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Mild traumatic brain injury (mTBI) is an injury to the brain that may result in immediate and chronic changes in cognition, language, emotion, or social interactions. The current means of assessing brain dysfunction following mTBI do not appear to accurately capture how the brain will responds to this type injury; therefore, there has been a limited ability to determine accurate prognosis from mTBI. The purpose of this study was to determine if data gathered in the initial stages of injury following mTBI could predict recovery and if so, which factors were most predictive. Participants admitted to the hospital with mTBI were evaluated within 48 hours after injury and again at approximately one month after injury. Regression analysis was used to determine if initial GCS score, initial head CT results, cognitive performance on ImPACT testing, or APOE genotype were most effective in predicting 1-month functional outcome after mTBI. Additionally, independent t-test procedures were conducted to determine whether cognitive recovery would vary across APOEe4 carriers as compared to participants without an APOEe4 allele. Results showed that none of the study variables significantly predicted one month GOS-E scores or DRS scores, however, cognitive differences were identified when APOE groups were compared. Participants who were noncarriers of an APOEe4 allele had significantly slower reaction times compared to APOEe4 carriers. Participants who were homozygous APOEe4 carriers had significantly lower instances of impulsivity than participants with other genotype combinations.

FACTORS INFLUENCING RECOVERY FROM

MILD TRAUMATIC BRAIN INJURY

by

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CHAPTER I

INTRODUCTION

Of the 1.7 million Americans who sustain a traumatic brain injury (TBI) annually (CDC, 2010), up to 85% of these are classified as mild TBI (mTBI) (Bazarian, Cernak, Noble-Haeusslein, Potolicchio & Temkin, 2009). Although mTBI is typically caused by a blow to the head, it can also occur when the head is shaken, and may or may not involve a loss of consciousness (LOC). The clinical physiological presentation of mTBI can vary from individual to individual depending on extent and location of injury (Faul, Xu, Wald & Coronado, 2010), and may not always be detected by standard neuroimaging assessments (Le et al., 2008). Additionally, changes affecting cognition, language, emotion, or social interactions may occur after mTBI and may not be readily apparent on standardized testing after the initial injury (Faul, Xu, Wald & Coronado, 2010). The current means of assessing mTBI do not appear to accurately capture how the brain responds to mTBI both initially and long-term; consequently, the ability to detect the extent of the injury and then determine accurate prognosis for this population has been limited (Bazarian et al., 2009).

Overview of Mild Traumatic Brain Injury

MTBI has been defined by a number of groups and organizations however the two definitions most frequently cited in the literature are the definition from the Brain Injury – Special Interest Group of the American Congress of Rehabilitation Medicine (BI-ISIG) and the definition from the *Diagnostic and Statistical Manual of Mental Disorders - IV (DSM-IV)*. The BI-ISIG (1993) defined mTBI as

> a traumatically induced physiologic disruption of brain function, as manifested by *one* of the following: loss of consciousness (LOC) for 30 minutes or less, any loss of memory for events immediately before or after the accident- with duration of post-traumatic amnesia (PTA) lasting 24 hours or less, any alteration in mental state at the time of the accident, or any focal neurologic deficits, which may or may not be transient in nature.

This definition is slightly different from the *DSM-IV* (APA, 2000) which uses similar criteria, except dictates that LOC last 5 minutes or less and PTA last 12 hours or less. More recently, the CDC (2005) defined a mTBI as

> an injury to the head as a result of blunt trauma or acceleration or deceleration forces that result in one or more of the following conditions: any period of observed or self-reported transient confusion, disorientation, or impaired consciousness; dysfunction of memory around the time of injury; LOC lasting less than 30 minutes; observed signs of neurological or neuropsychological dysfunction, such as—seizures, headache, dizziness, vomiting, lethargy, poor concentration, or irritability.

Because no one definition of mTBI has been universally accepted, and standard neuroimaging does not typically capture the extent of the brain injury, diagnosing mTBI remains a complex and challenging task for many medical professionals. The inability to collectively define mTBI has likely contributed to some individuals not seeking medical attention after sustaining a mTBI because the person may not realize that he has just experienced an injury to the brain (Barth, Varney, Ruchinskas & Francis, 1999; Delaney, Abuzeyad, Correa & Foxford, 2005). The difficulty in educating the general public about mild brain injury and ramifications associated with mTBI may have also contributed to society's view that mTBI implies that the injury is not serious and is without functional implications, thus leading to some individuals not seeking medical attention following a concussion.

The physical, cognitive, and emotional sequaelae of mTBI may be subtle and not apparent immediately after injury (Delaney, et al., 2005; Vanderploeg, Belanger & Curtiss, 2009) and the presentation of symptoms may vary from individual to individual. According to the Mayo Clinic (Ruff & Jurica, 1999), the hallmark initial symptoms of mTBI are confusion and amnesia, headache, loss of consciousness, or other neurological changes such as slowed mental processing, poor concentration, seizures, mood changes, or irritability.

Physical symptoms associated with mTBI can vary in severity or presentation, with headache being the most common physical complaint following mTBI (Ruff & Jurica, 1999). Other physical symptoms include nausea and/or vomiting, drowsiness,

numbness or tingling, balance issues, sensitivity to light/sounds/or smells, sleep disturbances, or visual disturbances.

Cognitive symptoms following mTBI may be initially overlooked after injury as they are typically not as overt as the physical symptoms of mTBI and may be difficult to assess due to the diffuse nature or the slight subtlety of many mTBI injuries. Yet impairments noted after mTBI can cross all cognitive domains including attention, memory, executive function, language, and/or visuo-spatial skills.

Attention deficits are frequently reported after TBI, regardless of the severity of the injury (Auerback, 1986; Chan et al., 2003; Eslinger et al., 2007; Lezak, 2004) and are pervasive in the mTBI population (Chan et al., 2003). People with mTBI have been noted to have attention deficits in sustained attention, selective attention, divided attention, and alternating attention (Lezak, 2004). Distractibility and impulsivity, two components of attention, have also been extensively reported after mTBI (Baddeley et al., 1997; Burgess et al., 1998).

Subjective and objective complaints of memory impairments after TBI are common across all TBI severity levels (Rimel et al., 1981). Impaired short-term memory has been reported to be the most frequently occurring symptom for people with mTBI (Lundin, de Boussard, Edman & Borg, 2006). Memory deficits can have significant ramifications, including impacting an individual's ability to live independently or to return to work (Drake et al., 2000). Hall & Chapman (2005) estimated that one in four people with mTBI will have short term memory problems after one year. Working

memory deficits have been noted to positively correlate with TBI severity (Smitts et al., 2009).

Decreased executive function ability, [e.g. planning and decision making] (as cited in Maruta et al., 2010) has been reported in people with mTBI. Executive function impairments such as working memory, sequencing, verbal fluency, planning, and set shifting have all been noted after mTBI (Grafman, Jones & Salazaar, 1990; Allegri & Harris, 2001). Deficits in metacognition, especially for memory demand and anosognosia, for people with frontal lobe damage after mTBI have both been reported (Hanten et al., 2004; Murrey, Hale & Williams, 2005).

Changes in visuospatial skills associated with mTBI include changes in attention to spatial cues or decreased memory of spatial patterns (Vanderplog et al., 2001; Vecera & Rizzo, 2003). Decreased speed and decreased accuracy of information processing, as well as longer reaction times have been demonstrated across TBI severity levels (Tinius, 2003; Mathias, Beall & Bigler, 2003), as well as after mTBI (Cicerone, 1996; Crawford, Knight & Alsop, 2007). Prolonged reaction times appear to be influenced by the type of task and the working memory load the task requires. Due to impairments in information processing speed and accuracy, people with mTBI must exert greater efforts in cognitive and occupational tasks, which may lead to increased physical and mental fatigue (Eslinger et al., 2007).

Although language deficits after TBI are not typically affected in terms of changes in fluency, oftentimes the social cues conveyed through language are impaired.

For example, Douglas (2010) listed several types of pragmatic, or proper social routine, impairments that have been reported after TBI including: (1) difficulties meeting the information needs of the listener, (2) lack of logical structure and coherence in discourse, (3) difficulty with implied meaning, (4) inappropriate choice of conversational content or topic, (5) inappropriate style of interaction, (6) inappropriate change in topic or tangentiality, or (7) impoverished content.

Symptom evolution or resolution, be it physical or cognitive, after mTBI varies depending on the individual, mechanism of injury, medical comorbidities, severity of injury, and pre- and post-psychosocial factors (King, 2003). Symptoms have been reported to resolve anywhere from two days (Theriault, Beaumont, Gosselin, Filipinni & Lassonde, 2009) to one month (Bruce & Echemendia, 2009) to three months (Stuss, Ely & Hugenholtz, 1985) after the incident, but some symptoms may never fully resolve. Friedman et al. (1995) reported that some symptoms may worsen with age or repeated injury. Fortunately, most people fully recover from a single concussion (Frey et al., 2006). Those who do not fully recover may experience lasting physical, emotional and/or cognitive deficits (Vanderploeg, 2009), often referred to as post-concussive syndrome.

These physical and cognitive symptoms associated with the original injury are used to determine severity ratings for TBI. Severity ratings for TBI are essential for establishing diagnosis of initial injury, developing prognostic statements, facilitating communication of injury severity among medical personnel, and qualifying patients for

rehabilitation services needed while in the hospital and upon discharge. Despite these benefits, labeling severity of TBI by initial injury presentation also has its drawbacks. Most importantly, severity level of TBI refers to the severity of the initial injury and initial symptoms, without taking into account the recovery pattern associated with the injury. For example, with mTBI *mild* refers to the extent of the initial physical and cognitive injury rather than the extent of the physiological changes in the brain following the injury. Consequences from the primary injury to the brain, as well as secondary injuries that may occur as a result of the primary injury, can affect an individual at two distinct levels-- physiologically and functionally. The culmination of these injuries to the brain may not be effectively measured during the initial evaluation of mTBI, thereby not accurately represented in the initial severity rating of TBI (Vital, 2002).

Structural and Functional Changes Following mTBI

The pathophysiology of mTBI is complex and many aspects of it are still not fully understood. In more severe TBI, structural changes to the brain, such as intracranial bleeding or fractures to the skull, can be readily observed by current neuroimaging techniques. However, with mTBI structural changes to the brain may not always be apparent on neuroimaging, especially changes at the neuronal or neurotransmitter level (Provenzale, 2007). Physiologically even mild injuries can have structural and cellular neuroanatomy damages associated with them which may lead to permanent disturbances of neural function.

A mTBI affects the brain at various levels, namely the cellular and neurotransmitter levels. The two main inertial forces active in mTBI are linear acceleration and rotational head movement (Giza & Hovada, 2001). These forces oftentimes produce axonal injuries which can occur with or without a direct blow to the head, (i.e. whiplash or blast-related injuries). These injuries have previously been described as diffuse axonal injuries (DAI); however, as researchers are learning more about the true nature of this type of injury, it is increasingly being referred to as traumatic axonal injury (TAI). TAI is one of the most common pathologies associated with TBI and is thought to contribute to enduring neurological impairments following TBI (Wang & Ma, 2010). With TBI neuronal axons can be stretched or sheared by rotational forces exerted during the initial impact of injury (Strich, 1961), and progressive changes such as alterations to the axon's cytoskeleton, impaired signal conduction, and axonal swelling have also been reported (Povlishock & Christman, 1995; Saatman, Graham & McIntosh, 1998; Smith et al., 1998). In animal models, researchers have reported that within the brain there are certain sub-populations of axons more susceptible to TAI (i.e. myelinated vs. unmyelinated or location of axons) (Reeves, Phillips & Povlishock, 2005; Reeves, Smith, Williamson & Phillips, 2012; Wang et al., 2011) and/or sub-populations of axons more likely to experience different forms of TAI (i.e. changes to the cytoskeleton vs. changes in signal transport) (Colley, Phillips & reeves, 2010; Stone, Singleton & Povlishock, 2001). In mTBI animal models, TAI has been reported to lead to increases in axon diameter immediately after injury (Kasahara, Hashimoto, Abo & Senoo, 2012) and

altered signal conduction both immediately after and several days after injury (Baker et al., 2002). Kasahara, Hashimoto, Abo & Senoo (2012) used diffusion tensor imaging to evaluate the pathophysiology associated with mTBI and reported that the axonal injuries of mice with mTBI are more focal in nature and significantly different than the DAI previously associated with the mTBI population.

In addition to axonal changes, injured neurons are also at a risk for experiencing neurochemical changes. For example, immediately after brain injury there is a sudden release of neurotransmitters causing a change in the ionization of the cell, thus affecting the neuronal membrane. In order to stabilize this imbalance, the cell's sodium potassium pump works to move sodium and potassium out of the cell, restoring the resting potential for the cell. To do this, it requires increased amounts of adenosine triphosphate, the form of energy needed for the cell to perform its vital functions, to continue to work properly. This time of accelerated glucose production within the cell is coupled with a decrease in cerebral blood flow (as typically seen in response to injury), ultimately leading to an "energy crisis" (Giza & Hovda, 2001, p 228) within the neuron. Following this initial increase in energy production by the cell, there is a dramatic decrease in the metabolism of the cell. This causes calcium to accumulate and this accumulation may contribute to neuronal dysfunction and eventual cell death.

Calcium accumulation also affects the cell's ability to produce the structural proteins needed to preserve the diameter of the neuron's axon. Changes in the neuron's axon affect the efficiency of the speed of the neural signal. This change occurs gradually

after the time of impact and may be responsible for the delay in symptoms that is sometimes observed after mTBI. Other important factors occurring at the cellular level after mTBI include the generation of lactic acid, inflammatory responses, and altered release of neurotransmitters (Giza & Hovda, 2001).

For those patients who survive the primary brain injury, morbidity and mortality are largely determined by the severity of secondary injury processes (Zink, Szmydynger-Chodobska & Chodobski, 2010). Swelling is an example of a secondary injury that can lead to increased intracranial pressure, which in turn can cause additional brain damage. This secondary damage has been reported to be more devastating than injuries associated with the initial impact (Sullivan et al., 2000; Vital, 2002). Unfortunately, initial severity levels do not take into account secondary injuries that often occur after mTBI. The initial mTBI simply sets into motion a series of neuropathological events including possible: rises in intracranial pressure; progressive axonal injury and damage; and ionic, chemical and/or cellular changes. In one retrospective review of patients who were admitted to the hospital with mTBI and perfect initial Glasgow Coma Scale (GCS) score of 15, 15-20% went on to develop an acute intracranial hematoma requiring surgical intervention (Miller, Murray & Teasdale, 1990). At later stages (several days or weeks post-injury), microscopic changes in the release of proteins that cause oxidative stress to neuronal cell membranes may continue which increases axonal swelling and causes continued degeneration of previously undamaged neurons. This may lead to additional injury that may or may not be noted by neuroimaging and clinical behavior (Giza & Hovda, 2001).

Secondary damages such as these to the brain can be life threatening, and may result in outcomes that are more severe than mild in nature.

The immediate and secondary physiological changes associated with mTBI are often manifested as changes in behavior and function. Functionally, researchers are only beginning to understand how 'mild' injuries affect cognition, both short-term and long-term, as well as psychological well-being (Bazarian, 2009). The effects of mTBI to an individual's cognitive ability may not be insignificant and may not appropriately describe the potential for long-term outcomes from this injury. In fact, mTBI may result in cognitive, social, emotional, financial and economic challenges (Bazarian et al., 2009; Vital, 2002), which are functionally significant and often chronic in nature. For some, cognitive deficits, such as difficulties with attention, memory, and executive function, are pervasive during the acute and post-acute stages of recovery. Researchers are only beginning to understand how these mild injuries affect long-term cognitive abilities (Bazarian et al., 2009). Changes in cognitive ability may impact the individual's ability to return to work or fully re-integrate back into community life after mTBI. Additionally, subjective distress described by the patient, such as persistent headaches following mTBI often seems out of proportion with the initial severity indicators, such as the absence of acute findings on neuroimaging studies. This may influence a patient's ability to return to work. Consequently, it is estimated that many people who experience a mTBI will not return to work until one to three months after injury and those who do go back to work report decreased productivity for several months afterwards (Boake et al., 2009).

Because of medical expenses and lost productivity in the work force, it is estimated that mTBI costs the nation nearly $17 billion annually (Paik et al., 2006).

Seemingly, the most accurate way to predict functional outcome after mTBI begins with an accurate diagnosis and assessment of mTBI.

Assessment of mTBI

MTBI has traditionally been assessed via neuroimaging techniques and / or neurobehavioral assessments. Neuroimaging allows for an indirect visualization of the brain by using a series of x-rays. This typically allows for gross or large scale representations of brain structure. The most commonly used neuroimaging tools for diagnosing mTBI and TBI in general are computed tomography (CT) and magnetic resonance imaging (MRI). Neurobehavioral assessments, such as the Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974) and length of post-traumatic amnesia (PTA), are also used to aid in the diagnosis of TBI. Neurobehavioral assessments involve both direct and indirect observations of the patient where the clinician evaluates the individual's state of consciousness, motor and verbal responses, and overall interaction with the environment. Neuroimaging and neurobehavioral assessments have been used to determine injury severity and predict outcome from injury. However, both neuroimaging and neurobehavioral techniques have their respective strengths and limitations.

An important component in the assessment of brain injury is to determine if there is intracranial injury. Neuroimaging allows for an evaluation of intracranial injury and is

important to (1) determine if life-threatening injuries are present and if so to rapidly plan for intervention, (2) to explain the findings on neurological examination, and (3) to help establish prognosis. The following types of neuroimaging assessments have been used in diagnosing mTBI, but are most commonly used in research settings (Gosselin et al., 2010) and are not standard practice for most clinic settings as a primary means of diagnosing mTBI. Electroencephalograms and brainstem evoked potentials (EP) have been used to evaluate concussion and these tests may detect subtle abnormalities over the first 24-48 hours after injury (Schoenhuber & Gentilini, 1989). Studies employing functional MRI have shown altered patterns of activation during working memory tasks for people diagnosed with mTBI (Matthews, Simmons & Strigo, 2011; Smits et al., 2009). Diffusion tensor imaging (DTI) can now detect microscopic white matter lesions associated with DAI (Maruta, Lee, Jacobs, Ghajar, 2010). Still, the most commonly used neuroimaging techniques for the assessment of mTBI are CT and MRI.

A head CT is often set protocol to evaluate intracranial damage and gather additional information on the extent of injury. Results from this test typically affect how the person's treatment is initially managed, especially if emergent neurosurgical treatment is required. A head CT is typically the first neuroimaging test performed to evaluate acute head injury as it is fast, relatively low-priced, widely available and highly accurate in the detection of skull fractures and intracranial hemorrhage (Le & Gean, 2009). Additionally, injuries such as epidural hematoma (EDH), subarachnoid hematoma, and subarachnoid hemorrhage (SAH) are usually clearly visualized on a head

CT (Provenzale, 2007). Because of a CT scan's ability to detect gross intracranial abnormalities, it may be most indicated in patients with moderate to severe brain injury as the majority of mTBI cases show no visible abnormality on CT (Le et al., 2008).

Still, some patients diagnosed with mTBI do show structural abnormalities on head CT. Tellier et al. (1999) noted that 31% of patients with mTBI had evidence of intracranial abnormalities on CT scan. Cerebral contusions were most common, followed by SAH, cerebral edema, intracerebral hemorrhage (ICH), subdural hematoma (SDH) and midline shift. Of patients who received CT scanning, those with a lower GCS score (score of 13) were more likely to have positive findings on CT scan. This group was biased as the participants were individuals who had been admitted to the hospital and did not include individuals who sustained a mTBI who did not seek medical attention or who were not admitted to the hospital from the emergency department. Haydel and colleagues (2000) reported that 10% of mTBI admissions with GCS score of 15 had cerebral lesion noted on CT. This subgroup of patients with positive CT scan findings has previously been labeled complicated mTBI (Williams, Levin, Eisenberg, 1990).

Although head CT remains the most widely used neuroimaging assessment for mTBI, MRI is increasingly being used in an attempt to evaluate the more subtle neurological changes noted after mTBI. Typically, MRI is recommended when head CT is unable to fully explain neurobehavioral presentation or to more extensively evaluate changes noted on head CT (Le & Gean, 2009; Provenzale, 2010). MRI is comparable to CT in the detection of hematomas and hemorrhages, but more sensitive in detecting

subtle nonhemorrhagic lesions or diffuse injuries (Le & Gean, 2009). In a 2008 study investigators demonstrated MRI as superior to CT for the detection of similar types of brain lesions (Le, Wintermark & Gean, 2008). The investigators used both techniques to evaluate 36 patients with mTBI. MRI was more sensitive than CT for the detection of parenchymal lesions, nonhemorrhagic axonal injury (detected by CT 0% of the time), hemorrhagic axonal injury, and contusion. Mitti and colleagues (2004) suggested that MRI has significant sensitivity for the majority of intracerebral lesions after the third day after injury, especially in the mTBI population who have negative findings on head CT. CT scans are often limited in detecting the presence and extent of TAI as they have decreased sensitivity and low resolution for this type of injury (Hammoud & Wasserman, 2002). Fluid attenuated inversion recovery (FLAIR) as well as Diffusion-Weighted Imaging (DWI), two types of MRI, are particularly helpful in detecting TAI (Hammoud & Wasserman, 2002; Kasahara, Hashimoto, Abo & Senoo, 2012) but are not widely available in most clinic settings. Despite these recent advances in neuroimaging techniques, oftentimes the subtle changes associated with mTBI go undetected by either CT or MRI (Rupp et al., 2009). Moreover, most people with mTBI only receive a head CT during hospitalization, with few actually receiving an MRI.

There are numerous benefits to completing neuroimaging techniques in the mTBI population. Many of the strengths of neuroimaging have already been addressed (i.e. fast, widely available), but one of the most beneficial uses of neuroimaging is that it allows for the assessment of life-threatening injuries. Both CT and MRI can be useful in

identifying the location and extent of primary injury. This provides doctors and clinicians with valuable information on extent of deficits, types of deficits likely to be sustained, and insights on prognosis. CT remains an essential diagnostic tool for emergency departments as it is relatively inexpensive, reliable, and easy to complete. It provides excellent information on soft tissue injuries that may be imperative in decisions of how to initially approach intervention (i.e. need to perform surgery or not). Neuroimaging can be used with patients who are nonresponsive or unable to demonstrate overt actions or behaviors. Additionally, the tests are not affected by intoxication, decreased participation or inability to cooperate.

