Physiological and Psychological Stress Markers in
Concussed Athletes from Injury to Post-Return to Play

by

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Graduate Department of Exercise Science
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ABSTRACT

Introduction: Concussions are a physiologically & psychologically stressful event. Stress markers may provide insight into concussion recovery, but have not been examined. Purpose & Method: To investigate the stress response of concussed athletes compared to controls from injury to post-RTP. Concussed athletes’ Mood states, Perceived Stress, HRV, and Morning & Afternoon Cortisol were assessed at 3 phases of recovery following concussion. Results: Repeated measures ANOVA revealed significant interactions for TMD, Depression, Anger, Confusion, Fatigue, HF norm (rest), LF norm (rest), HF norm (difference between sitting & standing), LF norm (difference between sitting & standing), and LF/HF ratio (difference between sitting & standing). Vigor & Tension demonstrated significant changes over time in the concussed group. Significant difference between the two groups for morning Cortisol levels at phase 3 was revealed. Conclusion: Concussed athletes display elevated levels of stress post-injury. Findings warrant further investigation of stress markers in concussed athletes during recovery.
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CHAPTER 1: INTRODUCTION

Sport concussions are a prominent issue for athletes involved in contact or collision sports; many of those athletes are at risk for concussions (Covassin & Elbin, 2011). Concussions, especially multiple concussions, can lead to severe and prolonged side effects (Henry & Beaumont, 2011). Athletes have a high risk for multiple concussions over their lifespan (Wilberg, Orega, & Solbonov, 2006). Those who sustain a concussion are estimated to be four to six times more likely to sustain a subsequent concussion (Wilberg, Orega, & Solbonov, 2006). Also, a concussed athlete is three times more likely to sustain a second concussion within the same season (Wilberg, Orega, & Solbonov, 2006; Guskiewicz et al., 2000).

Unlike a musculoskeletal injury, a concussion injury is not visible and healing cannot be seen by health professionals, coaches and trainers (Hutchison, Mainwaring, Comper, Richards, & Bisschop, 2009; Covassin & Elbin, 2011). A concussion is a mild traumatic brain injury caused by a traumatic biomechanical force that results in the pathophysiological process that affects the brain (McCrory et al., 2009). It typically results in a temporary alteration in cognitive abilities usually due to functional disturbance rather than structural injury (Covassin & Elbin, 2011). Concussion symptoms resolve in 2 to 10 days in 90% of athletes (Henry & Beaumont, 2011); however, prolonged symptoms can lead to post-concussion syndrome (Jotwani & Harmon, 2010).

Post-concussion syndrome is when a concussed individual continues to experience concussion-like symptoms 3 months after injury (Jotwani & Harmon, 2010; Henry & Beaumont, 2011). In order to avoid post-concussion syndrome, the
recommended treatment following a concussion is cognitive and physical rest (Jotwani & Harmon, 2010; Moore & DuBose 2011). Rest is also recommended in order to avoid physical and mental stress, which could aggravate symptoms (Moore & DuBose, 2011). Many athletes return to play (RTP) prematurely, which can aggravate symptom and/or inhibit recovery (Doolan, Day, Maerlender, Goforth & Brolinson, 2012). Premature RTP places athletes at risk for another concussion during a critical period of recovery (Doolan et al., 2012). A second concussion during this period may result in second impact syndrome, which can increase the chances of experiencing post-concussion syndrome (Doolan et al., 2012; Wilberg, Orega, & Solbonov, 2006; Guskiewicz et al., 2000).

Currently, concussion recovery is based on self-reported symptoms by athletes (Bigler, 2012). Basing recovery on symptoms often allows concussed athletes to RTP prematurely. Concussion symptoms may resolve before the injury is healed (Bigler, 2012) and athletes may also under report symptoms to RTP quicker (Nierengarten, 2011; McCrea et al., 2004). Premature RTP aggravates concussion injury as it is a form of physical stress (Doolan, Day, Maerlender, Goforth & Brolinson, 2012). Aggravating an injury to the brain can cause immediate and prolonged consequences that will affect the athletes’ career and life. Athletes with disrupted healing may experience slower reaction time, fogginess and disorientation, which will all affect their ability to play sports at a competitive level (Jotwani & Harmon, 2010). In order to preserve physical and cognitive abilities following concussion athletes should not RTP prematurely (Jotwani & Harmon, 2010; Moore & DuBose, 2011). Objective measures for concussions need to be devised in order to preclude premature RTP. Various imaging techniques are being examined for effectiveness in assessing concussion objectively (Bigler, 2012). However, these methods
may lack clinical and practical application due to their high cost, time consuming nature and limited availability (Dziemianowicz et al., 2012). The creation of clinically applicable markers to objectively measure concussion is needed to avoid returning athletes to play prematurely, in order to avoid subsequent injury and stress. Such markers may also provide a better understanding of the psychological and physiological changes occurring in concussed athletes post-injury.

Stress has been displayed to increase injury susceptibility and impair recovery in other athletic injuries (Perna & McDowell, 1995; Galamobos, Terry, Mayle & Locke, 2005). Similarly, stress can affect injury recovery in concussed athletes. Few studies have investigated psychological and physiological stress in concussed athletes. Stress in concussed athlete needs to be examined to gain a better understanding about how it affects concussion injury and to help identify practical objective markers for concussion.

**PURPOSE OF THE STUDY**

The purpose of this study is to investigate how stress is manifest in concussed athletes from injury to return to play (RTP). There have been no studies investigating stress in concussed athletes during the acute phase of injury. Such may illuminate the biochemical, physiological and psychological changes following concussions and can lead to the formation of practical and objective markers in concussion recovery beyond symptom profiles.

The following chapter provides a literature review of the neurometabolic cascade following concussion, an overview of stress and athletic injury literature, and a review of biochemical, physiological and psychological markers of stress. This includes a synopsis
of specific stress markers and how they can be measured and used to practically and objectively mark concussion recovery.
CHAPTER 2: LITERATURE REVIEW

Concussions are often referred to as invisible injuries (Hutchison et al., 2009) as the pathophysiology of the injury and recovery cannot be seen (Giza & Hovda, 2001; Mainwaring et al., 2004). Unlike many other sport injuries, the damage caused by a concussion is not only caused by initial injury, but also from underlying biochemical processes (Giza & Hovda, 2001).

After a concussion, the damage to nervous and brain tissue is caused either by the direct impact or the subsequent metabolic/chemical cascade (Giza & Hovda, 2001; Wilberg, Orega, & Solbonov, 2006). After a direct impact the brain experiences a high energy demand as it tries to repair damaged tissue (Giza & Hovda, 2001). The direct impact can also cause the compression and rupture of blood vessels compromising cerebral blood flow (Len & Neary, 2011; DeWitt & Prough, 2003; Wojtys et al., 1999). The lack of cerebral blood flow reduces glucose and oxygen availability to the brain (Giza & Hovda, 2001; Len & Neary, 2011; Wilberg, Orega, & Solbonov, 2006). The lack of glucose and oxygen makes it difficult to produce energy in the form of ATP (Wilberg, Orega, & Solbonov, 2006).

Additionally, the direct impact causes stretched neurons allowing greater amounts of potassium (K+) ions to leak out of the neuron cell. The high efflux of K+ ions causes the release of excitatory neurotransmitters. This causes the further release of K+ ions. In order to restore the ion gradient homeostasis, the sodium potassium (Na+K+) ATPase requires sufficient energy in the form of ATP; however, during a concussion there are inadequate availability of ATP to meet this demand (Giza & Hovda, 2001; Wilberg,
Orega, & Solbonov, 2006). Hence, the ion gradient is not quickly restored. The efflux of K+ causes the influx of calcium (Ca+) ions into the cell. High amounts of Ca+ ions within a cell causes dysfunctional mitochondrial activity (Wilberg, Orega, & Solbonov, 2006) due to changes in mitochondrial inner membrane permeability and uncoupling of oxidative phosphorylation (Signoretti, Lazzarino, Tavazzi, & Vagnozzi, 2011). This compromises mitochondrial ability to catalyze reduction of oxygen through the electron transport chain, which results in decreased energy production and the release of reactive oxidative species (ROS) (Signoretti et al. 2011). This can eventually lead to the activation of intracellular proteases, which will lead to apoptosis (cell death) (Signoretti et al., 2011; Wilberg, Orega, & Solbonov, 2006).

In an attempt to produce ATP to meet metabolic demands, surrounding tissue will rely on non-oxidative pathways (Wilberg, Orega, & Solbonov, 2006) causing the release of lactate (Giza & Hovda, 2001). Lactate will begin to accumulate as there is insufficient cerebral blood flow to remove it (Giza & Hovda, 2001; Wilberg, Orega, & Solbonov, 2006). The build-up of lactate will compromise cellular function and will result in the decrease of cognitive abilities experienced by those suffering from a concussion (Wilberg, Orega, & Solbonov, 2006).

The compromised cognitive abilities caused by concussions either by direct impact or its metabolic and chemical cascade can last for weeks (McCrea & Powell, 2012). Although athletes’ observable symptoms may be resolved, the underlying metabolic and chemical systems in the brain may not be restored. Simple pathways may be restored, but higher cognitive processes may not be working or restored; therefore,
giving the false appearance of recovery (Bigler, 2012). If metabolic processes have not fully recovered athletes are still at risk (Giza & Hovda, 2001).

The time taken to recover from a concussion injury is highly variable within and between individuals (Bigler, 2012; Griesbach, 2011; Giza & Hovda, 2001). Currently, concussion recovery duration is based on symptom resolution, which is inadequate as symptoms are a poor indicator of recovery since underlying cognitive and physiological processes may not be fully restored, despite the absence of symptoms (Bigler, 2012). Allowing athletes to compete during this vulnerable period can cause the re-emergence of symptoms or compromise the athletes’ ability to fully restore higher cognitive processes (Bigler, 2012; Henry & Beaumont, 2011). Additionally, allowing athletes to RTP during this vulnerable period places them in a position to potentially experience another concussion (Henry & Beaumont, 2011). Another concussion during this period can have dire consequences such as serious temporary or life-long cognitive and motor impairments or even death (Henry & Beaumont, 2011). After an initial concussion, cerebral metabolism is already at its limit; any further injury causing an increase in energy demand or a decrease in energy output can cause irreversible neuron damage (Giza and Hovda, 2009). Recent studies have also indicated that prolonged rest can also be detrimental. Supervised cardiovascular exercise has been displayed to alleviate concussion symptoms associated with cases of post-concussion syndrome (Griesbach, 2011). Also prolonged rest can cause depression and isolation as an athlete feels isolated from their normal activities (Driver & Ede 2009; Hoffmann et al. 2010). Hence it is important to for an athlete not to prematurely to RTP, but also not to prolong rest (Driver & Ede 2009; Griesbach, 2011; Hoffmann et al. 2010).
There are no objective physiological or biochemical markers to successfully assess concussion recovery and prognosis (Bigler, 2012). Studies investigating potential biomarkers, such as S100 proteins, NF kappa B, and neuron specific enolase, are inconclusive and have given contradictory results (Menascu, Brezner, Tshechmer & Rumeny, 2010). Although imaging techniques, such as functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI) or magnetic resonance (MR) spectroscopy, are promising avenues to detect concussions (Bigler, 2012), they lack clinical relevance as they are expensive, time consuming and unavailable to many (Dziemianowicz et al., 2012). These imaging techniques also haven displayed limited diagnostic capabilities in mild traumatic brain injuries (Dziemianowicz et al., 2012). As such, clinicians do not currently have definitive practical methods to assess concussion recovery.

Until metabolic and chemical pathways are restored after a concussion, the athlete’s body and brain are in a state of “stress” (Griesbach, 2011). Seyle (1973) described stress as the response of the body readjusting itself due to unusual demands placed upon it. Essentially, stress is the disruption of psychological and physiological homeostasis or the straining of mental and physical systems due to internal or external changes to an organism (Lin, Lin, Lin, & Huang 2011). An injury such as a concussion can cause a disruption to homeostasis due to the physical damages caused by the direct impact (Griesbach, 2011; Wilberg, Orega, & Solbonov, 2006) and subsequent metabolic/chemical cascade (Giza & Hovda, 2001). The brain following a concussion is not fully recovered until homeostasis is restored and the stress has been removed. A concussion is a form of stress on the brain and body (Griesbach, 2011) and should elicit
the same reaction as other forms of stress. Both physiological and mental stress, such as concussive, will manifest in biochemical, physiological and psychological markers.

Stress causes decreased heart rate variability (HRV), altered cortisol cycling, increased mood disturbance and increased perceived stress (Aubert, Seps & Beckers, 2003; Dickerson & Kemeny 2004; Bolger, DeLongis, Kessler, & Schilling, 1989). HRV is a physiological marker of stress; cortisol is a biochemical markers of stress; mood disturbance and perceived stress are psychological markers of stress (Aubert, Seps & Beckers, 2003; Dickerson & Kemeny, 2004; Bolger et al., 1989). These markers of stress can be used to assess the concussion recovery as continued elevation in stress levels can indicate a lack of homeostasis restoration in concussed athletes (Griesbach, 2011).

**STRESS & INJURY**

For an athlete an injury can be a stressful life event (Evan, Wadey, Hanton & Mitchell, 2012). Although, the basic reaction to stress is similar across all human, there are individual differences in the degree of how one responds to stress (Ellis, Jackson & Boyce, 2006). Certain individuals may be more resilient to stress and exhibit limited or no biological response to varying levels of stress (Ellis, Jackson & Boyce, 2006). Past experiences, genetics, environmental factors and personality traits all influence individual differences in response to stress (Ellis, Jackson & Boyce, 2006). Additionally, training and implementing coping strategies can improve stress resilience. Literature has displayed that coping strategies can help athletes reduce the negative impact acute stress has on their performance (Anshel, 1996). Furthermore physical activity and fitness level has been linked to resilience from physical and mental stress; however, the causality is unclear (Salmon, 2001). Exercise is a form of stress and with repetition loses its negative
effect and produces a tolerance (Salmon, 2001). Through conditioning stress resilience can be developed (Salmon, 2001).

For an athlete, the stress of an injury can vary based on injury severity, isolation, loss of identity, social support, individual versus team sport, and personal factors. Additionally, the level of stress experienced is also influenced by the phase of recovery. Evan, Wadey, Hanton & Mitchell (2012) demonstrated that an athlete experiences varying levels and types of stress at three distinct phases 1) the illness-injury phase (immediately post-injury) 2) the rehabilitation-recovery phase and 3) the return to full activity phase (return to play). Hence, it is important to assess these distinct phases in an athlete recovery when assessing stress levels.

The stress experienced by athletes post-injury is not solely a psychological response, but as well a physiological response to the injury. Hanna-Pladdy et al. (2001) exposed four groups: 1) asymptomatic uninjured; 2) symptomatic uninjured; 3) asymptomatic mild TBI; and 4) symptomatic mild TBI to either a high stress condition or a relaxation condition. Symptomatic mild TBI subjects exposed to high stress conditions displayed increased symptoms, decreased information processing speed, increased heart rate and greater change in skin conductance compared to the other groups. In the relaxation condition the symptomatic mild TBI group was not different from the other groups. This demonstrates that the symptomatic TBI change in measures were not a result of psychological stress experienced due to the injury, but from the physiological stress of the injury.

This study also demonstrates that symptomatic TBI individuals may be capable of performing or displaying normal ranges of physical measures when at rest or when
relaxed; however, when stressed they are unable to do so. This is due to higher cognitive processing in symptomatic TBI individuals being unable to meet the demands of high stress conditions. Therefore, an additional stimulus can help determine if there remains a physiological and/or psychological impairment in concussed athletes. It should be noted that subjects used in the TBI conditions in this study had a “history of TBI” and were not considered to be in the acute phase of their injury (greater than 3 months post-injury). Exposing concussed athletes to high stress conditions, such as exercise or cognitive/mental strain, during the acute phase of injury may be detrimental to their well-being (Griesbach, 2011).

The following section reviews the prominent models of stress and athletic injury. The theories lay the theoretical foundation for this interdisciplinary study of stress factors in sports concussion.

**Theoretical Models of Stress & Injury**

Empirical and theoretical work has established that athletic injuries are stressful events. Sport concussion is one type of athletic injury that has not been examined in terms of the stressful impact it may have on athletes. Current models of stress and athletic injury are based on the general stress literature and research as well as focused empirical study of athletic injuries (Brewer & Cornelius, 2008; Williams & Andersen, 1998). Theoretical models of stress and injury have been developed to explain the relationships between psychological, social and biological factors and their influence over occurrence of injury and recovery. They are reviewed below.

*The Stress and Injury Model (Andersen & Williams, 1988).* Andersen and Williams (1988) developed a multi-component theoretical model of stress factors that
influence the occurrence of injury. The model includes three factors that may influence the stress response experienced by an athlete: history of stressors, personality characteristics and coping resources. These factors increase or decrease the likelihood of injury and according to the revised model refined by the authors ten years later, the influence of these factors is bi-directional (Williams & Andersen, 1998). Previous histories of stressors are often associated with increased likelihood of injury or accidents. Fawkner, McMurray, & Summers (1999) confirmed athletes often have increased stressors the week prior to injury. Even minor daily hassle stressors can contribute to increased injury risk (Williams & Andersen, 1998). The model also displays that personality traits can influence the stress response or stress levels. Positive personality traits such as hardiness can help mediate stress responses whereas negative personality traits can exacerbate stress responses. The model implies those with positive moods had lower stress levels and as a result fewer injuries whereas those with negative moods had higher stress levels and as a result more injuries (Williams & Andersen, 1998). Fawkner (1995) confirmed athletes who experience injury had elevated mood disturbance immediately prior to injury. According to the model, coping resources such as social support, stress management and other psychological coping skills also affect the stress response (Williams & Andersen, 1998). Empirical work revealed that athletes with lower available coping resources had elevated incidences of injury (Hardy et al., 1991; Petrie, 1993). The appraisal of the situation also contributes to the stress response and incidences of injury. For example, an athlete many experience a higher level of stress during the competitive season and as a result has an increased risk of injury. The model suggests that intervention can decrease the stress response, which decreases the likelihood of
injury or re-injury (Williams & Andersen, 1998). Stress management programs, cognitive/physiological training programs have all been shown to reduce injury (Williams & Andersen, 1998).

