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Behavioral Symptoms, Functional and Cognitive Recovery Post-Mild Traumatic Brain Injury

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BEHAVIORAL SYMPTOMS AND FUNCTIONAL AND COGNITIVE RECOVERY IN POST-MILD TRAUMATIC BRAIN INJURY

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ABSTRACT

Mild traumatic brain injury (MTBI) accounts for 80–90% of the nearly two million traumatic brain injuries (TBI) that occur each year. The psychological consequences of MTBI can be extensive and can persist well beyond the acute injury, profoundly impacting the lives of the individual, their families, and society. A substantial number of MTBI patients suffer depressive mood, fatigue, and poor sleep (i.e., behavioral symptoms) for weeks and months post-injury. These symptoms reduce quality of life and delay the return to previous cognitive and functional status. Behavioral symptoms of depressed mood, fatigue, and poor sleep commonly co-occur and thus may constitute a symptom cluster, defined as co-occurring symptoms which share a common influence on an outcome. Symptoms of depression, fatigue, and poor sleep may share a common inflammatory etiology, and may develop as a result of pro-inflammatory cytokine elevation that occurs post-injury and which may persist beyond the acute phase of injury. Inflammatory molecules from sites of injury or infection are known to signal the brain to engender inflammatory-related sickness behaviors, such as depressed mood, fatigue, and poor sleep. It is possible that these co-occurring symptoms synergize to negatively impact cognitive and functional recovery. Yet investigation of these behavioral symptoms as a cluster and their association with MTBI recovery is limited.

Purpose: The purpose of this project is to identify different behavioral profiles of MTBI patients based on the intensity of depressive mood, fatigue, and sleep quality, to determine

whether there are differences in cognitive and functional outcomes at six months post-MTBI among the identified behavioral cluster profiles, and to explore differences in the intensity of behavioral symptoms at six months post-MTBI based on SNP genotype.

Research Design: This was a secondary data analysis of the database from the International Traumatic Brain Injury Initiative—TRACK-TBI pilot, which previously recruited TBI patients from two level I trauma centers. That study enrolled a total of 600 TBI patients; 340 of which suffered MTBI and who will thus be considered for potential inclusion in the current study. Participants in the original TRACK-TBI pilot study completed a battery of psychometric and health-related instruments and provided a blood sample for genetic analysis; these data were available to accomplish the aims of the present study.

Sample and Setting: From the TRACK-TBI pilot database, we selected a convenience sample (n=340) of male and females (ages >18years) who suffered external force trauma to the head, and who had an MTBI with classification by emergency department arrival Glasgow Coma Scale (GCS) as follows: mild (GCS 13–15). Only individuals who had completed follow-up at three months and six months were eligible.

Statistical Analysis: Latent Class Analysis was used to identify subgroups of MTBI patients with behavioral symptom cluster, using items derived from the psychological battery completed by participants in the TRACK-TBI pilot study completed; the presence and intensity of behavioral symptom cluster was analyzed with respect to cognitive and functional recovery. An analysis of covariance was used to explore differences in the intensity of behavioral symptoms at six months post-MTBI based on SNP genotype. The outcomes of this study will build a foundation upon which to establish clinically based strategies to identify MTBI patients

at risk for protracted recovery and to identify those who may require earlier and more intense intervention.

CHAPTER ONE

INTRODUCTION AND BACKGROUND OF THE PROBLEM

Nature of the Problem

Traumatic brain injury (TBI) is a significantly growing public health, social, and economic concern, as it can result in adverse outcomes that persist for an extended period of time. Mild traumatic brain injury (MTBI) accounts for 80–90% of the nearly two million traumatic brain injuries (TBI) that occur each year (Carroll et al., 2004; Kristman et al., 2014; R. Ruff, 2005; R. M. Ruff, 2011). The psychological consequences of MTBI can be extensive and can persist well beyond the acute injury, profoundly impacting the lives of the individuals, their families, and society (Center for Disease Control and Prevention, 2003). Advances in the diagnosis and management of TBI continue to reduce mortality for those who have incurred traumatic injuries, resulting in an increasing number of trauma survivors (Kristman et al., 2014; R. Ruff, 2005). Yet, surviving MTBI profoundly impacts the lives of the individual, their families, and society (Center for Disease Control and Prevention, 2003). The consequences of MTBIs can be extensive and wide ranging, and include physical, emotional, and financial difficulties. These consequences may be enduring (Center for Disease Control and Prevention, 2003). Traditionally the evaluation of the impact of TBIs has focused on survival, complications, and length of hospital stay. Few studies have evaluated the long-lasting psychological repercussions resulting from TBIs; yet such impairment can significantly reduce quality

of life outcomes and escalate health care costs (Center for Disease Control and Prevention, 2003).

Research suggests that only 20–25% of all patients who suffer MTBI are hospitalized, and of these MTBI patients, 80 to 90% recover without residual psychological adverse outcomes. The remaining 10–20% (referred to as the "miserable minority") (R. Ruff, 2005; R. M. Ruff et al., 2009); however, will suffer from long-term debilitating, unfavorable psychological outcomes and persistent physical, emotional, and cognitive symptoms (R. Ruff, 2005; R. M. Ruff et al., 2009). This could affect them for weeks or months after the injury, and possibly hinder them from returning to previous functional status and daily activities (J. Kraus et al., 2005). Such adverse outcomes lead to extensive economic costs for the healthcare system (Carroll et al., 2004; Cassidy et al., 2004; Kristman et al., 2014; R. Ruff, 2005). Nationally, MTBI costs nearly $17 billion each year (Center for Disease Control and Prevention, 2003).

Several studies have described the possible adverse behavioral outcomes following MTBI (Ayalon, Borodkin, Dishon, Kanety, & Dagan, 2007; Bay & Donders, 2008; Bay, 2009; Beetar, Guilmette, & Sparadeo, 1996; Levin et al., 2005; Ponsford, 2005). In particular, a substantial number of MTBI patients suffer depressive mood, fatigue, and poor sleep (i.e., behavioral symptoms) for weeks and months post-injury (Ayalon et al., 2007; Bay & Xie, 2009; Beaulieu-Bonneau & Morin, 2012; Beetar et al., 1996; Chaput, Giguere, Chauny, Denis, & Lavigne, 2009; Levin et al., 2005; Norrie et al., 2010; Ponsford et al., 2000; Rapoport, Kiss, & Feinstein, 2006). These symptoms not only reduce quality of life (Center for Disease Control and Prevention, 2003), but also likely delay the return to previous cognitive and functional status (J. Kraus et al., 2005). Behavioral symptoms of depressed mood, fatigue and poor sleep commonly co-occur and

thus may constitute a symptom cluster. Based on the oncology literature, a symptom cluster is when co-occurring symptoms share a common influence on an outcome (Fox & Lyon, 2007). Symptoms of depression, fatigue, and poor sleep may share a common inflammatory etiology, and may develop as a result of proinflammatory cytokine elevation (Kossmann, Hans, Imhof, Trentz, & Morganti-Kossmann, 1996; Shohami, Novikov, Bass, Yamin, & Gallily, 1994; S. H. Su et al., 2014; Woodcock & Morganti-Kossmann, 2013) that occurs post-injury and which may persist beyond the acute phase of injury. Inflammatory molecules from sites of injury or infection are known to signal the brain to engender inflammatory-related sickness behaviors, such as depressed mood, fatigue, and poor sleep (Dantzer, Wollman, Vitkovic, & Yirmiya, 1999; Dantzer, 2001; Dantzer & Kelley, 2007; Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Dantzer, 2009; Dantzer, O'Connor, Lawson, & Kelley, 2011; Kelley et al., 2003).

Evidence confirms that MTBI patients exhibit elevations in pro-inflammatory cytokines (Kossmann et al., 1996; Shohami et al., 1994; S. H. Su et al., 2014; Woodcock & Morganti-Kossmann, 2013), which may endure beyond the acute phase of injury. However, the pathogenesis of psychological long-term outcomes following MTBI is not fully understood. Low-grade systemic inflammation might contribute to the development of psychological long-term outcomes in patients with MTBI. Studies that focused on the systemic inflammation following MTBI are limited. According to findings from studies using animal models, MTBI could activate systemic inflammatory processes. For example, research findings demonstrate that circulating levels of IL-6 is increased in experimental rodent models of MTBI (Holmin et al., 1997; Shohami et al., 1994; S. H. Yang et al., 2013). Yet, it still remains unknown as to whether the systemic inflammatory process could be used to predict adverse psychological outcomes after

MTBI. Thus, it presents a fruitful area of research, in view of the fact that it is well established that systemic inflammatory processes activate the hypothalamic-pituitary-adrenal (HPA) axis (Murray, Buggey, Denes, & Allan, 2013) which may result in chronic stress, anxiety, and depression (Mustafa, 2013).

Furthermore, peripheral pro-inflammatory cytokines are capable of signaling the brain to induce behavioral symptoms like fatigue, sleep disturbance, and depressive mood (i.e., sickness behavior). It is possible that cytokine-to-brain signaling may contribute to behavioral symptoms of trauma patients. For example, pro-inflammatory cytokines that access the brain initiate a cascade of brain-derived cytokines that increase in indoleamine 2,3-dioxy-genase (IDO) expression (Yamada, Akimoto, Kagawa, Guillemin, & Takikawa, 2009). Increased IDO, in turn, can lead to overproduction of kynurenic and quinolinic acids and to less production of serotonin. Lower serotonin is linked to the pathogenesis of depression, which is primarily interferon-gamma-induced (Capuron & Miller, 2011; Haroon, Raison, & Miller, 2012; A. H. Miller, Maletic, & Raison, 2009).

Although experiences of MTBI patients are described in literature, there is lack of evidence to guide health care providers to identify which MTBI patients are at greater risk for behavioral symptoms. Explication of the psychobiological mechanisms that underlie behavioral symptom expression in MTBI survivors is a critical first step that will improve risk assessment and ultimately lead to prevention and/or better management of trauma-associated behavioral symptoms. It is possible that these co-occurring symptoms synergize to negatively impact cognitive and functional recovery. Yet investigation of these behavioral symptoms as a cluster and their association with MTBI recovery is limited. Thus, the primary aim of this proposal is to

determine the extent to which these behavioral symptoms, independently or as a cluster, predict worse cognitive and functional outcomes post-MTBI. Further, it is possible that genetic variants may predispose to more persistent behavioral symptoms post-MTBI. This proposal explores the relationship of these genetic variants to risk for depressive mood, fatigue, and poor sleep independently and as a cluster.

Size and Importance of the Problem

Behavioral Symptoms and MTBI

MTBI patients can suffer from anxiety, fatigue, poor sleep, and depressive mood for weeks and months after injury (Ayalon et al., 2007; Bay & Xie, 2009; Beaulieu-Bonneau & Morin, 2012; Beetar et al., 1996; Chaput et al., 2009; Levin et al., 2005; Norrie et al., 2010; Ponsford et al., 2000; Rapoport et al., 2006).

Ample research indicates that anxiety symptoms are prevalent in the aftermath of a mild TBI (Hiott & Labbate, 2002; Koponen et al., 2002; Ma et al., 2014; Mooney & Speed, 2001; Moore, Terryberry-Spohr, & Hope, 2006; Rao & Lyketsos, 2002; Rao et al., 2010; R. Ruff, 2005; R. M. Ruff, 2011; Stulemeijer et al., 2006; Woodcock & Morganti-Kossmann, 2013). Anxiety in general has been reported at rates as high as 70% in patients with TBIs (Rao & Lyketsos, 2002).

Likewise, fatigue is a frequent burdensome symptom post-TBI, and although the nature of fatigue may change with time, it can persist for years after the initial injury (Mollayeva et al., 2014). The incidence of fatigue after TBI varies from 21% to73%, depending on patient characteristics (e.g., severity of injury, time since injury, etc.) and how fatigue is measured (Belmont, Agar, Hugeron, Gallais, & Azouvi, 2006; Borgaro, Baker, Wethe, Prigatano, &

Kwasnica, 2005; Lidvall, Linderoth, & Norlin, 1974; Middleboe, Andersen, Birket-Smith, & Friis, 1992; Ponsford, Cameron, Fitzgerald, Grant, & Mikocka-Walus, 2011). Although fatigue is linked to poor recovery post-TBI, a recent systematic review concluded that the impact of fatigue on patient outcomes is unclear and more intensive investigation is essential (Mollayeva et al., 2014). The prevalence and persistence of fatigue after TBI has the potential to impact activities of daily functioning, occupational and leisure activities, and thus quality of life (Cantor et al., 2008; Ouellet, Savard, & Morin, 2004). Previous studies highlight the importance of fatigue after MTBI and the need for further investigation and identification of markers that could possibly identify MTBI patients who are at risk for more severe symptoms in order to implement interventions earlier for better quality of life in MTBI survivors.

Additionally, the increased incidence of sleep disorders after TBI relative to the general population has been increasingly recognized (Castriotta et al., 2007; Watson, Dikmen, Machamer, Doherty, & Temkin, 2007). Sleep disturbance is a common complaint following TBI, and it is more common with MTBI (Beetar et al., 1996; Clinchot, Bogner, Mysiw, Fugate, & Corrigan, 1998; Fichtenberg, Millis, Mann, Zafonte, & Millard, 2000; Mahmood, Rapport, Hanks, & Fichtenberg, 2004). In recent reviews, 30–70% of TBI survivors reported sleep disturbances (Orff, Ayalon, & Drummond, 2009). Sleepiness may present as a separate symptom or along with other sleep disorders (e.g., sleep apnea, narcolepsy, post-traumatic hypersomnia, delayed sleep phase, insomnia, fatigue, alteration of sleep-wake schedule to movement disorders) (Castriotta et al., 2007; Orff et al., 2009; Watson et al., 2007). However, insomnia has been found to be more prevalent in mild TBI individuals (Ouellet et al., 2004). Most of the time the sleep disturbances are directly related to the TBI, enduring for months and/or years after the

injury, consequently hindering the recovery process and return to pre-injury function (Orff et al., 2009).

Lastly, evidence reveals that MTBI patients with sleep disturbance are more likely to suffer depressive symptoms (Auxemery, 2012; Bay & Donders, 2008; Bay, 2009; Beaulieu-Bonneau & Morin, 2012; Chaput et al., 2009; Guskiewicz et al., 2007; Kristman et al., 2014; Levin et al., 2005; Mooney & Speed, 2001; Ponsford et al., 2011; Rapoport, McCullagh, Streiner, & Feinstein, 2003; Rapoport et al., 2006). Depression is commonly reported after MTBI—with a prevalence of 15% in the first three months post-MTBI (Rapoport et al., 2003) and a prevalence of 18% new onset depressive symptoms up to a year after MTBI (Rao et al., 2010)—and is highly correlated with poor recovery (Guskiewicz et al., 2007; Mooney & Speed, 2001). There are only a few studies that investigated the relationship between MTBI and depression, as well as the risk factors related to the development of depression after MTBI (Levin et al., 2005; Rao et al., 2010).

The results of these studies suggest that there are several possible predictive factors associated with MTBI, psychological adverse outcomes, and other biological factors that could be identified in future research. Using predictive parameters can help emergency department (ED) personnel to identify MTBI patients who are at higher risk before discharge from the ED; allowing the opportunity to make appropriate referrals and prevent suffering from debilitating symptoms. This is a clinically relevant and important area for research, as early identification with more knowledge about risk factors for MTBI behavioral symptoms soon after the injury can help initiate treatment early on, thus promoting optimal quality of life.

Depression, fatigue, and poor sleep have been independently associated with impeded

recovery from MTBI for cognitive function (Guskiewicz et al., 2007; Mooney & Speed, 2001; Orff et al., 2009) and with the resumption of pre-injury lifestyle and responsibilities (Patterson & Holahan, 2012; Silver, McAllister, & Arciniegas, 2009).

Although experiences of MTBI patients are described in literature, as summarized above, understanding the psychiatric morbidity following MTBI remains limited, even though these comorbidities are prevalent. Several studies have reported short- and long-term increased rates of comorbidities following TBI; most studies; however, combined mild and moderate to severe TBI in their analyses. Hence, it is difficult to draw conclusions regarding psychiatric outcomes following MTBI, as opposed to more severe forms of TBI.

However, predictive power may be gained by evaluating clusters of symptoms that co-occur and which may portend slower recovery. To date only six studies used cluster analysis to identify symptom profiles related to recovery (Bailie et al., 2016; Hellstrom et al., 2013; Hoffer et al., 2016; Snell, Surgenor, Hay-Smith, Williman, & Siegert, 2015; Velikonja, Warriner, & Brum, 2010). One study identified three clusters of psychological adaptation (high, medium, and low) which related to injury outcomes (Snell et al., 2015). A second study used cluster analysis to identify subgroups of MTBI patients based on a symptom intensity profile (Hellstrom et al., 2013). Findings revealed that those with minor symptoms had a reduced risk for a positive CT or MRI findings, whereas the high-symptom-level group experienced difficulty returning to work and reported high levels of anxiety, depression and disability. Although both of these studies support this proposal, neither evaluated inflammation-related behavioral symptoms as a cluster predictive of cognitive recovery. Thus, there is a critical need to further develop prognostic models of MTBI to identify those at greater risk for poorer cognitive and functional recovery,

who will thus most benefit from targeted therapy (McMahon et al., 2014). Explication of the cluster of behavioral symptoms (i.e., depressive mood, fatigue, and poor sleep) posited to underlie cognitive and functional recovery in MTBI survivors is a critical first step to improve risk assessment and to better manage post-MTBI outcomes (Lingsma et al., 2014).

Genetic Variants and Behavioral Symptoms Post-MTBI

Genetic variants may contribute to risk for clustering of behavioral symptoms (depressive mood, fatigue, and poor sleep) following MTBI. Yet most studies to date have not evaluated whether genetic variants predict a more intense and/or prolonged clustering of these behavioral symptoms. It is known that impairment of neuropsychological and cognitive functions are prevalent in MTBI patients with the APOE e4 allele (Isoniemi, Tenovuo, Portin, Himanen, & Kairisto, 2006; Liberman, Stewart, Wesnes, & Troncoso, 2002; Millar, Nicoll, Thornhill, Murray, & Teasdale, 2003; Potapov, Iusupova, Tendieva, Nikitin, & Nosikov, 2010; Sundstrom et al., 2004; Sundstrom et al., 2007; S. T. Yang et al., 2015) and although presence of the APOE4 allele is not associated with the initial severity of brain injury post-TBI, it is correlated with greater risk of poorer outcomes at six months post-injury (Zhou et al., 2008). The negative influence of the e4 allele on memory, executive function, and fine motor control (Ariza et al., 2006) has been highlighted in a meta-analysis (Zhou et al., 2008). In older (non-injured) adults, findings demonstrated a relationship between the APOE genotype and depressive symptoms (Rigaud et al., 2001; Yen et al., 2007) while other studies reported no such association (Cervilla, Prince, Joels, Russ, & Lovestone, 2004; Kessing & Jorgensen, 1999). With respect to fatigue, one study found that post-MTBI carriers of the APOE e4 allele had pronounced fatigue (Sundstrom et al., 2007). However, no studies have evaluated the linkage of the APOEe4 allele

to poor sleep post-MTBI or to the clustering of behavioral symptoms (depression, fatigue, and poor sleep) following MTBI. Thus, there is a need to explore the linkage of the APOEe4 allele to vulnerability for more intense and enduring depressive symptoms, fatigue and poor sleep—common behavioral symptoms which may share a similar inflammatory etiology in individuals following MTBI.

Further, genetic association analyses suggest certain common single nucleotide polymorphisms (SNPs) may negatively influence recovery from MTBI (Feng et al., 2015; Lanctot et al., 2010; McAllister et al., 2005; McAllister et al., 2008; Pap et al., 2012; Roetker et al., 2012). It is possible that certain SNPs may predispose individuals to experience persistent behavioral symptom clusters after MTBI, further impeding recovery. McAllister et al. (2005; 2008) found that rs1800497 allele status was associated with cognitive function post-mild to moderate TBI (McAllister et al., 2005; McAllister et al., 2008). Subsequently, others examined the influence of the (C/T) SNP rs1800497 on post-TBI outcome using data from two multicenter studies (the Citicoline Brain Injury Treatment trial and TRACK-TBI Pilot). Findings showed that the ANKK1 T/T genotype is related to poorer verbal learning performance at six months post-TBI (Yue et al., 2015). Previous evidence also suggests that SNPs play a role in predisposing patients to depression (Feng et al., 2015; Pap et al., 2012; Roetker et al., 2012) and also may explain differential response to treatment (Lanctot et al., 2010). Since previous studies focused on TBI in general, it is thus the purpose of this project to explore which alleles SNPs are associated with more intense and/or persistent behavioral symptom cluster (depressive mood, fatigue, and poor sleep) post-MTBI, which may negatively influence recovery.

Justification of the Importance

In light of the primary aim of this secondary analysis study research to determine the extent to which behavioral symptoms, independently or as a cluster, predict worse cognitive and functional outcomes post-MTBI, three important and innovative aspects of this project may be examined.

The first is the use of symptom clusters analysis as a predictive tool for profiling subgroups enduring behavioral symptoms post-MTBI. As it also to a certain extent reveals symptom interrelationships (Aktas, Walsh, & Rybicki, 2010), this aspect primarily facilitates in exploring the influence of symptoms on each other, and aids in tailoring specific treatments accordingly. This conceptualization of symptom clusters is visualized as a shift of the paradigm of symptom management research, which addressed the reality of concurrent symptoms experienced in different populations and may lead to more promising research that will potentially generate knowledge needed for rapid improvement in symptom management. Thus, the paradigm shift would bridge the gap between research and bedside nursing by addressing symptoms (as a cluster), which is the most common reason that individuals seek healthcare (Dodd et al., 2001). This paradigm shift might improve the management of symptoms, ultimately reducing symptom burden (Aktas et al., 2010). Thus, profiling subgroups of MTBI patients will improve clinical practice, inform clinical practice guidelines, and ultimately provide patients with the most effective and innovative treatment modalities (Barsevick, Whitmer, Nail, Beck, & Dudley, 2006; Dodd et al., 2001; Kim & Abraham, 2008). In addition, when symptoms are not treated the patient can suffer from lingering long-term negative outcomes. Therefore, enhancing

the knowledge regarding the symptom cluster experiences and cognitive and functional outcomes is crucial and can lead to innovative treatments.

The second innovative aspect involve the chosen frameworks (the psycho-neuro-immunology (PNI) framework and the Theory of Unpleasant Symptoms (TOUS) that guide this investigation. This integrative framework can lead to advancement in improving quality of life and cognitive and functional recovery post-MTBI. Specifically, the investigator will apply the field of genetics to explore a potential mechanism and to explain how genetic variants may predispose to more persistent behavioral symptoms post-MTBI. Understanding these physiological (genetic) factors may lead to effective symptom management approaches and/or tailored strategies. The PNI framework will guide the understanding of these relationships, where it is possible that these co-occurring symptoms synergize to negatively impact cognitive and functional recovery. Furthermore, the TOUS (Lenz, Suppe, Gift, Pugh, & Milligan, 1995; Lenz, Pugh, Milligan, Gift, & Suppe, 1997) will guide the symptom-clustering aim, since it illustrates the importance of inclusion and consideration of the symptom experience as clusters. Incorporating the experience of symptoms "as clusters" (adapted from TOUS) would allow researchers to have a broader view of the symptom-related variables (e.g., genetic variants) that contribute to the symptoms clusters, as well as the symptoms-related recovery outcomes (e.g., cognitive and functional recovery). Overall, it is hoped that the innovative 3-dimensionally conceptualized frameworks will creatively illustrate the variations in MTBI patients with the enhanced understanding regarding symptom clusters and long-term recovery outcome.

Lastly, the third innovative aspect is the objective to explore the extent to which genetic variants (SNPs) influence behavioral symptoms at six months post-MTBI. It is possible that

genetic variants may predispose to more persistent behavioral symptoms post-MTBI. There is a compelling impetus for further exploration of genetic variants linked to inflammatory-related behavioral symptoms in individuals who suffer MTBI. Determining the extent to which genetic variants might contribute directly or indirectly to the symptoms (depression, fatigue, and poor sleep) and might impact cognitive impairment in MTBI patients is innovative, as results may provide novel biomarkers to predict more intense and persistent symptoms as early as possible. This will provide a new and potentially important avenue for investigation into the biological basis for these behavioral symptoms. Understanding the role of these biomarkers (SNPs) in MTBI has potential to lead to predicting at discharge which MTBI patients are at risk for prolonged behavioral symptoms. The findings can guide the future development of personalized genetic-based approaches to help identify and treat trauma patients, in turn to promote quality of life and reduce symptom intensity and duration.

In summary, the long-range objective of this research is to develop novel approaches to predict risk for behavioral symptoms in mild traumatic brain-injured (MTBI) patients at discharge from the ED. The outcomes of the proposed study will build a foundation to establish clinically based strategies to identify MTBI patients at risk and to target interventions to reduce behavioral symptoms and improve quality of life in trauma survivors and their families. Thus, there is strong rationale for this research in its potential to improve long-term outcomes for MTBI survivors who overcome their acute injury but who remain at risk for chronic and disabling behavioral symptom clusters.

Central Hypothesis

There will be differences in cognitive and functional outcomes in patients at six months

post-MTBI based on inflammation-related behavioral symptoms (depressive symptoms, fatigue, and poor sleep), independently or as a cluster; and there will be differences in behavioral symptoms at six months post-MTBI based on SNP phenotype. The evaluation of inflammation-related behavioral symptom clusters post MTBI with respect to outcomes and genetic variants is an innovative approach that can result in novel predictive biomarkers for early risk assessment. Thus, there is strong rationale for the proposed research, which can improve long-term outcomes for MTBI survivors who overcome their acute injury but who remain at risk for chronic and disabling behavioral symptoms.

Specific Aims and Hypotheses

The following specific aims and hypotheses will be addressed:

Aim 1: Identify different behavioral profiles of MTBI patients based on the intensity of depressive mood, fatigue, and sleep quality.

Hypothesis 1: There will be individual differences in the profiles of MTBI patients based on the intensity of depressive mood, fatigue, and poor sleep.

Aim 2: Determine whether there are differences in cognitive and functional outcomes at six months post-MTBI among the identified behavioral cluster profiles.

Hypothesis 2: There will be differences in cognitive and functional outcomes at six months post-MTBI among the identified behavioral cluster profiles.

Aim 3: Explore differences in the intensity of behavioral symptoms at six months post-MTBI based on SNP genotype.

Hypothesis 3: There will be differences in behavioral symptoms at six months post-MTBI based on SNP genotype.

Expected Outcomes

For a sizeable subgroup of MTBI patients, recovery is protracted, and prediction of who will experience protracted recovery is not well defined. Thus, there is a critical need to identify those at risk for a poorer outcome. Findings from this study will increase understanding of the role of depressive mood, fatigue, and poor sleep—as a symptom cluster—on cognitive and functional recovery. Additionally, enhanced knowledge from this secondary analysis will provide a foundation to guide future studies that evaluate the usefulness of these biomarkers (genetic variants), as predictors for the risk of more intense and enduring behavioral symptoms in MTBI patients. As well, the identified symptom clusters profiles as predictors for risk for more cognitive and functional outcomes at six months post-MTBI. Ultimately, this knowledge can be used to develop clinical strategies for earlier identification (i.e., at discharge) of MTBI patients who are at risk of such behavioral symptoms. This crucial knowledge will have a positive impact on the care of MTBI patients, as it will stimulate the development and implementation of specific symptom profiles to be used clinically to stratify risk for poor recovery and to identify those who may require earlier and more intense intervention to promote better quality of life.

CHAPTER TWO

REVIEW OF THE LITERATURE

MTBI: Introduction and Definition of MTBI

Traumatic brain injury (TBI) is an acquired brain injury, which occurs when a sudden trauma produces damage to the brain. TBI can result when the head suddenly and violently strikes an object, or when an object penetrates the skull and enters brain tissue (National Institute of Neurological Disorders and Stroke, 2014). In the United States, TBI is a significantly growing public health, social, and economic concern. Of note, TBI can result in adverse outcomes, which may persist for an extended period of time. The annual incidence of TBI is estimated to be approximately 1.5–2 million, and of all TBIs—including mild traumatic brain injuries (MTBIs)—account for 80–90% (Carroll et al., 2004; Kristman et al., 2014; R. Ruff, 2005; R. M. Ruff, 2011). Research findings reveal that only 20–25% of all MTBI patients are hospitalized, and among these MTBI patients, 80–90% recover without residual psychological adverse outcomes. Yet, the remaining 10–20% (referred to as the "miserable minority") will continue to suffer from long-term debilitating, unfavorable psychological outcomes. These symptoms could affect these individuals for weeks or months after the injury, and possibly hinder them from returning to previous functional status and daily activities (J. Kraus et al., 2005). Such long-term symptoms result in extensive economic costs for the healthcare system (Carroll et al., 2004; Cassidy et al., 2004; Kristman et al., 2014; R. Ruff, 2005), with costs approaching nearly $17 billion each year (Center for Disease Control and Prevention, 2003).

It is important to highlight that past incidence data for MTBIs were primarily derived from patients evaluated in hospital emergency departments (ED). These ED-derived data underestimate TBI incidence because the majority of persons who sustain an MTBI either consult their primary care physician days after the injury or do not seek care at all (Langlois et al., 2003; Mellick, Gerhart, & Whiteneck, 2003). Consequently, the 1998 National Institute of Health (NIH) consensus statement concluded that MTBIs were under-diagnosed and the statistics likely underestimate the real extent of the problem (Rehabilitation of persons with traumatic brain injury.1998; Consensus conference. rehabilitation of persons with traumatic brain injury. NIH consensus development panel on rehabilitation of persons with traumatic brain injury.1999; Rose, 1999).

For some individuals, suffering an MTBI can lead to persistent behavioral symptoms long after sustaining the injury. Several studies described the possible adverse behavioral outcomes following MTBI (Bay & Donders, 2008; Bay & Xie, 2009; Bay, 2009). Those studies report that a substantial number of MTBI patients suffer from fatigue, sleep disturbances, cognitive impairment, and depression for weeks and months following the initial injury (Ayalon et al., 2007; Bay & Xie, 2009; Beaulieu-Bonneau & Morin, 2012; Beetar et al., 1996; Chaput et al., 2009; Levin et al., 2005; Norrie et al., 2010; Ponsford et al., 2000; Rapoport et al., 2006). Yet, few studies have attempted to investigate predictive factors which can be used to identify who is at risk for developing intense behavioral symptoms following MTBI (R. M. Ruff et al., 2009).

Conclusions from a comprehensive review emphasized the need for future research to develop diagnostic or predictive tools that would identify patients at risk for poor outcomes post-

MTBI. These tools would have a powerful clinical advantage to target vulnerable MTBI patients and would be cost-effective (R. Ruff, 2005). Although MTBI is not life-threatening, suffering from poor outcomes interferes with the ability to return to work or the resumption of social activities for up to six months after injury (J. Kraus et al., 2005). Thus, reliable predictive measures are essential to identify patients at increased risk of developing poor psychological outcomes, and to implement follow-up strategies for MTBI patients at risk early on. Establishment of protocols in clinical practice that demand early assessment and follow-up treatments would possibly prevent and improve the psychological burden for MTBI patients (Lingsma et al., 2014)

Although experiences of MTBI patients have been described in literature, understanding the psychiatric morbidity following MTBI remains limited, despite agreement that such comorbidities are common. Several studies have reported short- and long-term increased rates of comorbidities following TBI; most studies; however, combined mild and moderate to severe TBI in their analyses. Hence, it is difficult to draw conclusions regarding psychiatric outcomes following MTBI separately. Additionally, there is lack of evidence to guide health care providers to identify *which MTBI patients are at greater risk* for behavioral symptoms. Explication of the psychobiological mechanisms that underlie behavioral symptom expression in MTBI survivors is a critical first step that will improve risk assessment and ultimately lead to prevention and/or better management of trauma-associated behavioral symptoms.

In comparison with moderate and severe brain injuries, MTBIs are often more challenging to diagnose. The lack of a universally agreed-upon definition of MTBI contributes to many clinical and research challenges (R. Ruff, 2005). Therefore, it is essential to define MTBI.

The World Health Organization (WHO) Task Force proposed an operational definition that differs from the definition developed by the MTBI Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (ACRM) (Carroll et al., 2004; Kristman et al., 2014). The definition proposed by WHO and the one used for this study is as follows:

> MTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (1) 1 or more of the following: confusion or disorientation, LOC [Loss of Consciousness] for 30 minutes or less, posttraumatic amnesia for less than 24 hours, and/or other transient neurologic abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (2) GCS [Glasgow Coma Score] score of 13-15 after 30 minutes post-injury or later upon presentation for health care. (3) These manifestations of MTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g., systemic injuries, facial injuries, or intubation), caused by other problems (e.g., psychological trauma, language barrier, or coexisting medical conditions), or caused by penetrating craniocerebral injury. (Carroll et al., 2004), p. 115)

The WHO Collaborating Centre for Neurotrauma Task Force conducted a comprehensive critical review of the literature to determine the best evidence on the epidemiology, diagnosis, prognosis, and treatment of MTB. That Task Force concluded that identification of prognostic factors is a priority for research. Exploratory studies have suggested a number of potential prognostic factors for recovery after MTBI (Carroll et al., 2004; Kristman et al., 2014). Yet, no definitive study has yet been published that establish prognostic factors to predict outcomes post-MTBI.

Theoretical Frameworks

The psychoneuroimmunology (PNI) framework will be used to guide this investigation. In addition, the investigator will use the field of genetics to explore a potential mechanism to explain how genetic variants may predispose to more persistent behavioral symptoms post-

MTBI. Understanding these physiological (genetic) factors may lead to effective symptom management approaches and/or tailored strategies. Furthermore, the Theory of Unpleasant Symptoms (TOUS) (Lenz et al., 1995; Lenz et al., 1997) will guide the symptom-clustering aim, since it illustrates the importance of inclusion and consideration of the symptom experience as clusters. Incorporating the experience of symptoms "as clusters" (adapted from TOUS) would allow researchers to have a broader view of the symptom-related variables (e.g., genetic variants) that contribute to the symptoms clusters, as well as the symptoms-related recovery outcomes (e.g., cognitive and functional recovery). The PNI framework will guide the understanding of these relationships, where it is possible that these co-occurring symptoms synergize to negatively impact cognitive and functional recovery. Additionally, it is possible that genetic variants may predispose to more persistent behavioral symptoms post-MTBI; this also speaks to the mind and body connection. This suggests that this relationship is orchestrated by the unique mind and body connection.

Psychoneuroimmunology Framework

PNI is defined as the study of the interaction between behavioral, neural, endocrine (neuroendocrine), and immunological processes of adaptation (Ader, 1980). The interdisciplinary science of PNI examines an individual's emotional responses on a multidimensional level to determine if valid relationships exist among emotions, immune function, and health (Robinson, Mathews, & Witek-Janusek, 2000). Interdisciplinary researchers discovered the biological link between the brain on one hand and the cells and tissues of the immune system on the other, which built the foundation for this field of science (Kemeny & Schedlowski, 2007).The basic principle of the PNI framework is that an individual's adaptive response to the environment

involves coordinated interactions among the nervous, endocrine, and immune systems. The biological pathways that connect the brain to the cells and tissues of the immune system include direct innervations of lymphatic tissue by the central nervous system and a shared communication network in which cells of the nervous, endocrine, and immune systems use common molecules and receptors to jointly modulate one's biology and one's emotions and behavior. Moreover, an expanding body of evidence suggests that emotions play a role in the development and progression of disorders that involve immune processes (Kemeny & Schedlowski, 2007).

Of particular relevance to this investigation is the concept of sickness behavior. Sickness behavior refers to the non-specific adaptive response of the innate immune system, which results in behaviors associated with sickness including lethargy, lack of interest in the environment, decreased appetite, and fatigue (Dantzer & Kelley, 2007). It is proposed that sickness behavior represents an expression of a central motivational state mediated by release of cytokines (Aubert, Kelley, & Dantzer, 1997; Dantzer & Kelley, 2007). In essence cytokine-induced sickness behavior refers to a motivational state that belongs to the realm of physiology, similar to other motivational states, such as fear or hunger (Dantzer & Kelley, 2007). Withdrawing from the environment to seek rest and care for the body is as normal in response to infectious agents as being able to shift to a state of increased arousal and readiness for action when confronted with a potential external threat. In theory, cytokines released in response to infection or inflammation alert the brain of any real or potential threats and initiate behaviors that are important for survival (Frink et al., 2009).

The result of a hyperactive pro-inflammatory state marked by excess production of pro-inflammatory cytokines may contribute to the pathogenesis of various human diseases such as allergy, autoimmunity, obesity, depression and atherosclerosis (Sternberg, 2006). Some even refer to the ability of the immune system to alert or communicate information about the body to the brain as a "sixth sense" (Blalock & Smith, 2007). Sickness behavior is adaptive in that it forces an individual to rest and withdraw from activities so that physiological processes can effectively produce healing (Blalock & Smith, 2007; Kelley et al., 2003). However, sickness behavior is no longer adaptive if it goes beyond the organism's resources and/or occurs out of proportion to the triggering factors that initiated the adaptive response. This is prevalent during a variety of chronic inflammatory diseases (Dantzer & Kelley, 2007). Pro-inflammatory cytokines released during infection, inflammation, injury and even psychological stress can signal the brain to initiate behavioral changes that facilitate adaptation to these threats.

Cytokines signal the brain to induce sickness behaviors through neural, hormonal, and cellular pathways (Capuron & Miller, 2011). The purpose of the following section is to describe how cytokines access and signal the brain. Secondly, key evidence that supports the concept that cytokines signal the brain to induce sickness behaviors will be described. To accomplish this, two crucial models will be considered: Dantzer's Motivational Model of Sickness Behavior and the Two-Hit Model of Cytokine-Induced-Depression.

Cytokine signals access the brain. Cytokines are relatively large protein molecules, and as a result are prohibited from passing through the blood-brain barrier; however, the blood-brain barrier may be disrupted following TBI (Kumar & Loane, 2012). In view of the fact that cytokines signal the brain in a manner to influence behavior and the expression of emotion

(Capuron & Miller, 2011), there are specific mechanisms that differentially mediate cytokine effects on the central nervous system. The entry of peripheral cytokines into the brain initiates a cascade of signals, which become amplified within the context of the brain cytokine network. This network consists of cells within the brain (e.g., microglia and astrocytes) that are themselves capable of further cytokine secretion. The neural pathway of immune-to-brain signaling underlies the potent effects of peripheral proinflammatory cytokines on pathways involved in the pathophysiology of neuropsychiatric disorders, including the activation of the HPA axis and the alteration of the metabolism of key neurotransmitters, such as serotonin (Dantzer et al., 1999).

Cytokines access and signal the brain through hormonal, neural and cellular pathways. Hormonal pathways refer to the activation of monocytes and macrophages, which release the proinflammatory cytokine and enter the brain through the choroid plexus and circumventricular organs of the blood-brain barrier. Once inside the brain, the activation of endothelial cells is responsible for the subsequent release of second messengers that act on specific brain targets (Capuron & Miller, 2011). Cytokines also signal the brain via neural pathways in which activated monocytes and macrophages stimulate primary afferent nerve fibers in the vagus nerve; this, in turn, results in the release of proinflammatory cytokines. This information reaches the brain by sensory afferents of the vagus nerve, which connect with specific brain regions through the activation of the nucleus of the tractus solitarius and postrema area (Capuron & Miller, 2011). Lastly, D'Mello & Swain (2009) identified another new immune-to-central nervous system communication pathway in the setting of organ-centered peripheral inflammation. According to D'Mello & Swain (2009), evidence shows that there is a significant infiltration of

activated monocytes into the brain in mice with hepatic inflammation (D'Mello et al., 2009). This cellular pathway refers to the stimulation of microglia by pro-inflammatory cytokines to produce monocyte chemoattractant protein-1, which in turn is responsible for the recruitment of monocytes into the brain (D'Mello et al., 2009).

Dantzer's motivational model of sickness behavior. Dantzer's theory of sickness as a motivational state is built upon Bolles' definition of motivations as central states that reorganize perception and action (Bolles & Fanselow, 1980). Bolles (1974) emphasized that a motivational state enables the individual to detach perception from action, which results in a selective appropriate strategy depending on the encountered state. In order for the body to efficiently deal with an invading infectious organism, sickness takes precedence over other behavioral activities when the infected organism is at the death stage (Dantzer & Kelley, 2007). Bolles and Fanselow (1980) presented a fear motivation system, which by assumption activates a unique class of defensive behavior, such as freezing and flight from a frightening situation. This activation aims to defend the animal against predation of natural danger while reorganizing the perception of environmental events to facilitate the perception of danger and safety (Bolles & Fanselow, 1980). The following examples illustrate the expression of sickness behavior as a motivational state.

First, Neal Miller (1964) conducted the first series of experimental investigation that demonstrated a differential effect of bacterial endotoxin on behavior. Endotoxin administration decreased bar-pressing when the bar-pressing resulted in an appetitive stimulus like food or water, but endotoxin did not decrease bar-pressing when it resulted in the termination of an aversive event. Rats given an endotoxin injection increased bar-pressing to stop the rotation of a

drum, an aversive stimulus (N. E. Miller, 1964). Interestingly, these results revealed that the consequence of the behavior, which does not necessarily decrease following exposure to sickness-inducing agents, influences the effect of the sickness-inducing agent.

Second, Aubert, Goodall, and Dantzer (1995) compared the effects of cold and cytokines on spontaneous dietary self-selection of rats. First, they habituated rats to free access to carbohydrate, protein, and fat diets for 4 hours a day for 10 days. Then they randomly received physiological saline, IL-1 beta injection or lipopolysaccharide (LPS), or were exposed to cold (5 degrees C). Results revealed that LPS- and IL-1 beta-treated rats ate less, but ingested relatively more carbohydrates and less protein, whereas relative fat intake remained unchanged. The rats exposed to cold slightly increased their food intake, but in a non-significant manner. They also increased their relative intake of fat but did not change their relative intake of carbohydrate and protein. These results reveal interesting pyrogenic and metabolic effects of cytokines, which provides a clear-cut example of behavioral reorganization in response to sickness (Aubert et al., 1995).

In a subsequent study, Aubert, Goodall, Dantzer, & Gheusi (1997) investigated the sensitivity to LPS injection in lactating mice. They found that nest-building significantly decreased in LPS-treated mothers compared with saline-treated animals at an ambient temperature of 22 degrees C. Furthermore, they found that LPS-treated mice exposed to cold temperature (6 degrees C) expressed not only pup-retrieving but also nest-building activity. Therefore, these activities are a result of a motivational state due to the cooler environment. These differential results indicate that the maternal behavioral expressions of LPS-induced sickness are dependent on the comparative priority of the behavior under consideration (different

components of maternal care under consideration). Apparently, sickness prevents mice from displaying motor activities (pup-retrieving or nest-building) and from evaluating the situation under consideration efficiently (Aubert et al., 1997).

Finally, Aubert Kelley, & Dantzer (1997) compared the effects of LPS on food intake and food hoarding. Rats underwent tests under different motivational levels for food hoarding (receiving food supplement to maintain stable body weight or not receiving such a supplement). Interestingly, they found that LPS-injection significantly decreased total food intake in rats in general, whereas food-hoarding was less in LPS-treated rats compared to those who did not receive a supplement. The expression of a still salient secondary motivation in LPS-treated rats, which did not receive any food supplement, suggested the expression of an anticipatory feeding behavior along with a reduced immediate appetite. Their results demonstrated that LPS treatment disrupted food-hoarding in a minor way when rats received all of their food from hoarding, compared to rats that had supplemental food in their home cages (Aubert et al., 1997). LPS-treated animals still appear able to adjust their defensive behavioral strategies with regard to their needs and capacities. These findings support the adaptive value of the behavioral changes displayed by LPS-treated animals (Aubert et al., 1997).

In summary, the evidence described above confirms the hypothesis that sickness behaviors reflect the expression of motivational changes and reorganizations of behavioral priorities (Dantzer & Kelley, 2007). Additionally, Aubert, Kelley, & Dantzer (1997) confirmed that environmental conditions can be determinants of the behavioral change induced by illness or cytokines. In other words, when there are possible adverse effects of behavioral depression, behavior is less likely to suffer disruptions by infections and cytokines.

Motivational aspect of sickness behavior. From the previous discussion of the historical origin of the motivational model, it was clear that sickness has motivational properties that reorganize the function of the organism at subjective, behavioral, and visceral levels in order to cope with the threat encountered (Dantzer, 2009). The motivational aspect of sickness behavior is a vital perspective in pathophysiology; it entails that the neural pathways underlie the expression of sickness behavior, activated by immune stimuli but could possibly receive activations from non-immune stimuli (Dantzer et al., 1999).

Therefore, cytokines signal the brain by inducing sickness behavior as a result of expression of a motivational state triggered by activation of the peripheral innate immune system (Dantzer, 2009). As mentioned earlier it is an adaptive normal response to the exposure to a threat of a predator rather than being pathologic. In theory, cytokines released in response to infection or inflammation alert the brain to any real or potential threats and initiate behaviors that are important for survival (Frink et al., 2009). Some even refer to the ability of the immune system to alert or communicate with the brain as a "sixth sense" (Blalock & Smith, 2007). Sickness behavior is adaptive in that it forces an individual to rest and withdraw from activities so that physiological processes can more effectively produce healing (Blalock & Smith, 2007; Kelley et al., 2003).

Pro-inflammatory cytokines released during infection, inflammation, injury and even psychological stress can signal the brain to initiate behavioral changes that facilitate adaptation to these threats. However, similar to other responses, sickness behavior can become anomalous or pathologic outside its original context and in the absence of inflammatory stimulus (Dantzer, 2009). This pathologic state derives from several factors:

The hyperactive pro-inflammatory state marked by persistent excess production of pro-inflammatory cytokines like IL-1, IL-6 and TNF alpha and IFN gamma (Dantzer, 2009), which may also contribute to the pathogenesis of various human diseases in addition to sickness behaviors, such as allergy, autoimmunity, obesity, depression and atherosclerosis (Sternberg, 2006).

There is a predominance of pro-inflammatory cytokines over anti-inflammatory cytokines, which normally down-regulate the activation of the pro-inflammatory cytokines of the sickness response. This mismatch results in the exaggerated sickness response due to the peripheral immune system or direct activation of the brain cytokine system (Dantzer, 2009).

The sensitization of the neuronal circuits is another facet. Activation of afferent nerve fibers by peripherally released cytokines represents the fast pathway of transmission of immune signals from the periphery to the brain. This neural pathway certainly sensitizes the brain target areas of inflammatory mediators to the action of brain-produced cytokines that relay and amplify the action of peripheral cytokines (Dantzer, 2001).

The motivational competition between motivational states for behavioral output. Normally, hierarchal organization of motivational states is required for the expression of behaviors, along with continuous evaluation of the encountered internal context and external events occurrences (Dantzer, 2001). For example, if an individual is sick with the flu and experiences generalized muscle weakness, which cause them to stay in bed for the whole day, this individual is more likely to overcome this illness and will be better equipped to response to a threat.