Despite the relative strengths of neuroimaging techniques, there are several limitations for the use of these tools in the assessment of mTBI. CT's major limitations include the decreased ability to detect some types of intracranial injuries and exposing the patient to increased doses of radiation which can be problematic especially if multiple CT scans are required during the period of recovery. Additionally, some have noted that CT findings often worsen after the initial injury, which decreases the predictive outcome ability of early imaging tests (Le, Wintermark & Gean, 2008). MRI is able to provide sensitive information for those patients who may have negative findings on CT scans, but also has several drawbacks, namely it is expensive, time consuming, and not feasible for some patients (i.e. those who require mechanical ventilation, those with pacemakers or other types of metal devices). Although initial findings from CT scans (Wardlaw, Easton & Statham, 2002; Petroni et al., 2010; Hergenroeder, Redell, Moore & Dash, 2008) and

MRIs (Ingebrigtsen, Waterloo, Jacobsen, Langbakk & Romner, 1999) have been used as predictors of outcome, in many cases their sensitivity and specificity are not sufficient to alter clinical care (Berger, Beers, Richichi, Wiesman & Adelson, 2007). Moreover, the pathophysiological effects of mTBI are rarely detectible on either CT or MRI (Provenzale, 2007). Additionally, these methods have limited utility in detecting the more subtle damage at the cellular and neurochemical levels that are often associated with mTBI (Hergenroeder et al., 2010).

In addition to neuroimaging techniques, neurobehavioral assessments also play a critical role in the assessment and intervention of a person with a brain injury. Standardized rating scales are the most common form of neurobehavioral assessments. These scales involve a fixed administration and scoring criteria which are used to create a profile of the patient's cerebral function. Throughout the years, several standardized scales have been developed to evaluate brain injury. The GCS and presence of PTA are two of the most frequently used assessments for patients with TBI, especially at the beginning stages of evaluation.

Historically, medical professionals have classified TBI into 3 distinct categories: mild, moderate, or severe, using the GCS. The GCS is a behavioral assessment of level of consciousness that can be performed by first responders to the scene of the injury or by other medical professionals upon arrival to the hospital. To date, initial GCS score remains the most widely used scale to classify brain injury severity and most widely used indicator of prognosis from TBI (McNett, 2007; Wijdicks, 2006). Patients are assessed

and then scored based on their best response ability in 3 areas: best eye opening response, best verbal response, and best motor response. See Appendix A for a more detailed description of GCS scoring procedures. Patients who achieve scores of 8 or less are classified as severe, scores of 9-12 as moderate, and 13-15 as mild. Despite its wide-spread use the global nature of this assessment, renders it a poor evaluation tool for individuals with mTBI.

Another tool that is use to assist in determining outcome from TBI is length of PTA. The term PTA was first described by W. Richie Russell in 1932 to describe the period of acute confusion following head injury (Russell, 1932). PTA is a transitory state of impaired consciousness typically associated with disorientation and impaired short-term memory. The hallmark sign of this state of impaired consciousness is anterograde amnesia, the impaired ability to remember events after the onset of an event. Length of PTA is measured between the time of initial injury until the person meets a certain criterion for return of orientation and memory. The Galveston Orientation and Amnesia Test (GOAT) (Levin, O'Donnell & Grossman, 1979) is the most commonly used instrument to measure duration of PTA. Russell (1932) noted that after resolution of PTA, the patient will have 'continuous memory' for subsequent events, but will likely not recall events that occurred during PTA. Determination of length of PTA is important as it can yield an index of injury severity (Russell & Smith, 1961; Greenwood, 1997; Nakase-Thompson, Yablon & Sherer, 2006). Continuous evaluation of PTA is common practice in hospital settings as it provides an ongoing index of the patient's progress and

readiness for more formalized cognitive testing. For most definitions of mTBI, duration of PTA is limited to less than 24 hours.

A benefit in using neurobehavioral techniques such as the GCS and duration of PTA, is that they have been demonstrated to have prognostic value. Asikainen, Kaste & Sarna (1998) studied a group of 508 patients with moderate to severe TBI in an acute rehabilitation setting. The researchers aimed to investigate which variables in the acute stage of recovery were most predictive of long term functional and occupational outcome. Results indicated that initial GCS score, length of coma, and duration of PTA all have a strong predictive value in assessing outcome. Additionally, these neurobehavioral assessments allow for patients to be classified as having mild, moderate or severe level of injury. This classification allows the interdisciplinary team to communicate effectively with each other across disciplines and areas of care, and also allows for effective communication and education with the patient/family. Importantly, these neurobehavioral assessments can be done at the patient's bedside, require few tools or supplies (if any), and are very cost-effective.

Because of the subjective nature of behavioral observations and the fact that no two brain injuries or concussions manifest the same way clinically, diagnosing mTBI by neurobehavioral measures alone is difficult for even trained individuals (Bryant, 2008). Diagnosis is based primarily on the characteristics of the immediate symptoms following the injury including information obtained from the patient's self-report of the injury and the neurobehavioral assessment of the patient. This presents several difficulties for the

accurate assessment of the brain injury. A diagnosis largely depends on patient report. In many cases of mTBI, patients are likely dazed and confused and may unintentionally misrepresent the extent of their injury or severity of symptoms (Lange, Iverson, Brooks & Rennison, 2010). Rupp, Iverson, Barth, Bush & Broshek (2009) reported that the mTBI diagnosis is further confounded by several factors: patients who unintentionally misrepresent their length of LOC, the difficulty distinguishing between length of LOC and the period of PTA, the difficulty in accurately determining what the patient remembers and what the patient has been told, and important changes in clinical presentation that may occur if the injury was not witnessed.

To make accurate diagnoses, each behavioral assessment should be reliable, valid, and have adequate sensitivity (the ability to detect subtle clinical changes), and specificity (the ability to differentiate one severity of TBI from another). Unfortunately, despite the wide range of standardized neurobehavioral rating scales available, few have been shown to effectively satisfy these parameters, especially with regards to the more subtle variances of mTBI (Giacino & Smart 2007). Additionally, as with neuroimaging techniques, the sensitivity and specificity of neurobehavioral assessments have been reported to not be sufficient enough to alter clinical care (Berger, Beers, Richichi, Wiesman & Adelson, 2007).

Other limiting factors of neurobehavioral assessments are (1) difficulty in distinguishing between reflexive or involuntary movement, (2) concerns regarding response consistency, (3) scoring inconsistencies from one clinician to the next given the

subjective nature of these types of assessments, and (4) ratings may vary from one time period to the next depending on the patient's current clinical presentation. Moreover, techniques used in neurobehavioral assessments (ability to verbally communicate, ability to follow commands, eye gaze, motor movement, etc.) may be limited due to language deficits, motor impairments, or impaired arousal, though these oftentimes are not apparent in the mTBI population (Giacino et al., 2006).

Diagnosing mTBI has proved difficult for medical professionals for a variety of reasons. A primary problem is that despite the above mentioned diagnostic criteria for mTBI, there remains no set standard criterion used by all professionals. Therefore, there is no uniformity across practitioners and medical facilities in diagnosing mTBI. Additionally, depending on the individual, type of injury, and severity of injury, mTBI can present differently on neuroimaging and neurobehavioral assessments. Indeed, most people with mTBI complain of neurobehavioral changes, but typically show no sign of damage based on standard neurological exam or brain imaging techniques. This lack of objective measures for identifying mTBI leads to limited ways to predict the patient's course of recovery.

Predicting Outcome from mTBI

Neuroimaging techniques and neurobehavioral measures have not only been used in the assessment of mTBI, they have both also been used to aid in predicting outcome For example, findings on initial head CT have been linked with both short and long-term

outcome. Wardlow, Easton & Statham (2002) evaluated 425 head CTs from patients with all severities of head injury. They concluded that in addition to age, initial GCS score, and pupil reactivity, the presence of SAH on CT scan were all significant predictors of outcome. Williams et al. (1990) evaluated 215 patients admitted to the hospital with mild or moderate TBI. The investigators reported that those patients classified as uncomplicated mTBI (no findings on head CT) had better functional outcomes six months post-injury compared to the complicated mTBI (positive findings on head CT) group. Furthermore, the functional outcome of the complicated mTBI group, as measured by tests of memory, information processing, verbal fluency and Glasgow Outcome Scale score, was more similar to that of the moderate TBI group than the uncomplicated mTBI group. Similarly, Iverson (2006) compared the neuropsychological test performance of patients with complicated mTBI (n=50) to patients with uncomplicated mTBI (n=50) within 14 days of injury. Iverson found that those patients with complicated mTBI performed worse than those with uncomplicated mTBI on half of the neuropsychological measures tested, such as measures targeting short term recall and executive functioning. Others have demonstrated similar results on other neuropsychological subtests, such as post concussive symptom scales (Borago et al., 2003) and memory, selective attention and reaction time (Kurca, Sivak & Kucera, 2006). Importantly, the results from the above mentioned studies demonstrate worse neuropsychological performance on a small number of subtests, rather than globally diminished scores across all cognitive domains assessed. Also, taken collectively, the

effect sizes of the reported differences are generally small or medium and lower than expected (Lange, Iverson & Franzen, 2009). Additionally, there does not appear to be an obvious long term difference in neuropsychological function between these two groups at 6 month post-injury (Hanlon et al., 1999; Hofman et al., 2001). This is contrary to other studies that have reported that patients with complicated mTBI have worse 6-12 month functional status (as measured by the Glasgow Outcome Scale) compared to patients with uncomplicated mTBI (Williams, Levin & Eisenberg, 1990; van der Naalt et al., 1999; Wilson et al., 1996).

Others have reported no significant changes in neuropsychological functioning for patients with complicated mTBI versus patients with uncomplicated mTBI. Sadowski-Cron et al. (2006) found no differences in neuropsychological between 205 patients either with or without complicated mTBI as noted by CT findings. Lange, Iverson & Franzen (2009) reported significant differences on only three of 13 neuropyschological measures (Visual Reproduction Savings, Digit Span Forward, and the Controlled Oral Word Association Test), with patients with complicated mTBI performing worse than those patients with uncomplicated mTBI.

One might hypothesize that the greater sensitivity of MRI may identify an even larger amount of intracranial abnormalities within the mTBI population, thus identifying more patients at risk for neuropsychological impairments. However, Hughes and colleagues (2004) evaluated 80 patients with mTBI within the first 72 hours after injury and found that despite a notable trend between poor performance on neuropsychological

testing and an abnormal MRI, there was not enough evidence to show statistical significance. Similarly, for patients six-months post-injury, Hofman el at. (2001) found no difference in neuropsychological test performance for 21 patients with or without complicated mTBI as demonstrated on MRI.

In 1991, Marshall and colleagues proposed a scoring system for determining prognosis in head injury patients based on the head CT scan. This scale evaluates the following: presence of space-occupying lesions, intracranial abnormalities, and findings of increased intracranial pressure (Marshall et al., 1991). This scale is now widely accepted as a method of evaluating CT scans and predicting prognosis from injury (Provenzale, 2010), though has not sufficiently been applied to the mTBI population.

In a study that examined the ability of MRI versus CT to predict clinical outcome, investigators studied children who underwent CT within 24 hours of injury and MRI within 7 days of injury (Smits et al., 2008). Outcome was classified into normal, mild disability, or poor outcome. Results showed that CT results did not differentiate between any of the 3 outcome groups. Furthermore, within the poor outcome group, 40% of children had normal CT findings. MRI successfully discriminated between outcome groups by differences in amount of lesions noted and volume of those lesions. The authors concluded that MRI was superior to CT in predicting outcome. Still, as previously mentioned, this likely has limited clinical applications as most people with mTBI do not receive MRI testing. Additionally, this study was conducted with children under the age of 18.

Neurobehavioral assessment has also been proven to be predictive of outcome. For example, initial GCS scores have been shown to be a significant predictor of patient survival after head injury (Wardlaw et al., 2002; Wjidicks, 2006). Overall, studies have shown initial GCS to be a reliable predictor of general outcome as measured by the Glasgow Outcome Scale and capacity for employment after injury (Husson et al., 2010; Petroni et al., 2010; Asihainen, Kaste & Sarna, 1999). Murray and colleagues (2007) reported that initial GSC score is one of the most powerful independent prognostic variables in predicting outcome after TBI. Within the GCS scores of mTBI, researchers have reported that patients with a GCS score of 13 and 14 present with greater morbidity than those with a GCS score of 15 (Borg et al., 2004; Gomez, Lobato, Ortegao, Delacruz, 1996). Still, one group demonstrated this not to be the case (Tellier et al., 2009).

Other studies have shown discrepancies of using initial GCS score as the primary diagnostic or prognostic indicator (Woertgen, Rothoerl, Metz & Brawanski, 1999; Stocchetti et al., 2004). Stocchetti and colleagues (2004) reported that the GCS can overestimate injury severity and therefore overestimate prognostic ability, especially if GCS score was obtained not at the scene of the injury but upon admission to the hospital. Some suggest that initial GCS score is effective in diagnosing severe brain injury, but does not accurately reflect the full extent of injury for milder cases of brain injury (Wardlaw et al., 2002). Furthermore, initial GCS score does not take into account the ramifications of evolving secondary issues which can lead to further neurological impairment.

An accurate and complete GCS is difficult to obtain in many clinical situations, i.e. the patient is intubated and/or facial fractures or orthopedic injuries make assessment of motor or eye movement limited or prohibited. Because of this, researchers have attempted to determine which components of the GCS are most important in determining severity and predicting outcome. Marion & Carlier (1994) suggested that the motor score of the GCS is more important than the other two components in predicting severity of injury given the high rate of intubation and sedation for patients with brain injury and difficulties with properly assessing eye opening. Healey and colleagues (2003) reported that the motor score alone is predictive of outcome. Kung and colleagues (2010) demonstrated that for patients with an initial GCS score of 10 or above, severity and outcome was most determined by the verbal score. However, for patients with initial GCS score of below 7 (indicating severe TBI), clinical status was most closely determined by the motor score.

Similar to initial GCS score, length of PTA has been repeatedly shown to be another reliable indicator of TBI outcome (Brown et al., 2010; Asihainen, Kaste & Sarna, 1998; Walker et al., 2010). In a multi-center study evaluating the predictive value of PTA, Walker and colleagues (2010) reported that PTA was the strongest predictor of Glasgow Outcome Scale (GOS) score at both 1 year and 2 years after injury. Additionally, authors noted that when PTA ended within 4 weeks, severe disability was unlikely after the first year. However, when PTA lasted beyond 8 weeks, good recovery was highly unlikely at 1 year.

Still, the literature reports conflicting reliability for this measure due to difficulties associated with defining emergence from PTA (Ahmed et al., 2000; Tate et al., 2006; McMillan, Jongen & Greenwood, 1996; Katz & Alexander, 1994; Bishara et al., 1992; Nakase-Thompson, Yablon, & Sherer, 2007). In 1943, Symonds & Russell pointed out 2 problems associated with determining length of PTA: (1) most patients have 'islands' of memory which occur before actual continuity of memory is restored, and (2) determination of length of PTA is often done retrospectively rather than prospectively. Additionally, Forrester, Encel & Geffen (1994) reported that duration of PTA may be misrepresented by patients due to confabulations or poor insight, even in the mTBI population. Therefore, many clinicians use serial assessments of the Galveston Orientation and Amnesia Test to measure duration of PTA prospectively. Nakase-Thompson et al. (2004) and Sherer et al. (2005) studied confusion among TBI patients in an acute rehabilitation setting and found that traditional measures of length of PTA did not adequately reflect the range of other neurobehavioral impairments observed.

Challenges in Studying the mTBI Population and Predicting Recovery

Neuroimaging and neurobehavioral assessments offer limited and inconsistent prognostic information on outcome following mTBI. Additionally, the physiological and functional sequelae stemming from mTBI are oftentimes subtle and difficult to fully assess in clinical settings, as well as functional situations. The ability to determine who will have longstanding deficits after a mTBI and to accurately predict the functional

impact following a mTBI is challenging due to lack of evidence to support one or more prognostic indicators. Yet, prognostic information in the early aftermath of an injury would assist medical professionals with educating and counseling patients and families about potential outcome, and when making clinical decisions about best practices for the treatment and prevention of future chronic conditions.

Others have reported additional difficulties which further complicate studying the mTBI population. For example, the TBI population in general is an extremely heterogeneous group and findings from one set of patients may not be applicable to all. Tellier et al. (1999) concluded from their study of patients with mTBI that the "mild head injury group does not constitute a homogenous pool of patients, not only in terms of intracranial abnormalities in the group as a whole, but also with respect to the greater likelihood of finding abnormalities in patients with a GCS score of 13" p. 470. All of the definitions for mTBI presented above are limited because they are used to identify cases of mTBI that are treated at or admitted to the hospital, which are cases of mTBI that tend to be more severe in nature (Dikmen & Levin, 1993). Unfortunately, there is a large subset of patients with mTBI who are never evaluated by a medical professional (Langlois et al., 2006). The case can then be argued that within the mTBI population, there exists a less severe form of mTBI that has historically not been incorporated into the current definitions of mTBI.

Another complication of studying the mTBI population is that multiple factors have been noted to be associated with recovery from mTBI and researchers are only

beginning to understand how these factors influence outcome. In addition to severity and type of injury, other important factors to consider in determining likely outcome from mTBI are psychosocial factors, such as coping styles and personality factors, as well as premorbid function that may affect the individual's recovery (Finlayson, 2004). Furthermore, recent research has highlighted that recovery from mTBI is a highly variable process, and more complicated recoveries have been shown to be related to the younger patient (Field, Collins, Lovell, & Maroon, 2003), those patients with post-injury migraines (Mihalik et al., 2005), females (Collins et al., 1999; Colvin et al., 2009), and those with history of mTBI (Collins et al., 2002).

With a label of TBI severity often comes preconceptions about cognitive ability which may or may not be reflective of the individual's true ability or disability. Despite the strong evidence that physical, cognitive and emotional impairments can be longstanding after mTBI, some medical professionals continue to equate chronic deficits reported by patients with mTBI with malingering based on the notion that such mild injuries should not result in any permanent impairments (Tellier et al., 1999). While such patients likely do exist, it is unreasonable to deny that some patients with mTBI do have lingering deficits.

Despite a recent increase in research regarding evidenced-based prognostic indicators in the mTBI population, medical professionals still face challenges when predicting outcome for people with mTBI. The variability in terms of neuroimaging findings, as well as clinical presentation are two measures to evaluate and predict

outcome from mTBI. Still there remain discrepancies in the literature related to the accuracy of these measures. For example, some assert that the presence of positive CT findings should automatically exclude patients from the mTBI group (Williams, Levin & Eisenberg, 1990; Dikmen, McLean & Temkin, 1986). Moreover, documentation of positive CT findings provides a certain amount of credibility to the complaints voiced by many patients with mTBI. Additionally, while it is true that the milder the TBI, the better the recovery, some patients with mTBI are not immune to experiencing post-injury impairments lasting beyond the 3-month mark after their injury.

Seemingly, there are certain subgroups within the mTBI population that have yet to be fully defined or researched. Yet, few researchers have been able to demonstrate or distinguish subgroups of patients with mTBI who present with distinct clinical profiles early on in the recovery process. For example, Tellier et al. (2009) were not able to distinguish subgroups of mTBI based on initial GCS score, but did note partial support for subgroups of mTBI when duration of PTA was used as a measure of severity. Individuals who experienced PTA for greater than 20 minutes were more likely to have intracranial abnormalities on CT scanning and to report continued symptoms, namely disinhibition, at 6 months post-injury. Ponsford and colleagues (2000) noted a subgroup (24 of 84 participants) who were still suffering physical or neuropsychological problems at 3 months post-mTBI. Neither duration of PTA nor performance on neuropsychological testing were predictive of persistent symptoms. Rather, history of previous head injury, previous neurological or psychiatric problems, students, females,

and initial injury from motor vehicle accident were associated with persistent symptoms at the follow-up period. Interestingly, Hellstrom and colleagues (2013) also noted subgroups within the mTBI population that could be grouped according to their initial symptom complaints, as rated on the Rivermead Post Concussion Symptom Questionnaire. The generally "high" symptom cluster system subgroup (those participants with more physical and neuropsychological complaints after initial injury) scored significantly worse than the other grouped participants at the 6-8 week follow up period on both the Glasgow Outcome Scale –Extended (GOS-E) and measures of depression and anxiety.

Regardless of the strengths of the currently available neuroimaging and neurobehavioral assessment techniques, the above stated literature review demonstrates notable limitations in these techniques, especially when used to diagnose and predict outcome from mTBI. Additionally, although neuroimaging and neurobehavioral techniques have been shown to predict outcome from TBI, the literature shows conflicting evidence over the sensitivity of these measures (Berger et al., 2007; Hergenroeder et al., 2008). Despite the fact that people recovering from TBI typically follow a progression of recovery after initial injury, making prognostic statements about outcome for people with TBI, especially mTBI, remains challenging. There is little empirical evidence available to medical teams that allow them to predict outcome. This makes clinical decision making regarding prognosis extremely difficult and generally based on evidence that is only loosely supported by the literature.

Cognitive Ability as a Prognostic Indicator

Performance on initial cognitive testing may be one way to offer more objective and individualized information on predicting outcome from mTBI. Cognitive performance has been used as a prognostic indicator from mTBI, but there is limited evidence to support this (Comerford, Geffen, May, Medland & Geffen, 2002; Delaney et al., 2005). Numerous studies supporting cognitive ability as a predictor of outcome have been conducted within the moderate-to-severe TBI populations (Boake et al., 2001; Scheibel, Levin, & Clifton, 1998; Sherer et al., 2002); however the studies within the mTBI population are more divisive and few have linked acute cognitive ability with long-term functional recovery.

