceived quality of life did significantly differ between groups, these factors did not significantly interact with MRS outcomes in the mTBI group, when compared to controls. Therefore, the current findings suggest that mood and perceived quality of life do not significantly interact with cerebral metabolism in the mTBI population. These findings were fairly surprising as mood and quality of life showed the most robust difference between groups, therefore, it was expected that these variables would have had a significant relationship with cerebral metabolic ratios. However, more research is needed, with a larger sample size, to continue to explore the possible relationship between these variables. Overall, these findings demonstrate an important finding and possibly provide an explanation to the basic question asking why some mTBI patients experience residual cognitive and psychological symptoms while others do not. Additionally, the current results fill a gap in the literature, which, to date, has not evaluated the relationship between cerebral metabolism and neuropsychological performance, mood and quality of life, using MRS, following mTBI.

In general, the study is underpowered, which requires more subjects to evaluate true effects. When using a conservative estimate (0.15) of the effect size, many of the

measures (i.e., coping, quality of life) are more psychosocial in nature and therefore have less robust effects. However, in some cases the findings were rather robust and an effect was clearly seen. Specifically, both the significant and also many of the non-significant cerebral metabolic differences between groups showed small to large effect sizes. Therefore, it is likely that there are significant differences that this study, with its relatively small sample size, was unable to establish. Therefore, one should interpret non-significant findings with caution, as it is likely that type II errors have been made due to decreased power resulting from a low subject number.

It is important for future research, with larger sample sizes, to confirm the current findings in addition to exploring additional questions. Future studies should continue to evaluate the differences in cognitive, mood, coping style, and quality of life outcomes between children, adolescents, and adults following mTBI. These findings may provide an important understanding of how mTBI affects cognition, mood, coping style, and quality of life across the lifespan. Additionally, it may be interesting to better understand the psychological factors, including coping style, that may predispose some mTBI individuals to experience more chronic post-concussive symptoms than others. Future research in this area may also continue to examine differences in cerebral metabolism in this population. Specifically, researchers may seek to better understand possible cerebral metabolic differences in individuals with recent versus remote injuries. This may provide a better understanding of whether or not alterations in cerebral metabolism affect an individual's likelihood of experiencing chronic post-concussive symptoms over time. Another interesting question for future research is whether or not the type of injury has a significant impact on outcomes. Specific injuries that appear to be the most common

include sports related injuries, motor vehicle accidents and falls. It may be useful to better understand whether or not these injuries differ from other head injuries incurred in different ways. This may provide insight into the clinical implications of various types of mTBI.

In summary, this preliminary study has shown that mTBI subjects, when compared to healthy controls, performed poorer on various neuropsychological measures, displayed increased levels of depression and anxiety, demonstrate less effective coping strategies, and reported poorer quality of life. A significant difference in the metabolism of two cerebral metabolites in the corpus callosum was also found between groups. Additionally, significant relationships between cerebral metabolism in several brain regions and numerous neuropsychological variables were found in the mTBI, but not in the control group. Also, a significant relationship was found between cerebral metabolism and coping style in the corpus callosum of mTBI subjects, but not controls. Of note, non-significant differences in cerebral metabolism in various brain regions, showed surprisingly strong effect sizes. Using these findings as a guide, future studies should assess additional participants in order to increase statistical power to the current findings.

This study has been useful in filling a gap in the literature, which has failed to examine the potential relationship between cerebral metabolism and neuropsychological performance, mood, coping style, and perceived quality of life. The current findings provide clarification about the nature and extent of cognitive and psychological outcomes following TBI. More importantly, this study has established a new understanding of the alterations in cerebral metabolism following mTBI. Additionally, this study has provided

valuable information regarding the relationship between cerebral metabolism, as measured by MRS, and cognitive and psychological in the mTBI population. Specifically, current results show that neuropsychological performance and cerebral metabolism in various brain regions appear to be related differently in the mTBI population than in healthy controls. It is possible that differences in cerebral metabolism are influencing neuropsychological performance following mTBI. However, because these variables cannot be manipulated it is not possible to make inferences about causality. Overall, these findings provide a better understanding to the differences in the relationship between neurobiological and cognitive function in the mTBI population.

This study has shown that, following mTBI, there is a difference in the relationship between cerebral metabolism and performance on various neuropsychological measures. This finding directly affects treatment and can be translated to specific therapeutic interventions. Specifically, future research should eagerly strive to understand possible ways to alter cerebral metabolism, possibly through medication, diet, or other behavioural changes. This may lead to improvements in cognitive and functional outcomes. Additionally, the current study has demonstrated that neuropsychological performance, on tasks of non-verbal abstraction, visuoconstruction, processing speed, delayed non-verbal memory, verbal fluency, mental flexibility, and attention, have a significant relationship with cerebral metabolism in various brain regions in the mTBI population. Given the risk for mTBI patients to develop chronic post-concussive symptoms, it is important to identify factors that may intercept this conversion. It is possible that cognitive rehabilitation treatment strategies, specifically focused on improving non-verbal abstraction, visuoconstruction, processing speed,

delayed non-verbal memory, verbal fluency, mental flexibility, and attention may lead to reduced alterations in cerebral metabolism. This may in turn yield overall improvements in cognitive, psychological, and functional outcomes. Cognitive Remediation Therapy (CRT) aims to reduce an individual's cognitive deficits by employing evidence- based techniques to improve attention, memory, language, and executive functions. This therapeutic modality, with a focus on training the brain in deficient aspects of a cognitive function through regularly repeated exercises, may prove to dramatically reduce cognitive symptoms. It is hopeful that the findings from the current findings will affect therapeutic interventions, improving the overall prognosis of the mTBI patient.

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