The model provides a theoretical framework to determine risk factors for injury. It illustrates that elevated stress levels increases injury probability. With concussed athletes, second impact is a serious concern as a second concussion during vulnerable periods of recovery can have detrimental effect. This model implies that decreased levels of stress can reduce chances of re-injury. As such, markers of stress can determine if it is safe for concussed athletes to RTP. This model of stress does not address issues involved with injury recovery and how stress influences recovery timelines post-injury.

Psychological Response to Sports Injury & Rehabilitation Process Integrated Model (Wiese-Bjornstal, Smith, Shaffer & Morrey, 1998). The Psychological Response to sports Injury and Rehabilitation Process Integrated Model (Wiese-Bjornstal et al., 1998) demonstrates that pre-injury and post-injury factors influence the stress response an athletes has to injury. Wiese-Bjornstal et al. (1998) extended the model beyond pre-injury factors and included two post-injury factors: 1) personal factors and 2) situational factors. Personal factors include injury severity, general health status, and demographics variable. Situational factors include social support, type of sport played, and rehabilitation accessibility/availability. Several studies have confirmed that personal and situational factors influence the stress associated with a sports injury (Brewer & Cornelius, 2008). According to Wiese-Bjornstal (1998), these pre-injury and post-injury factors combined, influence the cognitive appraisal of the injury (e.g., the athlete’s appraisal of severity of injury, recovery status and support availability). This cognitive
appraisal elicits an emotional and behavioural response (Brewer & Cornelius, 2008), and this response, in turn, influences recovery outcome.

The Psychological Response to Sports Injury & Rehabilitation Process Integrated Model provides a detailed analysis of the psychological factors influencing athletic injury. The model provides a framework to help improve rehabilitation outcomes as the alteration of personal and situational factors can improve injury recovery outcome (Wiese-Bjornstal et al., 1998). However, the model fails to investigate the biological factors involved in injury recovery and rehabilitation as it only discusses the psychological response.

**Biopsychosocial Model of Sports Injury Rehabilitation (Brewer, Andersen & Van Raalte, 2002).** The Biopsychosocial Model of Sports Injury Rehabilitation model incorporates biological, social, medical and psychological factors. The Brewer et al. (2002) model incorporates the concepts from established models such as those developed by Wiese-Bjornstal et al. (1998) and Williams and Andersen (1998) (Brewer & Cornelius, 2008) and broadens the scope of influence by adding biological factors. The Biopsychosocial has seven components: 1) injury characteristics, 2) sociodemographics factors, 3) biological factors, 4) psychological factors, 5) social/contextual factors, 6) intermediate biopsychological outcomes and sports injury rehabilitation outcomes (Brewer & Cornelius, 2008). Although psychological factors are still the focus of this model, unlike previous models, it includes biological factors. Biological factors are an important component in the recovery process, such as proper nutrition, lack of sleep and immune functioning. Biological characteristics in this model are influenced by injury characteristics such as type and severity of injury, and bidirectional affect psychological
factors such as behaviour and cognition. Biological characteristics directly influence intermediate biopsychological outcomes and thus indirectly influence sports injury rehabilitation outcomes in this model. Sociodemographics factors and social/contextual factors are also included in this model and directly and indirectly influence intermediate biopsychological outcomes and sport injury rehabilitation outcomes.

The Biopsychosocial Model of Sports Injury Rehabilitation by Brewer et al. (2002) provides a comprehensive and in-depth analysis of a multitude of factors influencing athletic injury recovery. It also provides a framework to examine the relationships between these factors and how they influence injury rehabilitation outcomes. The inclusion of biological factors makes it an appropriate model to provide understanding of the psychological and physiological factors influencing stress response due to concussion injury.

**PHYSIOLOGICAL MEASURES OF STRESS**

**Heart Rate Variability.** During periods of stress the body displays physiological changes, including increased respiratory rate, changes to blood pressure, elevated heart rate and decreased heart rate variability. Heart rate variability is a reliable method to assess acute and chronic stress as changes in HRV reflect both physiological and psychological stress levels (Aubert, Seps & Beckers, 2003; Bilchick & Berger, 2006; Gall, Parkhouse & Goodman 2004; Vuksanovic & Gal 2006). Berntson et al. (1997) was critical of the use of HRV as there are shortcomings with its quantification and interpretation. HRV is controlled through a complex process and there are uncertainties associated with its regulation. However, since the Berntson et al. (1997) article many of the concerns regarding HRV have been rectified through more recent studies (Aubert,
Heart rate variability (HRV) is the change in beat-to-beat intervals between heartbeats, therefore the instantaneous change in heart rate (Bilchick & Berger, 2006). HRV is a reflection of the sympathetic and parasympathetic components of the autonomic nervous system (Bilchick & Berger, 2006). The autonomic nervous system is influenced by physiological and psychological stress (Lin et al., 2011). Therefore various types of mental and physical stress can influence HRV (Vuksanovic & Gal, 2006) through the autonomic nervous system. Studies have demonstrated decreases in some measures of HRV in cases of stress (Gall, Parkhouse & Goodman, 2004; Vuksanovic & Gal, 2006). Vuksanovic & Gal (2006) demonstrated a decrease in the High Frequency band of HRV during a stressful arithmetic task condition compared to a resting condition. Tan et al. (2011) demonstrated veterans with post-traumatic stress disorder (PTSD) exhibited decreased HRV compared to veterans without PTSD. Adults with attachment anxiety and increased levels of self-reported distress displayed an inverse relationship High Frequency band in HRV (Maunder, Lancee, Nolan, Hunter, Tannenbaum, 2006).

HRV is considered both a marker of sympathetic and parasympathetic activity, during periods of stress there is an increase in sympathetic activation (Aubert et al., 2003). The increase in sympathetic activation is reflected in the increase in the Low Frequency HRV (Aubert et al., 2003). During periods of stress there may be a decrease in parasympathetic activation, which is reflected in the decrease of High Frequency HRV (Aubert et al., 2003). Parasympathetic activation is dominant when sitting and
sympathetic activation is dominant when standing, which is reflected in the Low Frequency (LF) and High Frequency (HF) bands in HRV (Aubert et al., 2003).

In humans the LF range is between 0.04-0.15Hz, with the central frequency around 0.1Hz and the HF range is between 0.15-0.4Hz, with the central frequency around 0.25Hz (Aubert et al., 2003). The amount of variability or power of the frequency band is expressed in ms$^2$ or normalized units (n.u.). Normalized units minimize the effects of the change in total power when reporting LF and HF values (Aubert et al., 2003). LF/HF ratio can be calculated from the frequency bands and can reflect sympathovagal balance (Gall, Parkhouse, & Goodman, 2004).

There are concerns of the stability of HRV as few studies have investigated the stability of HRV over short durations (under 10 minutes) (Tarkiainen et al, 2005). Tarkiainen et al. (2005) investigated measures of HRV over short durations and demonstrated that most measures of HRV were stable with the exception of the standard deviation of all NN intervals (SDNN). The study indicated measures within the frequency domain were stable through repeated 5 minute interval measures (Tarkiainen et al, 2005).

Studies on HRV have been done in individuals with severe brain injuries. These studies have displayed the extent in HRV decrease is proportional to the injury severity (Gall, Parkhouse & Goodman 2004) and inversely associated with long-term outcomes (La Foutaine, Heffernan, Gossett, Bauman & Meersman, 2009). Rapenne et al. (2001) concluded that HRV is a useful predictor of imminent brain death and the outcome of patients with severe head injury. There was a statistically significant difference in numerous HRV measures (pNN50, rMSSD, natural logarithm of LF, and natural logarithm of HF) in the survivor groups and the group that progressed to brain death.
Other studies have also confirmed the use of HRV to predict outcomes in severe TBI (Gall, Parkhouse & Goodman, 2004).

HRV has not only been investigated in severe TBI, but as well in concussion injuries. Bauman, Meersman, Gossett, and La Fountiane (2011) conducted a study that assessed QT interval variability index (QTVI) in three concussed athletes compared to three matched controls. QTVI is inversely related to HRV and is a non-invasive measure of beat-to-beat fluctuation of the QT interval seen on electrocardiograph (Bauman et al., 2004). Initially within 48 hours of a concussion, athletes had a significantly higher QTVI measure than their matched control group. Within one week the concussed group’s QTVI measure was lower than their initial measure at 48 hours and was at the same level of control group’s QTVI measure. Two weeks post-injury the concussed groups and matched-control groups QTVI levels were not different. This pilot study indicates that QTVI or HRV can potentially help assess recovery in concussed athletes.

Another study by La Foutaine, Heffernan, Gossett, Bauman and Meersman (2009) assessed HRV (LF/HF ratio) and heart rate complexity (ApEn) in 3 concussed athletes and their 3 matched pair control during rest and during isometric hand grip at 48 hours and two weeks post injury. At both time points, during rest and the hand grip task, HRV demonstrated no difference in concussed athletes and the controls. Although not statistically significant concussed athletes exhibited a decrease in HRV during the hand grip task compared to rest at both time points. There was a significant change in heart rate complexity during the hand grip task in concussed athletes at 48 hours compared to their matched controls, as well as a significant difference in concussed athletes’ heart rate.
complexity at two weeks compared to 48 hours. This study had a small sample size making it lack statistical power.

A larger study on HRV and concussed athletes was conducted by Gall, Parkhouse and Goodman (2004). The study included 14 concussed athletes and their 14 matched-controls. The following measures were used to assess HRV: RR (ms), SDRR (ms), LF (ms²), HF (ms²), LF norm, HF norm, LF/HF ratio and total power (ms²). The study indicated that there was no significant HRV difference at rest between concussed athletes and their matched-control at 2 or 7 days post-injury. The concussed athletes’ and matched-controls HRV were assessed while exercising after resolution of symptoms and five days after the first exercise session. Across both tests the concussed group had significant lower mean RR interval, LF (ms²), and HF (ms²) compared to their matched-controls. Even though, the athletes’ HRV was normal at rest two weeks post-injury, the additional stress of exercise resulted in a more marked decrease of HRV. This neuroautonomic cardiovascular dysfunction indicates homeostasis could only be maintained at rest and the body is insufficiently prepared for additional stress of exercise. There is a difference between the two groups in HRV, implying the presence of physiological dysfunction, even after concussed athletes symptoms have disappeared (Gall et al., 2004). Therefore, even after the absence of symptoms the body and brain are still in a phase of recovery post-concussion.

These studies indicate that there is potential in using HRV to assess concussion recovery and determine if athletes are safe to RTP. HRV would be a powerful tool if proven effective as it can easily be tested. Previous studies assessing HRV have small sample sizes and use first time concussed athletes. Previous studies have also not
sufficiently observed HRV during recovery as no more than two time points were analyzed post-concussion. Further studies investigating the use of HRV in concussed athletes should be conducted with larger sample sizes, more time points and participants with varying severity levels and previous concussions status. When studying HRV, there are large individual differences that need to be taken into consideration such as gender, fitness level, diet, chronic stress, coffee consumption, smoking and genetic factors (Young & Leicht, 2011; Wang et al., 2009). The Heart Rate Task force has published normative values from the general population (Table 1).

Table 1: Normal value ranges for HRV

<table>
<thead>
<tr>
<th>Spectral Analysis of Stationary Supine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure</td>
</tr>
<tr>
<td>Total Power</td>
</tr>
<tr>
<td>Low Frequency</td>
</tr>
<tr>
<td>High Frequency</td>
</tr>
<tr>
<td>LF/HF ratio</td>
</tr>
</tbody>
</table>

Studies have displayed that athletes in general have higher resting levels of LF and HF measures due to increased sympathetic and parasympathetic activation compared to sedentary individuals (Aubert et al., 2003).

Previous studies have displayed HRV as a promising tool to assess concussion recovery. More research needs to be conducted as previous studies have limited sample sizes and do not assess HRV at a large range of time points in recovery. With more investigating, HRV can potentially be an instrumental tool in helping concussed athletes RTP safely.
**Cortisol.** Biochemical markers of stress such as hormones, proteins or metabolites may be elevated, inhibited or altered due to acute or chronic stress. The steroid hormone cortisol is secreted and produced by the adrenal glands (Lippi, De Vita, Salvagno, Gelati, Montagnana & Guidi, 2009). Cortisol secretions levels are a marker of both physiological and psychological stress (Dickerson & Kemeny, 2004; Koh & Koh, 2007; Lippi et al., 2009; Tsujita & Morimoto, 1998).

Cortisol is a hormone regulated by the hypothalamic-pituitary-adrenal (HPA) axis (Savaridas, Andrews & Harris, 2004). Similar to the sympathetic nervous system, the HPA helps maintain homeostasis within an organism (Savaridas et al., 2004; Dickerson & Kemeny, 2004). In humans, cortisol has a distinct cycling pattern, closely linked to circadian rhythms (Dahlgren, Kecklund, Theorell, Akerstedt, 2009). Cortisol reaches its peak approximately 30 minutes after awakening and steadily declines throughout the day (Dahlgren et al., 2009). During periods of acute stress, the HPA triggers a pathway that leads to the release of cortisol (Savaridas et al., 2004). Numerous studies have indicated cortisol as a reliable biomarker of psychological, social and physiological stress (Dickerson & Kemeny, 2004).

Cortisol studies have displayed that during periods of acute stress, there is a total rise in cortisol circulation throughout the body (Dickerson & Kemeny, 2004). Social or psychological stress before an examination or presentation has been correlated with increased levels of cortisol (Ng et al., 2003). In cases of individuals with burn injuries, cortisol levels were displayed to be elevated with accordance to the severity of the burn (Coombes & Batstone, 1981). Cortisol has also been used to monitor athletic training (Lippi et al., 2009). Studies have demonstrated cortisol levels can indicate overtraining.
syndrome (Neary, Maibon & McKenzie, 2002) and also recovery from overtraining in athletes (Perna & McDowell, 1995).

Even though in general cortisol levels increase in cases of acute stress, Savardas et al. (2004) demonstrated that after severe brain injury total serum cortisol was not elevated. In cases of severe TBI there was a decrease in plasma cortisol, which can be due to number of factors. During severe TBI patients are usually sedated (Savardas et al., 2004); therefore, the decreased activity of the brain may cause a reduction in cortisol release. Additionally, during severe TBI there may be damage to the CNS, affecting the HPA and its ability to release cortisol (Savardas et al., 2004). Therefore, it is important to understand the type and the severity of injury before using cortisol as an indication of injury.

Previous studies have displayed that the impaired cortisol release is not present in mTBI or concussion cases. During the acute phase of brain injuries, cortisol levels increase in patients with minor to moderate injuries, but decreased in patients with severe injuries (Cernak, Savic, Lazarov, Joksimovic & Markovic, 1999). Cernak et al., (1999) demonstrate a significant increase in cortisol levels including day of injury up till 2 days post-injury in mTBI; whereas cortisol levels initially significantly increased on the same day of injury, then significantly decreased for the first 1-3 days, but significantly increased 5-6 days post-injury in severe TBI. Koiv, Merisalu, Zilmer, Tomberg, & Kaasik (1997) demonstrated both mild-moderate and severe TBI patients had acute increase in plasma cortisol concentrations up to 7 days post-injury. This study also demonstrated that the amount of cortisol increase was correlated to injury severity (Koiv et al., 1997). On day 1 of injury, severe TBI patients who did not survive post-injury had a four-fold mean
increase in cortisol level compared to controls whereas mild-moderate TBI patients and severe TBI patients (who survived) had approximately two-fold mean increase in cortisol levels compared to controls (Koiv et al., 1997). Sojka, Stalnacke, Bjornstig, & Karlsson (2006) demonstrated that approximately 3 hours after mild TBI there was an elevation of serum cortisol compared to 10 hours post-injury. It should be noted that this study did not control for time of day or alcohol consumption, which both influence cortisol levels (Sojka et al., 2006). Based on the findings of these studies during the acute phase of a concussion, similar to other types of mild TBI, cortisol levels should be elevated; however, further research is required.

The continued deviation of normal cortisol in concussion patients can indicate the lack of full recovery. Bay, Sikorskii and Gao (2009) reported patients with post-concussion syndrome had hypo-cortisol levels in a 12 hour profile. Post-concussion syndrome is the prolonged experience of concussion symptoms (3 months post-injury) after mTBI. Therefore decreased levels of cortisol indicate that homeostasis has not been restored and in post-concussion syndrome cases symptoms have not been resolved. Decreased levels of cortisol are a reflection of down regulation of the HPA axis, which is often an indicator of chronic stress (Bay, Sikorskii & Gao, 2009).

Additionally, the disturbance of the cortisol cycling patterns can also be an indication of incomplete recovery in concussion patients. Typically cortisol peaks in the morning and gradually declines throughout the day (Koh & Koh, 2007). A change in this cycle is an indication of disrupted homeostasis and prolonged stress in the body (Koh & Koh, 2007). Athletes displayed altered cycling patterns on days of competition compared to control days, with no peaking of cortisol levels in the morning, but instead a
continuous increase of cortisol levels throughout the day (Iellamo et al., 2003). Stress caused by disruption in sleep cycles can also alter cortisol cycling (Bullock, Cox, Martin & Marino, 2009). Bullock et al. (2009), demonstrated athletes who had disrupted sleep patterns due to travelling to a new time zone exhibited suppressed morning cortisol levels up to 4 days after travel. Concussed athletes often exhibit disturbed sleep patterns post-injury (Jotwani & Harmon, 2010). Therefore those with concussion may experience an alteration in the cortisol cycling patterns.

