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The Frontal-Temporal Signature of TBI-Induced Acute Cerebral Metabolic Crisis

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The Frontal-Temporal Signature of TBI-Induced Acute Cerebral Metabolic Crisis

by

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

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ABBREVIATIONS

TBI	Traumatic Brain Injury
ACMC	Acute Cerebral Metabolic Crisis
CMR	Cerebral Metabolic Rate
CMRglc	Cerebral Metabolic Rate of Glucose
CMRlac	Cerebral Metabolic Rate of Lactate
FTI	Frontal-Temporal cognitive Integration
FTI-6	Frontal-Temporal Integration at 6 months
FTI-12	Frontal-Temporal Integration at 12 months
FTI-Recovery	Difference between FTI-12 and FTI-6
GCS	Glasgow Coma Score
PTA	Posttraumatic Amnesia
LOC	Loss Of Consciousness
DAI	Diffuse Axonal Injury
ALNS	Astrocyte-Neuron Lactate Shuttle model
MCBA	Metabolic Crisis-related Brain Atrophy
PET	Positron Emission Tomography
MRI	Magnet
ERGCS	Emergency Room GCS score
CT	Computerized Tomography
MVA	Motor Vehicle Accident
COWAT	Controlled Oral Word Association Test
FAS	COWAT for letters F, A, and S

SRT-6	Buschke Selective Reminding Test 6-trial version
CVLT	California Verbal Learning Test
LTS	Long-Term Storage
ICP	Intracranial Pressure
EEG	Electroencephalography
CMD	Cerebral Microdialysis
FDG	F^{19} deoxyglucose
AVDglc	Arterial-Venous Difference in glucose concentration
AVDlac	Arterial-Venous Difference in lactate concentration
$AVDO_2$	Arterial-Venous Difference in Oxygen concnetration
CBF	Cerebral Blood Flow
TMT-B	Trail Making Test Part B
ROCFT	Rey Osterrieth Complex Figure
GPT	Grooved Pegboard Test

ABSTRACT OF THE DISSERTATION

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Traumatic brain injury (TBI) often leads to acute cerebral metabolic crisis (ACMC), which appears to have the greatest impact on the frontal-temporal regions. A recent study demonstrated that atrophy in the frontal and temporal lobes related to acute metabolic crisis due to moderate or severe TBI was associated with poorer attention, executive functioning, and psychomotor abilities at 12 months post-injury. In addition, participants with greater frontal-temporal atrophy had T-scores on all of the standard tests that were in the deficit range indicating deficits in cognition. The purpose of the current study is to investigate the ability of direct measures of acute glucose and lactate metabolism to predict recovery of frontal-temporal cognitive integration in a sample of 26 moderate to severe traumatic brain injury participants. Cerebral metabolic rate of glucose (CMRglc) and lactate (CMRlac) were measured by the Kety-Schmidt method on days 0-7 post-injury. An index of frontal-temporal cognitive integration was calculated at 6 months (FTI-6) and 12 months (FTI-12) post-injury by averaging the T-scores of the phonemic fluency portion of the Controlled Oral Word Association Test and the long-term storage score of the 6-trial version of the Buschke Selective Reminding Test. A recovery index of frontal-temporal cognitive integration (FTI-Recovery) was derived by subtracting the 6 month FTI index (FTI-6) from the 12 month FTI index (FTI-12). Hierarchical linear

regression analysis was used to test acute CMRglc and CMRlac as predictors of FTI-6, FTI-12, and FTI-Recovery after controlling for severity of injury as measured by initial score on the Glasgow Coma Scale (GCS). The current study found an association between acute cerebral metabolic rates and frontal-temporal integration recovery (FTI-Recovery) for both glucose and lactate.

CHAPTER ONE

INTRODUCTION

Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide (Frattalone & Ling, 2013). The majority of TBI patients are between the ages of 15 and 44 (Tagliaferri et al., 2006) and are two times more likely to be male than female (Langlois, Rutland-Brown, & Wald, 2006). The incidence of TBI in the United States is estimated at 1.7 million patients per year, resulting in 50,000 deaths, 275,000 hospitalizations, and 80,000-90,000 patients with long-term disabilities (Kosty & Stein, 2013; Ma, Chan, & Carruthers, 2014). The actual statistics are most likely higher than these estimates, but cases that went undiagnosed were most likely mild in severity (Rusnak, 2013). Unfortunately, long-term cognitive and emotional disabilities associated with TBI often result in significant social and vocational consequences (Holloway, 2007). Furthermore, the total annual healthcare costs due to TBI for 2013 were estimated at between 60 to 80 billion dollars (Ma, Chan, & Carruthers, 2014). In addition to long-term disabilities and health care costs, TBI survivors report feeling stigmatized by society in response to their post-injury symptoms (Ralph & Derbyshire, 2013).

Given the gravity of this "silent epidemic," (Rusnak, 2013) emergency departments have developed a triage method to determine the severity of TBI based on the Glasgow Coma Scale (GCS) scores, and the durations of impaired consciousness and posttraumatic amnesia (PTA). The GCS is generally used within the first 24 hours to assess level of consciousness and triage patients who have sustained a head injury. Loss of consciousness (LOC) and PTA are neurobehavioral hallmarks of acute TBI that are also utilized in classification of TBI severity. A TBI with a GCS score between 13 and

15, or LOC less than 30 minutes, and/or PTA of 24 hours or less is considered to be mild. A TBI with a GCS score between 9 and 12, LOC between 30 minutes and 24 hours, and/or PTA between one and seven days is classified as moderate. A TBI with a GCS score of 8 or less, LOC greater than 24 hours, and/or PTA greater than seven days is considered severe (Blyth & Bazarian, 2010).