Cognitive performance on admission to the Emergency Department (ED) has been identified as one early predictor of outcome. One group of researchers noted subtle neurocognitive deficits in the areas of concentration, memory and performing simple math problems for patients in the ED with mTBI (Delaney et al., 2005). Peterson et al. (2009) showed that patients with mTBI admitted to the ED demonstrated cognitive deficits on ImPACT cognitive testing, but did not report if this could be used as a means of predicting functional outcome. Sheedy, Geffen, Donnelly, & Faux (2006) reported that patients with mTBI who demonstrated neurocognitive impairment while in the ED reported significantly more post-concussive symptoms compared to a group of controls at 1-month post-injury. Similarly, others have reported neurocognitive deficits noted during ED screen were predictive of 3-month functional outcome, as measured by the Glasgow

Outcome Scale, for patients with mTBI (Sheedy, Harvey, Faux, Geffen, & Shores, 2009). Moreover, immediate and delayed recall of words coupled with headache intensity provided 80% sensitivity and 76% specificity for predicting continued symptoms congruent with mTBI (such as headache and difficulties with concentration) 3-months post injury (Sheedy et al., 2009).

Others have screened neurocognitive function within 3 months post-injury and have reported on the prognostic applications of these assessments. For example, Kashluba, Hanks, Casey & Millis (2008) evaluated cognitive ability for patients with mTBI at discharge from inpatient rehabilitation and at 1 year post-injury. The researchers found that patients demonstrating cognitive deficits at discharge from inpatient rehabilitation, as measured by Functional Independent Measures, also demonstrated similar cognitive deficits at 1 year post-injury. Hanlon and colleagues demonstrated that memory function assessed at 3 months post-mTBI were significantly associated with employment 1-year post-injury. Sigurdardottier, Andelic, Roe, & Schanke (2009) reported that cognitive performance in the areas of Verbal/Reasoning, Visual/Perception, and Memory/Speed at 3 months after mTBI were near-significant predictors of 1-year outcome, as measured by the Glasgow Outcome Scale.

Seemingly, cognitive performance may be a useful prognostic indicator after mTBI; however, others have reported that neurocognitive measures do not effectively predict outcome from mTBI (Belanger et al., 2005; Ponsford et al., 2000; Stulemeijer et al., 2007).

As noted, the physiological changes associated with mTBI are frequently revealed in cognitive and functional changes, but not necessarily in the broad measures of GCS score or neuroimaging. Subsequently, subjective distress following mTBI often seems disproportionate with initial severity (King, 2003) and these sequelae may prove debilitating, impairing individuals' abilities to attend school, work, or perform other activities of daily living (CDC, 2008). Because even subtle neurocognitive deficits may prove debilitating for some patients, early identification of those patients at risk for poorer outcome may lead to better recovery. For example, some researchers have reported that people with mTBI who receive initial identification with a specialist (nursing or therapist) and who follow up after discharge from the hospital have been reported to describe fewer overall unresolved symptoms and decreased psychological sequelae (Ponsford et al., 2002; Wade et al., 1998).

ImPACT Cognitive Testing

One of the most commonly used screenings of cognitive ability in people with mTBI is the ImPACT (Immediate Post-Concussion Assessment and Cognitive Testing). Although typically used in the sports medicine setting, it is currently also being used by multiple researchers in numerous settings as a unified measure of neurocognitive ability. ImPACT screening is a computerized neurocognitive assessment tool that can be used by medical doctors, psychologists, athletic trainers, and other licensed healthcare professionals. It has traditionally been used to help these professionals determine an

athlete's ability to return to play after experiencing a concussion. ImPACT testing is recommended to occur within 24 – 72 hours after injury. ImPACT testing takes approximately 20 minutes to complete and measures multiple aspects of cognitive functioning, including: attention, memory, response variability, problem solving, and reaction time. This questionnaire has been adopted by the NFL, NHL, International Olympic Committee, and FIFA.

Like any neurocognitive test, test data often requires analysis at multiple levels or over various time periods, which prohibits any one test from over simplifying the effects of the injury to the particular individual. Therefore, ImPACT does not yield one summary score, but rather a series of indicators that have been demonstrated to be sensitive to mTBI. According to Iverson, Lovell & Collins (2003), the interpretation of ImPACT should follow a multi-level path of analysis including the evaluation of the five composite scores, change from baseline testing (as applicable) as assessed by the Reliable Change Index score, and comparison of ImPACT scores to established age and gender normative scores as included in the testing manual. Percentile rank for gender and age at time of testing is provided for each composite score as part of the ImPACT computer generated report. Specific analysis of the individual scores that comprise the composite scores is also essential in test interpretation. Analysis of patterns in performance, areas of strengths and weaknesses, and evaluation of speed and accuracy on specific modules are also important components of overall test interpretation which may not be entirely captured by the composite scores. Additionally, non-cognitive symptoms, such as

headache, nausea, balance problems and dizziness are common after mTBI and should be thoroughly assessed and documented as they may impact performance on neurocognitive testing. For example, a recent study utilizing ImPACT demonstrated that migraine-type headaches are associated with reduced neurocognitive performance (Collins et al., 2003), although this may not always be the case. Another study using the ImPACT test as a measure of cognitive function, reported that in athletes with mTBI fatigue significantly contributed to decreased Verbal Memory composite scores, but not for any of the other composite scores (Covassin, Weiss, Powell & Womack, 2007).

The reliability and validity of ImPACT has been demonstrated in several research studies. The reliability and validity of ImPACT has been explored primarily by assessing the correlation between one ImPACT subtest domain and one or multiple conventional measures (Iverson, Franzen, Lovell, & Collins, 2003; Iverson, Lovell, & Collins, 2005; Schatz & Putz, 2006). Schatz, Pardini, Lovell, Collins, & Podell (2006) demonstrated that ImPACT sensitivity was found to be 81.9% and specificity was 89.4% when differentiating concussed from non-concussed athletes. Maerlender and colleagues (2010) compared scores on the ImPACT to a comprehensive battery of traditional neuropsychological measures (approximately 2 hour testing time consisting of subtests from various neuropsychological batteries) and several experimental measures (i.e. N-back task, verbal continuous memory task) used in the assessment of mTBI. They demonstrated convergent validity for four of the five ImPACT domain scores. This group of researchers also reported two cognitive domains not directly identified by the

ImPACT battery: sustained attention and auditory working memory and concluded that in addition to ImPACT testing, other sources of data should be considered when identifying and managing mTBI. ImPACT has been shown to minimize practice effects through the use of randomization of stimuli presentation (Iverson, Lovell, Collins, & Norwig, 2002). Similarly, Iverson, Lovell, & Collins (2003) demonstrated that ImPACT testing reliably measured change in mTBI symptom presentation for a group of 41 athletes with mTBI as noted by repeated ImPACT testing over a 72-hour period.

ImPACT has been used as a primary neurocognitive evaluation after mTBI because of its ease of administration, speed, accuracy of assessment and ability to detect deficits that linger after physical symptom resolution (Fazio, Lovell, Pardini, & Collins, 2007; Grindel, Lovell, & Collins, 2001; Iverson, Lovell, & Collins, 2002; Maroon, Lovell, Norwig, Podell, Powell, Hartl, 2000; Schatz, Pardini, Lovell, Collins, & Podell, 2006). Although primarily used in outpatient clinic settings, ImPACT has also been used to evaluate cognitive function in the ED (Peterson et al., 2008; Thomas et al., 2011) and other acute hospital settings (Nance, Polk-Williams, Collins, Wiebe, 2009). Thomas and colleagues (2008) concluded that immediate assessment of neurocognitive deficits in the ED, as assessed by ImPACT, can predict neurocognitive deficits noted in follow-up (2-6 weeks post injury) assessment. Iverson (2001) utilized ImPACT to distinguish high school athletes with complex concussion from those with simple concussion. More specifically, Lau and colleagues (2009) reported that the reaction time composite score from ImPACT has significant prognostic value in determining time to clinical recovery.

Fazio et al (2007) revealed that patients with mTBI who denied symptoms within 4 days of injury performed significantly worse across all neurocognitive domains tested by ImPACT when compared to a matched control group. These researchers concluded that the ImPACT is able to accurately diagnose subacute mTBI when symptoms were not endorsed by the patient. Lau, Collins, & Lovell (2010) demonstrated that use of ImPACT testing in conjunction with symptom clusters (as noted on the post-concussion Total Symptom Scale) resulted in improved sensitivity, specificity, positive predictive value, and negative predictive value of predicting recovery as compared to using each test individually. VanKampen and colleagues (2006) concluded that the use of ImPACT neurocognitive testing increased sensitivity to detect prolonged post-concussive symptoms. They asserted that neurocognitive assessment tools, such as ImPACT, provide increased value to the more traditional assessment of mTBI. The results of many of these studies lend support to the added value of using neurocognitive testing early in the recovery process to aid in clinical decisions such as prognosis or readiness to return to athletic field/classroom/work.

The variability in outcome after TBI in only partly explained by the current most-widely used prognostic indicators such as initial GCS, neuroimaging findings, or performance on cognitive testing. Genetic factors that may influence the brain's susceptibility to brain injury and the capacity for repair and regeneration after injury may also aid in predicting outcome.

Introduction to APOE

Recently, researchers have begun to examine the potential role of genetics in determining functional outcome after TBI. Specifically, investigators have studied the role of apolipoprotein E (APOE) on cognitive recovery, long-term functional outcome, and onset of dementia (Teasdale, Murray, Nicoll, 2005; Mayeux et al., 1995). The APOE gene provides instructions for making a protein called apolipoprotein E (apoE). This protein combines with fats in the body to form molecules called lipoproteins. ApoE has been recognized for its importance in lipoprotein metabolism and cardiovascular disease, because of its functions related to the transport of fat-soluble vitamins and cholesterol into the lymph system and then into the bloodstream. It also plays an essential role in immunological regulation, including the inflammation and oxidation of various cells throughout the body, namely lipoproteins. Lipoproteins 'package' cholesterol and other fats, then carry them through the bloodstream. ApoE is the main lipoprotein found in the brain and the cerebrospinal fluid, where it appears to play a role in cell maintenance and growth (Maysinger et al., 2008). ApoE aids in transporting these lipoproteins throughout the cardiovascular system. The apoE protein is also necessary for the normal catabolism of triglyceride-rich lipoproteins (proteins that have been combined with fats). It is a major component of very low-density lipoproteins, which function to remove excess cholesterol from the blood and carry it to the liver for processing. Indeed, apoE is a key component in repair and regeneration following nerve damage by assisting with the delivery of cholesterol to damaged cells (Shea, Rogers, Ashline, Ortiz & Sheu, 2002).

Other ways apoE functions in immunological regulation include to suppress T cell proliferation and regulate macrophage function. APOE is the target gene of the liver X receptor. This allows the gene to play a role in the metabolism of regular cholesterol, fatty acids, and glucose homeostasis. In its normal functioning, apoE does not cross the blood-brain barrier. However, in response to injury, apoE may influence the central nervous system by acting as an anti-excitotoxic, antioxidant, and/or anti-inflammatory agent.

ApoE is principally synthesized in the liver, but also found in other tissues such as the brain, kidneys, and spleen. Within the nervous system, astroglia and microglia cells primarily produce apoE. ApoE is located on the long arm of chromosome 19 at position 13.2, between base pairs 45,409,038 and 45,412,649. It consists of 4 exons and 3 nitrons, totaling 3597 base pairs and is 299 amino acids long.

The APOE gene is polymorphic with 3 major isoforms, APOE2, APOE3, APOE4. These translate into 3 alleles of the gene: APOEe2, APOEe3, and APOEe4. The following table shows the estimated human genotype frequency of APOE. The APOE alleles differ from each other only by amino acid substitutions at positions 112 and 158. APOEe2 has CYS at positions 112 and 158 in the receptor-binding region of APOE. APOEe3 has CYS at 112 and ARG at 158. APOEe4 has ARG at both positions.

Table 1. Estimated Percentage of the Human Population for APOE Genotype Frequency

Allele	e2	e3	e4
e2	1-2%	15%	1-2%
e3		55%	25%
e4			1-2%

After CNS injury, apoE is locally upregulated and released by the astrocytes into the extracellular space where it is subsequently absorbed by the neurons (Horsburgh, Fitzpatrick, Nilsen & Nicoll, 1997). Several studies of animal models show that APOE influences the neuronal response to acute brain injury (Chen, Lomnitski, Michaelson & Shohami, 1997; Holtzman et al., 1995; Lomnitski et al., 1997; Poirier, 1994; Roses & Saunders, 1997; Teasdale, Nicoll, Murray & Fiddes, 1997). Still, the specific mechanisms by which the APOE genotype influences outcome after brain injury are largely unclear. Much of the work relating to mechanisms involving APOE has been undertaken using animal models and the direct relevance of these studies to humans is uncertain. Relevant mechanisms proposed range from basic cellular functions such as maintenance of cytoskeletal integrity (Roses et al., 1996), and protection from oxidative stress (Lomnitski et al., 1997) and excitotoxicity (Tolar et al., 1999), to general systemic dysfunction such as increased risk of atherosclerosis (Hixson, J.E. 1991) and altered blood coagulation (Weir et al., 2001).

There are several lines of evidence pointing to the critical role of apoE in maintaining the integrity of cerebral vasculature. Support for this has been noted in both the acquired and traumatic brain injury populations. For example, McCarron and colleagues (1998; 2003) reported APOE genotype influences outcome in patients with intracerebral hemorrhage. Similarly, others have demonstrated APOE genotype to affect outcome after subarachnoid hemorrhage (Dunn et al., 2001; Tang et al., 2003). Teasdale, Murray & Nicoll (2005) suggested that coagulation is relatively impaired in carriers of APOEe4, thus putting this group at an increased risk for hemorrhage. Methia (2001) reported that apoE deficiency compromises the strength of the blood brain barrier, especially after injury. ApoE deficiency can also lead to increased cerebral edema as noted in brain injury animal models (Lynch et al., 2002), though similar findings have not been confirmed in humans (Quinn et al., 2004).

ApoE works to deliver lipids (in the form of cholesterol) to the brain. The brain uses these lipids to maintain, restore, and/or stabilize its synaptic connections (Eisenstein, 2011). Therefore, it appears apoE is an essential component of the brain's capacity to rewire itself, otherwise known as plasticity. This plasticity is likely a key contributor in the rehabilitation process after brain injury. The overproduction of ApoE may lead to a prolonged inflammatory response which may result in the toxic build-up of chemicals that further accelerate the damage and possible death of neurons (Eisenstein, 2011). In the animal model, apoE has been reported to play a role in the acute sequelae of brain injury- with apoE levels peaking at 2 days after injury, returning to baseline within 2

weeks, and then gradually increasing through 6 months postinjury (Iwata, Browne, Chen, Yuguchi & Smith, 2005). This may potentially alter progressive neurodegenerative changes.

There is evidence to suggest that APOE responds to neurological change in an isoform-specific pattern (Horsburgh et al., 2001; Kandel, Schwartz, & Jessell, 2000; Ponsford et al., 2011). The APOE alleles have been recently shown to predict both acute and chronic outcomes after neurologic change. Mechanisms by which APOE genotype influences susceptibility to CNS disease and injury may include influencing the rate of cerebral amyloid deposition (Ramanen et al., 2013), impact on the body's inflammatory response (Guo, LaDu & Van Eldik, 2004), providing protection against oxidative injury (Jofre-Monseny, Minihane & Rimback, 2008), and subsequent lipid peroxidation that contributes to neuronal damage and cytoskeletal alterations (such as changes in synaptic repair and regeneration, reorganization) (Horsburgh et al., 2000). Of the three APOE alleles, APOEe3 is widely considered to be the neutral allele (Guo, LaDu & VanEldik, 2004; Roses et al., 1996).

APOEe2 has been associated with the genetic disorder hyperlipoproteinemia, type 3 and an increased risk for atherosclerosis. Homozygote carriers of APOEe2 may clear dietary fat slowly and be at a greater risk for early vascular disease. There is some evidence that APOEe2 may serve a protective role in preventing Alzheimer's disease. APOEe2 appears to be under-represented in the Alzheimer's disease population and is associated with a delayed age at onset (Corder et al., 1994). Qiu and colleagues (2004)

reported that the APOEe2 allele was only beneficial in protecting against Alzheimer's disease for adults under age 75.

APOEe4 is the most widely studied for its relationships to neurological functioning. APOEe4, a common variant of the APOE gene found in approximately one-quarter of the human population, has been associated with more extreme cognitive decline in the neurogenic population (see Dardiotis et al., 2010 for review). APOEe4 has long been associated with an increased risk for development of Alzheimer's disease (Corder et al., 1993; Schmechel et al., 1993) and a reduced capability for central nervous system plasticity response (Arendy et al., 1997). Some suggest the reason why APOEe4 is associated with cognitive impairment is because this genotype has been implicated in the hallmark pathologies associated with cognitive decline, including neurofibrillary tangles, neuritic plaques, and diffuse plaques- all of which are features that traditionally precede a diagnosis of dementia (Bennett et al., 2003; Breitner et al., 1999; Jonker, Schmand, Lindeboom, Havekes, Launer, 1998).

Perhaps the role of APOEe4 and cognitive decline has been most studied in the Alzheimer's disease population as the APOEe4 allele is the strongest known genetic risk factor for Alzheimer's disease (Elias-Sonnenschein, Viechtbauer, Ramakers, Verhey, & Visser, 2011). Some have reported that the presence of APOEe4 may lower the age of onset of the disease by as many as 4-9 years per allele (see Price et al., 1998 for review; Roses et al., 1996; Selkoe, 2001). Others have reported that head trauma leads to the subsequent deposition of amyloid β (Graham et al., 1999; Mannix & Whalen, 2012;

Tsitsopolous & Marklund, 2013), which may predispose these individuals to Alzheimer's disease (Heuvel, Thorton & Vink, 2007; Johnson, Stewart & Smith, 2010; Tang et al., 1996). Additionally, the extent of amyloid β deposition in long-term APOEe4 survivors of TBI is comparable with that of Alzheimer's patients, and noticeably higher than found in patients without the APOEe4 allele (Ewers et al., 2008; Nicoll et al., 1995). Memory deficits, typically found in both APOEe4 survivors of TBI and Alzheimer's patients, may be attributed to the amyloid β deposits found accumulating in cerebral areas commonly associated with memory function, namely the hippocampus and frontal lobe (Ramanen et al., 2013). Barger & Mattson (1997) reported that APOEe4 appeared less effective than the other isoforms of APOE in enhancing certain neuroprotective effects dealing with amyloid proteins.

People with mild cognitive impairment (MCI) have an increased risk for Alzheimer's disease, but not all will eventually develop dementia (Bennett et al., 2002). Elias-Sonnenschein and colleagues (2011) reported that carrying at least one APOEe4 allele was associated with a moderately increased risk for progression from MCI to Alzheimer's disease. Similarly, Farlow and colleagues (2004) prospectively evaluated the cognitive abilities of a group of participants (n= 494) diagnosed with MCI. The investigators concluded that participants carrying at least one APOEe4 (n= 198) allele showed distinct cognitive and neuroimaging profiles, which appeared to resemble those of early Alzheimer's disease patients. APOEe4 genotype was also associated with greater impairments in memory and functional activities, as well as hippocampal atrophy.

Bretsky, Guralnik, Launer, Albert & Seeman (2003) longitudinally evaluated cognitive function in a group of 965 normally aging adults. At 7 years follow-up, APOEe4 was associated with significant cognitive decline within this group of initially high-functioning elderly.

Mayeux et al. (1995) demonstrated that patients with APOEe4 who sustained a TBI were 10 times more likely to develop Alzheimer's disease than those without an e4 allele. Others have reported similar associations of increased risk of developing dementia after TBI for carriers of APOEe4 (Tang et al., 1996; O'Meara et al., 1997). Hippocampal atrophy is a common pathology associated with Alzheimer's disease (de Leon et al., 1993) and is also a common sequelae of TBI (Bigler et al., 1997). These studies lend support for other reports which have concluded that carriers of APOEe4 are at an increased risk for developing increased depositions of β-amyloid after TBI (a protein comprising the amyloid plaques associated with Alzheimer's disease) (Crawford et al., 2002; Nicoll, Roberts, & Graham, 1995). Additionally, the APOEe4 allele may be associated with other pathological conditions associated with Alzheimer's disease such as neurofibrillary tangles and neuritic plaques (Bennett et al., 2003; Breitner et al., 1999).

APOEe4 has also been linked to cardiovascular disease and risk for intracranial bleeding. Eisenstein (2011) suggested that apoE's role in the metabolism of cholesterol may play an important role in preventing atherosclerosis, coagulation, and/or maintaining the cerebral vasculature. Alberts et al. (1995) demonstrated that APOEe4 carrier patients who survived acute intracerebral hemorrhage were more likely to have a less favorable

outcome than those patients without an e4 allele. Alvim and colleagues (2010) evaluated risk for cardiovascular disease in a group of participants (n=1493) and reported that APOEe4 is associated with a worse lipid profile, but these lipid levels do not manifest into significant effects in arterial wall stiffness. Tardiff and colleagues (1994) reported that patients carrying an APOEe4 allele undergoing cardiac surgery recovered neuropsychological functions less efficiently than non-carriers. Nicoll and colleagues (1997) suggested that APOEe4 may play a significant role in determining the risk of intracranial hemorrhage in patients with Alzheimer's disease and cerebral amyloid angiopathy. Furthermore, APOEe4 has been associated with severity of atherosclerosis and predisposition to cerebral amyloid angiopathy (Greenburg et al., 1995). Similar findings were noted by Leclercq and colleagues (2005) in patients with TBI. Others have reported that APOEe4 carriers have larger volume intracranial hematomas after traumatic brain injury (Liaquat et al., 2002). Smith, Graham, Murray, Stewart, & Nicoll (2006) evaluated 239 cases of fatal TBI and reported that possession of APOEe4 was associated with a greater incidence of moderate to severe contusional injury and severe ischemic brain damage.

Increasingly researchers are discovering that APOE may play a dual role in neuroinflammation, serving in both anti-inflammatory activation as well as pro-inflammatory activation (Guo, LaDu & VanEldik, 2004). In normal functioning, apoE responds in an anti-inflammatory role by providing the CNS neurons with lipids for the repair of synapses and stabilizing microtubules within the neuron. However, over

production or over stimulation of this response (as noted in the APOEe4 allele), may indeed have a more detrimental effect. APOEe4 may cause an overproduction of apoE, leading to an increased inflammatory response, which over time may lead to significant changes in the brain's ability to perform certain functions. Alzheimer's disease has long been associated with inflammatory neurological processes (as noted by increased expression of C-reactive protein and interleukins, as well as formation of beta-amyloid plaques). These processes may be further expedited by the presence of APOEe4 (Finch & Morgan, 2007). Moreover, some have suggested that increased productions of apoE may have a neurotoxic effect on the neurons of the brain (Clay et al., 1995).