The effect of cytokines on maternal behavior provides a more representative example of

the competition of motivational states, in the sense that maternal behaviors are critical for the survival of the offspring. In the previously mentioned study by Aubert, Goodall, Dantzer, & Gheusi (1997), LPS-treated mice exposed to ambient temperature of 22 degrees C, compared to saline-treated mice, demonstrated pup-retrieving activity, but nest-building was significantly decreased. However, LPS-treated mice exposed to ambient cold temperature, compared with saline-treated mice, demonstrated both pup-retrieving and nest-building activity. Interestingly, their results signify that the behavioral expression of LPS-induced sickness depends on the priority of the behavior under consideration (Aubert et al., 1997). In motivational terms, maternal behaviors compete with sickness, and maternal-motivated behavior takes superiority over sickness behavior. This observation provides a valuable example of the motivational competition between behaviors.

The Two-Hit Model of Cytokine-Induced Depression

Production of pro-inflammatory cytokines induces sickness behavior, which is terminated by endogenous anti-inflammatory molecules. Sustained production of pro-inflammatory cytokines in the context of insufficient production of anti-inflammatory molecules causes depression in vulnerable individuals. Factors acquired or genetic can contribute to vulnerability. Vulnerability in the present context refers to an innate or acquired predisposition to develop a given pathology when causal factors are present. Dysfunction in genes controlling key proteins in cytokine production (e.g., IL-6) and serotoninergic neurotransmission (e.g., activity of the serotonin transporter) or serotonin receptor subtype are identified as vulnerability factors for cytokine-induced depression (M. R. Kraus et al., 2007). The association between IL-6 polymorphism and reduced risk of depressive symptoms confirms the role of the inflammatory

response system in the pathophysiology of IFN-alpha-induced depression. In contrast, the effect of the 5-HTT-serotonin transporter gene was reported to be small and perhaps dependent on the status of the inflammatory response (Bull et al., 2009).

There are several features that contribute to vulnerability and are considered markers of vulnerability. Firstly, psychological features can influence vulnerability to cytokine-induced depression. Patients who have high scores on depression scales at the start of cytokine treatment are more likely to develop depressive syndrome in response to immunotherapy than patients who have a low score at baseline (Capuron & Ravaud, 1999). Another example of psychological features is childhood adversity and maltreatment. Danese et al. (2007) conducted a cohort study and followed 1,000 individuals from birth to age 32. They found that patients with major depression and a documented history of childhood maltreatment showed higher levels of peripheral blood concentrations of high-sensitivity CRP compared with depressed patients without a history of childhood maltreatment (Danese et al., 2008)

Secondly, physiological features can also influence vulnerability. For example, patients who respond to the first injection of IFN-α by an exaggerated pituitary-adrenal response are more likely to become depressed in response to repeated administration of IFN-α than patients who display a lower pituitary-adrenal response (Capuron et al., 2003; Capuron & Miller, 2011). Aging is accompanied by several changes in the immune system and reflect immuno-senescence and an altered susceptibility of disease. Thus, the elderly respond to stressful events with a larger fluctuation of immune function and a greater propensity for the development or progression of disease than young or middle-aged individuals (Irwin & Miller, 2007). Godbout et al. (2005) investigated whether aging exacerbated neuro-inflammation and sickness behavior after

peripheral injection of lipopolysaccharide (LPS) in aged mice. Their data revealed that activation of the peripheral innate immune system leads to exacerbated neuro-inflammation in the aged mice compared with adult mice. The dysregulation link between the peripheral and central innate immune system is likely to be involved in the severe behavioral deficits that frequently occur in older adults with systemic infections.

Another example is obesity, an inflammatory condition. O'Connor et al. (2005) tested the hypothesis that obesity affects the IL-1beta system, with functional consequences in the brain of obese mice. Their results indicate IL-1beta-mediated innate immunity is augmented in diabetic obese mice at the periphery and in the brain, and the mechanism is due to diabetes-associated loss of IL-1beta counter-regulation. Obesity and aging is correlated with chronic low-grade inflammation that leads to priming or sensitization of brain microglial cells (Perry, 2004). Superimposed on this low-grade inflammation status, a peripheral infectious episode leads to exaggerated synthesis of inflammatory cytokines and other mediators in the brain that has an impact on behavior and mood or exacerbates the progression of chronic neurodegenerative disease.

Finally, immuno-compromised individuals, patients taking certain immune-altering medications, or drug abusers can be more vulnerable (Irwin & Miller, 2007). These groups may be more vulnerable as any alteration in the balance between pro-inflammatory and anti-inflammatory cytokines (in the sense of a predominance of pro-inflammatory cytokines over anti-inflammatory cytokines), results in an exaggerated sickness response to activation of the peripheral immune system or direct activation of the brain cytokine system (Dantzer, 2009). Patients who respond to the first injection of IFN-alpha with an exaggerated pituitary-adrenal

response are more likely to become depressed in response to repeated administration of IFN-alpha than patients who display a lower pituitary-adrenal response (Capuron et al., 2003)

The third vulnerability factor is genetic predisposition to particular diseases (e.g., autoimmune diseases, diabetes or cancer etc.) (Irwin & Miller, 2007). Dysfunction in genes controlling key proteins in cytokine production and serotoninergic neurotransmission are identified as vulnerability factors for cytokine-induced depression (Bull et al., 2009; M. R. Kraus et al., 2007). Krauset et al. (2007) conducted a study to investigate the impact of functional gene variants of the cerebral serotonin (5-HT) signaling pathway previously implicated in depression risk in hepatitis C-infected outpatients treated with interferon alfa-2b. Their findings suggest an impact of allelic variation in 5-HT1A receptor expressions on the development of interferon alpha-induced depression during antiviral treatment of chronic hepatitis C. Prediction models of interferon-induced depressive symptoms based on HTR1A variation offer a perspective for an antidepressant-selective serotonin reuptake inhibitor prophylaxis in patients genetically at risk for interferon-induced depression (M. R. Kraus et al., 2007).

In another study, Bull et al. (2009) determined if these polymorphisms were associated with the development of depression and fatigue during IFN-alpha and ribavirin treatment. Ninety-eight Caucasian patients who were receiving pegylated IFN-alpha and ribavirin treatment for chronic hepatitis C virus participated in this prospective cohort study. The association between the IL-6 polymorphism and reduced risk of depressive symptoms confirms the role of the inflammatory response system in the pathophysiology of IFN-alpha-induced depression. In contrast, the effect of the 5-HTT genes was small and perhaps dependent on the status of the inflammatory response (Bull et al., 2009).

The interaction between psychosocial factors and other psychobiological vulnerability (e.g., depression) is characterized by alteration of immune function and increased susceptibility to, or progression of, disease (Irwin & Miller, 2007). Collectively, the above features may help while using markers for prediction of patients at risk for depressive symptoms and a guide in the development of interventions to prevent the occurrence of depression thus improving the quality of life.

Cytokines and depression. Cytokine-to-brain signaling has been implicated in mood disorders, particularly depression that accompanies illness (Dantzer et al., 2008; Dantzer, 2009). Because of the close similarities between symptoms of sickness and clinical signs of depression, any of these conditions is likely a risk factor for the occurrence of major depressive disorders. Evidence for the possibility of a shift from sickness behavior to depression is available from two different sources: clinical research and experimental studies on animal models of depressive disorders (Dantzer, 2009). The growing body of evidence implicates pro-inflammatory cytokines in the etiology of depressive-like symptoms associated with chronic illness (Dantzer et al., 2008).

In the research field of PNI, accumulated evidence demonstrates reciprocal communication pathways between nervous, endocrine, and immune systems (Schiepers, Wichers, & Maes, 2005). Findings in the field of PNI stimulated increased interest in the involvement of the immune system in psychiatric disorders (Capuron & Miller, 2011). Research suggests that these reciprocal connections between nervous and immune systems are essential to understand the underlying pathophysiology of depression. More so, pro-inflammatory cytokines, such as IL-6, play a significant role in developing depression and can mediate its psychological, behavioral, and neurobiological manifestations (Dantzer et al., 2011). The cytokine hypothesis of

depression indicates that external psychological stressors and internal organic inflammatory diseases or condition stressors induce inflammatory process (Maes et al., 1999; Maes et al., 2009; Schiepers et al., 2005; Wichers & Maes, 2002). Additionally, it evident that psychological stress might induce an inflammatory response with increased production of pro-inflammatory cytokines (Maes et al., 1999; Maes et al., 2009; Schiepers et al., 2005; Steptoe, Hamer, & Chida, 2007; Wichers & Maes, 2002).

The conceptual model for the proposed investigation is grounded in the inflammatory theory of depression. Convergent findings from several lines of evidence reveal a robust association between depressive disorders and pro-inflammatory pathways, and some of this evidence is causal (Dantzer et al., 2008; A. H. Miller et al., 2009; Oxenkrug, 2013). Pro-inflammatory cytokines access the brain through multiple mechanisms and initiate a cascade of reactions that lower serotonin levels and increase glutamatergic effects (Dantzer et al., 2008). Depression is characterized by deficient serotonergic neurotransmission and enhanced glutamate receptor *N*-methyl-d-aspartate activation. Pro-inflammatory cytokines activate indoleamine 2,3-dioxygenase (IDO), which degrades tryptophan, a precursor to serotonin. In a pro-inflammatory environment, tryptophan is shunted toward production of kynurenine, via IDO, competing with the serotonin pathway. These pro-inflammatory cytokine-induced modifications promote the development of depressive symptoms. Within the microglia, kynurenine is metabolized to quinolinic acid, an agonist of glutamatergic NMDA receptors. This results in a serotonergic deficiency and glutamatergic overdrive in pro-inflammatory states that promotes the development of depressive symptoms (Heizmann, Koeller, Muhr, Oertli, & Schinkel, 2008; Oxenkrug, 2013)

The Theory of Unpleasant Symptoms

The Theory of Unpleasant Symptoms (TOUS) (Lenz et al., 1995; Lenz et al., 1997) is one of the guiding frameworks for this research. The original theory provides a model for the experience of, and relationships between, concurrent symptoms (Lenz et al., 1995). The theory was developed through collaboration among three researchers who initially were working with two concepts, dyspnea and fatigue. The investigators acknowledged shared characteristics between the dyspnea and fatigue that led to the ideas of developing an inclusive theory that addresses multiple unpleasant symptoms across clinical populations. The original theory included influencing factors—physiologic, psychological, and situational factors. The investigators emphasized that symptoms vary in several components—duration, intensity, quality, and distress. The experience of the symptoms ultimately produced an effect on a patient's level of performance across the three domains of functional status, cognitive functioning, and physical performance (Lenz et al., 1995). After the development of the original theory, the authors recognized that further refinements in the theory were necessary in order to address the possibility of experiencing several symptoms at the same time. Furthermore, they acknowledged the need to include the possibility for the experience of several symptoms to have multiple effects (Lenz et al., 1995). A revision of the TOUS was published in 1997 (Lenz et al., 1997). The revision reemphasized the three major concepts of the theory: the symptoms, the influencing factors which affect the symptom experience, and the performance of outcomes. The revised theory is useful in describing the possibility of interactions between the influencing factors. Lenz et al. (1997) stated that the symptom experience might have an effect on influential

factors and that there is a reciprocal relationship between the influencing factor and symptoms. The TOUS has been applied in research and practice.

The TOUS has three major concepts: the symptoms, influencing factors, and performance of outcomes. First, symptoms in the updated version are conceptualized as a multidimensional experience, which can be conceptualized and measured separately or in combination with other symptoms (Lenz et al., 1997). The dimensions of the symptom experience are the following: (a) intensity which refers to strength or severity, (b) timing which refers to duration and frequency of occurrence, (c) level of distress perceived which refers to degree of discomfort, and (d) quality which refers to the patient's description of what the symptom feels like. Lenz et al. (1997) stated that the dimensions are separable but related. Using these dimensions, each symptom can be conceptualized and measured separately or related to other symptoms. Quality is frequently the most difficult to discern because of individuals' varying levels of ability to describe a symptom or their ability to pinpoint or differentiate one symptom from another (Lenz et al., 1997). The second concept is influencing factors. Three categories are identified that influence the symptoms: physiological, psychological, and situational factors. In the updated version of the theory, the authors acknowledged the need to consider several interrelated aspects within each factor, in addition to the relations between these factors and interactions that could influence the symptom experience in return (Lenz et al., 1997). The third concept is performance of outcomes or effects of the symptom experience. The authors conceptualized performance to include functional and cognitive activities. Functional performance was conceptualized generally to include physical activities, activities of daily living, social activities, and role performance such as work-related roles (Lenz et al., 1997).

The main difference between the original and the revised model is that the original model represents a unidirectional influence moving from the influencing factors to the symptom experience to the performance or consequences. The revised model is more detailed and represents a bidirectional influence among all three of the major concepts of the model: symptoms, influencing factors, and performance of outcomes. Additionally, the revised model emphasizes the importance of the experience of multiple symptoms at the same time. It also advocates that one or more symptoms may aggravate effects on performance and provide a reciprocal influence on the influencing factors. Interaction occurs among symptoms, allowing for the multiplicity or additive nature of the symptom experience when more than one symptom is involved (Lenz et al., 1997).

It was emphasized by the authors that the experience of unpleasant symptoms could change the physiological, psychological, and situational status of a person. Therefore, the major theoretical statements of the updated version of the theory are as follows: (1) the performance of outcomes has a reciprocal relation to the symptom experience; (2) the decreased levels of performance can have a feedback loop of the influential factors, with a negative impact on physiological and psychological states and situational conditions; (3) the influential factors can display an interaction effect in their relation to the symptom experience; and (4) the symptom experience can have a moderating or mediating influence in the relationship between physiological or psychological status and performance (Lenz et al., 1997).

The two main assumptions, as Lenz says, are the following: (1) There are commonalities across different symptoms experienced by persons in varied situations; and (2) symptoms are

individual subjective phenomena occurring in family and community contexts (Lenz et al., 1997).

The elements of the theory provide perspective for research in both the basic and the clinical science of nursing. The Theory of Unpleasant Symptoms was examined in published research in different populations, such as cancer patients (Chen & Tseng, 2005), pregnancy (Milligan, Flenniken, & Pugh, 1996), childbirth (Pugh & Milligan, 1993), dyspnea in patients with chronic obstructive pulmonary disease (Gift, 1990), and cardiac patients (Jurgens et al., 2009). The theory has clearly demonstrated its usefulness in research to date. As the model continues to develop, it will serve as a framework quantitative research (Motl & McAuley, 2009; Rychnovsky, 2007; S. J. Woods, Kozachik, & Hall, 2010). The usefulness of the TOUS in practice has been demonstrated in a variety of clinical settings and various populations (Chen & Tseng, 2005; Gift, 1990; Gift, Jablonski, Stommel, & Given, 2004; Milligan et al., 1996; Pugh & Milligan, 1993).

The TOUS presents a holistic, comprehensive and dynamic view of the unpleasant symptoms experience. Managing the care for patient experiencing unpleasant symptoms is part of the real world of nursing and what patients encounter on a day-to-day basis. This model offers increased insight into the reality of unpleasant symptom experiences, and hopefully provides direction to guide management strategies aimed unpleasant symptoms. There is congruence with other theories such as symptom management theory (Dodd et al., 2001) and research internal and external to nursing. This theory contributes to other disciplines such as psychology and can be readily applied in clinical settings guided by other disciplines. For example, in the psychology discipline, Hutchinson & Wilson (1998) evaluated the emergent fit of the TOUS for Alzheimer's

disease (AD) patients in an effort to evaluate the usefulness of the theory with AD patients and designing nursing interventions. The researchers reported that the theory is useful because it emphasizes the complexity and interaction of symptoms and the interrelationships among symptoms, influencing factors and symptom consequences/performance outcomes (Hutchinson & Wilson, 1998). The importance of the caregiver and the social and environmental context, which are the situational factors in the theory, were especially relevant in AD (Hutchinson & Wilson, 1998).

Research has helped in the refinement of the original theory, and interactions among components and their interrelationships with other components were incorporated in the revised version of TOUS. The TOUS is an inclusive and interactive dynamic theory incorporating multiple concepts in one encompassing model. The theory is useful as it ranges from simple to complex depending on the number of unpleasant symptoms and variables a researcher decides to study. Additionally, the theory seems relevant to many cultural groups and it can be applied to many situations in different setting(Chen & Tseng, 2005; Gift, 1990; Gift et al., 2004; Hutchinson & Wilson, 1998; Jurgens et al., 2009; Milligan et al., 1996; Motl & McAuley, 2009; Pugh & Milligan, 1993; Rychnovsky, 2007; S. J. Woods et al., 2010).

Most importantly, the inclusion of multiple influencing factors that influence the patients' symptom experience makes the theory valuable because nurses can uniquely design interventions that are individualized for each patient's characteristics and patterns of symptoms. One of the goals of nursing care is to accomplish better outcomes and increase patients' satisfaction. With this theory, by individualizing the care, nurses can facilitate in accomplishing this goal. There are social policy issues related to the theory since Nursing's Policy Statement claims that theory

application in nursing is an essential tool that provides nurses with the framework for their clinical decision-making and ensures accountability by increasing transparency of their actions (Meleis, 2011). More specifically, one of the nursing accountabilities to society is to support the development of nursing theory and research to explain observations and guide nursing practice (American Nurses Association, 2010). Therefore, this TOUS could be useful guide to practice when assessing patients with unpleasant concurrent symptoms.

Finally, the TOUS has many practice implications and can be used to identify preventive interventions or develop innovative treatments that could be applied across similar symptoms. However, more attention needs to be paid to symptom assessment and management where recent findings suggest potentially useful interventions. These interventions need to be addressed and examined. For example, these interventions can include prevention interventions after a traumatic injury aimed to prevent the symptom of stress. Another example is restorative interventions after the experience of the symptom of stress aimed to restore rather than alleviate stress.

The concept of symptom clusters. The concept of symptom clusters has recently become an important concept in symptom related nursing research, especially in cancer (Donovan & Jacobsen, 2007; B. Given, Given, Azzouz, & Stommel, 2001; B. A. Given, Given, Sikorskii, & Hadar, 2007; C. W. Given, Given, Azzouz, Kozachik, & Stommel, 2001; Kirkova, Aktas, Walsh, Rybicki, & Davis, 2010; Kirkova, Walsh, Aktas, & Davis, 2010). The concept of symptom clusters was initially developed in psychology and psychiatry, and then developed to general medicine. It has been extensively utilized in these disciplines for many years now. However, the concept of symptom clusters is comparatively new to the nursing discipline. Even

though concurrent symptoms are frequently reported in clinical practice symptom management research, surprisingly, has not reflected this reality (Aktas et al., 2010; Barsevick et al., 2006; Dodd, Miaskowski, & Lee, 2004). According to Miaskowski, Dodd & Lee (2004), symptom clusters is the new frontier in symptom management research. Researchers suggest that specific symptom clusters have a cooperative effect on patient outcomes and prediction of morbidity (Aktas et al., 2010; Barsevick et al., 2006; Dodd et al., 2004). The purpose of this section is to explore the concept of symptom cluster by review of literature in three different disciplines: psychiatry and psychology, nursing, and general medicine.

Symptom clusters in psychology and psychiatry literature. The pathophysiology of associated symptoms is reasonably well understood and causal relationships are established in many known diseases. On the other hand, it is well known that it is not easy to identify etiologies of most mental disorders. More often, an agreement on specific symptoms is recommended for a common etiology, which is then regarded as sufficient to recognize a psychological syndrome (Collen, 2008).

It is evident in review of psychology and psychiatry literature that symptom clusters have long been the basis of disease diagnosis of psychological disorders. Several themes have been addressed in the literature review with regard to the concept of symptom cluster. These themes include empirical methods and factor analysis, the associative relationships among symptoms in a cluster, basic aspects, common etiology of psychological disorders and symptom construction expressed by symptom clusters, and clinical implication of the concept of symptom clusters (Eslick, Howell, Hammer, & Talley, 2004; Fernandez-Herlihy, 1988).

In a recent study by Hybels, Blazer, Pieper, Landerman and Steffens (2009), the researchers explored the basic aspects of symptom presentation in older adults with major depression by identifying homogeneous clusters of individuals based on symptom profiles. It was a secondary data analysis using latent class cluster analysis. In another classic study by Asmundson, Frombach, McQuaid, Pedrelli, Lenox and Stein (2000), the researchers described symptom clusters as corresponding to basic aspects of posttraumatic stress disorder (PTSD). But the researchers questioned whether PTSD symptom clusters derived by experts were truly corresponding to the basic aspects of PTSD and then proceeded to verify this assumption statistically by using factor analysis (Asmundson et al., 2000).

However, there has been controversy over the appropriate way to define symptom clusters for PTSD. Amdur and Liberzon (2001) tested the factor structure of the Impact of Event Scale (IES) in a sample of 195 male combat veterans with chronic PTSD by using confirmatory factor analysis. They found that the two-factor model including Intrusion and Avoidance deviated significantly from being a good fit. In spite of this, a four-factor model, including Intrusion and Effortful Avoidance subscales—as well as Sleep Disturbance and Emotional Numbing subscales—was significantly a better fit (Shevlin, Murphy, Dorahy, & Adamson, 2007; Shevlin, Dorahy, Adamson, & Murphy, 2007). They concluded that essential behavior became visible in the symptoms of a cluster. Conceptually, one can look at psychological disorder as a group of symptoms that may be constructed into precise symptom clusters, which distinguish characteristics of a specific disorder. Subsequently, these symptom clusters present the basis for diagnosis and classification of mental disorders and syndromes.

Shevlin, Murphy, Dorahy, and Adamson (2007) conducted a study to describe the distribution of positive psychosis-like symptoms in the general population by means of latent class analysis. They used latent class analysis to identify homogeneous sub-types of psychosis-like experiences. The latent class analysis showed that psychosis-like symptoms at the population level could be best explained by four groups that appeared to represent an underlying continuum (Shevlin et al., 2007).

Shevlin, Dorahy, Adamson, & Murphy (2007) conducted another study that examined the types of borderline personality profiles, associated psychological disorders and stressful life-events. They used data from the British Psychiatric Morbidity Survey to examine homogeneous subtypes of participants based on their responses to nine borderline personality disorder criteria (Shevlin et al., 2007).

In psychology and psychiatry, symptom cluster is described using the associative relationships between symptoms. Amdur and Liberzon (2001) acknowledged the strong relationship between symptoms within a cluster. Other properties of symptom clusters include the nature or type of symptoms in a cluster and the number of symptoms in a cluster (Shevlin et al., 2007).

The number of symptoms in a symptom cluster does not seem to be important. In a classic study, Rusch, Guastello and Mason (1992) attempted to delineate symptom clusters that may be considered most distinctive of patients diagnosed with borderline personality disorder (BPD). Medical records were examined to assess the extent to which each of the eight DSM-III-R BPD criteria was present in 89 psychiatric in-patients diagnosed with BPD. Structural analysis revealed three symptom clusters that could explain symptomatology for a majority of the sample.

It is also evident from the literature review that researchers are studying the etiology of psychological disorders and they are investigating symptom construction expressed by symptom clusters. For example, Dunn et al. (2002) determined clustering of depressive symptoms in a combined group of unipolar and patients with bipolar disorder using Principle Components Analysis of the Beck Depression Inventory. They also compared unipolar and bipolar. These symptom clusters were examined for interrelationships, and for relationships to regional cerebral metabolism for glucose measured by positron emission tomography. Different depressive symptom clusters may have different neural substrates in unipolar, but clusters and their substrates are convergent in bipolar (Dunn et al., 2002). These researchers have contributed essentially to the knowledge of brain regions involved in the expression of depressive symptoms.

Symptom clusters in general medicine literature. In medicine, the concept of symptom cluster has been used to explore symptom categorization. Siegel, Myers and Dineen (1987) evaluated premenstrual symptoms in a group of women with severe premenstrual tension syndrome. They performed a factor analysis to establish the nature of symptom clusters in their selected sample. Similar to clinical observations reported earlier, their results revealed two distinct clusters of emotional and behavioral symptoms and two of physical symptoms.

Symptom clusters would possibly help clinicians when looking at etiology of general medical disorders. For example, Cowey and Hardy (2006) defined metabolic syndrome as composed of cardiovascular risk factors including increased body mass index and waist circumference, blood pressure, plasma glucose, and triglycerides, as well as decreased high-density lipoprotein cholesterol. The researchers noted that essence of the metabolic syndrome lies in the clustering of these risk factors which are associated with cardiovascular disease.

Nock, Li, Larkin, Patel and Redline (2009) described Syndrome Z which involves individual components of Syndrome X (the metabolic syndrome). They performed a factor analysis that revealed five syndrome components that included insulin resistance, obesity, hypertension, dyslipidemia, and sleep disturbance (Nock et al., 2009)

Other researchers suggested that symptom clusters could be used to investigate the etiology in congestive heart failure patients (Martin & Pinkerton, 1983). They recommended that congestive heart failure in adults should be conceptualized as a clinical syndrome. They explained that patients with congestive heart failure exhibit clusters of symptoms that define sets of systemic congestion, pulmonary congestion and inadequate cardiac output. Some were found to have potentially correctable anatomic or metabolic defects, others had myocardial failure, while some had both as underlying causes of the syndrome.

Eslick, Howell, Hammer and Talley (2004) conducted a study to determine how clusters of patients with symptoms compare to a clinical diagnosis in patients with irritable bowel syndrome and non-ulcer dyspepsia. They used a factor analysis and a k-means cluster analysis. The factor analysis identified nine symptom factors. These are diarrhea, constipation, dysmotility, dyspepsia or reflux, nausea and vomiting, bowel, meal-related pain, weight loss, and abdominal pain. The k-means cluster analysis identified seven distinct subject groups that included an undifferentiated group.

Symptom cluster can also be used to plan treatment. In a study by Jurgens et al. (2009), the researchers identified the number, type, and combination of symptoms in hospitalized HF patients. They also identified the contribution of comorbid illness and age to symptom clusters. Three conceptually unique symptom clusters were recognized in individuals with heart failure:

(1) acute volume overload cluster which includes shortness of breath, fatigue and poor sleep;

(2) emotional cluster which includes depression, memory problems and worry; and

(3) chronic volume overload clusters which includes swelling, increased need to rest and dyspnea on exertion.

The knowledge of symptom clusters may improve the ability to recognize symptoms appropriately and make symptom-monitoring more meaningful for patients (Jurgens et al., 2009). This example demonstrates the clinical application of the concept of cluster in complicated illnesses.

It has been shown through the literature review that factor analysis and cluster analysis identify different symptom clusters in different diseases, such as gastrointestinal (GI) syndromes (Eslick et al., 2004). Talley, Boyce and Jones (1998) conducted a study to determine whether distinct symptom groupings exist in the community of Sydney residents in Penrith, Australia. In total, 60% of the population reported four or more gastrointestinal symptoms. There was considerable overlap of irritable bowel syndrome (IBS) with dyspepsia and among the dyspepsia subgroups by application of the Rome criteria. Independently, 10 symptom groupings were identified by factor analysis.

Another example is people with chronic hepatitis C infection. Quality of life has been shown to be poor among people living with chronic hepatitis C. However, it is not clear how this relates to the presence of symptoms and their severity. Lang et al. (2006) conducted a study to describe the typology of a broad array of symptoms that were attributed to hepatitis C viral (HCV) infection. Principal components analysis identified four symptom clusters of

neuropsychiatric basis which include mental tiredness, poor concentration, forgetfulness, depression, irritability, physical tiredness, and poor sleep.

With regard to somatic diseases, researchers found clusters in chronic fibromyalgia patients. Recent evidence points to the likelihood of heterogeneity in the presentation and etiology of fibromyalgia (FM). In order to gain insight regarding this condition, a clear understanding of the symptomatology and consideration of potential FM subtypes is needed. Rutledge, Mouttapa and Wood (2009)conducted a study to determine whether clusters could be identified among 20 symptoms that participants in a prior online study identified and to elucidate the underlying structure of resultant clusters. Factor analysis was used on data from a study sponsored by the National Fibromyalgia Association. Results revealed that in this well-educated, primarily Caucasian sample, morning stiffness, fatigue, and not feeling rested in the morning were the symptoms with the highest severity scores.

Another example of somatic diseases is in multiple sclerosis patients. Motl and McAuley (2009) examined the symptom cluster of fatigue, pain, and depression and its direct and indirect prediction of physical activity behavior in a sample of individuals with multiple sclerosis (MS). The data analysis indicated that fatigue, pain, and depression represented a symptom cluster. Additionally, the symptom cluster had a strong and negative predictive relationship with physical activity behavior.

Recently, symptom clusters have been used in general medicine as a statistical method to describe the relationships between symptoms. For the purposes of this paper, statistical associations may be essential in defining symptom clusters. On the contrary, a small number of researchers have clearly described relationships between symptoms when they defined symptom

clusters. Hunter, Battersby and Whitehead (2008) provided a detailed analysis of the relationships between menopausal status and psychological and somatic symptoms. They used a principal components analysis to examine the relationships between symptoms.

Kotagal et al. (1995) analyzed 91 psychomotor seizures from 31 patients, seizure-free at least one year after temporal lobectomy. The researchers explored fifty symptoms in every seizure and noted the time of onset and ending. They used statistical analysis to define symptom clusters and to identify the order of appearance of symptoms. They found that the eighteen most common symptoms they examined formed a tight cluster showing a high degree of correlation. They recommended that this high correlation is essential in defining symptom clusters.

In another study, Kay et al. (1996) tried to assess the clustering of abdominal symptoms in a random population. Data from a cohort study of a 70-year-old Danish population were analyzed. They indicated that the defined level of significance of clusters was set at 1%. Their results revealed that in this 70-year-old population, abdominal symptoms occur in clusters comparable to clusters in younger populations.

There is no evidence in the literature regarding statistical opinions and patients' real symptom experience except for one example regarding asthma symptoms and coping. Kinsman et al. (1973) explored characteristics of subjective symptomatology of asthma within a group of 100 asthma inpatients. Researchers suggested that complex patterning of subjective symptomatology is common in asthma. Symptom patterns described across each of their identified five symptom clusters may help to define coping styles related to the role of emotions in asthma and the course of illness.

Another evident aspect in the general medicine literature is the underlying dimension in defining symptom clusters. In factor analysis, the relationship between each symptom and factor is essential. Barrett et al. (2002)—in an attempt to develop a sensitive, reliable, responsive and easy-to-use instrument for assessing the severity and functional impact of the common cold using a factor analysis—identified four underlying symptom dimensions: cough, throat, nasal and fever aches. In another study, Alvir & Thys-Jacobs (1991) explored the effect of calcium therapy on peri-menstrual symptom clusters in a randomized, double blinded, crossover trial of calcium supplementation. Using a factor analysis, they identified four symptom clusters. Internal consistency was high for scales based on these factors which were negative affect, water retention, food, and pain. Correlations between the scores ranged from .35 to .69. Scores were low during the inter-menstrual phase and much higher during both luteal and menstrual phases. They also looked at dimensions of symptoms that were affected by calcium treatment. They found that calcium supplementation reduced negative affect, water retention, and pain during the luteal phase and pain during the menstrual phase.

Another important aspect in defining symptom cluster is concurrence of symptoms within a cluster as a criterion in defining symptom. However, there is little evidence in the literature to support this essential aspect. Groppel, Kapitany and Baumgartner (2000) as well as Kotagal et al. (1995) defined seizure-related symptom clusters in their research as symptoms that occurred together. However, they didn't address concurrence in relation to statistical methods; neither did they discuss the timing of coexisting occurrence for symptoms to form a cluster.

Regarding the number of symptoms involved in a cluster, the existence of several symptoms appears to be necessary for symptom clusters to develop. More so, there is no

restriction in the number of symptoms that can be involved in a cluster. For example, Alvir and Thys-Jacobs (1991) performed a factor analysis in order to investigate peri-menstrual symptoms. They identified two symptom clusters where each cluster contained two symptoms. The first cluster is food, which includes increased appetite and craving for sweets. The second cluster is pain, which includes abdominal cramps and back pain.

Hammer et al. (2003) performed cluster analysis and factor analysis in order to investigate gastrointestinal symptoms in a subsample of patients with diabetes mellitus. The researchers identified only one cluster which included two symptoms; nausea and vomiting. Groppel et al. (2000) performed a cluster analysis of clinical seizure of psychogenic non-epileptic seizures. They identified three clusters. Two of those clusters contained seven symptoms while the remaining one contained only one symptom clusters. Collectively, these results propose that there is no specific number of symptoms restricted in a cluster.

Symptom clusters in nursing literature. In nursing literature, the concept of symptom clusters is a relatively new one. Several approaches to the concept of symptoms have been addressed, including symptom occurrence, symptom distress, and unpleasant symptoms. However, there is limited research and publications in literature about the use of the term "symptom clusters" and additionally there are changeable definitions.

Some researchers borrowed this concept from general medicine, and the disciplines of psychology and psychiatry. Others used this term to explain several symptoms appearing together. Hall (1988) invented a very useful method of understanding and teaching about the multiplicity of symptoms in Alzheimer's disease (AD). Each person with AD presents many different symptoms that change over time (Richards, 1990). Rather than compile a list of

symptoms and losses associated with various stages, Hall (1988) identified four symptom clusters that groups change associated with AD. These are intellectual losses, personality losses, planning losses, and progressively lowered stress threshold. Richards (1990) noted that each patient exhibits some symptoms from each category. Using this approach, Richards discussed that the goal for planning care is to compensate for the losses and to help the patient function better within their neurological capacity. Richards concluded that this approach is promising for practice and research as it is based on existing theories of stress and coping.

Earlier works in the oncology nursing literature attempted to address concurrence of symptoms and associative relationships among symptoms presented in oncology patients (B. Given et al., 2001; B. A. Given et al., 2007; Lenz et al., 1997; Sarna, 1993; Sarna & Brecht, 1997).

However, although researchers in oncology nursing literature did not specifically relate their findings to the concept of symptom cluster, their contribution have formed the foundation for the newly promising concept of symptom clusters. Recently in the oncology nursing literature, there is a fair amount of research that relates oncology patients' symptoms to the concept of symptom clusters (Armstrong, Cohen, Eriksen, & Hickey, 2004; Barsevick et al., 2006; Cheung, Le, & Zimmermann, 2009; Donovan & Jacobsen, 2007; Fan, Hadi, & Chow, 2007; Fox & Lyon, 2007; Gift, 2007; B. A. Given et al., 2007; Kim, McGuire, Tulman, & Barsevick, 2005; Kirkova et al., 2010; Lacasse & Beck, 2007; Liu et al., 2009; Maliski, Kwan, Elashoff, & Litwin, 2008; Miaskowski & Aouizerat, 2007).

Following the previously addressed concept analysis, Armstrong et al. (2004) reviewed and analyzed the literature to provide a critical analysis of the state of the science of research on

symptom clusters in the general oncology population compared to symptom research in the primary brain tumor population. They addressed symptoms as multidimensional experiences that include perceptions of frequency, intensity, distress, and meaning as symptoms occur and are expressed. They emphasized that a symptom can influence the occurrence and meaning of other symptoms. They found that symptoms occur in clusters in general oncology patients, and these clusters have been shown to influence functional status. The potential effect of tumor biology on symptom clusters is shown by the cluster of symptoms theorized to be associated with pro-inflammatory cytokine production. Unfortunately, studies of symptom clusters have not been reported for patients with primary brain tumors. They recommended that application of the symptom cluster paradigm to guide research is needed.

With regard to defining the symptom cluster, Dodd et al. (2001) conducted a study to determine the effect of the symptom cluster of pain, fatigue, and sleep insufficiency on functional status during three cycles of chemotherapy. They defined the concept of symptom cluster as follows: “When three or more concurrent symptoms are related to each other, they are called a symptom cluster. The symptoms within a cluster are not required to share the same etiology.” (Dodd et al., 2001, p. 465). They identified *relationship* and *concurrence* as the key attributes of a symptom cluster in cancer patients. However, they did not address the associative relationships or timing of symptoms occurring together (Dodd et al., 2001).

With regard to underlying dimensions of symptoms in defining symptom clusters, Woods et al. (1999) identified the clusters of symptoms women experience during the premenstrual period and assessed the reliability of the symptom clusters as reported by women with three peri-menstrual symptom patterns. They also compared the levels of severity for the symptom clusters

across menstrual cycle phases and by symptom patterns and estimated the stability of the symptom cluster rankings across three menstrual cycle phases. Using a factor analysis, they identified four symptom clusters representing the underlying dimensions of symptoms: turmoil, fluid retention, somatic symptoms, and arousal symptoms. With regard to the number of symptoms included in a cluster, it appears to be very diverse in nursing literature. Dodd et al. (2001) addresses the number of symptoms in the oncology population as a minimum of three symptoms in a cluster.

With regard to shared etiology between symptom clusters, Dodd et al. (2001) noted that symptoms in a cluster are not required to share the same etiology. On the other hand, Gulick (1989), in an attempt to validate a multiple sclerosis-related symptom checklist, made an assumption that symptoms would cluster together according to neurological functional systems affected by multiple sclerosis. Using a factor analysis, the author tested this hypothesis and the results supported this hypothesis. Mitchell and Woods (1996) conducted a study to describe the type and stability of symptoms experienced by midlife women. They recommended that within the five different symptom clusters they identified, it is possible that the underlying etiology of each symptom cluster may be diverse.

Link Between the Frameworks

PNI, TOUS, and Genetics

The primary aim of this research is to identify behavioral symptom clusters post-MTBI and to determine if there are differences in functional and cognitive outcomes based on symptom cluster. It is possible that these behavioral symptoms (depression, fatigue, and poor sleep) may share a common inflammatory etiology, and may develop as a result of pro-inflammatory

cytokine elevation (Kossmann et al., 1996; Shohami et al., 1994; S. H. Su et al., 2014; Woodcock & Morganti-Kossmann, 2013) that occurs post-injury and which may persist beyond the acute phase of injury. Inflammatory molecules from sites of injury or infection are known to signal the brain to engender inflammatory-related sickness behaviors, such as depressed mood, fatigue, and poor sleep (Dantzer et al., 1999; Dantzer, 2001; Dantzer & Kelley, 2007; Dantzer et al., 2008; Dantzer, 2009; Dantzer et al., 2011; Kelley et al., 2003). This is congruent with the PNI framework, which seeks to understand the impact of environmental stimuli, especially psychosocial stimuli on behaviors, emotions, neuroendocrine stress responsivity, and immune functions (Mathews & Janusek, 2011).

Furthermore, there is a compelling impetus for further exploration of genetic variants linked to inflammatory-related behavioral symptoms in individuals who suffer MTBI. Determining the extent to which genetic variants might contribute directly or indirectly to the symptoms of depression, fatigue, cognitive impairment, and poor sleep in MTBI patients is innovative, as results may provide novel biomarkers to predict more intense and persistent symptoms as early as possible. Thus, there is strong rationale for this research, which can improve long-term outcomes for MTBI survivors, who overcome their acute injury but who remain at risk for chronic and disabling behavioral symptom clusters. The addition of genetics adds another dimension to the PNI framework, since it is possible that genetic variants may predispose to more persistent behavioral symptoms post-MTBI. Above and beyond, the interconnectivity between the brain, emotions, behaviors, and immunity may in fact be guided and coordinated genetically.

Understanding these physiological (genetic) factors may lead to effective symptom management approaches and/or tailored strategies. Furthermore, the Theory of Unpleasant Symptoms (TOUS) (Lenz et al., 1995; Lenz et al., 1997) will guide the symptom-clustering aim, since it illustrates the importance of inclusion and consideration of the symptom experience as clusters. Incorporating the experience of symptom "as clusters" (adapted from TOUS) would allow researchers to have a broader view of the symptom-related variables (e.g., genetic variants) that contribute to the symptoms clusters, as well as the symptoms-related recovery outcomes (e.g., cognitive and functional recovery). The theory has positively influenced researchers' viewpoint on many issues related to symptom management, which they are accounting for in their research (Barsevick et al., 2006; Barsevick, 2007; Dodd et al., 2001; Miaskowski, Aouizerat, Dodd, & Cooper, 2007). Additionally, the TOUS has been compared to the symptom management model published by Dodd et al. (2001). Although the symptom management model is focused more on the selection of symptom management strategies than on an explanation of the symptom experience, researchers have acknowledged the importance of this comparison.

The "Perfect Fit" of the Chosen Frameworks

Adding the TOUS framework as a third dimension to learn more about physiologic and psychological aspects and the experience of unpleasant symptoms "as clusters", and blending it with the PNI and genetic framework, will contribute significantly to the nursing body of knowledge in understanding unpleasant symptoms and guiding management strategies. Specifically, The PNI framework will help clarify these relationships, where it is possible that these co-occurring symptoms synergize to negatively impact cognitive and functional recovery, in addition, to the relationship between genetic variants and persistent behavioral symptoms

post-MTBI. This is suggestive that these relationships are correlated to the unique mind and body connection and that the frameworks of PNI, genetics, and TOUS are all a perfect fit. The use for these frameworks in viewing the aim of this research "3-dimensionally" and their "perfect fit/blend" will guide the discovery and lead to remarkable advancement in the knowledge regarding improvement of quality of life and cognitive and functional recovery post-MTBI.

MTBI and Health Outcomes: Overview

MTBI: Health Outcomes MTBI and Psychological Long-term Comorbidities

Symptoms experienced. Although experiences of MTBI patients are described in literature, there is lack of evidence to guide health care providers to identify which MTBI patients are at greater risk for behavioral symptoms. Explication of the psychobiological mechanisms that underlie behavioral symptom expression in trauma survivors is a critical first step that will improve risk assessment and ultimately lead to prevention and/or better management of trauma-associated behavioral symptoms. In the following section, previous evidence describing behavioral symptoms experienced by MTBI after the injury will be addressed; specifically, anxiety, depression, fatigue, and sleep disturbance. Then, evidence of symptom cluster in MTBI patients and outcomes (cognitive impairments) will be addressed in the following section.

MTBI and anxiety. Ample research indicates that anxiety symptoms are prevalent in the aftermath of a mild TBI (Hiott & Labbate, 2002; Koponen et al., 2002; Ma et al., 2014; Mooney & Speed, 2001; Moore et al., 2006; Rao & Lyketsos, 2002; Rao et al., 2010; R. Ruff, 2005; R. M. Ruff, 2011; Stulemeijer et al., 2006; Woodcock & Morganti-Kossmann, 2013). Anxiety in

general is reported at rates as high as 70% in patients with TBIs (Rao & Lyketsos, 2002). Mooney & Speed (2001) classified 24% of their participants with mild TBIs as having developed an acquired anxiety disorder. The most commonly reported anxiety symptoms after MTBI include free-floating anxiety, fearfulness, intense worry, generalized uneasiness, social withdrawal, inter-personal sensitivity, and anxiety dreams (Rao & Lyketsos, 2002).

Recently, Ma et al. (2014) conducted a study to determine the course of depression, anxiety, and sleep disturbance in patients with MTBI compared to healthy participants. They assessed patients at baseline after the injury and then at six weeks post-MTBI using the Beck Anxiety Inventory (BAI), the Beck Depression Inventory II (BDI), and the Pittsburgh Sleep Quality Index (PSQI). Their findings revealed that the average scores of the MTBI group were significantly higher than those of the control group only at baseline, and average scores all had improved and decreased significantly six weeks later.

Interestingly, only the PSQI score improved to a level that was not significantly different from that of the control group. They concluded that MTBI causes depression and anxiety and diminished sleep quality. However, patients recovered six weeks post-MTBI, and sleep quality improves to a pre-MTBI level (Ma et al., 2014). The researchers identified that one of the major limitations of this study was that some of the patients were using medications before or after suffering MTBI that may have influenced their results; however, there was no mention of the type of medications the study participants were using. It is a noteworthy limitation and other researchers should account for pre- and post-injury medications. Regardless of the limitations, these results provide valuable information for understanding the development and recovery of long term outcomes following an MTBI. This highlights the importance of the need for more

research in this area in combination with biomarkers to better identify which patients are at more at risk for suffering anxiety and other symptoms, allowing early intervention.

MTBI and fatigue. Fatigue is a prominent symptom following TBI, with self-report prevalence rates ranging from 43%–73% (Belmont et al., 2006). Fatigue can also endure as a predominant symptom several years after the TBI (Cantor et al., 2008; Ouellet et al., 2004). Fatigue after TBI has the potential to impact activities of daily functioning, occupational and leisure activities, and thus quality of life (Cantor et al., 2008; Ouellet et al., 2004). It has been emphasized that researchers need to conceptualize fatigue after TBI as a multidimensional symptom that includes components of physical, psychological, motivational, situational, and activity (Cantor et al., 2008; LaChapelle & Finlayson, 1998). Several factors are found to be highly correlated with post-TBI fatigue, including sleep disturbance, perceived stress, somatic symptoms, anxiety, and depression (Bay & Xie, 2009; Bushnik, Englander, & Wright, 2008; Ponsford et al., 2000). For example, Bushnik et al. (2008) conducted a prospective longitudinal study to quantify fatigue and associated factors during the first two years after TBI. Patients were assessed at three time points (6, 12, and 18-24 months after TBI). Self-reported fatigue improved during the first year, as did pain, sleep quality, cognitive independence, and involvement in productive activity. However, they found that further changes up to two years after TBI were not observed, but the subset of individuals who reported significant increases in fatigue over the first two years demonstrated poorer outcomes in regards to cognition, motor symptoms, and general functioning than those with decreased or stable fatigue (Bushnik et al., 2008)

Systematic and comparative studies on fatigue after MTBI are limited. However, in an important study (Bay & Xie, 2009), researchers examined the relationships between chronic

perceived stress, cortisol levels, and posttraumatic brain injury fatigue in outpatients. Seventy-five injured persons with TBI and their relatives/significant others participated in this cross-sectional study. Data collection including interviews and self-reported data from the Neuro-functional Behavioral Inventory, the Perceived Stress Scale, the Profile of Mood States-Fatigue subscale, the McGill Pain Scale, as well as self-collection of salivary cortisol over a 12-hour period (N = 50). In their analysis, researchers regressed fatigue on perceived health, cognitive, somatic, and depressive symptoms, present level of pain, cortisol levels, and perceived chronic stress. Interestingly, they found that only perceived stress and somatic symptoms were significantly associated with post-TBI fatigue (p = .03; p = .05, respectively). Additionally, perceived chronic stress alone explained 37% of the variance in post-TBI fatigue. When somatic symptoms were included in the model, perceived chronic stress accounted for 50% of the variance in post-TBI fatigue. The Centers for Disease Control Acute Concussion guidelines has strongly suggested fatigue and stress management interventions that are beneficial in reducing these post-MTBI symptom (Bay & Xie, 2009; Stulemeijer et al., 2006).

Subsequently, trauma comparison groups were examined to determine whether the persistence of fatigue was attributed to the brain injury. Stulemeijer et al. (2006) conducted the first study to determine the severity of fatigue six months after MTBI and its association to other outcomes. For example, these investigators tested whether injury indices, such as Glasgow Coma Scale scores, are related to higher levels of fatigue. In their study, they recruited a total of 299 MTBI patients and 287 minor-injury patients with an ankle or wrist distortion (control group). They reported that 32% of MTBI patients and 12% of the control patients were severely fatigued. They found that severe fatigue was highly correlated with the experience of other symptoms,

limitations in physical and social functioning, and fatigue-related problems like reduced activity. Furthermore, they reported that nausea and headache experienced in the ED were significantly related to higher levels of fatigue at six months (Stulemeijer et al., 2006). Their findings call for further investigation since higher levels of fatigue seems to be related to acute symptoms and mechanism of injury rather than injury severity indices.

