Heart Rate Variability Following Concussion in Youth Athletes: An Observational Pilot Study

by

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Abstract

Background/Rationale: Concussion is of great concern within the pediatric sport population due to its high prevalence and potential impact on neurological development. There is a need for additional inexpensive and objective measures for concussion assessment and management. Heart rate variability (HRV), an objective marker of physiological stress can be used as a measure of stress capacity and may fill this gap. Methods & Analyses: Participants included 29 healthy youth athletes (21 females; 8 males). The variables of interest in this thesis are post-concussion symptoms, concussion status, and time and frequency domain HRV measures.

Results: There was a main effect of PCS-I on measures of HRV in the mixed model analysis, whereby, increased post-concussion symptoms were associated with higher heart rate variability. Conclusion: Changes in HRV were associated with an increase in post-concussion symptom inventory scores. These preliminary data may guide future research in determining a physiological marker of stress post-concussion.
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### Acronyms

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<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACE</td>
<td>Acute Concussion Evaluation</td>
</tr>
<tr>
<td>ANS</td>
<td>autonomic nervous system</td>
</tr>
<tr>
<td>BCE</td>
<td>Before the Common/Current/Christian Era</td>
</tr>
<tr>
<td>CIHR</td>
<td>Canadian Institute of Health Research</td>
</tr>
<tr>
<td>cm</td>
<td>centimeters</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>FFT</td>
<td>Fast Fourier Transform</td>
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<tr>
<td>HF</td>
<td>High Frequency</td>
</tr>
<tr>
<td>hr</td>
<td>hours</td>
</tr>
<tr>
<td>HRV</td>
<td>heart rate variability</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>ID</td>
<td>identification</td>
</tr>
<tr>
<td>kg</td>
<td>kilograms</td>
</tr>
<tr>
<td>LF</td>
<td>Low Frequency</td>
</tr>
<tr>
<td>min</td>
<td>minutes</td>
</tr>
<tr>
<td>ms</td>
<td>milliseconds</td>
</tr>
<tr>
<td>ms^2</td>
<td>milliseconds squared</td>
</tr>
<tr>
<td>mTBI</td>
<td>mild Traumatic Brain Injury</td>
</tr>
<tr>
<td>PCS</td>
<td>post-concussion symptoms</td>
</tr>
<tr>
<td>PCSI</td>
<td>Post-Concussion Symptom Inventory</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>PCSI-C</td>
<td>Post-Concussion Symptom Inventory for Children</td>
</tr>
<tr>
<td>RHRV</td>
<td>R heart rate variability program</td>
</tr>
<tr>
<td>SE</td>
<td>standard error</td>
</tr>
<tr>
<td>SNR</td>
<td>signal to noise ratio</td>
</tr>
<tr>
<td>ULF</td>
<td>Ultra Low Frequency</td>
</tr>
<tr>
<td>VLF</td>
<td>Very Low Frequency</td>
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Chapter 1

1.1 Introduction

This thesis contributes to an emerging understanding of the use of heart rate variability (HRV) as an objective measure of concussion recovery in the youth athlete population. It describes the innovative development of HRV data collection protocols and analytic procedures for this population. Preliminary data that identifies the association between subjective reports of concussion symptoms and measures of HRV is presented.

The need for objective markers of physiological stress and recovery post-concussion is outlined and rationale is given for the utilization of heart rate variability (HRV) as an objective measure of neurophysiological stress among the pediatric population post-concussion. The purpose and objectives of this thesis are described. Chapter 1 concludes with a guide to the organization of this thesis.

A concussion is a type of traumatic brain injury (TBI) that is caused by impact to the head or body, which moves the brain inside the skull (McCrory et al., 2013). Concussion symptoms can manifest in a variety of physical, cognitive and emotional domains, and although the injury can be defined as a mild traumatic brain injury, the symptoms can cause sequellae of functional deficits (Halstead & Walker, 2010). Concussion often presents itself more as a functional brain injury rather than a structural injury (Giza & Hovda, 2014), whereby biomechanical insult elicits pathophysiological changes in the brain leading to functional deficits (McCrory et al., 2013). Because of the complexity of concussion symptoms among different individuals and its ambiguity on many traditional neuroimaging techniques (MRI, CT Scan), diagnosis and management of concussion can be challenging (McCrory et al., 2004, 2009). Research to date has primarily focused on adult populations, which is concerning due to the high incidence rates among youth, and the potential impact of concussion on their ongoing neurological development.

1.2 The Developing Brain

The child and youth brain is considered by some to be highly plastic; that is, unique physiologic and adaptive factors enable recovery after biomechanical insult (Browne & Lam, 2006; Kirkwood, Yeates, & Wilson, 2003; Sats, 1993). However, competing literature describes the
immature brain as more vulnerable and susceptible to brain injury than its mature adult counterpart (Kirkwood et al., 2006; McCrory et al., 2004). This vulnerability in children and youth can be explained in part by the physiological and biomechanical sensitivities associated with cognitive and physical maturation; that is, the mental faculties otherwise established in adults are still undergoing rapid neurodevelopment in youth and children (Adelson, 2000; Mazzola & Adelson, 2002; Sinopoli, et al., 2014). In addition to the immature brain’s vulnerability to injury, the prolonged recovery trajectory of the youth brain has been illustrated in both human and animal subjects, which suggest that age is a significant contributor to length of recovery in brain injury (Goldstrohm & Arffa, 2005).