The mechanisms of brain tissue trauma related to TBI have been classified as primary and secondary (Abdul-Muneer, Chandra, & Haorah, 2014). Primary injury is due to mechanical forces acting on the skull and brain during impact, and is thought to be irreversible. The primary injury results in brain contusions, intracranial hemorrhages, skull fractures, rupturing of blood vessels, and diffuse axonal injury. Secondary injuries develop over time in response to primary injuries and may be reversible if treated early enough. Secondary cerebral damage mechanisms involve a complicated series of biochemical reactions that can lead to brain edema, elevated intracranial pressure, ischemia, neuroinflammation, cerebral hypoxia, blood-brain barrier disruption, and delayed neurodegeneration.

The etiology and neuropathology of traumatic brain injury greatly varies (NIH, 1999; Williamson et al., 1996); however, the majority of moderate and severe cases are associated with acceleration-deceleration forces that result in contusions due to coup-contrecoup injury and diffuse axonal injury (DAI; Adams et al., 1989; Adams et al., 1980; Adams & Jennett, 2001; Bigler, 2001; Takaoka et al., 2002; Williamson et al., 1996). In addition, direct impact of parenchymal tissue against the bony processes in the skull due to these acceleration-deceleration forces cause lesions in the ventral frontal lobe and ventral anterior medial temporal areas (Adams et al., 1989; Adams et al., 1980;

Frattalone & Ling, 2013; Wilson et al., 1995). Other research has determined that early metabolic crisis may be another mechanism of chronic secondary brain injury following TBI (Wright et al., 2013).

In moderate to severe TBI (even in the absence of ischemia) decreases in oxygen metabolism and increases in glucose metabolism, as well as elevated lactate levels, commonly occur just after the TBI is sustained (Glenn et al., 2003; Vespa et al. 2005). This abnormal increase in glucose metabolism occurs during a period of increased demand for energy in the brain, which results in an increase in glucose metabolism followed by a period of metabolic depression, which the literature refers to as Acute Cerebral Metabolic Crisis (ACMC). Elevated lactate levels are a consequence of anaerobic metabolism of glucose, or glycolysis, that occurs after the primary injury when the brain does not have enough oxygen for aerobic metabolism (Jalloh et al., 2013). Recent studies have demonstrated that when the brain's glucose levels are low, lactate is utilized as an alternative fuel source (Bouzat et al., 2014; Jalloh et al., 2013). The astrocyte-neuron lactate shuttle model (ANLS) illustrates the posited process involved in lactate's use as an alternative fuel source. The ANLS model describes the transport of lactate produced by cerebral glycolysis from a lactate-producing cell (astrocyte) to a lactate-consuming cell (neuron) that preferentially metabolizes lactate as an oxidative fuel (Bouzat et al., 2014; Jalloh et al., 2013).

Lactate can be both a byproduct of glucose metabolism, and/or used as fuel by the brain similar to glucose. However, a number of studies of glucose and lactate metabolism after TBI have found that lactate is more commonly involved as a fuel than as a byproduct (Glenn et al, 2003). Holloway et al. (2007) determined that intravenous

infusions of lactate in rats following TBI improved cognitive impairment. Similarly, a study by Kokiko-Cochran, Michaels, and Hamm (2008) found that the performance of injured rats on the Morris Water Maze significantly improved after glucose was administered 11 days post-injury. However, this study also determined that the performance enhancement decreases as the time between glucose treatment and the cognitive assessment increases.

Previous research indicates that early metabolic dysfunction due to TBI varies greatly by brain region and time since injury (Hattori et al., 2003; Marcoux et al., 2008; Vespa et al., 2004; Vespa et al., 2007; Xu et al., 2010). Additionally, early metabolic dysfunction frequently results in chronic atrophy in the frontal and temporal lobes (Xu et al., 2010) and extends beyond pericontusional tissue to normal appearing brain tissue. While this chronic atrophy is not associated with ischemia and appears to be distinct from DAI (Hattori et al., 2003; Xu et al., 2010), it is related to long-term neuropsychological outcomes (Wright et al., 2013). Although chronic atrophy associated with early metabolic crises occurs in the parietal lobes, the frontal and temporal lobes generally exhibit the largest amount of atrophy (Xu et al., 2010). While the findings of the Xu et al. study (2010) suggest that impaired oxidative metabolism plays an important role in brain atrophy, the mechanisms that result in brain atrophy have not been determined.

Unlike mild TBI, chronic impairments in attention, processing speed, memory, and executive function are routinely observed in cases of moderate to severe TBI. Therefore, the cognitive profile generally seen in moderate to severe TBI patients has been identified as dysfunction that is frontal (Stuss & Gow, 1992; Vakil, 2005) or frontal-

temporal (Lezak et al., 2004) in nature, given that intact frontal and temporal lobes are essential for properly functioning memory, attention, and executive abilities.