In a longitudinal prospective study researchers examined fatigue prevalence, severity, predictors, and covariates over six months post-MTBI. Post-MTBI fatigue was prevalent at one week (68%), at three months (38%), and at six months (34%) (Norrie et al., 2010). Interestingly, depression and earlier prevalence of fatigue were highly correlated with later fatigue (Norrie et al., 2010). Although fatigue was exacerbated by depression, it was not related to increased anxiety. Another noteworthy finding is that fatigue was categorized or labeled as "laziness" by family or friends in 30% of cases, which could reduce care-seeking behavior. Most importantly, their findings revealed that fatigue was a persistent post-concussion symptom that mainly resolved in the first three months, and highly recommended that the optimum intervention placement be at three months post-MTBI. Thus, assessing fatigue early on post-injury is valuable and there is more need for studies regarding the prevalence and mechanism of fatigue post-TBI (Norrie et al., 2010)

Post-TBI fatigue appears to be persistent after mild-to-moderate TBI. For example, in those who were hospitalized and followed prospectively for symptom persistence and disability outcome, fatigue was present in 57% and persisted in 42% of the sample at one year (van der Naalt, van Zomeren, Sluiter, & Minderhoud, 1999). These studies highlight the importance of addressing fatigue after MTBI to identify biomarkers that can discern which MTBI patients are

at risk for more severe symptoms. Such identification will permit the implementation of interventions earlier for better quality of life.

MTBI and sleep disturbance. The increased incidence of sleep disorders after TBI relative to the general population has been increasingly recognized (Castriotta et al., 2007; Watson et al., 2007). Sleep disturbance is a common complaint following TBI, and it is more common with MTBI than severe or mild TBIs (Beetar et al., 1996; Clinchot et al., 1998; Fichtenberg et al., 2000; Mahmood et al., 2004). In recent reviews, 30–70% of TBI survivors reported sleep disturbances (Orff et al., 2009). Sleepiness may present as a separate symptom or along with other sleep disorder (e.g., sleep apnea, narcolepsy, or post-traumatic hypersomnia, delayed sleep phase, insomnia, fatigue, and alteration of sleep-wake schedule to movement disorders) (Castriotta et al., 2007; Orff et al., 2009; Watson et al., 2007). However, insomnia has been found to be more prevalent in mild TBI individuals (Ouellet et al., 2004). Most of the time the sleep disturbances are directly related to the TBI, enduring for months and/or years after the injury, consequently hindering the recovery process and return to pre-injury function (Orff et al., 2009).

In the previous section the importance of fatigue subsequent to traumatic brain injury was described. Although fatigue and poor sleep are related, the cause-effect relationship between MTBI-related sleep disturbance and MTBI-related fatigue remain unclear. Thus, it is important to include an assessment of sleep disturbance, along with fatigue, in this investigation of behavioral symptoms post-MTBI. In support of this, Beaulieu-Bonneau and Morin (2012) reported results of a prospective controlled study examining the correlation between sleepiness and fatigue in 22 adults with moderate to severe TBI, who were evaluated between one and 11

years post-head injury. These investigators assessed outcomes using polysomnography, maintenance of wakefulness test, Epworth Sleepiness Scale, Functional Outcomes of Sleep Questionnaire, Multidimensional Fatigue Inventory (MFI), Visual analogue scales (VAS), sleep diary, Insomnia Severity Index (ISI), Beck Depression Inventory (BDI-II), and State-Trait Anxiety Inventory (STAI-Trait). Their results revealed that the participants with TBI reported higher subjective fatigue as a more prominent symptom than sleepiness; the TBI participants also used compensatory strategies to reduce fatigue (e.g., napping and spending an increased amount of time in bed). This study is limited; however, due to the heterogeneity of the degree of brain trauma (i.e., moderate to severe) and the long time frame post-trauma of study participants (Beaulieu-Bonneau & Morin, 2012). Although this study excluded mild TBI patients, the findings have implications for research evaluating behavioral symptoms in this group.

Orff et al. (2009) summarized the current literature and remaining issues regarding the significant prevalence and potential consequences of sleep disturbance following mild TBI. Fascinatingly, the majority of research indicates that MTBI is highly correlated with increased sleep disturbances when compared to severe TBI (Orff et al., 2009). In their review they highlight the limitation of research in the inability to explain the reason why MTBI is more commonly associated with sleep disturbances. They speculated that it could be attributed to the differences in the nature of the injury, where diffuse injuries and axonal shearing (common with MTBI) could lead to impaired global functioning and arousal, as opposed to the more acute and focal trauma injuries (severe TBI). Another issue is differences in treatment modalities with less severe injuries. Most of these patients are discharged at the ED, thus they may not be receiving the adequate follow-up, which aggravates their recovery, impeding their sleep quality and quality

of life in general (Orff et al., 2009). Further, Mahmood et al. (2004) hypothesized that severe TBI patients maybe be unaware of their deficits and underreported sleep issues, which is most likely the case in this population. On the other hand, MTBI patients may be inflating their sleep disturbances issues because of the difficulties of going back to their daily routine in the face of increased stress in the aftermath of their injuries, which although mild, could be worrisome (Mahmood et al., 2004). It is also speculated that differences in neurobiological mechanisms between mild and severe brain injuries may explain the greater incidence of sleep disturbance with MTBI (Mahmood et al., 2004).

The above-mentioned studies emphasize the need for more research regarding sleep disturbance in those who suffered an MTBI. Sleep disturbance has many implications as it impedes the physical and cognitive recovery of TBI patients (Orff et al., 2009), hinders patients from the vitality of regaining lost functions, hampers patients from engaging in activities of daily living, and further reduces quality of life (Parcell, Ponsford, Rajaratnam, & Redman, 2006). In addition, MTBI patients with sleep disturbances are more likely to suffer from concomitant headaches, depressive symptoms, and irritability. Of note, patients with MTBI who experienced sleep disturbance also reported feeling depressed at ten days and six weeks after their injury (Chaput et al., 2009).

Furthering the understanding of sleep disorders after MTBI is needed which will lead to earlier diagnosis and earlier treatments of sleep disorder to provide better care to the patients and to understand this less communicated and recognized symptom. Future research to elucidate the nature and extent of the relationship between MTBI and sleep disturbance is needed, especially to uncover the specific types, causes, and severity of TBI that most often lead to sleep problems,

as well as the specific consequences of sleep disturbance post- MTBI (e.g., impaired physical or cognitive recovery)(Orff et al., 2009).

MTBI and depression. MTBI patients are at risk of depression (Auxemery, 2012; Bay & Donders, 2008; Bay, 2009; Beaulieu-Bonneau & Morin, 2012; Guskiewicz et al., 2007; Kristman et al., 2014; Levin et al., 2005; Mooney & Speed, 2001; Ponsford et al., 2011; Rapoport et al., 2003; Rapoport et al., 2006) and depression is highly correlated with poor recovery (Guskiewicz et al., 2007; Mooney & Speed, 2001). Prevalence of depression is 15% in the first three months post-MTBI (Rapoport et al., 2003) and 18% up to a year after MTBI (Rao et al., 2010). Few studies have investigated the relationship between MTBI and depression, as well as the risk factors related with the development of depression after MTBI (Levin et al., 2005; Rao et al., 2010). Of those studies, older age and abnormal computerized tomography (CT) scans are reported as risk factors for developing major depression in MTBI within three months of injury and could possibly predict the development of depression within the first three months post-TBI (Levin et al., 2005).

These findings are similar to a longitudinal study that followed a sample of 43 MTBI patients for one year and found that increased age and presence of frontal subdural hemorrhage were the only two significant findings noted in the depressed group compared to the non-depressed group (Rao et al., 2010). The results of these studies are suggestive that other biological factors could be identified as predictors in future research. Using predictive parameters can help ED personnel identify MTBI patients, who are at higher risk before discharge and thus appropriate referrals can be made to prevent the suffering from debilitating symptoms.

In conclusion, although experiences of MTBI patients are described in literature, understanding the psychiatric morbidity following MTBI remains limited, even though these comorbidities are prevalent. Several studies have reported short- and long-term increased rates of comorbidities following TBI; most studies however, combined mild and moderate to severe TBI in their analyses. Hence, it is difficult to draw conclusions regarding psychiatric outcomes following MTBI separately. Additionally, there is lack of evidence to guide health care providers to identify which MTBI patients are at greater risk for behavioral symptoms clusters.

MTBI: Symptom Clusters and Cognitive and Functional Outcomes

Symptom clusters in MTBI population. In this literature review, we demonstrated that MTBI research has primarily focused on studying symptoms (single, paired, or all symptoms) experienced three, six, and twelve months or years post-injury. As mentioned earlier, MTBI patients can suffer from depressive mood, fatigue, and poor sleep for weeks and months after injury (Ayalon et al., 2007; Bay & Xie, 2009; Beaulieu-Bonneau & Morin, 2012; Beetar et al., 1996; Chaput et al., 2009; Levin et al., 2005; Norrie et al., 2010; Ponsford et al., 2000; Rapoport et al., 2006). Prevalence of depression is 15% in the first three months post-MTBI (Rapoport et al., 2003) and 18% up to a year after MTBI. (Rao et al., 2010) Sleep disturbance is also a common complaint, (Beetar et al., 1996; Clinchot et al., 1998; Fichtenberg et al., 2000; Mahmood et al., 2004) and MTBI patients with sleep disturbance are more likely to suffer depressive symptoms (Chaput et al., 2009). Likewise, fatigue is a frequent burdensome symptom post-TBI, and although the nature of fatigue may change with time, it can persist for years after the initial injury (Mollayeva et al., 2014). The incidence of fatigue after TBI varies from 21% to73%, depending on patient characteristics (e.g., severity of injury, time since injury, etc.) and

how fatigue is measured (Belmont et al., 2006; Borgaro et al., 2005; Lidvall et al., 1974; Middleboe et al., 1992; Ponsford et al., 2011). Although fatigue is linked to poor recovery post-TBI, a recent systematic review concluded that the impact of fatigue on patient outcomes is unclear and more intensive investigation is essential (Mollayeva et al., 2014). Depression, fatigue, and poor sleep have been independently associated with impeded recovery from MTBI for cognitive function (Guskiewicz et al., 2007; Mooney & Speed, 2001; Orff et al., 2009) and the resumption of pre-injury lifestyle and responsibilities (Patterson & Holahan, 2012; Silver et al., 2009). However, predictive power may be gained by evaluating clusters of symptoms that co-occur and which may portend slower recovery. Determining the existence of symptom clusters is vital in MTBI patients and will lead to further crucial investigation into the mechanisms that underlie these clusters that will advance the knowledge regarding cognitive and functional outcomes. Although there is ample of research in the literature about symptoms experienced post-MTBI, to date only six studies used cluster analysis to identify symptom profiles related to recovery (Goldstein, Allen, & Caponigro, 2010; Hellstrom et al., 2013; Hoffer et al., 2016; Snell et al., 2015; Velikonja et al., 2010).

In one study, Snell et al. (2015) conducted a prospective observational study to examine associations between baseline demographic, clinical, psychological variables, and six-month follow-up outcome. They analyzed the data using a two-step approach to cluster analysis, which revealed three clusters of psychological adaptation (high, medium, and low) related to injury outcomes (Snell et al., 2015). The identified cluster-group membership was significantly correlated with outcomes squeal. This study supports the notion that groups could be identified

early post-injury based on psychological factors, and that different group membership is correlated with different recovery outcomes and sequelae.

A second study used cluster analysis to identify subgroups of MTBI patients based on a symptom intensity profile (Hellstrom et al., 2013). Findings revealed that those with minor symptoms had a reduced risk for a positive CT or MRI findings, whereas the high symptom level group experienced difficulty returning to work and reported high levels of anxiety, depression, and disability.

In a recent study, researchers (Hoffer et al., 2016) compared MTBI patients to controls to examine the use of vestibular testing to diagnose MTBI. They identified five symptom clusters: (1) Post-Traumatic Headache/Migraine, (2) Nausea, (3) Emotional/Affective, (4) Fatigue/Malaise, and (5) Dizziness/Mild Cognitive Impairment. They highlighted the importance of considering other symptoms to critically provide prognostic value and treatment for best short-term outcomes or prevention of long-term complications (Hoffer et al., 2016).

Goldstein, Allen, and Caponigro (2010) performed two cluster analyses using retrospective data from veterans with TBIs to explore whether subtypes emerged based on cognitive performance on test batteries. They found cluster membership was associated with education, age, and employment status, but not with neurological findings (e.g., lesion location) (Goldstein et al., 2010)

In addition, Velikonja, Warriner, and Brum (2010) used the Personality Assessment Inventory (PAI) to detect emotional and behavioral profiles in acquired brain injury (ABI) patients (n=440). They analyzed their data by a three-step cluster analytic approach, and seven clusters were identified: (1) multiple high symptoms with antisocial and borderline personality

features and substance use; (2) high somatic and depressive symptoms; (3) high depression; (4) normal/no major concerns; (5) high substance use with antisocial personality features; (6) normal with possible minimization of concerns; and (7) multiple high symptoms with borderline personality features but no substance use.

An interesting approach when taking the demographic information in combination would provide descriptive insight into the nature of post-injury affective and behavioral symptoms, which in turn could lead to establishing a more inclusive conceptualization of needs with specifically customized treatment modalities (Velikonja et al., 2010)

Lastly, Bailie et al. (2016) explored the taxonomy of combat-related MTBI (n=1341 military personnel) based on symptom patterns within two years of evaluation. Cluster analysis revealed four subtypes (primarily psychiatric PTSD group, a cognitive group, a mixed symptom group, and a good recovery group. Their results are indicative of the need for unique treatment resources and programs (Bailie et al., 2016).

However, although each of these studies supports this proposal, neither evaluated inflammation-related behavioral symptom clusters as a potential predictor *of* cognitive recovery. Thus, there is a critical need to further develop prognostic models of MTBI to identify those at greater risk for poorer cognitive and functional recovery and who will most benefit from targeted therapy (McMahon et al., 2014). Explication of the cluster of behavioral symptoms (i.e., depressive mood, fatigue, and poor sleep) posited to underlie cognitive and functional recovery in MTBI survivors is a critical first step to improve risk assessment and to better manage post-MTBI outcomes (Lingsma et al., 2014).

Symptom clusters and outcomes. Cognitive impairment is prevalent in the acute phase after MTBI, and these impairments include impaired verbal memory and slowed speed of language comprehension and information processing (De Monte, Geffen, May, & McFarland, 2004), difficulties in attention, episodic memory, executive functions, working memory, information-processing speed, language functions, and visio-spatial processing that can last for months or even years (Kinnunen et al., 2011). MTBI patients with a decreased Glasgow Coma Scale score in the acute phase exhibit significantly decreased and disturbed cerebral perfusion in the frontal and occipital grey matter as seen on a normal non-contrast CT; moreover, these observations correlated with severity of injury and cognitive impairment (Metting et al., 2009).

While these acute cognitive impairments are overwhelming, MTBI patients also have long-term cognitive impairments related to trauma-induced neuro-degeneration. These impairments include impairment of memory, changes in executive cognitive function affecting the accomplishment of tasks involving complex cognition, emotional instability causing deficient judgment and insight, impaired attention and concentration, struggles with speed of information processing (slowed), and sensorimotor impairments (Binder, Rohling, & Larrabee, 1997; Patterson & Holahan, 2012; Silver et al., 2009). In general, MTBI patients experience problems with attention and concentration to accomplish one goal for a given time, they are unable to efficiently shift attention to another goal, and/or they are unable to handle interruptions effectively (Binder et al., 1997).

The long-term higher-level cognitive processes impairments following MTBI are more problematic to these patients than simpler cognitive tasks, such as keeping track of daily activities, responsibilities, and/or appointments that might not be affected as much (Silver et al.,

2009). The incidence of these long-term cognitive impairments following MTBI lead to a debilitating failure to resume their pre-injury lifestyle, such as returning to work, academic, and/or social life. In addition, MTBI patients can have adverse long-term psychiatric, neurologic, and psychosocial morbidities (Vanderploeg, Curtiss, Luis, & Salazar, 2007). For example, MTBI patients report poor psychosocial outcomes, including an increased self-reported disability, under-employment, low income, and marital problems (Vanderploeg et al., 2007). Usually, the expected recovery from cognitive impairments after MTBI varies from week to months. Yet, 10-20% of MTBI patients will experience persistent cognitive impairments beyond the acute phase, which significantly disrupts their capacity to resume many pre-injury activities (Patterson & Holahan, 2012; Silver et al., 2009)

At present, it still remains indistinguishable whether the long-term cognitive impairments correlate with pathophysiological factors of the injury itself, or if these impairments are a result of the influence of other psychological adverse outcomes such as fatigue, sleep, anxiety, and depression (Bigler, 2008; Wood, 2004).

Historically, researchers attempted to theorize and explain the development of long-term cognitive impairment post-TBI. Some suggested that psychological distress post-MTBI influences the occurrence and maintenance of cognitive impairments experienced by MTBI (Ryan & Warden, 2003). Yet, the research related to the influence of symptoms on cognitive and functional outcomes in MTBI patients is limited. However, relevant to this proposal, Ramati et al. (2009) examined the association between psychiatric morbidity and cognitive functioning in 86 electrical injury patients. They found that patients with multiple psychiatric morbidities showed worse cognitive impairment (verbal memory, executive functioning, and attention) when

compared to electrical injury patients with one or no post-injury psychiatric morbidities. Their results delineate the relationship between psychological symptoms and cognitive and functional recovery, and this worthy of investigation in the MTBI population. Others noted a relationship between level of depression and performance on cognitive tests. The incidences of depression were correlated with worse cognitive impairment and poor social functioning (Busch & Alpern, 1998). In particular, worse prognosis of depression was highly associated with impaired mental flexibility and visuomotor tracking (Veiel, 1997). This is suggestive of the association between depression and TBI, and there is a need for more research to explore whether subgroups of patients with MTBI could be identified according to their symptom clusters to delineate those who are at risk poor cognitive and functional outcomes.

On the other hand, it is well established that one of the causative factors linked to cognitive impairment following MTBI is neuro-inflammation. For example, the proinflammatory cytokine IL-1β is known to affect hippocampal-dependent memory tasks (Huang & Sheng, 2010). Increased pro-inflammatory cytokines IL-1beta, IL-6 and TNF-alpha are known to play a role in complex cognitive processes at the molecular and cellular level, as these cytokines reduce synaptic plasticity, affect neurogenesis and neuromodulation, and result in neurodegeneration (McAfoose & Baune, 2009; J. A. Smith, Das, Ray, & Banik, 2012). In other words, cognitive functions are at risk when disruption of cytokine levels exists. Most importantly, it is suggested that cytokine dysregulation could orchestrate the long-term development and pathogenesis of neuropsychiatric disorders such as major depression (McAfoose & Baune, 2009). When the microglia are activated post-injury, they release pro-inflammatory cytokines (e.g., IL-1, IL-6, and TNF-α). Acute microglial activations of these pro-inflammatory cytokines are beneficial and

neuroprotective, but chronic microglial activation may also be toxic and lead to neurodegeneration (J. A. Smith et al., 2012).

Recent findings suggest that microglial activation and pro-inflammatory cytokines could be used as targets in the treatment of neuro-degeneration (J. A. Smith et al., 2012). Briones, Woods, and Rogozinska (2013) conducted a study to determine the effects of environmental enhancement (EE) (refers to conditions that provide increased social, cognitive, and physical stimulation) in attenuating the long-term consequences of MTBI subsequent to neuro-inflammation, alterations in brain energy metabolism, and cognitive impairment. The study was conducted using rodents that were randomly assigned to receive either MTBI using the controlled cortical injury model or sham surgery. The animals were then randomized again to EE housing or standard laboratory housing. Cognitive and behavioral testing, and the levels of the pro-inflammatory cytokines IL-1β and TNF-α and the anti-inflammatory cytokine IL-10 were measured after 4 weeks of recovery in the brains tissue, specifically the ipsilateral region. The results revealed that EE correlated with decreased levels of the pro-inflammatory cytokines IL-1β and TNF-α and enhanced levels of the anti-inflammatory cytokine IL-10 after MTBI. Additionally, EE alleviated MTBI-induced cognitive impairment. Thus, these findings demonstrate the potential of EE to attenuate the persistent neuro-inflammatory state, which occurs after MTBI.

Primarily, it is crucial to advance the knowledge symptom clusters and cognitive and functional outcomes especially in this understudied MTBI population. Despite the evidence that supports the association between specific symptoms and cognitive impartment, the research on symptom clusters and their influence on cognitive and functional outcomes remains limited,

suggesting the need for more research regarding their associations. Thus, it is imperative to attempt to identify subgroups within the MTBI patients that may account for the differences in experiences, symptoms, and variation in cognitive and functional recovery outcomes following MTBI. This will address the gap in the literature and improve understanding of symptom-clustering in MTBI patients and will aid in the development of rehabilitation programs that are tailored to specific profiles.

It is hoped that the symptom cluster approach and analyzing the symptoms that are experienced concurrently will aid in profiling MTBI patients. The evolution of innovative cognitive and functional outcome initiatives and treatment modalities aimed to manage the consequences of MTBI, along with evidence from behavioral psychotherapy and cognitive remediation, could be applied to help improve cognitive function in MTBI (Tiersky et al., 2005). This highlights the need for more studies to identify predictive tools to identify patients who are at more risk for these persistent long-term cognitive impairments in order to intervene early on. Again, the devastation resulting from long-term impaired cognitive functioning could correlate to other adverse long-term outcomes. There is a need for the earlier assessment of cognitive and functional impairments for the purposes of identifying patients at risk for long-term outcomes. More broadly, there is a need for increasing the knowledge regarding the most prevalent impaired cognitive functions, understanding the recovery timeframe for these patients, and early interventions.

MTBI and Biological Mechanisms

MTBI and Genetic Variants (SNPs)

Several studies have described the possible adverse behavioral outcomes following MTBI

(Bay & Donders, 2008; Bay & Xie, 2009; Bay, 2009). In particular, study findings reveal that patients suffer from fatigue, sleep disturbances, and depression for weeks and months following MTBI (Ayalon et al., 2007; Bay & Xie, 2009; Beaulieu-Bonneau & Morin, 2012; Beetar et al., 1996; Chaput et al., 2009; Levin et al., 2005; Norrie et al., 2010; Ponsford et al., 2000; Rapoport et al., 2006). Yet, few studies have attempted to investigate predictive factors to identify the long-term development of symptoms following MTBI (R. M. Ruff et al., 2009). A comprehensive review emphasized the need for research to develop predictive tools to identify risk for poor outcomes post-MTBI (R. Ruff, 2005). Furthermore, as Lingsma et al. (2014) has pointed out, "explication of the psychobiological mechanisms that underlie behavioral symptoms in MTBI survivors is a critical first step to improve risk assessment, and ultimately prevent and/or better manage post-MTBI behavioral symptoms" (Lingsma et al., 2014). The pathogenesis of psychological long-term outcomes following MTBI is not fully understood.

Genetic variants might contribute to the development of psychological long-term outcomes in patients with MTBI. Studies that focused on the relationship between behavioral outcomes and genetic variants following MTBI are limited and it still remains unknown as to whether the genetic variants could be used to predict adverse psychological outcomes post-MTBI. Thus, it presents a fruitful area of research, in view of the fact that although experiences of MTBI patients are described in literature, there is lack of evidence to guide health care providers to identify which MTBI patients are at greater risk for behavioral symptoms. Explication of the psychobiological mechanisms that underlie behavioral symptom expression in MTBI survivors is a critical first step that will improve risk assessment and ultimately lead to prevention and/or better management of trauma-associated behavioral symptoms. It is prevalent

that the recovery from MTBI is a nonlinear process and the time-frame for complete recovery, for some, may endure for months and years or never be achieved (R. M. Ruff, 2011). First there is a need to develop standardized behavioral measures linked to behavioral symptoms, which would greatly benefit MTBI patients by attending to those who are at risk for behavioral symptoms at their early stages of treatment. Furthermore, since it is shown in many studies that the behavioral outcomes seem to be independent of severity of injury, it is therefore useful to examine the role of other unique factors of MTBI, such as genetic variants which may contribute to the development or susceptibility of persistent behavioral symptoms clusters. Researchers have suggested and highlighted the need for the development of prognostic models of MTBI that will serve the symptomatic subgroups of MTBI patients that warrant elucidation (McMahon et al., 2014).

Genetic variants and symptoms clusters. Genetic variants may contribute to risk for clustering of behavioral symptoms (depressive mood, fatigue, and poor sleep) following MTBI. Yet most studies to date have not evaluated whether genetic variants predict a more intense and/or prolonged clustering of these behavioral symptoms. Further, genetic association analyses suggest that certain common single nucleotide polymorphisms (SNPs) may negatively influence recovery from MTBI (Feng et al., 2015; Lanctot et al., 2010; McAllister et al., 2005; McAllister et al., 2008; Pap et al., 2012; Roetker et al., 2012). It is possible that certain SNPs may predispose individuals to experience persistent behavioral symptom clusters after MTBI, further impeding recovery. Identification of such associations will permit earlier intervention for those at risk for behavioral symptoms clusters. McAllister et al. (2005) found that rs1800497 allele status was associated with cognitive function post-mild-to-moderate TBI (McAllister et al., 2005;

McAllister et al., 2008). Subsequently, others examined the influence of the (C/T) SNP rs1800497 on post-TBI outcome using data from two multicenter studies: the Citicoline Brain Injury Treatment trial and the TRACK-TBI Pilot. Findings showed that the ANKK1 T/T genotype is related to poorer verbal learning performance at six months post-TBI(Yue et al., 2015). Previous evidence also suggests that SNPs play a role in predisposing patients to depression (Feng et al., 2015; Pap et al., 2012; Roetker et al., 2012) and also may explain differential response to treatment (Lanctot et al., 2010). The identification of these genetic variants may shed light on the mechanisms involved in treating non-response and lack of tolerance to treatment in TBI patients (Lanctot et al., 2010).

Moreover, depression has been linked to inflammation and has been strongly associated with increased inflammatory cytokines (Haroon et al., 2012; A. H. Miller et al., 2009), and there is possibly interaction between SNPs and inflammatory cytokines (Lotrich, Albusaysi, & Ferrell, 2013). Thus, patients with Val/Met polymorphisms rs6265 are at greater risk for inflammatory cytokine-associated depression, where Val66Met BDNF polymorphism (rs6265) and BDNF levels have been associated with depression (Lotrich et al., 2013)—notably, the distinct genetic variant APOE genotype (Feng et al., 2015) and polymorphism (e.g., rs6265) (Lotrich et al., 2013), The variants rs1800479 (Roetker et al., 2012) and rs4680 (Nyman et al., 2011; Pap et al., 2012; Vrijsen et al., 2014) may aid in predicting distinct sets of depression symptoms (Lotrich et al., 2013), greater treatment response and tolerability (Lanctot et al., 2010), and/or occurrence of intense adverse events (Lanctot et al., 2010) . SNPs, therefore, are viable targets for improving resiliency against developing inflammatory cytokine-associated depression (Lotrich et al., 2013).

Additionally, SNP rs6311 is correlated with fatigue and reveals allele-specific binding of a transcription factor at that serotonergic system locus.(A. K. Smith et al., 2008). Meanwhile, SNP rs6311 can affect both transcription factor-binding and promoter methylation, and this along with stress response can influence the rate of HTR2A transcription in a genotype and methylation-dependent manner. This highlights the importance of molecular determinants of transcriptional regulation of major genes and the medical importance of integrating functional genomics (Falkenberg, Gurbaxani, Unger, & Rajeevan, 2011). Since previous studies focused on TBI in general, it is thus the purpose of this project to explore which SNPs are associated with more intense and/or persistent behavioral symptom cluster (depressive mood, fatigue, and poor sleep) post-MTBI, which may negatively influence recovery. Thus, there is a need to explore the linkage of the SNPs to vulnerability for more intense and enduring depressive symptoms—fatigue and poor sleep—common behavioral symptoms which may share a similar inflammatory etiology in individuals following MTBI.

In conclusion, several SNPs have been proposed in earlier studies, yet there is a need for replication or validation that the SNPs may be useful in the clinical setting. Genetic variants underlying behavioral symptoms clusters might eventually aid in predicting prognoses and responses to treatment. Therefore, investigation of these biomarker genetic variants (SNPs) may provide a valuable means to predict persistent and lingering behavioral symptoms in MTBI patients. This investigation is significant because it will fundamentally advance knowledge of behavioral symptoms in the subgroup of MTBI patients, as well as the genetic variants and their role in the etiology of behavioral symptom clusters post-MTBI.

Clinical Implications and Future Directions

Clinical Implications

One of the important contributions of the symptom clusters analysis is that in addition to profiling subgroups, it also to a certain extent reveals symptom interrelationships (Aktas et al., 2010). This notion primarily facilitates in exploring the influence of symptoms on each other, and aids in tailoring specific treatments accordingly. Historically, clinicians and researchers acknowledged the multiple, concurrent symptom-experience reality and highlighted the literature gap posited by the single-symptom focus of the majority symptom-management research, which led to the development of the concept of symptom clusters (Barsevick et al., 2006; Dodd et al., 2001). This conceptualization of symptom clusters is visualized as a paradigm shift in the symptom management research, which addresses the reality of the concurrent symptoms experiences in different populations and is supposed to lead to more promising research that will potentially generate knowledge needed for rapid improvement in symptom management. The shift helped bridge the gap between research and bedside nursing by addressing symptoms (as a cluster), which is the most common reason that individuals seek healthcare (Larson et al., 1994).

Furthermore, advancing the knowledge regarding symptom interrelationships within a cluster might overall help manage symptoms, ultimately leading to reducing symptom burden (Aktas et al., 2010). A more recent study demonstrated that military MTBI patients with a self-reported history of an MTBI who completed multidisciplinary treatment reported a reduction in both persistent post-concussive and PTSD symptoms (Janak et al., 2015). Thus, it is hoped that with profiling subgroups of MTBI patients this will improve clinical practice, inform clinical

practice guidelines, and ultimately provide patients with the most effective and innovative treatment modalities (Barsevick et al., 2006; Dodd et al., 2001; Kim & Abraham, 2008).

Additionally, enhanced understanding of cluster symptoms related to the development of specific cognitive profiles of MTBI patients would allow for the development of future rehabilitation programs that target specific cognitive deficits. Furthermore, clinicians will identify patients at risk for poor cognitive and functional outcomes based on post-MTBI symptoms experiences/presentations (perhaps symptom clusters), which will allow tailoring earlier interventions to better serve this population promoting better quality of life.

Moreover, the above-mentioned paradigm shift will potentially help in identifying underlying mechanisms such that treating the mechanism may relieve or prevent several different symptoms. Specifically, this may lead to new discoveries at the molecular level of genetics-epigenetic and inflammation-cytokines:

Implications for Genetics and Epigenetics

Epigenetic modifications have revitalized the interest in the interaction between the environment and the genome. Results from numerous studies demonstrate that the environment influences epigenetic modification. However, a key feature that distinguishes epigenetic modifications from genetic changes is their reversible nature that provides opportunities for identification of a multitude of preventive and/or therapeutic interventions for a disease across the lifespan. It also ascertains the fact that our genes are not our destiny (Stein, 2012). Further knowledge and understanding regarding epigenetic modifications may help in identifying susceptibility for certain diseases through categorization of molecular mechanisms that are triggered in vulnerable populations. Humans are found to differ in gene expression because of

changes in methylation caused by factors such as diet, chemicals in the environment, and relational experiences during early development, including the quality of caregiver-infant interactions (Hochberg et al., 2011).

The development of interventions will aid in adjusting the influence of the environment upon the genome while reversing and/or preventing epigenetic modifications in order to improve health and quality of life. There are several behavioral, nutritional, and pharmacological strategies that may target adverse epigenetic marks with the potential for reducing the risk of diseases over the human lifespan.

First of all, behavioral therapies could be exploited to alleviate stress and other adverse environmental factors that may potentially lead to epigenetic modification. For example, exercise can result in weight loss and help provide resistance to stress-induced chromatin remodeling within the brain. It has been shown that rats that were exposed to greater physical activity prior to stress exposure exhibit resistance to stress-induced chromatin remodeling within the dentate gyrus (Bilang-Bleuel et al., 2005). These findings demonstrate that stress-related learning results in hippocampal chromatin remodeling, which may facilitate behavioral adaptation to environmental changes. This presents an opportunity for the exploration of other behavioral lifestyle changes that could aid in the prevention or restoration of epigenetic modification (Mathews and Janusek, 2011).

Recently, Yehuda et al. (2013) examined the association between methylation of the GR and FKBP5 genes, downstream neuroendocrine measures, cortisol, and NPY, and before-and-after prolonged exposure psychotherapy in combat veterans with PTSD (n = 8). The purpose was to determine if cytosine methylation in promoter regions of the glucocorticoid-related NR3C1

and FKBP51 genes would predict or correlate with treatment outcome (prolonged exposure psychotherapy) in these patients. Blood samples were analyzed for methylation at three-time points (pre-treatment, 12 weeks post-treatment and 3-month post-treatment follow-up). In addition, glucocorticoid receptor (GR) activity (i.e., plasma and 24-hr. urinary cortisol, plasma ACTH, lymphocyte lysozyme IC50-DEX, and plasma neuropeptide-Y) was assessed. Findings revealed that the methylation of the GR gene (NR3C1) exon 1F promoter at pre-treatment predicted treatment outcome. On the other hand, methylation of the FKBP5 gene (FKBP51) exon 1 promoter region decreased in association with treatment, but was not predictive of treatment outcomes. These results denote that specific genes can be correlated with prognosis and symptom state. Although these preliminary results require replication and validation, they support research indicating that some glucocorticoid related genes are subject to environmental regulation throughout lifespan, and also that psychotherapy treatment may alter epigenetic state through environmental regulation. This is the first longitudinal study of an epigenetic alteration in association with behavioral treatment outcomes. This study represents an important initial step in establishing relevant molecular markers for PTSD therapies (Yehuda et al., 2013), and perhaps injury-related traumatic events that results in MTBI.

It is widely known that epigenetic modification is reversible. This makes modulation of epigenetic states a potential therapeutic option for cancer and other diseases (Corpet & Almouzni, 2007). A number of agents that alter patterns of DNA mythelation are being tested in clinical trials (Egger, Liang, Aparicio, & Jones, 2004) along with ongoing research for agents that can inhibit methyltranferases directly to target other epigenetic regulators (Corpet & Almouzni, 2007). There is a promising potential regarding the development of epigenetic

therapies that have shown positive anti-tumorigenic effects for some malignancies. These epigenetic therapies could include several inhibitors of enzymes controlling epigenetic modifications through DNA methyltransferases and histone deacetylases (Egger et al., 2004). Finally, the development of more specific agents capable of targeting discrete brain regions is another area that needs more research (Mathews & Janusek, 2011).

Implications for Cytokine Brain-Signaling

Several symptoms (e.g., pain, sleep disruption, and fatigue) can result from the persistent release of cytokine as a response to inflammation; thus, specific treatments aimed to block the cytokine production would have a direct effect on symptoms relief. Furthermore, the model of cytokine-induced depression provides valuable insights into the relationship between cytokines and depression (Dantzer, 2009). Clinicians may explore the implications of sickness behavior related to depression and specific disease-related symptoms. Nurses would benefit from awareness and understanding of the relationship between pro-inflammatory cytokine and sickness behaviors. Enhanced knowledge in this arena will aid nurses in assessing and identifying vulnerable patients at risk for these sickness behavior symptoms. Additionally, nurses can participate in educating patients to promote quality of life.

There are several interventions that can interrupt the cytokine brain-signaling pathway, such as pharmacological and non-pharmacological interventions. First, for pharmacological interventions, there is a crucial need for the discovery and the development of novel antidepressant drugs that target the brain immune system or its secondary consequences of activating IDO or the enzymes responsible for degradation of kynurenine. These neural circuits process affective and reward-based information for optimal cost-benefit decision-making, a

function that may link cytokine-evoked changes in synaptic plasticity to translatable measures of specific behavioral impairments observed in depressed patients (Piser, 2010). For example, the administration of insulin-like Growth Factor-I into the lateral ventricles of the brain inhibits sickness behavior induced by a central injection of LPS (Dantzer, Gheusi, Johnson, & Kelley, 1999). Furthermore, evidence shows that central administration of IGF-I decreases depressive-like behavior and brain cytokine expression in mice (Park, Dantzer, Kelley, & McCusker, 2011). The anti-depressant activity of IGF-I may have clinical implications for psychiatric conditions with or without the presence of inflammatory diseases (Park et al., 2011). Park et al. (2011) conducted a study to investigate the extent to which central IGF-I would impair the development of depressive-like behavior by tempering the neuro-inflammatory processes within the brain. Additionally, they examined the extent it would do so by inducing expression of the brain-derived neurotropic factor while decreasing pro-inflammatory cytokine expression in the brain. Their results revealed that the central IGF-I significantly impaired development of depressive-like behavior in LPS-challenged mice by an anti-inflammatory response in the brain, which in turn decreases the expression of inflammatory proteins in naïve and LPS-challenged mice. In other words, these findings showed how IGF-I down-regulates glial activation and induces expression of an endogenous growth factor that shares anti-depressant activity. This is the first study which evaluated IGF-I for anti-depressive actions within the brain, which forms the basis for future studies defining the mechanism for IGF-I's anti-depressant activity in humans (Park et al., 2011).

Another example is the use of anti-cytokine therapies for depressed mood. In a large double-blind placebo-controlled trial, the administration of TNF-alpha antagonist in patients with

psoriasis showed significant improvement in depressive symptoms independent of symptoms related to the disease etiology (Tyring et al., 2006). Furthermore, in a small double-blind placebo-controlled trial, a COX-2 inhibitor administered to healthy patients with major depression increased the antidepressant efficacy of the norepinephrine reuptake inhibitor (Muller et al., 2006). These implications emphasize the importance and significance of targeting signaling pathways of cytokines to enhance antidepressant activity. Additionally, chemokines, such as MCP-1, which can attract monocytes to multiple tissue sites including the brain, enable inflammatory responses (D'Mello et al., 2009). These is another class of targets that have unique applicability to behavioral disorders associated with increased inflammation (Capuron & Miller, 2011). Finally, the cytosolic enzyme indoleamine 2, 3-dioxygenase (IDO) can be manipulated to treat a range of chronic inflammatory diseases. There are studies of IDO inhibitors to improve T cell activity in inflammatory states and cancer, thus indicating broad interest in the development of pharmacologic agents that target IDO (Johnson, Baban, & Mellor, 2009). These are some examples of the development of pharmacological interventions relevant to immuno-biology and neurobiology, which emphasize the need for implication, and support opportunities for collaborative effort between disciplines to advance the understanding of the mind-body connection (Capuron & Miller, 2011)

For non-pharmacological interventions, the immuno-modulatory and anti-inflammatory effects of specific nutritional factors help prevent or modulate neuropsychiatric symptomatology in chronic low-grade inflammation using nutritional interventions. For example, polyunsaturated fatty acids are essential nutrients and essential components of neuronal and glial cell membranes (Laye, 2010). These polyunsaturated fatty acids regulate prostaglandin and pro-inflammatory

cytokine production. For example, n-3 fatty acids are anti-inflammatory, while n-6 fatty acids are precursors of prostaglandins. Inappropriate amounts of dietary n-6 and n-3 fatty acids can lead to neuro-inflammation because of their abundance in the brain. However, future investigations need to account for the two key enzymes in the metabolism of polyunsaturated fatty acids such as phospholipase A2 (PLA2) and cyclooxygenase 2 (COX2). These enzymes have significantly crucial roles in cytokine-induced depression. Elucidation of the genetic variations in the COX2 and PLA2 genes increase the risk of IFN-alpha-induced depression, possibly by affecting the levels of docosahexaenoic and eicosapentaenoic acid (K. P. Su et al., 2010).

Additionally, the abovementioned vulnerability features may help in using cytokines as markers for prediction of patients at risk for depressive symptoms, as well as a guide in the development of interventions to prevent the occurrence of depression and improve life. For example, since obesity is correlated with low-grade inflammation status (Perry, 2004), weight loss intervention will benefit obese vulnerable patient accordingly. Finally, it is well established that stress predisposes laboratory animals and humans to activate the inflammatory response (A. H. Miller et al., 2009). Behavioral interventions focused on stress management, as well as coping strategies that adjust sympathetic and parasympathetic tone (e.g., meditation, behavioral cognitive therapies, and yoga), should also be implemented and considered for further research.

In conclusion, advancing the knowledge regarding the interrelationships among symptoms and addressing their influence on cognitive and functional outcome will pose important implications for clinical practice through development of specific innovative-therapeutic interventions.

Future Directions and Research

The evidence described in this paper reveals the increasing knowledge regarding the body-to-brain communication, but there is a need to increase such evidence in human paradigms for translation to clinical practice. Furthermore, the neurobiological mechanisms underlying the behavioral effects of pro-inflammatory cytokines have not been investigated in a manner that correlates a given behavioral effect of a cytokine to a specific action in a well-defined area in the brain. For this reason, micro-pharmacology experiments that target inflammatory mediators in specific brain areas must be implemented to define the cause-effect relationships (Dantzer et al., 2008). The identification of the intracellular association between inflammation and depression will provide valuable targets for the development of new antidepressant drugs if the activation of brain pro-inflammatory cytokine signaling is proven to represent the final common pathway for the various conditions that lead to depression (Dantzer et al., 2008).

Investigation of the responses of acute circulating inflammatory markers is a fruitful area which may provide insight into the role of psycho-neuro-immunological processes in patients. Additionally, standardization of appropriate markers of inflammation and a systematic approach for investigation of the risk factors will improve outcomes and quality life. Furthermore, it is possible to develop clinical trials aimed at blocking cytokine production or action, attenuating the production of second messengers, or deactivating glial cells which produce excessive quantities of pro-inflammatory cytokines. More research is needed in this area to enhance its innovative potential and avoid the duplication of efforts likely to occur because of the diversity of pathological conditions that lead to non-specific clinical signs of sickness behavior (Dantzer & Kelley, 2007).

Taken together, future studies are warranted to illuminate the precise effects of certain cytokines and explore targets for interventions and therapies. For example, the potential targeting of inflammatory pathways for depression treatment, such treatments can provide valuable starting points for the identification of vulnerable subgroups of depressed patients who may be most appropriate for immune-targeted therapies. For example, the potential targeting of inflammatory pathways for depression treatment can provide valuable starting points for the identification of vulnerable subgroups of depressed patients who may be most appropriate for immune-targeted therapies. Finally, findings from warranted studies can lead to the development of feasible effective interventions aimed at identifying patients at risk for sickness behaviors, preventing or decreasing the negative effects of cytokine-induced inflammatory responses to improve outcomes of quality of life.

Environmental exposures have been shown to affect the activity of the methylation machinery, and would also lead to behavioral and mental pathologies. Future studies should address and explore the specific mechanisms responsible for the observed epigenetic drift of MZ twins. Such studies can provide key insights into the impact of environment-gene interaction on behavior and vulnerability to diseases over the human lifespan. In conclusion, it is likely that epigenetic patterns affect and/or contribute to the relationship between the environment and human health (Mathews & Janusek, 2011). The good news is that evidence shows that epigenetic modifications are reversible; the supportive evidence addressed earlier opens a window for a variety of novel epigenetic-based interventions that could be implemented at periods of biological vulnerability to prevent the harmful effects of stress and reduce incidences of diseases.

More specific to symptom clusters paradigm shift, in order to address gaps in the literature, identification and comparison of symptom clusters within the MTBI population is warranted with the consideration of profiling subgroups and identifying those who are at risk for intense behavioral symptom clusters while accounting for influencing factors causing symptom clusters and assessing symptom intensity overtime. It has been long emphasized that longitudinal research regarding post-discharge cognitive impairment in MTBI patients is needed, as it is possible that persistent intense behavioral symptoms sustain cognitive and functional outcomes in the absence of long-term structural damage (Bernstein, 1999). These studies will help inform the development of the most appropriate and treatment approaches for MTBI patients with persistent intense symptoms and poor cognitive and functional outcomes. Following the aims of the TRACK-TBI initiative, it is hoped through this current secondary analysis that we will help in identifying if symptom clusters account for variability in cognitive and functional outcomes post-MTBI.

The aforementioned clinical implications are suggestive of the need for more future prospective studies of symptom management designed to identify components of specific innovative therapeutic interventions that will be collaborative and multidisciplinary and will specifically contribute to symptom reduction and improvement of cognitive and functional outcomes. Then, future research will call for further investigation of the prevalence of cognitive impairments after the reduction or elimination of symptoms.

The evidence reveals the increasing knowledge regarding genetic-to-brain communication, but again there is a need to increase such evidence in human paradigms for translation to clinical practice. Experienced symptoms could negatively affect patients who

sustain injury, like MTBI. Further, preliminary evidence also suggests that specific pre-existing genetic variants may predispose certain individuals to more persistent behavioral symptoms post-injury. Determining the extent to which genetic variants contribute to the symptomatology of depression, fatigue, and poor sleep in MTBI patients can lead to novel biomarkers to predict behavioral symptoms as early as possible. The identification of these genetic variants may shed light on and aid development of viable targets in predicting distinct sets of behavioral symptoms, and eventually help in genetic-targeted intervention tailored for greater treatment response and tolerability, and improvement of resiliency against developing inflammatory cytokine-associated behavioral symptoms.

Collectively, the compelling evidence provides impetus for further exploration in the genetic and PNI paradigm. The possibility that symptom clusters might participate directly or indirectly in the symptomatology of cognitive impairment in trauma patients is fascinating and worth further investigation. This is especially so due to the lack of evidence about predicting symptom clusters in MTBI patients. Investigation of genetic variants might provide valuable information for the prediction of symptom clusters as early as possible in MTBI patients. As such, this proposal presents promising areas in genetics, symptom clusters, PNI, and MTBI research.

CHAPTER THREE

RESEARCH METHODOLOGY

Review of the Study Purpose, Research Questions, Aims, and Hypotheses

In summary, the long-range objective of this research is to develop novel approaches to predict risk for behavioral symptoms in mild traumatic brain-injured (MTBI) patients at discharge from the emergency department (ED). The outcomes of the proposed study will build a foundation to establish clinically based strategies to identify MTBI patients at risk and to target interventions to reduce behavioral symptoms and improve quality of life in trauma survivors and their families. Thus, there is strong rationale for this research in its potential to improve long-term outcomes for MTBI survivors who overcome their acute injury but who remain at risk for chronic and disabling behavioral symptom clusters.

The central hypothesis is the following: There will be differences in cognitive and functional outcomes in patients at six months post-MTBI based on inflammation-related behavioral symptoms (depressive symptoms, fatigue, and poor sleep), independently or as a cluster; and there will be differences in behavioral symptoms at six months post-MTBI based on SNP phenotype. The evaluation of inflammation-related behavioral symptom clusters post MTBI with respect to outcomes and genetic variants is an innovative approach that can result in novel predictive biomarkers for early risk assessment. Thus, there is strong rationale for the proposed research, which can improve long-term outcomes for MTBI survivors who overcome their acute injury but who remain at risk for chronic and disabling behavioral symptoms.

Specific Aims and Hypotheses

Aim 1: Identify different behavioral profiles of MTBI patients based on the intensity of depressive mood, fatigue, and sleep quality. Hypothesis 1: There will be individual differences in the profiles of MTBI patients based on the intensity of depressive mood, fatigue, and poor sleep.