More specifically, others have proposed that the APOEe4 genotype influences the transportation of lipids, increases accumulation of beta amyloid, impairs growth and branching of neuronal dendrites, and increases cerebral edema (as cited in Hiekkanen, Kurki, Brandstack, Kairisto, & Tenovuo, 2007). Houlden & Greenwood (2006) state that it is not known whether APOEe4 acts by increasing neurological susceptibility to the consequences of neurotoxic agents (such as amyloid b-peptides), or if pre-injury effects on vascular wall pathology of blood clotting mechanisms impact outcome. Additionally, Mahley, Weisgraber & Haung (2006) suggest that age, extent of traumatic injury, oxidative stress, ischemia, and/or inflammation may also be confounding variables on the effects of APOEe4.

There are strong links between APOEe4 and mitochondrial dysfunction that might explain APOEe4's influence on injury and disease (James et al., 2011). Matteson,

Gleichmann & Cheng (2008) reported that mitochondria are critical in regulating normal neuronal functions and are typically disrupted in injury or disease. Additionally, these organelles are often influenced by the presence of APOEe4 (Matteson, Gleichmann & Cheng, 2008). deLeon et al. (2008) stated that a notable feature detectable in the brains of carriers of APOEe4 is regional cerebral hypometabolism, likely a reflection of decreased mitochondrial function. This regional cerebral hypometabolism is further exacerbated in disease as demonstrated in APOEe4 mice who exhibit structural and functional mitochondrial abnormalities (Choi et al., 2004; Mielke, Zerres, Uhlhaas, Kessler & Heiss, 1998; Shenk et al., 2009; Strum et al., 2007). Huang, Weisgraber, Mucke & Mahley (2004) suggested that the structural and subsequent biological difference between the APOE protein isoforms may explain the differential mitochondrial functions. James and colleagues (2011) attempted to determine the protein signature of mitochondria in different APOE genotypes and reported that APOE genotype has a differential effect on the mitochondrial protein expression in the absence and presence of injury. The researchers postulated that this may underlie the differences in mitochondrial function (as noted by regulation of energy production, metabolism, oxidative stress, and organelle dynamics) for varying genotypes.

Interestingly, in populations without neurological injury, there is evidence to support that APOEe4 carriers may perform equal to or better than APOEe4 non-carriers on a number of neurocognitive measures. For example, Keltikangags-Jarvinen et al. (1993) noted that possession of an APOEe4 allele was associated with increased “mental

vitality, social ability, and positive emotionality" among 1577 participants who consisted of healthy children, adolescents, and young adults. Others have found that APOEe4 carriers achieved a mean higher level of education than those with APOEe2 (Hubacek et al., 2001). Mondadori et al. (2007) reported that APOEe4 was associated with better and more efficient memory performances on neuropsychological measures in a group of 340 healthy young adults. Moreover, Han et al. (2007) concluded that possession of an APOEe4 allele may serve as a neurocognitive benefit among young active military personnel approximately 1 month following mild to moderate TBI.

The Role of APOE in the TBI Population

Overall, the APOE data in the TBI population is limited and the role of APOE after brain injury has yet to be fully understood. Current themes in the literature are attempting to determine how the e4 allele affects both the severity and nature of the acute consequences of injury and the processes of neural regrowth and repair involved in recovery (Houlden & Greenwood, 2006). Other genetic factors are also likely playing a part in APOE's role after brain injury, including those aspects controlling neurotrophic factors associated with synaptic plasticity and the response to training and rehabilitation (Kleim et al 2006), though there is minimal research in this area at this time.

Taken collectively, the literature suggests that the APOEe4 allele may influence outcome following TBI, possibly resulting in greater injury severity, as well as greater cognitive and functional impairments. Still, the literature is divided with some

investigators reporting significant changes in short-term (Ariza et al., 2006; Chiang et al., 2003) and long-term (Ost et al., 2008; Ponsford et al., 2011) outcome for those participants with APOEe4, while others show no significant changes associated with short-term (Jiang et al., 2008; Noe, Colomer, Moliner, Chirivella, 2010) and long-term (Hiekkanan et al., 2009; Shadli et al., 2011) outcome.

Some have looked at the relationship between APOE genotype and recovery during the acute stages of TBI recovery. Sorbi and colleagues (1995) reported that patients admitted to the hospital with TBI who were APOEe4 carriers, had a higher risk of prolonged unconsciousness over the first year after injury when compared to patients with other APOE genotypes. Others have reported that APOE genotype was not associated with worsening of CT findings (i.e. hemorrhagic extension or delayed hemorrhage) in the acute stage (within 1 week) of TBI recovery (Jiang et al., 2007). Conversely, Liaquat, Dunn, Nicoll, Teasdale & Norrie reported that APOEe4 predicted larger intracranial hematoma in the acute stages of TBI. Jiang and colleagues (2006) evaluated acute (within 7 days of injury) clinical deterioration of patients with TBI. They reported that carriers of APOEe4 were predisposed to clinical deterioration (as characterized by decreased of GCS, increase in hematoma volume, or delayed hematoma detected by repeat head CT) in this acute phase. Using the same cohort of participants, Jiang and colleagues (2007) further analyzed the role of APOEe4 in outcome after TBI and reported that the APOE -491AA promoter in APOEe4 carriers significantly

contributed to poor acute outcome. No such relationship was noted for other APOE promoters.

Smith and colleagues (2006) postulated that patients with TBI who were carriers of APOEe4 were predisposed to one or more different pathological features in response to TBI (such as ischemic damage, axonal damage) and that this underlies the association of APOEe4 with poor clinical outcome. These researchers concluded that possession of APOEe4 was associated with a greater incidence of moderate or severe contusions only, but no significant differences were noted in other pathological features (ischemic brain damage, skull fracture, axonal injury, epidural hemorrhage, subdural hemorrhage, intracerebral hemorrhage, or increased intracranial pressure).

Teasdale and colleagues (1997) reported that 57% of APOEe4 carriers had a GOS score of dead, vegetative state, or severe disability compared with 27% of non-carriers of APOEe4 after TBI; however this study was limited to 93 participants, of whom only 30 possessed an APOEe4 allele, and the groups with and without e4 differed in several parameters including injury severity. A more extensive study, conducted by the same researchers (Teasdale, Murray, & Nicoll, 2005) reported there was no significant association between APOE genotype and outcome for 1094 participants admitted to the neurosurgical unit with acute brain injury. Interestingly, they did note a significant interaction between age and APOE genotype on outcome, reporting that possession of APOEe4 reduced the prospect of a favorable outcome in children and young adults (<15 years).

Friedman and colleagues (1999) demonstrated that the e4 allele of APOE predicted both short-term and long-term morbidity for patients with various levels of TBI severity. These researchers showed that patients with the e4 allele were more likely to remain unconscious for more than 7 days and were less likely to have a good outcome, as measured by independence in activities of daily living. Chiang, Chang, & Hu (2003) prospectively studied a group of 100 patients with TBI to evaluate the effect of APOE genotype on outcome after TBI. APOEe4 carriers, a total of 19 participants, had significantly longer hospital stays and unfavorable outcomes, as measured by the GOS, after TBI.

Ost, Nylen, Csajbok, Blennow, Rosengren, & Nellgard (2008) reported that APOEe4 correlated to worse outcome at 1 year after severe TBI. Additionally, this group found that males with APOEe4 had poorer outcome, while females did not, thus indicating a possible gender influence. Crawford and colleagues (2002) showed decreased performance on memory tasks for 30 participants with TBI and the APOEe4 allele compared to 80 participants who were not carriers of an APOEe4 allele. This relationship was not demonstrated in other aspects of cognitive functioning such as executive functioning. The researchers suggested that these findings may add support to the role APOE plays in neuronal repair. Additionally, Ariza and colleagues (2006) demonstrated that at 6-months post-injury performance on neuropsychological tasks that were presumably related to temporal lobe, frontal lobe and white matter integrity were worse in participants with an APOEe4 allele than in those without it.

Regarding long-term outcome, Ponsford et al. (2011) reported that after TBI, APOEe4 may be associated with poorer long-term outcome (as measured by GOS), but genotype does not appear to impact acute injury severity. In a population with a high prevalence of the APOEe4 allele, Nathoo, Chetty, van Dellen, Connolly & Naidoo (2003) demonstrated no relationship between APOEe4 allele status and 6 month outcome, as measured by Glasgow Outcome Scale after TBI. Millar et al. (2003) reported that cognitive decline 15-25 years post severe TBI was not related to APOE genotype.

Isoniemi, Kurki, Tenovuo, Kairisto & Portin (2006) evaluated 58 people with TBI of varying severity an average of 31.3 years after injury. They reported that the APOEe4 allele was not associated with the development of hippocampal or global cerebral atrophy after TBI. The authors suggested that if the APOEe4 allele is associated with an unfavorable outcome after TBI as many reports in the literature propose, this association may involve mechanisms other than those responsible for the development of brain atrophy. Hiekkanen and colleagues (2009) reported that APOE genotype was not predictive of 1-year outcome following TBI, rather duration of PTA and findings on MRI were more accurate predictors of significant changes on MRI at the follow up period. Still, others have reported that a portion of APOEe4 carriers who developed long-term cognitive decline after TBI do indeed demonstrate significant global cerebral atrophy on neuroimaging (Himanen et al., 2006; Koponen et al., 2004). Still, it remains unclear if these cerebral changes were due to APOEe4 or due to trauma-related factors, such as TBI severity or contusion volume.

Conversely, Willemse-van Son and colleagues (2008) found that patients with moderate-to-severe TBI possessing an APOEe4 allele had a significantly better outcome on the Glasgow Outcome Scale Extended (GOS-E). Interestingly, an animal study of closed head injury demonstrated that APOEe4 may actually be neuroprotective, although less so than the other two alleles, e2 and e3 (Chen et al., 1997), and these results have yet to be replicated.

There is a limited number of research studies designed to assess the relationship between APOE genotype and outcome after mTBI. Moreover, it is difficult to compare the results of each of the previous studies based on methodological and outcome measurement differences. However, it remains important to review the findings of these studies.

Sundstrom and colleagues (2007) assessed the incidence of fatigue for participants with mTBI, then evaluated the relationship between fatigue and APOE genotype. They concluded that fatigue is a common concern after mTBI and is especially pronounced for carriers of an APOEe4 allele. Han et al. (2009) questioned if APOE genotype would predict outcome, as measured by a change in job status at 1 month post-injury, for a group of 52 participants with mTBI. Although not singularly statistically significant, APOE genotype, in association with other neurocognitive and clinical postconcussive symptom measures, was noted to be an important factor to consider when predicting outcome after mTBI. The authors also concluded that results from this study provided tentative support that young adults who are APOEe4 carriers may experience a

neurocognitive change following mTBI, but note that future longitudinal research would be essential in clarifying these results.

Liberman et al. (2002) studied the neuropsychological performance of 87 patients with mTBI at 3 and 6 weeks after injury. They determined that APOE genotype may influence the severity of the acute injury, however, there were no noted consistent patterns of recovery and the investigators could not clearly determine if APOE genotype influenced the rate of recovery, or outcome after injury as measured by performance on a battery of neuropsychological subtests. Sundstrom et al. (2004) evaluated the relationship between neuropsychological outcome and APOE genotype for a group of 34 participants with mTBI. Pre-injury and post-injury performances on a battery of 9 neuropsychological tests were compared within person, and the post-injury performance was compared with that of age- and gender-matched control participants. Researchers concluded that the 11 participants with at least one APOEe4 allele had a significantly decreased post-injury performance on 3 of the neuropsychological tests, whereas the post-injury performance for the participants without APOEe4 was unchanged. Overall, there was no significant difference in post-injury performance between participants with an APOEe4 allele and those without an APOEe4 allele, and neither group was impaired relative to controls.

Shadli, Pieter, Yaacob & Rashid (2011) evaluated the influence of APOE genotype on neuropsychological outcome in 19 participants with mTBI and 14 aged-matched healthy controls. The researchers demonstrated no clear APOE genotype

influence on neuropsychological outcome for participants with mTBI at 6 weeks and 6 months post-injury, but reported that larger-scale studies with longer follow-up duration are warranted.

Chamelian, Reis & Feinstein (2004) investigated the influence of APOEe4 in 90 participants with mTBI on neuropsychological outcome. Outcome was measured at 6 months using the following indices: a neuropsychological battery, an index of emotional distress, diagnosis of major depression, GOS-E, an index of psychosocial outcome, and a measure of symptoms congruent with post-concussion syndrome. No association was noted between the presence of an APOEe4 allele and poor outcome across all measures.

Rahida and colleagues (2008) reported that for 19 participants with mild to moderate TBI, carriers of an APOEe4 allele showed no significant differences from noncarriers of an APOEe4 allele in measures of executive function, verbal learning and memory, verbal fluency, abstract reasoning, speed of processing and an index of emotional distress. Participants were evaluated at 6 weeks post-injury and again at 6 months after injury.

Although the most widely studied within the neurogenic population, the apoE protein and APOE gene are only one gene and protein of interest to researchers. Increasingly, researchers are looking at how proteins produced by various genes may interact together to influence outcome after CNS injury. These possible protein interactions may provide additional valuable information into how the brain responds to injury. Other recognized genes, such as MAPT, COMT, DRD2, p53 and ACE, have been

less extensively studied and have not had extensive replication of initial findings (see Dardiotis et al., 2010 for review; Jordan, 2010). Moreover, little is known how or if these genes interact with the APOE gene or apoE protein, especially following TBI.

For example, the tau gene, found on chromosome 17 is responsible for the production of the tau protein (Terrel et al., 2008) which has been implicated in chromosome 17 frontotemporal dementia (Poorkaj at al., 1998) and chronic traumatic encephalopathy (Kounang, 2012). Increased tau protein levels have been reported after severe TBI and linked to poorer GOS-E scores (Liliang et al., 2010). Terrell and colleagues (2008) investigated the association between APOE, APOE promoter, and tau protein exon 6 polymorphisms in college athletes with a history of concussion. The researchers reported an association between APOE promoter G-219T polymorphism and history of concussion, leading to a nearly 3 times increased risk for history of concussion. However, they did not note a link between APOE genotype and tau polymorphism with prior concussion.

Inflammation is a pathophysiological event often initiated in the minutes, hours and days following a TBI and is, in part, mediated by the interleukin genes (Jordan, 2010). An association between various interleukin polymorphisms and poorer outcome after TBI has been noted in experimental TBI models (Hadjigeorgiou et al., 2005; Uzan et al., 2005). Others have noted no relationship between interleukin polymorphisms and outcome after TBI (Dardoitis, Dardioti, Hadjigeorgiou & Paterakis, 2006; Tanriverdi et al., 2006).

The accumulation of Aβ proteins can be found in the brain of both people with TBI (Roberts et al., 1994) and Alzheimer's disease (Mortimer et al., 1991) and is likely the result of an imbalance between production and clearance of Aβ. Neprilysin has been reported to play an important role in the degradation of Aβ as it has been shown to have an effect on preventing the formation of new amyloid plaques (Mohajeri et al., 2004). In patients with TBI, the amount of Aβ deposition was shown in part to be determined by the presence of an APOEe4 allele (Nicoll, Robers & Graham, 1995).

Investigators are also looking at the role of biomarkers in the assessment of TBI. Few have studied the effect APOE may have on the release of various biomarkers associated with TBI, but one group of researchers reported significant increases in S100B and NSE levels for participants with severe TBI who were carriers of an APOEe4 allele compared to participants who were APOEe4 noncarriers (Olivecrona & Koskinen 2012).

Although a promising area of future research, the current data linking specific genes or protein interactions is in its earliest stages of investigation. These current studies are based on small sample sizes with differing outcome measures. Additionally, the investigations of these genes are limited to single studies with limited or no replication to date (Conley & Alexander, 2011). Still, they do provide us with insights into the pathophysiology of TBI and how genetic information may be used to further predict outcome from TBI.

Purpose of the Current Study

To date, medical professionals depend largely on initial GCS score and neuroimaging results to determine prognosis from TBI. Little is known about how acute cognitive abilities play a role in eventual recovery from TBI. Even less is known about how certain genetic factors may influence outcome. Furthermore, many of the studies evaluating prognostic indicators after TBI have targeted the population of individuals with moderate to severe brain injury, with few studies measuring outcome indicators within the population of mTBI. Therefore, there is a gap in the evidenced based knowledge of mTBI for what initial factor is most predictive of outcome after injury.

The *overall objective* of this study is to determine which initial factors are most predictive of functional recovery from mTBI. The *specific aim* of this study is to determine whether initial severity of injury, initial head CT results, cognitive performance on a standardized measure, or genotyping most effectively predicts 1-month functional outcome. Based on these objectives, and a noted lack of evidenced-based research in this specific area related to mTBI, the below proposed study was developed to answer the following research questions.

Research Question #1: Does initial GCS, initial head CT findings, performance on ImPACT cognitive testing, or APOE genotype most effectively predict 1-month functional outcome after mTBI?

Working Hypothesis #1: It is hypothesized that performance on ImPACT cognitive testing will most effectively predict 1-month GOS-E.

Research Question #2: Do carriers of an APOEe4 allele exhibit a slower 1-month recovery from mTBI? ***Working Hypothesis #2:*** It is hypothesized that carriers of an APOEe4 allele will show a relatively weaker recovery from mTBI as compared to APOEe4 non-carriers.

CHAPTER II

METHODS

This was a joint study between The University of North Carolina – Greensboro (UNCG) and The University of North Carolina Hospitals (UNCH). Institutional Review Board approval was obtained from both sites, with the UNCG IRB maintaining primary oversight of the project.

The study used regression analysis to determine which dependent variable (initial GCS score, initial head CT results, cognitive screening using ImPACT, or APOE genotyping) most effectively predicted 1-month functional outcome as measured by GOS-E score or DRS (independent variables). Independent t-test procedures were used to determine the relationship between APOE genotype and functional outcome.

Participants

Participants were recruited at UNCH and identified upon initial inpatient consult to UNCH's Department of Speech Pathology. Recruitment occurred between September 2012 – October 2013. Inclusion criterion included males or females, admitted to UNCH with a diagnosis of acute mTBI (GCS score > or equal to 13); age 18-65; closed head injury; not intoxicated at the time of injury; no history of learning disabilities; high school graduate; no other neurological history; no post-traumatic seizures experienced during hospitalization; no cardiac arrest at the scene; was admitted to the hospital within 24

hours of the injury; and was able to provide informed consent. Exclusion criterion included previous concussion or TBI, left-handedness, and English as not the primary language. Potential participants were identified by the primary investigator after a brief case history was conducted based off the speech pathology consult. Findings from the case review were matched to the participant recruitment criterion and collaboration with other members of the research team was completed to determine candidacy for participation in the study. After appropriateness for candidacy was determined, the potential participant was provided extensive information about the study and written informed consent was obtained. To ensure that participants fully understood the nature of the data (i.e. Protected Health Information) they were agreeing to release as part of the study, informed consent was again obtained at the follow up data collection session.

79 participants were recruited for this study. Of these 79, 61 participants provided informed consent and participated in most of the study requirements. Of these 61, 49 participants completed the study requirements in its entirety and the results from these 49 were used in the data analysis. This participant sample should be representative of the general TBI population as UNCH is a state-supported hospital that receives traumatized patients from across the entire state, serving people of various ethnic, socioeconomic, and racial backgrounds.

Procedures and Measures

There were 2 data collection periods for each participant- one within 48 hours after mTBI and the other at approximately 1-month post-mTBI. These time points were chosen based on methodology of previous studies which used data collection at the time of initial injury (Borago et al., 2003; Delaney et al., 2005; Hughes et al., 2004; McNett, 2007; Wijdicks, 2006) and within the 1 to 2 month period after initial injury (Barkhoudarian, Hovda & Giza, 2011; Han et al., 2007; King, 2003; Wade et al., 1998). King (2003) describes a "window of vulnerability" for people with mTBI at this time period and suggests that follow-up at this time is essential to assess for possible emerging risk factors, such as concerns regarding the potential permanence of the symptoms and detection of negative coping strategies possibly developed by the individual. The majority of the initial data collection (case review, initial GCS score, head CT results, ImPACT testing, and DNA sampling) occurred at UNCH while the participant remained hospitalized. The remaining data (GOS-E, DRS, and repeat ImPACT testing) was obtained at the patient's convenience, either at home or during follow-up appointments upon return to UNCH.

Case Review, Including Initial GCS Score and Head CT Results

After obtaining written informed consent, all participants received a detailed review of their case history. This included information on previous neurological history, reason for current hospitalization, medications used to medically stabilize the person after

the initial injury, and results of various tests and screens commonly used in the assessment of mTBI. Information regarding the mechanism of injury (i.e. fall, motor vehicle collision) was collected for each participant. Determination of loss of consciousness was determined by patient report or bystander report and categorized as either positive (the participant had LOC) or negative (the participant did not have LOC). Information on length of LOC was not collected for each participant given length of LOC has been previously shown to be grossly misrepresented when based on patient report alone (Rupp, Iverson, Barth, Bush, Broshek, 2009).

Data was also collected on the participant's initial GCS score and when the GCS was completed. Initial GCS is typically completed by first responders (i.e. EMS), but sometimes is not completed until the person arrives to the Emergency Department of the hospital. For participants in this study, the initial GCS score documented within the participant's medical record, either by first responders or emergency medicine physician, was used as the participant's GCS score.

All participants received a head CT upon arrival to the hospital. Information on head CT results was collected for each participant based off the Radiologist's read of the neuroimaging scan. Based on the Radiologist's impression of the scan, head CT results were grossly generalized as positive (there were acute changes noted on the scan per the Radiologist) or negative (no acute changes were noted on the scan per the Radiologist). If a positive head CT was noted, additional information was collected about the specific type of change noted on the head CT, either epidural hemorrhage (EDH), subarachnoid

hemorrhage (SAH), intraparenchymal hemorrhage (IPH), or subdural hematoma (SDH), and the location of the injury.