Numerous studies have been conducted to determine the neuropathology that predicts the cognitive outcome of TBI survivors. It is well established that the presence of DAI and focal lesions, frequently located in the frontal and temporal lobes, is one of the predictors of cognitive outcome in TBI (Auerbach, 1986; Bigler, 2001; Fork et al. 2005; Kraus et al., 2007; Lehtonen et al., 2005; Levine et al., 2002; Wallesch et al., 2001; Williamson et al., 1996). A recent study investigated the possible relationship between chronic TBI-induced cognitive deficits and acute metabolic crisis (Wright et al., 2013). The rationale for this hypothesized association was the frontal-temporal nature of the TBI cognitive profile and the corresponding frontal-temporal influence of the metabolic crisis-related brain atrophy (MCBA). Specifically, atrophy was most prominent in the frontal-temporal regions that are associated with persistent metabolic crisis due to abnormal glucose (Wright et al., 2013) and lactate metabolism (Xu et al., 2010). The experimental protocol accounted for all identified contusions and lesions to rule out the possibility that the frontal-temporal cognitive profile of TBI was due to factors other than MCBA. The results of this study demonstrated that non-ischemic MCBA was strongly correlated with attention, executive functioning, and psychomotor abilities at 12 months post-injury (Wright et al., 2013). Moreover, the participants of this study with gross frontal and/or temporal atrophy displayed numerous clinically significant neuropsychological deficits, unlike participants with other brain atrophy patterns.

In the current study, we assessed neuropsychological function at 6 and 12 months post-injury in a sample of TBI participants who exhibited non-ischemic MCBA. Unlike

the Wright et al. (2013) investigation that studied abnormal glucose metabolism and MCBA indirectly using positron emission tomography (PET) and magnetic resonance imaging (MRI), the current study investigated both abnormal glucose and lactate metabolism directly via Kety-Schmidt jugular bulb catheterization. Given the frontal-temporal cognitive signature of TBI and the impact of acute metabolic crisis on the frontal and temporal lobes, our goal was to determine if early markers of glucose and lactate metabolism predict indices of cognitive skills that require interactive processing in the frontal and temporal lobes. These indices were calculated at 6 (FTI-6) and 12 months (FTI-12) post-injury. In addition to evaluating short- and long-term outcomes of frontal-temporal cognitive integration, this study examined the degree of recovery. A recovery index of frontal-temporal cognitive integration (FTI-Recovery) was derived from the difference between FTI-6 and FTI-12. In all cases (FTI-6, FTI-12, and FTI-Recovery), severity of initial injury was measured by GCS assessed upon admission to the emergency department (ERGCS).

Because metabolic rate is a measurement of the brain's response to injury, we hypothesized that greater rates of glucose and lactate metabolism (Cerebral Metabolic Rate of glucose, CMRglc, and Cerebral Metabolic Rate of lactate, CMRlac) would predict better recovery in frontal-temporal processing (FTI-Recovery) after controlling for severity of injury. In addition, we hypothesized that greater rates of CMRglc and CMRlac would be predictive of improved performance on indices of memory and executive function at 6 months (FTI-6) and 12 months (FTI-12) post injury after controlling for severity of injury. However, we hypothesized that CMRglc and CMRlac would be less predictive of the index of integrated cognitive skills at 6 months (FTI-6)

post-injury than they would be for the index at 12 months (FTI-12) post injury and would be less predictive of both cognitive indices (FTI-6 & FTI-12) than the recovery index (FTI-Recovery), due to the brain being more fully recovered after 12 months than at 6 months.

CHAPTER TWO

METHOD

Participants

The current study was approved by the institutional review board of the University of California, Los Angeles and all participants consented directly or by proxy to voluntary participation. The current study initially included 27 TBI participants who completed brief neuropsychological testing at 6 and 12 months post-injury. One participant was removed from the data as an outlier. All of the TBIs were due to acceleration-deceleration forces and were moderate to severe in nature. Eligible patients consisted of all patients with moderate to severe head injuries who were admitted to UCLA Medical Center within 24 hours of injury. The patient inclusion criteria comprised a GCS score of 8 or less, or a GCS between 9 and 15 if an initial computerized tomography (CT) brain scan showed evidence of intracranial bleeding, and completion of the majority of a brief neuropsychological test battery administered at approximately 6 and 12 months post-injury.

The average patient age was 29.08 (*SD* = 11.22). The sample consisted of 85% male (*N* = 22) and 15% female (*N* = 4). The racial/ethnic composition of the sample was 53.8% Caucasian, 15.4% African American, 15.4% Hispanic/Latino, 11.5% Asian, and 3.9% other. The average level of education was 13.21 years (*SD* = 2.99). The sample consisted of 53.8% closed head injury and 46.2% open head injury. In terms of injury mechanism, the sample included 38.5% motor vehicle accident (MVA), 23.1% long fall (fall from a height greater than or equal to the height of the patient), 15.4% MVA versus pedestrian, 11.5% bicycle, 7.7% blunt force trauma, and 3.8% gunshot. The average

patient ERGCS score was 7.96 (*SD* = 3.54), which falls within the severe TBI range (Table 1).

Table 1. Participant Demographics.