Aim 2: Determine whether there are differences in cognitive and functional outcomes at six months post-MTBI among the identified behavioral cluster profiles.

Hypothesis 2: There will be differences in cognitive and functional outcomes at six months post-MTBI among the identified behavioral cluster profiles.

Aim 3: Explore differences in the intensity of behavioral symptoms at six months post-MTBI based on SNP genotype.

Hypothesis 3: There will be differences in behavioral symptoms at six months post-MTBI based on SNP genotype.

Research Design and Methods

Research Design

This investigation was a secondary data analysis of the database from the International Traumatic Brain Injury Initiative (TRACK-TBI), which previously recruited TBI patients from two level I trauma centers. Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) study (NCT01565551) is a prospective cohort study of all TBI patients presenting to one of two level I trauma centers with in-house neurosurgical coverage(Dams-O'Connor et al., 2013; McMahon et al., 2014; Yue et al., 2013). Institutional review board approval was obtained for this study from the participating institutions. For the secondary data analysis, approval was received from the Loyola University Health Science Division Institutional Review Board.

Participants in the original TRACK-TBI study completed a battery of psychometric and health-related instruments and provided a blood sample for genetic analysis; these data were available to accomplish the aims of the present study. Latent cluster analysis was used to evaluate the differences in functional and cognitive outcomes at six months post-MTBI with respect to behavioral symptom cluster (depressive mood, fatigue, and poor sleep.

Sample and Setting

From the TRACK-TBI database, a convenience sample (n=304) of male and females (ages >18years to 85 years) who suffered external force trauma to the head, and who had an MTBI with classification by emergency department arrival Glasgow Coma Scale (GCS) is as follows: mild (GCS 13–15, TRACK-pilot has 83 % mild) was selected. Only individuals who completed the three- and six-month follow-ups were eligible.

Sample size. That primary study enrolled a total of 600 TBI patients; 340 of which suffered MTBI and who were thus considered for potential inclusion in the current study. Six hundred TBI patients were enrolled in the TRACK- TBI Pilot study. However, of these, 68 cases were excluded because of Glasgow Coma Scale < 13 upon arrival to the ED; 17 cases were excluded because of a reported LOC > 30 minute; 13 cases were excluded because of reported PTA > 24 hours; and 76 cases were excluded because of assault as mechanism of injury and reported injuries inflicted by other persons or resulted from domestic violence. Then 31 cases were excluded because of serious psychiatric disorders that interfere with outcome assessment. A sample of N=340 who suffered MTBI and who met the inclusion criteria were considered for potential inclusion in the current study. However, 139 MTBI patients had missing data and uncompleted biological data. Thus, the final sample for Aim1 and 2 consisted of 201 patients.

Also, of the sample that met the inclusion criteria (n=340), 187 MTBI patients had missing data and uncompleted biological data, and so the final sample for Aim 3 consisted of 153 patients.

Sample Characteristics

Sample. A convenience sample of male and females (ages >18 years) who suffered external force trauma to the head, an MTBI with classification by emergency department arrival GCS as follows: mild (GCS 13–15, TRACK-pilot has 83 % mild), and who have completed the three- and six-month follow-ups.

Sample inclusion criteria. Concussion/MTBI patients who suffered minor injuries who were alert, oriented, read, write and speak English. All races are included. Mechanisms of injury to be included are the following: motor vehicle accident, motorcycle/bicycle accident, pedestrian struck by vehicle, struck by/against object, falls, and other accidental causes of injury.

Exclusion criteria. Patients who had history of sleep apnea, cognitive impairment, and/or serious psychiatric and neurologic disorders that interfere with outcome assessment were excluded. Individuals who suffered assault as mechanism of injury in which other persons inflicted the injury or if the injury resulted from domestic violence were excluded. Covariates (age, race, education, gender, demographics, and injury/health history) were controlled statistically.

Data Collection & Management

The Study Procedure and Recruitment

The Transforming Research and Clinical Knowledge for Traumatic Brain Injury (TRACK-TBI) is a series of two large-scale prospective multicenter observational trials for improving TBI diagnosis, and therapeutic targeting (Yue et al., 2013). The TRACK-TBI pilot phase

(ClinicalTrials.gov Identifier: NCT01565551, 2010–13) consisted of three centers and collected data from 600 TBI patients from April, 2010 until December, 2013 with a primary completion of data collection on August, 2012. This secondary data analysis used only data derived from the pilot study.

The TRACK-TBI project applies the official NIH/NINDS TBI Common Data Elements (TBI- CDEs) and standardized collection protocols for bio-specimens (Diaz-Arrastia et al., 2014), imaging (Yue et al., 2013; Yuh et al., 2013; Yuh et al., 2014), and neurocognitive and neuropsychiatric outcome metrics (Dams-O'Connor et al., 2013). These processes have been expanded upon in the current TRACK-TBI study (ClinicalTrials.gov Identifier: NCT02119182, ongoing 2014–18) funded for 11 centers with goals of an estimated enrollment of 3000 TBI-patients from February 2014 until August 2018 (estimated study completion date).

The TRACK-TBI pilot study was conducted by UCSF/SFGH. Patients were asked to participate in the study if they suffered a traumatic brain injury (TBI) within the preceding 24 hours and had had a CT scan completed at San Francisco General Hospital as part of their clinical care. The main study procedures took place at SFGH and the UCSF China Basin Imaging Center. Upon enrolment, medical information regarding the injury was obtained from SFGH medical record and general history were obtained from the patient as well. SFGH medical record, including your CT scan were reviewed. The study consisted of five components and the entire study required approximately five hours over the course of six months:

(1) Component 1 (Case Report Forms) takes approximately 30 minutes after enrollment.

(2) Component 2 (blood draw) will take 10 – 15 minutes after enrollment.

(3) Component 3 (MRI in one or two weeks after enrollment) takes about one hour

(4) Component 4 (three-month follow-up phone call) takes up to 30 minutes included functional and neuropsychological questionnaires.

(5) Component 5 (six-month follow-up phone call or meeting here at San Francisco General Hospital) takes approximately 2–3 hours and included behavioral symptoms and cognitive impairments questionnaires.

Study Variables Instrumentations with Psychometric Evidence

For this secondary data analysis, genetic variants (i.e., SNPs) and symptoms cluster of behavioral symptoms (i.e., fatigue, depression and sleep) were the main independent variables. The dependent variables are the functional outcomes, cognitive outcome (i.e., nonverbal processing speed, mental, and verbal learning), and quality of life outcomes. Also, behavioral symptoms included were the following: Post-Traumatic Stress Disease (PTSD), somatization, depression, and anxiety. In addition**,** this study controlled for the following confounding variables: history of depression and anxiety. These variables were clearly and explicitly linked to the framework and aims of the study.

In this section, conceptual and operational definitions will be addressed for each variable along with corresponding measurement instruments, which are utilized in quantitative research for the purposes of quantifying phenomenon to resolve research questions and inquiries. Researchers acknowledge that inappropriate measures can lead to inaccurate data (DeVellis, 2012). As such, evaluation of measurements is essential. Although it might be time consuming, evaluation helps to prevent problems and errors that could result from the selection and use of inappropriate or psychometrically inadequate measures (Waltz, Strickland, & Lenz, 2010).

Therefore, the purpose of this section is to review the measurements used in this research. Table 1 lists study variables, and Table 2 list instruments and time points (refer to Appendix B)**.**

Biological Measures

Serum Sample Collection and Biomarker Measurement

The blood samples for DNA genotyping analysis for TRACK-TBI Pilot patients were collected within 24 hours of injury, processed and stored in a -80°C freezer within two hours of collection, as previously described (Manley et al., 2010). Specimen acquisition is previously described (Yue et al., 2013), detailed protocols for collection, processing, and shipping of blood bio specimen, developed for the TRACK-TBI pilot are available on the NINDS TBI-CDE website (TBI Standards–NINDS Common Data Elements, 2016). The TBI-CDE bio specimens protocol was used effectively to collect, process, and store blood bio specimens for proteomic and genetic analyses (Manley et al., 2010).

In brief, blood samples for DNA genotyping analysis were collected via peripheral venipuncture or existing peripheral venous indwelling catheters within 24 h of injury. Samples were collected in BD Vacutainer K2-EDTA vacutainer tubes, and subsequently aliquoted and frozen in cryotubes at −80 °C within 2 h of collection in accordance with recommendations from the NIH-CDE Biomarkers Working Group (Manley et al., 2010). DNA was extracted then the Single nucleotide polymorphisms (SNPs) (rs1800497 (ANKK1) rs1799971 (OPRM1), rs279836 (GABRA2), rs279845 (GABRA2), rs279871 (GABRA2), and rs4680 (COMT) was genotyped (please refer to Table 3). SNPs are variations at a single position in a DNA sequence among individuals and patients were categorized by genotype, and each SNP was categorized into the following six groups:

- SNP rs1800497 (ANKK1) categorized into 3 groups (A1/A1, A1/A2, and A2/A2).
- SNP rs1799971 (OPRM1) categorized into 3 groups (A/A, A/G, and G/G).
- SNP rs279836 (GABRA2) categorized into 3 groups (A/A, A/T, and T/T).
- SNP rs279845 (GABRA2) categorized into 3 groups (A/A, A/T, and T/T).
- SNP rs279871 (GABRA2) categorized into 3 groups (C/C, C/T, and T/T).
- SNP rs4680 (COMT) categorized into 3 groups (Met/Met, Met/Val, and Val/Val).

Functional Outcomes

Glasgow Outcomes Scale—Extended (GOS-E). Global functional outcome and functional dependence was assessed using the GOSE (Jennett, Snoek, Bond, & Brooks, 1981; Shukla, Devi, & Agrawal, 2011; Wilson, Pettigrew, & Teasdale, 1998). GOSE is used with patients 18 years and older, and includes eight questions with subparts. Research assistants trained to uniformly assess the GOS-E administered the GOSE at three and six months post-MTBI through structured phone-interview with each participant, employed to measure the impact of the TBI on the patient's level of functioning. The GOSE is a multi-dimensional scale (depression, anxiety, and somatization subscales), which assesses various aspects of functional outcome. Specifically, it measures patient's consciousness; independence; ability to return to work and/or previous lifestyle including social and leisure activities, social relationships, and other sequelae of TBI (Wilson et al., 1998). A major strength of the GOSE as opposed to other functional outcomes measures is that it includes activity or participation components that importantly illustrate patient recovery and aids in measuring functional outcome and burden of illness (Nichol et al., 2011) It is a revision of the original Glasgow Outcome Scale (GOS), which was the most widely used method for classifying outcome in TBI survivors (Wilson et al., 1998).

The GOSE is considered the ‘‘gold standard’’ for assessing patient outcomes after TBI (Shukla et al., 2011). Another acknowledged strength of the GOSE is that it attempts to deal with the potential confounding effects of pre-existing factors in post-TBI patients (Nichol et al., 2011).

Several limitations of the GOS led to the development of the extended version; such as the perceived allocation bias in the higher functional end of the scale, and the ‘open ended’ and unstructured format of the interviews (Wilson et al., 1998). These limitations speculate the insensitivity of the GOS, which was addressed in GOSE by separating each of the three higher function categories into two (Jennett et al., 1981). The GOSE (extended version of the GOS) provides eight, rather than five, categories of outcome: (1) Dead, (2) Vegetative State, (3) Lower Severe Disability, (4) Upper Severe Disability, (5) Lower Moderate Disability, (6) Upper Moderate Disability, (7) Lower Good Recovery, and (8) Upper Good Recovery (Nichol et al., 2011). Structured interviews are provided to facilitate ratings patient outcome and the assignment of an ordinal score of 1 to 8. The severely disabled category is indicative of ability to follow commands yet cannot live independently, while a moderately disabled category indicates the ability to live independently with reduced work capacity. Lastly, a good recovery category is indicative of ability to return to work to full functional capacity (Jennett et al., 1981). Overall, the scores are either **favorable** (Lower Moderate Disability, Upper Moderate Disability, Lower Good Recovery, Upper Good Recovery) or **unfavorable** (Dead, Vegetative State, Lower Severe Disability, Upper Severe Disability) outcomes. Thus, the Upper Good Recovery (GOS-E score of 8) indicates return to pre-injury baseline with no residual effects of the TBI. In general, a given score of 7 or more as (good recovery) is indicative of return to full functional status at work and in daily activity (McMahon et al., 2014).

Distinctively, the GOSE differentiates between specific aspects of functional disabilities within mild-to-moderate, rather than mild-to-severe TBI and it is most commonly utilized post-MTBI global functional outcomes measure (Levin, O'Donnell, & Grossman, 1979) and there is an extensive literature demonstrating its reliability and validity (Nichol et al., 2011). The GOSE is a reliable measure with added practical usefulness advantage of the ability to be administered through structured phone-interview, with an interrater reliability that ranges from 0.85 to 0.89 (Pettigrew, Wilson, & Teasdale, 2003; Wilson et al., 1998), specifically shows a good reliability in patients with TBI (Wilson, Pettigrew, & Teasdale, 2000). The criterion validity of the GOSE demonstrated that it is better and more sensitive to change than the GOS (Levin et al., 2001; Wilson et al., 1998). The GOSE has been shown to be associated with other functional outcome measures: initial injury severity, the Disability Rating Scale, and self-reported measures of health outcomes (Wilson et al., 2000)

Researchers identified limitations of the functional outcome measures including the following: insensitivity to function outcomes, limited domains of functional assessments, insufficient operational definitions, lack of evaluation for unconscious patients, and the inability to incorporate categories of morbidity and mortality (Nichol et al., 2011; Shukla et al., 2011). However, the GOSE has been valued by researchers as fulfilling all criteria for a reliable and valid outcome scale, and is regarded in combination with neuropsychological tests as a near comprehensive and inclusive outcome post-TBI (Shukla et al., 2011).

Cognitive Outcome

California verbal learning trial–II. The California Verbal Learning Test, Second Edition (CVLT-II) Trials 1-5 Standard Score (Delis D. C., Kramer J. H., Kaplan E., & Ober B.

A., 2000), is a verbal learning and memory task which consists of the following: five learning trials, an interference trial, an immediate recall trial, and a post-20 min recall trial. The CVLT-II Trials 1–5 Standard Score (CVLT-TSS) is normed for age and sex, and provides a global index of verbal learning ability (Delis D. C. et al., 2000). It was used in this current study as one of the measures for cognitive impairment; specifically, verbal learning at the six-month follow-up. It measures both recall and recognition memory (Delis et al., 2000).

The CVLT-II consists of a word list task of 16 words that are randomly presented, each of which belongs to one of four categories, including animals, vegetables, ways of traveling, and furniture, and the participants are asked to recall them across a series of trials. The words were selected after careful study of their frequency of use across multiple demographic variables (Delis D. C. et al., 2000). The participants are instructed to recall them in any order and as many as they can. There are a series of recall trials, followed by a 20-minute delay, at which point more recall trials are given, in addition to a yes/no recognition component. Following another delay of 10 minutes, a forced choice recognition component of 16 items is given (Delis D. C. et al., 2000). The CVLT-II is known for higher reported consistency on between-norm sets (Stallings, Boake, & Sherer, 1995). The forced-choice an item is useful for detecting malingering, thereby helping to reduce false results. In addition to recall and recognition scores, CVLT–II measures encoding strategies, learning rates, error types, and other process data (Delis D. C. et al., 2000).

The recent revision of the CVLT led to improved psychometric properties (Delis D. C. et al., 2000; Stallings et al., 1995). The new items provide more comprehensive and inclusive results. Additionally, the second edition includes new options that provide administration

flexibility when the Standard or Alternate Forms impractical. A Short Form can be used with limited exam time is limited, less detailed test information needed, fatigued patients, and/or severe memory or cognitive impairments. The Short Form consists of nine words in three categories and is administered in only 15 minutes with two delay periods of 15 minutes. Additionally, an alternate form can be utilized when re-testing to prevents falsely inflated scores. The Standard and Alternate Forms can be administered in 30 minutes, with an additional 30-minute delay (Delis D. C. et al., 2000).

When comparing CVLT-II Trials 1-5 Free Recall results to the norms, researchers provide normative data from large samples of 285 outpatients in a mixed neurologic sample with low executive functioning (M=34.86, SD= 16.66), medium executive functioning (M= 43.10 SD=17.26), and high executive functioning (M= 45.02, SD=22.72) (Hill, Alosco, Bauer, & Tremont, 2012).

Wechsler Adult Intelligence Scale IV (WAIS IV). The Wechsler Adult Intelligence Scale Processing Speed Index (WAIS IV-PSI; consists of Digit Symbol Coding and Symbol Search subtests) (Wechsler, 2008). WAIS-IV PSI is a test of nonverbal processing speed with additional contribution from working memory (Kennedy, Clement, & Curtiss, 2003; Lichtenberger & Kaufman, 2013; Wechsler, 2008) comprised of two nonverbal tasks (Digit Symbol Coding and Symbol Search subtests of the WAIS IV) which involves both visual attention and motor speed (Wechsler, 2008). Briefly, it measures the amount of time it takes to process a set amount of information, or vice versa. It is considered one of the most clinically culturally, racially, and ethnically sensitive cognitive measures to neurological conditions, and is known for its usability across different literacy levels (Lichtenberger & Kaufman, 2013;

Wechsler, 2008). The Wechsler Adult Intelligence Scale is known to have an extensive normative data and excellent psychometric properties (Wechsler, 2008). Researchers investigated the extent to which working memory, motor speed and perceptual processing speed influence WAIS-III-PSI scores in a sample of 68 TBI outpatients of varying severity. In hierarchical multiple regression analyses, findings confirmed that the WAIS-III PSI scores of TBI patients reflect perceptual processing speed, with an additional component attributable to working memory (Kennedy et al., 2003). The composite score which is used in this study refers to a scale that ranged from 50 to 150 to resemble a certain percentile (0.1st to 99.9th percentile) of performance across different age groups. For example, the 25th percentile represented a score of □90, the 50th percentile represented a score of 100, and the 75th percentile represented a score of □110 (Wechsler, 2008). However, previous research with TBI patients revealed that it mainly reflects cognitive impairment in perceptual processing speed with a minimal attribution to working memory and slight contribution from motor speed (Kennedy et al., 2003). In this secondary data analysis, the WAIS-PSI was used to measure one of the cognitive outcomes—specifically, nonverbal processing speed at the six-month follow-up post-MTBI. When comparing WAIS-IV Processing Speed Index Composite Score results to the norms, researchers provide normative data for a clinical sample that scored lowest and highest on WAIS-IV Processing Speed Index: The means that the lowest scores included autistic disorders (M=75.1), traumatic brain injury (M=80.5), major depressive disorder (M=95.8), ADHD (M=94), intellectually gifted (M=112.4), and probable Alzheimer's dementia-mild (M=76.6). The highest score included mathematics disorders (M=93.2), borderline intellectual functioning (M=80.9),

and reading disorder (M=94.5). WAIS-IV Processing Speed Index score between the range of 90 and 109 are considered average (Wechsler, 2008).

Trail-Making Test and B (TMT). In general, The TMT measures attention, speed, and mental flexibility (Reitan, 1958). The TMT consists of two parts, A and B, and takes about 5 minutes to be completed, as it measures the number of seconds needed for the patient to complete the tasks (Reitan, 1958). These tests are used to measure neuro-cognitive performance, where TMT-A assesses visual processing, and TMT-B assesses mental flexibility and processing speed (Reitan, 1958). In this secondary data analysis, the difference score between the TMT-B and TMT-A—TMT B-A—was used to measure one of the cognitive outcomes; specifically, mental flexibility at the six-month follow-up. TMT B-A represents a purer index of executive control and mental flexibility separate from visual processing and motor speed (Sanchez-Cubillo et al., 2009). The lower the score, the higher and more improved the performance will be concluded.

On both components A and B, patients are instructed to complete the task quickly and accurately (Reitan & Wolfson, 2004). The TMT is known for its sensitivity to cognitive impairment post-TBI, and it is also used extensively for its good reliability with demographically adjusted normative data available for a wide age range (Tombaugh, 2004). Normative data for the TMT A and B are presented for 911 community-dwelling individuals aged 18-89 years. Researchers found that the performance on the TMT decreased with increasing age and lower levels of education. Based on these results, the norms were stratified for both age (11 groups) and education (2 levels). These current norms represent a more comprehensive set of norms than previously available and will increase the ability of neuropsychologists to determine more

precisely the degree to which scores on the TMT reflect impaired performance for varying ages and education (Tombaugh, 2004).

For comparing TMT B-A results to the norms, with the notion that the lower score correlates with better performance, researchers provide normative data from large samples of patients with traumatic brain injury (TBI) (n=90; M=102.1, SD=80.1), and healthy controls as well (n=223; M=36.4, SD=35) (Perianez et al., 2007). More specifically, the groups are the following: the young group 16–24 (M= 24.99, SD=23), middle-aged 25–54/education 0-12 years (M= 38.46, SD=27.1), middle aged 25–54/education 13+ (M=27.69, SD= 15.52), and the elderly group 55–88 (M=56.58, SD= 38; Perianez et al, 2007). Statistical properties of the demographic and TMT variables for each normative group of patients with TBI were the following: education: 0–11 years M=135.24, SD= 106.5, education: 12+ years M=81.95, SD= 58 (Perianez et al., 2007).

Behavioral Symptoms

Post-Traumatic Stress Disease (PTSD). PTSD will be measured using the PTSD Checklist–Civilian Version (PCL-C). The PCL is a standardized self-reported rating scale for PTSD, comprising 20 items that correspond to the key symptoms of PTSD. Two versions of the PCL exist: (1) PCL-M is specific to PTSD caused by military experiences, and (2) PCL-C is applied generally to any traumatic event and asks about symptoms in relation to generic "stressful experiences" and can be used with any population. The PCL is self-administered and patients indicate how much they have been bothered by a symptom over the past month/week using a 5-point Likert scale, ranging from (**1** Not at All – **5** Extremely) (Weathers et al., 2013).

It was administered at the six-month follow-up, as the PCL can be easily modified to fit specific time frames or events (Kaloupek et al., 2010).

As for the PCL-C psychometric properties, a good test-retest reliability was reported after one week using computerized PCL-C total scores with a civilian community population with slightly lower reliability found using mixed administration (computer vs. paper administration) (Campbell et al., 1999). Researchers reported average PCL- C scores for the computerized administration with only 1.5 points difference. For validity, internal consistency was reported in 14 studies investigating psychometric properties in a variety of samples (e.g., military samples, patients with severe mental illness, patients with HIV, women with substance use disorders, women treated for breast cancer, patients with recent limb loss, female undergraduates, and community adults), and these studies reported total score values above .75 (Wilkins, Lang, & Norman, 2011). The PTSD Checklist Civilian Version (PCL-C) is a widely used self-administered screening tool for identification of patients who need further evaluation for PTSD (Kaloupek et al., 2010).

Brief Symptoms Inventory-18 items (BSI-18). The BSI-18 is a screening tool to assess the level of psychological distress after TBI (Meachen, Hanks, Millis, & Rapport, 2008). The BSI-18 a short form of the Symptom Checklist-90-R and consists of three subscales (somatization, depression, and anxiety) as well as a Global Severity Index. Each subscale contains six questions that rate the level of distress over the past seven days using a 4-point Likert-scale, ranging from “not at all” to “extremely often” (Meachen et al., 2008). The overall reliability of the GSI is high, with a kappa of 0.89 and a retest reliability kappa of approximately 0.66 (Meachen et al., 2008). In tests of validity, the BSI correlates significantly with other

validated psychosocial and functional tests in TBI patients (Meachen et al., 2008). The BSI-18 is commonly used as a measure of psychological distress post TBI, and is known for its comprehensive psychometric characteristics (Derogatis, 2000; Meachen et al., 2008).

Post-concussion symptoms. Post-concussion symptoms will be measured using the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) (King, Crawford, Wenden, Moss, & Wade, 1995). The RPQ consists of 16 items and patients are asked to rate the degree of experienced symptoms for the last 24 hours compared to symptoms prior to head injury. Items include symptoms such as headaches, dizziness, nausea, noise sensitivity, sleep disturbance, fatigue, irritability, depression, frustration, poor memory, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision, and restlessness. It is a 5-point Likert scale that ranges from 0 to 4, ranging from "not experienced at all" to " a severe problem." The total RPQ score is the sum of all of the 16 symptom items. Possible total scores range from 0 (no change in symptoms since the injury) to 64 (most severe problems symptoms) (King et al., 1995). RPQ has demonstrated validity and reliability in studies using classical test theory (King et al., 1995). A well-established internal consistency of 0.71 was reported in MTBI patients (Lannsjo, Borg, Bjorklund, Af Geijerstam, & Lundgren-Nilsson, 2011). The test is divided into the RPQ-3 and the RPQ-13, with the RPQ-3 items assessing headaches, nausea and/or vomiting, and dizziness that are considered to be early concussion symptoms (headaches, dizziness, and nausea/vomiting) typically experienced as short term outcomes post MTBI. The RPQ-13 items assess cognitive, mood, sleep, and other psychological symptoms (i.e., hyperacusis, sleep disturbances, fatigue, irritability, depressed mood, frustration, forgetfulness, poor concentration, requiring longer times to think, blurred vision, light sensitivity, double vision, and restlessness)

(Eyres, Carey, Gilworth, Neumann, & Tennant, 2005; King et al., 1995). The separate scores for analysis method is known for good test-retest reliability and construct validity. The RPQ-13 is considered as a long-term outcome post-MTBI (Eyres et al., 2005; Potter, Leigh, Wade, & Fleminger, 2006; Sveen, Bautz-Holter, Sandvik, Alvsaker, & Roe, 2010), thus used in this secondary data analysis. It is widely known for its psychometric characteristics and capability of detecting clinical changes in patients post MTBI.

Quality of Life Outcome:

Satisfaction With Life Scale (SWLS). The Satisfaction with Life Scale (SWLS) was developed as a measure of the judgmental component of subjective well-being (SWB) (Diener, Emmons, Larsen, & Griffin, 1985). The SWLS is a series of five statements that assess current patient life satisfaction. Patients rank each question from 1 (“strongly disagree”) to 7 (“strongly agree”) (Diener et al., 1985). The total score ranges from a maximum very high score between 30–35 indicating “highly satisfied,” high score 25–29, “slightly below average in life satisfaction” score between 15–19, “dissatisfied’ score between 10–14, and “extremely dissatisfied” score between 5–9 (Diener et al., 1985). In this secondary analysis, we used the SWLS as the aqality of life outcome measure.

The average score for economically developed nations ranges between 20–24, indicating general satisfaction, but with desire for improvement in certain aspects of life (Diener et al., 1985). A cut-off value of 19 or below was used to indicate significant dissatisfaction. The SWLS is considered to have good reliability and validity and is believed to be an accurate measure of subjective wellbeing (Diener et al., 1985; Pavot, Diener, Colvin, & Sandvik, 1991). As for reliability**,** initial and subsequent studies have examined the internal consistency of the SWLS

and alpha coefficients have continually exceeded .80 (Pavot et al., 1991) also in the Diener and colleagues examined a two-month test-retest correlation coefficients for 76 students and it was reported at .82. Interestingly, the SWLS is known for sensitivity to differences and consistency between different populations with expected different qualities of life, such as psychiatric patients and male prison inmates, as well as different life directions and major life-events changes, and in patients receiving psychotherapy (Diener et al., 1985; Pavot et al., 1991).

When comparing SWLS results to the norms, the reported mean of for TBI patients (n = 95, six months to five years after inpatient rehabilitation; mean age = 32.4 years) was 19 (SD=7.6), and time post-injury was significantly associated with higher SWLS total score (Corrigan, Smith-Knapp, & Granger, 1998). Undergraduates at the University of Illinois who were enrolled in psychology classes (n = 176) had a mean score of 23.5 (SD= 6.43) (Diener et al., 1985). In a Turkish sample cross-sectional assessment of the SWLS, university students (n = 547) had a mean of 21.91 (SD= 6.18), correctional officers (n = 166) had a mean of 15.68 (SD=6.97), and elderly adults (n=123) had a mean age = 68.18 (5.10) years. In the elderly population, 2 reported their health as “very poor,” 10 as “poor,” 51 as “average,” 46 as “well,” and 14 as “very well,” with a mean of 23.82 (SD=7.44) (Durak, Senol-Durak, & Gencoz, 2010).

Additional Variables

Covariates. This study controlled for the following confounding variables: health history, pre-injury functional status, and a history of behavioral symptoms (i.e., history of depression, anxiety, and sleep disturbance).

Data Analysis

Statistical Analysis

The independent variables to be evaluated for this study include genetic variants (i.e., SNPs), and symptoms cluster of behavioral symptoms (i.e., fatigue, depression and sleep). Dependent variables will include functional outcomes (i.e., Glasgow Outcome Scale Extended (GOSE)), cognitive out-come (i.e., nonverbal processing speed assessed by Wechsler Adult Intelligence Scale-IV (WAIS-IV), mental flexibility assessed by the difference score between the Trial Making Test (TMT) B and TMT A (TMT B-A). The main independent variables in this study will be verbal learning assessed by California Verbal Learning Test-II (CVLT-II), and quality of life outcomes assessed by the Satisfaction with Life Scale (SWLS). In addition, this study will control for the following confounding variables through a history of behavioral symptoms: history of depression, anxiety, and sleep disturbance. These variables are clearly and explicitly linked to the framework and aims of the study.

Preliminary analysis will assess variable distribution, residuals for normality, linearity, homoscedasticity, homogeneity, and multicollinearity. Data transformations to correct for non-normal distribution will be completed as needed. Descriptive statistics will summarize the sample's general health histories, injury type, severity, and demographics. Analysis will be performed using the SPSS Grad Pack Mac Version 20 (SPSS, 2011). First, the assumption of normality and homogeneity of variances and outliers will be assessed for all outcome measures. Normality will be assessed by examining histogram plots and z scores, while homogeneity of variances will be assessed by Levene's test. All variables will be checked for skewness and kurtosis. If results indicate that all outcome variables are normally distributed, no

transformations will be necessary.

For the first aim, Latent Class Analysis (LCA) will be used to identify profiles of MTBI patients based on the intensity of behavioral symptom, using items derived from the Rivermead Post-Concussion Questionnaire that was administered at six-months follow-up. These assess presence and intensity of depressive mood, fatigue, and poor sleep, and are to be completed by participants in the TRACK-TBI study.

LCA analysis will be conducted using Mplus 7.4 (Muthén & Muthén, 1998-2011) for running the LCA. The analysis was performed by fitting a two-class model, and gradually increasing the number of classes one at a time for model comparison, setting a random starting value arbitrarily from 500 to 100. Several criteria were used to guide the decision on the number of classes in mixture modeling, including the Akaike Information Criterion (AIC), the Bayesian Information Criterion (BIC) (Schwarz, 1978), the sample-size-adjusted aBIC, the Vuong-Lo-Mendell-Rubin (VLMR) test (requested using TECH 11 in Mplus), and the bootstrapped parametric likelihood ratio test (LRT; requested using TECH 14 in Mplus). Both tests compared the model of the currently chosen number of classes (K) to a model of K−1 classes. For AIC, BIC, and aBIC, lower observed values indicate better model fit. In case of entropy, values closer to 1.00 suggest better fit. In addition, a nonsignificant p value for the BLMR LR test indicates that the model with the K-1 class is preferred to the model with K classes. The final classes were determined by small AIC, BIC, and aBIC values comparing each class (K) with each of the K-1 classes, as well as nonsignificant BLMR LR and strong entropy values.

For the second aim, analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were conducted to determine (after identifying the latent class solution that best fit the data) the

differences among the predicted classes and outcome variables (functional, cognitive, and quality of life) at six-months follow-up. The extent to which membership in an identified cluster predicts functional, cognitive, and quality of life outcomes at six-months post-MTBI was explored. We will assess the association between predicted classes and the three main outcomes: Functional outcomes assessed by Glasgow Outcome Scale Extended (GOSE), cognitive outcome and nonverbal processing speed assessed by Wechsler Adult Intelligence Scale-IV (WAIS-IV; Coding Subset Total Raw Score, Symbol Search Subset), mental flexibility assessed by the difference score between the Trial Making Test (TMT) B and TMT A (TMT B-A), verbal learning assessed by the California Verbal Learning Test-II (CVLT-II), and quality of life outcomes assessed by the Satisfaction with Life Scale (SWLS).

For the third exploratory aim, an Analysis of Covariance (ANCOVA) was performed to explore the extent to which SNPs predict risk for more intense behavioural symptoms (somatisation, anxiety, depression, PTSD, and post-concussive syndrome) at six months post-MTB. We assessed the association between SNPs genotype and three main measures: (1) BSI-18 (the BSI-18 is a brief screen of psychological distress with a Global Severity Index (GSI), and three clinical subscales: BSI-somatisation, BSI-anxiety, and BSI-depression); (2) PTSD-PCL (3 subscales; hyper-vigilance, avoidance, Re-experiencing); and (3) the Rivermead Post Concussion Symptoms Questionnaire 13 (RPQ-13). For all follow-up posthoc tests, the Hochberg's GT2 was used to correct for the unequal sample size (Field, 2009).

The outcomes of this study will build a foundation upon which to establish clinically based strategies to identify MTBI patients at risk for protracted recovery and to identify those who may require earlier and more intense intervention.

Ethical Considerations

Protection of Human Subjects

The TRACK-TBI pilot study is an example of Multi-Dimensional Data Sharing, where multicenter patients' data and protected health information (PHI) are collected under informed consent into a central, custom-designed storehouse (QuesGen Systems, Inc., Burlingame, CA). In order to protect the privacy of patient enrolled in the study, each patient is assigned a globally unique identifier (Sorani et al., 2015). The permission for access ranged from 'no-PHI', to 'local PHI only', to 'full-access'. For the purpose of this secondary data analysis, a completed and approved research collaboration proposal was submitted to the TRACK TBI executive committee, which was reviewed and accepted. Then, the Data Use Agreement between the Regents of the University of California, on behalf of its San Francisco campus ("UCSF") and Loyola University of Chicago was acknowledged and signed by the data user's research team members who will access and/or analyze data. Access to TRACK-TBI and access to clinical data is provided to the data user for the purpose of collaboration in TBI research and will be used only as described in research proposal agreed upon by the TRACK-TBI executive committee and is data access was effective as of March, 18, 2016.

Additionally, an approval form from the Loyola University Medical Center (LUMC) institutional review boards (IRB) for conducting this secondary data analysis study was obtained. Federally sponsored studies are subject to strict guidelines for evaluation and before undertaking any study; researchers need to submit their research plans to the IRB, and must also go through a formal human subjects training and certification process that can be completed online (Polit &

Beck, 2008). The duty of the IRB is to ensure that the proposed plans meet the federal requirements for ethical research (Polit & Beck, 2008).

This is a no-benefit project; however, there are several anticipated benefits to MTBI populations in the future. It is hoped that results from this study will help in identifying MTBI patients who are at risk of fatigue, depression, cognitive impairment, and poor sleep at discharge and as early as possible. Findings may stimulate the development and implementation of programs for early interventions with these trauma patients to prevent these symptoms and to promote better quality of life.

Study Limitations

Overall secondary data analysis has been a widespread method in promoting the proficiency of the health research initiative; however, there are some advantages and disadvantages of analyzing existing secondary data (Cheng & Phillips, 2014). The major disadvantage is that the available data were not collected to address the particular research question or to test the particular hypothesis (Cheng & Phillips, 2014). However, overall the purpose of the analysis is to follow the TRACK-TBI initiative to improve long-term outcomes of TBI patients in general. Therefore, though a limitation of this study, it is not uncommon that valuable confounding variables were not available for the analysis (Cheng & Phillips, 2014).

First, the threat from confounding variables is one of the most important threats the investigator needs to account for. The confounding variables, as described earlier, will be controlled for.

Second, another threat to internal validity was the missing data. Third, selection bias, since the sample was a convenient and nonrandom sample. Convenience sampling is known as

one of the weakest sampling techniques and available subjects might be atypical of the population of interest with regard to critical variables. Selection bias is the most problematic and frequently occurring threat to internal validity of studies not using an experimental design (Polit & Beck, 2008). Fourth, the threat of history refers to the occurrence of external events that take place concurrently with the independent variable that can affect the dependent variable (Polit & Beck, 2008). A case in point is when something happens to the patient between follow-up points or even before enrollment that causes depression, fatigue, or poor sleep; for example, events such as death in the family or loss of job. Preinjury stress has been hypothesized to play a role in long-term maintenance of symptoms (van Veldhoven et al., 2011). For example, using the Life Events Scale could have assessed major life events. In fact, there is support for this notion, where research shows that incidence of stressful life events was a significant predictor of anxiety, depression, and mental health in MTBI patients. Thus, the experience of stressful events prior to the injury may predispose those with MTBI to suffer from lingering poor long-term outcomes. Assessment of stressful life events during acute stages post-MTBI is essential (van Veldhoven et al., 2011). Since this is a secondary data analysis, the researcher was limited and might not be able to overcome some of the threat.

Lastly, the threat to instrumentation is a minor threat in the use of self- report questionnaires as the measure for symptoms. There were no measures for each behavioral symptom (i.e., anxiety, depression, fatigue, poor sleep); they were either subscales from BSI-GSI (i.e., BSI-Depression, BSI-anxiety, BSI- Somatization), or for the cluster analysis, the items that address these factors were taken from the Rivermead Post-Concussion Questionnaire that was administered at the six-month follow-up.

Generalizability is identified as a threat to external validity. According to Polit and Beck (2008), generalizability is the criterion used in quantitative research to assess the extent to which the findings can be applied to other groups and setting. The population is a sample of MTBI patients with a range of ethnic diversity. Despite the study limitations, this study may not be generalizable to all MTBI patients. However, it could provide information that will help MTBI patients in the future by advancing the ability of clinicians to predict those who are at greater risk for more intense and/or prolonged depressive symptoms, fatigue, poor sleep, cognitive impairment, and anxiety.

Another threat to external validity is the relatively small size. The TRACK-TBI pilot phase consisted of three centers and collected data on 599 patients (only 340 MTBI patients; with only 201 eligible for the study due to missing data). With regard to generalizability of the current findings, the results are not generalizable beyond the institutions where data was collected and cannot be generalizable to all MTBI patients.

However, despite these limitations, ultimately, the knowledge acquired can be used to develop and implement improved risk assessment protocols for behavioral symptoms and to target prevention programs to those most vulnerable, and it can be tested in future intervention studies accordingly.

Conclusion

Overall, secondary data analysis has been a widespread method in promoting the proficiency of the health research initiative; however there are some advantages and disadvantages of analyzing existing secondary data (Cheng & Phillips, 2014). The most valuable advantage of the secondary data analysis involves the novel ideas about possible creative

research approaches when looking at the bigger picture of the readily available collected data rather than collecting primary data (Cheng & Phillips, 2014). This would inspire innovative usage of collected variables—for example, the use of symptom clusters analysis as a predictive tool for profiling subgroups enduring behavioral symptoms post-MTBI. Thus, this approach can bridge the gap between research and bedside nursing by addressing symptoms (as a cluster), which is the most common reason that individuals seek healthcare (Dodd et al., 2001). This paradigm shift might help better manage symptoms, ultimately reducing symptom burden (Aktas et al., 2010).

The second innovative aspect are the chosen frameworks (the psycho-neuro-immunology (PNI) framework, the Theory of Unpleasant Symptoms (TOUS), and the genetics field) that guide this investigation. These frameworks can potentially lead to remarkable advancement in the knowledge regarding improvement of quality of life and cognitive and functional recovery post-MTBI and will provide insight into the role of psycho-neuro-immunological processes in MTBI patients. Overall, the innovative conceptualized framework creatively addresses the depth of the interaction between symptoms experienced and their impact on recovery outcome, and explains the variations seen in MTBI patients.

The availability of the Track-TBI Pilot database, which provided a real-life data with a very un-accessible population and helped in accomplishing this secondary study, will eventually aid in identifying new treatment modalities to improve outcome of MTBI patients that can tested in future intervention studies (Cheng & Phillips, 2014).

This secondary data analysis represents a fortunate example of clinical research collaboration. Van Horn and Ball (date?) write that although it will not be “a pain-free process,

with increased data availability, scientists from multiple fields can enjoy greater opportunity for novel discoveries about the brain in health and disease." Sorani et al. (2015) add that "The ability to integrate clinical, genetic, imaging, and other types of biomedical data will be of tremendous value in ongoing efforts to discover and develop biomarkers and drugs to address unmet medical needs."

CHAPTER FOUR

RESULTS

This chapter describes the findings from the study in the following manner. First, the descriptive characteristics of the sample and all study variables are summarized. Second, the results of the study aims are delineated. As previously stated, there were three aims to this study. The first aim was to identify different profiles of MTBI patients based on the intensity of depressive mood, fatigue, and poor sleep. The second aim was to determine whether there are differences in cognitive and functional outcomes at six months post-MTBI among the identified behavioral cluster profiles. The third aim was to explore differences in the intensity of behavioral symptoms at six months post-MTBI based on SNP genotype.

Data Analysis: Aim 1

Results Summary of Sample Characteristics/Demographic Statistics

Data for 340 MTBI patients extracted from the TRACK-TBI pilot database. Of the 340 MTBI patients, 202 patients were included in the Latent Class Analysis (LCA) due to missing data. The sample characteristics of the 202 patients are described below and in Table 4. The majority of the sample were males (67.3%), white (99.5%) and single (50.5%), with a mean age of 45±18 years. Nearly half (44.6%) of the sample worked full time (35 hours or more per week) and had either a High school diploma (34.7%) or Bachelor's degree (25.7%). Nearly 20% of the sample had a previous TBI (With and Without Hospital Admission). Past history of anxiety, depression and sleep disorder was reported by 14.4%, 20.8%, and 5.9% of the sample,

respectively. Use of tobacco, alcohol, and drugs was reported by 31.7%, 51.5%, and 18.8% of the sample, respectively.

Upon arrival to the ED, the majority of patients (77.7%) had a GCS of 15 and 71% reported LOC with varied duration (i.e., 11.4% <1 minute,35.1% 1-29 minutes, 5% 30-59 minutes, and 20.3% unknown LOC duration). While the majority (62.4%) reported no Post Traumatic Amnesia (PTA), of those reporting PTA the duration was: 5.9% <1 minute, 23.8% 1-29 minutes, 6.9% 30-59 minutes, 7.9% 1-24 hours, and 17.3% unknown PTA duration. Data on injury severity, using the Injury Severity Score (ISS), was available for 88.1% of the sample. The ISS rates traumatic injury based on worst injury of 6 body systems, and ranges from 1 to75; 1-9 Minor, 10-15 Moderate, 16- 24 Moderate/Severe, and ISS > 25 Severe/Critical (Baker, O'Neill, Haddon, & Long, 1974). The majority (56.9%) of the sample had ISS scores ≥ 16, placing them in the moderate to severe range. Nearly all injuries (99.5%) were closed head injuries; roughly half (47.5%) were motor vehicle accidents (MVA). Accidental falls accounted for 36.6% of the injuries and 0.5% were due to explosive injury. Please refer to Table 5.

Descriptive statistics for key study outcome variables. Fatigue, sleep disturbance and depression were assessed by the items from the Rivermead Post-Concussive Questionnaire (RPQ). The items were measured on a Likert scale in which respondents rated items from a minimum score of 0 (not experienced at all) to a maximum score of 4 (severe problem). Means and standard deviations are shown in Table 1 (all variables were normally distributed), see Table 1

Table 1. Descriptive Statistics

	N	Mean	Std. Deviation	Skewness		Kurtosis	
	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic	Std. Error
RPQ Fatigue	202	1.27	1.233	.475	.171	-.972	.341
RPQ Sleep Disturbance	202	1.00	1.333	.984	.171	-.413	.341
RPQ Feeling Depressed or Tearful	202	.75	1.050	1.162	.171	.280	.341

Note: RPQ = Rivermead post-concussive symptoms questionnaire (each question ranges from 0-not experienced to 4-severe problem). STD = Standard

Aim 1 Data Analysis and Results

Latent Class Analysis of Behavioral Symptoms at six-month post MTBI

Latent Class Analysis (LCA) was performed to identify profiles of MTBI patients based on the intensity of depressive symptoms, fatigue, and poor sleep. The items that address these factors were taken from the Rivermead Post-Concussion Questionnaire that was administered at the six-month follow-up. Mplus 7.4 (Muthén & Muthén, 1998-2011) was used to conduct the LCA. The analysis was performed by fitting a two-class model, and gradually increasing the number of classes one at a time for model comparison, setting a random starting value arbitrarily from 500 to 100. A range of random start values was used to confirm that the true minimum was reached.

Several criteria were used to guide the decision on the number of classes in mixture modeling, including the Akaike Information Criterion (AIC), the Bayesian Information Criterion (BIC (Schwarz, 1978), the sample-size-adjusted aBIC, the Vuong-Lo-Mendell-Rubin (VLMR) test (requested using TECH 11 in Mplus) and the bootstrapped parametric likelihood ratio test (LRT; requested using TECH 14 in Mplus). Both tests compared the model of the currently

chosen number of classes (K) to a model of K−1 classes. For AIC, BIC, and aBIC, lower observed values indicate better model fit. In case of entropy, values closer to 1.00 suggest a better fit. In addition, a nonsignificant p value for the BLMR LR test indicates that the model with the K-1 class is preferred to the model with K classes. The final classes were determined by small AIC, BIC, and aBIC values comparing each class (K) with each K-1 classes, as well as nonsignificant BLMR LR and strong entropy values.

The four-class model suggested the best fit to the data with the lowest observed AIC, BIC and the sample-size-adjusted BIC. Entropy value was the highest also for the four-class model. Also, when the number of latent classes was increased from four to five classes, the p value of the VLMR test was not statistically significant (p= .5754), indicating that the addition of a fifth class did not significantly improve the fit of the model. However, BLMR LR remained significant for the five-class model (see Table 2).

Research suggests that BLMR LR is in general a more accurate indicator of the classes than the VLMR test (Nylund, Asparouhov, & Muthén, 2007). For this reason, the discrepancy between these two indices was further investigated by examining which model has most conceptual as well as empirical value. The examination of the three-, four-, and five-class solutions revealed that the four-class solution had the clearest interpretation. The three-class solution largely combined Classes 3 and 4, which masked the important distinction in the levels of depression between these two classes, whereas the five-class solution essentially divided Class 1 into two subclasses that differed in what appeared to be substantively unimportant ways. The decision was made to disregard the BLMR LR test and retain the four-class model as the final model.

The means of the three variables used to generate the latent classes are shown in Table 3. The first column shows the overall means for the full sample, and subsequent columns show the means for the four latent classes. Class 1 was the largest class, constituting 67.7% of the cases, and was characterized by low endorsement of depression, fatigue, and sleep disturbance. Class 4 accounted for 15.9% and had the highest ratings of depression, fatigue, and sleep disturbance. Class 3 (9.5%) was characterized by low depression and high fatigue, whereas Class 2 (7%) was characterized by low fatigue and high depression; both classes had the same ratings of sleep disturbance. The difference between latent class on demographic and injury-related characteristics are addressed in the following section (AIM 2).