**PSYCHOLOGICAL MEASURES OF STRESS**

Concussions are different from other physical injuries as they affect the brain. The brain controls psychological, emotional and social factors. Injury to the brain can manifest as psychological, emotional and social stress symptoms. This is demonstrated by common concussion symptoms such as depression and/or irritability, which are forms of mood disturbance (Bigler, 2012). Therefore mood disturbance and perceived stress, both markers for psychosocial stress, might be useful markers for concussions.

**Mood Disturbance.** Mood and emotions are controlled by the limbic structures in the brain, which include the hippocampus, amygdala and prefrontal cortex (Duman & Monteggia, 2006). During periods of stress expression of certain factors are altered within the brain, which would affect function. Expression of factors brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3) and vascular endothelial growth factor (VEGF) are decreased in the limbic regions during stress (Duman & Monteggia, 2006). Changes in the expression of these proteins affect the structures of hippocampal neurons altering their structure and function (Duman & Monteggia, 2006). This alteration has been linked to behavioural despair and depression
Studies have linked the down regulation of BDNF in the brain to mood disorders (Duman & Monteggia, 2006). Mood disturbance is caused by changes in genetic expression, which causes an alteration to the limbic structures (Duman & Monteggia, 2006). Since, stress causes the change in expression of BDNF, NGF, NT-3 and VEGF, it essentially causes mood disturbance.

Stress caused by physical injuries can cause negative mood states in individuals (Bolger et al., 1989). Traumatic injuries can elicit a variety of emotional responses such as anxiety, depression or post-traumatic stress disorder (Mason, Turpin, Woods, Wardrope & Rowlands, 2006). There is a correlation between injury severity and emotional reaction felt by individuals in non-athletic populations (Mason et al., 2006). Mason et al., (2006) study discovered a positive correlation between pain scores at 1 month post injury and psychological symptoms at 6 and 18 months post injury. The study also found higher levels of perceived stress were correlated with poorer outcomes at 6 and 18 months (Mason et al., 2006). The 2010 study by vanWilgen, Kaptein, & Brink found athletes experience a similar reaction as they experience higher incidents of mood disturbance during severe injuries compared to milder injuries. The study also found signs of negative mood states were negatively related to functional outcome after 12 months.

Concussed athletes also experience an increase in total mood disturbance after post-injury compared to control groups (Mainwaring et al., 2004). Mainwaring, Hutchison, Bisschop, Comper, & Richards (2010) compared the mood profiles of athletes with concussions and anterior cruciate ligament (ACL) injuries with uninjured controls. Compared to un-injured controls, concussed athletes reported significant changes in Total
Mood Disturbance and Depression, whereas ACL injured athletes reported only significant changes in Depression post-injury. This illustrates that concussed athletes do experience changes in mood and emotional functioning and they seem to differ from other athletic injuries.

Common symptoms associated with concussions, such as depression, irritability, or agitation, are all forms of mood disturbance. Often mood disorders have a deleterious effect on the recovery process and psychological outcome of brain injury patients (Jorge & Robinson, 2003). Although, the mood disturbance following a concussion can be a result of psychological variables such as loss of identity, social isolation, and inability to play, there is an underlying biological base. Studies have displayed mood disruption can last up to a year after a concussion (Bowen, Chamerlain, Tennant, Neuman, & Conner, 1999) similarly metabolic depression in concussed athletes can also last up to a year (Wojtys et al., 1999). Schonberger et al. (2011) in a MRI study linked post-concussion depression with the imbalance of left-right frontal and parietal brain volumes. These findings suggest that there is a physiological link to the arising of symptoms associated with mood disturbance after a concussion. Further investigation of mood disturbance after a concussion is important to better understand its physiological bases.

**Perceived Stress.** Perceived stress is the self-appraised chronic or acute psychological and physical stress experienced by an individual. Studies have demonstrated that even minor daily stressors can affect mood, heart rate, blood pressure, cortisol levels and overall well-being (Bolger, DeLongis, Kessler & Schilling, 1989; Perna & McDowell, 1999; Chatkoff, Maier & Klein, 2010).
Bay, Sikorskii, and Gao (2009) demonstrated that post-concussion syndrome was associated with increased levels of perceived life stress. The study correlated decreased cortisol levels and mood disturbance with increased life stress in individuals with post-concussion syndrome 24 months after injury.

Increased chronic stress prolongs the recovery process (Perna & McDowell, 1995). During the recovery process injured athletes, especially concussed athletes, are in a period of susceptibility to illness and re-injury (Perna & McDowell, 1995; Perna, Antoni, Kumar, Cruess & Sehneiderman, 1998; Perna, Antoni, Baum, Gordon, Sehneiderman, 2003). Perna et al. (1998) demonstrated that decreasing life stress through cognitive behavioural intervention decreased negative mood states and cortisol. In 2003 Perna et al. demonstrated decreased life stress through cognitive behavioural stress management reduced injury and illness amongst athletes. Literature has consistently displayed a relationship between stressful life events and increased injury (Galambos, Terry, Mayle & Locke, 2005). In athletes increased life stressors are precursors for injury (Galambos et al., 2005). Hence, athletes with higher perceived stress levels are more prone to injury. As such, in concussed athletes it is important to monitor their perceived stress levels, as injury during this periods could be detrimental especially if they have not fully recovered from their first injury.

**CONCLUSION**

Few studies have examined stress or stress measures in concussed athletes at various stages of recovery. Since a concussion is a form of stress on the body and mind it is an important issue that needs to explored. Stress markers can potentially fill the void of objective practical markers for concussion. The selected stress markers: HRV, cortisol,
mood states and perceived stress, could potentially help in the evaluation of concussion recovery and prognosis. Each of these stress markers has its own advantage and disadvantage in its potential ability to assess concussion recovery. These markers in combination with each other and the current method of symptomology could provide a more holistic picture of concussion prognosis and provide a better understanding of the underlying homeostasis dysfunction following a concussion.

Each concussion will emerge differently based on individual factors (Henry & Beaumont, 2011). Health status, previous concussions history, gender, severity of injury, mechanism of injury and other factors all influence the manner in which a concussion is manifested within a person (Henry & Beaumont, 2011; Bigler, 2012). The recovery time frame and emerging symptoms will also differ based on personal and injury factors (Henry & Beaumont, 2011). There is no definitive pattern or timeline on how a concussion will manifest; although, there will be a biochemical and metabolic change following a concussion, which will cause a disruption in homeostasis within a concussed individual. This fact will remain consistent for all cases. The appearance of stress markers during a concussion could indicate continued homeostasis disruption, which would indicate recovery is still ongoing. The present study will explore stress markers HRV, cortisol, mood states and perceived stress in concussed athletes. These stress markers may prove to be a multidimensional tool to provide clinically applicable, non-invasive, and objective markers to help concussed athletes RTP safely.

The following chapter will outline the methods to examine the selected stress markers: HRV, cortisol, mood states and perceived stress, in concussed athletes.
compared to matched-controls from injury to RTP. The Method chapter will also outline the purpose, research questions, hypothesis, and procedure of the study.
CHAPTER 3: METHOD

RESEARCH QUESTIONS

The purpose of this study was to investigate how stress is manifest in concussed athletes from injury to RTP. Stress was measured through the following psychological and physiological markers: Heart Rate Variability, morning saliva cortisol, afternoon saliva cortisol, mood disturbance and perceived life stress.

1. How will stress measures in concussed athletes compare to matched-controls from injury to post-RTP?
2. How will stress levels in concussed athletes compare to their baseline stress levels?
3. How will stress measures correlated to the time it takes concussed athletes to Return to Play?
4. How will concussed athletes’ stress measures exhibit even after the absences of symptoms at phase 2 and 3 of recovery?

HYPOTHESES

1. Concussed athletes’ stress measures will be higher than matched controls values from injury until post-RTP.
2. Concussed athletes’ stress measures will be higher than baseline from post-injury until post-RTP.
3. Concussed athletes with higher stress measure levels will take a longer period of time to RTP.
Concussed athletes will continue to have elevated levels of stress measures even after the resolution of symptoms at phase 2 and 3 of recovery.

**Participants**

University of Toronto intercollegiate male and female athletes from varsity teams were the participants for this study: basketball, volleyball, football, ice hockey, lacrosse, rugby and soccer. Baseline measures were obtained from willing members of varsity teams with a significant risk of concussion: hockey, football and soccer. Two separate groups from this pool of varsity athletes were recruited, the concussed and the matched-control group. Upon consent, participants were asked to provide a baseline measure of morning and afternoon saliva cortisol, as well as complete Profile of Mood States (POMS) and Perceived Stress Scale (PSS) questionnaires. A general demographic form, including injury history, age, weight and height, and sleep information was collected after participants were recruited into the study (Appendix D).

*Concussed Group.* After physician diagnosis of concussion, 11 athletes were recruited to complete a series of repeated measures at 3 phases of recovery post-injury.

*Matched-Control Group.* Eleven participants were recruited as a matched-control for the concussed group based on similar sport and academic background as the concussed athletes. They were required to complete the same series of 3 repeated measures at the same times as the concussed athletes.

**Physical Characteristics of Participants**

Table 2 identifies the physical characteristics and concussion history for the concussed and matched control group. An Independent t-test was conducted for differences between groups for height, weight and age. Although the concussed group
was taller, weighed more and were older, there were no significant difference in groups
between height, weight and age. There was a significant differences in number of
concussions experienced by the two groups with the concussed group experiencing on
average 2.18 concussions, including their current concussions compared to the matched
control group experiences an average of 0.64 (p<0.01).

Table 2: Physical Characteristics and concussion history for concussed and matched-
control group

<table>
<thead>
<tr>
<th>Group</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Age (years)</th>
<th>Concussion (#)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Concussed</td>
<td>170.9</td>
<td>10.9</td>
<td>84.8</td>
<td>28.9</td>
</tr>
<tr>
<td>Control</td>
<td>175.9</td>
<td>9.8</td>
<td>75.8</td>
<td>13.7</td>
</tr>
</tbody>
</table>

Table 3 identifies the number of participants from each varsity sports team in the
concussed and matched control group. It also identifies the number of female and male
participants in each group. Table 4 identifies the living situation of participants during
the study period.

Table 3: Varsity Sports Team Represented in Concussed & Matched Control Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Football (M=2)</th>
<th>Rugby (M=2)</th>
<th>Hockey (F=2)</th>
<th>Volleyball (F=1)</th>
<th>Lacrosse (F=2)</th>
<th>Basketball (F=1)</th>
<th>Soccer (F=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concussed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Football (M=2)</td>
<td>Rugby (M=2)</td>
<td>Hockey (F=2)</td>
<td>Volleyball (F=1)</td>
<td>Lacrosse (F=2)</td>
<td>Basketball (F=1)</td>
<td>Soccer (F=1)</td>
</tr>
</tbody>
</table>

M=males
F=females
Table 4: Living Situation of Concussed & Matched Control Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Living with Parents</th>
<th>Residences</th>
<th>Off-Campus Housing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concussed</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Controls</td>
<td>2</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

**RECRUITMENT**

Participants were recruited by the investigator through a presentation about the study to varsity sport teams that are at a high risk of concussions prior to the start of the teams’ athletic season. Each participant was read an information sheet outlining the objectives, procedures and time commitment of the study and then agreed to and signed a consent form prior to the start of the athletic season (Appendix A). Team therapists were required to inform the University of Toronto Concussion Laboratory via email about any concussion occurrences on their team. This information was passed along to the investigator who directly contacted the participants and invited them to participate in the study. Matched-controls were chosen, based on the same sport and similar academic background, and invited to participate in the study.

**PRIVACY AND CONFIDENTIALITY**

Participants were assured anonymity, privacy and confidentiality. In order to maintain confidentiality, participants were assigned a subject number, which was used when collecting, entering and storing data. Information identifying the athlete was only accessible to the student investigator and faculty supervisor.

**RESEARCH DESIGN**
Table 5: Research Study Design for Concussed and Matched Control Groups at three Phases of Recovery

<table>
<thead>
<tr>
<th>Groups</th>
<th>Baseline</th>
<th>Phase 1 72-96 hours post-injury</th>
<th>Phase 2 Pre- RTP (Exercise Clearance)</th>
<th>Phase 3 Post-RTP (1 week after)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concussed</td>
<td>O1</td>
<td>C O2</td>
<td>O3</td>
<td>O4</td>
</tr>
<tr>
<td>Matched-Control</td>
<td>O1</td>
<td>O2</td>
<td>O3</td>
<td>O4</td>
</tr>
</tbody>
</table>

The three phases of recovery assessed are displayed in the research design in Table 5. The phases were determined based on recovery milestones from the University of Toronto Return to Play protocol (Appendix I), which adheres to the McCrory et al., 2009 Return to Play guidelines. The protocol was overseen by the physicians at the David L. Macintosh Sports Medicine Clinic at the University of Toronto.

**Measures**

**Demographics.** Participants completed a demographics questionnaire to assess background information including age, sex, height, weight and previous injury history.

**Heart Rate and Heart Rate Variability.** Heart rate variability (HRV) is the reflection of the autonomic nervous system (Bilchick & Berger, 2006) and a physiological marker of stress (Vuksanovic & Gal, 2006). Stress decreases HRV (Vuksanovic & Gal, 2006). Previous initial studies have displayed success in using HRV to assess concussion (Bauman, Meersman, Gossett, & Fountiane, 2011; Gall, Parkhouse & Goodman, 2004).

HRV was measured at the three phases of recovery after injury in concussed athletes and their matched-controls. During these phases HRV was measured at rest and sitting/standing (baseline measures were not made due to procedural and time constraints).
Morning and Afternoon Cortisol. The study assessed cortisol through saliva samples as it is convenient, non-invasive and accurate (Koh & Koh, 2007). Salivary cortisol was displayed to be accurate reflection of plasma cortisol (Lipp et al., 2009). Saliva samples were collected from participants once at baseline and twice at each of the subsequent phases of recovery. In order to analyze the cycling patterns of cortisol, participants were required to provide saliva samples approximately 30 minutes after awakening and in the afternoon between 2-5pm at baseline and each phase. Cortisol has a distinct cycling pattern in humans reaching its peak approximately 30 minutes after awakening and steadily declines throughout the day (Dahlgren et al., 2009). Stress can disrupt the cortisol circadian patterns (Llompart-Pou et al., 2010; Koh & Koh, 2007). Participants were required to collect morning saliva samples themselves and would come in the laboratory between 2-5pm to give afternoon saliva samples. The afternoon saliva sample timeframe was chosen to minimize diurnal effect.

Mood Disturbance. POMS (Appendix B) was used to assess mood disturbance as it is frequently used to measure the emotional states of injured athletes in research (Brewer, 2001). The shortened version of POMS developed by Grove and Prapavessis (1992) was used, in order to minimize time demands on the participants. This version has been used in previous studies with this population (Mainwaring et al., 2010).

The short version of POMS consists of 40 adjectives organized into seven categories: tension, depression, anger, vigour, fatigue, confusion and self-esteem. Participants rated how they felt right now for each adjective on a five point Likert scale ranging from 0 (not at all) to 4 (extremely). Total mood disturbance was calculated by subtracting positive moods scores from negative mood scores, then adding a constant of
100 (Grove and Prapavessis, 1992). The sub-scales with POMS were also calculated and analysed. The sub-scales of POMS have been assessed for reliability and validity, demonstrating Cronbach’s alphas ranging from 0.66–0.95 with a mean of 0.80 (Mainwaring et al. 2010). The Self-esteem subscale was not evaluated as previous research has displayed it to have inadequate reliability (Grove and Prapavessis, 1992).

POMS scores were measured at baseline and 3 phases of recovery after injury during laboratory visits between 2-5pm.

**Perceived Stress.** Increased perceived stress levels are correlated with delayed recovery and increased likelihood of injury (Perna & McDowell, 1995). To quantify perceived stress, the PSS developed by Cohen 1994 (Cohen, Kessler, & Gordon, 1995) (Appendix C) was administered to participants. The PSS is a well-established tool used to determine chronic stress (Bay, Sikorskii, & Gao, 2009). The PSS questionnaire has been used to assess chronic stress in individuals with post-concussion syndrome (Bay, Sikorskii, & Gao, 2009) and was chosen to investigate concussed athletes during the recovery process to determine if they exhibit increased levels of perceived stress. The PSS is a 14 item Likert-type scale, which retrospectively measures the extent which an individual finds his/her life unpredictable, uncontrollable and overloaded in the last month (Cohen, Kessler, & Gordon, 1995). Higher scores indicate increased stress levels (Cohen, Kessler, & Gordon, 1995). The Cronbach’s alpha for the 14-item PSS versions was determined to be .89 (Mitchell, Crane & Kim, 2008). PSS was measured at baseline and 3 phases of recovery post-injury.
INSTRUMENTS

Saliva Collection Tubes. The Saliva Collection Tubes consists of a large outer tube, with a small insert and snap cap. The saturated oral swab was placed in the small insert after saliva collection.

The speed, convenience and easy self-collection make this method a good choice to collect saliva samples (DeCaro, 2008). Although, this method may under estimate protein, this error can be reduced by having sufficient saliva sample volume (over 0.25 mL) (DeCaro, 2008). Therefore, during collection it was ensured consistent and adequate volume of saliva was collected in order to analyze data (DeCaro, 2008).

Polar Heart Rate Monitors and Associated Software. Polar Heart Rate Monitors were used to assess heart rate variability of participants. Polar Precision Performance Program software and Kubious software were used to upload, analyze and store data.

PROCEDURE

Before the start of the sports season, an advisory meeting was held with the head therapist of the varsity teams to outline the study’s objectives and procedures. The procedure of reporting injuries was reviewed at this time. Therapists were reminded about the study through emails and personal visit to the clinic by the investigator throughout the season. Additionally, before the start of the season an overview about the study was given to student athletes explaining its objectives, procedures and time commitment. Athletes were then given information to read and consent forms to sign.