	N (%)	*Mean (SD)*	*Median*	*Range*
Demographics				
Age (yrs) at Injury	26	29.08 (11.22)	25.00	42.00
Education (yrs) at Injury	26	13.21 (2.99)	13.00	14.00
Sex (% male)	22 (84.62)			
Ethnicity (%)				
Caucasian	14 (53.85)			
African American	4 (15.38)			
Hispanic/Latino	4 (15.38)			
Asian	3 (11.54)			
Other	1 (3.85)			
Injury Characteristics				
ERGCS	26	7.96 (3.54)	7.00	11.00
Best in 8 GCS	26	7.27 (1.80)	7.00	8.00
Closed Head Injury	14 (53.85)			
Open Head Injury	12 (46.15)			
Injury Type (%)				
MVA	10 (38.46)			
MVA vs. Pedestrian	4 (15.38)			
Bicycle	3 (11.54)			
Long Fall	6 (23.08)			
Blunt	2 (7.69)			
Gun Shot	1 (3.85)			
Cerebral Metabolic Rates				
CMRglc	26	.174 (.057)	.163	.216
CMRlac	26	.065 (.067)	.044	.235
Frontal-Temporal Performance				
FTI-6	26	1.81 (1.61)	2.00	5.00
FTI-12	26	1.54 (1.45)	1.50	3.50
FTI-Recovery	26	.27 (.94)	0.00	4.50

Measures

Glasgow Coma Scale

The GCS (Teasdale & Jennett, 1974) is an instrument widely used in hospitals to assess level of consciousness in acute trauma patients. The GCS was utilized in the

current study as a measure of injury severity. Each patient was initially assessed with the GCS upon entering the ER and then eight more times over the course of acute care. The "best in 8" GCS score was the best of eight GCS scores obtained during the hospital stay. The current study used ERGCS as a measure of injury severity. The scale consists of three elements: eye opening response, verbal response, and motor response. The eye opening response subscale consists of four possible responses, '"spontaneous" eye opening is worth 4 points, eye opening "to verbal stimuli" is worth 3 points, eye opening "to pain only" is worth 2 points, and "no response" is worth 1 point. The verbal response subscale comprises five possible responses, "oriented" is worth 5 points, "confused conversation but able to answer questions" is worth 4 points, "inappropriate words" is worth 3 points, "incomprehensible speech" is worth 2 points, and "no response" is worth 1 point. The motor response subscale comprises six possible responses, "obeys commands for movement" is worth 6 points, "purposeful movement to pain stimulus" is worth 5 points, "withdraws in response to pain" is worth 4 points, "flexion in response to pain" is worth 3 points, "extension response in response to pain" is worth 2 points, and "no response" is worth 1 point. The points for the three response subscales are then summed to yield the GCS score. Although the GCS is a widely used measure, evidence is mixed about its inter-rater reliability. Reith et al's (2016) review of 52 GCS reliability studies found that good-quality studies gave reliability estimates described as "adequate".

Neuropsychological Instruments

A number of studies have determined that distinct frontal and temporal components play a role in various types of memory deficits observed following severe

TBI (Schmitter-Edgecombe et al., 2004; Schmitter-Edgecombe & Wright, 2003; Schmitter-Edgecombe & Wright, 2004; Wright & Schmitter-Edgecombe, 2011; Wright et al., 2010). One of these studies of verbal memory showed that memory deficits associated with severe acceleration-deceleration TBI were primarily due to encoding problems and secondarily to consolidation difficulties (Wright et al., 2010). In addition, this study indicated that these encoding and consolidation deficits play significant roles in the memory impairments observed in the study's sample of TBI patients both independently and through their interaction. However, it should be noted that moderate to severe TBI does not necessarily disrupt all abilities that depend on intact frontal and temporal lobe function (e.g., language; Schmitter-Edgecombe et al., 1993).

The neuropsychological instruments that were used to measure the cognitive skills required for interactive processing in the frontal and temporal lobes were the Controlled Oral Word Association Test for letters F, A, and S (COWAT FAS; Benton, Hemsher, Varney, & Spreen, 1983), and the 6-trial version of the Buschke Selective Reminding Test (SRT-6; Hannay & Levin, 1985).

Controlled Oral Word Association Test

The COWAT phonemic fluency measure was utilized in the derivation of the recovery index because the task requires frontal-executive and temporal-verbal abilities. The phonemic fluency (FAS) portion of the COWAT evaluates the spontaneous verbal production of words beginning with a specific letter, given a set of restrictions such as omitting proper nouns and repeating words with different suffixes over a fixed time period. In addition, the areas of the brain chiefly responsible for phonemic word

generation are the left dorsolateral prefrontal cortex, anterior cingulate gyrus, and inferior frontal cortex (Mitrushina et al., 2005), the areas frequently seen affected in head injuries due to acceleration-deceleration accidents. However, injuries to the temporal lobes also affect performance on this test. The COWAT was chosen as the phonemic fluency measure due to the high degree of internal consistency among the letter trials (r = .83; Tombaugh et al., 1999) and high test-retest reliability after more than five years (r = .74; Tombaugh et al., 1999). In addition, previous research shows this test is sensitive to severity of TBI in that patients with mild, moderate, or severe TBI all evidenced reduced verbal fluency and demonstrated a clear association with severity (Iverson et al., 1999).

Buschke Selective Reminding Test

The SRT-6 evaluates verbal memory and learning utilizing a six trial list-learning paradigm. Unlike other list-learning tasks such as the California Verbal Learning Test (CVLT), on each subsequent trial after the first, the examinees are only presented with the word stimuli that they did not recall during previous trials. The SRT-6 long-term storage (LTS) score is the number of words that have been recalled on two consecutive trials and thus are assumed to have entered long-term storage on the first of these trials. The SRT-6 LTS score was included in the recovery index because it is a measure of memory storage (encoding and consolidation), which requires the interaction of the frontal and medial temporal areas. Additionally, the degree of long-term memory impairment as measured by the SRT one year after a severe TBI corresponds to the overall level of disability in TBI survivors (Levin et al., 1979).