ImPACT Cognitive Testing

All participants completed ImPACT testing within 48 hours after their injury. This is a computerized cognitive test that takes approximately 20 minutes to complete. All patients admitted to UNCH with a diagnosis of mTBI already receive cognitive testing from a trained Speech Language Pathologist (SLP) prior to discharge from the hospital. ImPACT testing used as part of this study served as the SLP's cognitive evaluation; therefore, the participant did not receive redundant cognitive assessments. The ImPACT has been repeatedly used to evaluate cognitive function after concussion (Iverson, Lovell & Collins, 2003; Schatz et al., 2005; Thomas et al., 2011). Moreover, it has also been used to evaluate cognitive abilities after mTBI during acute hospitalization (Nance, Polk-Williams, Collins, Wiebe, 2009; Peterson et al., 2008; Thomas et al., 2011).

The ImPACT consists of 6 modules. Module 1: Word Memory evaluated attentional processes and verbal recognition memory utilizing a word discrimination paradigm. Twelve target words were presented for 750 milliseconds each. This list was presented twice to facilitate list learning. The participant was tested for recall using a 24 word list, comprised of the 12 target words and 12 additional non-target distractor words. Distractor words were chosen from the same semantic category as the target word. There are five different forms of the target word list used in various versions of the ImPACT to

reduce test learning effects. All other test modules have 5 versions as well to minimize learning of the test. Following administration of all other test modules, the participant was again tested for memory of the initial target words via the same method. The delay in testing is approximately 20 minutes.

Module 2: Design Memory evaluated attentional processes and visual recognition memory utilizing a design discrimination paradigm. This module uses similar methods as the ones used for Module 1, but this module targeted abstract designs, rather than targeting words. Non-target, distractor designs were simply the target designs rotated 180°. There was also a delay condition (approximately 20 minutes) for this module.

Module 3: X's and O's measured visual working memory as well as visual processing speed and consisted of a visual memory paradigm with a distractor task. The distractor task served also as a reaction time test and impulsivity test. It consisted of either a blue square or a red circle flashed on the screen. The participant as quickly as possible pressed the Letter Q on the keyboard if the blue square was presented, or the Letter P on the keyboard if the red circle was presented. After completion of the distractor task, the memory task was presented. The memory task presented a random assortment of X's and O's displayed for 1.5 seconds. A total of three X's or O's were highlighted in yellow. The participant was charged with remembering which X's or O's had been highlighted within the larger group. Immediately after the presentation of the highlighted X's and O's, the distractor tasks again reappeared on the screen. Following completion of the distractor task, the memory screen of X's and O's reappeared and the

participant was asked to click on the previously highlighted X's and O's. There were a total of 4 trials of this module.

Module 4: Symbol Matching evaluated visual processing speed, learning, and memory. During this module, the participant was presented with a screen displaying 9 common shapes (triangle, square, circle, diamond, etc.). Directly under each symbol was a numbered button from 1 to 9. Below this grid of shapes and numbers, a shape was presented and the participants were asked to click on the above number that corresponded to that shape as quickly as possible. Correct answer was reinforced through the highlighting of the correctly clicked shape in green, while incorrect answers were indicated by the shape changing color to red. Following the completion of 27 trials, the shapes disappeared from the top grid, with just the numbers remaining. A shape was then again presented below the grid and participants were asked to recall the correct shape/number pairing by clicking on the appropriate number button. This module provided a component of the reaction time score, in addition to a component of the memory score.

Module 5: Color Match represented a reaction time task and a measurement of impulsivity and response inhibition. The participant was first tested for color blindness. Next, a word was displayed on the screen in the same colored ink as the word (i.e. RED), or in a different colored ink as the word (i.e. BLUE). The participant was instructed to only click the words that were presented in the matching ink, and to do so as quickly as

possible. The number of errors made by the participant during this task was provided in impulsivity score calculations.

Module 6: Three Letter Memory measured working memory and visual-motor response speed. This task consisted of the learning and recalling of 3 letters, while being distracted by a backward number tracking task. 3 letters were initially presented on the screen. Immediately following this display, the distracter task appeared. The distracter task consisted of 25 numbered buttons in a 5 x 5 grid. The participant was instructed to click as quickly as possible on the numbered buttons, counting backward starting with number 25. After 18 seconds, the numbered grid disappeared and the participant was asked to recall the three letters by typing them from the keyboard. Both the number placement on the grid and the three letters displayed were randomized for each trial. Five trials of this task were presented.

The ImPACT does not yield one summary score, but rather a series of indicators that have been demonstrated to be sensitive measures in the mTBI population (ImPACT Clinical Interpretation Manual, 2011). There are six composite scores calculated from the neurocognitive modules administered: Verbal Memory, Visual Memory, Visual Processing Speed, Reaction Time, Impulse Control, and Cognitive Efficiency. The Verbal Memory composite score represents the average performance on the Word Memory (both immediate and delayed recall) (Module 1), the Symbol Match (Module 4), and the Three Letters (Module 6). Scores are represented in an age-referenced percentile. A higher score indicates a better performance on the Verbal Memory composite score.

The Visual Memory composite score measures visual attention, scanning, visual learning, and attention. This score is comprised of the average of Design Memory total percent correct (Module 2) and the X's & O's total correct memory score (Module 3). A higher score indicates a better performance on the Visual Memory composite score. The Visual Processing Speed composite score is determined based on the average of the following scores: X's & O's total number correct (Module 3) and Three Letters average counted correctly from the countdown phase (Module 6). A higher score indicates a better performance on the Visual Processing Speed composite score. The Reaction Time composite score is comprised of the average of the X's & O's average correct (Module 3), Symbol Match average correct (Module 4), and Color Match average correct (Module 5). A lower score indicates a better performance on the Reaction Time composite score. The Impulse Control composite provides a measure of errors on testing and can be used to determine test validity. It is derived from the total errors in X's & O's (Module 3) and the total commissions from the Color Match (Module 5). A lower score indicates a better performance on the Impulse Control composite. Normative data is available for these composite scores for sex and age, as well as level of education (see Iverson, Lovell & Collins, 2003 for further detail).

The Cognitive Efficiency score measures the interaction between accuracy (percentage correct) and speed (reaction time). It is calculated using the Symbol Match Test (Module 4). It can be used in determining the extent to which the participant tried to work very fast, and thus perhaps decreasing accuracy; or the extent to which the

participant attempted to improve accuracy, but then perhaps jeopardized speed (ImPACT Clinical Interpretation Manual, 2011). The range of scores is approximately zero to approximately 0.70, with a mean of 0.34. A higher score indicates the participant did well in both the speed and accuracy domains on the Symbol Match Test. A low score (below 0.20) indicates poor performance on both the speed and accuracy components. If the score is a negative number, the participant performed very poorly on the reaction time component.

Importantly, ImPACT testing also includes a 22 item self-report questionnaire of physical, cognitive, and emotional symptoms typically experienced after mTBI. Individual symptoms are scored on a Likert scale from 0 to 6, with 0 indicating the participant is not experiencing that symptom. Participants are asked to only report symptoms experienced in the past 24 hours. Appendix B lists the various symptoms described on this scale. Points are totaled from all 22 symptoms and are reported in the Total Symptom score. A lower score indicates fewer endorsed symptoms by the participant.

The ImPACT was also administered at the 1-month follow up period. The test consisted of the same 6 modules, with the same composite scores calculated based off performance on these modules. Repeat Total Symptom score was assessed using the same 22 item self-report questionnaire. Several researchers have demonstrated the effectiveness of using ImPACT after mTBI to evaluate recovery, functional outcome, or in making return to play decisions for athletes (Iverson, Lovell, Collins, 2003; Lau,

Collins, Lovell, 2010; VanKampen et al., 2006). ImPACT testing has been shown to minimize practice effects through the use of randomization of stimuli presentation (Iverson, Lovell, Collins, & Norwig, 2002).

DNA Collection, Analysis, and Genotyping

During the initial data collection session, Isohelix SK-2S buccal swabs were used to collect saliva samples from each participant. Samples were collected according to the manufacturer's protocols (Isohelix, Inc). Swabbing occurred at least one hour after eating, drinking, or cleaning the mouth. All participants rinsed their mouth with water immediately prior to swabbing. According to the manufacturer, the anticipated DNA yield from the Isohelix SK-2S swab averages 5µg DNA in adults. The quality of the collected DNA sample affects the quality and amount of the DNA that is then isolated from that sample. Several measures were taken to store the collected DNA sample swabs under the most optimal conditions to preserve DNA integrity. For example, immediately after collection, swabs were stored in a locked freezer at -20°C where they remained until they were transported to the lab at UNCG for genotyping analysis, swabs were stored in a cooler with ice packs for transport, and upon arrival to the lab swabs were again stored in a freezer at -20°C until analysis was started. Repeated freezing and thawing of the frozen samples was minimized as much as possible.

For each participant in the study, DNA was extracted from the buccal swab using the Maxwell® 16 MDx instrument (©Promega Corporation) with the Maxwell® 16

Buccal Swab LEV DNA Purification kit. Under this system, 16 samples can be processed simultaneously, yielding 50µl of DNA at an average concentration of 5-20ng/µl. The DNA samples were stored at -20°C until genotyping could be performed.

Wenham, Price & Blandell (1991) established PCR protocols for amplifying the common alleles of APOE genes and similar protocols were followed for the completion of this study. The genotyping platform used to process the study samples was Applied Biosystems® 7500 Fast instrumentation with Custom Taqman® SNP Assays (Life Technologies™). This methodology employs primers and sequence specific probes with fluorophores (VIC and FAM) to distinguish the presence of a specific allele at the SNP site of interest. SNP kits rs429358 and rs7412 were used to determine APOE genotype. APOE genotyping requires the coding of 2 SNPs, rs 429358 and rs7412, to determine allele type. This methodology has been established elsewhere in the literature (Lescai et al., 2001; Wenham, Price & Blandell, 1991). Table 2 shows the method used to determine APOE allele genotype based on SNP analysis. APOE has six standard genotypes presented in Table 2 (2/2, 2/3, 2/4, 3/3, 3/4, 4/4); however, most studies categorize APOE genotype into a dichotomous variable which becomes coded as the presence or absence of any e4 allele (Bretsky et al., 2003, Crawford et al., 2002; Elias-Sonnenschein et al., 2011; Hiekkanen et al., 2007; Liberman et al., 2002; Ost et al., 2008; Smith et al., 2006; Sundstrom et al., 2007). The standard method of grouping participants based on presence or absence of any e4 allele was used for this study.

Table 2. APOE Allele Determination based on SNPs rs429358 and rs7412

rs429358	rs7412	APOE allele
T;T	T;T	APOE 2/2
T;T	C;T	APOE 2/3
C;T	C;T	APOE 2/4
T;T	C;C	APOE 3/3 *most common
C;T	C;C	APOE 3/4
C;C	C;C	APOE 4/4

Glasgow Outcome Scale – Extended

In 1997, Wilson, Pettigrew & Teasdale modified and extended the traditionally used Glasgow Outcome Scale (GOS) (Jennett & Bond, 1975) to encompass a broader range of functional outcome and published guidelines on this new version, known as the Glasgow Outcome Scale – Extended (GOS-E). Since then, the GOS-E has been frequently cited in the literature as a primary measure of functional outcome after TBI (Alexander et al, 2007; Brichtova & Kozak, 2008; Chamelian, Reis & Feinstein, 2004; Diaz-Arrastia et al., 2003; Ost et al., 2008; Ponsford et al., 2011). Teasdale and colleagues (1998) and Wilson and colleagues (2007) have both demonstrated excellent test-retest reliability for the GOS-E. Lu et al. (2010) reported good to excellent inter-rater reliability, and Pettigrew et al. (2003) reported excellent inter-rater reliability.

Others have demonstrated validity measurements of the GOS-E (Hall et al., 2001; Levin et al., 2001; Wilson et al., 2000). Hiekkanen et al., (2009) reported that the GOS-E was more sensitive than the GOS for patients with mild or moderate TBI because of the scale's more detailed description of the upper range of outcome.

The GOS-E is a list of 19 structured interview questions that target the individual's level of independence in and out of the home, current employment, social and leisure activities, and family and friend relationships. See Appendix C for the GOS-E structured interview questions. GOS-E scores range from 1 to 8 with each score correlating to a severity level of disability or extent of recovery. Based on this scale, outcome results have typically been divided to either good (GOS-E scores of 7 or 8) or bad (GOS-E scores of 1, 2, 3, 4, 5, or 6) (Hiekkanen et al., 2009; Ost et al., 2008; Ponsford et al., 2008; Teasdale, Murray & Nicoll, 2005). Table 3 provides a description of GOS-E scores and outcome levels.

Table 3. GOS-E Score and Functional Outcome Levels (Adapted from Rehabilitation Measures Database, 2012)

GOS-E Score	Functional Outcome Level	Description
1	Death	Dead
2	Vegetative State	Condition of unawareness with only reflex responses; periods of eye opening
3	Lower Severe Disability	Dependent for daily support for mental and/or physical disability
4	Upper Severe Disability	Dependent for daily support for mental and/or physical disability but can be left alone for periods of time
5	Lower Moderate Disability	Some level of physical or mental disability, but generally able to care for themselves within a controlled environment
6	Upper Moderate Disability	Some level of physical or mental disability, but able to return to work even if special arrangement is needed
7	Lower Good Recovery	Resumption of normal life with the capacity to work, even if pre-injury status has not been achieved; may have minor neurological or psychological deficits
8	Upper Good Recovery	Minor neurological or psychological deficits persist, but are not disabling

Disability Rating Scale

The purpose of the Disability Rating Scale (DRS) (Rappaport et al., 1982) is to track the recovery of an individual from coma to community and to measure general functional changes over the course of this recovery. It was developed to address the limitations of the commonly used Glasgow Outcome Scale. It was originally tested in the moderate and severe TBI population, although it has been used in mTBI population as well (Struchen et al., 2001). Still others have reported the DRS has poor sensitivity in the evaluation of mTBI (DRS < 3) or severe TBI (DRS > 22) (Hall et al., 1996). Gouvier and colleagues (1997) demonstrated excellent test-retest reliability as well as excellent interrater reliability for the DRS. Others have demonstrated both criterion validity (Flemming et al., 1999; Fryer & Haffey, 1987; Nichol et al., 2011) and construct validity (Hall et al., 1985; Gouvier et al., 1987) for the DRS. Acute inpatient discharge DRS scores have been used to predict return to work with 86% accuracy (Rao et al., 1992). Hall and colleagues (1985) compared the DRS with the GOS and found that 71% of individuals showed improvements on the DRS compared to 33% with the GOS between acute inpatient admission and discharge.

The DRS is a series of structured checkpoints that can either be obtained through personal interview with the individual or through direct observations of the individual. The checklist targets consciousness, cognitive ability, dependence on others, and employability. See Appendix D for a list of DRS observations and correlating scores. A 30-point scale is used to provide quantitative information, with lower numbers indicating

better recovery and less level of disability. Table 4 depicts DRS scores with associated level of disability. The DRS addresses all three World Health Organization (1980) categories used across various stages of recovery: impairment, disability, and handicap. Impairment is targeted by the first three items of the DRS, eye opening, communication ability, and motor response. Cognitive ability for feeding, toileting, and grooming measure disability. The level of function and employability items are used to measure handicap.

Table 4. Disability Rating Scale Scores and Associated Level of Disability

DRS	Level of Disability	General Description
0	None	No impairments in consciousness or communication status; not restricted in cognitive abilities or self-care activities, independent, not restricted in employment
1	Mild	No impairments in consciousness or communication status; may be minimally restricted in cognitive ability, self-care activities, independence, or employment
2 – 3	Partial	No impairments in consciousness; may be restricted in communication status, cognitive ability, self-care activities, independence, or employment
4 – 6	Moderate	Poor attention, requires moderate assistance with cognitive and self-care activities; may have moderate restrictions on independence or employment abilities
7 – 11	Moderately Severe	Poor attention, requires moderate to severe assistance with cognitive and self-care activities; likely has restrictions on independence; likely unable to be employed without special arrangements
12 – 16	Severe	Maintains periods of arousal, poor attention, likely requires maximum assistance for all activities of daily living; likely unable to be employed
17 – 21	Extremely Severe	Severe but likely fluctuating impairment in arousal and attention, fluctuating awareness of self and environment; requires maximum assistance for all activities of daily living; unable to be employed
22 – 24	Vegetative State	Profound impairments in consciousness; no attempts at communication; does not show awareness of self or environment
25 - 29	Extreme Vegetative State	Profound impairments in consciousness- may only respond to painful stimuli; no attempts at communication; does not show awareness of self or environment; may require certain forms of medical intervention to sustain life
30	Death	Dead

Statistical Analysis

Statistical analyses were conducted using SPSS 21 statistical software. Descriptive statistics were used to assess participants' background characteristics, as well as for study outcome measures. The following statistical analyses were used to answer the following research questions.

Research Question #1: Does initial GCS, initial head CT findings, performance on ImPACT cognitive testing, or APOE genotype most effectively predict 1-month functional outcome after mTBI?

Statistical Analysis: Logistic regression procedures were conducted to determine which variables would significantly predict the likelihood of recovery. The GOS-E and DRS variables were coded into binary variables for the purpose of this analysis. Participants with a score of 7 or below on the GOS-E were grouped into the GOS-E Group A and participants with a GOS-E score of 8 were grouped into the GOS-E Group B. Similarly, participants who scored a one or more on the DRS were grouped the DRS Group A, whereas participants with a score of zero on the DRS were grouped into the DRS Group B. Logistic regression procedures were also used to determine if demographic variables would significantly predict the odds of being categorized into GOS-E Group A or GOS-E Group B, or DRS Group A or DRS Group B.

Research Question #2: Do carriers of an APOEe4 allele exhibit a slower 1-month recovery from mTBI compared to APOEe4 non-carriers?

Statistical Analysis: Independent t-test procedures were conducted to determine whether cognitive recovery would vary across APOEe4 carriers as compared to APOEe4 noncarriers. Participants were grouped by presence or absence of an e4 allele as previously described in the literature. Independent t-test procedures were also conducted to determine whether cognitive recovery varied across homozygous APOEe4 carriers. A 2 x 2 x 2 analysis of variance (ANOVA) were conducted for all composite scores of the ImPACT to determine if these scores changed significantly across time, as well as to assess if other variables impacted this change in score.

The level of statistical significance was $p < 0.05$ for all analyses.

CHAPTER III

RESULTS

Description of the Sample

Participants in this study were between 19 and 64 years old. The mean age was 36.02 (SD = 14.49). There were slightly more males (57.1%) than females (42.9%). Most of the participants were Caucasian (75.5%). Years of education ranged between 12 and 20 years, with a mean of 14.82 (SD = 2.02). The majority of the brain injuries resulted from a motor vehicle collision (n = 40, 81.6%). Other causes for brain injury were fall (n = 4), assault (n = 2), all-terrain-vehicle accident (n = 1), and pedestrian hit by car (n = 2). Initial GCS is typically completed by first responders (i.e. EMS), but sometimes cannot be completed until the person arrives to the Emergency Department of the hospital. For participants in this study, GCS was completed at the scene of the injury for 89.8%, with the remaining 11.2% of participants having initial GCS completed by the Emergency Department physician. Most participants had an initial GCS score of 15 (n = 28, 57.1%). 19 (38.7%) participants had an initial GCS of 14 and 2 (4.1%) participants had an initial GCS of 13.

The Radiology report was used to collect information on head CT results. Head CT results were grossly generalized as positive (the radiology report noted acute brain changes on the scan) or negative (the radiology report noted no acute brain changes on

the scan). The majority of participants had a negative head CT (n = 31; 63.3%). Of the participants with a positive head CT (n = 18; 36.7%), additional information was gathered about the specific type of change noted on the head CT, either epidural hemorrhage (n = 3), subarachnoid hemorrhage (SAH) (n = 5), intraparenchymal hemorrhage (n = 3), or subdural hematoma (SDH) (n = 7).

ImPACT testing was completed within 24 hours of injury for 30.6% of participants, and within 48 hours of injury for the other 69.4% of participants. All DNA samples were gathered within 48 hours of injury. Results of DNA genotyping indicated that 40.8% (n = 20) of the participants were either heterozygous (n = 17) or homozygous (n = 3) for the APOEe4 allele. The rest of the participants, n = 29 (59.2%), did not carry an APOEe4 allele. The frequencies and percentages for the participant demographic variables are presented in Table 5.

Table 5. Frequencies and Percentages for the Demographic Variables

Variable	Frequency	Percentage
Gender		
Male	28	57.1
Female	21	42.9
Education in Years		
12 years	22	44.9
13 – 16 years	24	49.0
16+ years	3	6.1
Race		
Caucasian	37	75.5
African American	9	18.4
Native American	3	6.1
Cause of Brain Injury		
Motor vehicle crash	40	81.6
Fall	4	8.2
Assault	2	4.1
All-terrain vehicle accident	1	2.0
Pedestrian hit by car	2	4.1
Initial GCS Score		
13	2	4.1
14	19	38.7
15	28	57.1
When GCS Completed		
On scene of trauma	44	89.8
Upon arrival to the hospital	5	10.2
When ImPACT Conducted		
Within 24 hours of trauma	15	30.6
Within 48 hours of trauma	34	69.4
Head CT Scan Results		
Negative	31	63.3
Positive	18	36.7
Epidural hemorrhage	(3)	(8.2)
Subarachnoid hemorrhage	(5)	(13.6)
Intraparenchymal hemorrhage	(3)	(8.2)
Subdural hematoma	(7)	(19.1)
APOE Genotype		
2/3	8	16.3
3/3	21	42.9
2/4	1	2.0
3/4	16	32.7
4/4	3	6.1
APOEe4 Carriers		
2/3 or 3/3	29	59.2
2/4, 3/4, or 4/4	20	40.8

Other Study Variables

Demographic and current situation variables were also collected that were considered important variables to evaluate when measuring outcome. The number of days until follow-up was completed ranged from 28 to 74, with the mean number of days until follow-up was completed being 50.31 (SD = 11.50). GOS-E scores ranged from 6 to 8. The mean GOS-E score was 7.63 (SD = .57). DRS scores ranged from 0 to 3. The mean DRS score was 0.33 (SD = .72). As shown in Table 6, mean Verbal Memory scores increased from 62.78 (SD = 14.84) to 75.55 (SD = 10.42). Similarly, mean Visual Memory scores increased from 55.84 (SD = 16.18) to 70.61 (SD = 12.78). Mean Visual Processing Speed scores also increased from 29.42 (SD = 7.56) to 39.67 (SD = 6.49). Mean Reaction Time scores decreased from 0.89 (SD = .24) to 0.67 (SD = .16) and mean Impulse Control scores similarly dropped from 3.67 (SD = 2.46) to 1.71 (SD = 1.22). Cognitive Efficiency scores increased from .10 (SD = .17) to .29 (SD = .11). Total Symptom scores decreased from 11.78 (SD = 7.86) to 2.39 (SD = 1.96). Table 6 is a display of the descriptive statistics for the study's other variables.