After consent, participants were required to provide a baseline afternoon saliva cortisol, and complete both PSS and POMS. After injury the concussed athletes and their
matched-control were measured at 3 subsequent phases of recovery: 1) 72-96 hours post-injury, 2) Pre-RTP (exercise clearance), and 3) Post-RTP (one week after RTP clearance). Phase 1 was chosen as symptoms typically are at their peak 72-96 hours post-injury; therefore it is assumed stress levels were also at their peak during this time. Phase 2 was when the athlete was approved to participate in exercise due to resolution of symptoms, but had not returned to play yet. Stress levels were assessed after symptoms have been resolved to see if stress levels remain elevated. Phase 3 was used to assess the stress levels after returning to normal activities. It was used to evaluate if stress levels were still elevated even if symptoms had resolved and athletes were engaged in physical contact sport. Evan et al. (2012) also demonstrated that an athlete experiences varying levels and types of stress at these three phases of recovery, hence making it important to assess these specific phases.

At each subsequent phase after injury, participants were required to visit the laboratory for collection of 1) saliva sample, 2) measure HRV at rest and during sitting/standing 3) PSS & 4) POMS. At each phase participants were required to collect a saliva sample after 30 minutes of awakening by themselves.

**SALIVA ANALYSIS**

Participants were asked not to consume any food or drinks approximately one hour prior to saliva collections. In order to collect morning saliva samples, participants were required to collect a saliva sample by themselves 30 minutes after awakening the day of each phase of recovery. Participants were also required to visit the laboratory between 2 pm and 5 pm at each phase. During these periods another saliva sample was collected for afternoon cortisol. Saliva samples were collected using saliva collection
tubes and were frozen in a -20°C freezer until analysis. Samples were analyzed by a technician using Salimetrics salivary cortisol assay kits (Steps in Appendix H). All samples were analyzed twice and the mean value was used for analysis.

**Heart Rate Variability Analysis**

HRV data for participants were gathered over a 20-25 minute time period during laboratory visits at each phase post-injury. HRV was recorded using Polar heart rate monitors. The chest straps for the Polar heart rate monitors were placed on participants after arriving to the lab. Data collection would then begin. HRV would be monitored during completion of the questionnaires and a 5 minute resting period. HRV was recorded as participants stood and remained standing for 5 minutes. Data were continuously collected as participants gave their saliva samples.

Polar Precision Performance Program software and Kubios HRV (Biosignal Analysis and Medical Imaging Group, Kuopio, Finland) was used to upload, analysis and store collected data. HRV was assessed: 1) during rest and 2) during sitting/standing task. Two 5 minute segments were obtained during the completion of the questionnaires and rest period. Statistical analyses were conducted to determine if these segments differed. They were then averaged to obtain a resting HRV period for analysis. HRV during the sitting/standing task was assessed from a single 5 minute interval during standing. Fast Fourier Transform (FFT) Frequency domain measures were used to assess HRV including: LF, HF, LF/HF ratio and total power. LF is a marker of mainly sympathetic activity and HF is a marker of parasympathetic activity (Gall, Parkhouse, & Goodman, 2004). LF/HF ratio was calculated and used as an indicator of sympathovagal balance (Gall, Parkhouse, & Goodman, 2004). Total power reflects the overall variability of the
signal balance (Gall, Parkhouse, & Goodman, 2004). The minimum duration needed to assess the frequency domain of HRV is 50 seconds; however, the recommended duration is between 5-10 minutes (Aubert et al., 2003). Therefore the frequency domain was the most appropriate for this study as it allows for shorter readings and discriminates between the activities of the sympathetic and parasympathetic nervous system (Aubert et al., 2003). All data collection and analysis were performed in accordance to the recommendation by the Task for Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology (Heart Rate Variability Task Force, 1996).

**Procedure Timeline**

![Timeline](image)

Figure 1: Timeline for each data collection session (total time approximately 25 minutes)

**Data Analysis**

SPSS 20 was used to analyze all the data. Descriptive statistics (mean standard deviations, etc.) were calculated for all the variables at each phase. Differences between each of the variables at each phase in each group were examined with a series of 2 (Group) by 3 (Phase) repeated measures ANOVAs. Pairwise comparisons were used to assess within group differences at different phases. Independent t-tests were calculated to compare group difference at each phase of recovery. A $P$ value of $<0.05$ was considered statistically significant.

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SAMPLE SIZE AND POWER ANALYSIS

Based on similar studies power and sample size estimate calculations were conducted. Calculated power of 0.8 was chosen. Based on the calculated variance and effect size from previous studies, HRV sample size of 12 for each group was determined (Gall, Parkhouse & Goodman, 2004; Bauman, Meersman, Gossett, & La Fountiane, 2011). A power of 0.8 for cortisol in concussed athletes was difficult to discern since no studies have assessed cortisol and concussion. Cernak et al. (1999) examined cortisol in mild to moderate TBI and had an effect size of 0.41 and sample size of 8. Perna & Mcdowell (1995) investigated stress and cortisol recovery in elite athletes and had an effect size of 0.246 and sample of 39. Based on this information it is approximated that 14 subjects are needed for each group. Based on the effect size of 0.273 and sample of 50 from Bay, Sikorskii, & Gao (2009), a sample size of 12 is needed to assess PSS. Based on the partial eta square from Mainwaring et al. (2010) it is estimated that 4 participants for each group is needed to assess mood disturbance. Therefore the aim for this study was to sample a minimum of 15 participants for each group.
CHAPTER 4: RESULTS

The purpose of this study was to investigate the stress response of concussed athletes post-injury until post-RTP. Four hypotheses were examined:

1. Concussed athletes’ stress measures will be higher than matched controls from injury until post-RTP.

2. Concussed athletes’ stress measures will be higher than baseline post-injury until post-RTP.

3. Concussed athletes with higher stress measure levels will take a longer period of time to RTP.

4. Concussed athletes will continue to have elevated levels of stress measures even after the resolution of symptoms at phase 2 and 3 of recovery.

A concussed group and a matched-control group consisting of 11 athletes were recruited from the University of Toronto varsity level teams. Baseline measures were only obtained for teams with high incidence of concussion; however, many of the concussed athletes were not on these specific teams. Additionally, some of the athletes on baselined teams were absent during the period when baseline measures were obtained. Consequently, of a total 22 possible baseline assessments only 2 concussed and 4 matched control baselines were obtained.

In this study, concussed athletes returned to play an average of 15.5 ± 6.7 days post-injury with a range of 10-31 days. The concussed group was assessed at three phases: 1) within one week of injury (4.7 ± 1.8 days post-injury); 2) after return to exercise (18.1 ± 6.8 days post-injury); and 3) approximately one week after RTP (25.6 ±
6.8 days post-injury). The concussed athletes’ corresponding matched-control was assessed within the same week for each phase of recovery. Note that these phases were not assessed at even intervals of time. During these sessions HRV, POMS, PSS and afternoon cortisol was collected. The following morning participants were asked to collect morning cortisol by themselves to assess if cortisol levels were cycling normally. Information about the sleep was collected using a sleep scale (see Appendix G for analysis).

**EVALUATION OF HYPOTHESIS 1: CONCUSSED ATHLETES’ STRESS MEASURES WILL BE HIGHER THAN MATCHED CONTROLS FROM INJURY UNTIL POST-RTP**

In order to evaluate hypothesis 1, four separate sub-hypotheses were tested, one for each specific stress measure:

1. Total Mood Disturbance, as measured by the POMS, for concussed athletes will be higher than matched controls from injury until post-RTP.
2. Perceived stress, as measured by the Perceived Stress Scale, for concussed athletes will be higher than matched controls from injury until post-RTP.
3. HRV, as measured by the frequency domain, for concussed athletes will show elevated stress levels from injury until post-RTP.
4. Cortisol both AM and PM levels for concussed athletes will be higher than matched controls from injury until post-RTP.

**HA1a: Total Mood Disturbance, as measured by the POMS, for concussed athletes will be higher than matched controls from injury until post-RTP.** Total Mood Disturbance and the subscales of POMS were calculated for each group at each
phase. Figures 2-8 presents findings graphically. Table 6 displays the calculated mean score and standard error for each group over the three phases of recovery.

*Table 6: Mean score and standard error for POMS subscales and Total Mood Disturbance at three phases of recovery for 11 concussed and 11 matched control subjects.*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concussed</td>
<td>Control</td>
<td>Concussed</td>
</tr>
<tr>
<td>Depression</td>
<td>5.0 ± 1.1</td>
<td>1.2 ± 0.5</td>
<td>2.5 ± 1.0</td>
</tr>
<tr>
<td>Anger</td>
<td>3.6 ± 1.1</td>
<td>0.8 ± 0.4</td>
<td>3.2 ± 1.4</td>
</tr>
<tr>
<td>Vigor</td>
<td>4.6 ± 1.5</td>
<td>8 ± 1.5</td>
<td>8.8 ± 1.7</td>
</tr>
<tr>
<td>Confusion</td>
<td>4.8 ± 0.9</td>
<td>2.5 ± 0.6</td>
<td>2.4 ± 0.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.1 ± 0.8</td>
<td>5.3 ± 0.8</td>
<td>3.4 ± 0.8</td>
</tr>
<tr>
<td>Tension</td>
<td>5.5 ± 1.2</td>
<td>3.4 ± 1.3</td>
<td>9.9 ± 2.3</td>
</tr>
<tr>
<td>TMD</td>
<td>117.5 ± 4.5</td>
<td>101.8 ± 3.1</td>
<td>102.2 ± 5.6</td>
</tr>
</tbody>
</table>

Note: TMD: Total Mood Disturbance

A 2 (Group) x 3 (Phase) repeated measures ANOVA revealed analysis demonstrated a significant group × phase interaction [F (2, 40) = 9.143), p=0.001, \( \eta^2 = 0.314 \)] in Total Mood Disturbance scores. Pairwise comparisons demonstrated a significant difference (p=0.001) between phase 1 & 3 and significant difference (p=0.019) between phase 2 & 3 in the concussed group. Pairwise comparisons demonstrated no significant difference in the matched-control group between phases. Independent t-tests determined significant difference between the two groups at phase 1 (p=0.009) and 3 (p=0.012). Figure 2 presents these findings.
A 2 (Group) x 3 (Phase) repeated measures ANOVA revealed a significant group × phase interaction \[ F (2, 40) = 6.601, p=0.003, \eta_p^2 = 0.248 \] in Depression Scores.

Pairwise comparisons demonstrated a significant difference \( p=0.004 \) between phase 1 & 3 in the concussed group. Pairwise comparisons demonstrated no significant difference in matched-control groups between phases. Independent t-tests determined significant difference between the two groups at phase 1 \( p=0.004 \). Figure 3 displays these findings.
A 2 (Group) x 3(Phase) repeated measures ANOVA revealed a significant group × phase interaction \[ F (2, 40) = 4.761, p = 0.014, \eta^2_p = 0.192 \] in Anger scores. Pairwise comparison demonstrated a significant difference \( p = 0.021 \) between phase 1 & 3 in the concussed group. Pairwise comparisons demonstrated no significant difference in the matched-control group between phases of recovery. Independent t-tests determined significant difference between the two groups at phase 1 \( p = 0.033 \). These findings are displayed in Figure 4.

* = \( p < 0.05 \) between phase 1 and 3
# = \( p < 0.05 \) between matched control and concussed group

Figure 3: Mean and standard error of Depression scores for the concussed and matched control groups over 3 phases of recovery.
Figure 4: Mean and standard error of Anger scores for the concussed and matched control groups over 3 phases of recovery.

A 2 (Group) x 3 (Phase) repeated measures ANOVA demonstrated no significant group × phase interaction in Vigor. Pairwise comparisons demonstrated a significant difference (p=0.034) between phase 1 & 3 in the concussed group. There were no significant differences in the matched-control group between phases and no significant difference between the two groups at any of the phases of recovery. Figure 5 displays these findings.
A 2 (Group) x 3 (Phase) repeated measures ANOVA revealed significant group x phase interaction \([F (2, 40) = 8.541], p=0.001, \eta^2_p = 0.299\) in Confusion scores. Pairwise comparison demonstrated significant difference \((p=0.003)\) between phase 1 & 3 in concussed group. No significant difference in the matched-control group between phases. Independent t-tests determined significant difference between the two groups at phase 1 \((p=0.040)\) and 3 \((p=0.047)\) (Figure 6).
A 2 (Group) x 3(Phase) repeated measures ANOVA revealed significant group × phase interaction \([F (2, 40) =2.619], \, \eta^2_p = 0.116\) in Fatigue scores. Pairwise comparisons demonstrated significant difference \((p=0.006)\) between phase 1 & 3 in concussed group. No significant difference in matched-control group between phases of recovery. Independent t-tests determined significant difference between the two groups at time phase 3 \((p=0.005)\). These findings are displayed in Figure 7.
A 2 (Group) x 3 (Phase) repeated measures ANOVA with a Greenhouse-Geisser correction revealed no significant group × phase interaction in Tension scores. Pairwise comparison demonstrated significant difference (p=0.018) between phase 1 & 2 and significant difference (p=0.020) between phase 1 & 3 in concussed group. There were no significant differences in the matched-control group between phases and no significant difference between the two groups at any of the phases. Figure 8 displays these findings.
Figure 8: Mean and standard error of Tension scores for the concussed and matched-control groups over 3 phases of recovery.

**HA1b: Perceived stress, as measures by the Perceived Stress Scale, for concussed athletes will be higher than matched controls from injury until post-RTP.**

Perceived stress score was calculated from the perceived stress scale for each group at each phase of recovery. Group profiles for each phase are presented below (Fig 9). These figures illustrate the mean score for each group over the three phases. Table 7 displays the calculated mean score and standard error for each group over the three phases of recovery.

*= p< 0.05 between phase 1 and 3
@ = p< 0.05 between phase 1 and 2
Table 7: Mean score and standard error for PSS at three phases of recovery for 11 concussed and 11 matched control subjects.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Phase 1 Concussed</th>
<th>Phase 1 Control</th>
<th>Phase 2 Concussed</th>
<th>Phase 2 Control</th>
<th>Phase 3 Concussed</th>
<th>Phase 3 Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSS score</td>
<td>22.8 ± 1.8</td>
<td>22.0 ± 2.0</td>
<td>21.7 ± 2.0</td>
<td>23.4 ± 1.8</td>
<td>17.7 ± 1.6</td>
<td>22.2 ± 2.0</td>
</tr>
</tbody>
</table>

Mean Perceived Stress in Concussed & Matched Control Groups over Three Phases of Recovery

Figure 9: PSS scores for the concussed and matched control groups over 3 phases of recovery.

No significant within group or between group were displayed in PSS analysis. Figure 12 displays these findings.

**HA1c: HRV, as measured by the frequency domain, for concussed athletes will show elevated stress levels from injury until post-RTP.** Heart rate Variability was assessed using the FFT frequency domain measures: HF (n.u.), LF (n.u.) and LF/HF ratio
at rest (Fig 10-12), while standing (Fig 13-15) and the absolute difference between sitting and standing (Fig 16-18). Tables 8-10 display calculated mean scores and standard errors for each group over the three phases of recovery. Calculations and analysis for Total Power were calculated and can be found in Appendix F. Total Power was not included in the Results as it produced no significant results.

Table 8: HF, LF and LF/HF ratio at rest (sitting at three phases of recovery for 11 concussed and 11 matched control subjects.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concussed</td>
<td>Control</td>
<td>Concussed</td>
</tr>
<tr>
<td>HF norm</td>
<td>32.9 ± 3.6</td>
<td>47.5 ± 5.7</td>
<td>37.6 ± 5.1</td>
</tr>
<tr>
<td>LF norm</td>
<td>67.1 ± 3.6</td>
<td>56.7 ± 5.3</td>
<td>62.6 ± 5.1</td>
</tr>
<tr>
<td>LF/HF Ratio</td>
<td>2.5 ± 0.4</td>
<td>1.8 ± 0.4</td>
<td>2.4 ± 0.4</td>
</tr>
</tbody>
</table>

A 2 (Group) x 3(Phase) repeated measures ANOVA with a Greenhouse-Geisser correction revealed significant group × phase interaction \( [F (1.149, 29.812) =3.934], \) \( p=0.041, \eta^2_p = 0.164 \) in HF norm at rest. Pairwise comparisons demonstrated significant difference \( (p=0.015) \) between phase 1 & 3 in concussed group. No significant difference in the matched-control group between phases of recovery. Independent t-tests determined significant difference between the two groups at phase 1 \( (p=0.043) \). These Findings are displayed in Figure 10.
A 2 (Group) x 3(Phase) repeated measures ANOVA revealed significant group × phase interaction [F (2, 40) =3.458, \( p=0.041, \eta^2_p= 0.147 \) in LF norm at rest. Pairwise comparisons demonstrated significant difference (\( p=0.014 \)) between phase 1 & 3 in the concussed group. No significant difference in the matched-control group between phases and no significant difference between the two groups at any of the phases were found. Figure 11 displays these findings.
* = p< 0.05 between phase 1 and 3

Figure 11: Mean and standard error of LF norm at rest (sitting) for the concussed and matched control groups over 3 phases of recovery.

When analyzed, no significant findings were uncovered in LF/HF ratio. These findings are displayed in Figure 12.
Figure 12: Mean and standard error of LF/HF ratio at rest (sitting) for the concussed and matched control groups over 3 phases of recovery.

At standing the mean and standard error for the HF norm, LF norm and LF/HF ratio were calculated (Table 9).