Table 2. Information Criteria and Entropy for Different Class Solutions

Model	AIC	BIC	aBIC	Entropy	VLMR	BLMR LR
2 class	1545.078	1578.210	1546.528	0.945	>.001	>.001
3 class	1518.639	1565.024	1520.669	0.943	.1534	>.001
4 class	1454.946	1514.584	1446.556	0.951	>.03	>.001
5 class	1443.224	1516.115	1459.413	0.932	0.5754	>.001

Table 3. Means and Standard Errors of the Fatigue, Depression and Sleep Disturbance by Latent Class Membership

Variable	Full Sample	Class 1	Class 2	Class 3	Class 4
Fatigue					
Mean	1.27	0.165	0.431	1.953	2.538
SE	.087	0.034	0.142	0.166	0.127

Table 3 (cont.)

Depression					
Mean	0.75	0.184	2.569	0.605	2.536
SE	.074	0.039	0.221	0.162	0.122
Sleep Disturbance					
Mean	1.00	0.394	1.373	1.062	1.837
SE	.094	0.065	0.318	0.202	0.238

Figure 1. Mplus profile plot based on estimated means.

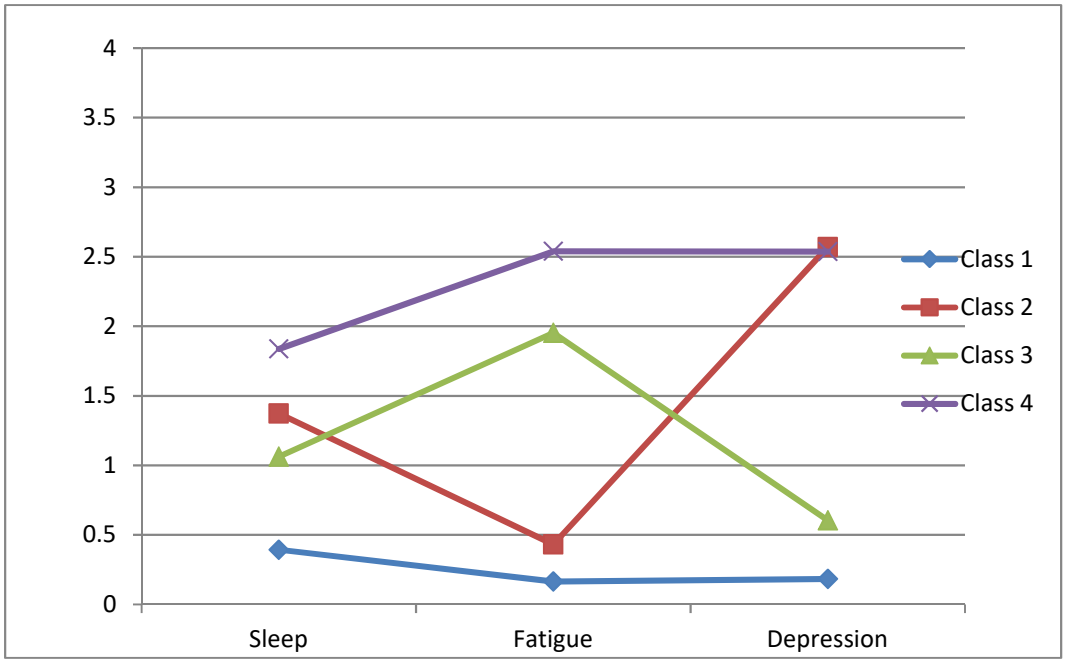


Figure 1. The means of the three variables used to generate the latent classes are shown in Table X. Class 1 was the largest class, constituting 67.7% of the cases, and was characterized by low endorsement of depression, fatigue, and sleep disturbance. Class 4 accounted for 15.9% and had the highest ratings of depression, fatigue, and sleep disturbance. Class 3 (9.5%) was characterized by low depression and high fatigue, whereas Class 2 (7%) was characterized by low fatigue and high depression; both classes had the same ratings of sleep disturbance. The items that address these factors were taken from the Rivermead Post-Concussion Questionnaire that was administered at six-months follow-up. (RPQ-13 questions; RPQ Fatigue: Tiring More

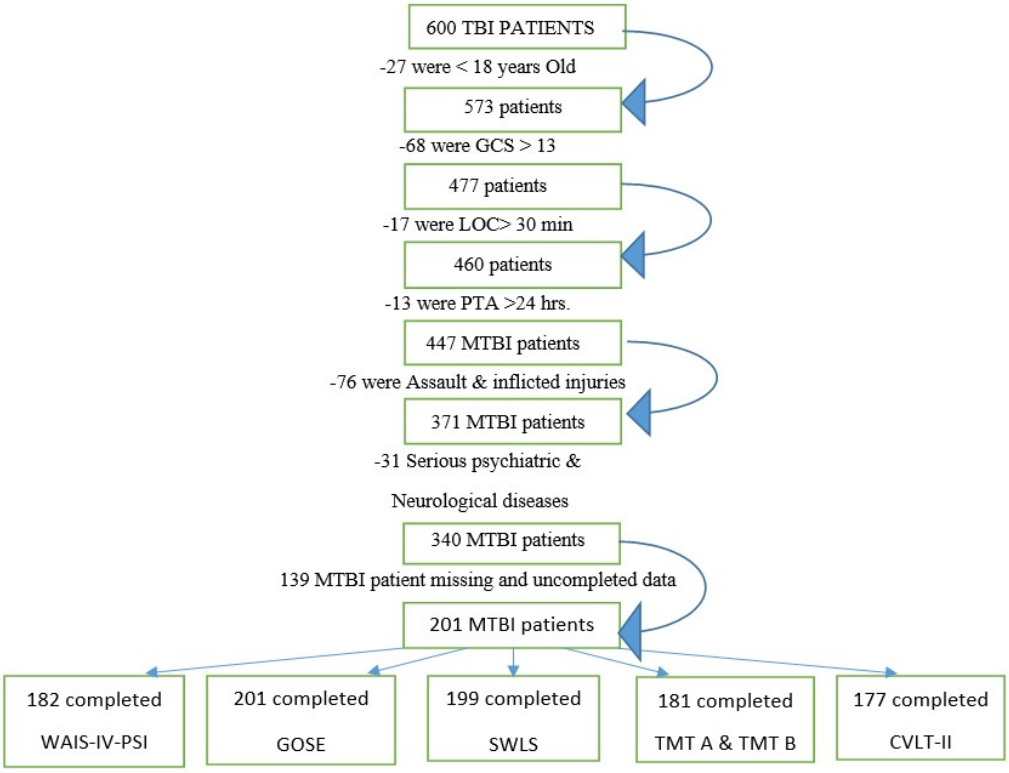
Easily, RPQ Sleep Disturbance, RPQ Feeling Depressed or Tearful). It is a 5-point Likert scale that ranges from 0 to 4, ranging from ‘‘not experienced at all’’ to ‘‘a severe problem’’.

Data Analysis: Aim 2

Sample Exclusion and Inclusion Criteria

Six hundred TBI patients were enrolled in the TRACK-TBI Pilot study (See Figure X for enrollment diagram); however, 68 cases were excluded because of Glasgow Coma Scale < 13 upon arrival to the ED, 17 cases were excluded because of reported LOC > 30 minutes, 13 cases were excluded because of reported PTA > 24 hours, 76 cases were excluded because their injury was a result of assault by others or a result of domestic violence. Additionally, 31 cases were excluded because of serious psychiatric disorders that would interfere with outcome measures. Of the sample that met the inclusion criteria (n=340), 139 MTBI patients had missing data and uncompleted biological data as shown in Figure 2. The final sample consisted of 201 patients (see Figure 2).

Figure 2: Enrollment flow diagram



Inclusion criteria were both males and females (ages >18years) who suffered external force trauma to the head, an emergency department arrival GCS score between 13 and 15 (mild) and who have completed the three- and six-month follow-up. Concussion/MTBI patients who suffered minor injuries, who were alert, oriented, and who could read, write and speak English were included. Mechanisms of injury included were motor vehicle accident, motorcycle/bicycle accident, pedestrian struck by vehicle, struck by/against object, falls, and other accidental causes of injury.

Sample Characteristics/Demographic Statistics

The sample characteristics by LCA class as describe in Aim 1 are presented below (see Table 4). The demographic and health characteristics of the individuals grouped into the four Classes were similar; however, there were some minor trending differences and other significant

differences (i.e., employment status and GCS score). Among the trending differences were those in social behaviors and history of behavioral symptoms (i.e., anxiety, depression, sleep disturbance), and causes of injury.

For social behaviors, Class 4 (high symptoms) reported more alcohol consumption (65.6%) compared to other Classes; yet, it is not clear if this was a pre-existing behavior or if it developed in association with the post-MTBI symptoms. We attempted to conduct a chi-square test of independence between LCA groups and social behaviors; however, all expected cell frequencies were below five, and therefore we did not have an adequate sample size to run the chi-square test of independence.

As for history of behavioral symptoms (i.e., anxiety, depression, sleep disturbance), Class1 had the least reported history of behavioral symptoms—anxiety (9.5%), depression (15.4%), and sleep disorder (3.6%). A comparison of the history of behavioral symptoms (i.e., anxiety, depression, poor sleep) between Class 2 and Class 3 revealed that Class 2 reported a lower percentage of history of behavioral symptoms (i.e., anxiety (21.4%), depression (28.5%), sleep disorder (7.1%)); whereas Class 3 reported a higher percentage of history of behavioral symptoms prior to MTBI (i.e., anxiety (26.3%), depression (36.8%), sleep disorder (15.8%)). These findings suggest that history of behavioral symptoms does not necessarily predict the intensity of symptoms post-TBI. Along the same lines, another interesting finding is that only 9.4% of those in Class 4 reported some history of a sleep disorder, while a low percentage reported history of anxiety (25%) and history of depression (31.3%). Although it is valuable to asses for history of behavioral symptoms that could relate to susceptibility of poor long-term outcome recovery, no such relationship was found in this sample. We attempted to conduct a chi-square test of independence between LCA groups and social behaviors; however, all expected

cell frequencies were below five, and therefore, we did not have an adequate sample size to run the chi-square test of independence.

With respect to the causes of injury, the majority of patients in Class 2 were involved in accidental falls (43%), while the remainder presented with a mix of MVA, accidental fall, or other injury. However, the present findings revealed that the symptom cluster intensity post-MTBI was not associated with severity of injury, as the ISS Score was ≥ 16 for similar across Classes (i.e., 56 % for Class 1, 43% for Class 2, 58 % for Class 3, and 65.6% for Class 4). A chi-square test of independence was conducted, there were no statistically significant differences between the LCA groups and causes of injury.

Lastly, the findings revealed few significant demographic differences across LCA groups; that is, differences were observed in employment status and arrival GCS score. A chi-square test of independence was conducted between LCA groups and Employment status. All expected cell frequencies were greater than five. There were statistically significant differences between LCA groups and Employment status $\chi 2(21) = 38.364$, $p < .012$. The association was moderately strong (Cohen, 1988), Cramer's V = .254. Additionally, a chi-square test of independence was conducted between LCA groups and arrival GCS score. All expected cell frequencies were greater than five. There were statistically significant differences between LCA groups and arrival GCS $\chi 2(6) = 14.094$, $p < .029$. The association was small (Cohen, 1988): Cramer's V = .188.

Overall, the findings revealed no major demographic differences across LCA groups; that is, no differences were observed in age, gender, and marital status. An ANOVA was conducted between LCA groups and age; however, there were no statistically significant differences. A chi-square test of independence was conducted between LCA groups, and gender and marital

status; however, there were no statistically significant differences. Also, the findings revealed no major injury-related characteristics differences across LCA groups. A chi-square test of independence was conducted between LCA groups and injury-related characteristics; however, there were no statistically significant differences.

Descriptive Statistics of Outcome Variables

For Aim II, differences in the functional and cognitive abilities as well as the quality of life factors were investigated as a function of the class membership that was identified in Aim 1. The functional outcomes were assessed by the Glasgow Outcome Scale Extended (GOSE); Cognitive outcomes were assessed by the Trial Making Test (Part B-Part A Difference and Part B/Part A ratio), California Verbal Learning Test-II (CVLT-II; Trials 1-5 Free Recall), Wechsler Adult Intelligence Scale-IV (WAIS-IV; Coding Subset Total Raw Score, Symbol Search Subset). Quality of life outcomes were assessed by the Satisfaction with Life Scale (SWLS). For means and standard deviations of main outcome variables, see Table 6. All variables were normally distributed; see Table 6 for Skewness and Kurtosis values.

For functional outcomes, MTBI patients had a GOSE mean of 6.96 (SD= 1.108) for functional level. More specifically, low symptoms (M=7.37, SD=.933) performed better than all other groups: high depression/low fatigue symptoms group (M=6.29, SD=1.204), low depression/high fatigue symptoms group (M=6.11, SD=.875), as well as high symptoms group (M=6.03, SD=.897).

When comparing satisfaction with life results to the norms, overall MTBI patients (M=22. 30, SD=7.645) reported greater level of satisfaction when compared to TBI patients (Corrigan et al., 1998) and university students, but a lower level of satisfaction when compared to elderly adults (Durak et al., 2010) and undergraduate students (Diener et al., 1985). More

specifically, the low symptoms group (M=25.22, SD=6.590) reported greater level of satisfaction when compared to TBI patients (Corrigan et al., 1998), undergraduate students (Diener et al., 1985), university students, correctional officers and elderly adults (Durak et al., 2010). While both high depression/low fatigue (M=18.71, SD=5.717) symptoms and low depression/high fatigue symptoms group (M=16.89, SD=7.203) had lower level of satisfactions when compared to all above mentioned groups they had a greater level of satisfaction than correctional officers (Durak et al., 2010). Also, high symptoms group (M=14.81, SD=4.967) had the lowest level of satisfaction when compared to TBI patients (Corrigan et al, 1998), undergraduate students (Diener et al., 1985), university students and correctional officers (Durak et al, 2010).

When comparing non-verbal learning results, MTBI patients (M=102.55, SD=15.543) performed better in WAIS-IV Processing Speed Index Composite Score when compared to all the lowest and highest index except for the intellectually gifted (Wechsler, 2008). More specifically, three classes—low symptoms group (M= 105.211, SD=14.773), low depression/high fatigue symptoms group (M= 99.611, SD=14.034), and high symptoms group (M= 97.143, SD=16.788)—performed better than all the highest and lowest score index clinical population except for the intellectually gifted (Wechsler, 2008). Meanwhile, the high depression/low fatigue symptoms group (M= 93.154, SD=16.201) performed better than some of the highest and lowest except for major depressive disorder, ADHD, intellectually gifted, and reading disorder (Wechsler, 2008).

When comparing mental flexibility results, overall TMT B-A performance was poorer in MTBI patients (M=49.070, SD=45.40) as compared to healthy control (young group 16 to 24 and middle aged 25-54) (Perianez et al., 2007), but better than TBI patients and elderly healthy controls (55–80 years old) (Perianez et al., 2007). For LCA groups, the low symptoms group

(M=42.58, SD=35.26) and both high depression/low fatigue symptoms group (M=61.96, SD=46.31) symptoms and low depression/high fatigue symptoms group (M=56.58, SD=36.61) symptoms, as well as high symptoms group (M=66.54, SD=75.84) performed better than TBI patients and elderly healthy controls but worse when compared with young and middle healthy controls (Perianez et al., 2007).

When comparing verbal learning (CVLT-II Trials 1-5 Free Recall) results to the norms, researchers provide normative data from large samples of 285 outpatients in a mixed neurologic sample with low executive functioning (M=34.86, SD= 16.66), medium executive functioning (M= 43.10 SD=17.26), and high executive functioning (M= 45.02, SD=22.72) (Hill et al., 2012). In our sample, overall MTBI patients (M=49.08, SD=12.770) performed better in CVLT-II Trials 1-5 Free Recall when compared to all levels of executive functioning. More specifically, low symptoms group (M= 49.64, SD= 12.736), both high depression/low fatigue symptoms group (M= 49.54, SD= 15.125) and low depression/high fatigue symptoms group (M= 47.83, SD= 13.840), as well as high symptoms group (M= 47.22, SD= 11.430) had better scores when compared to all levels executive functioning.

Table 4. Sample Characteristics for Aim 2

	class 1		*class 2*		*class 3*		*class 4*	
	n = 136		*n* = 14		*n* = 19		*n* = 32	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Male	95	70%	8	57%	10	53%	22	69%
Ethnicity								
Hispanic or Latino	13	10%	1	7%	3	16%	10	31%
Non-Hispanic or Non-Latino	123	90%	13	93%	16	84%	21	66%
Race								
Asian	8	6%	1	7%	0	0%	3	9%
Black	5	4%	0	0%	0	0%	2	6%
White	114	84%	12	85.7	18	95%	25	78%
American Indian or Alaska Native	0	0%	0	0%	1	5%	0	0%
Native Hawaiian or Other Pacific Islander	5	4%	0	0%	0	0%	1	3%
Other	3	2%	1	7%	0	0%	1	3%
Employment								
Working full time with 35 hours or more per week and at least minimum wage	69	51%	2	14%	3	16%	16	50%
Working 20-34 hours per week at least minimum wage	12	9%	2	14%	4	21%	2	6%
Working less than 20 hours per week and at least minimum wage	5	4%	0	0%	2	11%	1	3%
Special employment (sheltered workshop, supportive employment, job coach)	0	0%	0	0%	1	5%	0	0%
Temporary or odd jobs and less than minimum wage jobs	2	14%	0	0%	0	0%	1	3%
Not in paid workforce	26	19%	4	29%	4	21%	5	16%
Unemployed	18	13%	4	29%	3	16%	7	22%

Table 4 (cont.)

Education Highest Level								
High school diploma	42	31%	7	50%	9	47%	12	38%
Associate degree	12	9%	1	7%	0	0%	2	6%
GED	4	3%	2	14%	0	0%	2	6%
Bachelor's degree	39	29%	1	7%	4	21%	8	25%
Master's degree	16	12%	0	0%	1	5%	2	6%
Doctoral degree	6	4%	0	0%	1	5%	1	3%
Marital Status								
Divorced	4	3%	3	21%	2	11%	5	16%
Married or living together	54	40%	2	14%	7	37%	9	28%
Separated	1	1%	0	0%	0	0%	0	0%
Single	71	52.2%	9	64%	9	47%	13	41%
Widowed	2	1%	0	0%	1	5%	3	9%
Unknown	3	2%	0	0%	0	0%	0	0%

Note. GED = general education development

Table 5. Sample Characteristics for Study Aim 2: Injury-Related Characteristics

	class 1		*class 2*		*class 3*		*class 4*	
	n = 136		*n* = 14		*n* = 19		*n* = 32	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Arrival GCS								
13	2	1.5%	0	0.0%	1	5.2%	0	0.0%
14	21	15.7%	1	7.1%	4	21.0%	13	40.6%
15	111	82.8%	13	92.9%	14	74.0%	19	59.4%
LOC	84	61.7%	9	64.2%	13	68.0%	23	72.0%
LOC Duration								
<1 minute	15	11.0%	2	14.3%	2	0.9%	4	13.0%
1-29 minutes	46	33.8%	5	36.0%	7	36.8%	13	41.0%
30-59 minutes,	6	4.4%	0	0.0%	2	10.5%	2	6.2%
Unknown	26	19.0%	3	21.0%	3	16.0%	8	28.0%
PTA	76	55.8%	6	43.0%	10	53.0%	20	63.0%
PTA Duration								
<1 minute	12	8.8%	0	0.0%	0	0.0%	0	0.0%
1-29 minutes	30	22.0%	3	21.0%	5	26.3%	10	31.0%
30-59 minutes	11	8.0%	0	0.0%	1	5.3%	2	6.2%
1-24 hours	11	8.0%	1	7.0%	0	0.0%	4	12.5%
Reported injury severity	120	88.0%	11	79.0%	17	89.0%	29	90.6%
Poly-trauma with any two body regions,	7	5.1%	1	7.0%	2	10.5%	4	13.8%
Poly-trauma with Head or neck Injury	7	5.1%	1	7.0%	2	10.5%	3	10.3%
ISS Score ≤ 16	43	31.6%	5	36.0%	6	31.5%	8	27.6%
ISS Score ≥ 16.	77	56.0%	6	43.0%	11	58.0%	21	65.6%
Closed head injuries	135	99.3%	14	100.0%	19	100.0%	32	100.0%
previous TBI	24	17.6%	2	14.3%	3	15.8%	11	34.4%

Table 5 (cont.)

MVA	54	40.0%		4	28.5%		9	47.0%		14	45.1%
Accidental Fall	46	34.0%		6	43.0%		9	47.0%		13	40.6%
Cutting and piercing Object	1	0.7%		0	0.0%		0	0.0%		0	0.0%
Firearm accident by explosive material	1	0.7%		0	0.0%		0	0.0%		0	0.0%
Striking Accidents	5	3.6%		0	0.0%		0	0.0%		1	3.1%
Struck accidentally by falling object	2	1.4%		0	0.0%		0	0.0%		0	0.0%
Other environmental or accidental causes	0	0.0%		1	7.1%		0	0.0%		0	0.0%
Other vehicle accident	10	7.3%		2	14.3%		0	0.0%		4	12.5%
Motor vehicle accident but not traffic related	4	2.9%		0	0.0%		0	0.0%		0	0.0%
Unknown	14	10.2%		1	7.0%		1	5.2%		0	0.0%

Note, GCS=Glasgow Coma Scale, PTA= Post Traumatic Amnesia, LOC= Loss of Consciousness, MVA= Motor vehicle accident, ISS= Injury Severity Score.

Table 6. Descriptive for Main Study Outcome Variables

	N	Range	Mean	Std. Dev.	Skewness	Std. Error	Kurtosis	Std. Error
GOSE	201	5	6.96	1.108	.172	-1.034	.341	.749
SWLS	199	28	22.30	7.645	.172	-.241	.343	-1.045
TMT Part B-Part A\	181	328.5	49.070	45.40	.181	2.971	.359	12.252
CVLT-II Trials 1-5 Free Recall	177	63	49.08	12.770	.183	-.275	.363	-.303
WAIS-IV-PSI Composite Score	182	91	102.55	15.543	.180	.179	.358	.407

Note. GOSE= Glasgow Outcome Scale Extended, WAIS-IV PSI= Wechsler Adult Intelligence Scale-IV Processing Speed Index, TMT = Trial Making Test (TMT) CVLT-II trials 1– 5= California Verbal Learning Test-II (five learning trials, an interference trial, an immediate recall trial, and a post-20 min recall trial); SWLS= Satisfaction with Life Scale.

Aim 2: Data Analysis and Results

Statistical strategy. First, the assumption of normality and homogeneity of variances and outliers was assessed for all outcome measures. Normality was assessed by examining histogram plots and z scores. Homogeneity of variance was assessed by Levene's test. All variables were checked for skewness and kurtosis (see Table 6). Results indicated that all outcome variables were normally distributed and no transformations were necessary.

The second aim of this study was to determine (after identifying the latent class solution that best fit the data) the differences among the predicted classes and outcome variables (functional, cognitive, and quality of life) at six-months follow-up. Functional outcomes were assessed by Glasgow Outcome Scale Extended (GOSE), cognitive outcome and nonverbal processing speed were assessed by Wechsler Adult Intelligence Scale-IV (WAIS-IV; Coding Subset Total Raw Score, Symbol Search Subset), mental flexibility was assessed by the difference score between the Trial Making Test (TMT) B and TMT A (TMT B-A), verbal learning was assessed by the California Verbal Learning Test-II (CVLT-II trials 1–5; five learning trials, an interference trial, an immediate recall trial, and a post-20 min recall trial); and quality of life outcomes assessed by the Satisfaction with Life Scale (SWLS). An analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were conducted to address this aim. For all follow-up post hoc tests the Hochberg's GT2 was used to correct for the unequal sample size (Field, 2009).

Functional outcome and LCA groups. A one-way ANOVA was conducted to investigate differences in the main functional outcome (Glasgow Outcome Scale Extended (GOSE) among the four LCA Groups: low symptoms (n = 136), high depression/low fatigue (n = 14), low depression\ high fatigue (n = 19), and high symptoms (n = 32)). Since the subgroup

sizes were unequal, the Hochberg's GT2 posthoc test which explicitly allows for unequal sample sizes was used (Field, 2009).

Results revealed significant group differences in the level of functional outcome as assessed by GOSE at six months post-injury, ($F(3,197) = 26.40$, $p < .05$, partial $\eta 2 = .287$). The assumption of homogeneity of variances was met, as assessed by Levene's test for equality of variances ($p = .813$). The follow-up Hochberg's GT2 post-hoc test revealed that group differences in GOSE were significant between low symptoms (M=7.37, SD=.933) and high depression/low fatigue symptoms (M=6.29, SD=1.204) (95% CI .38 to 1.79, $p = .0003$), as well between low symptoms and low depression/high fatigue (M=6.11, SD=.875) symptoms (95% CI .65 to 1.88, $p< .05$), and between low and high (M=6.03, SD=.897) symptoms (95% CI .84 to 1.83, $p< .05$). This indicates that those with low symptoms (M=7.37, SD=.933) had significantly greater levels of functional outcomes and good recovery as compared to high depression/low fatigue (M=6.29, SD=1.204) symptoms and, with low symptoms, had significantly greater levels as compared low depression/high fatigue symptoms, and high symptoms. See Tables 7 and 8.

Table 7. Tests of _____ Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	70.449[a]	3	23.483	26.400	.000
Intercept	4088.928	1	4088.928	4596.844	.000
LCAclass	70.449	3	23.483	26.400	.000
Error	175.233	197	.890		
Total	9983.000	201			
Corrected Total	245.682	200			

a. R Squared = .287 (Adjusted R Squared = .276)
b. Computed using alpha = .05

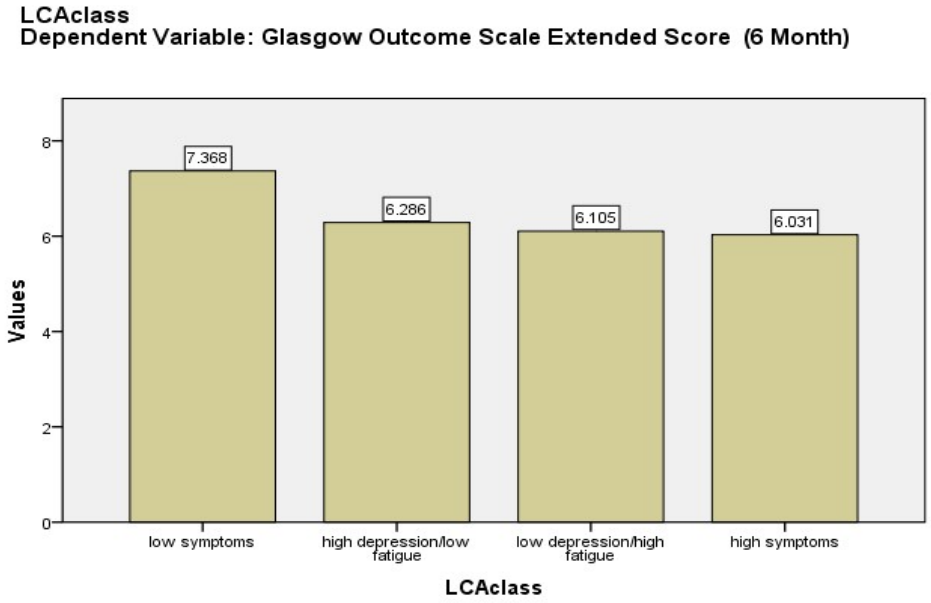
Note. The Glasgow Outcome Scale Extended provides eight categories of outcome, ranges from (1) Dead to (8) Upper Good Recovery.

Table 8. LCA Class

Dependent Variable: Glasgow Outcome Scale Extended (6 Month)				
			95% Confidence Interval	
LCAclass	Mean	Std. Deviation	Lower Bound	Upper Bound
low symptoms	7.368	.933	7.208	7.527
high depression/low fatigue	6.286	1.204	5.789	6.783
low depression/high fatigue	6.105	.875	5.679	6.532
high symptoms	6.031	.897	5.702	6.360

Note. The Glasgow Outcome Scale Extended provides eight categories of outcome, ranges from (1) Dead to (8) Upper Good Recovery.

Figure 3. Glasgow Outcome Scale Extended (6-month).



Note. Patients (n=201) were classified into 4 groups: low symptoms (n = 136), high depression/low fatigue (n = 14), low depression\ high fatigue (n = 19), and high symptoms (n = 32), The follow-up Hochberg's GT2 post-hoc test revealed that group differences in GOSE were significant between low symptoms (M=7.37, SD=.933) and high depression/low fatigue symptoms (M=6.29, SD=1.204) (95% CI .38 to 1.79, p = .0003), as well between low symptoms and low depression/high fatigue (M=6.11, SD=.875) symptoms (95% CI .65 to 1.88, p< .05), and between low and high (M=6.03, SD=.897) symptoms (95% CI .84 to 1.83, p< .05). The Glasgow Outcome Scale Extended provides eight categories of outcome, ranges from (1) Dead to (8) Upper Good Recovery.

Satisfaction with life and LCA groups. A one-way ANOVA was conducted to investigate differences in the main quality of life outcome measure assessed by the Satisfaction

with Life Scale (SWLS) among patients (n=201) in the four LCA groups: low symptoms (*n* = 134), high depression/low fatigue (*n* = 14), low depression\high fatigue (*n* = 19), and high symptoms (*n* = 32). Since the subgroup sizes were unequal, the Hochberg's GT2 post hoc test, which explicitly allows for unequal sample sizes was used (Field, 2009).

Results revealed significant group differences in the level of Satisfaction with Life at six-months follow-up, (F *(3, 195) = 30.239,* p < *.0005,* partial η2 = .318). The assumption of homogeneity of variances was met, (p = .270). The follow-up Hochberg's GT2 post hoc test revealed that group differences in Satisfaction with Life were significant between low (M=25.22, SD=6.590) and high depression/low fatigue (M=18.71, SD=5.717) symptoms (95% CI 1.76 to 11.26, *p* = .002), as well as the between low symptoms and low depression/high fatigue (M=16.89, SD=7.203) symptoms (95% CI 4.18 to 12.47, *p*< .05), and between low and high (M=14.81, SD=4.967) symptoms (95% CI 7.08 to 13.74, *p*< .05). This indicates that those with low symptoms (M=25.22, SD=6.590) had significantly greater levels of satisfaction with life as compared to high depression/low fatigue symptoms (M=18.71, SD=5.717) and low depression/high fatigue symptoms (M=16.89, SD=7.203); both groups are considered slightly below average in life satisfaction. Also, low symptoms (M=25.22, SD=6.590) had a significantly greater level of satisfaction with life as compared to high symptoms (M=14.81, SD=4.967), which are considered dissatisfied according to the SWLS scoring (see Tables 9 and 10).

Table 9. Tests of Between-Subjects Effects

Dependent Variable: SWLS Total Score (6 Month)					
Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	3674.702[a]	3	1224.901	30.239	.000
Intercept	35154.680	1	35154.680	867.873	.000
LCA class	3674.702	3	1224.901	30.239	.000
Error	7898.805	195	40.507		
Total	110503.000	199			
Corrected Total	11573.508	198			

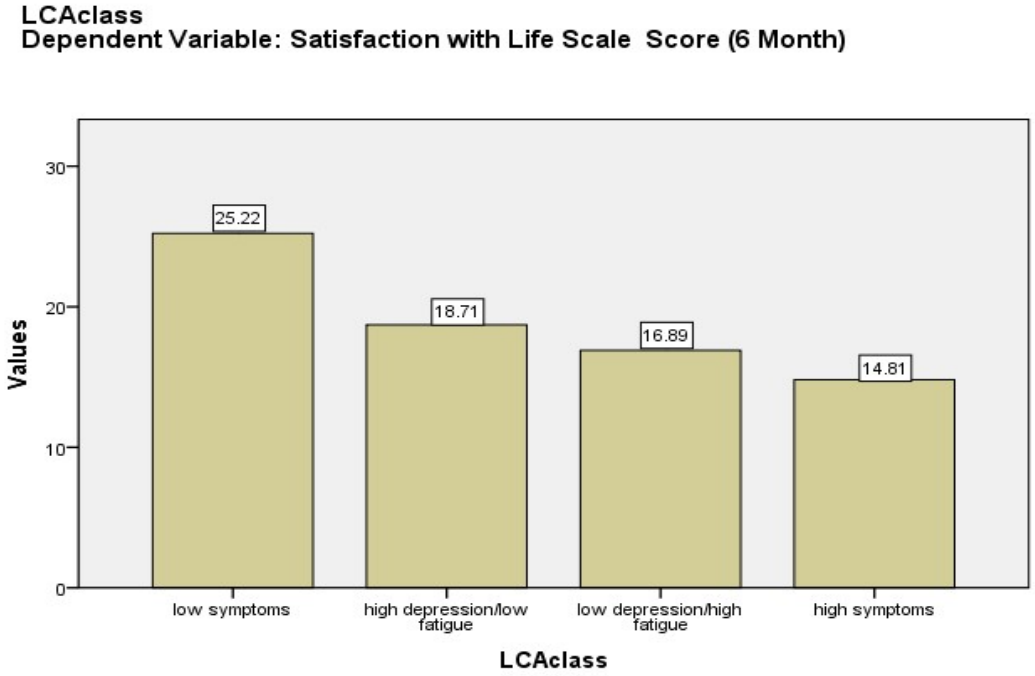
a. R Squared = .318 (Adjusted R Squared = .307)

Note. SWLS- Satisfaction with Life scale. The SWLS is a series of five statements ranges from 1 (‘‘strongly disagree’’) to 7 (‘‘strongly agree’’). The total score ranges from a maximum very high score between 30 – 35 indicating ‘‘highly satisfied’’, high score 25- 29, “slightly below average in life satisfaction” score between 15 – 19, “dissatisfied’ score between 10 – 14, and “extremely dissatisfied” score between 5 – 9

Table 10. Descriptive Statistics: SWLS

Dependent Variable: SWLS Total Score (6 Month)				
		Std.	95% Confidence Interval	
LCA class	Mean	Deviation	Lower Bound	Upper Bound
low symptoms	25.224	6.590	24.140	26.308
high depression/low fatigue	18.714	5.717	15.360	22.069
low depression/high fatigue	16.895	7.203	14.015	19.774
high symptoms	14.813	4.967	12.594	17.031

Figure 4. Satisfaction with Life Scale.



Note. Patients (n=201) were classified into 4 groups: Low symptoms (*n* = 134), high depression/low fatigue (*n* = 14), low depression\ high fatigue (*n* = 19), and high symptoms (*n* = 32). The follow-up Hochberg's GT2 post-hoc test revealed that group differences in Satisfaction with Life were significant between low (M=25.22, SD=6.590) and high depression/low fatigue (M=18.71, SD=5.717) symptoms (95% CI 1.76 to 11.26, *p* = .002), as well as the between low symptoms and low depression/high fatigue (M=16.89, SD=7.203) symptoms (95% CI 4.18 to 12.47, *p*< .05), and between low and high (M=14.81, SD=4.967) symptoms (95% CI 7.08 to 13.74, *p*< .05). Note. SWLS- Satisfaction with Life scale. The SWLS is a series of five statements ranges from 1 (''strongly disagree'') to 7 (''strongly agree''). The total score ranges from a maximum very high score between 30 – 35 indicating ''highly satisfied'', high score 25-29, "slightly below average in life satisfaction" score between 15 – 19, "dissatisfied' score between 10 – 14, and "extremely dissatisfied" score between 5 – 9

Cognitive abilities and LCA groups. A one-way ANOVA was conducted to investigate differences in cognitive abilities among patients (n=201) who are classified into four LCA groups: low symptoms (*n* = 136), high depression/low fatigue (*n* = 14), low depression/high fatigue (*n* = 19), and high symptoms (*n* = 32). Cognitive measures evaluated were: **nonverbal processing speed** assessed by Wechsler Adult Intelligence Scale-IV (WAIS-IV; Coding Subset Total Raw Score, Symbol Search Subset); **mental flexibility** assessed by the difference score

between the TMT B and TMTA (TMT B-A); and **verbal learning** assessed by California Verbal Learning Test-II (CVLT-II trials 1– 5; five learning trials, an interference trial, an immediate recall trial, and a post-20 min recall trial). Since the subgroup sizes were unequal, the Hochberg's GT2 post hoc test, which explicitly allow for unequal sample sizes, was used (Field, 2009).

Nonverbal processing speed. Results revealed significant group differences in the level of nonverbal processing speed as assessed by WAIS-IV Processing Speed Index Composite Score at the six-month follow-up, F (3, 178) = 4.360, p =.005, partial $\eta 2$ = .068. The assumption of homogeneity of variances was met *(*p = .905). The Hochberg's GT2 post hoc test revealed significant group differences in nonverbal processing speed between low (M= 105.21, SD= 14.733) and high depression/low fatigue (M= 93.15, SD= 16.201) symptoms (95% CI .33 to 23.97, p = .041). This indicated that those with low symptoms (M= 105.21, SD= 14.733) had significantly greater level of nonverbal processing speed corresponding to the 50th percentile of performance across age groups as compared to high depression/low fatigue (M= 93.15, SD= 16.201) symptoms corresponding to 25th percentile of performance across age groups. There are no group differences in nonverbal processing speed between individuals with low depression/high fatigue symptoms and those with high symptoms (see Tables 11 and 12).

Table 11. Tests of Between-Subjects Effects

Dependent Variable: Wechsler Adult Intelligence Scale-IV\Processing Speed Index Composite Score (6 Month)					
Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	2993.048[a]	3	997.683	4.360	.005
Intercept	885415.856	1	885415.856	3869.302	.000
LCA class	2993.048	3	997.683	4.360	.005
Error	40731.903	178	228.831		
Total	1957913.000	182			
Corrected Total	43724.951	181			

a. R Squared = .068 (Adjusted R Squared = .053)

Note. The Wechsler Adult Intelligence Scale-IV-Processing Speed Index Composite Score ranges from 50 to 150 to resemble a certain percentile (0.1st to 99.9th percentile) of performance across different age groups. For example, the 25th percentile represent score of □90, the 50th represent a score of 100, and 75th percentiles represent a score of □110.

Table 12. Descriptive statistics: Wechsler Adult Intelligence Scale-IV Processing Speed Index Composite Score

LCA class				
Dependent Variable: Wechsler Adult Intelligence Scale-IV Processing Speed Index Composite Score (6 Month)				
		Std.	95% Confidence Interval	
LCA class	Mean	Deviation	Lower Bound	Upper Bound
low symptoms	105.211	14.773	102.520	107.903
high depression/low fatigue	93.154	16.201	84.874	101.433
low depression/high fatigue	99.611	14.034	92.575	106.647
high symptoms	97.143	16.788	91.501	102.784

Mental flexibility. TMT-A assesses visual processing, and TMT-B assesses mental flexibility and processing speed, and therefore the difference between TMT-B and TMT-A provides an index of executive control and mental flexibility separate from visual processing and motor speed (Sanchez-Cubillo et al., 2009; Tombaugh, 2004). Results revealed significant group differences in the level of Mental Flexibility at six-months follow-up, (F (3, 177) = 2.806, $p <$ .041, partial η2 = .045). The assumption of homogeneity of variances was violated, (p = .002).

The follow-up Games-Howell post hoc procedure, was chosen to correct for the unequal variances. Results revealed that the differences between these LCA groups were not statistically significant, Welch's F (3, 31.968) = 1.997, p = .134.

In an exploratory analysis, results revealed that mental flexibility was positively correlated with age (r (181) = .405, p < .01) and negatively with number of years of education completed (r (168) = -.270, p < .01); thus these variables were controlled for in the subsequent ANOVA. However, there were no statistical significant group differences in the level of mental flexibility as assessed by TMT B-A between LCA Groups at six-months follow- (F (3, 94) = 1.163, p < .328, partial η2 = .036).

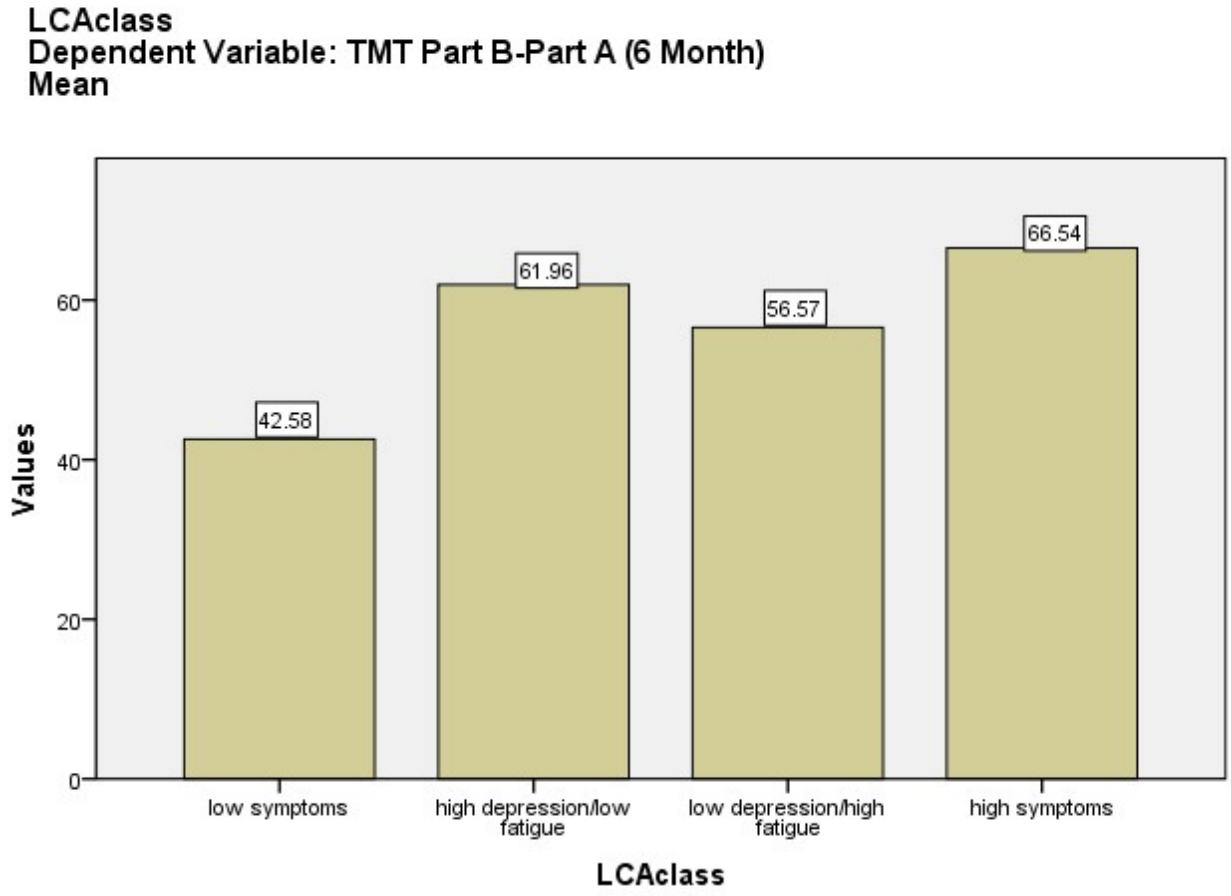
Table 13. Tests of Between-Subjects Effects

Dependent Variable: TMT\Part B-Part A (6 Month)					
Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	16848.534[a]	3	5616.178	2.806	.041
Intercept	293793.302	1	293793.302	146.788	.000
LCA class	16848.534	3	5616.178	2.806	.041
Error	354262.502	177	2001.483		
Total	806940.471	181			
Corrected Total	371111.036	180			

a. R Squared = .045 (Adjusted R Squared = .029)

Note. The Trail-Making Test (TMT), the difference score between the Trial B and Trial A (TMT B-A) A lower is a two-part timed test (TMT-A and TMT-B), and both scores are measured in number of seconds needed for the patient to complete the task. In this test, a lower score suggests improved performance.

Figure 5. Wechsler Adult Intelligence Scale-IV processing speed index composite score.



Note. Patients (n=201) were classified into 4 groups: Low symptoms (n = 136), high depression/low fatigue (n = 14), low depression\ high fatigue (n = 19), and high symptoms (n = 32). The follow-up Games-Howell post-hoc procedure, was chosen to correct for the unequal variances. Results revealed that the differences between these LCA groups were not statistically significant, Welch's F (3, 31.968) = 1.997, p = .134. In this test, a lower score suggests improved performance, and results were trending toward indicating that the Low symptoms group appears to have more improved performance compared to other groups; however, results revealed that the differences between these LCA groups were not statistically significant. Note. The Trail-Making Test (TMT), the difference score between the Trial B and Trial A (TMT B-A) A lower is a two-part timed test (TMT-A and TMT-B), and both scores are measured in number of seconds needed for the patient to complete the task. In this test, a lower score suggests improved performance.

Verbal learning. Results of the ANOVA revealed no significant differences in the level of verbal learning as assessed by (i.e., CVLT-II trials 1– 5; five learning trials, an interference trial, an immediate recall trial, and a post-20 min recall trial) among LCA Groups.

In an exploratory analysis, results revealed that verbal learning was positively correlated with injury severity as assessed by ISS ($r(153) = .215$, $p < .01$), thus this variable was controlled for in the subsequent ANOVA; however, there were no statistical significant group differences in the level of Verbal Learning as assessed by (i.e., CVLT-II trials 1– 5) between LCA Groups at six-months follow-up ($F(3, 48) = .180$, $p < .910$, partial $\eta 2 = .004$).

Summary of Aim 2

First, there was a significant difference among predicted LCA Groups and functional outcomes. Results revealed significant group differences in the level of functional outcomes as assessed by GOSE, indicating that those with low symptoms had significantly greater levels of functional outcomes and good recovery as compared to those reporting high depression/low fatigue symptoms. Also, those with low symptoms had significantly greater levels of functional outcomes and good recovery as compared to individuals who reported low depression/high fatigue symptoms, and high symptoms.

Second, there were significant differences among predicted LCA Groups and quality of life. Results revealed significant group differences in the level of Satisfaction with Life, indicating that those reporting low symptoms had significantly greater levels of satisfaction with life as compared to individuals reporting high depression/low fatigue symptoms and low depression/high fatigue symptoms; the reported life satisfaction scores reported are considered slightly below average. Also, individuals with low symptoms had a significantly greater level of satisfaction with life as compared to individuals who reported high symptoms; the life

satisfaction scores of that group is considered "dissatisfied with their life" according to the SWLS scoring.