Reliability coefficients for the 12-trial SRT are variable (r = .48 to .92) for normal and neurological samples. The reliability coefficients for the 6-trial SRT are most likely similar to those determined for the 12-trial, as a number of studies found that the scores obtained by the 6-trial SRT were highly consistent with those obtained by the 12-trial SRT, with the exception of the random long-term recall score (Strauss, Sherman, & Spreen, 2006). In fact, correlations between the 6- and 12-trial LTS score ranged from .91 to .95 (Larrabee, Trahan, & Levin, 2000). The validity of the SRT has been demonstrated in closed-head injury, Alzheimer's disease, multiple sclerosis, and epilepsy patient populations.

CHAPTER THREE

PROCEDURES

Acute Care Protocol

After initial stabilization in the emergency room or surgery, all patients were admitted to a neurointensive care unit. Hematomas and intracranial mass lesions were evacuated by craniotomy. Intracranial pressure (ICP) was maintained below 20mmHg by means of a standardized stepwise treatment protocol that included head of bed elevation to 30 degrees, mild hyperventilation ($PaCO_2$ = 30-35mmHg), external ventricular drainage, low doses of propofol for moderate sedation, maintenance of normal blood sugar (80 to 120mg/dL), and maintenance of mildly elevated sodium level (sodium = 140 to 145 mmol/L) (Wright et al., 2013). If these measures did not control ICP, pentobarbital was used to induce burst suppression coma. Cerebral perfusion pressure was maintained above 60mmHg using volume repletion and anti-hypertensive medication. Jugular venous oxygen saturation was continually monitored and maintained between 60% and 70% by adjusting cerebral perfusion pressure. Continuous electroencephalography (EEG) was used to monitor for possible seizure activity and barbiturate effects. Acute rehabilitation was provided to all participants.

Assessment of Glucose and Lactate Cerebral Metabolic Rates

There are three methods used to measure the cerebral metabolic rate of glucose (CMRglc) and lactate (CMRlac): cerebral microdialysis (CMD), PET scan, and jugular bulb catheterization. Cerebral microdialysis is a well-established research tool that provides continuous analysis of brain biochemistry through a thin dialysis catheter

inserted into the interstitium of the brain (de Lima Oliveira et al., 2014). Unfortunately, the microdialysis technique only provides biochemical data for a small volume around the catheter, and there are considerable differences in blood flow and glucose metabolism between regions of injured and normal brain tissue. Therefore, the cerebral insult must be focal rather than diffuse and the position of the focal injuries must be known in order to properly position the catheter (Nordström, 2010). Unlike microdialysis, PET imaging is a non-invasive technique that evaluates regional brain glucose metabolism by measuring the concentration of positron emitting radionuclides distributed in the brain tissue (Rostami, Engquist, & Enblad, 2014). F^{19} deoxyglucose (FDG) is utilized to determine brain glucose metabolism because it is analogous to glucose in the brain. Given that FDG is not further metabolized after being taken up into brain cells, it can be imaged to produce metabolic maps of the brain. The advantage of the PET imaging technique is that it provides quantitative results that can be compared across different brain regions, time, subjects, and studies (Byrnes et al., 2014). Unfortunately, PET imaging metabolism measurement is not continuous, cannot be performed bedside (Rostami, Engquist, & Enblad, 2014), and exhibits inaccuracy due to poor spatial resolution and partial volume effects (Hoffman et al., 1991).

The Kety-Schmidt jugular bulb catheterization method is widely recognized as the most accurate technique for the evaluation of global cerebral metabolism (Nybo et al., 2002). This technique for measuring CMRglc and CMRlac was chosen for the current study because it provides continuous bedside glucose metabolism monitoring. The catheter is inserted into the jugular bulb, which is the preferred location for sampling blood from the brain. The jugular bulb is the dilated or enlarged portion of the internal

jugular vein that is situated just below the base of the skull (Schell & Cole, 2000). The blood in the jugular bulb originates from both cerebral hemispheres (approximately 70% ipsilateral and 30% contralateral); however, it is commonly accepted that there is a dominant side of venous drainage, generally the right, in the majority of patients. The reason there is a dominant side of venous drainage is that in 88% of patients the two lateral sinuses that drain into the jugular bulbs differ in size and the cerebral venous blood is not completely mixed within these sinuses (Schell & Cole, 2000). The disadvantage of the jugular bulb catheterization technique is that the patient must be unconscious throughout the procedure. However, this is an effective method of monitoring cerebral metabolism in more severe cases of TBI.

In the current study, all participants underwent intubation and jugular bulb catheterization via the Kety-Schmidt method (Figure 1; Glenn et al., 2003) and their cerebral metabolic rates of glucose (CMRglc) and lactate (CMRlac) were assessed on days 0-7 post-injury. Participants had a jugular bulb catheter inserted as soon as possible following admission to allow serial measurements of cerebral blood flow (CBF), and the differences in arterial and venous glucose (AVDglc), lactate (AVDlac), and O_2 concentrations ($AVDO_2$). The catheter was inserted in the dominant jugular vein, which was selected based on the CT scan performed when the patient was admitted. In accordance with standard techniques, the catheter was inserted in the vein until resistance was encountered, approximately 15 cm, and then placement was verified by lateral skull x-ray. The catheter was calibrated *in vivo* and calibration was conducted every 12 hours. Arterial and venous samples were collected every 12 hours for the first 7 days post-injury

while the bedside CBF was scheduled every 12 hours for the first 48 hours and then daily on days 2-7 post-injury.