**Table 9: HF, LF and LF/HF ratio at standing in concussed athletes and their matched-control.**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Phase 1</th>
<th></th>
<th>Phase 2</th>
<th></th>
<th>Phase 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concussed</td>
<td>Control</td>
<td>Concussed</td>
<td>Control</td>
<td>Concussed</td>
<td>Control</td>
</tr>
<tr>
<td>HF norm</td>
<td>14.8 ± 2.4</td>
<td>20.9 ± 3.6</td>
<td>19.8 ± 3.5</td>
<td>21.8 ± 4.3</td>
<td>22.2 ± 4.4</td>
<td>26.6 ± 5.6</td>
</tr>
<tr>
<td>LF norm</td>
<td>85.2 ± 2.4</td>
<td>79.0 ± 3.6</td>
<td>80.1 ± 3.5</td>
<td>77.9 ± 4.3</td>
<td>77.7 ± 4.4</td>
<td>73.4 ± 5.7</td>
</tr>
<tr>
<td>LF/HF Ratio</td>
<td>7.2 ± 1.0</td>
<td>5.2 ± 0.9</td>
<td>5.9 ± 1.2</td>
<td>5.8 ± 1.3</td>
<td>5.5 ± 1.3</td>
<td>7.1 ± 2.5</td>
</tr>
</tbody>
</table>
No significant findings were uncovered in HF norm, LF norm and LF/HF ratio at standing analysis. These Findings are displayed in Figures 13-15.

Figure 13: Mean and standard error of HF norm at standing for the concussed and matched control groups over three phases of recovery.
Figure 14: Mean and standard error of LF norm at standing for the concussed and matched control groups over 3 phases of recovery.
Figure 15: Mean and standard error of LF/HF ratio standing for the concussed and matched control groups over 3 phases of recovery.

The mean and standard error for the absolute difference between sitting and standing were calculated for the HF norm LF norm and LF/HF ratio (Table 10).

Table 10: HF, LF and LF/HF ratio absolute difference between sitting and standing at three phases of recovery for 11 concussed and 11 matched control subjects.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concussed</td>
<td>Control</td>
<td>Concussed</td>
</tr>
<tr>
<td>HF norm</td>
<td>18.1 ± 3.4</td>
<td>26.6 ± 5.0</td>
<td>17.5 ± 2.7</td>
</tr>
<tr>
<td>LF norm</td>
<td>18.1 ± 3.4</td>
<td>22.3 ± 3.6</td>
<td>17.5 ± 2.7</td>
</tr>
<tr>
<td>LF/HF Ratio</td>
<td>4.7 ± 0.8</td>
<td>3.4 ± 0.7</td>
<td>3.5 ± 1.1</td>
</tr>
</tbody>
</table>
A 2 (Group) x 3(Phase) repeated measures ANOVA revealed significant group × phase interaction \[F(2, 40) = 4.262, \ p = 0.021, \ \eta^2_p = 0.176\] for HF norm absolute difference between sitting and standing. No significant difference between phases in concussed group and the matched-control group and difference between the two groups at any of the phases of recovery was assessed. These Findings are displayed in Figure 16.

![Figure 16: Mean and standard error of HF norm absolute difference between sitting and standing for the concussed and matched control groups over 3 phases of recovery.](image)

A 2 (Group) x 3(Phase) repeated measures ANOVA revealed a significant group × phase interaction \[F(2, 40) = 3.662, \ p = 0.035, \ \eta^2_p = 0.155\] for LF norm absolute difference between sitting and standing. No significant difference between phases in the
concussed group and matched-control group and no significant difference between the
two groups at any of the phases were found. Figure 17 displays these findings.

Figure 17: Mean and standard error of LF norm absolute difference between sitting and standing for the concussed and matched control groups over 3 phases of recovery.

A 2 (Group) x 3(Phase) repeated measures ANOVA revealed a significant group × phase interaction [F (2, 40) =0.965, p=0.39, η²p = 0.046] for LF/HF ratio absolute difference between sitting and standing. No significant difference between phases in the concussed group and matched-control group and no significant difference between the two groups at any of the phases were found. Figure 18 displays these findings.
HA1d: Cortisol both AM and PM levels for concussed athletes will be higher than matched controls from injury until post-RTP. Average Cortisol levels were calculated for each phase between 2-5pm (PM) and in the morning 30 minutes after rising (AM) and the following day) for each group. Group profiles for each phase are presented below (Fig 19). These figures present the mean score for each group over the three phases of recovery. Table 11 displays the calculated mean score and standard error for each group over the three phases of recovery.
Table 11: Mean levels (µg/dL) and standard error for PM & AM Cortisol levels at three phase of recovery at for 11 concussed and 11 matched control subjects.

<table>
<thead>
<tr>
<th>Group</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PM</td>
<td>AM</td>
<td>PM</td>
</tr>
<tr>
<td>Concussed</td>
<td>0.109 ± 0.010</td>
<td>0.217 ± 0.024</td>
<td>0.098 ± 0.013</td>
</tr>
<tr>
<td>Control</td>
<td>0.124 ± 0.017</td>
<td>0.262 ± 0.060</td>
<td>0.117 ± 0.014</td>
</tr>
</tbody>
</table>

No significant group × phase interaction or within group differences were revealed by a 2 (Group) x 3 (Phase) repeated measures ANOVA for cortisol levels. Independent t-tests determined significant difference between the two groups at phase 3 at AM time point (p=0.19). These Findings are displayed in Figure 19. It should be noted that both groups have large standard errors and group means at each phase and time point are not reflective of individual data, refer to Appendix E for individual data.
Overall Evaluation of Hypothesis 1. At phase 1, compared to the matched-control group, the concussed group was significantly (p<0.5) different in the following measures: Total Mood Disturbance, Depression, Anger and HF norm at rest. Although not significant at phase 1 concussed athletes displayed higher measures in Confusion, Fatigue and LF norm at rest and lower measures in Vigor. Therefore concussed athletes do display high levels of stress compared to matched controls during phase 1, which is when they are still experiencing symptoms. There were no significant differences in any of the measures between the two groups at phase 2. There was a significant (p<0.05) difference at phase 3 between the groups in Fatigue and Total Mood Disturbance.
Cortisol levels revealed a significant (p<0.05) difference at AM phase 3 of recovery between the concussed and matched control group. Concussed athletes are still experiencing significant differences to their matched-control at phase 3, after they have returned to play.

During the standing task concussed athletes compared to their matched-control at all three phases displayed a lower measure of HF norm and a higher measure of LF norm. This trend can indicate that concussed athletes even after the resolution of symptoms and RTP may still display higher levels of stress during a reaction task, such as standing HRV compared to sitting HRV.

**EVALUATION OF HYPOTHESIS 2: CONCUSSED ATHLETES’ STRESS MEASURES WILL BE HIGHER THAN BASELINE POST-INJURY UNTIL POST-RTP**

Only two concussed athletes and four matched-control athletes’ baseline measures were obtained. Therefore this hypothesis could not be evaluated.

**EVALUATION OF HYPOTHESIS 3: CONCUSSED ATHLETES WITH HIGHER STRESS MEASURE LEVELS WILL TAKE A LONGER PERIOD OF TIME TO RTP**

a) Concussed athletes with higher Total Mood Disturbance will take a longer period of time to RTP.

b) Concussed athletes with increased Perceived Stress Levels will take a longer period of time to RTP.

c) Concussed athletes with higher LF norm and lower HF norm will take a longer period of time to RTP.

d) Concussed athletes with increased Cortisol levels at both AM and PM will take a longer period of time to RTP.
Pearson Correlations were calculated between the different stress measures and the time it took athletes to return to play. There were significant correlations between time it took to RTP and the following stress measures at phase 1: Total Mood Disturbance (p=0.009, Pearson correlation= 0.74), Depression (p=0.005, Pearson correlation = 0.77), and Fatigue (p=0.048, Pearson correlation =0.61) (Fig 20 & 21). These correlations indicate that concussed athletes who experience higher levels of Total Mood Disturbance, Depression and Fatigue during the acute phase of their injury take longer time to RTP.

Figure 20: Scatter Plot of Days Taken to Return to Play vs. Total Mood Disturbance at phase 1 of recovery.
Although not significant, there was a correlation between days taken to return to play and LF (n.u.) (p=0.102, Pearson correlation = 0.519) and HF (n.u.) (p= 0.103, Pearson correlation = - 0.518) values at phase 1 (Fig 22). These trends indicate concussed athletes who exhibit higher LF (n.u.) and lower HF (n.u.) values during the acute phase of their injury take longer time to RTP.

Figure 21: Scatter Plot of Days Taken to Return to Play vs. Depression and Fatigue Scores at phase 1 of recovery.
Also not significant, there was a correlation between time taken to return to play and AM Cortisol levels at phase 3 (p=0.79, Pearson correlation = -0.551) (Fig 23). This trend indicates concussed athletes that took longer to RTP exhibit lower AM cortisol levels at phase 3.
EVALUATION OF HYPOTHESIS 4: CONCUSSED ATHLETES WILL CONTINUE TO HAVE ELEVATED LEVELS OF STRESS MEASURES EVEN AFTER THE RESOLUTION OF SYMPTOMS

a) Concussed athletes will continue to have elevated levels Total Mood Disturbance after the resolution of symptoms

b) Concussed athletes will continue to have elevated levels Perceived Stress Levels after the resolution of symptoms

c) Concussed athletes will continue to have elevated levels of LF norm and lower levels of HF norm after the resolution of symptoms

d) Concussed athletes will continue to have elevated levels of cortisol at both AM and PM after the resolution of symptoms
Table 12 displays the mean and standard error of the symptom levels of both groups. The Concussed group displays a significant difference from phase 1 to 2 in symptom levels; hence, a decrease in their symptom levels.

Table 12: Symptom profiles of concussed and matched control group at 3 phases of recovery

<table>
<thead>
<tr>
<th>Group</th>
<th>Phase of Recovery</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0 ± 0 score</td>
<td>0 ± 0 score</td>
<td>0 ± 0 score</td>
<td></td>
</tr>
<tr>
<td>Concussed</td>
<td>23.3 ± 2.42 score</td>
<td>8.5 ± 3.09 score</td>
<td>3.5 ± 1.27 score</td>
<td></td>
</tr>
</tbody>
</table>

Pearson correlations were calculated between symptoms score levels in concussed athletes and stress measures. Symptoms score levels at phase 2 significantly correlated with Depression (p= 0.004, r =0.783), Anger (p=0.002, r =0.823), Confusion (p<0.0005, r=0.879), Fatigue (p=0.022, Pearson correlation =0.677), Total Mood Disturbance (p=0.005, r=0.780) and Sleep Scale values (p=0.001, r =-0.835) (Fig 24-26). This indicates that concussed athletes with higher symptoms levels at phase 2 exhibited increased negative mood states and disrupted sleep.
Figure 24: Scatter Plot of Symptom Scale Score vs. POMS subscale Scores at phase 2 of recovery.

Figure 25: Scatter Plot of Symptom Scale Score vs. Total Mood Disturbance Scores at phase 2 of recovery.
Symptoms score levels at phase 3 significantly correlated with phase 2 scores in Depression (p= 0.002, Pearson correlation =0.855), Anger (p=0.005, Pearson correlation =0.778), Total Mood Disturbance (p=0.002, Pearson correlation =0.811) and Sleep scale values (p=0.014, Pearson correlation =-0.711) (Fig 27-29). There were no correlations between phase 3 symptoms score levels at phase 3 stress measures. This indicates that concussed athletes with higher symptoms levels at phase 3 exhibited increased negative mood states and disrupted sleep at phase 2.
Figure 27: Scatter Plot of phase 3 Symptom Scale Score vs. phase 2 POMS Subscale Scores (Depression and Anger).

Figure 28: Scatter Plot of Symptom Scale Score at phase 3 vs. Total Mood Disturbance Scores at phase 2.
Symptoms score levels at phase 1 significantly correlated with phase 3 Difference between Sitting and Standing scores in HF (p=0.034, Pearson correlation =-0.641) and LF (p=0.034, Pearson correlation =-0.639) values (Fig 30 & 31). This indicates that concussed athletes with higher symptom levels at phase 1 exhibit a decreased change in HF and LF values when standing from sitting at phase 3 of recovery.
Figure 30: Scatter Plot of Symptom Scale Score at phase 1 vs. HF norm difference between Sitting and Standing scores at phase 3.

Figure 31: Scatter Plot of Symptom Scale Score at phase 1 vs. LF norm difference between Sitting and Standing scores at phase 3.
CHAPTER 5: DISCUSSION

The main objective of the study was to investigate changes in selected stress measures (Mood States, Perceived Stress, Heart Rate Variability, and Cortisol) in concussed athletes from injury to post-RTP. Three of the initial four hypotheses were analysed:

1. Concussed athletes’ stress measures will be higher than matched controls from injury until post-RTP.
2. Concussed athletes’ stress measures will be higher than baseline post-injury until post-RTP (Not analysed due to lack of baseline data)
3. Concussed athletes with higher stress measure levels will take a longer period of time to RTP.
4. Concussed athletes will continue to have elevated levels of stress measures even after the resolution of symptoms at phase 2 and 3 of recovery.

The study extends the current knowledge of the psychological and physiological changes occurring in concussed athletes during the recovery process. The findings suggest that post-injury concussed athletes exhibit elevated levels of stress and increased stress levels correlate with a longer time to RTP.

CONCUSSED ATHLETES’ CHANGES IN STRESS MEASURES FROM INJURY TO POST-RTP COMPARED TO MATCHED-CONTROLS

POMS. The POMS subscales and Total Mood Disturbance scores in the concussed group display significantly more negative mood states during the acute phase of injury and more positive mood states at post-RTP compared to controls. Although, this is consistent with current literature and recent research, previous studies did not assess
mood states of concussed athletes at post-RTP (Mainwaring et al., 2004; Mainwaring et al., 2010, Hutchison et al., 2009). Assessment at phase 3 of the present study was conducted at post-RTP and revealed concussed athletes had more positive mood states compared to controls at this phase of recovery. This elevation in positive mood states can be explained by the Hedonic Adaption Theory, which states individuals have a set point of happiness and changes to circumstances, not necessarily the circumstances themselves effect people happiness or mood (Diener et al., 2006). This increase in positive mood states can be attributed to the concussed athletes exhibiting more positive feelings about their ability to return back to their normal activities after a period of time.

Compared to controls, Total Mood Disturbance scores of concussed athletes were higher at the acute stage of injury and lower at post-RTP. This confirms results of previous studies that concussed athletes experience increased Total Mood Disturbance post-injury (Mainwaring et al., 2004; Mainwaring et al., 2010; Hutchinson et al., 2009). At phase 2, an average of approximately 18 days post-injury, concussed athletes display similar levels of Total Mood Disturbance as controls. This is also constant with previous research, which found concussed athletes Total Mood Disturbance levels are no longer increased at two weeks post-injury, but are at the previously assessed pre-injury baseline levels (Mainwaring et al., 2004; Hutchinson et al., 2009). The present study found that, during the acute phase, concussed athletes displayed significantly increased levels of negative mood states compared to scores at post-RTP and controls. Athletic injuries are stressful life events (Evan et al., 2012), and, as expected based on previous literature, concussed athletes display more negative mood states post- injury (Mainwaring et al., 2004; Mainwaring et al., 2010; Hutchinson et al., 2009). The increased in negative mood
states indicates that concussed athletes are experiencing elevated levels of stress post-injury.

Depression scores in Concussed athletes were higher at the acute stage and lower at post-RTP compared to Matched Controls. This is consistent with previous literature, which has displayed athletes often experience symptoms of depression post-concussion (Mainwaring et al., 2004; Mainwaring et al., 2010; Hutchinson et al., 2009).

In this study concussed athletes displayed elevated Anger scores during the acute phase of injury compared to their Anger scores at post-RTP, and Matched Controls. Previous literature suggests increased levels of anger are associated with the injuries (Hutchinson et al., 2009); however, studies within the concussed population have not displayed significant elevated levels of Anger during the acute phase (Mainwaring et al., 2004; Hutchinson et al., 2009). The current study used Matched Controls controlling for sport and academic influences, which may have allowed for group differences to be detectable.

Immediately, post-injury concussed athletes displayed lower Vigor scores compared to Matched Controls. This indicates concussed athletes are lacking energy and alertness, which is often a symptom of a concussion injury. A decrease in vigor with athletic injuries and concussion injuries has been reported in the literature (Mainwaring et al., 2004; Mainwaring et al., 2010; Hutchinson et al., 2009). Concussed athletes are advised to cease all physical activity as well as other normal activities, which could be a contributing factor in the decrease of Vigor (Hutchinson et al., 2009). Additionally, concussion symptoms such as headaches, lack of energy, fogginess or nausea may be contributing to decreases in Vigor (Hutchinson et al., 2009).
Confusion scores were higher during the acute stage of injury compared to controls. This is consistent with previous research that demonstrated an increase in Confusion scores post-concussion (Mainwaring et al., 2004). Increased post-injury confusion can be due to athletes receiving insufficient information about their injury or prognosis (Mainwaring, 1999). Cognitive impairments post-concussion can also cause increased Confusion levels (Mainwaring et al., 2004).

The present study found Fatigue scores in Concussed athletes were not elevated at the acute phase of injury compared to Matched Controls contrary to literature (Mainwaring et al., 2004; Mainwaring et al., 2010; Hutchinson et al., 2009). Lethargic feelings are often an associated concussion symptom. Based on literature it was expected that concussed athletes would display increased levels of fatigue post-injury, but this was not found. At phase 3 (post-RTP) concussed athletes did show a significant decrease in fatigue scores compared to controls. At phase 1, concussed athletes may have not reported decreased levels of fatigue, but were able to notice a change in their fatigue levels as they progressed through to RTP.