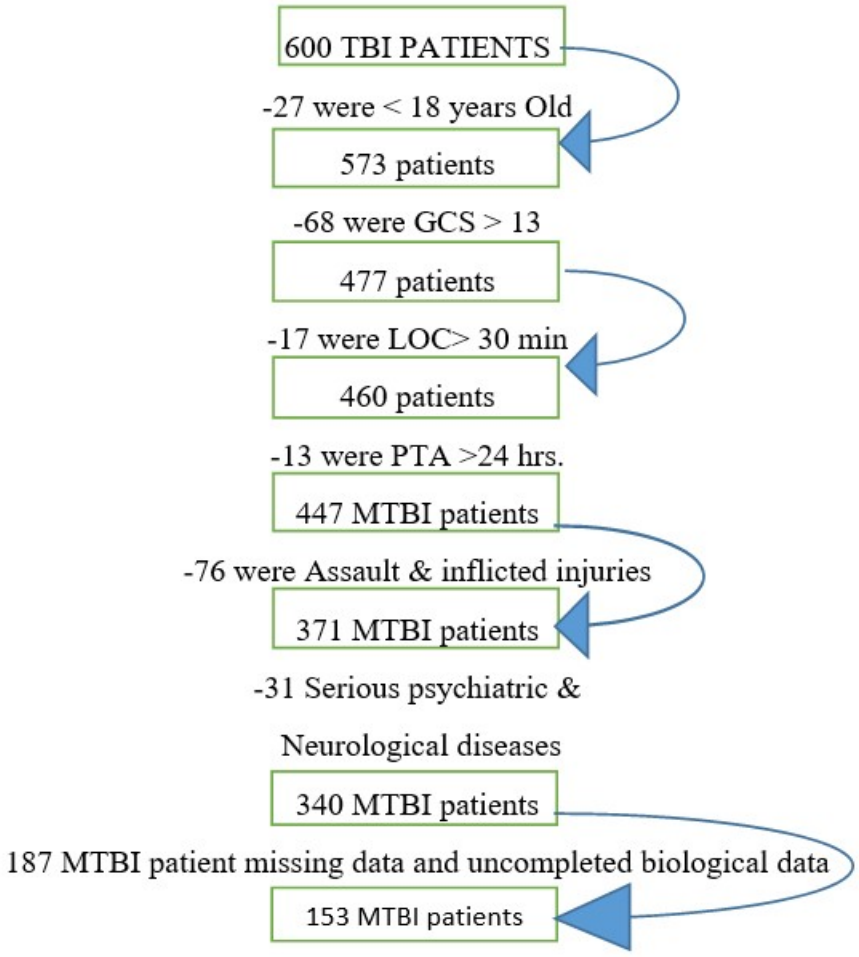
Third, for cognitive outcomes, there were significant differences among LCA Groups and the level of nonverbal processing speed as assessed at the six-month follow-up, indicating that those with low symptoms had levels of nonverbal processing speed/that processing speed corresponded to the 50th percentile of performance across age groups, which were significantly greater as compared to individuals reporting high depression/low fatigue symptoms, whose processing speed corresponded to the 25th percentile of performance across age groups. There were no group differences in nonverbal processing speed between individuals with low depression/high fatigue symptoms and those with high symptoms. Additionally, there was a significant difference between predicted LCA Groups and the level of mental flexibility as assessed by the difference between TMT-B and TMT-A at the six-month follow-up. In this test, a lower score suggests improved performance, and results were trending toward indicating that the low symptoms group appears to have more improved performance compared to other groups. However, there were no group differences among the predicted LCA Group and the level of mental flexibility. Lastly, there was no significant relationship between predicted LCA Groups and verbal learning as assessed by CVLT-II trials 1– 5.

Data Analysis: Aim 3—Exploratory Aim

Sample Exclusion and Inclusion Criteria

Of the sample that met the inclusion criteria (n=340), 187 MTBI patients had missing data and uncompleted biological data (i.e., genetic) as shown in Figure 6. The final sample consisted of 153 patients (see Figure 6).

Figure 6: Enrollment flow diagram.



Inclusion criteria were the following: males and females (ages >18years) who suffered external force trauma to the head, an emergency department arrival GCS score between 13 and 15 (mild) and completion of three- and six-month follow-ups. In addition, only those concussion/MTBI patients who suffered minor injuries, and who were alert, oriented, and were able to read, write and speak English were eligible. Mechanisms of injury included; motor vehicle accident, motorcycle/bicycle accident, pedestrian struck by vehicle, struck by/against object, falls, and other accidental causes of injury.

Sample Characteristics/Demographic Statistics

The majority of the sample was male (66%) and single (52.9%), with a mean age of 18 to 84 years (M = 44.18, SD = 17.93). Most were working full time (46.4%) with 35 hours or more per week and at least minimum wage. Eighteen percent had a history of anxiety, 24% had a history of depression, 7% had some history of sleep disorders. Nearly 23% had a previous TBI (with & without hospital admission). Tobacco use was reported by 31.4% patient, and alcohol use was reported by 51.6%, while drug use was reported by 19% patients (see Table 14).

Injury-related characteristics. Upon arrival to the ED, the majority had a GCS of 15 (77.1%). For reference, a GCS score of 8 or less indicates severe injury, GCS of 9-12 moderate injury, and a GCS score of 13-15 indicate minor injury. As with mild TBI, 13-15 GCS is one of the criteria for MTBI and is indicative of minor injury. Additionally, the majority of the sample (76.5%) reported LOC of varied duration; of these 13% had LOC of less than 1 minute, 37.9% had LOC between 1-29 minutes, 5.2% between 30-59 minutes, and 20.3% participants had unknown LOC duration. PTA was reported by 61.4% patients with varied duration; of these 0.6% patients had PTA for less than1 minute, 26.7% had PTA between 1-29 minutes, 5.8% had PTA between 30-59 minutes, 8.4% had PTA between 1-24 hours, and 16.3% had unknown PTA duration. Injury severity scores (ISS) was reported for 87.6% patients. Fourteen suffered poly-trauma involving two body regions, and 13 suffered poly-trauma with head or neck injury. The majority had an ISS Score ≥ 16 (53.5%). All injuries were closed head injuries. The majority of patients were involved in a MVA and accidental falls (see Table 15).

Descriptive Statistics for Main Study Outcome Variables

The three main measures were the following: Brief Symptom Inventory 18 (the BSI-18 is a brief screen of psychologic distress with a Global Severity Index (GSI) and three clinical

subscales: BSI-somatization, BSI-anxiety, and BSI-depression), PTSD-PCL (3 subscales—hypervigilance, avoidance, re-experiencing), and the Rivermead Post Concussion Symptoms Questionnaire 13 (RPQ-13). Table 16? lists mean and standard deviations for main study outcome variables. All variables were normally distributed.

Table 14. Sample Characteristics for Study Aim 3

Characteristic	Actual Sample Analyzed			
	MTBI *n* = 153			
	N	*%*		
Male	101	66.0%		
Ethnicity				
Hispanic or Latino	129	84.3%		
Non-Hispanic or Latino	23	15.0%		
Race				
Asian	10	6.5%		
Black	7	4.6%		
White	126	82.4%		
American Indian or Alaska Native	1	0.7%		
Native Hawaiian or other Pacific Islander	5	3.3%		
Other	3	2.0%		
Employment				
Working full time with 35 hours or more per week and at least minimum wage	71	46.4%		
Working 20-34 hours per week at least minimum wage	16	10.5%		
Working less than 20 hours per week and at least minimum wage	4	2.6%		
Special employment (sheltered workshop, supportive employment, job coach)	1	0.7%		
Temporary or odd jobs and less than minimum wage jobs	2	1.3%		
Not in paid workforce (including child, retired, student, homemaker, disabled pre-injury)	29	19.0%		
Unemployed	25	16.3%		
Unable to obtain information	3	2.0%		
Education Highest Level				
None, not currently in school	5	3.3%		
None, but currently in diploma or degree-oriented program	2	1.3%		

Table 14 (cont.)

Vocational training (no high school diploma or GED)	1	0.7%		
Table 14 (cont.)				
Vocational training (post high school)	6	3.9%		
GED, 53 (34.6%) High school diploma	8	5.2%		
Bachelor's degree	39	25.5%		
Master's degree	15	9.8%		
Doctoral degree	5	3.3%		
Unable to obtain information	2	1.3%		
Unknown	4	2.6%		
Marital Status				
Divorced	12	7.8%		
Married or living together or common law	50	32.7 %		
Separated	3	2.0%		
Single	81	52.9%		
Widowed	5	3.3%		
Unknown	2	1.3%		

Table 15. Sample Characteristics for Study Aim 3: Injury-Related Characteristics

Characteristic	Actual Sample Analyzed			
	MTBI *n* = 153			
	N	*%*		
Arrival GCS				
13	2	1.3%		
14	31	20.3%		
15	118	77.6%		
LOC	117	76.9%		
LOC Duration				
<1 minute	20	13.1%		
1-29 minutes	58	38.8%		
30-59 minutes,	8	5.2%		
Unknown	31	20.3%		
PTA	94	61.8%		

Table 15 (cont.)

PTA Duration				
<1 minute	6	3.9%		
1-29 minutes	41	26.9%		
30-59 minutes	9	5.9%		
1-24 hours	13	8.5%		
Unknown	25	16.4%		
Reported injury severity	134	88.1%		
Poly-trauma with any two body regions,	14	9.2%		
Poly-trauma with Head or neck Injury	13	8.5%		
ISS Score ≤ 16	52	34.2%		
ISS Score ≥ 16.	82	53.9%		
Closed head injuries	151	99.3%		
MVA	61	39.9%		
Accidental Fall	61	39.9%		
Firearm accident by explosive material	1	0.7%		
Striking Accidents	3	2.0%		
Struck accidentally by falling object	1	0.7%		
Other environmental or accidental causes	1	0.7%		
Other vehicle accident,	11	7.2%		
Motor vehicle accident but not traffic-related	2	1.3%		
Unknown	12	7.8%		
LOC= Loss of Consciousness, PTA= Post Traumatic Amnesia, ISS= Injury severity score.				

Table 16. Descriptive Statistics

	N	Range	Mean	Std. Deviation	Skewness		Kurtosis	
					Statistic	Std. Error	Statistic	Std. Error
BSI-GSI (6 Month)	153	60	11.18	11.291	1.356	.196	2.037	.390
BSI-Depression (6 Month)	153	20	3.75	4.493	1.274	.196	.947	.390
BSI-Somatization (6 Month)	153	18	3.66	4.005	1.311	.196	1.297	.390
BSI-Anxiety (6 Month)	153	22	3.77	4.201	1.456	.196	2.232	.390

Table 16 (cont.)

PTSD -Re-experiencing (6 Month)	152	20	8.41	4.319	1.504	.197	1.894	.391
PTSD - Hypervigilance (6 Month)	152	20	9.71	4.632	1.049	.197	.271	.391
PTSD - Avoidance (6 Month)	152	24	12.78	5.755	1.125	.197	.660	.391
PTSD PCL-C Total Score (6 Month)	152	60	30.89	13.615	1.178	.197	.801	.391
RPQ-13 Score (6 Month)	152	49	11.70	11.356	.942	.197	.267	.391

Aim 3 Data Analysis and Results

Statistical strategy. First, the assumption of normality and homogeneity of variances and outliers was assessed for all outcome measures. Normality was assessed by examining histogram plots and z scores, homogeneity of variances was assessed by Levene's test. All variables were checked for skewness and kurtosis (see Tables 16). Results indicated that all outcome variables were normally distributed and no transformations were necessary.

Differences in behavioral symptoms (somatization, anxiety, depression, PTSD, and post concussive syndrome) among the SNPs genotype (rs1800497 (ANKK1), rs1799971 (OPRM1), rs279836 (GABRA2), rs279845 (GABRA2), rs279871 (GABRA2), and rs4680 (COMT)) were determined. Behavioural symptoms were assessed by three main measures: (1) BSI-18 (the BSI-18 is a brief screen of psychological distress with a Global Severity Index (GSI), and three clinical subscales: BSI-somatisation, BSI-anxiety, and BSI-depression); (2) PTSD-PCL (3 subscales; hyper-vigilance, avoidance, Re-experiencing); and (3) the Rivermead Post Concussion Symptoms Questionnaire 13 (RPQ-13). An analysis of variance (ANOVA) and

analysis of covariance (ANCOVA), were conducted to address this aim. For all follow-up post hoc tests the Hochberg's GT2 was used to correct for the unequal sample size (Field, 2009).

To identify potential covariates, an independent sample t-test statistical test was conducted between medical history of depression, anxiety, and poor sleep, ethnicity, and outcome variables (i.e., Somatization, Anxiety, Depression, PTSD, and Post-Concussive Syndrome) to determines statistically significant differences between the means. Those variables that were significantly different were included as covariates in the subsequent ANOVAs (Table 17a, 17b, and 17c). Somatization was associated with history of depression ($t\ (151) = 4.423$, $p < .01$) and Ethnicity ($t\ (150) = 3.114$, $p < .01$); thus these variables were controlled for in the subsequent ANOVA. Also, anxiety was associated with history of anxiety *($t\ (151) = 4.572$, $p < .01$),* Ethnicity *($t\ (150) = 2.760$, $p < .01$).* These variables were controlled for in the subsequent ANOVA. Refer to Tables 17, 18, and 19.

Table 17. Independent Sample T-Test Analysis Between Medical History of Depression and Outcome Variables

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Brief Symptom Inventory 18- GSI (6 Month)	Equal variances assumed	3.970	.048	4.195	151	.000	8.492	2.024	4.493	12.492
	Equal variances not assumed			3.584	48.975	.001	8.492	2.369	3.731	13.253
Brief Symptom Inventory 18- Depression (6 Month)	Equal variances assumed	7.562	.007	3.351	151	.001	2.752	.821	1.129	4.374
	Equal variances not assumed			2.841	48.559	.007	2.752	.968	.805	4.698
Brief Symptom Inventory 18- Somatization (6 Month)	Equal variances assumed	1.567	.213	4.423	151	.000	3.158	.714	1.747	4.568
	Equal variances not assumed			3.959	51.771	.000	3.158	.798	1.557	4.758

Table 17 (cont.)

Brief Symptom Inventory 18-Anxiety (6 Month)	Equal variances assumed	5.547	.020	3.365	151	.001	2.583	.768	1.067	4.100
	Equal variances not assumed			2.840	48.308	.007	2.583	.910	.755	4.412
PTSD Checklist-Civilian-Domain Score Reexperiencing (6 Month)	Equal variances assumed	2.879	.092	3.439	150	.001	2.712	.789	1.154	4.270
	Equal variances not assumed			3.168	53.862	.003	2.712	.856	.995	4.428
PTSD Checklist-Civilian-Domain Score Hypervigilance (6 Month)	Equal variances assumed	.434	.511	2.008	150	.046	1.740	.867	.027	3.453
	Equal variances not assumed			2.123	67.165	.037	1.740	.820	.104	3.376
PTSD Checklist-Civilian-Domain Score Avoidance (6 Month)	Equal variances assumed	.144	.705	1.796	150	.075	1.939	1.080	-.195	4.072
	Equal variances not assumed			1.781	60.112	.080	1.939	1.088	-.238	4.116

Table 17 (cont.)

PCL-C Total Score (6 Month)	Equal variances assumed	.195	.660	2.527	150	.013	6.391	2.529	1.394	11.387
	Equal variances not assumed			2.521	60.653	.014	6.391	2.535	1.321	11.460
RPQ-13 Score (6 Month)	Equal variances assumed	3.856	.051	3.316	150	.001	6.893	2.079	2.786	11.000
	Equal variances not assumed			3.020	53.042	.004	6.893	2.283	2.315	11.471
RPQ-3 Score (6 Month)	Equal variances assumed	5.762	.018	2.653	150	.009	1.136	.428	.290	1.983
	Equal variances not assumed			2.287	49.553	.026	1.136	.497	.138	2.134
SWLS Total Score (6 Month)	Equal variances assumed	.184	.669	-4.704	150	.000	-6.481	1.378	-9.203	-3.759
	Equal variances not assumed			-4.770	59.707	.000	-6.481	1.359	-9.199	-3.763
GOSE Score (6 Month)	Equal variances assumed	.688	.408	-2.371	151	.019	-.504	.212	-.924	-.084
	Equal variances not			-2.216	54.832	.031	-.504	.227	-.959	-.048

Table 18. Intendent Sample T-Test Analysis Between Medical History of Anxiety and Outcome Variables

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Brief Symptom Inventory 18- GSI (6 Month)	Equal variances assumed	2.423	.122	4.372	151	.000	9.897	2.263	5.425	14.369
	Equal variances not assumed			3.536	31.965	.001	9.897	2.799	4.195	15.599
Brief Symptom Inventory 18- Depression (6 Month)	Equal variances assumed	2.124	.147	3.298	151	.001	3.045	.923	1.221	4.869
	Equal variances not assumed			2.747	32.590	.010	3.045	1.108	.789	5.301
Brief Symptom Inventory 18-Somatization (6 Month)	Equal variances assumed	1.762	.186	3.703	151	.000	3.021	.816	1.409	4.633
	Equal variances not assumed			3.109	32.770	.004	3.021	.972	1.044	4.999

Table 18 (cont.)

Brief Symptom Inventory 18- (6 Month)	Equal variances assumed	8.627	.004	4.572	151	.000	3.831	.838	2.175	5.486
	Equal variances not assumed			3.489	30.884	.001	3.831	1.098	1.591	6.070
PTSD Checklist-Civilian-Domain Score Reexperiencing (6 Month)	Equal variances assumed	2.054	.154	3.626	150	.000	3.197	.882	1.455	4.939
	Equal variances not assumed			3.268	34.603	.002	3.197	.978	1.210	5.184
PTSD Checklist-Civilian-Domain Score Hypervigilance (6 Month)	Equal variances assumed	.005	.945	2.171	150	.031	2.108	.971	.190	4.027
	Equal variances not assumed			2.193	38.472	.034	2.108	.961	.163	4.054
PTSD Checklist-Civilian-Domain Score Avoidance (6 Month)	Equal variances assumed	.025	.875	2.128	150	.035	2.569	1.207	.184	4.954
	Equal variances not assumed			2.200	39.454	.034	2.569	1.168	.207	4.930

Table 18 (cont.)

PCL-C Total Score (6 Month)	Equal variances assumed	.014	.906	2.786	150	.006	7.874	2.827	2.289	13.460
	Equal variances not assumed			2.814	38.483	.008	7.874	2.798	2.212	13.536
RPQ-13 Score (6 Month)	Equal variances assumed	1.267	.262	3.507	150	.001	8.151	2.325	3.558	12.745
	Equal variances not assumed			3.170	34.687	.003	8.151	2.572	2.929	13.374
RPQ-3 Score (6 Month)	Equal variances assumed	15.806	.000	3.157	150	.002	1.504	.477	.563	2.446
	Equal variances not assumed			2.406	30.884	.022	1.504	.625	.229	2.780
SWLS Total Score (6 Month)	Equal variances assumed	2.047	.155	-3.682	150	.000	-5.789	1.572	-8.895	-2.683
	Equal variances not assumed			-4.087	43.026	.000	-5.789	1.417	-8.646	-2.932

Table 18 (cont.)

GOSE Score (numerical) (6 Month)	Equal variances assumed	.089	.766	-1.906	151	.059	-.458	.240	-.932	.017
	Equal variances not assumed			-1.875	37.361	.069	-.458	.244	-.952	.037

Table 19. Independent Sample T-Test Analysis Between Ethnicity, and Outcome Variables

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	T	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Brief Symptom Inventory 18-GSI (6 Month)	Equal variances assumed	5.913	.016	3.273	150	.001	8.129	2.483	3.222	13.035
	Equal variances not assumed			2.692	26.642	.012	8.129	3.020	1.929	14.328
Brief Symptom Inventory 18-Depression (6 Month)	Equal variances assumed	11.715	.001	3.114	150	.002	3.084	.990	1.127	5.041
	Equal variances not assumed			2.488	26.249	.020	3.084	1.240	.538	5.631
Brief Symptom Inventory 18-Somatization (6 Month)	Equal variances assumed	2.470	.118	2.792	150	.006	2.480	.888	.725	4.236
	Equal variances not assumed			2.397	27.294	.024	2.480	1.035	.358	4.602
Brief Symptom Inventory 18\Raw Score Anxiety (6 Month)	Equal variances assumed	3.396	.067	2.760	150	.006	2.564	.929	.729	4.400
	Equal variances not assumed			2.353	27.184	.026	2.564	1.090	.329	4.799

Table 19 (cont.)

PTSD Checklist-Civilian-Domain Score Reexperiencing	Equal variances assumed	1.842	.177	2.638	149	.009	2.530	.959	.635	4.424
	Equal variances not assumed			2.341	27.894	.027	2.530	1.080	.316	4.743
PTSD Checklist-Civilian-Domain Score Hypervigilance	Equal variances assumed	.310	.578	2.905	149	.004	2.935	1.010	.939	4.931
	Equal variances not assumed			2.810	29.636	.009	2.935	1.045	.801	5.070
PTSD Checklist-Civilian-Domain Score Avoidance (6 Month)	Equal variances assumed	4.368	.038	2.866	149	.005	3.646	1.272	1.132	6.160
	Equal variances not assumed			2.370	26.751	.025	3.646	1.539	.488	6.805
PCL-C Total Score (6 Month)	Equal variances assumed	1.848	.176	3.050	149	.003	9.111	2.987	3.208	15.014
	Equal variances not assumed			2.740	28.115	.011	9.111	3.325	2.301	15.921
RPQ-13 Score (6 Month)	Equal variances assumed	2.259	.135	3.126	149	.002	7.748	2.479	2.850	12.645
	Equal variances not assumed			2.781	27.936	.010	7.748	2.786	2.040	13.455
RPQ-3 Score (6 Month)	Equal variances assumed	.935	.335	1.170	149	.244	.612	.523	-.422	1.646
	Equal variances not assumed			1.095	28.920	.283	.612	.559	-.531	1.756

Table 19 (cont.)

SWLS Total Score (6 Month)	Equal variances assumed	.320	.572	-1.214	149	.227	-2.122	1.747	-5.574	1.331
	Equal variances not assumed			-1.135	28.883	.266	-2.122	1.870	-5.946	1.703
GOSE Score (numerical) (6 Month)	Equal variances assumed	.118	.732	-1.135	150	.258	-.294	.259	-.805	.217
	Equal variances not assumed			-1.281	34.123	.209	-.294	.229	-.759	.172

Exploratory analysis of SNP rs1800497 ANKK1 on outcome measures. There were marginal differences at $\alpha = 0.05$ between SNP rs1800497ANKK1 and outcome variables included: BSI18 Global Severity Index (GSI), BSI-somatisation, BSI-anxiety, and BSI-depression, PTSD- hyper-vigilance, PTSD-avoidance, PTSD-Re-experiencing, and RPQ-13 total score, which warrant further exploration. To identify potential covariates, independent sample t-test analysis was conducted between medical history of depression, medical history of depression anxiety, ethnicity, and outcome variables. Those variables that were significantly correlated ($p < .01$) were included as covariates in the subsequent ANOVAs.

Then, Analysis of Covariance (ANCOVA) was conducted to investigate differences between patients who were classified into 3 groups**:** A1/A1 (*n* = 10), A1/A2 (*n* = 56), A2/A2 (*n* = 86), with respect to distress, posttraumatic symptoms, and post concussive symptoms. The outcome variables included: BSI18 Global Severity Index (GSI), BSI-somatisation, BSI-anxiety, and BSI-depression, PTSD- hyper-vigilance, PTSD-avoidance, PTSD-re-experiencing, and RPQ-13 total score. Since the subgroup sizes are greatly unequal, the Hochberg's GT2 post hoc test explicitly allows for unequal sample sizes (Field, 2009).

***Somatisation and SNP rs1800497ANKK1*.** Results revealed that somatization was associated with history of depression ($t (151) = 4.423$, $p < .01$) and ethnicity ($t (150) = 3.114$, $p < .01$), thus these variables were controlled for in the subsequent ANOVA. Significant group differences in the level of somatisation were found, ($F (2,146) = 3.859$, $p < .023$, partial $\eta 2 = .050$). The assumption of homogeneity of variances was met, as assessed by Levene's test for equality of variances ($p = .177$). The follow-up Hochberg's GT2 post hoc test revealed that group differences in somatization were significant between A1/A1 (M=7.416, SD=1.188) and A1/A2 (M=4.366, SD= .571) genotypes (95 % CI .03 to 6.09, $p = .047$). However, no

differences were observed between A1/A1 and A2/A2 (M=5.651, SD=.537) genotypes, and A2/A2 and A1/A2 genotypes. Please refer to Tables 20 and 21.

Table 20. Tests of Between-Subjects Effects

Dependent Variable: Brief Symptom Inventory 18 Somatization (6 Month)						
Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	471.845[a]	4	117.961	8.851	.000	.195
Intercept	1557.248	1	1557.248	116.849	.000	.445
SNP1800497ANKK1	102.863	2	51.432	3.859	.023	.050
Ethnicity	102.176	1	102.176	7.667	.006	.050
MHPSYCDEP	268.709	1	268.709	20.163	.000	.121
Error	1945.745	146	13.327			
Total	4487.000	151				
Corrected Total	2417.589	150				

a. R Squared = .195 (Adjusted R Squared = .173)

Note. Brief Symptom Inventory 18- somatization subscale consists of 6 question (each question ranges from 0 “not at all” to 4 “extremely”), total score for somatization subscale ranges from 0 to 18, a higher score is indicative of higher level of somatization.

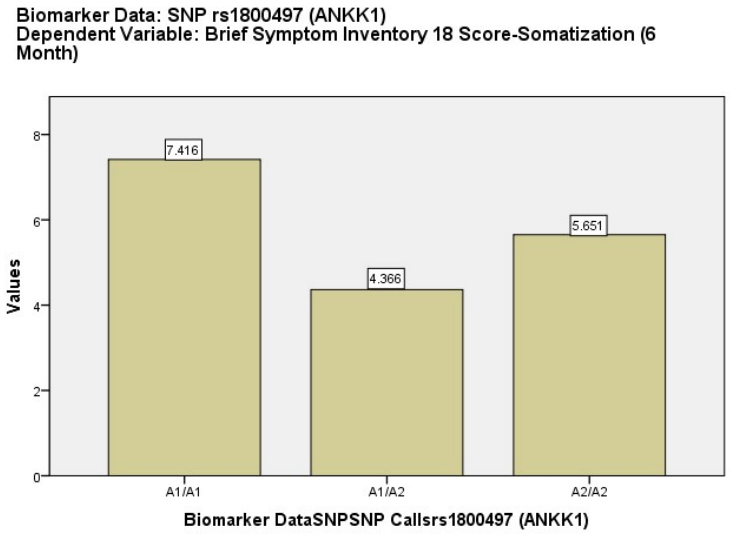
:

Table 21. Descriptive statistics: Brief Symptom Inventory 18-Somatization

Dependent Variable: Brief Symptom Inventory 18-Somatization (6 Month)				
SNP rs1800497 (ANKK1)	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
A1/A1 (*n* = 10)	7.416	1.188	5.068	9.763
A1/A2 (*n* = 56)	4.366	.571	3.237	5.495
A2/A2 (*n* = 86)	5.651	.537	4.589	6.712

Note. Brief Symptom Inventory 18- somatization subscale consists of 6 question (each question ranges from 0 “not at all” to 4 “extremely”), total score for somatization subscale ranges from 0 to 18, a higher score is indicative of higher level of somatization.

Figure 7. Brief symptom inventory 18- Somatization.



Note. Patients were classified into 3 groups**:** A1/A1 (*n* = 10), A1/A2 (*n* = 56), A2/A2 (*n* = 86). The follow-up Hochberg's GT2 post-hoc test revealed that group differences in somatization were significant between A1/A1 (M=7.416, SD=1.188) and A1/A2 (M=4.366, SD= .571) genotypes (95 % CI .03 to 6.09, p = .047). However, no differences were observed between A1/A1 and A2/A2 (M=5.651, SD=.537) genotypes, and A2/A2 and A1/A2 genotypes. Note. Brief Symptom Inventory 18- somatization subscale consists of 6 question (each question ranges from 0 "not at all" to 4 "extremely"), total score for somatization subscale ranges from 0 to 18, a higher score is indicative of higher level of somatization.

Anxiety and SNP rs1800497ANKK1. Results revealed that also, anxiety was associated with history of anxiety *(t (151)* = 4.572*, p < .01),* and ethnicity *(t (150) = 2.760, p < .01);* these variables were controlled for in the subsequent ANOVA. Significant group differences in the level of anxiety were found, (*F* (2,145) = 5.060, *p* < .008, partial η2 = .065). The assumption of homogeneity of variances was met, as assessed by Levene's test for equality of variances (p = .269). The follow-up Hochberg's GT2 post-hoc test revealed that group differences in anxiety were significant between A1/A1 (M=7.982, SD= 1.264) and A1/A2 (M= 4.266, SD= .604) genotypes (95 % CI .27 to 6.67, p = .029); however, no differences were observed between

A1/A1 and A2/A2 (M=5.824, SD=.572) genotypes and A2/A2 and A1/A2 genotypes. Please refer to Tables 22 and 23.

Table 22. Tests of Between-Subjects Effects

Dependent Variable: Brief Symptom Inventory 18- Anxiety (6 Month)						
Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	588.101[a]	4	147.025	10.386	.000	.222
Intercept	1736.771	1	1736.771	122.685	.000	.457
SNP1800497ANKK1	143.633	2	71.816	5.073	.007	.065
MHPSYCANX	345.789	1	345.789	24.426	.000	.143
Ethnicity	117.038	1	117.038	8.268	.005	.054
Error	2066.826	146	14.156			
Total	4769.000	151				
Corrected Total	2654.927	150				

a. R Squared = .222 (Adjusted R Squared = .200)

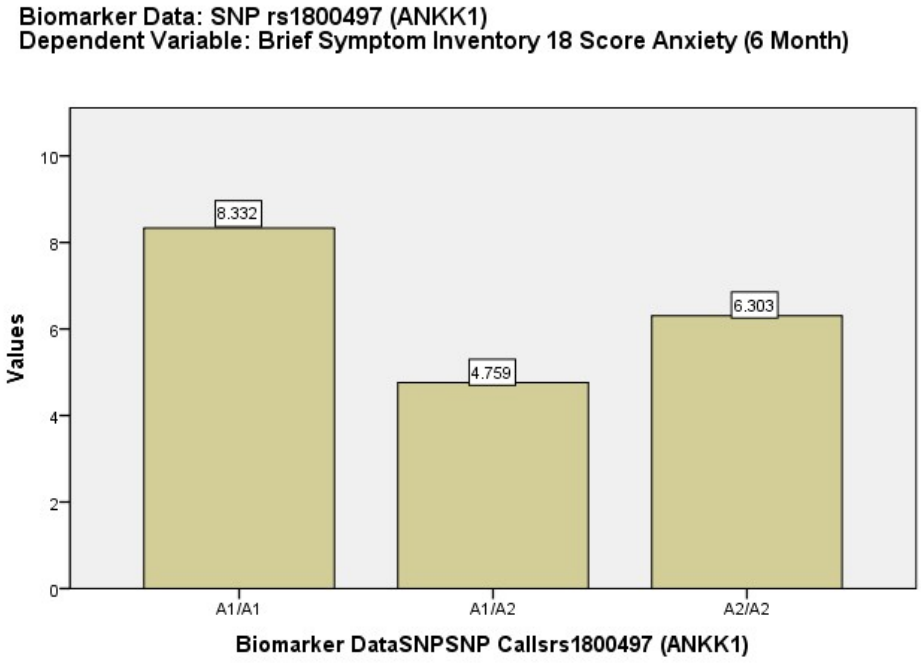
Note. Brief Symptom Inventory 18- Anxiety subscale consists of 6 question (each question ranges from 0 "not at all" to 4 "extremely"), total score for anxiety subscale ranges from 0 to 18, a higher score is indicative of higher level of anxiety.

Table 23. Descriptive Statistics: Brief Symptom Inventory 18-Anxiety

Dependent Variable: Brief Symptom Inventory 18-Anxiety (6 Month)				
Biomarker Data\SNP\SNP			95% Confidence Interval	
Calls\rs1800497 (ANKK1)	Mean	Std. Error	Lower Bound	Upper Bound
A1/A1 (*n* = 10)	7.982	1.264	5.485	10.480
A1/A2 (*n* = 56)	4.266	.604	3.072	5.459
A2/A2 (*n* = 86)	5.824	.572	4.693	6.955

Note. Brief Symptom Inventory 18- Anxiety subscale consists of 6 question (each question ranges from 0 "not at all" to 4 "extremely"), total score for anxiety subscale ranges from 0 to 18, a higher score is indicative of higher level of anxiety.

Figure 8. Brief symptom inventory 18- Anxiety.



Note. Patients were classified into 3 groups: A1/A1 (n = 10), A1/A2 (n = 56), A2/A2 (n = 86). The follow-up Hochberg's GT2 post-hoc test revealed that group differences in anxiety were significant between A1/A1 (M=7.982, SD= 1.264) and A1/A2 (M= 4.266, SD= .604) genotypes (95 % CI .27 to 6.67, p = .029); however, no differences were observed between A1/A1 and A2/A2 (M=5.824, SD=.572) genotypes and A2/A2 and A1/A2 genotypes. Note. Brief Symptom Inventory 18- Anxiety subscale consists of 6 question (each question ranges from 0 "not at all" to 4 "extremely"), total score for anxiety subscale ranges from 0 to 18, a higher score is indicative of higher level of anxiety.

Post-concussive syndrome and SNP rs1800497ANKK1. Results of the ANOVA revealed no significant differences in the level of post-concussive syndrome (i.e., as assessed by RPQ-13) between the SNP rs1800497ANKK1 genotypes ($F(2,148) = .642$, $p < .537$).

PTSD symptoms and SNP rs1800497ANKK1. The ANOVA was performed to assess the differences between SNP rs1800497ANKK1 genotype groups, with respect to PTSD-PCL (hypervigilance, avoidance, re-experiencing). The ANOVA was done for each outcome variable.

Results revealed no significant SNP rs1800497ANKK1 genotype group differences for any of the PTSD-PCL subscales (i.e., hypervigilance, avoidance, re-experiencing)

Exploratory analysis of SNP1799971 OPRM1 on outcome measures. A one-way Analysis of variance (ANOVA) was conducted to investigate differences between patients who were classified into 3 groups: A/A (*n* = 111), A/G (*n* = 39), G/G (*n* = 2) with respect to distress, posttraumatic symptoms and post concussive symptoms. The outcome variables included: BSI18 Global Severity Index (GSI), BSI-somatization, BSI-anxiety, and BSI-depression, PTSD-hypervigilance, PTSD-avoidance, PTSD-Re-experiencing, and RPQ-13 total score. The assumption of homogeneity of variances was met, as assessed by Levene's test for equality of variances for all outcome measures. No differences in any outcome measures were observed among SNP1799971 OPRM1 Genotype groups.

Exploratory analysis of SNP rs279836 (GABRA2) on outcome measures. A one-way analysis of variance (ANOVA) was conducted to investigate differences between patients (n=151) who were classified into 3 groups: A/A (n = 30), A/T (n = 70), T/T (n = 51) with respect to distress, posttraumatic symptoms and post-concussive symptoms. The outcome variables included: BSI18 Global Severity Index (GSI), BSI-somatisation, BSI-anxiety, and BSI-depression, PTSD- hyper-vigilance, PTSD-avoidance, PTSD-Re-experiencing, and RPQ-13 total score. The assumption of homogeneity of variances was violated, as assessed by Levene's test for equality of variances for all outcome measures. No differences in any outcome measures were found among SNP rs279836 GABRA2 Genotype groups.

Exploratory analysis of rs279845 (GABRA2) on outcome measures. A one-way analysis of variance (ANOVA) was conducted to investigate differences in distress, posttraumatic symptoms and post-concussive symptoms among patients (n=151) who were

classified into 3 groups**:** A/A (n = 29), A/T (n = 73), T/T (n = 49). The outcome variables were assessed using: BSI18 Global Severity Index (GSI), BSI-somatisation, BSI-anxiety, and BSI-depression, PTSD- hyper-vigilance, PTSD-avoidance, PTSD-Re-experiencing, and RPQ-13 total score. Results revealed no differences in these behavioural outcome measures between SNP rs279845 GABRA2 Genotype groups.

Exploratory analysis of rs279871 (GABRA2) on outcome measures. A one-way Analysis of variance (ANOVA) was conducted to investigate differences between patients (n=152) who were classified into 3 groups**:** C/C (n = 29), C/T (n = 70), T/T (n = 53), with respect to distress, posttraumatic symptoms and post concussive symptoms. The outcome variables included: BSI18 Global Severity Index (GSI), BSI-somatisation, BSI-anxiety, and BSI-depression, PTSD- hyper-vigilance, PTSD-avoidance, PTSD-Re-experiencing, and RPQ-13 total score. No differences in any outcome measures among SNP rs279871 GABRA2 Genotype groups were found.

Exploratory analysis of rs4680 (COMT) on outcome measures. A one-way Analysis of variance (ANOVA) was conducted to investigate differences between patients (n=153) who were classified into 3 groups**:** Met/Met (n = 40), Met/Val (n = 74), Val/Val (n = 39), with respect to distress, posttraumatic symptoms and post concussive symptoms. The outcome variables were assessed using the following measures: BSI18 Global Severity Index (GSI), BSI-somatisation, BSI-anxiety, and BSI-depression, PTSD- hyper-vigilance, PTSD-avoidance, PTSD-Re-experiencing, and RPQ-13 total score. No differences in any outcome variables were found among the SNP rs4680 (COMT) Genotype groups.

Additional exploratory analysis. Additional exploratory analysis was conducted to further explore group differences among SNP rs1800497 (ANKK1) genotypes and the level of

fatigue, depression, and sleep disturbance. The three RPQ-13 questions used for Aim 1 (LCA) that addressed fatigue, depression, and sleep were used to measure the dependent variables. To identify potential covariates, an independent sample t-test statistical test was conducted between medical history of depression, anxiety, ethnicity, and outcome variables (i.e., RPQ-13 questions; RPQ Fatigue: Tiring More Easily, RPQ Sleep Disturbance, RPQ Feeling Depressed or Tearful) to determine statistically significant differences between the means. Those variables that were significantly different were included as covariates in the subsequent ANOVAs (See Tables 24, 25, and 26). For all follow-up post hoc tests the Hochberg's GT2 was used to correct for the unequal sample size (Field, 2009).

Table 24. Independent Sample T-Test Analysis Between Medical History of Anxiety and Outcome Variables (RPQ-13 questions; RPQ Fatigue: Tiring More Easily, RPQ Sleep Disturbance, RPQ Feeling Depressed or Tearful)

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
RPQ Fatigue, Tiring More Easily (numerical) (6 Month)	Equal variances assumed	1.668	.198	3.943	150	.000	.962	.244	.480	1.444
	Equal variances not assumed			3.448	33.787	.002	.962	.279	.395	1.529
RPQ Feeling Depressed or Tearful (numerical) (6 Month)	Equal variances assumed	4.101	.045	3.601	150	.000	.809	.225	.365	1.254
	Equal variances not assumed			3.145	33.754	.003	.809	.257	.286	1.333
RPQ Sleep Disturbance (numerical) (6 Month)	Equal variances assumed	2.370	.126	1.799	150	.074	.508	.283	-.050	1.067
	Equal variances not assumed			1.633	34.809	.112	.508	.311	-.124	1.141

Table 25. Independent Sample T-Test Analysis Between Medical History of Depression and Outcome Variables (RPQ-13 Questions; RPQ Fatigue: Tiring More Easily, RPQ Sleep Disturbance, RPQ Feeling Depressed or Tearful)

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
RPQ Fatigue, Tiring More Easily (numerical) (6 Month)	Equal variances assumed	2.254	.135	2.985	150	.003	.662	.222	.224	1.100
	Equal variances not assumed			2.723	53.168	.009	.662	.243	.174	1.150
RPQ Feeling Depressed or Tearful (numerical) (6 Month)	Equal variances assumed	3.618	.059	3.530	150	.001	.708	.201	.312	1.104
	Equal variances not assumed			3.179	52.261	.002	.708	.223	.261	1.155
RPQ Sleep Disturbance (numerical) (6 Month)	Equal variances assumed	2.684	.103	1.560	150	.121	.394	.252	-.105	.893
	Equal variances not assumed			1.457	54.876	.151	.394	.270	-.148	.936

Table 26. Independent Sample T-Test Analysis Between Ethnicity and Outcome Variables (RPQ-13 questions; RPQ Fatigue: Tiring More Easily, RPQ Sleep Disturbance, RPQ Feeling Depressed or Tearful)

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
RPQ Fatigue, Tiring More Easily (numerical) (6 Month)	Equal variances assumed	.959	.329	1.624	149	.107	.441	.272	-.096	.978
	Equal variances not assumed			1.518	28.898	.140	.441	.291	-.153	1.036
RPQ Feeling Depressed or Tearful (numerical) (6 Month)	Equal variances assumed	5.839	.017	3.050	149	.003	.739	.242	.260	1.219
	Equal variances not assumed			2.573	27.052	.016	.739	.287	.150	1.329
RPQ Sleep Disturbance (numerical) (6 Month)	Equal variances assumed	6.502	.012	2.108	149	.037	.636	.301	.040	1.231
	Equal variances not assumed			1.786	27.117	.085	.636	.356	-.094	1.366

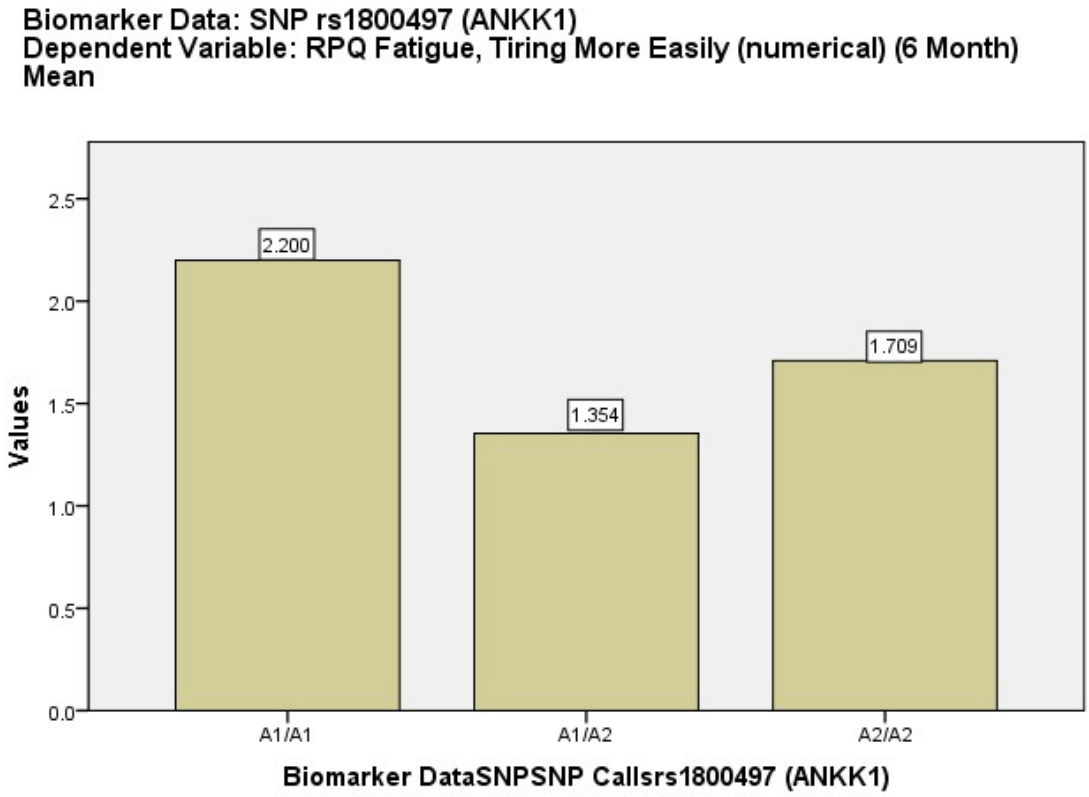
Fatigue and SNP rs1800497ANKK1. Results revealed that fatigue was associated with history of anxiety (t (150) = 3.943, p < .01); thus, this variable was controlled for in the subsequent ANOVA. Significant group differences in the level of fatigue were found, (*F* (2,147) = 3.057, *p* = .050 partial η2 = .040). The assumption of homogeneity of variances was violated, as assessed by Levene's test for equality of variances (p = .008). The follow-up Hochberg's GT2 post-hoc test revealed that there were no differences in fatigue between A1/A1 (M=2.200, SD= .366) and A1/A2 (M= 1.354, SD= .166) genotypes. Also, no differences in fatigue were observed between A1/A1 and A2/A2 (M=1.709, SD=.150) genotypes and A2/A2 and A1/A2 genotypes (see Table 27 and Figure 9).

Table 27. Descriptive Statistics: RPQ Fatigue, Tiring More Easily

Dependent Variable: RPQ Fatigue, Tiring More Easily (6 Month)				
			95% Confidence Interval	
SNP \rs1800497 (ANKK1)	Mean	Std. Error	Lower Bound	Upper Bound
A1/A1	2.200	.366	1.476	2.923
A1/A2	1.354	.166	1.027	1.682
A2/A2	1.709	.150	1.412	2.006

Note. RPQ = Rivermead post-concussive symptoms questioner (each questions ranges from 0-not experienced to 4-severe problem).

Figure 9. RPQ-Fatigue, tiring more easily.



Note. Patients were classified into 3 groups: A1/A1 (n = 10), A1/A2 (n = 55), A2/A2 (n = 86). The follow-up Hochberg's GT2 post-hoc test revealed that there were no differences in fatigue between A1/A1 (M=2.200, SD= .366), A1/A2 (M= 1.354, SD= .166) genotypes, no differences were observed between A1/A1 and A2/A2 (M=1.709, SD=.150) genotypes and A2/A2 and A1/A2 genotypes (See Table x, and Figure X). Note: RPQ = Rivermead post-concussive symptoms questioner (each question ranges from 0- not experienced to 4-severe problem).

Depression, sleep disturbance and SNP rs1800497ANKK1. No significant differences in levels of depression and sleep disturbance were found among SNP rs1800497ANKK1 genotype groups.

Summary of Exploratory Aim

The results of this aim indicated that there are no differences in behavioural symptoms outcomes on the three main measures—BSI-GSI, BSI-somatisation, BSI-anxiety, and BSI-depression, PTSD-PCL (hyper-vigilance, avoidance, re-experiencing), and RPQ-13—among the five SNP genotypes—(rs279836 (GABRA2), rs279845 (GABRA2), rs279871 (GABRA2), SNP1799971 (OPRM1), and rs4680 (COMT)). However, differences were found for patients with different SNP rs1800497 ANKK1 genotype and their level of BSI-somatisation and BSI-anxiety.

First there was a significant difference in somatisation among SNP rs1800497 ANKK1 genotype groups while controlling for history of depression and ethnicity. Results revealed significant group differences in the level of somatisation, ($F(2,146) = 3.859$, $p < .023$, partial $\eta 2 = .050$), indicating that those with A1/A1 (M=7.416, SD=1.188) had significantly greater levels of somatisation as compared to A1/A2 (M=4.366, SD= .571) genotype. However, no differences were observed between A1/A1 and A2/A2 (M=5.651, SD= .537) genotypes, and A2/A2 and A1/A2 genotypes.