Table 6. Descriptive Statistics for the Study Variables

Variable	Immediately after Injury			At Follow - Up		
	Range	*M*	*SD*	Range	*M*	*SD*
Age in years	19 to 64	36.02	14.49	--	--	--
Education in years	12 to 20	14.82	2.02	--	--	--
Days until follow up	28 to 74	50.31	11.50	--	--	--
Initial GCS Score	13 to 15	14.53	.58	--	--	--
GOS-E	--	--	--	6 to 8	7.63	.57
DRS	--	--	--	0 to 3	.33	.72
Verbal Memory	40 to 94	62.78	14.84	58 to 95	75.55	10.42
Visual Memory	28 to 86	55.84	10.18	45 to 93	70.61	12.78
Visual Processing	9.32 to 44.28	29.42	7.56	19.85 to 48.87	39.67	6.49
Reaction Time	.55 to 1.71	.89	.24	.41 to 1.09	.67	.16
Impulse Control	.00 to 11.00	3.67	2.46	.00 to 5.00	1.71	1.22
Total Symptom	.00 to 36.00	11.78	7.86	.00 to 6.00	2.39	1.96
Cognitive Efficiency	-.48 to .38	.10	.17	.02 to .54	.29	.11

Preliminary Screening Procedures

Univariate normality was assessed via the skewness and kurtosis indices of the variables. According to Kline (2005), skew indices (i.e. skewness statistic/SE) above three indicate non-normality. Kurtosis indices (i.e. kurtosis statistic/SE) between 10 and 20 also indicate non-normality. The findings, presented in Table 7, indicate that the GOS-E and the DRS measures were highly skewed. Initially, to correct for non-

normality, these two variables were transformed via a natural log function (per Tabachnick & Fidell, 2007). But the skewness and kurtosis indices of these transformed variables did not drop to acceptable levels. The histograms of these two variables were examined (see Appendix E) and revealed that responses to these variables were practically binary. Thus, the two variables were recoded into binary variables.

First, participants with a GOS-E score of seven or less were categorized into GOS-E Group A and participants with a GOS-E score of eight were categorized into GOS-E Group B. GOS-E Group A was defined as participants who scored a seven or less on the GOS-E and who had some level of physical or cognitive impairment, but were generally able to resume function as normal before the brain injury with minimal need for special arrangements or accommodations to complete activities of daily living. GOS-E Group B was defined as participants who scored an eight on the GOS-E and who had possible persistent, minor neurological or psychological deficits after the injury, but these were not disabling.

Second, participants who scored a one or more on the DRS were classified into DRS Group A and participants who scored a zero on the DRS were classified into DRS Group B. DRS Group A was defined as participants who scored a one or more on the DRS and who were minimally restricted in cognitive ability, independence or employability. DRS Group B was defined as participants who scored a zero on the DRS and who were not restricted in cognitive ability, independence or employability.

To detect for univariate outliers, the composites were standardized. Cases whose standardized values exceeded the absolute value of 3.29 were considered outliers (Tabachnick & Fidell, 2007). None of the cases had standardized values above this absolute value; therefore, none of the cases were deleted from the data set.

Table 7. Skewness and Kurtosis Statistics for the Study Variables

Variables	Immediately after Injury		At Follow-Up	
	Skewness	Kurtosis	Skewness	Kurtosis
Age in years	.67	-1.02	--	--
Education in years	.94	.43	--	--
Days until follow up	.00	-.76	--	--
Initial GCS score	-.79	-.33	--	--
GOS-E	--	--	-1.27	.72
DRS	--	--	2.58	6.74
Verbal Memory	.39	-.79	.04	-.84
Visual Memory	.11	-.81	-.23	-.83
Visual Processing Speed	-.08	.16	-.76	.67
Reaction Time	1.06	1.42	.60	-.31
Impulse Control	.74	.79	.86	.37
Total Symptom Score	.85	.54	.17	-1.17
Cognitive Efficiency	-.91	1.65	-.32	.19

Note. *SE* for skewness statistic = .34. *SE* for kurtosis statistic = .67.

Predictors of Functional Recovery

Because the GOS-E and DRS variables were recoded into binary variables, two logistic regression procedures were conducted to determine which variables would significantly predict the likelihood of recovery. The findings from these analyses are presented in Tables 8 through 21. Overall, neither initial GCS score, head CT findings, performance on individual ImPACT composite scores, nor genotype significantly predicted the likelihood that a participant would be classified into a higher outcome group (GOS-E Group A versus GOS-E Group B) using GOS-E as the outcome measurement. Similarly, neither initial GCS score, head CT findings, performance on individual ImPACT composite scores, nor genotype significantly predicted the likelihood that a participant would be classified into a higher outcome group (DRS Group A versus DRS Group B) using DRS as the outcome measurement.

Table 8. Logistic Regression Results for the GOS-E Model – with the ImPACT Verbal Memory Subscale

Variable	*B*	*SE*	Sig.	*OR*	95% CI for *OR*	
					Lower	Upper
Glasgow coma scale	.54	.57	.344	1.72	.56	5.30
Positive vs. negative head CT	1.15	.68	.089	3.17	.84	11.98
APOEe4 carriers vs. non	-.29	.68	.674	.75	.20	2.86
Verbal Memory (immediately after injury)	-.01	.02	.639	.99	.94	1.04

Note. *OR* = odds ratio. Overall model $\chi^2(4) = 4.88$, $p = .300$.

Table 9. Logistic Regression Results for the GOS-E Model – with the ImPACT Visual Memory Subscale

Variable	*B*	*SE*	Sig.	*OR*	95% CI for *OR*	
					Lower	Upper
Glasgow coma scale	.49	.57	.395	1.63	.53	5.10
Positive vs. negative head CT	1.14	.67	.090	3.11	.84	11.57
APOEe4 carriers vs. non	-.27	.67	.686	.76	.21	2.82
Visual Memory (immediately after injury)	-.02	.02	.387	.98	.94	1.02

Note. *OR* = odds ratio. Overall model $\chi^2(4) = 5.42$, $p = .247$.

Table 10. Logistic Regression Results for the GOS-E Model – with the ImPACT Visual Processing Speed Subscale

Variable	*B*	*SE*	Sig.	*OR*	95% CI for *OR*	
					Lower	Upper
Glasgow coma scale	.48	.57	.393	1.62	.54	4.92
Positive vs. negative head CT	1.07	.66	.107	2.92	.79	10.74
APOEe4 carriers vs. non	-.38	.69	.585	.69	.18	2.64
Visual Processing Speed (immediately after injury)	.04	.05	.365	1.04	.95	1.14

Note. *OR* = odds ratio. Overall model $\chi^2(4) = 5.50$, $p = .239$.

Table 11. Logistic Regression Results for the GOS-E Model – with the ImPACT Reaction Time Subscale

Variable	*B*	*SE*	Sig.	*OR*	95% CI for *OR*	
					Lower	Upper
Glasgow coma scale	.48	.56	.391	1.62	.54	4.88
Positive vs. negative head	1.04	.66	.119	2.81	.77	10.35
CT	-.36	.68	.601	.70	.18	2.66
APOEe4 carriers vs. non	-1.31	1.39	.343	.27	.02	4.06
Reaction Time (immediately after injury)						

Note. *OR* = odds ratio. Overall model $\chi^2(4) = 5.59$, $p = .232$.

Table 12. Logistic Regression Results for the GOS-E Model – with the ImPACT Impulse Control Subscale

Variable	*B*	*SE*	Sig.	*OR*	95% CI for *OR*	
					Lower	Upper
Glasgow coma scale	.51	.57	.373	1.66	.55	5.04
Positive vs. negative head CT	1.08	.66	.103	2.94	.80	10.75
APOEe4 carriers vs. non	-.14	.67	.832	.87	.24	3.21
Impulse Control (immediately after injury)	.07	.14	.604	1.07	.82	1.40

Note. *OR* = odds ratio. Overall model $\chi^2(4) = 4.93$, $p = .294$.

Table 13. Logistic Regression Results for the GOS-E Model – with the ImPACT Total Symptom Score Subscale

Variable	*B*	*SE*	Sig.	*OR*	95% CI for *OR*	
					Lower	Upper
Glasgow coma scale	.53	.56	.346	1.70	.56	5.13
Positive vs. negative head CT	1.00	.67	.132	2.73	.74	10.06
APOEe4 carriers vs. non	-.17	.66	.794	.84	.23	3.07
Total Symptoms (immediately after injury)	-.03	.04	.482	.97	.89	1.06

Note. *OR* = odds ratio. Overall model $\chi^2(4) = 5.14$, $p = .273$.

Table 14. Logistic Regression Results for the GOS-E Model – with the ImPACT Cognitive Efficiency

Variable	*B*	*SE*	Sig.	*OR*	95% CI for *OR*	
					Lower	Upper
Glasgow coma scale	.46	.56	.411	1.59	.53	4.80
Positive vs. negative head	1.16	.67	.083	3.20	.86	11.95
CT	-.32	.67	.640	.73	.20	2.73
APOEe4 carriers vs. non	2.12	1.93	.272	8.33	.19	365.23
Cognitive Efficiency (immediately after injury)						

Note. *OR* = odds ratio. Overall model $\chi^2(4) = 5.88$, $p = .209$.

Table 15. Logistic Regression Results for the DRS Model – with the ImPACT Verbal Memory Subscale

Variable	*B*	*SE*	Sig.	*OR*	95% CI for *OR*	
					Lower	Upper
Glasgow coma scale	-.43	.61	.479	.65	.20	2.15
Positive vs. negative head CT	-.84	.73	.250	.43	.10	1.80
APOEe4 carriers vs. non	-.24	.74	.742	.79	.19	3.33
Verbal Memory (immediately after injury)	-.00	.02	.880	1.00	.96	1.04

Note. *OR* = odds ratio. Overall model $\chi^2(4) = 2.58$, $p = .631$.

Table 16. Logistic Regression Results for the DRS Model – with the ImPACT Visual Memory Subscale

Variable	*B*	*SE*	Sig.	*OR*	95% CI for *OR*	
					Lower	Upper
Glasgow coma scale	-.41	.61	.501	.66	.20	2.20
Positive vs. negative head CT	-.81	.73	.268	.44	.11	1.87
APOEe4 carriers vs. non	-.07	.76	.931	.94	.21	4.19
Visual Memory (immediately after injury)	-.04	.05	.406	.96	.87	1.06

Note. *OR* = odds ratio. Overall model $\chi^2(4) = 3.26$, $p = .515$.

Table 17. Logistic Regression Results for the DRS Model – with the ImPACT Visual Processing Speed Subscale

Variable	*B*	*SE*	Sig.	*OR*	95% CI for *OR*	
					Lower	Upper
Glasgow coma scale	-.41	.61	.501	.66	.20	2.20
Positive vs. negative head CT	-.81	.73	.268	.44	.11	1.87
APOEe4 carriers vs. non	-.07	.76	.931	.94	.21	4.19
Visual Processing Speed (immediately after injury)	-.04	.05	.406	.96	.87	1.06

Note. *OR* = odds ratio. Overall model $\chi^2(4) = 3.26$, $p = .515$.

Table 18. Logistic Regression Results for the DRS Model – with the ImPACT Reaction Time Subscale

Variable	*B*	*SE*	Sig.	*OR*	95% CI for *OR*	
					Lower	Upper
Glasgow coma scale	-.43	.61	.486	.65	.20	2.17
Positive vs. negative head	-.75	.74	.310	.47	.11	2.01
CT	.01	.77	.988	1.01	.22	4.57
APOEe4 carriers vs. non	2.09	1.50	.165	8.08	.43	153.04
Reaction Time (immediately after injury)						

Note. *OR* = odds ratio. Overall model $\chi^2(4) = 4.61$, $p = .330$.

Table 19. Logistic Regression Results for the DRS Model – with the ImPACT Impulse Control Subscale

Variable	*B*	*SE*	Sig.	*OR*	95% CI for *OR*	
					Lower	Upper
Glasgow coma scale	-.43	.61	.479	.65	.20	2.15
Positive vs. negative head CT	-.86	.73	.239	.43	.10	1.77
APOEe4 carriers vs. non	-.18	.75	.813	.84	.19	3.67
Impulse Control (immediately after injury)	.05	.14	.726	1.05	.79	1.39

Note. *OR* = odds ratio. Overall model $\chi^2(4) = 2.68$, $p = .613$.

Table 20. Logistic Regression Results for the DRS Model – with the ImPACT Total Symptom Score Subscale

Variable	*B*	*SE*	Sig.	*OR*	95% CI for *OR*	
					Lower	Upper
Glasgow coma scale	-.53	.62	.390	.59	.18	1.97
Positive vs. negative head CT	-.72	.73	.329	.49	.12	2.06
APOEe4 carriers vs. non	-.31	.75	.682	.74	.17	3.18
Total Symptoms (immediately after injury)	.06	.05	.186	1.06	.97	1.16

Note. *OR* = odds ratio. Overall model $\chi^2(4) = 4.29$, $p = .368$.

Table 21. Logistic Regression Results for the DRS Model – with the ImPACT Cognitive Efficiency Subscale

Variable	*B*	*SE*	Sig.	*OR*	95% CI for *OR*	
					Lower	Upper
Glasgow coma scale	-.39	.61	.524	.68	.21	2.24
Positive vs. negative head	-.92	.74	.212	.40	.09	1.69
CT	-.11	.75	.883	.90	.20	3.92
APOEe4 carriers vs. non	-2.33	2.05	.256	.10	.00	5.40
Cognitive Efficiency (immediately after injury)						

Note. *OR* = odds ratio. Overall model $\chi^2(4) = 3.85$, $p = .427$.

The logistic regression findings presented in Table 22 indicate that age, gender, race, education, and cause of brain injury did not significantly predict the odds of being categorized into GOS-E Group A or GOS-E Group B. Further, the findings in Table 23 indicate that none of these demographic variables significantly predicted the likelihood that patients would be categorized into DRS Group A or DRS Group B.

Table 22. Logistic Regression Results for the Demographics and GOS-E Model

Variable	*B*	*SE*	Sig.	*OR*	95% CI for *OR*	
					Lower	Upper
Age	-.00	.02	.847	.99	.95	1.04
Race	-.57	.42	.729	.42	.26	1.09
Years of Education	-.62	.49	.561	.52	.31	1.32
Males vs. females	-.72	.64	.262	.49	.14	1.71
Motor vehicle crash vs. other	-1.09	.78	.160	.34	.07	1.54

Note. *OR* = odds ratio. Overall model $\chi^2(5) = 3.86$, $p = .277$.

Table 23. Logistic Regression Results for the Demographics and DRS Model

Variable	*B*	*SE*	Sig.	*OR*	95% CI for *OR*	
					Lower	Upper
Age	.00	.02	.988	1.00	.95	1.05
Race	.52	.63	.592	1.27	.52	2.97
Years of Education	.38	.49	.635	1.52	.81	3.43
Males vs. females	.55	.70	.434	1.74	.44	6.89
Motor vehicle crash vs. other	.61	.83	.459	1.85	.36	9.41

Note. *OR* = odds ratio. Overall model $\chi^2(5) = 1.33$, $p = .723$.

The Relationship between Genotype and Cognitive Recovery

Independent t-test procedures were conducted to determine whether cognitive recovery, as measured by performance on follow-up ImPACT subscales, would vary across participants who were carriers of an APOEe4 allele versus those participants who were noncarriers of the APOEe4 allele. The findings presented in Table 24 reveal that Reaction Time scores differed significantly across allele groups, $t(47) = 2.33$, $p = .024$. Participants who were noncarriers of an APOEe4 allele had significantly slower reaction times (*M = .71, SD = .16)* than participants who were APOEe4 carriers (*M = .61, SD = .15).* An adjustment was not completed at this time given the independent variable (Reaction Time) could not be divided into multiple subscales.

Table 24. Means, Standard Deviations, and Independent t-test Results for Genotype and Cognitive Recovery

	APOEe4 Noncarriers		APOEe4 Carriers			
Variables	*M*	*SD*	*M*	*SD*	*df*	*t*
Verbal Memory	77.34	10.11	72.95	10.57	47	1.47
Visual Memory	73.28	10.95	66.75	14.47	47	1.80
Visual Processing	38.54	6.99	41.30	5.44	47	-1.49
Reaction Time	.71	.16	.61	.15	47	2.33 *
Impulse Control	1.86	1.33	1.50	1.05	47	1.02
Total Symptom Score	2.31	2.07	2.50	1.54	47	-.35
Cognitive Efficiency	.28	.09	.29	.13	47	-.34

* $p < .05$. ** $p < .01$. *** $p < .001$.

Independent t-test procedures were conducted to determine whether cognitive recovery, as measured by performance on follow-up ImPACT subscales, would vary across participants who were homozygous APOEe4 carriers and all other APOE allele genotypes. The findings in Table 25 show that Impulse Control scores differed significantly across allele groups, $t(45) = 4.13$, p = .001. Participants who were homozygous APOEe4 carriers had significantly lower instances of impulsivity (*M = 1.00, SD = .00)* than participants with other genotype combinations (*M = 1.76, SD = 1.25).* Again, adjustments were not completed at this time given the independent variable (Impulse Control score) could not be divided into multiple subscales.

Table 25. Means, Standard Deviations, and Independent t-test Results for Homozygous APOEe4 Genotype and Cognitive Recovery

	Others		APOE 4/4			
Variables	*M*	*SD*	*M*	*SD*	*df*	*t*
Verbal memory	75.46	10.28	77.00	14.93	47	-.25
Visual memory	70.52	12.24	72.00	23.39	47	-.19
Speed	39.53	6.44	41.76	8.33	47	-.57
Reaction time	.67	.16	.67	.19	47	-.05
Impulse Control	1.76	1.25	1.00	.00	47	4.13 ***
Total symptoms	2.46	1.83	1.33	2.31	47	1.02
Cognitive index	.29	.11	.30	.16	47	-.17

* $p < .05$. ** $p < .01$. *** $p < .001$.

Other Factors Impacting Change in Cognitive Recovery

The following section evaluates whether any of the original dependent variables (initial GCS score, head CT results, or genotype) affected the individual composite scores of the ImPACT test across time. This is useful information in determining what, if any factors, most impact cognitive recovery at the follow-up period, as measured by the ImPACT's composite scores. Initial GCS score was used as the covariate because it has 3 possible categories (i.e. a score of 13, 14, or 15). Head CT results and genotype were used as between subject variables because each of these variables can only be grouped into 2 categories (i.e. positive or negative head CT; APOEe4 carrier or APOEe4 non-carrier). Therefore, each analysis uses a 2 x 2 x 2 mixed analysis of covariance (ANCOVA). Initial GCS score was not included as a between subjects variable because doing so would have decreased the study's statistical power due to the low sample size.

Change in Verbal Memory across Time at the Follow-Up Period

A 2 x 2 x 2 mixed ANCOVA was conducted to determine whether Verbal Memory scores changed significantly across time, and, if so, did a certain factor(s) have an impact on this change in scores. The covariate was initial GCS score. The within subjects variable was time (i.e., immediate vs. one month). The between subjects variables were head CT scan findings (i.e., positive vs. negative) and genotype (i.e., APOEe4 carriers vs. non-carriers). The findings in Table 26 indicate that the change in Verbal Memory scores varied across head CT scan findings, $F(1, 44) = 6.91$, $p = .012$. As shown in Figure 1, the improvement in Verbal Memory scores was steeper for participants whose head CT results were positive in comparison to participants whose head CT results were negative.

Figure 1. Verbal Memory Scores across Time as a Function of Head CT Scan Findings.

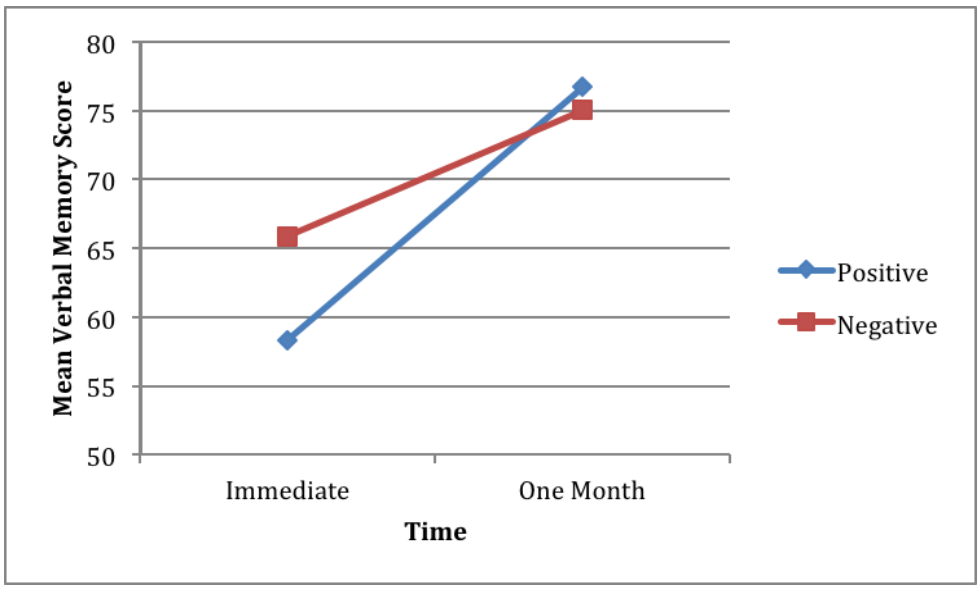

Table 26. Mixed ANCOVA Findings for Verbal Memory across Time

Source	*MS*	*df*	*F*
Between subjects			
Glasgow coma scale	168.71	1	.68
Head CT scan	6.12	1	.03
Genotype	669.22	1	2.70
Head scan x genotype	734.93	1	2.96
Error	248.19	44	
Within subjects			
Time	14.74	1	.33
Time x head scan	310.99	1	6.91 *
Time x genotype	54.08	1	1.20
Time x head x genotype	128.82	1	2.86
Error	45.00	44	

* $p < .05$. ** $p < .01$. *** $p < .001$.