CBF was measured using the intravenous ^{133}Xenon clearance technique. The cerebral metabolic rate for glucose (CMRglc) was calculated as the product of CBF_{15} and the difference in concentration of glucose between arterial and venous blood (AVDglc), and the cerebral metabolic rate for lactate (CMRlac) was the product of CBF_{15} and the difference in concentration of lactate between arterial and venous blood (AVDlac). CBF_{15} is a cerebral blood flow parameter that was calculated utilizing a two-component mathematical model. CBF_{15} represents the mean blood flow of the fast clearing (gray matter) and slow clearing (white matter) compartments of the brain (Obrist et al., 1984). CBF_{15} was used to calculate CMRglc and CMRlac because it has been shown to be very stable in patients with reduced blood flow (Glenn et al., 2003). For this study, the CMRglc and CMRlac values were averaged over the first 7 days post injury.

Neuropsychological Assessment

Neuropsychological assessments were conducted by a clinical neuropsychologist using a modified version of a test battery designed for TBI clinical trials (Clifton et al., 1992). All tests were administered and scored in accordance with standard instructions. The battery of six tests required approximately 65 minutes to complete. The battery comprised the Symbol Digit Modalities Test (SDMT; Smith, 1991), the COWAT (FAS; Benton, Hemsher, Varney, & Spreen, 1983), the 6-trial version of the Buschke Selective Reminding Test (SRT-6; Hannay & Levine, 1985), Trail Making Test Part B (TMT-B; Army Individual Test Battery, 1944), Rey Osterrieth Complex Figure Test (ROCFT;

Corwin & Bylsma, 1993), and Grooved Pegboard Test (GPT; Matthews & Klove, 1964). The assessments were conducted at approximately 6 and 12 months post-injury. Test scores were normed by age and education for group comparisons. This was accomplished by calculating *T*-scores using common normative datasets.

The COWAT FAS score and SRT-6 long-term storage score were chosen to calculate the recovery index of frontal-temporal cognitive integration (FTI-Recovery) over the other test scores because of all the test scores these two scores provide the greatest sensitivity to cognitive deficits due to the interaction of the areas most affected by TBI, the frontal and medial temporal regions. The COWAT raw scores were normed using metanorms (Mitrushina et al., 2005), and the SRT-6 scores were normed with norms from Larrabee et al. (2000). Metanorms were chosen for the COWAT because many of the normative studies have small sample sizes. After the long-term storage score from the SRT-6 and the total FAS score were normed, they were converted to *T*-scores, and averaged for both the 6 and 12 month performances to produce indices of frontal-temporal cognitive integration. The 6 month combined *T*-score was subtracted from the 12 month combined *T*-score to provide a recovery index, FTI-Recovery.

CHAPTER FOUR

RESULTS

A threshold of $p < .05$ for statistical significance was set for all analyses. Initially, a hierarchical regression model was planned to be utilized to determine if acute CMRglc was more predictive of the frontal/medial temporal indices assessed at 6 months (FTI-6) and 12 months (FTI-12) and recovery index of frontal-temporal cognitive integration (FTI-Recovery) than ERGCS, and if acute CMRlac was more predictive than acute CMRglc. However, prior to analysis, the data were evaluated for outliers and multicollinearity and it was discovered that there was a very high degree of collinearity between the CMRglc and CMRlac variables which would biase the coefficients and standard errors. Therefore the model was split into two hierarchical regression models, one for each variable of cerebral metabolism. Each hierarchical regression model was used to determine if the particular cerebral metabolism variable was more predictive of the frontal-temporal cognitive integration indices than ERGCS. The data were also evaluated to determine if they violated the assumptions of homoscedasticity, independence of residuals, and normality of residuals. None of the assumptions were violated by the data; however, one outlier was removed from the original data set for FTI-6, FTI-12, and FTI-Recovery.

Correlations among the variables used in the regression models demonstrated positive relationships between CMRglc and CMRlac, CMRglc and FTI-Recovery, CMRlac and FTI-Recovery, FTI-6 and FTI-12, as well as FTI-6 and FTI-Recovery (Table 2).

Table 2. Intercorrelations among Covariates and Cognitive Test Performances.

Measure	1	2	3	4	5	6
1. ERGCS	--					
2. CMRlac	.141	--				
3. CMRglc	.080	**.916**	--			
4. Frontotemporal Index, 6 months	-.089	.281	.264	--		
5. Frontotemporal Index, 12 months	-.246	.010	-.008	**.816**	--	
6. Frontotemporal Recovery Index	.226	**.467**	**.464**	**.457**	-.140	--

Note. Bold correlation values are significant at $p < .05$.

The author hypothesized that the average cerebral metabolism of a specific fuel source over 7 days (glucose or lactate) would be more predictive than ERGCS of the results of verbal memory and phonemic fluency measures at 6 months and 12 months post injury. Results of these regression models can be seen in Tables 3-8. Contrary to these hypotheses, higher values of ERGCS, glucose metabolism, and lactate metabolism did not result in significantly better scores on the memory and phonemic fluency measures at either 6 or 12 months post injury, $p > 0.5$ (Tables 3, 4, 6, and 7).