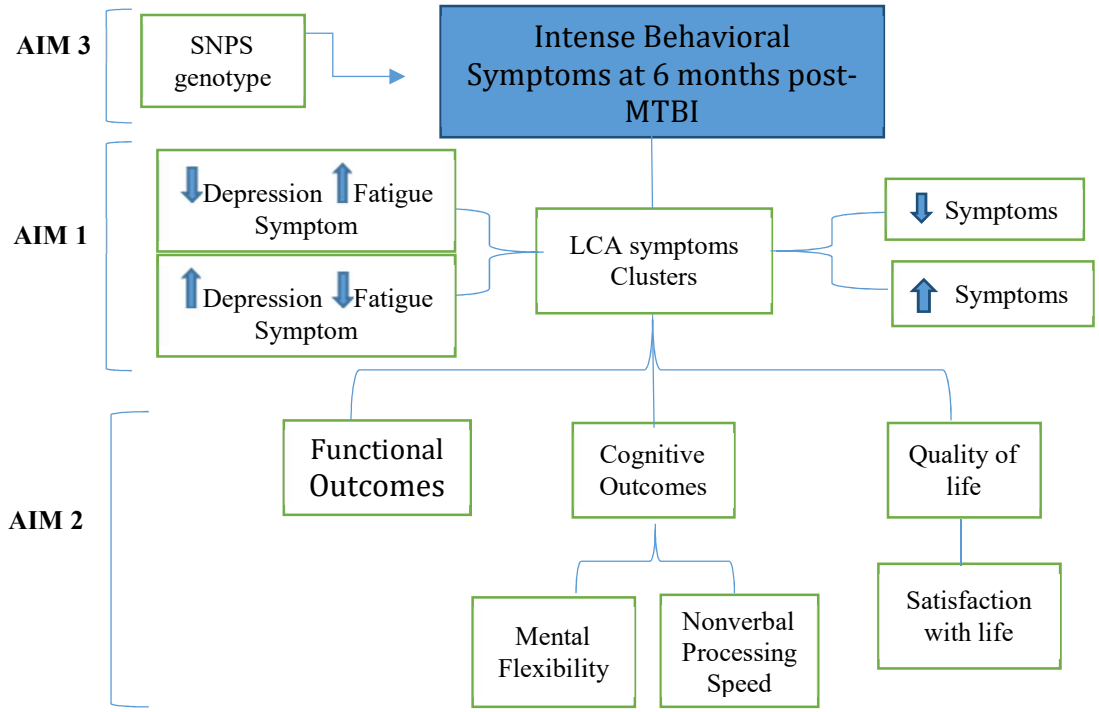
Second, there was a significant difference in anxiety among SNP rs1800497 ANKK1 genotype groups while controlling for history of anxiety and ethnicity. Results revealed significant group differences in the level of anxiety ($F(2,145) = 5.060$, $p < .008$, partial $\eta 2 = .065$). Specifically, those with A1/A1 (M=7.982, SD= 1.264) reported significantly greater levels of anxiety than patients with A1/A2 (M= 4.266, SD= .604) genotype. However, no differences were observed between A1/A1 and A2/A2 genotypes and A2/A2 and A1/A2 genotypes.

In conclusion, it is important to note that although the differences observed were significant, there was very little difference among the means, which warrants replication with a larger sample. Also, perhaps a larger sample size may produce different findings regarding differences between groups with different six types of SNPs genotype (rs1800497 (ANKK1), rs1799971 (OPRM1), rs279836 (GABRA2), rs279845 (GABRA2), rs279871 (GABRA2), and rs4680 (COMT).

Schematic of the Variables

The primary aim of this investigation was to use latent class cluster analysis to identify behavioral symptom clusters in MTBI patients; and to then determine whether there were differences in quality of life, and in cognitive and functional outcomes among the symptom groups. An exploratory aim assessed whether there were differences in the intensity of behavioral symptoms among SNP genotypes (see Figure 10).

Figure 10. Diagram of the final study variables.



Note. Aim 1: to identify different profiles of MTBI patients based on the intensity of depressive mood, fatigue, and poor sleep. Aim 2: to determine whether there are differences in cognitive and functional outcomes at six months post-MTBI among the identified behavioral cluster profiles. Aim 3: to explore differences in the intensity of behavioral symptoms at six months post-MTBI based on SNP genotype.

CHAPTER FIVE

DISCUSSION

This chapter summarizes and integrates results for each research question, aim and hypothesis; derives conclusions and provide explanations for findings; integrates findings with extant literature and discusses areas of convergence and divergence; discusses how findings address knowledge gaps; identifies and discusses realistic implications of the findings for nursing; addresses strengths and limitations of the study; and identifies directions for further study.

Overview of Findings

For Aim 1, Latent Class Analysis (LCA) was performed to identify profiles of MTBI patients based on the intensity of depressive symptoms, fatigue, and poor sleep. The measurements for these variables were derived from the Rivermead Post-Concussion Questionnaire, which was administered six months post-MTBI. Mplus 7.4 (Muthén & Muthén, 1998-2011) was used to conduct the LCA. The means of the three variables (depressive symptoms, fatigue, and poor sleep) were used to generate the latent classes. Results for Aim 1 revealed four predicted LCA Groups with different symptom intensity that were classified into four groups (Class 1—low symptoms, Class 2—high depression/low fatigue, Class 3—low depression/high fatigue, and Class 4—high symptoms). Class 1 was the largest class, constituting 67.7 % of the sample, and was characterized by low endorsement of depression, fatigue, and sleep disturbance. Class 4 accounted for 15.9% of the sample and had the highest ratings of depression, fatigue, and sleep disturbance. Class 3 consisted of low depression and

high fatigue and accounted for 9.5 % of the sample, whereas Class 2 was characterized by low fatigue and high depression and accounted for 7 % of the sample; both Class 2 and 3 had the same ratings of sleep disturbance.

After identifying the LCA groups, the second aim of this study was to determine whether there were differences among outcome variables (functional, cognitive, and quality with life) among the predicted LCA groups. An analysis of variance (ANOVA) and analysis of covariance were conducted to address this aim. The results for Aim 2 indicated that there were group differences in functional and quality of life outcomes among the four predicted LCA Groups. First, findings revealed significant group differences in the level of functional outcomes as assessed by GOSE, indicating that those with low symptoms had significantly greater levels of functional outcomes and good recovery as compared to those reporting high depression/low fatigue symptoms, low depression/high fatigue symptoms, and high symptoms. Second, results revealed significant group differences in the level of Satisfaction with Life, indicating that those reporting low symptoms had significantly greater levels of satisfaction with life as compared to individuals reporting high depression/low fatigue symptoms and low depression/high fatigue symptoms; the reported life satisfaction scores reported are considered slightly below average. Also, individuals with low symptoms had a significantly greater level of satisfaction with life as compared to individuals who reported high symptoms; the life satisfaction scores of that group is considered "dissatisfied with their life" according to the SWLS scoring. Third, group differences were found in both nonverbal processing speed and mental flexibility; findings revealed that those with low symptoms had levels of nonverbal processing speed, which corresponded to the 50th percentile of performance across age groups. This level was significantly greater as compared to individuals reporting high depression/low fatigue symptoms,

whose processing speed corresponded to the 25th percentile of performance across age groups. Additionally, there was a significant difference between predicted LCA Groups and the level of mental flexibility as assessed by the difference between TMT-B and TMT-A at the six-month follow-up. In this test, a lower score suggests improved performance. Results revealed a trend, such that the low symptoms group had better performance (approaching significance) compared to other groups. No differences in verbal learning were found among the LCA groups.

For the third exploratory aim, differences in intensity of behaviour symptoms (Somatisation, Anxiety, Depression, PTSD, and Post-Concussive Syndrome) among SNP genotypes (rs1800497 (ANKK1,) rs1799971 (OPRM1), SNPs genotype (rs1800497 (ANKK1), rs1799971 (OPRM1), rs279836 (GABRA2), rs279845 (GABRA2), rs279871 (GABRA2), and rs4680 (COMT)) was explored. An analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were conducted to address this aim. The results for Aim 3, revealed no differences in intensity of behavioural symptoms at six months post-MTBI for the five different SNP genotypes (rs279836 (GABRA2), rs279845 (GABRA2), rs279871 (GABRA2), SNP1799971 (OPRM1), and rs4680 (COMT)). However, group differences in the level of BSI-somatisation and BSI-anxiety were found for patients with different SNP rs1800497 ANKK1 genotypes. Yet, it is important to note that although the differences were statistically significant, the magnitude of these differences was small, and warrants replication with a larger sample. Also, it is likely that a larger sample size would reveal significant differences for other functional outcomes, especially cognitive function (i.e., non-verbal processing speed and mental flexibility). As well, a larger sample may also yield significant differences in functional outcomes among the six types of SNPs genotype (rs1800497 (ANKK1), rs1799971 (OPRM1), rs279836 (GABRA2), rs279845 (GABRA2), rs279871 (GABRA2), and rs4680 (COMT).

Relevance to Guiding Frameworks/Theories

This study was guided by a psychoneuroimmunology (PNI) framework. The field of PNI posits bidirectional networks that underlie the manifestation of behaviour; in this case inflammatory-related behaviour. The type and extent of such interaction and a given behavioural phenotype is also influenced by an individual's genetic make-up; and these behavioural phenotypes may influence cognitive and functional outcomes post-MTBI. Thus, consistent with this concept, this investigation explored genetic variants as a potential mechanism to explain individual differences in cognitive and functional outcomes post-MTBI. Understanding these physiological (genetic) factors may lead to tailored strategies to improve outcomes. Furthermore, the Theory of Unpleasant Symptoms (TOUS) (Lenz et al., 1997) guided the symptom-clustering analysis. The TOUS emphasizes the importance of consideration of symptom experiences as clusters. Incorporating the experience of symptoms "as clusters" (adapted from TOUS) would allow researchers to have a broader view of the symptom-related variables that contribute to the symptoms clusters, as well the symptoms-related recovery outcomes (e.g., cognitive and functional recovery).

The PNI framework guided the investigation of these relationships, and the results revealed that co-occurring symptoms synergize to negatively impact cognitive and functional recovery. Additionally, the findings revealed that genetic variants (i.e., SNP rs1800497 ANKK1) could predispose MTBI patients to more intense behavioural symptoms post-MTBI, which is consistent with the embodiment of mind and body. That is, a unique genetic phenotype may predispose an individual who suffers mild traumatic brain injury to exhibit more intense psychological symptoms. This line of thought is consistent with this study's finding that patients with different SNP rs1800497 ANKK1 genotype had differences in their level of somatisation

and anxiety. That is, those with A1/A1 had a significantly greater level of somatisation and anxiety as compared to A1/A2 genotype. Thus, we could perhaps, speculate that different genotypes could have a positive relationship with such psychological symptoms post MTBI. These preliminary results offer compelling impetus for further exploration of genetic variants linked to mental health outcomes in individuals who suffer MTBI. Such findings are innovative, as they may lead to novel genotype-based biomarkers predictive of who is at risk for worse outcomes as early as possible.

Discussion of Study Aims

Aim 1: Different Profiles of MTBI Patients and Intensity of Behavioral Symptoms

The first aim of this study was to identify different profiles of MTBI patients based on the intensity of depressive mood, fatigue, and poor sleep. First, symptom clusters analysis was used as a predictive tool for profiling subgroups with enduring behavioral symptoms post-MTBI. Such an analysis can reveal symptom interrelationships (Aktas et al., 2010) and facilitate exploring the influence of symptoms on each other (AIM 1) and on cognitive and functional outcomes (AIM 2). It is well established from previous research that MTBI patients can suffer from anxiety, fatigue, poor sleep, and depressive mood for weeks and months after injury (Ayalon et al., 2007; Bay, 2009; Beaulieu-Bonneau & Morin, 2012; Beetar et al., 1996; Chaput et al., 2009; Levin et al., 2005; Norrie et al., 2010; Ponsford et al., 2000; Rapoport et al., 2006). However, few studies have identified behavioral symptom clusters in MTBI patients, and no prior study has addressed the extent to which clusters of these symptoms influence functional and cognitive outcomes over time.

The results for Aim 1 extend the existing literature regarding persistence of behavioral symptoms post MTBI, in that most of previous studies have either evaluated individual

symptoms or the co-occurrence of two symptoms. For example, it has been shown that MTBI patients who experience sleep disturbance are also more likely to suffer depressive symptoms (Auxemery, 2012; Bay & Donders, 2008; Bay, 2009; Beaulieu-Bonneau & Morin, 2012; Chaput et al., 2009; Guskiewicz et al., 2007; Kristman et al., 2014; Levin et al., 2005; Mooney & Speed, 2001; Ponsford et al., 2011; Rapoport et al., 2006). Prevalence of depression is 15% in the first 3 months post-MTBI (Rapoport et al., 2003) and 18% up to a year after MTBI (Rao et al., 2010). These prevalence rates are similar to what was observed in the present study, as the present findings found that 25.3 % of the sample reported sleep disturbance (17.4 % mild, 6.5 % moderate, and 1.5% severe) at six-month post-MTBI. Also, the LCA results revealed that 7 % of cases had high depression symptoms/low fatigue symptoms (Class 2) and 15% of cases had high levels of depressive symptoms along with other symptoms (Class 4). In addition; however, the present results also demonstrate that high levels of sleep disturbance and fatigue accompanied such high levels of depression.

Fatigue is a prominent symptom following TBI, with self-report prevalence rates ranging from 43%–73% (Belmont et al., 2006). Fatigue can also endure as a predominant symptom several years after the TBI (Cantor et al., 2008; Ouellet et al., 2004). In comparison, the present findings reveal that 43.3 % of the sample (24.4 % mild, 14.9 % moderate, and 4% severe) report fatigue at six-month post-MTBI; while the LCA revealed prevalence of high fatigue in 9.5% of the cases (Class 3), and 15.9% of the cases reported high levels of fatigue symptoms along with other symptoms (Class 4). Fatigue after TBI has the potential to impact activities of daily functioning, occupational and leisure activities, and thus quality of life (Cantor et al., 2008; Ouellet et al., 2004). Although cluster analysis has not been conducted, correlational studies reveal several factors to be highly correlated with post-TBI fatigue; these include sleep

disturbance, perceived stress, somatic symptoms, anxiety and depression (Bay & Xie, 2009; Bushnik et al., 2008; Ponsford et al., 2000), which resonate with the clustering of symptoms (i.e., fatigue, depression, and sleep disturbance) in Class 4. Along the same line, a prospective longitudinal study assessed fatigue and associated factors in patients at 6, 12, and 18-24 months after TBI (Bushnik et al., 2008). Results of that study revealed self-reported fatigue improved during the first year, as did pain, sleep quality, cognitive independence, and involvement in productive activity. On the other hand, the subset of individuals who reported significant increases in fatigue over the first two years demonstrated poorer outcomes in regard to cognition, motor symptoms, and general functioning than those with decreased or stable fatigue (Bushnik et al., 2008).

In comparison, our results revealed significant group differences in the level of satisfaction with life. Those results showed that those who reported low symptoms had significantly greater levels of functional outcomes and good recovery, and greater levels of satisfaction with life as compared to individuals reporting high levels of fatigue. Further, those reporting high fatigue symptoms reported a level of satisfaction considered slightly below average. As for cognitive outcomes, there were significant group differences in the level of mental flexibility and results were trending toward indicating that the low symptoms group appears to have more improved performance compared to individuals reporting high fatigue symptoms.

Although systematic and comparative studies of fatigue after MTBI are limited, severe fatigue has been shown to be highly correlated with the experience of acute symptoms (Stulemeijer et al., 2006). In a longitudinal prospective study, post-MTBI fatigue was prevalent at one week (68%), at three months (38%), and at six months (34%) (Norrie et al., 2010).

Interestingly, depression and earlier prevalence of fatigue were highly correlated with later depression. Although fatigue was exacerbated by depression, it was not related to increased anxiety (Norrie et al., 2010). Post TBI fatigue appears to be persistent after mild-to-moderate TBI. For example, in those who were hospitalized and followed prospectively for symptom persistence and disability outcome, fatigue was present in 57% and persisted in 42% of the sample at one year (van der Naalt et al., 1999). Collectively, the findings of this secondary analysis and that of others highlight the importance of addressing fatigue after MTBI to identify biomarkers that can discern which MTBI patients are at risk for more severe symptoms. Such identification will permit the implementation of interventions earlier for better quality of life.

Sleep disturbance is a common complaint following TBI, and it is more common with MTBI (Beetar et al., 1996; Clinchot et al., 1998; Fichtenberg et al., 2000; Mahmood et al., 2004). In recent reviews, 30–70% of TBI survivors reported sleep disturbances (Orff et al., 2009). Most of the time the sleep disturbances are directly related to the TBI, enduring for months and/or years after the injury, consequently hindering the recovery process and return to pre-injury function (Orff et al., 2009). In comparison, the present findings are similar to the literature as the findings revealed that sleep disturbance was prevalent in 32.2% of the sample (14.4 % mild, 10.9 % moderate, and 7% severe) at six-month post-MTBI; and the LCA revealed that 15.9% of the cases had high levels of sleep disturbance (i.e., Class 4).

The above described how fatigue, depression, and sleep disturbance are relevant long-term outcomes in MTBI patients, in approximately 15% of MTBI survivors. MTBI research has primarily focused on studying symptom(s) (single, parried or all symptoms) experienced 3, 6, 12 months or years post injury. As mentioned earlier, MTBI patients can suffer from depressive mood, fatigue, and poor sleep for weeks and months after injury (Bay & Xie, 2009; Beaulieu-

Bonneau & Morin, 2012; Beetar et al., 1996; Chaput et al., 2009; Levin et al., 2005; Norrie et al., 2010; Ponsford et al., 2000; Rapoport et al., 2006). Although there is ample research regarding symptoms experienced post-MTBI, to date only six studies used cluster analysis to identify symptom profiles related to recovery (Bailie et al., 2016; Goldstein et al., 2010; Hellstrom et al., 2013; Hoffer et al., 2016; Snell et al., 2015; Velikonja et al., 2010). These studies attempted to explain the cluster of behavioral symptoms posited to underlie cognitive and functional recovery in MTBI survivors, which is a critical first step to improve risk assessment and to better manage post-MTBI outcomes (Lingsma et al., 2014). In contrast, analysis of symptom clusters has been a focus of research in oncology, in which a symptom cluster is defined as co-occurring symptoms that share a common influence on an outcome (Fox & Lyon, 2007). That literature provides overwhelming evidence that fatigue, depression, and insomnia commonly co-occur and exacerbate each other in cancer patients (Donovan & Jacobsen, 2007). For example, pain, fatigue, anxiety, insomnia, and depression are commonly co-occurring symptoms in breast cancer (Fiorentino, Rissling, Liu, and Ancoli-Israel, 2011). These findings suggest potential for practitioners to develop customized and comprehensive approaches that target not only one symptom but multiple symptoms; thus, breaking the vicious cycle whereby individual symptoms exacerbate each other.

Another closer look at the results of Aim 1 revealed that Class 3 (9.5%) was characterized by low depression and high fatigue, whereas Class 2 (7%) was characterized by low fatigue and high depression; both classes had the same ratings of low levels of sleep disturbance. These results appear contradictory, given the strong relationship between fatigue and depression across different healthcare settings and populations, from community samples to those in specialist care (Afari & Buchwald, 2003; Ball et al., 2010; Skapinakis, Lewis, &

Mavreas, 2003; Skapinakis, Lewis, & Meltzer, 2003). However, fatigue has long been a very challenging and elusive concept to comprehend by researchers and health care providers. Results are unclear, yet interesting, in that they do not co-occur in Class 2 and Class 3 (each are high without the other being high). Yet, they co-occur in 15% of cases in Class 4. Nevertheless, there are some factors, which may explain why fatigue and depression do not necessarily always co-occur. First, it is important to acknowledge that they are district concepts and independent of each other despite sharing some similarities and connections. Beyond that acknowledgement, there are several differences why fatigue and depression do not always co-occur:

(1) There are symptom presentation differences (Leone, 2010); that is, feeling depressed and tearful is different than feeling fatigued and tiring more easily (King et al., 1995). Also depression is operationally defined as feeling blue, feeling no interest in things, feeling lonely, feeling hopeless about future, feeling worthlessness, and/or having auicidal thoughts (Meachen et al., 2008).

(2) There are biological differences in the regulation of the hypothalamic–pituitary–adrenal (HPA) axis associated with fatigue and depression. Interestingly, with chronic fatigue syndrome a down-regulation of the HPA axis is observed, while with depression an up-regulation of the HPA axis is observed (Parker, Wessely, & Cleare, 2001).

(3) There are differences in epidemiology and etiology determinants. For example, one study evaluated genetic and environmental antecedents of fatigue, anxiety, depression and psychological distress in healthy adult twin pairs (n= 1004; 533 monozygotic and 471 dizygotic, age >50). Results distinctively reveled the etiological independence of prolonged fatigue; both genetic and environmental determinants were independent for other psychiatric symptoms. Multivariate genetic modeling revealed an independent

genetic factor influenced anxiety and depression, while another independent genetic factor solely influenced fatigue. Congruently, fatigue was linked to unique particular non-overlapping independent environmental factors, incomparable to environmental factor influencing psychological distress. Others note that despite some overlap, fatigue is independent from psychiatric symptoms, specifically depressive symptoms (Hickie, Kirk, & Martin, 1999).

On the other hand, there is growing evidence that supports the association between depression and fatigue, where both may predict and influence each other over time, and this may be partially explained by similar risk factors (Harvey, Wadsworth, Wessely, & Hotopf, 2008; Huibers, Leone, van Amelsvoort, Kant, & Knottnerus, 2007; Skapinakis, Lewis, & Mavreas, 2004). This notion emphasizes the importance and necessity of prolonged measurement of long term outcomes, as MTBI patients can suffer from depressive mood, fatigue, and poor sleep for weeks and months after injury (Ayalon et al., 2007; Bay & Xie, 2009; Beaulieu-Bonneau & Morin, 2012; Beetar et al., 1996; Chaput et al., 2009; Levin et al., 2005; Norrie et al., 2010; Ponsford et al., 2000; Rapoport et al., 2006). If untreated, individuals who fall into Class 2 and Class 3 may be predisposed to more severe, debilitating long-term outcomes; specifically, those in Class 2 may be predisposed to depression, whereas those in Class 2 maybe be predisposed to fatigue.

The demographic and health characteristics of the individuals grouped into the four classes were similar; however, there were some minor trending differences and other significant differences (i.e., employment status and GCS score). First, there were trending differences in social behaviors, history of behavioral symptoms (i.e., anxiety, depression, sleep disturbance), and causes of injury. For social behaviors, Class 4 (high symptoms) reported more alcohol

consumption (65.6%) compared to other classes; yet, it is not clear if this was a pre-existing behavior or if it developed in association with the post-MTBI symptoms. We attempted to conduct a chi-square test of independence between LCA groups and social behaviors; however, we did not have an adequate sample size to run the chi-square test of independence. As for history of behavioral symptoms (i.e., anxiety, depression, and sleep disturbance), Class1 had the least reported history of behavioral symptoms (anxiety (9.5%), depression (15.4%), and sleep disorder (3.6). A comparison of the history of behavioral symptoms (i.e., anxiety, depression, poor sleep) between Class 2 and Class 3 revealed that Class 2 reported a lower percentage of history of behavioral symptoms (i.e., anxiety (21.4%), depression (28.5%), sleep disorder (7.1%); whereas Class 3 reported a higher percentage of history of behavioral symptoms prior to MTBI (i.e., anxiety (26.3%), depression (36.8%), sleep disorder (15.8%). These findings suggest that history of behavioral symptoms does not necessarily predict the intensity of symptoms post MTBI. Along the same lines, another interesting finding is that only 9.4% of those in Class 4 reported some history of a sleep disorder, while a low percentage reported history of anxiety (25%) and history of depression (31.3%). Although it is valuable to assess for history of behavioral symptoms that could relate to susceptibility of poor long-term outcome recovery, no such relationship was found in this sample. We attempted to conduct a chi-square test of independence between LCA groups and social behaviors; however, we did not have an adequate sample size to run the chi-square test of independence.

Lastly, the findings revealed few significant demographic differences across LCA groups, with the only differences observed being differences in employment status and arrival GCS score. The difference found between LCA groups and employment status was moderately strong

(Cohen, 1988). Also, there were statistically significant differences between LCA groups and arrival GCS.

Overall, the findings revealed no major demographic differences across LCA groups; that is, no differences were observed in age, gender, and marital status. It is possible that a larger more heterogeneous sample could yield such differences. If so, this could lead to tailored treatment of behavioral symptoms based on age, gender and marital status. This could also provide descriptive insight into the nature of post-injury affective and behavioral symptoms, which in turn could lead to establishing a more inclusive conceptualization of needs with specifically, customized treatment modalities (Velikonja et al., 2010). Other studies were able to delineate such differences between their predicted profile patterns and associated demographic factors (Demakis et al., 2007; Velikonja et al., 2010; Warriner, Rourke, Velikonja, & Metham, 2003). For example, researchers found cluster membership was associated with education, age and employment status, but not with neurological findings (e.g., lesion location) (Goldstein et al., 2010). It is possible that relationships between demographic factors (i.e., age, gender, marital status, education, and employment status) and symptom experience will be found in the TRACK-TBI cohort study; thus emphasizing the importance of replicating this analysis with a larger sample.

Taken together, the results demonstrate that LCA can be used to reliably and objectively detect subtypes of behavioral symptom clusters post MTBI. These findings go beyond the prior research, which primarily focused on single, paired or all symptoms experienced at 3, 6, 12 months or years post injury. Although there is ample literature describing symptoms experienced post-MTBI, to date only six studies used cluster analysis to identify symptom profiles related to recovery (Bailie et al., 2016; Goldstein et al., 2010; Hellstrom et al., 2013; Hoffer et al., 2016;

Snell et al., 2015; Velikonja et al., 2010). The findings from the current study, therefore, encourage further studies of the relationship between symptoms experience and evaluation of inflammation-related behavioral symptom clusters as a potential predictor of cognitive and functional recovery. Thus, there is a critical need to further develop prognostic models of MTBI to identify those at greater risk for poorer cognitive and functional recovery and who will most benefit from targeted therapy (McMahon et al., 2014). Explication of the cluster of behavioral symptoms (i.e., depressive mood, fatigue, and poor sleep) posited to underlie cognitive and functional recovery in MTBI survivors is a critical first step to improve risk assessment and to better manage post-MTBI outcomes (Lingsma et al., 2014).

In addition, an important cluster that emerged from these findings is a group of individuals who experience a cluster of high levels of depression, fatigue, and sleep disturbance. It is likely that the co-occurrence of these distressing symptoms presents a vicious cycle, in which these symptoms reinforce each other making them more difficult to manage. Understanding the etiology of this symptom cluster and treatment of these symptoms as a whole may be more effective. However, to accomplish this, mechanistic studies of the linkages among sleep, fatigue, pain, and depression are needed to more fully understand the etiology of this symptom cluster, as a common biological pathway may underlie this cluster. Such understanding can guide new approaches to manage these symptoms as a group. For example, further understanding the relationship among symptom clusters could lead to the development of algorithms and decision trees for assessment and management. It is important that practitioners comprehensively assess symptoms and make informed decisions as to which interventions could target single and multiple symptoms to improve quality of life in the MTBI survivor.

Aim 2: Latent Cluster Analysis Groups and Cognitive, Functional, and Quality of Life Outcomes

The second aim of this study was to determine (after identifying the latent class that best fit the data) if there were any differences among the predicted classes and outcome variables (functional, cognitive, and quality with life) at the six-month follow-up. The extent to which membership in an identified cluster predicts functional, cognitive, and quality of life outcomes at six-months post -MTBI was explored. Specifically, we assessed the association between the four predicted Classes (low symptoms, high depression/low fatigue, low depression\ high fatigue, and high symptoms) and three outcomes (functional outcomes assessed by GOSE, cognitive outcome: nonverbal processing speed assessed by WAIS-IV Processing Speed Index; mental flexibility assessed TMT B-A, and verbal learning assessed by CVLT-II; and quality of life outcomes assessed by SWLS. An analysis of variance (ANOVA) and analysis of covariance were conducted to address this aim.

Depression, fatigue, and poor sleep have been independently associated with impeded cognitive recovery from MTBI (Guskiewicz et al., 2007; Mooney & Speed, 2001; Orff et al., 2009) and the resumption of pre-injury lifestyle and responsibilities (Patterson & Holahan, 2012; Silver et al., 2009). This aim presents a novel approach since predictive power may be gained by evaluating clusters of symptoms that co-occur and which may portend slower recovery. Determining the existence of symptom clusters is vital in MTBI patients and will lead to further crucial investigation into the mechanisms that underlie these clusters, which will advance the knowledge regarding cognitive and functional outcomes. Although there is ample literature about symptoms experienced post-MTBI, to date only six studies used cluster analysis to identify

symptom profiles related to recovery (Bailie et al., 2016; Goldstein et al., 2010; Hellstrom et al., 2013; Hoffer et al., 2016; Snell et al., 2015; Velikonja et al., 2010).

The results of Aim 2 identified group differences in functional outcomes between the four LCA symptom cluster groups. Findings revealed that those with low symptoms had significantly higher levels of functional outcomes and better recovery as compared to high depression/low fatigue symptoms, low depression/high fatigue symptom, and between high symptoms. Although, fatigue has been linked to poor recovery post-TBI a recent systematic review concluded that the impact of fatigue on patient outcomes is unclear and more intensive investigation is essential (Mollayeva et al., 2014). The prevalence and persistence of fatigue after TBI has the potential to impact activities of daily functioning, occupational and leisure activities, and thus quality of life (Cantor et al., 2008; Ouellet et al., 2004). Previous studies highlight the importance of fatigue after MTBI and the need for further investigation and identification of markers that could possibly identify MTBI patients who are at risk for more severe symptoms in order to implement interventions earlier for better quality of life in MTBI survivors. Thus, the result of this study revealed the potential importance of evaluating clusters of symptoms as an approach to increases predictive power to identify trajectories of recover (good versus poor).

The findings also revealed that six months post-MTBI, those with low symptoms had significantly greater levels of satisfaction with life as compared to high depression/low fatigue symptoms, and low depression/high fatigue symptoms (M=16.89, SD=7.203). [Note - both of these groups reported slightly below average in life satisfaction based on SWLS scoring]. Also, individuals with low symptoms also reported significantly greater levels of satisfaction with life as compared to those reporting high symptoms (i.e., those considered dissatisfied according to

the SWLS scoring). In fact, there is some support for this notion, as others have showed that post- concussive symptoms associated with MTBI reduce psychological quality of life for veterans who experienced deployment-related MTBI (Sofko, Currier, Hill, & Drescher, 2016).

In regard to cognitive outcomes, the results revealed that there were group differences in cognitive outcomes between the four predicted LCA Groups with different symptom intensity. Specifically, LCA group differences were found in both nonverbal processing speed and mental flexibility (i.e., TMT B-A). This is congruent with previous research that demonstrate that MTBI patients also have long-term cognitive impairments related to trauma-induced neuro-degeneration, and these impairments include impairment of memory, changes in executive cognitive function affecting the accomplishment of tasks involving complex cognition, impaired attention and concentration, and struggles with speed of information processing (slowed) (Binder, Rohling, & Larrabee, 1997; Patterson & Holahan, 2012; Silver et al., 2009).

Our results indicate that those with low symptoms had significantly greater levels of nonverbal processing speed, corresponding to the 50th percentile of performance across age groups, as compared to high depression/low fatigue symptoms, whose performance corresponded to the 25th percentile of performance across age groups. Few identified differences could explain the difference in nonverbal processing. There were trending differences between LCA groups and education background and statistically significant differences between LCA groups and employment status. For example, the majority of Class 1 (Low symptoms) were working full time and received at least minimum wage (50.7%); also the majority had either a Bachelor's degree (39 %) high school diploma (30.8%), or a master's degree (11.7%); while for Class 2 (high depression/low fatigue), the majority were not in the paid workforce or unemployed (57%) and the majority had a high school diploma (50%). This

could partially explain the differences in nonverbal processing, perhaps a larger sample could explain these differences better.

As mentioned earlier, there were minor trending differences between LCA groups and history of depression, with 15.4% of Class 1 reporting a history of depression, while 28.5% of Class 2 reported history of depression (this could also explain how Class 2 patients clustered in the Class; high depression/low fatigue). Others have previously reported a relationship between level of depression and performance on cognitive tests, with higher levels of depression correlating with worse cognitive impairment and poor social functioning (Busch & Alpern, 1998). In particular, worse prognosis of depression was highly associated with impaired mental flexibility and visio-motor tracking (Veiel, 1997). This suggests that subgroups of patients with MTBI could be identified according to their symptom clusters to delineate those who are at risk poor cognitive and functional outcomes.

Additionally, relevant to this study, Ramati et al. (2009) examined the association between psychiatric morbidity and cognitive functioning in 86 electrical injury patients. They found that patients with multiple psychiatric morbidities showed worse cognitive impairment (verbal memory, executive functioning and attention) when compared to electrical injury patients with one or no post-injury psychiatric morbidities. Again, this is consistent with the present study results, as they reveal a relationship between psychological symptoms and cognitive and functional recovery (Ramati et al., 2009). On the other hand, previous researchers have established that MTBI patients with a decreased Glasgow Coma Scale score in the acute phase exhibit significantly decreased and disturbed cerebral perfusion in the frontal and occipital grey matter as seen on a normal non-contrast CT performed directly after admission. Moreover, these observations correlated with severity of injury and cognitive impairment (Metting et al., 2009).

Such relationships could not be determined in this study. This is likely because the majority had a GCS of 15. Nevertheless, the above-mentioned differences between classes could relate to the importance of considering the causes of injuries and cognitive recovery.

Although the present study revealed a significant difference among LCA Groups and the level of Mental Flexibility, as assessed by the difference between TMT-B and TMT-A at six-months follow-up, unfortunately there were no group differences between the LCA Groups on the post hoc test. Perhaps a larger sample size could delineate these differences in the future. Also, there were no group differences in verbal learning. This again is likely due to the small sample size. However, this finding is important when considered with other research in that only 10-20% of MTBI patients will experience persistent cognitive impairments beyond the acute phase; such cognitive impairment significantly disrupts their capacity to resume many pre-injury activities (Patterson & Holahan, 2012; Silver et al., 2009). Perhaps the small sample size could explain these results and a larger sample size could more reflective of the symptom experience of the miserable minority (who suffer from a plethora of persistent physical, emotional, and cognitive symptoms) (R. Ruff, 2005). In general, the small sample size hindered finding meaningful statistical or clinical differences in verbal learning and mental flexibility for the "miserable minority."

This study is unique and the first of its kind to link behavioral symptom clusters with cognitive outcomes post-MTBI. In one of the few previous investigations Snell et al. (2015), conducted a prospective observational study to examine associations between baseline demographic, clinical, psychological variables, and six-months follow-up outcome. Using a two-step approach for cluster analysis, their findings reveled three clusters of psychological adaptation (high 36.3%, medium 38.3%, and low 25.3%) related to injury outcomes (Snell et al.,

2015). Furthermore, they found that the identified cluster-group membership was significantly correlated with outcomes. This study supports the notion that groups could be identified early post injury based on psychological factors, and that different group membership is correlated with different recovery outcomes. Yet again, low adapters were only 25.3% of the whole sample, representing a miserable minority. This is also comparable to the work by Bailie et al. (2016). That study explored the taxonomy of combat-related MTBI (n=1341 military personnel) based on symptom patterns within two years of evaluation. Cluster analysis revealed four subtypes (primarily psychiatric PTSD group, a cognitive group, a mixed symptom group, and a good recovery group). Once more, the largest cluster had an overall low symptom profile, which was the "good recovery" group.

Overall, previous research was limited to identifying whether the long-term cognitive impairments correlate with patho-physiological factors of the injury itself, or if these impairments are a result of the influence of other psychological adverse outcomes such as fatigue, sleep, and depression (Bigler, 2008; Wood, 2004). Historically, researchers attempted to theorize and explain the development of long-term cognitive impairment post-TBI (Ryan & Warden, 2003). In this secondary analysis, we identified different behavioral profiles of MTBI patients based on the intensity of depressive mood, fatigue, and sleep quality, and determined differences in quality of life (i.e., satisfaction with life), cognitive (i.e., non-verbal learning and mental flexibility), and functional outcomes at six months post-MTBI among the identified behavioral cluster profiles.

It is crucial to advance the knowledge of how symptom clusters can influence cognitive and functional outcomes especially in this understudied MTBI population (as opposed to the TBI population). The research on symptom clusters and their influence on cognitive and functional

outcomes remain limited. Further research on such associations can provide insight as to who might be at high risk for poor recover. Thus, it was imperative to attempt to identify subgroups within the MTBI patients that may account for the differences in symptom experiences and variation in cognitive and functional recovery outcomes over time.

The results revealed that those with low symptoms had significantly better cognitive and functional and quality of life outcomes, concluding that the intensity of experienced symptom clusters can influence long term outcomes negatively. Although there is ample literature about symptoms experienced post-MTBI, to date only six studies used cluster analysis to identify symptom profiles related to recovery (Bailie et al., 2016; Goldstein et al., 2010; Hellstrom et al., 2013; Hoffer et al., 2016; Snell et al., 2015; Velikonja et al., 2010). Given this discussion and our analysis, one might argue that simply inquiring about symptoms experienced post-MTBI by healthcare professionals will improve long term outcomes and predict those who are more at risk for poor recovery. Thus, the results of this study along with previous cluster analysis studies, highlights the importance of evaluating symptom clusters to critically provide treatment or prevention of long-term complications. Further, these findings highlight the need for unique tailored treatment resources and programs (Bailie et al., 2016; Goldstein et al., 2010; Hellstrom et al., 2013; Hoffer et al., 2016; Snell et al., 2015; Velikonja et al., 2010).

Aim 3: SNPs and Behavioural Symptoms

The third aim of this study was to explore whether the intensity of behavioral symptoms differed with respect to SNPs (rs1800497 (ANKK1,) rs1799971 (OPRM1), SNPs genotype (rs1800497 (ANKK1), rs1799971 (OPRM1), rs279836 (GABRA2), rs279845 (GABRA2), rs279871 (GABRA2), and rs4680 (COMT)). We assessed the differences among SNPs genotypes and three main measures: BSI18 (The BSI-18 is a brief screen of psychologic distress

with a Global Severity Index (GSI), and 3 clinical subscales: BSI-somatization, BSI-anxiety, and BSI-depression), PTSD-PCL (3 subscales; hypervigilance, avoidance, Re-experiencing), and RPQ-13, and Rivermead Post Concussion Symptoms Questionnaire 13 (RPQ-13). An analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were conducted to address this aim.

Findings revealed no differences in the intensity of behavioral symptoms, as assessed by three main measures (BSI-GSI, BSI-somatization, BSI-anxiety, and BSI-depression, PTSD-PCL (hypervigilance, avoidance, Re-experiencing), and RPQ-13) at six months post-MTBI based on t five types of SNPs genotype (rs279836 (GABRA2), rs279845 (GABRA2), rs279871 (GABRA2), SNP1799971 (OPRM1), and rs4680 (COMT)). However, differences were found for patients with different SNP rs1800497 ANKK1 genotype and their level of BSI-somatization and BSI-anxiety at six months post-MTBI. Specifically, findings revealed a significant difference between SNP rs1800497 ANKK1 and somatization, while controlling for history of depression and ethnicity. These findings showed that individuals with A1/A1 had significantly greater levels of somatization as compared to A1/A2 genotype. However, no differences were observed between A1/A1 and A2/A2 genotypes, and A2/A2 and A1/A2 genotypes.

Second, there was a significant difference between SNP rs1800497 ANKK1 and anxiety, while controlling for history of anxiety and ethnicity. Individuals with A1/A1 reported significantly greater levels of anxiety than patients with A1/A2 genotype. However, no differences were observed between A1/A1 and A2/A2 genotypes and A2/A2 and A1/A2 genotypes.

Ample research has shown that anxiety symptoms are prevalent in the aftermath of a mild TBI (Hiott & Labbate, 2002; Koponen et al., 2002; Ma et al., 2014; Mooney & Speed, 2001; Moore et al., 2006; Rao & Lyketsos, 2002; Rao et al., 2010; R. Ruff, 2005; R. M. Ruff, 2011;

Stulemeijer et al., 2006; Woodcock & Morganti-Kossmann, 2013). Our results revealed that ANKK1 might predispose individuals to experience persistent symptoms of anxiety and somatization) after MTBI, which could impede cognitive recovery. These results are important when considered in combination with other research. For example, McAllister et al. showed rs1800497 (T allele) to be negatively associated with poorer performance on cognitive outcomes, specifically poorer verbal learning, at one-month post mild to moderate TBI (McAllister et al., 2005; McAllister et al., 2008). Subsequently, others examined the influence of the (C/T) SNP rs1800497 on post-TBI outcome using data from two multicenter studies: Citicoline Brain Injury Treatment trial and TRACK-TBI Pilot. Findings from that study showed that the ANKK1 T/T genotype is related to poorer verbal learning performance at six-months post-TBI (Yue et al., 2015). Identification of such associations between ANKK and cognitive outcome, will permit earlier intervention for those at risk for behavioral symptoms clusters, since behavioral symptoms could impede cognitive outcomes as seen in AIM 2.

Genetic association analyses suggest certain common single nucleotide polymorphisms (SNPs) may negatively influence recovery from MTBI (Feng et al., 2015; Lanctot et al., 2010; McAllister et al., 2005; McAllister et al., 2008; Pap et al., 2012; Roetker et al., 2012). Although results from this study did not reveal group differences in behavioral symptoms among five SNPs (rs1799971 (OPRM1), rs279836 (GABRA2), rs279845 (GABRA2), rs279871 (GABRA2), and rs4680 (COMT)), we did observe differences in the levels of BSI-somatization and BSI-anxiety at six months post-MTBI in those patients with different SNP rs1800497 ANKK1 genotype.

This study is unique and the first of few studies to link behavioral symptoms to SNPs post-MTBI. If replicated in a larger sample, it may open up new approaches to identify and treat

the “miserable minority.” Ruff et al. (2005) hypothesized that 10- 20 % of MTBI patients will suffer long term symptoms, and defined this subgroup as the "miserable minority." New approaches can aid in improving the quality of life of these miserable minority who continue to experience high levels of behavioral symptoms long after MTBI. Also, perhaps the TRACK-TBI cohort with a larger sample size may produce significant differences in symptoms among groups that differ with respect to other SNPs genotypes (rs1800497 (ANKK1), rs1799971 (OPRM1), rs279836 (GABRA2), rs279845 (GABRA2), rs279871 (GABRA2), and rs4680 (COMT)). The lack of statistically significant findings may be attributed to the small sample size and inadequate power to detect statistically significant findings. However, controlling for possible correlated covariates added strength and importance to the analysis and produced statistically significant differences among groups. As such, these findings highlight the importance of considering other variables that could be cofounders for the miserable minority.

In conclusion, several SNPs have been proposed to be implicated in outcomes post MTBI and TBI. Yet there is a need for replication or validation of those SNPs that may underlie individual differences in behavioral symptoms post-MTBI. Only then can this evidence be translated to the clinical setting. If genetic variants predict risk for more intense and enduring behavioral symptoms clusters, this might eventually aid in predicting prognoses and responses to treatment. Therefore, investigation of these biomarkers genetic variants (SNPs) may provide a valuable means to predict persistent and lingering behavioral symptoms in MTBI patients. This investigation is significant because it will fundamentally advance knowledge of behavioral symptoms in the at risk subgroup of MTBI patients, as well as provide information as to the role of genetic variants in the etiology of behavioral symptom clusters post-MTBI.

Summary of Major Findings

Results revealed that for a sizeable subgroup of MTBI patients, recovery is protracted, and prediction of who will experience protracted functional and cognitive recovery was explored. Findings from this secondary analysis study increased knowledge as to whether certain behavioral symptoms clusters (i.e., depressive mood, fatigue, and poor sleep), differentiate cognitive (i.e., mental flexibility and non-verbal learning) and functional recovery; and quality of life. Additionally, the LCA identified 4 classes of symptom clusters profiles: Class 1 was the largest class, constituting 67.7% of the cases, and was characterized by low endorsement of depression, fatigue, and sleep disturbance. Class 4 accounted for 15.9% and had the highest ratings of depression, fatigue, and sleep disturbance. Class 3 (9.5%) was characterized by low depression and high fatigue, whereas Class 2 (7%) was characterized by low fatigue and high depression; both class2 and 3 had the same ratings of sleep disturbance.

Based on LCA symptom clusters profiles (i.e., Class 1, 2, 3 and 4), significant differences in functional outcomes, quality of life, and cognitive outcomes (nonverbal processing speed and mental flexibility) were found at six-months post-MTBI. These differences were:

- Individuals with low symptoms (Class 1) had significantly greater levels of functional outcomes and good recovery as compared to those reporting high depression/low fatigue symptoms, low depression/high fatigue symptoms, and high symptoms.

For both high depression/low fatigue symptoms and low depression/high fatigue symptoms the reported life satisfaction scores are considered slightly below average. Meanwhile, those with high symptoms the reported life satisfaction scores of that group is considered "dissatisfied with their life" according to the SWLS scoring.

- For cognitive outcomes, individuals with low symptoms had levels of nonverbal processing speed that corresponded to 50th percentile of performance across age groups; this performance level was significantly greater as compared to individuals reporting high depression/low fatigue symptoms, whose processing speed corresponded to the 25th percentile of performance across age groups. There were no group differences in nonverbal processing speed between individuals with low depression/high fatigue symptoms and those with high symptoms.
- Results revealed significant group differences in the level of mental flexibility at six-months follow-up. Those results showed a trend indicating that the low symptoms group appears to have better performance compared to other groups.

Lastly, for the exploratory aim focused on genetic variants, results revealed that the ANKK1 genotype might predispose individuals to experience persistent behavioral symptoms (i.e., anxiety and somatization) after MTBI; such symptoms could further impede cognitive recovery, as well as reduce quality of life.

Study Strength and Limitations

A primary strength of this investigation is the chosen frameworks; namely, the PNI framework and the Theory of Unpleasant Symptoms (TOUS). In combination, these frameworks offered an integrated and holistic perspective to guide discovery, which can lead to remarkable advancement in symptom science. It is clear that behavioral symptoms arise from complex interactions among biological, psychological and social factors; consistent with a PNI framework. Overall, the use of an integrated framework in combination with a theory of symptom clusters creatively addresses the depth of the interaction among symptoms experienced, their impact on recovery outcomes, and may explain individual variation in symptom intensity and duration seen in MTBI patients.

This study acquired data from an existing database, which has both strengths and limitations. Overall, secondary data analysis has been a widespread and useful method in health promotion research. Nevertheless, there are clear advantages and disadvantages of analyzing existing secondary data (Cheng & Phillips, 2014). One of the most valuable advantages of secondary data analysis is the accessibility and ease of data collection; often from large data sets than would be impractical to achieve with primary data collection. This can speed the procurement of findings, saving time for the investigator, and stimulating more rapid translation of findings to the targeted population (Cheng & Phillips, 2014). Secondary data analysis can lead to unexpected findings and new insights, which can spur hypothesis generation to guide future primary data collection. From a practical point of view, analyzing an existing data set requires few resources and is cost effective. On the other hand, secondary data analysis has its disadvantages. For example, an investigator may not be able to ask a specific question or test a

specific hypothesis due to the nature and measures used to obtain the original data set. In contrast, with primary data collection an investigator can design the study and choose the measures to address a specific question. For the current study, measurement of fatigue, depression, and sleep had to be obtained from several measures, which may not have adequately captured the variables of interest. Also, there were no biomarkers of inflammation in the data set, and these biomarkers were assumed to underlie the clustering of these symptoms. Furthermore, the investigator does not have control of data quality or control of potential confounders. However, given the nature, purpose, and oversight of the TRACK-TBI database, the data collected could be assumed to be of good quality. Further, the overall the purpose of the TRACK-TBI initiative is to improve long-term outcomes of TBI patients in general, and this purpose is consistent with the objectives of the present study. Therefore, these limitations are minimized. Lastly, the availability of the Track-TBI Pilot database provided real-life data from a population that is difficult to access single handedly, and this allowed the accomplishment of the objectives of this investigation.