Change in Visual Memory across Time at the Follow-Up Period

A 2 x 2 x 2 mixed ANCOVA was conducted to determine whether Visual Memory scores changed significantly across time and whether specific factors had an impact on this change in scores. The covariate was initial GCS. The within subjects variable was time (i.e., immediate vs. one month). The between subjects variables were head CT scan findings (i.e., positive vs. negative) and genotype (i.e., APOEe4 carriers vs. non-carriers). The findings in Table 27 show that the change in Visual Memory scores did not vary across any of the variables.

Table 27. Mixed ANCOVA Findings for Visual Memory across Time

Source	*MS*	*df*	*F*
Between subjects			
Glasgow coma scale	59.00	1	.17
Head CT scan	20.78	1	.06
Genotype	362.7	1	1.04
Head scan x genotype	758.41	1	2.18
Error	348.28	44	
Within subjects			
Time	4.51	1	.06
Time x head scan	121.54	1	1.59
Time x genotype	10.38	1	.14
Time x head x genotype	26.58	1	.35
Error	76.48	44	

$^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

Change in Visual Processing Speed across Time at the Follow-Up Period

A 2 x 2 x 2 mixed ANCOVA was conducted to determine whether Visual Processing Speed scores changed significantly across time and whether specific factors had an impact on this change in scores. The covariate was initial GCS. The within subjects variable was time (i.e., immediate vs. one month). The between subjects variables were head CT scan findings (i.e., positive vs. negative) and genotype (i.e., APOEe4 carriers vs. non-carriers). The findings in Table 28 reveal that the change in Visual Processing Speed scores did not vary across any of the variables.

Table 28. Mixed ANCOVA Findings for Verbal Processing Speed across Time

Source	*MS*	*df*	*F*
Between subjects			
Glasgow coma scale	.29	1	.00
Head CT scan	9.64	1	.12
Genotype	268.77	1	3.26
Head scan x genotype	27.89	1	.34
Error	82.48	44	
Within subjects			
Time	19.67	1	1.12
Time x head scan	36.38	1	2.06
Time x genotype	9.36	1	.53
Time x head x genotype	5.06	1	.29
Error	17.64	44	

$^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

Change in Reaction Time across Time at the Follow-Up Period

A 2 x 2 x 2 ANCOVA was conducted to determine whether Reaction Time scores changed significantly across time and whether specific factors had an impact on this change in scores. The covariate was initial GCS. The within subjects variable was time (i.e., immediate vs. one month). The between subjects variables were head CT scan findings (i.e., positive vs. negative) and genotype (i.e., APOEe4 carriers vs. non-carriers). The findings in Table 29 reveal that the change in Reaction Time scores did not vary across any of the variables.

Table 29. Mixed ANCOVA Findings for Reaction Time across Time

Source	*MS*	*df*	*F*
Between subjects			
Glasgow coma scale	.02	1	.31
Head CT scan	.02	1	.27
Genotype	.23	1	3.36
Head scan x genotype	.00	1	.04
Error	.07	44	
Within subjects			
Time	.00	1	.13
Time x head scan	.01	1	.89
Time x genotype	.00	1	.12
Time x head x genotype	.00	1	.28
Error	.02	44	

$^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

Change in Impulse Control across Time at the Follow-Up Period

A 2 x 2 x 2 mixed ANCOVA was conducted to determine whether Impulse Control scores changed significantly across time and whether specific factors had an impact on this change in scores. The covariate was initial GCS. The within subjects variable was time (i.e., immediate vs. one month). The between subjects variables were head CT scan findings (i.e., positive vs. negative) and genotype (i.e., APOEe4 carriers vs. non-carriers). The findings in Table 30 reveal that the change in Impulse Control scores did not vary across any of the variables.

Table 30. Mixed ANCOVA Findings for Impulse Control across Time

Source	*MS*	*df*	*F*
Between subjects			
Glasgow coma scale	.16	1	.03
Head CT scan	1.24	1	.25
Genotype	8.99	1	1.81
Head scan x genotype	5.40	1	1.09
Error	4.97	44	
Within subjects			
Time	.01	1	.00
Time x head scan	.15	1	.05
Time x genotype	2.51	1	.91
Time x head x genotype	8.87	1	3.22
Error	2.76	44	

* $p < .05$. ** $p < .01$. *** $p < .001$.

Change in Total Symptom score across Time at the Follow-Up Period

A 2 x 2 x 2 mixed ANCOVA was conducted to determine whether Total Symptom scores changed significantly across time and whether specific factors had an impact on this change in scores. The covariate was initial GCS. The within subjects variable was time (i.e., immediate vs. one month). The between subjects variables were head CT scan findings (i.e., positive vs. negative) and genotype (i.e., APOEe4 carriers vs. non-carriers). The findings in Table 31 reveal that the change in Total Symptom score did not vary across any of the variables.

Table 31. Mixed ANCOVA Findings for Total Symptom Score across Time

Source	*MS*	*df*	*F*
Between subjects			
Glasgow coma scale	2.15	1	.05
Head CT scan	58.01	1	1.42
Genotype	18.15	1	.45
Head scan x genotype	6.72	1	.17
Error	40.83	44	
Within subjects			
Time	1.20	1	.05
Time x head scan	70.80	1	2.68
Time x genotype	8.07	1	.31
Time x head x genotype	5.80	1	.22
Error	26.46	44	

$^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

Change in Cognitive Efficiency across Time at the Follow-Up Period

A 2 x 2 x 2 mixed ANCOVA was conducted to determine whether Cognitive Efficiency scores changed significantly across time and whether certain factors had an impact on this change in scores. The covariate was initial GCS. The within subjects variable was time (i.e., immediate vs. one month). The between subjects variables were head CT scan findings (i.e., positive vs. negative) and genotype (i.e., APOEe4 carriers vs non-carriers). The findings in Table 32 indicate that the change in Cognitive Efficiency scores did not vary across any of the variables.

Table 32. Mixed ANCOVA Findings for Cognitive Efficiency across Time

Source	*MS*	*df*	*F*
Between subjects			
Glasgow coma scale	.02	1	.58
Head CT scan	.02	1	.41
Genotype	.01	1	.29
Head scan x genotype	.00	1	.05
Error	.04	44	
Within subjects			
Time	.00	1	.03
Time x head scan	.00	1	.05
Time x genotype	.01	1	1.02
Time x head x genotype	.01	1	1.14
Error	.01	44	

$^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

CHAPTER IV

DISCUSSION

The purpose of this study was to investigate which initial factors, initial GCS score, head CT results, performance on cognitive testing, or genotype, were most predictive of one month outcome following mTBI. The hypothesis that performance on ImPACT cognitive testing would most effectively predict 1-month GOS-E was not supported. Moreover, results revealed no significant relationship between the ability of any of the dependent variables to predict outcome as measured by the GOS-E or DRS. This study also aimed to describe whether genotype influenced progression or rate of recovery. The hypothesis that carriers of the APOEe4 allele would show a relatively weaker recovery from mTBI as compared to noncarriers of APOEe4 was not supported as results failed to show a significant relationship between genotype and overall outcome.

The Relationship between Initial GCS Score, Head CT Results and Cognitive Ability to Outcome

The finding of no significant predictive value of initial GCS score, head CT results, performance on initial cognitive testing, and genotype are consistent with some aspects of findings from previous studies, but does not reflect the overall trend in the literature.

As previously noted, the physiological changes associated with mTBI may be readily apparent as cognitive and/or functional changes, but not necessarily as apparent in broader measures, such as GCS score or head CT neuroimaging results. Within the mTBI population, few researchers have been able to show the effectiveness of initial GCS as a means to predict either short term or long term outcome, based on return to work (van der Naalt et al., 1999) or GOS / GOS-E (McCullagh et al., 2001, Fischer & Mathieson, 2001). Although the GCS has been used to predict outcome from TBI at all severity levels, fewer researchers have shown it to be as effective in the mTBI population as compared to the moderate and severe populations (Shores et al., 2008). Indeed, many researchers report combining initial GCS score with other variables, namely length of PTA, as a more appropriate method of predicting outcome within the mTBI population (Drake et al., 2006; Mena et al., 2011). Hiekkanen and colleagues (2009) reported that when initial GCS score was combined with APOE genotype, these two variables were not found to be predictive of follow up (1 year) GOS-E. Similarly, the results of this current study failed to demonstrate a statistically significant relationship between initial GCS score in predicting outcome after mTBI, even when grouped with the other dependent variables.

People with mTBI who are treated in a medical center almost always receive a head CT upon arrival. This may provide very useful information in determining the presence of life-threatening situations (such as active bleeding in the brain), but the information derived from the head CT in predicting prognosis after mTBI may be less

helpful (Brown et al., 2007). Indeed, some have argued that within the mTBI population, routine head CT neuroimaging does not lead to necessary intervention, unless neurologic changes are noted clinically; therefore, has nominal use as a predictor of prognosis (Metting et al., 2009; Servadei, Teasdale & Merry, 2001). The results of this current study found no significant predictive value of head CT results on short term outcome.

Initial cognitive ability has been used as a prognostic indicator from mTBI, but there is limited evidence to support this (Comerford, Geffen, May, Medland & Geffen, 2002; Delaney et al., 2005). Numerous studies supporting cognitive ability as a predictor of outcome have been conducted within the moderate-to-severe TBI populations (Boake et al., 2001; Scheibel, Levin, & Clifton, 1998; Sherer et al., 2002); however the studies set in the mTBI population are more conflicting and few have linked acute cognitive ability with long-term functional recovery. This study failed to show that performance on acute cognitive testing was statistically significant in predicting outcome after mTBI. Others have reported similar results (Belanger et al., 2005; Ponsford et al., 2000; Stulemeijer et al., 2007).

The discrepancy in the findings from this study as compared to some of the others in the literature may related to the smaller sample sizes in this and some of the previous studies (thus providing limited statistical power); different time periods used to measure outcome (ranging from one month to several years after injury); and different measures used to determine outcome (i.e. GOS, GOS-E, DRS, return to work) which make it difficult to compare studies.

The Relationship between APOEe4 and Outcome

Results of this study failed to demonstrate a significant interaction between participants who were carriers of an APOEe4 allele and overall outcome. Others have shown no clear relationship between APOEe4 and outcome (as measured by the GOS or GOS-E), but many of these studies have been within the moderate to severe TBI population (Chamelian et al., 2004; Millar et al., 2003; Nathoo et al., 2003; Ponsford et al., 2007; Teasdale et al., 2005). Other studies have grouped participants with mTBI with participants with moderate to severe TBI and have demonstrated APOEe4 allele status to be associated with poorer outcome and slower recovery rates as measured by either the GOS or GOS-E (Alexander et al., 2007; Chiang et al., 2003; Friedman et al., 1999; Jiang et al., 2007; Lichtman et al., 2000; Teasadale et al., 1997). This study serves as a counter to previous studies which have demonstrated support for an association between APOE genotype and overall functional outcome, though it does demonstrate a relationship between APOE genotype and certain aspects of cognitive ability.

Few studies have evaluated the effects of APOEe4 status and cognitive function as this study did. Rather than looking at a global, summed score of cognitive function, this study looked at various subcategories of cognitive function. This study found that Reaction Time scores differed significantly across allele groups and that participants who were noncarriers of an APOEe4 allele had significantly ($p < .05$) slower reaction times ($M = .61$, $SD = .16$) than participants who were APOEe4 carriers ($M = .61$, $SD = .15$) at the follow-up period. Han and associates (2007) reported that participants with mild to

moderate TBI who were carriers of the APOEe4 performed significantly or marginally better on select neuropsychological measures (WAIS-III Digit Symbol Age subscale, D-KEFS Color-Word Interference Inhibition/Switching subscale, and CVLT-II List A Trials 1-5 Total Learning T score) than noncarriers of an APOEe4, but reaction time was not one of these measures.

Independent t-test procedures revealed that Impulsivity scores at the follow up period differed significantly ($p < .001$) across groups when APOEe4 homozygous carriers were compared to all other participants. Participants who were homozygous APOEe4 carriers had significantly lower instances of impulsivity than participants with other genotype combinations. This relationship has to date not been reported in the literature. Others have shown an APOEe4 dose-dependent relationship between other aspects of outcome, for example faster rate of decline in short term memory function in patients with mild cognitive impairment (Caselli, et al. 2007), though none have specifically observed a relationship between homozygous APOEe4 carriers and impulsivity. Others have demonstrated no significant differences regarding an APOE4 allele dose effect on GOS-E (Ponsford et al., 2011). Ponsford and colleagues (2011) reported that to most effectively study the effects of homozygous APOEe4 carriers a sample size in excess of 1000 may be required given the relatively small incidence of homozygous carriers in the human population (1-2%). Reports like this should be considered in follow up studies that may attempt to replicate the findings of this study.

Although others have not demonstrated a relationship between APOEe4 carrier status and impulsivity, APOEe4 status has been linked with other aspects of cognitive ability, leading to the idea that perhaps there are possible subgroups of people with TBI in which APOEe4 carrier status may influence recovery. For example, Farlow and associates (2004) reported that participants who were APOEe4 carriers had significantly worse memory performance than APOEe4 noncarrier participants. Similarly, Crawford and colleagues (2002) demonstrated that memory performance on the California Verbal Learning Test was worse for carriers of APOEe4 allele, than those who were not carriers. Groups in this study did not differ on demographic variables or measures of executive functioning. Interestingly, Han et al. (2007) suggested a possible compensatory mechanism underlying cognitive function for APOEe4 carriers, finding improved performance on neurocognitive measures of memory and executive function one month after injury.

Disagreement between these previous studies and the present findings of this study may again be related to sample size and associated power limitations of the previous studies. Additionally, some have argued that the potentially detrimental effects of the APOEe4 allele may only become more apparent over longer periods of time (Alexander et al., 2009; Ponsford et al., 2011). This idea was also supported in a meta-analysis of studies conducted up to 2007 by Zhou and associates (2008). Still, perhaps the most important reason for disparity between findings in this study and previous ones

in the literature may be that many of the previous studies were conducted within the moderate to severe TBI population, not within the mTBI one as was this one.

The mechanism of how APOEe4 relates to outcome after TBI is not well understood. Shadli and colleagues (2011) note that studies targeting the APOEe4 allele have found it to be responsible for poorer overall recovery in both the animal and human research models, but this has not been consistently replicated in investigations targeting neurocognitive outcome specifically. A possible explanation could be in how a carrier of an APOEe4 allele responds to severity of injury, especially at the acute stages of injury, with much of the literature supporting the view that the APOEe4 allele adversely affects outcome after TBI during the first 6 months after injury (Hiekkanen et al., 2007; Liberman et al., 2002). Its effects over a much longer period of time are less clear. For example, the damaging effects of the APOEe4 allele may only be evident in cases where the primary injury is very severe and neuropyschologically may only be noted in the later stages of life (Isoiemi et al., 2006). Mechanisms involving ApoE in response to acute TBI include the deposition of the amyloid β protein, maintenance of cytoskeletal integrity, modulation of excitotoxic responses, and protection from oxidative stress. As for the long term role of ApoE after brain injury, the literature suggests it is involved in the delivery of cholesterol to the neurons required for neurite outgrowth and synaptic capabilities, clearance of degeneration products, microglial activation and maintenance of the cholinergic system (as cited in Hiekkanen et al., 2007). Alexander and colleagues (2007) postulated that the long term effects of APOEe4 are likely more detrimental than

the short term effects given that the full extent of neuronal damage, difficulty with neuronal repair, and subsequent reperfusion complications may not be apparent until 6 months after injury.

Interestingly, research on younger participants has shown that the APOEe4 allele may be associated with neuroprotective abilities (Brictova & Kozak, 2008). Willemse-van Son et al. (2008) studied the adolescent population and reported improved outcomes between 12-36 months on the GOS for participants who were APOEe4 carriers as compared to participants who were noncarriers. Additionally, some have questioned if there is an APOEe4 and environment interaction (Farrer et al., 1997; Shadli et al., 2011; Tzourio et al., 2008). Taken collectively, the recent findings suggest the need for caution in accepting of the hypothesis that APOE genotype is a factor in outcome after TBI.

Clinical Implications

The implications of these results are important, as they, like the findings of many other studies (Alexandre, et al., 1983; Bishara, et al., 1992; Ellenberg, Levin, & Saydari, 1996) suggest that the dominating role of initial GCS score as a means to predict outcome from mTBI should be questioned. At the time the GCS was introduced in the literature (1974), there were no other standardized measures for evaluating level of consciousness.

The GCS provided first responders and clinicians alike with a mechanism for quickly evaluating the severity of a brain injury and a means to communicate this information effectively to other members of the healthcare team. The GCS gained

popularity because it was an easy to use and cost-effective way to standardize the initial evaluation of TBI. Unfortunately, there was little evidence at the time of the inception to support the reliability or validity of this measure before it became commonplace practice, with much of the literature supporting its effectiveness for measuring TBI severity being conducted years after the GCS had become incorporated into a routine standard of care (McNett, 2007). The ability of the GCS to predict outcome after TBI has been repeatedly demonstrated in the literature (Asikainen, Kaste & Sarna (1998); Husson et al. (2010); Petroni et al. (2010); Wardlow, Easton & Statham (2002), however, many of these studies were completed with more severe populations of TBI and the application of their results to the mTBI population are likely not entirely appropriate. Others have reported that the predictive ability of the GCS is substantial only with very high or very low initial GCS scores (Changaris et al. 1987; Pal, Brown & Fleiszer, 1989; Young, 1981). Still, few of these studies have demonstrated that the GCS should be the sole variable when predicting outcome for people with TBI, with many suggesting that combining GCS with other variables, such as age and pupillary response, increases the accuracy of predicting outcome (Balestreri et al., 2004; Diringer & Edwards, 1997; Choi et al., 1983; Narayan et al., 1981; Zafronte et al., 1996). Taken collectively, previous studies documented in the literature as well as results from this current study suggest at least using caution when using GCS as a primary predictor of outcome from TBI.

There is a gap in the evidenced based knowledge of the mTBI population as to what initial factor is most predictive of outcome after injury. Because of this, many

people with mTBI may not be receiving appropriate treatment plans, suitable medical follow up, or rehabilitative services after their injury. Moreover, medical professionals may have difficulty determining which patients are most appropriate for treatment and which treatment options would be most effective. Unfortunately, clinicians have minimal objective and individualized prognostic data to provide patients and family members. This lack of knowledge and information could possibly lead to the development of inappropriate treatment plans or discharge recommendations, ultimately contributing to increased anxiety and confusion over the prognosis for recovery. Without an accurate means of predicting recovery, we are not able to provide appropriate and cost-effective treatment services to our patients. Because of the limitations of neuroimaging and neurobehavioral assessments in determining accurate diagnosis and prognosis from TBI, researchers are increasingly looking to a more objective, individualized means of providing additional diagnostic and prognostic information. Performance on acute cognitive testing is one relatively simple tool clinicians can incorporate into their intervention for people with TBI, especially mTBI. Based on the results of this study, performance on acute cognitive testing was not significantly predictive of one month outcome; however, of the four variables used it was the one that most neared significance. Others have also demonstrated the importance of using acute cognitive performance as a measure of prognosis from mTBI (Comerford, Geffen, May, Medland & Geffen, 2002; Delaney et al., 2005).

A measure of global cognitive function may not be the most specific means of assessing recovery from mTBI. Some have identified certain aspects of cognition that may be more predictive of recovery than others, thereby identifying specific subgroups within the mTBI population who may be at risk for poorer outcome after mTBI. For example, Delaney and colleagues (2005) revealed that difficulties noted in the Emergency Department in the areas of concentration, memory and performing simple math problems may be indicative of poorer outcome following mTBI. Similarly, Peterson et al. (2009) showed that patients with mTBI admitted to the Emergency Department do demonstrate deficits on ImPACT testing, but this group did not report if this could be used as a means of predicting functional outcome. Hanlon and colleagues demonstrated that memory function assessed at 3 months post-mTBI were significantly associated with employment 1-year post-injury. Sigurdardottier, Andelic, Roe, & Schanke (2009) reported that cognitive performance in the areas of Verbal/Reasoning, Visual/Perception, and Memory/Speed at 3 months after mTBI were near-significant predictors of 1-year outcome (as measured by the GOS).

Despite the strong evidence that physical, cognitive and emotional impairments can be longstanding after mTBI, some medical professionals continue to equate the chronic deficits reported by patients with mTBI with malingering based on the notion that such mild injuries should not result in any permanent impairments (Tellier et al., 1999). While such patients likely do exist, it is unreasonable to deny that some patients with mTBI do have lingering deficits. The failure to recognize the presence of these deficits

would be a terrible disservice to this patient population. Hence there is a need for supplementary tests to enable early prediction of recovery from mTBI. Initial and / or follow up cognitive testing may be one way to offer objective and individualized data to confirm or refute continued patient subjective complaints.

In addition to cognitive functions, there may be other ways to identify subgroups within the mTBI population who remain at an increased risk for poorer outcome after injury. For example, Tellier et al. (2009) were not able to distinguish subgroups of mTBI based on initial GCS score, but did note partial support for subgroups of mTBI when duration of PTA was used as a measure of severity. Individuals who experienced PTA for greater than 20 minutes were more likely to have intracranial abnormalities on CT scanning and to report continued symptoms, namely disinhibition, at 6 months post-injury. Typically, head CT scans do not readily detect the neuroanatomical changes associated with mTBI. However, a handful of people with mTBI do have positive findings on head CT imaging. Changes associated with head CT findings may be another way to categorize individuals with mTBI based on expected prognosis. Kurca, Sivak & Kucera (2006) and Iverson (2006) have reported that positive findings on head CT imaging have been linked to poorer outcome for people with a GCS of 13, 14, of 15. Williams and associates (1990) argued that positive findings on head CT should automatically place the person into the moderate TBI severity level, rather than the mTBI one. Moreover, documentation of positive CT findings provides a certain amount of credibility to the complaints voiced by many patients with mTBI. This may ensure

proper medical management and rehabilitation services for this group of patients who often are overlooked or met with cynicism.