Tension scores revealed no significant findings, which is consistent with previous research (Mainwaring et al., 2004; Hutchison et al., 2009). Both Concussed and Matched Control groups increased in their tension levels at each subsequent phase of recovery. This increase in tension can be due to other non-injury associated factors, such as academics, personal or athletic issues. Although not significant, Concussed athletes displayed higher levels of tension than their Matched Controls at all three phases. This increase in Tension may be because the acute phase of injury is a tense period as concussed athletes are not receiving sufficient information about their injury. After the
acute phase, returning back to normal activities can be stressful or overwhelming as one has to “catch-up” on one’s academic, social and athletic aspects of life, causing an increase in tension scores at Phase 2 and Phase 3. Also the state of being injured may be sufficient to elevate Tension levels.

The results for mood disturbance are similar to previous findings in this population. Previous studies found increases in negative mood states post-injury and as athletes’ progress to RTP the negative mood states resolve to levels similar to matched controls. Previous literature has demonstrated that concussed athletes display different mood disturbance compared to athletes with skeletomuscular injuries (Mainwaring et al., 2010). This difference in mood states is due to the limbic system, which controls emotions and mood, in the brain being directly affected during a concussion (Duman & Monteggia, 2006). Based on the results of the present study, concussed athletes display clear mood changes during their recovery process.

**Perceived Stress.** No significant findings were uncovered with the Perceived Stress Scale Scores. This is can be due to the small sample size, or the Perceived Stress Scale might not be a suitable tool for concussion assessment. There is however a trend displayed in scores similar to mood states with an increased level of stress at the acute phase of injury and a decreased level of stress at post-RTP compared to controls. Further studies need to be conducted to assess the utility of the Perceived Stress Scale in concussed athletes.

**Heart Rate Variability.** Previous studies assessing HRV have been limited. Gall, Parkhouse & Goodman (2004) assessed the frequency domain in HRV in concussed athletes. They did not find significant difference between the concussed and control
The changes within the LF and HF norm in the concussed group are consistent with previous stress literature (Aubert et al., 2003; Bilchick & Berger, 2006). LF is a reflection of sympathetic activity and HF is a reflection of parasympathetic activity (Aubert et al., 2003; Bilchick & Berger, 2006). Increased levels of sympathetic activation and decreased levels of parasympathetic activation are often associated with periods of stress (Aubert et al., 2003).

Contrary to the present study, other studies with TBI and HRV have displayed an overall decrease in HRV measures including LH and HF norms. This decrease in HRV measures is due to the uncoupling between the autonomic and cardiovascular system due to the disruption in neuroautonomic pathways in TBI (Gall, Parkhouse & Goodman, 2004). Previous studies indicate that the severity of the brain injury is proportional to the degree of uncoupling between the two systems (Gall, Parkhouse & Goodman, 2004). Hence an mTBI such as a concussion may be insufficient to cause an uncoupling of the
autonomic and cardiovascular system at rest; however under additional stress this uncoupling may be detectable (Gall, Parkhouse & Goodman, 2004). Gall, Parkhouse & Goodman (2004) observed a change in HRV measures during exercise, which is a form of additional stress. In this study, when standing from sitting (a minor physical stress), compared to controls, the concussed group displayed decreased LF and HF norm values at all three phases. Therefore, this perturbation can be due to group difference with the concussed group normally having lower values when standing. Alternatively, the difference can be due to the uncoupling of the autonomic and cardiovascular system in the concussed group when experiencing additional stress. The absolute difference between sitting and standing values was calculated to assess the reactivity of the two groups. A significant group by phase interaction was revealed with the concussed group displaying a smaller change in LF and HF norm measures when standing compared to sitting at phase 1 and 2. This can be an indication of a disconnection between the autonomic and cardiovascular system experienced by the concussed group during the acute phase of injury and when returning to exercise as they displayed a decreased reaction to the change between sitting and standing.

The information revealed in this study is consistent with literature and previous research. It gives a good indication of the underlying physiological changes experienced by concussed athletes and with more investigation HRV can be a potential tool in the understanding and assessment of concussion recovery.

**Cortisol.** A review of the literature revealed that cortisol is expected to have a defined circadian cycling rhythm with it peaking within 30 minutes of awakening and declining throughout the day. This cycling is observed in both the concussed and control
group at all three phases. There is no significant difference between the two groups at phase 1 or 2. Savardas et al. (2004) also demonstrated no elevation in cortisol levels post-injury in severe brain injuries due to the reduction in brain activity as a result of sedation or damage to the CNS/HPA axis. Similarly, no acute increase in cortisol in concussed athletes may be due to the cognitive, physical and mental rest imposed on the athletes, post-injury, causing a reduction in brain activity.

Other literature contradicts the findings in this study and has displayed increases in cortisol levels at the acute phase of mTBI. Cernak et al. (1999), Kovi et al. (1997) and Sojka et al. (2006) all found increased cortisol levels during the acute phase of mTBI. It should be noted that the first session (phase 1) in this study was an average of 4.5 days post-injury and the study by Cernak et al. (1999) found the increase in cortisol was only present in the first 2 days post-injury. Similarly, Sokja et al. (2006) found a significant decrease in cortisol levels 10 hours post-injury compared to the first 2 hours. Therefore, phase 1 in the present study may have missed a possible increase in cortisol levels during the acute phase of injury. Contrary to this Kovic et al. (1997) found that up to 7 days post mTBI serum cortisol levels were elevated. This acute increase in cortisol levels is not observed in the mean cortisol levels for the concussed group at phase 1; however, the mean of the group is not an accurate reflection individual data collected (Appendix E). When examining the individual data there is an increase in cortisol levels in many of the concussed athletes at phase 1, which is consistent with literature and can be explained by the physical/metabolic stress caused by the concussion injury in the acute phase.

In some individual cases there is an increase in cortisol levels at phase 2 when given exercise clearance and allowed to resume normal activities. Returning back to
normal activities can be a psychologically stressful event as many athletes are stressed by having to “catch-up” on their sport, academic and social endeavors. This is also reflected through individual data in the other collected stress measures. This increase in cortisol can also be a result of physiological stress as the athletes are not physically prepared to return to back to normal activities and this additional stress is displayed through an increase in cortisol levels.

At phase 3 there is a significant difference at the AM time point between the two groups with the concussed group showing a decrease in cortisol levels. Decreased levels of cortisol can be an indicator of reduced levels of stress. In the present study, the psychological measures displayed that concussed athletes were less stressed and exhibited more positive mood states at phase 3. The reduction in cortisol levels at this time point can be a reflection of less stress. Although, awakening cortisol levels are a reflection of the hypothalamus-pituitary adrenal (HPA) axis activity. The peak in cortisol in the morning is a result of the activation of the pituitary adrenal axis upon awakening; therefore, decreased levels of AM cortisol may not be positive. It has been displayed that those who suffer from post-concussion syndrome have decreased cortisol levels (Bay, Sikorskii, & Gao, 2009). The present study has displayed a negative correlation between days taken to RTP and AM cortisol levels at phase 3. Literature has also displayed hypocortisolism in the morning can be a reflection of hypopituitarism in TBI cases (Agha et al., 2007; Tanriverdi et al., 2010). In TBI cases, hypopituitarism is the decrease in pituitary activity caused by the physical or metabolic damage to the brain (Tanriverdi et al., 2010; Zaben et al., 2013). Hypopituitarism is displayed in both severe and mild TBI, especially in the case of multiple mild TBI (Tanriverdi et al., 2010; Zaben et al., 2013).
Symptoms of hypopituitarism are often overlooked as they are similar to acute concussion and post-concussion syndrome symptoms (Agha et al., 2007; Ives et al., 2007). Hypopituitarism reflected through hypo-cortisol is not usually present during the acute phases of concussion and is capable of presenting itself several weeks post-concussion (Tanriverdi et al., 2010). Studies have found that the majority of cases of hypopituitarism often resolve after varying periods of time (Agha et al., 2007; Tanriverdi et al., 2010). Similar to phases 1 and 2, group means of phase 3 are not reflective of the individual data. Many concussed athletes at phase 3 do not exhibit hypo-cortisol levels and show ranges of morning cortisol comparable to controls. A few concussed athletes do display a decrease in cortisol levels which has caused the overall mean to be decreased.

It may be possible, especially with a small sample size, that the two groups differ in normal cortisol levels with the concussed group naturally exhibiting a lower level of morning cortisol as cortisol levels are highly individualized. Therefore, this decrease in cortisol levels would be the concussed athletes returning back to their normal levels and the other two previous phases would have been an increase level of cortisol secretion in the concussed athletes, which would have been expected (an increase in cortisol levels during the acute phase on injury) based on the literature.

Concussed athletes’ cortisol levels post-injury seem to be very individualized. Cortisol levels are not only a reflection of stress in TBI injuries, but are a reflection of other processes in the brain. Cortisol release is due to a hormone cascade initiated by the hypothalamus in the brain (Fries et al., 2009). Concussions disrupt brain processes affecting normal cortisol response; as such cortisol may not be released similarly as other forms of stress. Although, it is clear that many concussed athletes based on their cortisol
levels experience some form of disruption at varying phases. Further research must be conducted before any conclusions can be drawn and to gain a better understanding of cortisol levels in mTBI cases.

**Concussed Athletes’ Stress Measures in Relation to Days Taken to RTP**

The present study found that levels of Total Mood Disturbance and Depression at phase 1 were significantly correlated with days taken to RTP. Concussed athletes who displayed higher levels of Total Mood Disturbance and Depression during the acute phase of injury took a longer time to RTP. Therefore, Total Mood Disturbance and Depression scores can be predictive in determining time needed to RTP. Total Mood Disturbance and Depression scores though are not necessarily a reflection of injury severity. Usually more severe injuries take longer time period to recover than less severe injuries. However, injury severity is not the only factor affecting recovery time as additional stress on an injury can impede or slow the recovery process (Perna & McDowell, 1995). Increased levels of Total Mood Disturbance and Depression may be a reflection of a more severe injury, which will require a longer time to RTP; alternatively increased levels of Total Mood Disturbance and Depression may be causing concussed athletes additional psychological stress, which slows their recovery process resulting in a longer time to RTP. It is unclear if this correlation between mood states and days taken to RTP is due to injury severity reflected in increased levels of Total Mood Disturbance /Depression or increased levels if stressing slowing the recovery process.

Although not a significant correlation, concussed athletes with increased LF and deceased HF took longer to RTP. This implies concussed athletes exhibiting elevated stress levels during the acute phase of injury took more time to recover. The increased
sympathetic activation and decreased parasympathetic activation can be a reflection of physiological stress as a result of the injury (Aubert et al., 2003; Bilchick & Berger, 2006). The severity of the injury can be reflected in the LF and HF values (Gall, Parkhouse & Goodman, 2004). The increase in LF and decrease in HF values may correspond to injury severity can predict the time needed to RTP. HRV measures including LF and HF can be reflective of psychological stress as well as physiological stress (Aubert et al., 2003; Bilchick & Berger, 2006). Similar to Total Mood Disturbance and Depression, the levels of LF and HF may reflect increased levels of psychological stress experienced by the concussed athlete, which may be disrupting the recovery processing cause an increase time taken to RTP (Perna & McDowell, 1995).

There is an association between Mood Levels and HRV stress measures and days taken to RTP in concussed athletes. But it is unclear if increased stress measures reflect injury severity or increased stress measures are slowing the recovery process causing more days taken to RTP.

**EVALUATION OF SYMPTOM PROFILES USING STRESS MEASURES**

The correlations between symptom scale scores and stress measures revealed that at phase 2, mood states reflected symptom levels. Concussed athletes at this phase with increased symptoms displayed more negative mood states. There was no correlation between symptom levels and mood levels at phase 1. Symptom levels were at their highest during phase 1 and mood states were also the most negative at this phase, but no correlation was found. The lack of correlation can be due to other factors contributing to mood states other than symptoms. At phase 1, concussed athletes are removed from their daily routines and told to rest. Athletes will react differently to this change hence there
will be mood differences. At phase 3, symptoms scale scores are correlated with Depression, Anger and Total Mood Disturbance Scores at phase 3. There were no significant correlations between phase 3 symptoms scale scores and phase 3 mood scores. Mood scores at phase 3 are the most positive, which is most likely due to concussed athletes being able to return back to their normal lifestyles. Hence, even if athletes are still experiencing minor symptoms, these symptoms may not be impacting their mood sufficiently, and their ability to RTP and other activities may be a stronger predictor of their mood at this phase. Phase 2 mood states may be a better predictor of symptom levels at phase 3. Increased negative mood states at phase 2 correlates with more symptoms at phase 2 and those with more symptoms at phase 2 usually have more symptoms at phase 3. Also those experiencing more negative mood states may be placing upon themselves additional stress due to their negative moods, which can slow recovery causing symptoms to still be present at phase 3.

Phase 1 symptom levels displayed a correlation between difference between sitting and standing at phase 3 in LF and HF values. Those with increased symptom levels at phase 1 displayed decreased change in LF and HF values when standing from sitting. The lack of change can imply an uncoupling of the autonomic and cardiovascular system in the concussed group when experiencing the additional stress of standing (Aubert et al., 2003). If symptoms levels at phase 1 were a reflection of injury severity, then this finding would imply those with more severe injuries would display a disconnect between the mind and body when additional stress is placed upon them even after post-RTP. This implies that concussed athletes continue to experience elevated levels of stress or are unable to cope with additional stress even after the resolution of symptoms.
It should be noted that the symptom scale accuracy relies on the concussed athletes’ honesty. Athletes often underreport symptom levels in order to RTP sooner; also they may be aware when they received exercise clearance that it is expected that they are symptom free. Therefore at phase 2 and 3 concussed athletes may be reporting less symptoms or less severe symptoms because they are aware that it is expected for them to no longer have symptoms. The score of the symptom scale is also based on severity, which is subjective and perception of severity differs.

There was no correlation between symptom levels at all three phases and days taken to RTP. Symptoms do not appear to predict when concussed athletes will to RTP and may not reflect injury severity. If time (needed) to RTP corresponds to injury severity, then symptoms lack of correlation to time needed to RTP indicates symptoms may not reflect of injury severity. This can be due to the lack of objectivity of the symptom scale.

Symptoms levels do correlate to some of the indicators of stress, especially the mood states at phase 2. However, symptom scores are not objective and do not reflect concussion recovery. Stress scores can provide more insight beyond symptoms levels, in concussion recovery and prognosis by providing more information about the physiological and psychological changes happening post-concussion.

**Relationship Between Assessed Stress Markers**

This study’s results imply that measures of stress have a relationship to time taken to RTP and symptoms score levels. These measures of stress—mood states, perceived stress, cortisol and HRV— are directly and/or indirectly related and together influence the biopsychological and sports rehabilitation outcome post-injury. Based on the principles of
the Biopsychosocial Model of Sports Injury Rehabilitation (Brewer et al. 2002), Figure 32 outlines the relationship between the assessed stress measures, injury characteristics, sociodemographic factors, intermediate biopsychological outcomes and sports injury rehabilitation outcome. In this model Cortisol and HRV are considered Biological Factors, Mood States is considered a Psychological Factor and Perceived Stress is considered a Psychosocial Factor.

The injury characteristics of concussed athletes are widespread and result in a variety of psychological and pathophysiological irregularities including cerebral blood flow reduction, cognitive dysfunction, and autoregulatory impairment (Giza & Hovda, 2001; Len & Neary, 2011; Wilberg, Orega, & Solbonov, 2006). These changes elicit a stress response in concussed athletes causing the alteration in cortisol level, HRV, mood states and perceived stress. The study observed a significant change in mood states and HRV measures and a trend in perceived stress and cortisol levels during recovery. A concussion can directly affect limbic structures in the brain and their regulation (Duman & Monteggia, 2006). The limbic structures control mood and emotions; therefore, unlike other athletic injuries, the injury characteristic of a concussion directly affects psychological functioning (Duman & Monteggia, 2006). Furthermore, sociodemographics factors, such as age or gender, influence these markers of stress. Social factors, such as social support and other situational factors can either help mediate the stress response or create additional sources of stress during injury recovery (Anshel, 1996, Bloom, et al., 2004; Brewer & Cornelius, 2008; Williams & Andersen, 1998). The measures of stress in this study also have a bidirectional effect on each other as the psychological and physiological responses post-concussion are not exclusive. Stress
measures influence either directly or indirectly and bi-directionally the Biopsychological Outcomes, such as rate of recovery. This study has demonstrated athletes with increased levels of stress take longer to RTP; therefore, there is a relationship between stress levels and Biopsychological Outcomes. Furthermore, Biopsychological Outcomes can also affect stress measures as the recovery process can be a stressful event. Finally the Biopsychological Outcomes and Stress Measures also bi-directionally affect the Sports Injury Rehabilitation Outcomes. Currently concussion recovery is based on the resolution of symptoms and this study has shown some correlation to symptom levels and markers of stress (Bigler, 2012). Similar to the Biopsychological Outcomes, Sports Injury Rehabilitation Outcomes such as treatment outcomes and readiness to RTP can also be stressful and influence these measures of stress. The model creates a framework to help examine the relationships between markers of stress (cortisol level, HRV, mood states and perceived stress) and how they influence injury rehabilitation outcomes.
Figure 32: Relationship between Injury Characteristics, Sociodemographic Factors, Cortisol Levels, HRV, Mood States, Perceived Stress, Intermediate Biopsychological Outcomes and Sports Injury Rehabilitation Outcomes in sports concussion.
LIMITATIONS

As with all research there were limitations to this study. Baseline data for most of the participants was unattainable due to practical constraints. Baseline data (POMS, PSS and PM Cortisol) was taken for teams with high incidences of concussion. Many of the athletes that experienced concussions this season were not on these particular teams and did not have baseline values. Furthermore, many of the concussed participants on these teams were absent during the baseline procedure day. Literature provides a basis to overcome this limitation. Previous studies have displayed no pre-season difference between concussed athletes and their teammates on mood states determined by POMS (Mainwaring et al., 2004). HRV is stable within subjects, but varies between individuals; however, obtaining baseline data would be a time consuming process (Aubert et al., 2003; Bilchick & Berger, 2006). Other studies involving HRV and concussion/TBI have not been used baseline data to assess study results (Gall, Goodman, Parkhouse; 2004; Bauman et al., 2011; La Fountiane et al., 2011). Cortisol is stable within individuals (if other factors are kept consistent), but does vary between individuals (Fries, Dettenborn, Kirschbaum, 2009). Obtaining AM cortisol levels would be difficult; however, baseline values or normative values for this measure would provide useful information for further understanding.