There were limitations in this study based on threats to internal and external validity. First, the threat from confounding variables is one of the most important threats the investigator needs to account for. Therefore, this study did control for several confounding variables. For example, to address Aim 3 potential, covariates were controlled (i.e., history of behavioral symptoms), and this added strength and validity to the findings. However, it is likely that other uncontrolled covariates may confound findings, especially as relates to those suffering more intense and persistent behavioral symptoms post-MTBI (i.e., the “miserable minority”).

Another threat to internal validity was missing data. For this study, data were missing for both the biological variables and the self-reported questionnaires. As a result, this decreased the

sample size from n=340 to n= 201 for (AIM 1 AND Aim 2), and further reduced the N to 153 for Aim 3. Also, there were missing data regarding injury severity and acute histories. For example, duration of LOC and PTA associated with a MTBI has been shown to contribute to worse behavioral avoidance and psychological well-being for veterans who experienced deployment-related MTBI (Sofko et al., 2016). Therefore, missing data regarding LOC and PTA duration is very crucial. Since this is a secondary data analysis, the research did not have control over data that was missing.

A third threat is selection bias. For this study, the sample was a convenient and nonrandom sample and subject to selection bias. Convenience sampling is known as one of the weakest sampling techniques, as available subjects might be atypical of the population of interest with regard to critical variables. Selection bias is the most problematic and frequently occurring threat to internal validity of studies not using an experimental design (Polit & Beck, 2008). For example, because of the sampling techniques, the majority of the sample was white (84%) and male (67%), which limits generalizability. Also, history of behavioral symptoms was not controlled for during enrollment; however, it was accounted for in this analysei to address the potential impact of this threat to validity; thus attenuating this limitation.

A fourth threat to validity is history. History refers to the occurrence of external events that take place concurrently with the independent variable and which can affect the dependent variable (Polit & Beck, 2008). A case in point is when something happens to the patient between follow-up data collection or even before enrollment that influences depression, fatigue, or poor sleep. Such events might be a death in the family or loss of a job. Pre-injury stress has been hypothesized to play a role in long-term maintenance of symptoms (van Veldhoven et al., 2011). A way to control for this would be to administer a Life Events Scale to assess occurrence

of major life events. In fact, there is support for this notion, as research shows that incidence of stressful life events to be a significant predictor of anxiety, depression, and mental health in MTBI patients (van Veldhoven et al., 2011). Thus, the experience of stressful events prior to the injury may predispose those with MTBI to suffer from poor long-term outcomes. Assessment of stressful life events during acute stages post-MTBI is essential (van Veldhoven et al., 2011). Again, since this is a secondary data analysis and the researcher was unable to overcome this threat.

Lastly, the use of self-report questionnaires to measure symptoms is considered a minor threat to validity. For this secondary analysis, there were no data available that used specific validated measures for each behavioral symptom (i.e., anxiety, depression, fatigue, poor sleep). Measures for these variables were obtained from either subscales of the BSI- GSI (i.e., BSI-Depression, BSI-anxiety, BSI- Somatization), or the Rivermead Post-Concussion Questionnaire. Use of validated instruments, containing more items, may have revealed more significant differences in outcomes among symptom cluster groups. Again, this was a secondary analysis and the researcher was limited by the measurements used in the original investigation. Perhaps, replication of this study with more comprehensive and specific measures of behavioral symptoms could produce more representative and valid results.

Generalizability is identified as a threat to external validity. According to Polit and Beck (2008), generalizability is the criterion used in quantitative research to assess the extent to which the findings can be applied to other groups and settings. The target population for this study is MTBI patients with a range of ethnic diversity. Due to the study limitations, this study may not be generalizable to the general population of MTBI patients. However, the findings could provide information to generate hypotheses and guide future studies, which can advance the

ability of clinicians to predict those who are at greater risk for worse cognitive/functional outcomes. Another threat to external validity is the relatively small sample size. The TRACK-TBI pilot phase recruited subjects from three centers, resulting in data collection from 599 patients (only 340 MTBI patients; with only 201 eligible for the study due to missing data). With regard to this secondary data analysis, the results are not generalizable beyond the institutions where data was collected and the demographics of the sample; hence, the findings cannot be generalizable to all MTBI patients.

Nevertheless, despite these limitations, ultimately, the knowledge acquired can be used to develop and implement improved risk assessment protocols and targeted interventions to those most vulnerable for behavioral symptoms and poor outcomes.

Nursing Implications

One of the important contributions of the symptom clusters analysis is that in addition to profiling subgroups, it also to a certain extent reveals symptom interrelationships (Aktas et al., 2010). This conceptualization of symptom clusters is visualized as a paradigm shift in symptom management research. The goal of symptom cluster research is to address the reality of concurrent symptom experiences in different populations and to lead to more promising research that will potentially generate knowledge needed to rapidly improve symptom management. Thus, the findings from this study can contribute to bridging the gap between research and bedside nursing by addressing symptoms (as a cluster), which is the most common reason that individuals seek healthcare (Larson et al., 1994). Furthermore, advancing knowledge of symptom interrelationships within a cluster might lead to more efficient approaches that target multiple symptoms as opposed to a single symptom approach. This may more effectively

leverage scarce recourses and ultimately reduce the symptom burden (Aktas et al., 2010). Consistent with this notion, a recent study demonstrated that military MTBI patients who completed multidisciplinary treatment reported a reduction in both persistent post-concussive and PTSD symptoms (Janak et al., 2015). Thus, profiling subgroups of MTBI patients has potential to improve clinical practice, inform clinical practice guidelines, and ultimately provide patients with the most effective and innovative treatment modalities (Barsevick et al., 2006; Dodd et al., 2001; Kim & Abraham, 2008).

Additionally, enhanced understanding of which clusters of symptoms relate to the development of specific cognitive profiles of MTBI patients would allow for the development of future rehabilitation programs that target specific cognitive deficits. Furthermore, clinicians could identify patients at risk for poor cognitive and functional outcomes based on post-MTBI symptoms experiences/presentations (perhaps symptom clusters). Such identification may facilitate the tailoring of earlier interventions to better serve this population and promote better quality of life.

Collectively, several implications can be derived from the findings of this study. Nurses are the first line of contact with MTBI patients at their ER visits post-MTBI. In most cases, it is the only time they are seeking medical help. Often a diagnosis of a "mild" traumatic brain injury could be misleading. After discharge from the ER, they may never return for a follow-up visit at a concussion clinic or even to their primary physician. Although a few, but identifiable, number of MTBI patients will suffer from lingering long-term symptoms, it is important for nurses to know and understand the prevalence of symptom clusters in MTBI patients and their relationship with long-term cognitive and functional outcomes. ER nurses need to be sensitive to long-term outcomes

of MTBI and to teach these patients when to seek help prior to being discharged from the ER. It is imperative that nurses are aware of the long-term cognitive and functional outcome that are disabling and hinder MTBI patients from retuning to life before the injury. In follow-up concussion clinics, it may be necessary to include self-reported measures of depression, fatigue, and sleep quality along with the usually addressed questions about physical symptoms (such as headache). For those who report these symptoms, a follow-up teaching session is necessary to address the relationship between symptom clusters and cognitive and functional outcomes. Health care providers may want to consider earlier screening for history of behavioral symptoms that could be aggravated by the injury.

Also, involved family members or supportive people of MTBI patients should be educated on the risks of symptom clusters. MTBI patients will most probably need help in recognizing these symptom clusters and guidance to see medical help accordingly. If the family and support system of the MTBI patients are educated about symptom clusters, and cognitive and functional outcomes, they may be more likely to support and even recognize the need for MTBI patients to seek medical treatment. MTBI patients' need to be reassured by nurses (the first line of help) that symptom clusters are common and there is treatment designed to help them deal with these symptoms. In order to bridge the gap between research and nursing practice, it should a high priority for nurses to provide sympathetic and compassionate care for these patients, while emphasizing that although some can experience these symptoms clusters, early treatment can lead to better recovery.

One interesting contribution of this study is the consideration of predictive biomarkers that can predict risk of symptom clusters and long-term outcomes. Evaluation

of genetic markers may lead to new ways to prevent, predict, and treat behavioral symptoms, and directly or indirectly improve long-term cognitive and functional outcomes. Specifically, the preliminary findings of this study suggest that those with SNP rs1800497 ANKK1 who had the A1/A1 allele had significantly greater levels of somatization as compared to A1/A2 genotype. Additionally, those with A1/A1 reported significantly greater levels of anxiety than patients with A1/A2 genotype. Confirming these genetic findings in larger studies can lead to genetic risk profiling for such symptoms. Somatization is a very elusive concept, which has been defined in many ways (De Gucht & Fischler, 2002). For example, somatization has been defined as "the tendency to experience and communicate somatic distress and symptoms unaccounted for by pathological findings, to attribute them to physical illness, and to seek medical help for them" (Lipowski, 1988). Furthermore, some researchers distinguish between presenting and functional somatization, with presenting somatization defined as "the predominantly or exclusively somatic presentation of psychiatric disorder, most commonly depression and anxiety," (Kirmayer & Robbins, 1991); and functional somatization defined as "high levels of medically unexplained symptom reporting in multiple physiological systems" (Kirmayer & Robbins, 1991). This added distinction draws attention to hidden psychiatric morbidity, especially anxiety and depressive disorders (De Gucht & Fischler, 2002).

Shifting the paradigm to view symptoms as clusters will potentially assist in identifying common underlying mechanisms, which can then lead to single approaches to treat multiple symptoms. For example, this may lead to new discoveries that target biological processes related to inflammation (which may underlie behavioral symptom

clusters and cognitive impairment) and/or targeting symptoms at the genetics-epigenetic level. Using predictive parameters can help ED personnel identify MTBI patients who are at higher risk before discharging them from the ED; allowing the opportunity to make appropriate referrals and prevent prolonged suffering from debilitating symptoms. This is a clinically relevant and important area for research, as early identification and providing more knowledge about risk factors for MTBI behavioral symptoms soon after the injury can help initiate preemptive treatment; thus, promoting optimal quality of life in the long run.

Implications for Cytokines-Brain Signaling

It is well established that one of the causative factors implicated in cognitive impairment following MTBI is neuro-inflammation, which is likely related to dysregulation of pro-inflammatory cytokines (Huang & Sheng, 2010; McAfoose & Baune, 2009; J. A. Smith et al., 2012). For example, ample evidence shows that when the microglia are activated post-injury, they release pro-inflammatory cytokines (e.g., IL-1, IL-6, and TNF-α), which, in turn, alter neuro-cognitive function. Thus, it is possible that cytokine dysregulation could orchestrate the long-term development and pathogenesis of neuropsychiatric disorders (McAfoose & Baune, 2009). Emerging research suggests that enhancing the environment may improve cognition by restoring cytokine balance, as discussed below.

Interventions to reduce long-term consequences of MTBI. Environmental enhancement (EE) refers to conditions that provide increased social, cognitive, and physical stimulation. Such enhancement could help decrease the negative long-term consequences of MTBI subsequent to neuro-inflammation. EE may also decrease the alterations in brain energy metabolism linked to cognitive impairment. EE has been shown to be correlated with decreased

levels of the pro-inflammatory cytokines IL-1β and TNF-α and enhanced levels of the anti-inflammatory cytokine IL-10 after MTBI (Briones et al., 2013). Also, there is evidence that EE alleviated MTBI-induced cognitive impairment in rodent models (Briones et al., 2013). Thus, these findings demonstrate the potential of EE to attenuate the persistent neuro-inflammatory state, which occurs after MTBI (Briones et al., 2013).

Behavioral therapies implications. Behavioral therapies could be exploited to alleviate stress and other adverse environmental factors that may potentially lead to epigenetic modification within the brain and restoration of brain function. For example, exercise can result in weight loss and help provide resistance to stress-induced chromatin remodeling within the brain. It has been shown that rats that were exposed to greater physical activity prior to stress exposure exhibited resistance to stress-induced chromatin remodeling within the dentate gyrus (Bilang-Bleuel et al., 2005). These findings demonstrate that stress-related learning results in hippocampal chromatin remodeling, which may facilitate behavioral adaptation to environmental changes. This presents an opportunity for the exploration of other behavioral life-style changes that could aid in the prevention or restoration of epigenetic modification (Mathews & Janusek, 2011) and may offer potential to prevent and/or restore cognitive function after MTBI.

Recently, Yehuda et al. (2013) examined the association between methylation of the GR and FKBP5 genes, downstream neuroendocrine measures, cortisol, and NPY, and before and after prolonged exposure to psychotherapy in combat veterans with PTSD (N=8). The purpose was to determine if cytosine methylation in promoter regions of the glucocorticoid-related NR3C1 and FKBP51 genes would predict or correlate with treatment (prolonged exposure psychotherapy) outcome in these patients. These results denote that specific genes can be correlated with prognosis and symptom state. Although these preliminary results require

replication and validation, they support research indicating that some glucocorticoid-related genes are subject to environmental regulation throughout lifespan, and also that psychotherapy treatment may alter epigenetic state through environmental regulation. This is the first longitudinal study of an epigenetic alteration in association with behavioral treatment outcomes. This study represents an important initial step in establishing relevant molecular markers for PTSD therapies (Yehuda et al., 2013), and perhaps injury-related traumatic events that results in MTBI and risk for PTSD post-injury (Yehuda et al., 2013).

Several symptoms (e.g., pain, sleep disruption, and fatigue) can result from the persistent release of cytokines as a response to inflammation; thus specific treatments aimed to block cytokine production may have a direct effect on symptoms relief. Furthermore, the model of cytokine-induced depression provides valuable insight into the relationship between cytokines and depression (Dantzer, 2009). Clinicians may explore the implications of sickness behavior related to depression and specific disease-related symptoms. For example, nurses could benefit from increased awareness and understanding of the relationship between pro-inflammatory cytokines and sickness behaviors. Enhanced knowledge in this arena will aid nurses in assessing and identifying vulnerable patients at risk for these sickness behavior symptoms.

Future Research

Collectively, the results from this study provide compelling impetus for further exploration of behavioral symptom clusters post-MTBI using genetic and PNI paradigms. Findings that suggest symptom clusters participate directly or indirectly in the symptomatology of functional cognitive impairment in trauma patients is fascinating and worth further investigation. Future investigation of genetic variants could provide information for the prediction of symptoms as early as possible in MTBI patients; specifically, somatization and

anxiety. As such, this study enhanced the knowledge regarding relationships among genetic variants, symptom clusters, and functional outcomes post MTBI. Yet, given that many of the findings in the current study were trending toward significance, a larger study is needed to determine if there are additional statistically significant differences in cognitive outcomes, specifically, verbal learning. A well-powered study may reveal significant findings regarding differences among groups based on the six different SNP genotypes evaluated in this study (i.e., rs1800497 (ANKK1), rs1799971 (OPRM1), rs279836 (GABRA2), rs279845 (GABRA2), rs279871 (GABRA2), and rs4680 (COMT). Additionally, future studies could benefit from use of additional and more comprehensive symptom measurement instruments and a longitudinal design which evaluates patients beyond six months. As well, the addition of reliable measures for each symptom (fatigue, depression, and poor sleep) could yield more favorable results.

Second, it has been long emphasized that longitudinal research regarding post-discharge cognitive impairment in MTBI patients is needed, as it is possible that persistent intense behavioral symptoms sustain cognitive and functional outcomes in the absence of long-term structural damage (Bernstein, 1999). These studies will help inform the development of the most appropriate treatment approaches for MTBI patients with persistent intense symptoms and poor cognitive and functional outcomes.

Following the aims of the TRACK-TBI initiative, this current secondary analysis identified symptom clusters that account for variability in cognitive and functional outcomes post-MTBI. The above-mentioned clinical implications are suggestive of the need for more future prospective studies of symptom management designed to identify components of specific collaborative multidisciplinary innovative-therapeutic interventions that contribute to symptom reduction and improvement of cognitive and functional outcomes. Future research would then

call for further investigation of the prevalence of cognitive impairments after the reduction or elimination of symptoms. Also, the results can open the venue for more research in specific areas; studies of genetic, epigenetic, neurobiological and inflammatory mechanisms underlying MTBI; as well as intervention studies that incorporate PNI (mind-body) framework.

Future Genetic Studies

There is increasing knowledge of gene-to-brain communication and the complex ways in which genes regulate brain function and behavior. Yet, there is a need to increase such evidence in human paradigms for translation to clinical practice. Results from this study revealed that the symptom experience negatively affects MTBI patients. Further, results suggest specific pre-existing genetic variants (i.e., ANKK) predispose certain individuals to more persistent behavioral symptoms post-injury (i.e., anxiety and somatization). Determining the extent to which genetic variants contribute to the symptomatology of more intense behavioral symptoms in MTBI patients can result in novel biomarkers to predict behavioral symptoms as early as possible. The identification of these genetic variants may shed light on viable targets to predict distinct sets of behavioral symptoms. Such knowledge may eventually help in genetic-targeted intervention tailored for greater treatment response and tolerability, and improvement of resiliency against developing inflammatory cytokine-associated behavioral symptoms.

Future Epigenetic Studies

Environmental exposures have been shown to affect the activity of the methylation machinery, leading to behavioral and mental pathologies. Future epigenetic studies can provide key insight into the impact of environment-gene interaction on behavior and vulnerability to poor health over the human lifespan (Mathews & Janusek, 2011). Since evidence shows that epigenetic modifications are reversible; the supportive evidence addressed earlier opens a

window for a variety of novel epigenetic-based interventions that could be implemented at periods of biological vulnerability (i.e., post-trauma) to prevent the harmful effects of stress and reduce incidences of intense behavioral symptoms post MTBI.

Individuals who suffer traumatic brain injury are at risk for post-traumatic stress disorder (PTSD). Recently, traumatic events have been found to induce epigenetic modifications for genes that encode immuno-regulatory proteins in individuals with PTSD (Segman et al., 2005). Evidence reveals that for PTSD patients, the experience of a traumatic event triggers downstream alterations in immune function by decreasing methylation of immune-related genes (Uddin et al., 2010). These findings demonstrate the capacity of a traumatic event to trigger long-lasting epigenetic-induced alterations (i.e., DNA methylation) in immune function, possibly through brain-immune interactions (Uddin et al., 2010). Although currently there is little evaluation of stress-related epigenetic modification in trauma survivors, the findings in individuals with PTSD provide preliminary evidence suggesting this possibility (Uddin et al., 2010). Investigation of these biomarkers (DNA methylation and pro-inflammatory cytokines) may provide valuable information for understanding the link between behavioral symptoms and cognitive/functional outcomes in MTBI patients. Such understanding is a critical first step that will improve risk assessment and ultimately lead to prevention and/or better management of trauma-associated behavioral symptoms. Moreover, future studies that enhance the knowledge regarding the role of epigenetic modification (i.e., DNA methylation) has potential to lead to predicting at discharge, which MTBI patients are at risk for prolonged behavioral symptoms. These studies can guide the future development of personalized epigenetic-based approaches to identify and treat trauma patients to promote quality of life, and reduce symptom intensity and duration.

Future Neurobiological Mechanisms and Pro-Inflammatory Cytokines Studies

The results from this secondary analysis study have increased knowledge of the importance of body-to-brain communication, but there is a need to further increase such evidence in human paradigms for translation to clinical practice. Furthermore, the neurobiological mechanisms underlying the behavioral effects of pro-inflammatory cytokines have not been investigated in a manner that correlates to a given behavioral effect of a cytokine on a well-defined area of the brain. For this reason, micro-pharmacology experiments that target inflammatory mediators in specific brain areas must be implemented to define cause-effect relationships (Dantzer et al., 2008). The identification of the intracellular association between inflammation and behavioral symptoms (i.e., depression) will provide valuable targets for the development of new antidepressant drugs, if the activation of brain pro-inflammatory cytokine signaling is proven to represent the final common pathway for the various conditions that lead to depression (Dantzer et al., 2008).

With respect to MTBI, low-grade systemic inflammation might contribute to the development of psychological long-term morbidities in patients with MTBI. Yet, studies focused on the systemic inflammation following MTBI are limited. Findings from animal models of MTBI do show that systemic inflammatory processes are activated post-MTBI; specifically circulating IL-6 levels are increased in rodent models of MTBI (Holmin et al., 1997; Shohami et al., 1994; S. H. Yang et al., 2013). Similarly, Yang et al. (2013) found serum cytokines interleukin-6 and keratinocyte-derived chemokine to be significantly increased within 90 minutes after MTBI in a murine model. In a rat model of closed head injury, Shohami et al. (1994) found elevated levels of IL-6 following injury, and suggested that rapid production of IL-6 following closed head injury is a local inflammatory response of brain tissue to the primary insult.

Yet, it still remains unknown whether the systemic inflammatory process could be used as predictive markers for psychological outcomes after MTBI. Thus, it presents a fruitful area of research, in view of the fact that it is well established that systemic inflammatory processes activate the neuroendocrine HPA axis (Murray et al., 2013) and were found to result in chronic stress linked to anxiety and depression (Mustafa, 2013). Also, systemic inflammation results in an increase in indoleamine 2, 3-dioxy-genase (IDO) expression (Yamada et al., 2009), which leads to an overproduction of kynurenic and quinolinic acids, and subsequent reduction of serotonin within the brain. Lower serotonin is established to result in depression and other psychological and behavioral problems (Capuron & Miller, 2011; Haroon et al., 2012; A. H. Miller et al., 2009). Therefore, investigation of acute circulating inflammatory marker responses is a fruitful area which may provide insight into the role of psycho-neuro-immunological processes in MTBI patients. Additionally, standardization of appropriate markers of inflammation and a systematic approach for investigation of the risk factors will improve outcomes and quality of life. Furthermore, it is possible to develop clinical trials aimed at blocking cytokine production or action, attenuating the production of second messengers or deactivating glial cells and halting excessive quantities of pro-inflammatory cytokines. More research is needed in this area to enhance its innovative potential and avoid the duplication of efforts likely to occur because of the diversity of pathological conditions that lead to non-specific clinical signs of sickness behavior (Dantzer & Kelley, 2007).

Taken together, future studies are warranted to illuminate the precise effects of certain cytokines and explore targets for interventions and therapies in the MTBI population. For example, targeting of inflammatory pathways for depression treatments post-MTBI can provide valuable starting points for the identification of vulnerable subgroups of depressed patients who

may be most appropriate for immune-targeted therapies. Such studies can lead to the development of feasible and effective interventions to identify patients at risk for sickness behaviors; thus, preventing or decreasing the negative effects of cytokine-induced inflammatory responses, which reduce quality of life post-MTBI.

Intervention Studies

Findings from this secondary data analysis revealed that somatization and anxiety were common symptoms after MTBI. Further, a significant relationship between SNP rs1800497 ANKK1 and anxiety and somatization was revealed; suggesting that this genetic variant predisposed these individuals to these particular behavioral symptoms. Therefore, perhaps screening MTBI patients for genetic variants linked to risk of these symptoms could lead to early targeting of treatment and improvement in recovery.

Also, since symptom clusters predicted poor function and cognitive recovery, future intervention studies may want to use EE to treat depression, stress, and anxiety at the same time. The successful treatment of those symptom clusters may improve cognitive and functional outcomes and subsequently quality of life for those most affected (i.e., the "miserable minority"). Also, the consideration of controlling for previous history of behavioral symptoms and prior stressful life events could yield better results. Early implementation of treatment modalities for the "miserable minority" could improve or even prevent long-term cognitive impairment. Future studies are needed to evaluate novel interventions that target symptom clusters, so that such treatment could be incorporated into cognitive and functional rehabilitation programs for those who suffer MTBI. Promising interventions include cognitive behavioral therapy or mindfulness-based stress reduction (MBSR).

Conclusion

For a sizeable subgroup of MTBI patients, recovery is protracted, and prediction of who will experience protracted recovery was explored. Findings from this secondary analysis study attempted to increase the understanding of the role of depressive mood, fatigue, and poor sleep as a symptom cluster, on cognitive and functional recovery. This enhanced knowledge can guide future studies that may pursue the following: (1) evaluate use of behavioral symptom clusters as risk factors for poor cognitive/function outcomes and poor quality of life post-MTBI, and (2) evaluate the usefulness of biomarkers (genetic variants, epigenetic modifications and pro-inflammatory cytokines) as predictors for the risk of more intense and enduring behavioral symptoms in MTBI patients. Ultimately, the knowledge from this secondary analysis can be used a starting point to build on and develop clinical strategies for earlier identification (i.e., at discharge) of MTBI patients who are at risk of such behavioral symptoms. This crucial knowledge can positively impact the care of MTBI patients, as it will stimulate the development and implementation of specific symptom profiles to be used clinically to stratify risk for poor recovery and to identify those who may require earlier and more intense intervention to promote better quality of life.

APPENDIX A

DATA COLLECTION TOOLS

The Brief Symptom Inventory 18

The Brief Symptom Inventory 18 (BSI 18) is designed with reliability in mind. The BSI 18 assessment gathers patient-reported data to help measure psychological distress and psychiatric disorders in medical and community populations. As the latest in an integrated series of test instruments that include the SCL-90-R®, BSI® (53 questions), and DPRS® instruments, the BSI 18 test offers a more effective, easy-to-administer tool to help support clinical decision-making and monitor progress throughout treatment.

How To Use This Test: Quickly Measure and Monitor Psychological Distress in Oncology and Primary Care Patients. Psychologists, psychiatrists, physicians, nurses and other health care professionals can use the BSI 18 assessment to help:

- Assess patients at intake for psychological problems
- Measure patient progress during and after treatment to monitor change
- Support managed care decisions
- Provide outcomes measurement for treatment programs

Key Features

- The BSI 18 test can be completed in approximately 4 minutes. Designed to be brief and easy to administer, the BSI 18 assessment is well-suited for helping measure symptom change throughout treatment.
- The test helps measure three primary symptom dimensions and is designed to provide an overview of a patients symptoms and their intensity at a specific point in time.
- Dimension and global scores form the BSI 18 test correlate highly (i.e., > .90) with analogous score from the SCL-90-R test based on a large community population.

BSI®18 Scales

- **SOM**—Somatization
- **DEP**—Depression
- **ANX**—Anxiety

Global Severity Index (GSI) Designed to help measure overall psychological distress level

Psychometric Information: **Adult community norms**: The adult community norms are based on 1,122 individuals—605 males and 517 females. **Oncology Norms:** The oncology norms are based on 1,543 individuals—802 males and 741 females.Shortened form of the BSI® instrument that provides a highly sensitive assessment of psychological factors

Ages / Grades	18 Years and Older Reading Level: 6th Grade
Administration Setting	18, 5-Point Rating Scale
Qualification	Level B

PTSD Checklist – Civilian Version (PCL-C)

PTSD CheckList – Civilian Version (PCL-C)

Client's Name: _____

Instruction to patient: Below is a list of problems and complaints that veterans sometimes have in response to stressful life experiences. Please read each one carefully, put an "X" in the box to indicate how much you have been bothered by that problem *in the last month*.

No.	Response	Not at all (1)	A little bit (2)	Moderately (3)	Quite a bit (4)	Extremely (5)
1.	Repeated, disturbing *memories, thoughts, or images* of a stressful experience from the past?					
2.	Repeated, disturbing *dreams* of a stressful experience from the past?					
3.	Suddenly *acting* or *feeling* as if a stressful experience *were happening* again (as if you were reliving it)?					
4.	Feeling *very upset* when *something reminded* you of a stressful experience from the past?					
5.	Having *physical reactions* (e.g., heart pounding, trouble breathing, or sweating) when *something reminded* you of a stressful experience from the past?					
6.	Avoid *thinking about* or *talking about* a stressful experience from the past or avoid *having feelings* related to it?					
7.	Avoid *activities* or *situations* because they *remind you* of a stressful experience from the past?					
8.	Trouble *remembering important parts* of a stressful experience from the past?					
9.	Loss of *interest in things that you used to enjoy?*					
10.	Feeling *distant* or *cut* off from other people?					
11.	Feeling *emotionally numb* or being unable to have loving feelings for those close to you?					
12.	Feeling as if your *future* will somehow be *cut short*?					
13.	Trouble *falling* or *staying asleep*?					
14.	Feeling *irritable* or having *angry outbursts*?					
15.	Having *difficulty concentrating*?					
16.	Being *"super alert"* or watchful on guard?					
17.	Feeling *jumpy* or easily startled?					

PCL-M for DSM-IV (11/1/94) Weathers, Litz, Huska, & Keane National Center for PTSD - Behavioral Science Division

Rivermead Post-Concussion Symptoms Questionnaire (RPQ)

Rivermead Post Concussion Symptoms Questionnaire

Modified (Rpq-3 And Rpq-13)[42] Printed With Permission: Modified Scoring System From Eyres 2005 [28]

Name: Date:

After a head injury or accident some people experience symptoms that can cause worry or nuisance. We would like to know if you now suffer any of the symptoms given below. Because many of these symptoms occur normally, we would like you to compare yourself now with before the accident. For each symptom listed below please circle the number that most closely represents your answer.

0 = not experienced at all
1 = no more of a problem
2 = a mild problem
3 = a moderate problem
4 = a severe problem

Compared with **before** the accident, do you **now** (i.e., over the last 24 hours) suffer from:

	not experienced	no more of a problem	mild problem	moderate problem	severe problem
Headaches	0	1	2	3	4
Feelings of dizziness	0	1	2	3	4
Nausea and/or vomiting	0	1	2	3	4
Noise sensitivity (easily upset by loud noise)	0	1	2	3	4
Sleep disturbance	0	1	2	3	4
Fatigue, tiring more easily	0	1	2	3	4
Being irritable, easily angered	0	1	2	3	4
Feeling depressed or tearful	0	1	2	3	4
Feeling frustrated or impatient	0	1	2	3	4
Forgetfulness, poor memory	0	1	2	3	4
Poor concentration	0	1	2	3	4
Taking longer to think	0	1	2	3	4
Blurred vision	0	1	2	3	4
Light sensitivity (easily upset by bright light)	0	1	2	3	4
Double vision	0	1	2	3	4
Restlessness	0	1	2	3	4
Are you experiencing any other difficulties? Please specify, and rate as above.					
1.	0	1	2	3	4
2.	0	1	2	3	4

Administration only:

RPQ-3 *(total for first three items)*	
RPQ-13 *(total for next 13 items)*	

Cognitive Outcomes

Mental Flexibility assessed by TMT B-A

Trail Making Test (TMT) Parts A & B

Instructions:

Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time the patient as he or she connects the "trail." If the patient makes an error, point it out immediately and allow the patient to correct it. Errors affect the patient's score only in that the correction of errors is included in the completion time for the task. It is unnecessary to continue the test if the patient has not completed both parts after five minutes have elapsed.

Step 1:	Give the patient a copy of the Trail Making Test Part A worksheet and a pen or pencil.
Step 2:	Demonstrate the test to the patient using the sample sheet (Trail Making Part A – *SAMPLE*).
Step 3:	Time the patient as he or she follows the "trail" made by the numbers on the test.
Step 4:	Record the time.
Step 5:	Repeat the procedure for Trail Making Test Part B.

Scoring:

Results for both TMT A and B are reported as the number of seconds required to complete the task; therefore, higher scores reveal greater impairment.

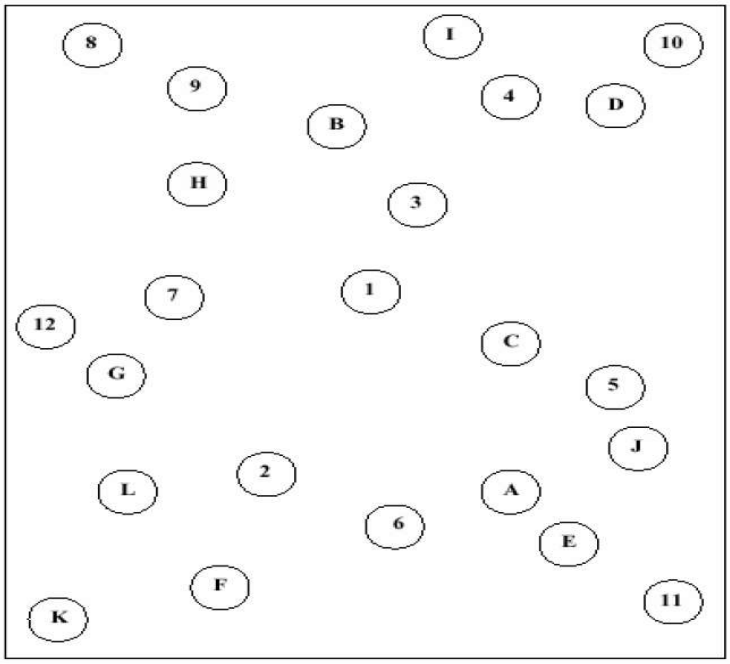
	Average	Deficient	Rule of Thumb
Trail A	29 seconds	> 78 seconds	Most in 90 seconds
Trail B	75 seconds	> 273 seconds	Most in 3 minutes

Sources:

- Corrigan JD, Hinkeldey MS. Relationships between parts A and B of the Trail Making Test. *J Clin Psychol*. 1987;43(4):402–409.
- Gaudino EA, Geisler MW, Squires NK. Construct validity in the Trail Making Test: what makes Part B harder? *J Clin Exp Neuropsychol*. 1995;17(4):529-535.
- Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment*. 4th ed. New York: Oxford University Press; 2004.
- Reitan RM. Validity of the Trail Making test as an indicator of organic brain damage. *Percept Mot Skills*. 1958;8:271-276.

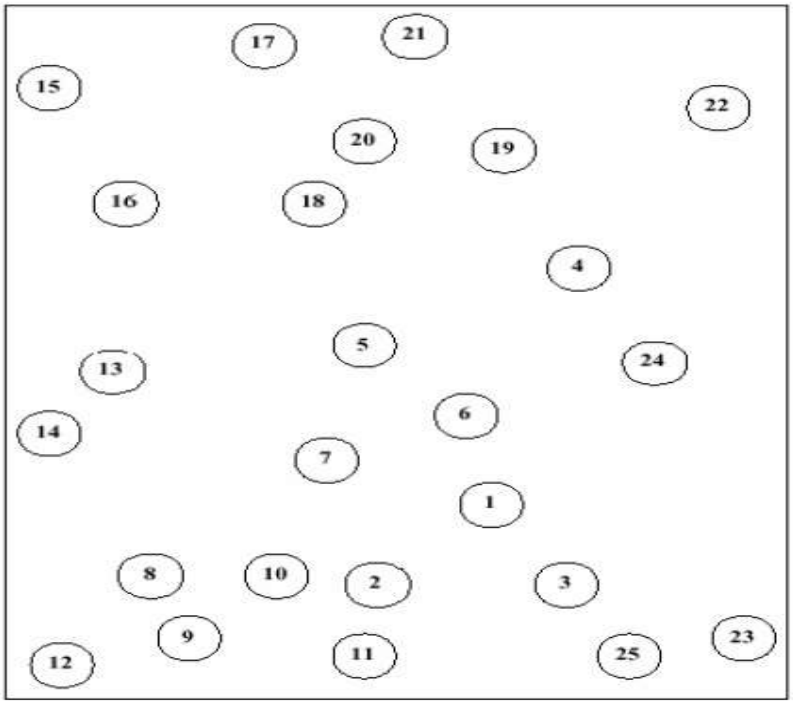
Trail Making Test Part B

Patient's Name: _____ Date: _____



Trail Making Test Part A

Patient's Name: _____ Date: _____



Quality of life

Satisfaction with Life Scale

Scale:

Instructions: Below are five statements that you may agree or disagree with. Using the 1 - 7 scale below, indicate your agreement with each item by placing the appropriate number on the line preceding that item. Please be open and honest in your responding.

- 7 - Strongly agree
- 6 - Agree
- 5 - Slightly agree
- 4 - Neither agree nor disagree
- 3 - Slightly disagree
- 2 - Disagree
- 1 - Strongly disagree

____ In most ways my life is close to my ideal.

____ The conditions of my life are excellent.

____ I am satisfied with my life.

____ So far I have gotten the important things I want in life.

____ If I could live my life over, I would change almost nothing.

Scoring:

Though scoring should be kept continuous (sum up scores on each item), here are some cut-offs to be used as benchmarks.

- 31 - 35 Extremely satisfied
- 26 - 30 Satisfied
- 21 - 25 Slightly satisfied
- 20 Neutral
- 15 - 19 Slightly dissatisfied
- 10 - 14 Dissatisfied
- 5 - 9 Extremely dissatisfied

Functional outcome

Glasgow Outcome Scale Extended (GOSE)

Glasgow Outcome Scale

The Glasgow Outcome Scale (GOS) is a global scale for functional outcome that rates patient status into one of five categories: Dead, Vegetative State, Severe Disability, Moderate Disability or Good Recovery. The Extended GOS (GOSE) provides more detailed categorization into eight categories by subdividing the categories of severe disability, moderate disability and good recovery into a lower and upper category:
Table 1: Extended Glasgow Outcome Scale (GOSE)

1	Death	D
2	Vegetative state	VS
3	Lower severe disability	SD -
4	Upper severe disability	SD +
5	Lower moderate disability	MD -
6	Upper moderate disability	MD +
7	Lower good recovery	GR -
8	Upper good recovery	GR +

Use of the structured interview is recommended to facilitate consistency in ratings.

References:
Jennett B, Bond M: Assessment of outcome after severe brain damage. Lancet 1:480–484, 1975.

Teasdale GM, Pettigrew LE, Wilson JT, Murray G, Jennett B. Analyzing outcome of treatment of severe head injury: A review and update on advancing the use of the Glasgow Outcome Scale. *Journal of Neurotrauma* 1998;15:587-597.

Wilson JTL, Pettigrew LEL, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: Guidelines for Their Use. J Neurotrauma 15(8): 573-85. 1997.

Wilson JT, Slieker FJ, Legrand V, Murray G, Stocchetti N, Maas AI. Observer variation in the assessment of outcome in traumatic brain injury: experience from a multicenter, international randomized clinical trial. Neurosurgery. Jul;61(1):123-8; discussion 128-9. 2007 .

Recommended time for assessment:			
	Basic	Intermediate	Advanced
3 months outcome		X	X
6 months outcome	X	X	X
12 months outcome			X

POST DISCHARGE
STRUCTURED INTERVIEW FOR GOSE

Respondent: ☐ 0 = Patient alone 1 = Relative/friend/caretaker alone 2 = Patient plus relative/friend/caretaker

Conciousness:

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

◯ Yes ◯ No (VS)

Note: anyone who shows the ability to obey even simple commands or utter any word or communicate specifically in any other way is no longer considered to be in vegetative state. Eye movements are not reliable evidence of meaningful responsiveness. Corroborate with nursing staff and/or other caretakers. Confirmation of VS requires full assessment.

Independence at home:

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

◯ Yes ◯ No (VS) **If no: go to 3**

Note: for a NO answer they should be able to look after themselves at home for 24 hours if necessary, though they need not actually look after themselves. Independence includes the ability to plan for and carry out the following activities: getting washed, putting on clean clothes without prompting, preparing food for themselves, dealing with callers and handling minor domestic crises. The person should be able to carry out activities without needing prompting or reminding and should be capable of being left alone overnight.

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

◯ Yes (lower SD) ◯ No (upper SD)

Note: for a NO answer they should be able to look after themselves at home up to eight hours during the day if necessary, though they need not actually look after themselves

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

◯ Yes ◯ No

Independence outside home:

3a. Are they able to shop without assistance?

◯ Yes ◯ No (upper SD)

Note: this includes being able to plan what to buy, take care of money themselves and behave appropriately in public. They need not normally shop, but must be able to do so.

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

◯ Yes ◯ No

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

◯ Yes ◯ No (upper SD)

Note: they may drive or use public transport to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and instruct the driver.

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 6** ◯ No

5b. How restricted are they?

a. Reduced work capacity? ◯ a. (Upper MD)

b. Able to work only in a sheltered workshop or non-competitive job or currently unable to work? ◯ b. (Lower MD)

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

◯ Yes ◯ No

Social and Leisure activities:

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

◯ Yes **If yes, go to 7** ◯ No

Note: they need not have resumed all their previous leisure activities, but should not be prevented by physical or mental impairment. If they have stopped the majority of activities because of loss of interest or motivation, then this is also considered a disability.

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 injury ◯ a. (Lower GR)

b. Participate much less: less than half as often ◯ b. (Upper MD)

c. Unable to participate: rarely, if ever, take part ◯ c. (Lower MD)

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

◯ Yes ◯ No

Family and friendships:

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

◯ Yes ◯ No **If no, go to 8**

Note: typical post-traumatic personality changes are: quick temper, irritability, anxiety, insensitivity to others, mood swings, depression and unreasonable or childish behaviour.

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

a. Occasional - less than weekly ◯ a. (Lower GR)

b. Frequent - once a week or more, but not tolerable ◯ b. (Upper MD)

c. Constant - daily and intolerable ◯ c. (Lower MD)

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

◯ Yes ◯ No

Note: if there were some problems before injury, but these have become markedly worse since the injury then answer yes to question

Return to normal life:

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

◯ Yes (Lower GR) ◯ No (Upper GR)

Note: other typical problems reported after head injury: headaches, dizziness, sensitivity to noise or light, slowness, memory failures and concentration problems.

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?

◯ a. Effects of head injury

◯ b. Effects of illness or injury to another part of the body

◯ c. A mixture of these

Note: extended GOS grades are shown beside responses on the CRF. The overall rating is based on the lowest outcome category indicated.
Areas in which there has been no change with respect to the pre-trauma situation are ignored when the overall rating is made

APPENDIX B

TABLES

Table 1. Study Variables

PRIMARY VARIABLES TO BE USED IN THE ANALYSIS				
Biological	Psychological/Behavioral	Cognitive	Quality of life	Functional
SNPs rs1800497 (ANKK1) rs1799971 (OPRM1), rs279836 (GABRA2), rs279845 (GABRA2), rs279871 (GABRA2), and rs4680 (COMT)	PTSD-PCL	Nonverbal Processing Speed assessed by WAIS-IV	SWLS	GOSE
	RPQ (Sleep Disturbance, Fatigue, Depression items)	Verbal Learning assessed by CVLT-II		
	BSI-18 (Depression, Anxiety, & Somatization subscales)	Mental Flexibility assessed by TMT B-A		

Note: BSI-18= Brief Symptom Inventory=18, PTSD-PCL= The Post-Traumatic Stress Disorder Checklist Civilian Version, RPQ=The Rivermead Post-Concussion Symptoms Questionnaire, SNP= single-nucleotide polymorphism, GOSE= Global outcomes Glasgow Outcome Scale-Extended score, WAIS-IV= Wechsler Adult Intelligence Scale-IV, CVLT-II= California Verbal Learning Test-II, TMT B-A= the difference score between the Trial Making Test B and TMT A, SWLS= Satisfaction with -Life Scale

Table 2. Tools and Data Collection Time Points

	T1: 3-month	T2: six-month
Background information		
Demographic Information & health assessment	X	
Age & Gender	X	
Biological Variables		
SNPs rs1800497 (ANKK1) rs1799971 (OPRM1), rs279836 (GABRA2), rs279845 (GABRA2), rs279871 (GABRA2), and rs4680 (COMT)	X	
Psychological/Behavioral Variables		
PTSD-PCL		X
RPQ (Sleep Disturbance, Fatigue, Depression items)		X
BSI-18 (Depression, Anxiety, & Somatization subscales)		X
Cognitive outcomes		
Nonverbal Processing Speed assessed by WAIS-IV		X
Verbal Learning assessed by CVLT-II		X

Table 2 (cont.)

Mental Flexibility assessed by TMT B-A	X
Quality of life	
SWLS	X
Functional outcomes	
GOSE	X

Note: BSI-18= Brief Symptom Inventory=18, PTSD-PCL= The Post-Traumatic Stress Disorder Checklist Civilian Version, RPQ=The Rivermead Post-Concussion Symptoms Questionnaire, SNP= single-nucleotide polymorphism, GOSE= Global outcomes Glasgow Outcome Scale-Extended score, WAIS-IV= Wechsler Adult Intelligence Scale-IV, CVLT-II= California Verbal Learning Test-II, TMT B-A= the difference score between the Trial Making Test B and TMT A, SWLS= Satisfaction with -Life Scale

Table 3. SNPs Information

SNPs Genotype	Official Name and type	Biological and Functional Significance
rs1800497 (ANKK1)	ankyrin repeat and kinase domain containing 1 protein coding	A frequently studied SNP, known as TaqI polymorphism Dopamine D2 receptor reduction DRD2 gene (rs1800497 allele (T)) is associated with neurobiological correlate evidenced by the decreased dopamine binding sites in the brain (Pohjalainen et al., 1998) There is some evidence suggesting that ANKK1 pays a role in comorbid substance use disorder (Blum et al. 1996), diminished reaction to negative action consequences, which may explain an increased risk for addictive behaviors in A1-allele carrier specifically (Klien et al, 2007), and risk for chronic renal disease and high blood pressure (Jiang et al., 2014). Also, traumatic brain injury patients who are carriers of rs1800497(A) alleles recover slower as assessed by memory and attention tests (McAllister et al., 2008)
rs1799971 (OPRM1)	opioid receptor mu 1 protein coding	Carriers of at least one rs1799971(G) allele are more at higher risk for alcoholism than carriers of two A alleles. (van den Wildenberg et al., 2007; Bart et al., 2005; Bergen et al., 1997; Crowley et al., 2003; Miranda et al., 2010); however, in alcoholics treated with naltrexone, rs1799971(G) carriers had better clinical outcome when compared to rs1799971(A: A) carriers (Anton et al., 2008). In regards to influences of opioids consumption (i.e., heroin, codeine or morphine): rs1799971(G) allele carriers consumed more opioids for analgesia but still reported higher pain scores and less nausea and vomiting than rs1799971(A: A) allele carriers during the first 24-hour postoperative period (Ren et al., 2015). A118G Polymorphism of OPRM1 Gene is Associated with Schizophrenia (Sery et al., 2010)
rs279836 (GABRA2) rs279845 (GABRA2)	gamma-aminobutyric acid type A receptor alpha2 protein coding	This SNP in the GABRA2 gene has been linked to Alcoholism (Rangaswamy and Porjesz, 2008; Lind et al, 2008), and has been found to be associated with human cocaine addiction (Dixon et al., 2010). Some research suggests it can be used as a marker for alcoholism (Zintzaras, 2012). Evidence are suggestive that GABRA2 might influence susceptibility to alcohol dependence by modulating the level of neural excitations specifically in carriers of these alleles:rs279871(A) + rs279845(T) + rs279836(A) alleles (Edenberg et al, 2004)

Table 3 (cont.)

rs4680 (COMT)	catechol-O-methyltransferaseprovided protein coding	Associated condition: panic disorder 1 and schizophrenia (Gupta et al., 2009), cocaine dependence (Lohoff at el., 2008), breast cancer (Onay et al., 2008), venous thrombosis (Gellekink et al., 2007). Val alleles have increased COMT activity and lower prefrontal extracellular dopamine compared with those with the Met substitution (Stein et al., 2006). Val158 alleles may be associated with an advantage in the processing of aversive stimuli (warrior strategy). Under stressful situations that cause increased dopamine release, carriers of Val158 alleles may have improved dopaminergic transmission and better performance. Some evidence suggests that Val158 alleles are associated with schizophrenia (Stein et al., 2006) However, Met158 alleles may be associated with an advantage in memory and attention tasks (worrier strategy). Under stressful situations that cause decreased dopamine release, carriers of Met158 alleles may have less efficient neurotransmission and worse performance. Some evidence suggests Met158 alleles are associated with anxiety (Stein et al., 2006)

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VITA

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