Interestingly, this study demonstrated that participants who had a positive finding on head CT imaging had a steeper recovery at one month follow up on verbal memory scores, as compared to participants who had negative head CT results. No significant relationship was noted between the other variables (initial GCS score or APOE genotype) in increasing verbal memory scores. Perhaps these participants had more severe injuries in general, including more severe cognitive impairments at the time of initial injury. If this was the case, these participants would have more likely to be referred on for rehabilitative services during the follow up periods. This more intense intervention may have caused an increase in verbal memory performance by either direct treatment targeting this area of cognition, or by teaching the person compensatory strategies to aid in managing this cognitive function. Still, this study lacks information on whether or not this group of participants received neurorehabilitation services during the interim follow up period or not. To date, no other studies support this finding and results should be replicated prior to incorporating this into clinical management. Of note, this study provides some support for the findings of Noe and colleagues (2010) that APOE genotype did not influence efficacy of verbal memory rehabilitation for people with TBI.

A combination of clinical (cognitive ability) and imaging (results of head CT scans) variables seems to be an alternate and acceptable approach to predict outcome for

people with mTBI. Boake & High (1996) reported that the use of combining variables like these would likely be a more accurate reflection of the multifactorial pathophysiology associated with mTBI.

Limitations of the Study

There are several limitations of this study which warrant discussion. One major limitation of this study is the relatively small sample size. 12 participants were withdrawn from the study given that they were unable to complete the follow-up ImPACT test, despite having completed all other study conditions. For all of these 12 participants, ImPACT testing could not be completed due to issues with internet connectivity. Ultimately, this decreased the sample size from 61 to 49. A larger sample size may have enabled investigators to divide participants into more refined groups (i.e. those with positive or negative loss of consciousness, or isolate various mechanisms of injury) which may help to better elucidate why some participants did better than others at the follow-up session.

Moreover, the sample size may have been unintentionally biased to only encompass mTBI which was more severe by nature. For example, only people with mTBI who were admitted to the hospital were recruited for this study. People with mTBI who never sought medical attention or who were only seen in the Emergency Department, but not admitted to the hospital, were not recruited. The ones admitted to the hospital may represent a slightly more impaired, rather physically and/or cognitively,

subgroup of people with mTBI, which may have impacted the results of this study. Furthermore, not all participants were assessed at exactly the same post-injury time point, although all participants completed initial testing within 48 hours after injury.

This study followed similar methods to Collie and colleagues (2004) who suggested that grouped assessments by repeated measures analysis of variance would be most effective for testing for cognitive differences between APOEe4 carriers and noncarriers. Grouping participants in a slightly different way, as Sundstrom and colleagues (2004) did, yielded slightly different results. These investigators too reported a lack of association between APOEe4 and poorer functional outcome when grouped by APOEe4 carriers and APOEe4 noncarriers. However, when the researchers compared cognitive performance as within-person comparisons, they found that participants who were APOEe4 carriers declined significantly in three of the neurocognitive measures, divided attention, recognition of faces, and recall of actions. Conversely, this study found that APOEe4 carriers performed better than APOEe4 noncarriers in the domains or Reaction Time and Impulsivity.

Another limitation of this study is the lack of controlling for medications used during the participant's hospitalization at the time of cognitive assessment. Many of the participants had confounding orthopedic injuries in addition to their brain injury for which they were on various types of pain medications, including acetaminophen (Tylenol), oxycodone (Percocet), hydrocodone (Vicodin), morphine (MS Contin), ondansetron (Zofran), haloperidol (Haldol), fentanyl (Fentora), and/or lorazepam

(Ativan). Use of these types of medications have been shown to globally impact cognitive function, as well as negatively impact cognitive abilities such as short term memory and attention (Kamboj et al., 2005; McMorn, Schoedel & Sellers, 2011; Woodward et al., 2007). Some participants did not have pain that was well controlled and required frequent rest breaks during cognitive testing, which may have impacted their performance on the ImPACT evaluation. Fatigue has been shown to significantly increase after mTBI (Sundstrom et al., 2007) and oftentimes can be increased due to the use of pain medications. Additionally, pain may have influenced effort on ImPACT testing, though this was not objectively measured. Effort testing is typically not a routine part of acute TBI assessment (Luethcke et al., 2010); therefore, was not included in this study. In addition to pain medications, other medications which may have influenced cognitive abilities or overall medical status were not controlled for or documented. Anti-inflammatory medications and sleep-aid medications have both been demonstrated to affect overall medical and mental status and may have influenced results of this study (McMorn, Schoedel & Sellers, 2011). More thorough documentation of medications used while in house should be included in any follow-up studies studying cognitive abilities in the mTBI population.

Similarly to pain, post-traumatic stress disorder has also been reported to affect outcome after mTBI (Bryant, 2011) and may have influenced the data set of this study, especially at the follow up session. Others have reported that these two patient populations likely overlap in some cases, making it difficult to distinguish symptoms

associated with one or the other (Vasterling, Verfaellie & Sullivan, 2009). Participants in this study were not screened for post-traumatic stress disorder at either time of data collection.

Despite these limitations, the results of this study have important clinical implications and provide further avenues of areas of future research.

Future Directions

Longitudinal studies that track recovery over longer periods would be exceedingly valuable in determining the eventual outcome of people with mTBI. Given the discrepancies noted in this study regarding which prognostic indicators are most predictive of outcome following mTBI, further research in this area should be conducted with larger sample sizes over a longer period of time.

Various complaints of the physical and cognitive symptoms reported in the Total Symptom Score of the ImPACT may have greatly impacted performance on this test, and may have ultimately contributed to outcome. However given the small sample size of this study, participant subgroups related to type of symptom complaints were not able to be statistically measured with sufficient power. Future researchers should take this into account when designing upcoming studies so that they may better understand the relationship between initial symptom complaints and overall outcome. This may provide valuable information in understanding at what time point during recovery the impact of the APOEe4 allele may be most apparent or most detrimental.

The variability in outcome after mTBI seems to be only partly explained by prognostic factors, such as age and severity of initial injury. There are likely other factors that may influence the brain susceptibility to injury and its subsequent capacity for repair and regeneration. For example, some studies have demonstrated a negative effect of APOEe4 carriers on long term outcome that was more pronounced in females than in males (Ponsford et al., 2011; Raber et al., 1998); whereas another group demonstrated APOEe4 status was more pronounced in males than females (Ost et al., 2008). Others have demonstrated a negative effect of the APOEe4 allele on outcome that was most pronounced in younger aged participants (Teasdale, et al., 2005) or as related to ethnicity (Farrer et al., 1997) or race (Nathoo et al., 2003). These confirm the importance of controlling for other variables which may influence outcome, variables which may be used to make statements about probable prognosis.

Associations between APOEe4 carrier status and impulsivity have not been reported in other populations, such as ADHD (Lesch et al., 2008), though this area has not been extensively researched and this may be an avenue for additional studies. Similarly, associations between APOEe4 carrier status and reaction time have not only not been demonstrated previously within the TBI population, but have yet to be demonstrated in other populations as well.

Future studies should aim to gain a better understanding of the exact role of ApoE within the neuronal metabolism and how this is affected after injury to the brain. Studies targeting the role of the ApoE protein as well as the APOE gene may provide some

clarification on the conflicting results within this area of interest. Understanding how ApoE responds to CNS injury, especially how it responds in isoform specific ways would allow clinicians to better understand what, if any, treatment options may be best for their patients with TBI. This may be helpful in developing or guiding treatments such as pharmacological agents used to block the harmful effects of the APOEe4 allele (Chiang et al., 2003; Laskowitz et al., 2010), or to augment neuronal sprouting (Teasdale et al., 2005). More information is needed on the role of APOE in cognition. Replication of this study using a control group of participants of the same age, but without brain injury may further the knowledge base within this area. Additionally, other genes, or areas of genes that may affect other genes, may influence the role of ApoE or APOE gene expression. For example, polymorphism within the promoter region of APOE may increase the expression of ApoE and thus exacerbate the response to TBI (Hiekkanen et al., 2007), but little is known about the extent of this relationship.

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APPENDIX A

GLASGOW COMA SCALE SCORING AND SEVERITY (TEASDALE & JENNETT, 1974)

The following details the 3 areas of response scored for the GCS. Each patient is given a score in each of the three response areas, based on the description of the patient's best response in each category. GCS score is derived from summing the 3 areas of response. Corresponding severity levels are provided below based on total GCS score.

Area of Response	Description of Finding	Score
EYES OPEN	Spontaneous	4
	To speech	3
	To pain	2
	None	1
BEST VERBAL RESPONSE	Oriented	5
	Confused	4
	Inappropriate	3
	Incomprehensible	2
	None	1
BEST MOTOR RESPONSE	Obeys commands	6
	Localizes to pain	5
	Withdraws from pain	4
	Flexion to pain	3
	Extension to pain	2
	None	1

Severity Level of TBI	GCS Score
Mild	13 - 15
Moderate	9 – 12
Severe	3 – 8

APPENDIX B

TOTAL SYMPTOM SCORE FROM THE IMPACT

Symptom	None	Mild		Moderate		Severe	
Headache	0	1	2	3	4	5	6
Nausea	0	1	2	3	4	5	6
Vomiting	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
Numbness or tingling	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Balance problems	0	1	2	3	4	5	6
Sleeping less than usual	0	1	2	3	4	5	6
Sensitivity to light	0	1	2	3	4	5	6
Sensitivity to noise	0	1	2	3	4	5	6
Feeling slowed down	0	1	2	3	4	5	6
Feeling as if ‘in a fog’	0	1	2	3	4	5	6
Difficulty concentrating	0	1	2	3	4	5	6
Difficulty remembering	0	1	2	3	4	5	6
Trouble falling asleep	0	1	2	3	4	5	6
More emotional than usual	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6
Nervousness	0	1	2	3	4	5	6
Visual problems (blurry/double)	0	1	2	3	4	5	6
Balance issues	0	1	2	3	4	5	6
Fatigue	0	1	2	3	4	5	6
Sleeping more than usual	0	1	2	3	4	5	6

APPENDIX C

STRUCTURED INTERVIEW FOR THE GLASGOW OUTCOME SCALE – EXTENDED (WILSON, PETTIGREW & TEASDALE, 1997)

CONCIOUSNESS:

1. Is the head-injured person able to obey simple commands or say any words?

___ Yes ____ No (If no, Vegetative State)

INDEPENDENCE AT HOME:

2a. Is the assistance of another person at home essential every day for some activities of daily living?

___ Yes ____ No (If no, Vegetative State)
(If no, go to Question 3)

2b. Do they need frequent help of someone to be around at home most of the time?

____ Yes (Lower Severe Disability) ____ No (Upper Severe Disability)

2c. Was the patient independent at home before the injury?

____ Yes ____ No

INDEPENDENCE OUTSIDE THE HOME:

3a. Are they able to shop without assistance?

____ Yes ____ No (If no, Upper Severe Disability)

3b. Were they able to shop without assistance before the injury?

____ Yes ____ No

4a. Are they able to travel locally without assistance?

____ Yes ____ No (If no, Upper Severe Disability)

4b. Were they able to travel locally without assistance before the injury?

____ Yes ____ No

WORK:

5a. Are they currently able to work (or look after others at home) to their previous capacity?

____ Yes (If yes, go to Question 6) ____ No

5b. How restricted are they?

a) Reduced work capacity? ____ Yes (If yes, Upper Moderate (Disability)

b) Able to work only in a sheltered workshop or non-competitive job or currently unable to work? ____ Yes (If yes, Lower Moderate Disability)

5c. Does the level of restriction represent a change in respect to the pre-trauma situation?

____ Yes ____ No

SOCIAL AND LEISURE ACTIVITES:

6a. Are they able to resume regular social and leisure activities outside the home?

____ Yes (If yes, got to 7) ____ No

6b. What is the extent of restriction on their social and leisure activities?

a) Participate a bit less: at least half as often as before the injury
____ Yes (Lower Good Recovery)

b) Participate much less: less than half as often
____ Yes (Upper Moderate Disability)

c) Unable to participate: rarely, if ever, take part
____ Yes (Lower Moderate Disability)

6c. Does the extent of restriction in regular social and leisure activities outside the home represent a change in respect to pre-trauma?

____ Yes ____ No

FAMILY AND FRIENDSHIPS:

7a. Has there been family or friendship disruption due to psychological problems?

____ Yes ____ No (If no, got to Question 8)

7b. What has been the extent of disruption or strain?

a) Occasional – less than weekly ____ Yes (Lower Good Recovery)

b) Frequent – once a week or more, but not tolerable
____ Yes (Upper Moderate Disability)

c) Constant – daily and intolerable ____ Yes (Lower Moderate Disability)

7c. Does the level of disruption or strain represent a change in respect to pre-trauma situation?

____ Yes ____ No

RETURN TO NORMAL LIFE:

8a. Are there any other current problems relating to the injury which affect daily life?

____ Yes (Lower Good Recovery) ____ No (Upper Good Recovery)

8b. If similar problems were present before the injury, have these become markedly worse?

____ Yes ____ No

9. What is the most important factor in outcome to you?

a) Effects of head injury
b) Effects of illness or injury to another part of the body
c) A mixture of these

APPENDIX D

DISABILITY RATING SCALE OBSERVATION FORM (RAPPAPORT ET AL., 1982)

A. <u>EYE OPENING</u>

- **a. 0 = SPONTANEOUS** : eyes open with sleep/wake rhythms indicating active arousal mechanisms, does not assume awareness
- **b. 1 = TO SPEECH** : to speech and / or sensory stimulation; a response to any verbal approach, whether spoken or shouted, no necessarily the command to open the eyes; response to touch, mild pressure
- **c. 2 = TO PAIN** : tested by a painful stimulus
- **d. 3 = NONE** : no eye opening even to painful stimulation

B. <u>COMMUNICATION ABILITY</u>

- **a. 0 = ORIENTED** : implies awareness of self and the environment; patient able to tell you a) who he is; b) where he is; c) why he is there; d) year; e) season; f) month; g) day; h) time of day
- **b. 1 = CONFUSED** : attention can be held and the patient responds to questions but responses are delayed and / or indicate varying degrees of disorientation and confusion
- **c. 2 = INAPPROPRIATE** : intelligible articulation but speech is used only in an exclamatory or random way (such as shouting and swearing); no sustained communication exchange is possible
- **d. 3 = INCOMPREHENSIBLE** : moaning, groaning or sounds without recognizable words, no consistent communication signs
- **e. 4 = NONE** : no sounds or communication signs from the patient

C. <u>MOTOR RESPONSE</u>

- **a. 0 = OBEYING** : obeying command to move finger on best side; if no response or not suitable try another command such as “move lips”, “blink eyes”; do not include grasp or other reflex responses
- **b. 1 = LOCALIZING** : a painful stimulus at more than one site causes a limb to move (even slightly) in an attempt to remove it; it is a deliberate motor act to move away from or remove the source of noxious stimulation; if there is doubt as to whether withdraw or localization has occurred after 3 or 4 painful stimulation, rate as localization

c. **2 = WITHDRAWING** : any generalized movement away from a noxious stimulus that is more than a simple reflex response
d. **3 = FLEXING** : painful stimulation results in either flexion at the elbow, rapid withdrawl with abduction of the shoulder or a slow withdrawl with adduction of the shoulder; if there is confusion between flexing and withdrawing, then use pinprick on hands
e. **4 = EXTENDING** : painful stimulation results in extension of the limb
f. **5 = NONE** : no response can be elicited; usually associated with hypotonia; exclude spinal transection as an explanation of lack of response; be satisfied that an adequate stimulus has been applied

D. <u>FEEDING (COGNITIVE ABILITY ONLY)</u>

a. **0 = COMPLETE** : continuously shows awareness that he knows how to feed and can convey unambiguous information that he knows when this activity should occur
b. **1 = PARTIAL** : intermittently shows awareness that he knows how to feed and/or can intermittently convey reasonably clear information that he knows when the activity should occur
c. **2 = MINIMAL** : shows questionable or infrequent awareness that he knows in a primitive way how to feed and/or show infrequently by certain signs, sounds, or activities that he is vaguely aware when the activity should occur
d. **3 = NONE** : show virtually no awareness at any time that he knows how to feed and cannot convey information by signs, sounds, or activity that he knows when the activity should occur

E. <u>TOILETING (COGNITIVE ABILITY ONLY)</u>

a. **0 = COMPLETE** : continuously shows awareness that he knows how to toilet and can convey unambiguous information that he knows when this activity should occur
b. **1 = PARTIAL** : intermittently shows awareness that he knows how to feed and/or can intermittently convey reasonable clearly information that he knows when the activity should occur
c. **2 = MINIMAL** : shows questionable or infrequent awareness that he knows in a primitive way how to feed and/or shows infrequently by certain signs, sounds, or activities that he is vaguely aware when the activity should occur

d. **3 = NONE** : shows virtually no awareness at any time that he knows how to toilet and cannot convey information by signs, sounds, or activity that he know when the activity should occur

F. <u>GROOMING (COGNITIVE ABILITY ONLY)</u>

a. **0 = COMPLETE** : continuously shows awareness that he knows how to groom self and can convey unambiguous information that he knows when this activity should occur
b. **1 = PARTIAL** : intermittently shows awareness that he knows how to groom self and/or can intermittently convey reasonable clearly information that he knows when the activity should occur
c. **2 = MINIMAL** : shows questionable or infrequent awareness that he knows in a primitive way how to groom self and/or shows infrequently by certain signs, sounds, or activities that he is vaguely aware when the activity should occur
d. **3 = NONE** : shows virtually no awareness at any time that he knows how to groom self and cannot convey information by signs, sounds, or activity that he knows when the activity should occur

G. <u>LEVEL OF FUNCTIONING (PHYSICAL, MENTAL, EMOTIONAL OR SOCIAL FUNCTION)</u>

a. **0 = COMPLETELY INDEPENDENT** : able to live as he wishes, requiring no restriction due to physical, mental, emotional or social problems
b. **1 = INDEPENDENT IN A SPECIAL ENVIRONMENT** : capable of functioning independently when needed requirements are med (mechanical aids)
c. **2 = MILDLY DEPENDENT – LIMITED ASSISTANCE NEEDED** : able to care for most of own needs but requires limited assistance due to physical, cognitive and/or emotional problems (needs non-resident helper)
d. **3 = MODERATELY DEPENDENT – MODERATE ASSISTANCE NEEDED** : able to care for self partially but needs another person at all times (person in home)

e. **4 = MARKEDLY DEPENDENT – ASSISTANCE NEEDED IN ALL MAJOR ACTIVITES, ALL TIMES** : needs help with all major activities and the assistance of another person at all times

f. **5 = TOTALLY DEPENDENT – 24 HOUR NURSING CARE** : not able to assist in own care and requires 24-hour nursing care

H. **<u>"EMPLOYABILITY" (AS A FULL TIME WORKER, HOMEMAKER, OR STUDENT)</u>**

a. **0 = NOT RESTRICTED** : can compete in the open market for a relatively wide range of jobs commensurate with existing skills; or can initiate, plan, execute and assume responsibilities associated with homemaking; or can understand and carry out most age relevant school assignments

b. **1 = SELECTED JOBS, COMPETITIVE** : can compete in a limited job market for a relatively narrow range of jobs because of limitations of the type described above and/or because of some physical limitations; or can initiate, plan, execute and assume many but not all responsibilities associated with homemaking; or can understand and carry out many but not all school assignments

c. **2 = SHELTERED WORKSHOP, NON-COMPETITIVE** : cannot compete successfully in a job market because of limitations described above and/or because of moderate or severe physical limitations; or cannot without major assistance initiate, plan, execute and assume responsibilities for homemaking; or cannot understand and carry out even relatively simple school assignments without assistance

d. **3 = NOT EMPLOYABLE** : completely unemployable because of extreme psychosocial limitations of the type described above, or completely unable to initiate, plan, execute and assume any responsibilities associated with homemaking; or cannot understand or carry out any school assignments

APPENDIX E

HISTOGRAMS FOR THE GLASGOW OUTCOME SCALE – EXTENDED AND THE DISABILITY RATING SCALE

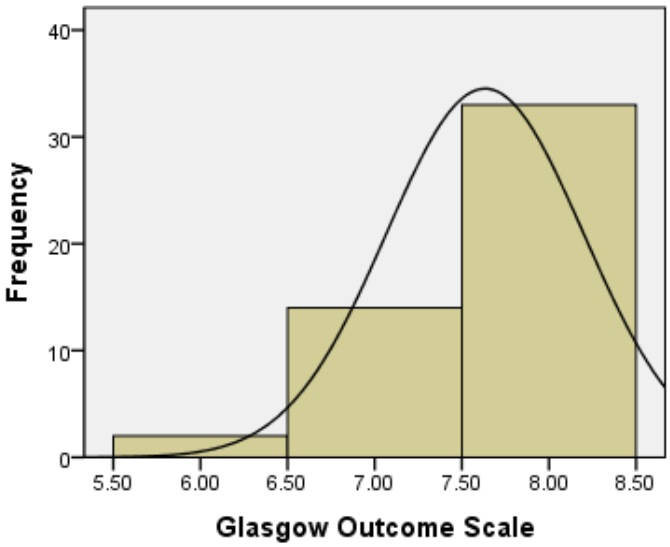

Figure 2. Histogram for the Glasgow Outcome Scale – Extended

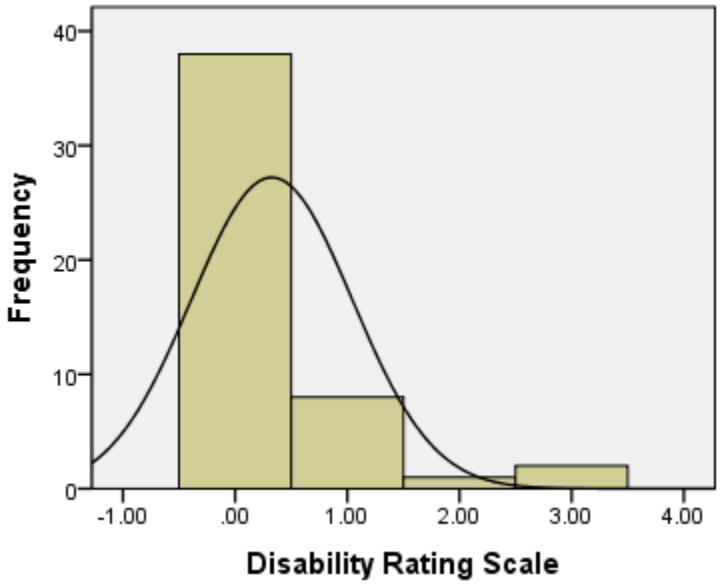

Figure 3. Histogram for the Disability Rating Scale