Participants were required to collect AM cortisol samples on their own after awakening; therefore the accuracy of this measure relies on the participants taking the samples correctly and at the appropriate time. The accuracy of the questionnaires (POMS, PSS, symptoms profiles and sleep scale) used in this study requires the honestly of
participants. Concussed athletes were assured that the results of this study would not affect their ability to RTP and should answer as honestly as possible.

The study was also unable to differentiate injury stress from other forms of stress. Matched controls were chosen based on similar academic and sport background as it is assumed that these controls would have similar academic and athletic stress as concussed athletes. Personal forms of stress or other stressors experienced by both the matched-controls and concussed athletes were not controlled.

It should be noted that an ideal marker of concussion recovery reduces the chance of athlete returning to play too soon and being at risk for subsequent injury; unfortunately this study was unable to assess this aspect. Although these markers of stress provide insight into the recovery process, further studies need to be conducted to determine if they can be used as an accurate marker of concussion recovery.

Another limitation was that there was a change in environment that may have impacted study results. A few of the participants were unable to complete their three testing sessions in the same room due to a laboratory move uncontrollable by the researcher. Individual data displayed in Appendix E shows that the Control participants who experienced a lab move did not have consistent HRV results, unlike other Controls, who had more stable measures. Studies have displayed that environment can affect HRV. Environmental changes even subtle can impact HRV; hence, it is important to measure HRV in constant environments for the most accurate results (Gao et al., 2013).

Sample size was a limitation also as the study was unable to reach 15 participants as initially planned. The season had a lower than expected number of reported concussions, which may reflect an unusually low number of concussions or there could
Underreporting is a problem with sport-related concussion research as previous studies have identified (Williamson & Goodman, 2006). The sample size may have been too small for certain findings to reach significance. Based on power analysis it was determined that a sample size of at least 15 would be ideal. Nevertheless, Total Mood Disturbance, most of the subscales of POMS and HF norm at rest reached significance when analyzing group differences. LF norm at rest did not reach significance with the current sample and calculations using the means and standard error of each group, displayed a sample size of 15 is needed to reach significance. The sample also had an uneven number of males and females, with 4 males and 7 females. The stress measures in this study as explained in the following paragraph do exhibit gender differences, but this study was unable to evaluate this due to the small sample size.

The fluctuation of hormones in females creates a gender difference that was not evaluated in this study. Information about female menstrual cycle was not gathered. Based on literature, mood states, stress levels, HRV and cortisol levels all indicate gender differences. These measures in females are also influenced by the phase of menstrual cycle and use of oral contraceptives. Natale & Albertazzi (2006) used POMS to evaluate women’s, both oral contraceptive users and non-users, mood states during their menstrual cycle. The study demonstrated women had a significant increase in depression scores during the premenstrual phase. The study also found women on oral contraceptives displayed similar mood changes to non-oral contraceptive users; however, oral contraceptives users had less drastic fluctuation in mood. It also has been hypothesized that phase of menstrual cycle does not only affect mood, but also mood/stress affects menstrual cycle as higher levels of stress causes menstrual cycle abnormalities/
disruption. Sandes & Bruce (1999) demonstrated women with irregular menstrual cycles had less favorable mood states. Other studies have displayed that menstrual cycle in only a small influence compared to other factors. Romans et al. (2013) demonstrated physical health, perceived stress and social support were much stronger predictors of mood than menstrual cycle phase.

Heart rate variability has been displayed to have a gender difference as well. Compared to females, males exhibit significantly greater LF and LF/HF ratio measures and significantly lower HF measures (Young & Leicht, 2011). Phase of menstrual cycle also has an effect on HRV measures. However, Leicht et al., 2003 demonstrated no significant difference in the frequency domain between menstrual cycle phases at rest. However, Sato & Niyake, 2004 demonstrated that during the luteal phase LF and LF/HF measures were higher and decrease HF measures compared to the follicular phase. Therefore, the stability of HRV measures in this study may be influenced by menstrual cycle. Cortisol also displays a gender difference with females displaying a significant (p=0.05) net increase in awakening cortisol levels during the ovulation phase compared to menses, follicular and luteal phases (Wolfram, Bellingrath, & Kudielka, 2011) potentially impacting accuracy of the present study’s results. Therefore, there are gender differences associated with these stress measures, but could not be evaluated in this study.

**Practical Knowledge**

This study adds to current literature and has confirmed that concussed athletes experience elevation in measures purported to stress levels during their recovery process. It has confirmed the findings of previous studies with this population that post-concussion athletes experience psychological changes in mood states. It has also
demonstrates that, even though concussions are mild traumatic brain injuries, they still influence physiological changes post-injury.

The study found that concussion recovery and the post-concussion response is individualized as concussed athletes displayed varying levels of symptoms, sleep patterns, times taken to RTP and stress measures. Many of the stress measures had large standard deviations indicating that group means were not necessarily reflective of individual data implying recovery is not predicable and individualized. Therefore, concussion recovery must be evaluated on an individual basis and recovery timelines should be tailored for individual needs. This concept should be made clear to health professionals and athletes, as they may have set expectations or timeframes about concussion recovery.

Based on this study, athletes with increased levels of stress take a longer period to RTP. All the stress measures used in this study can be reflective of both psychological and physiological stress; consequently it is unclear if the increase level of stress is due to the physiological stress of injury or the psychological stress of being placed on “rest”. The correlation between increased stress levels and days taken to RTP implies that reduced stress levels during this period may help with the recovery process. Previous studies have indicated that increased stress levels impedes recovery (Perna & McDowell, 1995), therefore, it will be beneficial to aim to reduce the amount of stress concussed athletes experience post-injury. It is important that concussed athletes do not RTP too soon to avoid extra physical stress during recovery. It is also important to reduce psychological stress and prolonged recovery may be detrimental as it may increase psychological stress because athletes may feel isolated, depressed and helpless.
Psychology techniques, such as support groups and enhanced coping mechanisms may be beneficial to help reduce stress during the recovery process (Bloom, et al., 2004). Caron et al. (2013) demonstrated that concussed athletes often felt a lack of understanding and isolation. The psychological stress associated with concussion injuries due to lack of social support can be detrimental to the recovery process. Therefore it is important during the recovery process that concussed athletes receive sufficient social support and understanding during this period and the implementation of support groups can help in this respect. Concussion recovery requires a multi-disciplinary team with the support and understanding from coaches, teammates, physicians and therapists.

Concussed athletes need to be made aware that there are physiological and psychological changes occurring post-injury. Since a concussion is an “invisible injury” it may be difficult for athletes to understand the magnitude of changes they are experiencing. The acknowledgement of the changes happening to them post-injury may provide concussed athletes with the realization that it is important they take sufficient physical and cognitive rest before RTP. Concussed athletes must realize that RTP is a progression that cannot be rushed and that they should seek the advice of health professionals during their recovery process.

Health professionals must also be made aware of these physiological and psychological changes occurring post-concussion. They should be aware that hypopituitarism is a possibility even in mTBI especially cases of multiple concussions. It is important for health professionals to have up to date information about patients’ concussion history when assessing their recovery process. Hypopituitarism often has similar symptoms as post-concussion syndrome and may be mistaken for it; therefore
athletes, especially those with multiple concussions, should be tested for hypopituitarism if they are experiencing post-concussion syndrome (Agha et al., 2007; Ives et al., 2007).

**Future Directions**

The findings in this study indicate that concussed athletes do exhibit increased levels of stress post-injury and display psychological and physiological changes. Further research should be conducted examining the changes in these stress markers in concussed athletes. The three phases assessed in this study are insufficient to get a proper understanding of the changes occurring in post-concussion. Assessment of additional phase during the recovery process will provide more understanding. To gain a better understanding of the cortisol cycling patterns in concussed athletes, cortisol should be measured at more phases within each assessment session; however, this may be practically constraining as concussed athletes would be required to collect sample on their own. Ensuring participants collect samples on at the proper time and correctly was difficult as many forget and may not check their phones/emails sufficiently for reminders.

Future research would benefit from investigating the gender differences in concussed athletes and stress markers. Also investigating how menstrual cycle affects concussed female athletes and their stress measures is important. Also evaluating how stress markers differ in those with multiple concussions would be beneficial for understanding. The use of other psychological and physiological markers of stress, such as other stress questionnaires or biomarkers would be valuable in future studies. Investigating how concussed athletes cope with additional forms stress may be important to assess if higher cognitive processes have been restored in concussed athletes. The resolution of symptoms may not be indicative of restoration of higher cognitive processes
in the brain. The sitting and standing task with HRV has demonstrated that concussed athletes even after RTP may not be able to cope with additional forms of stress as they displayed a smaller change in LF and HF compared to controls. Cierone (1996) investigated mild TBI patients’ attention ability (6 to 30 months post-injury) using dual task by testing their processing speed when performing two stimulus the control conditions there were no significant differences between the control group and mTBI group; however, during the dual task condition the mTBI group displayed a significant decrease in processing speed compared to the control group and their control condition. Therefore, mTBI patients may continue to exhibit cognitive deficiencies which are apparent only under conditions that exceed their cognitive resources (Cierone, 1996).

Gall, Parkhouse & Goodman (2004) found concussed athletes HRV was normal at rest two weeks post-injury, but during exercise 5 days post-resolution of symptoms HRV was decreased during an exercise task. This indicated a neuroautonomic cardiovascular disconnect and homeostasis could only be maintained at rest (Gall, Parkhouse & Goodman, 2004). Even after the resolution of symptoms, concussed athletes are insufficiently prepared for the additional stress of exercise (Gall, Parkhouse & Goodman, 2004). Future studies on how additional forms of stress affect concussed athletes post-RTP by measuring HRV during exercise or using dual process tests would be beneficial.

This study found that increased levels of stress resulted in longer times to RTP. Increased stress levels are detrimental to the recovery process. Future studies to investigate how coping mechanism, support group and other stress reducing techniques impact recovery time are warranted.
CONCLUSION

The purpose of this study was to assess stress levels in concussed athletes with a series of post-injury assessments to gain a better understand of the psychological and physiological process post-concussion. Overall the study found that concussed athletes do display increased stress through physiological and physiological changes post-injury. The findings demonstrated concussed athletes exhibited elevated negative mood states post-injury indicating increased levels of psychological stress, which returns back to normal levels at exercise clearance. Concussed athletes also displayed increased physiological stress during the acute phase of injury as seen through the changes in their HRV measures. Furthermore, large standard deviations of the cortisol measures highlighted the individual variability in concussion recovery and response. As such the decisions to return back to play post-concussion should be made on an individual basis as the reaction to a concussion injury varies based on individual factors. The study also revealed that concussed athletes that display increased levels of stress levels post-injury take longer to RTP and symptoms profiles show minimal correlation to stress measures. It is important that concussed athletes aim to reduce the amount of stress they experience post-injury by reducing physical and mental activity. This study provides evidence that there are physiological, biochemical and psychological changes happening in athletes post-concussion. Both health care providers and athletes should be educated about these changes to ensure that athletes receive proper treatment and sufficient rest to reduce the adverse effects of injury. Stress measures can provide more insight into concussion recovery and prognosis beyond symptom profiles and should be monitored during the recovery process.
References


Appendix A

Consent Form

Title of Research Project
Manifestation of stress in concussed athletes from injury to RTP

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Medical Director
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Investigator’s
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 FKPE
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647-622-5001

Background
The purpose of this study is to investigate how stress is manifested in concussed athletes from injury to RTP. Stress will be measured through the following psychological and physiological markers: Heart Rate Variability, morning saliva cortisol, afternoon saliva cortisol, mood disturbance and perceived life stress. These stress markers will be measured in concussed athletes at various milestones from injury to RTP. The information obtained from this study will aim to help in the creation of objective and practical markers to assess concussion recovery and when it is safe to RTP post-concussion.

University of Toronto intercollegiate varsity athletes on teams with a high risk of concussion will be recruited to participate in the study and provide baseline measures. It is estimated 30-40 athletes will participate in the study as either concussed athletes or match-controls.

Eligibility
To participate in this study you must be participating in university level sports that are considered to be at risk for concussions. Both male and females athletes are invited to participate in the study.

Procedure
If you consent to participate in the study you will be asked to give a baseline saliva sample and complete mood profile, perceived stress, symptoms check-list and a sleep scale questionnaires. If you are concussed and consent to participate you will be contacted by the Ms. Arrani Senthinathan (investigator). You can also be contacted to participate in the study if you are a suitable match for the control group and have consented to participation.

You will be required to arrive at the lab between 2-5pm at 3 time points. For accurate results, you will be asked to refrain from food consumption for 1 hour and caffeine for 4 hours prior to testing and also to refrain from any vigorous exercise 2 hours prior to your visit. Upon arrival to the lab you will first have a chest strap (to measure heart rate) place on you. You will then be asked to fill out the Profile of Mood States (POMS) and Perceived Stress Scale (PSS) questionnaires; these will assess your current mood state and your perceived level of stress respectively. You will also be asked to complete a symptoms check-list and sleep scale for comparison purposes. A short rest period will follow completion of the questionnaires. Next, you will be asked to stand up at a comfortable pace and remain standing for a period of 5 minutes. Then you will be asked to give a saliva sample to analysis afternoon cortisol levels. Saliva samples will be collected by a cotton swab you will be instructed to chew for 90 seconds and place in a tube for analysis. This will conclude laboratory data collection.
Figure 1. Timeline for each data collection session, total time approximately 25 minutes

At home you will also be asked to collect a saliva sample by yourself approximately 30 minutes after awakening. Once again you must ensure that you do not consume any food one hour prior to collection. This collection will be done in the same manner as in the lab and will be done the day after your lab visit. After samples are collected, you will be required to store them in a cool place, such as the refrigerator or freezer. You will be asked to hand in the sample to the laboratory as soon as possible.

You will be asked to visit the lab as well collect morning samples by yourself 4 times: 1) 72-96 hours post-injury 2) Pre-RTP (after exercise clearance), and 3) Post-RTP (one week after RTP clearance). Each visit will be approximately 25-30 minutes long.

Through your preferred method of contact (email, phone, and text message) you will be reminded of scheduled morning saliva collection and in laboratory testing dates and times.

**Voluntary Participation and Early Withdrawal**
Your participation in this study is completely voluntary and you can withdraw anytime by informing the investigator. Withdrawal or refusal to participate in the study does not affect your medical access or care and/or academic career.

**Risk/Benefits**

**Risks**

Risks to participating in this study are minimal. However, there is a chance during data collection post-concussion of experiencing concussion-related symptoms. You will be allowed to take breaks until you feel ready to participate or the experiment can be terminated immediately upon your request.

**Benefits**

There will be no immediate direct benefit to you. However, the study will benefit the athletic student community as it would provide better insight into the biochemical, physiological and psychological stress associated with concussions. This will help inform RTP guidelines and help concussed athletes RTP safely. A summary of the group findings will be provided upon request.

**Privacy and Confidentiality**
Only the investigators will have access to the collected data from the study. After initial collection all data records are made anonymous by the use of confidential number codes as the only identify factor. Data will be stored in locked cabinets in a locked room with limited access to only the investigators. Data may be kept in archives to help inform future research direction. However, no identifiable information about your participation will be available after the completion of this study.
Publication of Findings
Following the completion of the study results may be published, however no information revealing your participation in the study will be released.

New findings
If anything is uncovered during the course of the study that will influence you decision to continue participating, you will be informed.

Compensation
Upon completion of the study you will be given $10 Starbucks gift certificates for your time. Participants, who withdrew after 3 time points will be provided with half the compensation amount for their time.

Rights of the Subject
You are not waving any legal rights by participating in the study.

Dissemination of Results
As a research participant you have the right to request a final report of the research findings in this study.

Copy of informed consent
You will be given a copy of the informed consent form you sign.

Consent to Participate:

Year of Study: 

Program of Study:

Email Address:

By signing in any of the spaces below I acknowledge that any questions and concerns I have were addressed adequately by investigators and I have read and understand the information sheet. I acknowledge that I know I can withdraw anytime from the study without penalty. I understand if I have any questions I can contact the investigators of the study.

I hear by consent to participate in all the components (salvia collection, HRV, questionnaires) of this study as a

☐ Post-concussion participant
☐ Control participant
☐ Both

______________________________
Signature
## Appendix B

### POMS QUESTIONNAIRE

Respond to the following questions based on how you are feeling **RIGHT NOW**.

The boxes refer to the phrases:

- **0 = Not at all**
- **1 = A Little**
- **2 = Moderately**
- **3 = Quite a bit**
- **4 = Extremely**

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<td>Worn out</td>
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<td>Cheerful</td>
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<td>Restless</td>
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<td>Embarrassed</td>
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<td>Bewildered</td>
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<td>Blue</td>
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<td>Weary</td>
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<td>Bitter</td>
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<td>Vigorous</td>
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<td>Nervous</td>
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<td>Ashamed</td>
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<td>Forgetful</td>
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<td>Helpless</td>
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<td>Bushed</td>
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<td>Resentful</td>
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<td>Full of pep</td>
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<td>On-edge</td>
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<td>Annoyed</td>
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<td>Proud</td>
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<td>Confused</td>
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<td>Sad</td>
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<td>Fatigued</td>
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<td>Grouchy</td>
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<td>Active</td>
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<td>Tense</td>
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<td>Confident</td>
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<td>Unable to concentrate</td>
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<td>Worthless</td>
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<td>Exhausted</td>
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<td>Angry</td>
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<td>Energetic</td>
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<td>Uneasy</td>
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<td>Satisfied</td>
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<td>Uncertain about things</td>
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<td>Unhappy</td>
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<td>Furious</td>
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<td>Lively</td>
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<td>Anxious</td>
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<td>Discouraged</td>
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Appendix C

Perceived Stress Scale

The questions in this scale ask you about your feelings and thoughts. In each case, you will be asked to indicate your response by placing an “X” over the circle representing HOW OFTEN you felt or thought a certain way. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer fairly quickly. That is, don’t try to count up the number of times you felt a particular way, but rather indicate the alternative that seems like a reasonable estimate.