The author also hypothesized that the average cerebral metabolism of a fuel source over 7 days would be more predictive than ERGCS of patient recovery. The results of the current study indicate that the average of cerebral metabolism of glucose (CMRglc) over a 7-day period was predictive of patient recovery as measured by neuropsychological measures of memory and phonemic fluency ($B = 7.37$, $p = .021$. 95%CI [1.227, 13.512]; Table 5). Unlike glucose metabolism, ERGCS was not predictive of patient recovery. In addition, CMRglc accounted for 19% ($R^2_{adj} = .186$) of the variance in patient scores on the recovery index of frontal-temporal cognitive integration (FTI-Recovery), which was significant, $F(2, 25) = 3.86$, $p = .036$ (Table 5). The results of a power analysis for this model showed that this study had a 52% chance of detecting a

truly significant effect of R^2_{adj} = .186. Similar results were found for cerebral lactate metabolism. Average cerebral lactate metabolism over a 7-day period was also predictive of patient outcome (B = 6.21, p = .024, 95% CI [.904, 11.506]; Table 8). ERGCS was again not predictive of patient recovery. CMRlac accounted for 18% (R^2_{adj} = .178) of the variance in patient scores on FTI-Recovery, which was significant, $F(2, 25) = 3.71$, p = .040 (Table 8). The results of a power analysis for this model showed that this study had a 50% chance of detecting a truly significant effect of R^2_{adj} = .178.

Table 3. Results of a Multiple Linear Regression Analysis Predicting FTI-6 From ERGCS and CMRglc.

	Model 1			Model 2		
Variable	*B*	*SE B*	95% CI	*B*	*SE B*	95% CI
ERGCS	-.041	.093	[-.232, .151]	-.051	.091	[-.240, .139]
CMRglc	-	-	-	7.669	5.640	[-3.997, 19.335]
R^2		.008			.082	
Adj. R^2		-.033			.002	
ΔR^2		.008			.074	
F for ΔR^2		.191			1.849	

Note. Significant results were determined by a p < .05. ERGCS = Glascow Coma Scale score obtained in the emergency department; CMRglc = average cerebral metabolic rate of glucose over days 0-7 post-injury.
*p < .05

Table 4. Results of a Multiple Linear Regression Analysis Predicting FTI-12 From ERGCS and CMRglc.

	Model 1			Model 2		
Variable	*B*	*SE B*	95% CI	*B*	*SE B*	95% CI
ERGCS	-.101	.081	[-.268, .067]	-.101	.083	[-.273, .071]
CMRglc	-	-	-	.300	5.123	[-10.299, 10.898]
R^2		.060			.060	
Adj. R^2		.021			-.021	
DR^2		.060			.0001	
F for ΔR^2		1.540			.003	

Note. Significant results were determined by a $p < .05$. ERGCS = Glascow Coma Scale score obtained in the emergency department; CMRglc = average cerebral metabolic rate of glucose over days 0-7 post-injury.
*$p < .05$

Table 5. Results of a Multiple Linear Regression Analysis Predicting FTI-Recovery From ERGCS and CMRglc.

	Model 1			Model 2		
Variable	*B*	*SE B*	95% CI	*B*	*SE B*	95% CI
ERGCS	.060	.053	[-.049, .169]	.050	.048	[-.049, .150]
CMRglc	-	-	-	7.369*	2.969	[1.227, 13.512]
R^2		.051			.251	
Adj. R^2		.011			.186	
DR^2		.051			.200	
F for ΔR^2		1.287			6.160*	

Note. Significant results were determined by a $p < .05$. ERGCS = Glascow Coma Scale score obtained in the emergency department; CMRglc = average cerebral metabolic rate of glucose over days 0-7 post-injury.
*$p < .05$

Table 6. Results of a Multiple Linear Regression Analysis Predicting FTI-6 From ERGCS and CMRlac.

	Model 1			Model 2		
Variable	*B*	*SE B*	95% CI	*B*	*SE B*	95% CI
ERGCS	-.041	.093	[-.232, .151]	-.060	.091	[-.249, .129]
CMRlac	-	-	-	7.194	4.804	[-2.744, 17.133]
R^2		.008			.096	
Adj. R^2		-.033			.017	
DR^2		.008			.088	
F for ΔR^2		.191			2.242	

Note. Significant results were determined by a p < .05. ERGCS = Glascow Coma Scale score obtained in the emergency department; CMRlac = average cerebral metabolic rate of lactate over days 0-7 post-injury.
*$p < .05$

Table 7. Results of a Multiple Linear Regression Analysis Predicting FTI-12 From ERGCS and CMRlac.

	Model 1			Model 2		
Variable	*B*	*SE B*	95% CI	*B*	*SE B*	95% CI
ERGCS	-.101	.081	[-.268, .067]	-.103	.084	[-.276, .070]
CMRlac	-	-	-	.989	4.395	[-8.102, 10.080]
R^2		.060			.062	
Adj. R^2		.021			-.019	
DR^2		.060			.002	
F for ΔR^2		1.540			.051	

Note. Significant results were determined by a p < .05. ERGCS = Glascow Coma Scale score obtained in the emergency department; CMRlac = average cerebral metabolic rate of lactate over days 0-7 post-injury.
*$p < .05$

Table 8. Results of a Multiple Linear Regression Analysis Predicting FTI-Recovery From ERGCS and CMRlac.