<table>
<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Fairly Often</th>
<th>Very Often</th>
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<tbody>
<tr>
<td>1. How often have you been upset because of something that happened unexpectedly?</td>
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<td>2. How often have you felt that you were unable to control the important things in your life?</td>
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<td>3. How often have you felt nervous and “stressed” in the last few days?</td>
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<td>4. How often have you dealt successfully with day to day problems and annoyances in the last few days?</td>
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<td>5. How often have you felt that you were effectively coping with important changes that were occurring in your life?</td>
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<td>6. How often have you felt confident about your ability to handle your personal problems?</td>
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<td>7. How often have you felt that things were going your way?</td>
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<td>8. How often have you found that you could not cope with all the things that you had to do?</td>
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<td>9. In the last month, how often have you been able to control irritations in your life?</td>
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<td>10. How often have you felt that you were on top of things?</td>
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<td>11. How often have you been angered because of things that happened that were outside of your control?</td>
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<td>12. How often have you found yourself thinking about things that you have to accomplish?</td>
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<td>13. How often have you been able to control the way you spend your time?</td>
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<td>14. How often have you felt difficulties were piling up so high that you could not overcome them in the last few days?</td>
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Appendix D

UNIVERSITY OF TORONTO / TORONTO REHABILITATION INSTITUTE
VARSITY ATHLETE CONCUSSION RESEARCH PROJECT

BASELINE HISTORY AND DEMOGRAPHICS FORM

Instructions: Please complete the following information as best you can. The information that you provide will be kept strictly confidential. Only the investigators will have access to the information. If you have questions about a particular question, leave it blank and ask the researcher for clarification. Thank you very much for your cooperation.

NAME: ____________________________________________________________

1. What is your sex? 1. MALE       2. FEMALE

2. What is your date of birth? (mm/dd/yyyy) _________ / _________ / _________

3. What is your height? _______________ (Feet) or ______________ (cm)

4. What is your weight? ______________ (Lbs.) or ______________ (kg)

5. Do you consider yourself to be: 1. LEFT HANDED 2. RIGHT HANDED 3. BOTH

6. To what ethnoracial group do you belong?
   i. CAUCASIAN (WHITE)  v. HISPANIC
   ii. AFRICAN ORIGIN (BLACK)  vi. EAST INDIAN
   iii. ASIAN  vii. WEST INDIAN
   iv. SOUTH ASIAN  viii. OTHER/MIXED ______________ (SPECIFY)

7. What is the highest level of education completed by your father and mother?

   FATHER   MOTHER
   i. SOME HIGH SCHOOL OR LESS  i. SOME HIGH SCHOOL OR LESS
   ii. HIGH SCHOOL GRADUATE   ii. HIGH SCHOOL GRADUATE
   iii. POST-SECONDARY VOCATIONAL  iii. POST-SECONDARY VOCATIONAL TRAINING
      training
   iv. COLLEGE GRADUATE   iv. COLLEGE GRADUATE
   v. SOME UNIVERSITY   v. SOME UNIVERSITY
   vi. UNIVERSITY GRADUATE (e.g., BSC)   vi. UNIVERSITY GRADUATE (e.g., BSc)
   vii. MASTERS DEGREE (e.g., MSc)   vii. MASTERS DEGREE (e.g., MSc)
   viii. DOCTORAL DEGREE (e.g., PhD)   viii. DOCTORAL DEGREE (e.g., PhD)
   ix. PROFESSIONAL DEGREES (e.g., DOCTOR, LAWYER)

8. What varsity team do you play for (e.g. Men's hockey / Women's soccer)? ______________________________________________________

9. How many years have you played with this team (before this year)? ________________________
10. What position do you play? ________________________________________________

11. What academic program are you registered in at U of T? _________________

12. Is English your first language? 1. YES 2. NO
   If NO, at which age did you begin to acquire the English language? _______

For the purpose of the next few questions, an injury is defined as any physical harm resulting in pain or discomfort that causes one or more of the following:

a. Unable to participate in sport activity during one or more practices, training sessions, or competitions

b. A need to modify physical activities during practice, training, or competition.

c. Sufficient distraction or emotional distress to interfere with concentration or focus during one or more practices, training sessions, or competitions.

13. Are you currently injured? 1. YES 2. NO

14. Please circle the numbers below that indicate the location of any current injuries.

<table>
<thead>
<tr>
<th>Injury #1</th>
<th>Injury #2</th>
<th>Injury #3</th>
<th>Injury #4</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Right</td>
<td>o Right</td>
<td>o Right</td>
<td>o Right</td>
</tr>
<tr>
<td>o Left</td>
<td>o Left</td>
<td>o Left</td>
<td>o Left</td>
</tr>
<tr>
<td>o Both</td>
<td>o Both</td>
<td>o Both</td>
<td>o Both</td>
</tr>
<tr>
<td>o Head</td>
<td>o Head</td>
<td>o Head</td>
<td>o Head</td>
</tr>
<tr>
<td>o Neck</td>
<td>o Neck</td>
<td>o Neck</td>
<td>o Neck</td>
</tr>
<tr>
<td>o Shoulder, armpit</td>
<td>o Shoulder, armpit</td>
<td>o Shoulder, armpit</td>
<td>o Shoulder, armpit</td>
</tr>
<tr>
<td>o Upper arm, elbow</td>
<td>o Upper arm, elbow</td>
<td>o Upper arm, elbow</td>
<td>o Upper arm, elbow</td>
</tr>
<tr>
<td>o Lower arm, wrist</td>
<td>o Lower arm, wrist</td>
<td>o Lower arm, wrist</td>
<td>o Lower arm, wrist</td>
</tr>
<tr>
<td>o Hand, fingers</td>
<td>o Hand, fingers</td>
<td>o Hand, fingers</td>
<td>o Hand, fingers</td>
</tr>
<tr>
<td>o Upper back, rib cage</td>
<td>o Upper back, rib cage</td>
<td>o Upper back, rib cage</td>
<td>o Upper back, rib cage</td>
</tr>
<tr>
<td>o Low back, pelvis, abdomen</td>
<td>o Low back, pelvis, abdomen</td>
<td>o Low back, pelvis, abdomen</td>
<td>o Low back, pelvis, abdomen</td>
</tr>
<tr>
<td>o Hip, thigh / upper leg, knee</td>
<td>o Hip, thigh / upper leg, knee</td>
<td>o Hip, thigh / upper leg, knee</td>
<td>o Hip, thigh / upper leg, knee</td>
</tr>
<tr>
<td>o Lower leg, ankle</td>
<td>o Lower leg, ankle</td>
<td>o Lower leg, ankle</td>
<td>o Lower leg, ankle</td>
</tr>
<tr>
<td>o Foot, toe</td>
<td>o Foot, toe</td>
<td>o Foot, toe</td>
<td>o Foot, toe</td>
</tr>
</tbody>
</table>
15. Are you receiving any treatment for the injury at present?  1. Yes  2. No
   If "YES", please describe briefly: __________________________________________________________

16. Have you ever had an injury to the head (e.g. from a collision, a fall, a punch, a car accident) that
resulted in any of the symptoms in the table below?
   If so, for each injury, indicate the date and the associated symptoms.

<table>
<thead>
<tr>
<th>1st injury</th>
<th>2nd injury</th>
<th>3rd injury</th>
<th>4th injury</th>
<th>5th injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Injury (month / year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Momentary disorientation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory problems:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred vision or &quot;seeing stars&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skull fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brief loss of consciousness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged loss of consciousness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood changes (e.g. irritability, sadness, other):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specify ____________</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

17. Are the symptoms of the most recent head injury still present or completely cleared?
   1. Still Present
   2. Completely Cleared

18. Please list ALL medications, pills, drugs, vitamins/supplements that you are now taking:

   _______________________________________
   _______________________________________
   _______________________________________
Appendix E
Individual Graphs

POMS

Figure 1: Individual Depression scores of Matched Controls participants

Figure 2: Individual Depression scores of Concussed participants
Figure 3: Individual Anger scores of Matched Control participants

Figure 4: Individual Anger scores of Concussed participants
Figure 5: Individual Vigor scores of Matched Control participants

Figure 6: Individual Vigor scores of Concussed participants
Figure 7: Individual Confusion scores of Matched Control participants

Figure 8: Individual Confusion scores of Concussed participants
Figure 9: Individual Fatigue scores of Matched Control participants

Figure 10: Individual Fatigue scores of Concussed participants
Figure 11: Individual Tension scores of Matched Control participants

Figure 12: Individual Tension scores of Concussed participants
Figure 13: Individual Total Mood Disturbance scores of Matched Control participants

Figure 14: Individual Total Mood Disturbance scores of Concussed participants
Heart Rate Variability

**High Frequency**

![Graph showing high frequency levels for Matched Control participants](image)

Figure 15: Individual High Frequency norm levels at rest of Matched Control participants

![Graph showing high frequency levels for Concussed participants](image)

Figure 16: Individual High Frequency norm levels at rest of Concussed participants
Figure 17: Individual High Frequency norm levels at standing of Matched Control participants

Figure 18: Individual High Frequency norm levels at standing of Concussed participants
Figure 19: Individual High Frequency norm levels at difference between sitting and standing of Matched Control participants

Figure 20: Individual High Frequency norm levels at difference between sitting and standing of Concussed participants
Low Frequency

Figure 21: Individual Low Frequency norm levels at rest of Matched Control participants

Figure 22: Individual Low Frequency norm levels at rest of Matched Control participants
Figure 23: Individual Low Frequency norm levels at standing of Matched Control participants

Figure 24: Individual Low Frequency norm levels at standing of Concussed participants
Figure 25: Individual Low Frequency norm levels at difference between standing and sitting of Matched Control participants

Figure 26: Individual Low Frequency norm levels at difference between standing and sitting of Concussed participants
Figure 27: Individual LF/HF ratio levels at rest of Matched Control participants

Figure 28: Individual LF/HF ratio levels at rest of Concussed participants
Figure 29: Individual LF/ HF ratio levels at standing of Matched Control participants

Figure 30: Individual LF/ HF ratio levels at standing of Concussed participants
Figure 31: Individual LF/ HF ratio levels at difference between standing and sitting of Matched Control participants

Figure 32: Individual LF/ HF ratio levels at difference between standing and sitting of Concussed participants
Figure 33: Individual Cortisol PM and AM levels at three phases in Matched Control participants
Figure 34: Individual Cortisol PM and AM Levels at three phases in Concussed participants
## Appendix F

### Total Power

No significant differences were found for Total Power Measures.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Phase 1 Concussed</th>
<th>Phase 1 Control</th>
<th>Phase 2 Concussed</th>
<th>Phase 2 Control</th>
<th>Phase 3 Concussed</th>
<th>Phase 3 Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting</td>
<td>8146.8 ± 4772.2</td>
<td>4938.5 ± 995.8</td>
<td>4195.8 ± 1193.6</td>
<td>8039.0 ± 1383.2</td>
<td>5563.9 ± 1132.4</td>
<td>6868.1 ± 1685.2</td>
</tr>
<tr>
<td>Standing</td>
<td>7350.909 ± 1848.5</td>
<td>6415.0 ± 1848.5</td>
<td>3793.7 ± 1051.4</td>
<td>6724.5 ± 1051.4</td>
<td>4725.7 ± 900.3</td>
<td>4161.9 ± 900.3</td>
</tr>
<tr>
<td>Difference between Sitting and Standing</td>
<td>795.9 ± 3210.9</td>
<td>1486.4 ± 1130.7</td>
<td>402.0 ± 1063.0</td>
<td>1314.5 ± 860.2</td>
<td>838.2 ± 652.5</td>
<td>795.9 ± 3210.9</td>
</tr>
</tbody>
</table>
Appendix G

Stanford Sleepiness Scale

This is a quick way to assess how alert you are feeling. If it is during the day when you go about your business, ideally you would want a rating of a one. Take into account that most people have two peak times of alertness daily, at about 9 a.m. and 9 p.m. Alertness wanes to its lowest point at around 3 p.m.; after that it begins to build again. Rate your alertness at different times during the day. If you go below a three when you should be feeling alert, this is an indication that you have a serious sleep debt and you need more sleep.

An Introspective Measure of Sleepiness
The Stanford Sleepiness Scale (SSS)

<table>
<thead>
<tr>
<th>Degree of Sleepiness</th>
<th>Scale Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling active, vital, alert, or wide awake</td>
<td>8</td>
</tr>
<tr>
<td>Functioning at high levels, but not at peak; able to concentrate</td>
<td>7</td>
</tr>
<tr>
<td>Awake, but relaxed; responsive but not fully alert</td>
<td>6</td>
</tr>
<tr>
<td>Somewhat foggy, let down</td>
<td>5</td>
</tr>
<tr>
<td>Foggy; losing interest in remaining awake; slowed down</td>
<td>4</td>
</tr>
<tr>
<td>Sleepy, woozy, fighting sleep; prefer to lie down</td>
<td>3</td>
</tr>
<tr>
<td>No longer fighting sleep, sleep onset soon; having dream-like thoughts</td>
<td>2</td>
</tr>
<tr>
<td>Asleep</td>
<td>1</td>
</tr>
</tbody>
</table>

How many Hours of Sleep did you get last night? _____.
Sleep Scale Analysis

Table 5: Mean score and standard error for sleep scale score at three phases of recovery

<table>
<thead>
<tr>
<th>Measure</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Scale Score</td>
<td>Concussed</td>
<td>Control</td>
<td>Concussed</td>
</tr>
<tr>
<td>5.41 ± 0.200</td>
<td>6.46 ± 0.207</td>
<td>6.36 ± 0.432</td>
<td>6.46 ± 0.231</td>
</tr>
</tbody>
</table>

* = p< 0.05 between phase 1 and 3
# = p<0.05 between matched control and concussed group

Figure 9: Sleep Scale scores for the concussed and matched control groups over 3 phases of recovery

A 2 (Group) x 3(Phase) repeated measures ANOVA with a Greenhouse-Geisser correction revealed significant group × phase interaction [F (1.468, 29.368) =5.079), p=0.020, ηp² = 0.203] in Sleep Scale scores. Pairwise comparisons demonstrated significant difference (p<0.001) between phase 1 & 3 in concussed group. No significant difference in matched-control group between phases. Independent t-tests determined significant difference between the two groups at phase 1 (p=0.002) and phase 3 (p=0.019).
Appendix H

Cortisol Analysis

1. Bring all reagents to room temperature and mix before use.
2. Bring plate to room temperature and prepare for use with NSB wells. (Use of NSB wells is optional.)
3. Prepare 1X wash buffer.
4. Prepare tube with 24 mL of assay diluent for conjugate dilution, which will be made later.
5. Pipette 25 μL of standards, controls, and unknowns into appropriate wells.
6. Pipette 25 μL of assay diluent into zero and NSB wells.
7. Make final 1:1600 dilution of conjugate (15 μL into 24 mL assay diluent), mix, and immediately pipette 200 μL into each well. Note any pH indicator color changes.
8. Mix plate for 5 minutes at 500 rpm. Incubate for an additional 55 minutes at room temperature.
9. Wash plate 4 times with 1X wash buffer. Blot.
10. Add 200 μL TMB solution to each well.
11. Mix plate for 5 minutes at 500 rpm. Incubate in dark at room temperature for 25 additional minutes.
12. Add 50 μL stop solution to each well. Mix for 3 minutes at 500 rpm.
13. Wipe plate bottom clean and read within 10 minutes of adding stop.

Calculations

1. Compute the average optical density (OD) for all duplicate wells.
2. Subtract the average OD for the NSB wells (if used) from the average OD of the zero, standards, controls, and unknowns.
3. Calculate the percent bound (B/Bo) for each standard, control, and unknown by dividing the average OD (B) by the average OD for the zero (Bo).
4. Determine the concentrations of the controls and unknowns by interpolation using software capable of logistics. We recommend using a 4-parameter sigmoid minus curve fit.
5. If a dilution of the sample is used, multiply the results by the dilution factor. Samples with cortisol values greater than 3.0 μg/dL (82.77 nmol/L) should be diluted with assay diluent and rerun for accurate results.
Appendix I

University of Toronto RTP Guidelines

Await resolution of symptoms. Rehab neck.

Fail* Pass ¹

Low-impact Exercise Test

Fail*

NP Assessment
Interpretation by NPsych

Pass

Non-contact exercise progression
low acceleration > high acceleration
body weight exercise > valsalva exercise
Continue neck rehab

Fail

NP Assessment
Interpretation by NPsych

Pass

Return to contact / collision sport

1. No Symptoms
2. No Recurrence of Symptoms
* Re-occurrence of Symptoms
Appendix J

Commonly Used Abbreviations

DTI- Diffusion Tensor Imaging
fMRI- Functional Magnetic Resonance Imaging
FFT- Fast Fourier Transform
HF- High Frequency
HRV-Heart Rate Variability
LF- Low Frequency
MR- Magnetic Resonance
mTBI - Mild Traumatic Brian Injury
N.U.- Normalized Units
POMS- Profile of Mood States
PSS- Perceived Stress Scale
PTSD- Post-Traumatic Stress Disorder
ROS-Reactive Oxidative Species
RTP- Return to Play
TBI-Traumatic Brain Injury
TMD- Total Mood Disturbance