	Model 1			Model 2		
Variable	*B*	*SE B*	95% CI	*B*	*SE B*	95% CI
ERGCS	.060	.053	[-.049, .169]	.043	.049	[-.057, .144]
CMRlac	-	-	-	6.205*	2.562	[.904, 11.506]
R^2		.051			.244	
Adj. R^2		.011			.178	
DR^2		.051			.193	
F for ΔR^2		1.287			5.864*	

Note. Significant results were determined by a $p < .05$. ERGCS = Glascow Coma Scale score obtained in the emergency department; CMRlac = average cerebral metabolic rate of lactate over days 0-7 post-injury.
*$p < .05$

CHAPTER FIVE

DISCUSSION

The results of regression models predicting integration indices representative of cognitive function of the frontal and temporal lobes did not confirm the hypotheses that the more glucose or lactate metabolism in the brain, the better the performance on measures of long-term memory and phonemic fluency at 6 and 12 months post injury. However, the regression models predicting participant recovery as measured by the difference between the performance on tests of long-term memory and phonemic fluency at 6 and 12 months post injury confirmed the hypotheses that the more metabolism of fuel, the more improvement over the recovery period on cognitive tasks governed by the area that appears to sustain the most damage in acceleration-deceleration head injuries. This result was found for both forms of fuel, glucose and lactate. A possible explanation for these results is that performance on the integrated frontal-temporal measures at the two time points is influenced more by injury severity than by cerebral metabolism of either glucose or lactate. Recovery depends not just on the severity of the injury, but also on the ability of the brain to repair damage. Such repair requires the energy produced by metabolism of fuels such as glucose and lactate.

While the psychology literature (Ferguson, 2009) considers the effect sizes found by both models to be small, because they are less than .25 for both glucose and lactate metabolism, this is still a promising result. Nearly a fifth of the variance in FTI-Recovery is explained by cerebral metabolic rates, even though this study did not control for the range of severity of injury, different types of injuries, and differences between the subjects, such as psychiatric symptoms and possible post-hospital substance use due to

the small sample size. If we could improve cognitive outcomes by about 20%, then many more TBI survivors could resume normal daily activities such as employment.

GCS was used in this study because it is commonly used in emergency departments to assess injury severity, but its reliability is at best "adequate" (Reith et al, 2016) and is only predictive of very broad descriptions of TBI outcome (e.g., "good" vs. "bad"; McNett, 2007). Unfortunately, there does not presently seem to be any better method of evaluating initial injury severity. In addition, due to the inclusion criteria, there were two sub-groups of participants, those with low ERGCS scores (less than or equal to 8), and those with higher ERGCS scores whose initial CT showed the presence of intracranial bleeding. In the former group, the ERGCS may be a reasonable measure of injury severity, while in the latter group, there is evidence of injury severity (intracranial bleeding) that is not captured in the ERGCS score. Although the `best in 8` GCS score might more accurately measure overall injury severity, we used ERGCS as an approximation of initial injury severity, because GCS measured later in hospitalization has been found to be significantly associated with glucose metabolism (Hattori, et al, 2003), and so might lead to problems with multicollinearity. Therefore, it is not surprising that initial GCS was not predictive of frontal-temporal cognitive performance at either time point or of frontal-temporal cognitive recovery.

Glucose and lactate are the major fuel sources used by the brain, and as such their metabolic rates are very strongly positively correlated. These metabolic rates play a critical role in repairing damage, and so are strongly positively correlated with the frontal-temporal integrated recovery index. Given that the same battery was administered to the same participants at both 6 and 12 months, the frontal-temporal indices at those

times are strongly positively correlated. The change in a participant's scores over time is generally smaller than the differences between individual participants' scores. The positive correlation between the 6-month index and the recovery index, and the lack of correlation between the 12 month index and the recovery index, were unexpected. This pattern may be due to a correlation between true severity of injury (inadequately measured by GCS) and both 6 month and recovery indices; more severely injured patients performed worse at 6 months and recovered less than patients with moderate TBIs. The lack of correlation between the 12 month and recovery indices may be because at both the high and low ends of the 12 month score distribution, one would likely see less recovery than in the mid-range. In other words, the 12-month and recovery indices can vary somewhat independently of each other.

While the current study was novel in that it investigated the ability of a direct measure of acute glucose (CMRglc) and lactate (CMRlac) metabolism to predict recovery of frontal-temporal cognitive integration in moderate to severe TBI participants, the results are based on data from a small sample of participants. The small sample size means that this investigation may have missed significant relationships between fuel metabolism and frontal-temporal cognitive integration due to the current study's relatively low statistical power. Another methodological limitation was the lack of a control group to examine the natural fluctuations in frontal-temporal cognitive integration over a 6-month span in uninjured participants. The final methodological limitation of the current study was the use of an opportunistic sample. The only practical way to obtain a truly random sample for a study of brain injury would require the use of animal subjects

instead of humans, which would not fully answer the question and result in greater limitations in cognitive assessment.

Given that the connection between cerebral metabolism and neuropsychological outcome after TBI is a relatively new area of study, there are a number of promising avenues for future research. One such avenue involves investigating interventions intended to increase acute glucose metabolism and their impact on cognitive outcomes of moderate to severe TBI. Other areas to investigate include extending the current study to examine other metabolic variables such as cerebral oxygen metabolism, or to examine other aspects of long-term recovery such as daily functioning and mood.

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