Delayed, differential recovery patterns, and protracted cognitive deficits have been reported in youth athletes as compared to college-aged and professional athletes (Adirim, 2007; Field, Collins, Lovell, Maroon, 2003). Moreover, youth progress through unique developmental milestones as they age and in turn, recovery from brain injury may be further stratified by age within the youth population. For example, research has observed that unlike school aged children, and adolescents with moderate to severe TBI, the recovery curve of younger children is flat, and this recovery pattern suggests no significant ‘catch-up’ or improvement in scores compared to healthy controls (Ewing-Cobbs, Prasad, Kramer, & Landry, 1999). The effect of TBI in younger children leads to a more protracted recovery when compared to non-injured age matched controls (Ewing-Cobbs, Prasad, Kramer, & Landry, 1999). This protracted recovery may result in long-term implications in physical and cognitive outcomes, and less improvement on scores associated with attention/arousal, emotional regulation, and motor coordination (Ewing-Cobbs, Prasad, Kramer, & Landry, 1999). The developmental impact of concussion on youth is currently unknown, and further investigation is required to understand the differential recovery pattern of youth with concussion. Strategies to optimize recovery from brain injury are essential to rehabilitating youth back to their daily activities.

1.3 Epidemiology of Concussion in the Youth Population

While the incidence of concussion in children is not well documented, it is estimated that in children 15 years and younger, the incidence rate of TBI is 180 per 100,000, of which 85% of injuries can be categorized as mild (McCrory, Collie, Anderson, & Davis, 2004). In Canada (Ontario) the rates of emergency room and physician visits for concussion have steadily
increased, as the rate per 100,000 increased from 466.7 to 754.3 for boys and from 208.6 to 440.7 for girls between 2003 and 2010 (Macpherson, Fridman, Scolnik, Corallo, Guttmann, 2014). Of these injuries, falls accounted for approximately 1/3 of the concussions in the pediatric population and hockey/skating were the most commonly specified sport related causes of injury (Macpherson et al., 2014). These numbers are thought to be an underestimate since concussions can go unrecognized or may be underreported (Register-Mihalik et al., 2013; Mrazik, Bawani, & Krol, 2011). The incidence of injury largely speaks to the importance of examining concussion in sport, as sport is the second-leading cause of concussion behind motor vehicle accidents (Marar, McIlvain, Field, & Comstock, 2012).

One of the most commonly reported injuries in children who participate in sports is concussion (Browne & Lam, 2006). Youth involved in organized sports are nearly six times more likely to endure a concussion compared to those involved in leisure physical activities (Browne & Lam, 2006). Traditionally, concussion research has focused on contact sport such as hockey, and football; however, current research suggests that all sports pose a risk of concussion for youth athletes. Marar et al (2012) corroborated that contact sports put youth at the highest risk of concussion compared to non-contact sports; however, concussion still occurred in non-contact sports such as basketball, swimming, and track and field. These findings suggest that concussion can occur in any contact or non-contact sport, and the breadth of this injury is far reaching within the youth sport population. Concussions commonly occur in both adult and youth populations, and although concussion results in common sequelae for adult and youth populations, the consequences of this injury on the developing and immature brain remain largely unknown.

1.4 Concussion Diagnosis and Recovery Management

One of the most puzzling issues surrounding the clinical management of concussion is when to return an athlete to school or activity (e.g., sport) following a concussion (Toledo et al., 2012). An early return to daily activity following concussion may result in delayed recovery (McCrory et al., 2009), prolonged functional deficits (Reed, Taha, Tremblay, Monette, & Keightley, 2012), the inability to navigate complex environments (Fait, Swaine, Cantin, Leblond, & McFadyen, 2012), or more serious injury (e.g., second impact syndrome [Cantu, 1998]). Beyond the physical and cognitive sequelae, these symptoms may have a significant impact on functional performance in activities that children and youth find important and meaningful (i.e., school,
social interactions, community participation [McCrory, Collie & Anderson, 2004; Ponsford, Willmott & Rothwell, 1999]).

Guidelines have been established for returning to physical and cognitive demands, such as sport and school (Kissick & Johnston, 2005, McCrory et al., 2009, 2013; Zemek, Duval, Dematteo, et al., 2014). These clinical guidelines are facilitated by the presence or absence of self-report symptoms, and augmented by tests of cognition, neuroimaging and other markers of recovery (Toledo et al., 2012). To date, there is no gold standard for the management of concussion, and the evidence base to support the use of standardized treatment interventions is lacking. Current post-concussion return to play and return to learn guidelines (Zemek, et al., 2014) direct an injured youth to engage in a graded and stepwise reintegration of physical and cognitive exertion, where the presence or absence of self-reported concussion symptoms determines their stage in the program (McCrory et al., 2013). Traditionally, decisions regarding youth athletes’ return to activity following sport-related concussion have been based on the subjective self-report of post-concussion symptoms (e.g. headaches, fatigue, nausea) and the assessment of cognitive performance (Chen et al., 2007; McCullough & Jarvik, 2011).

Utilizing self-report diagnostic tools for assessing acute concussion, such as the Post-Concussion Symptom Inventory (PCSI) have proven to be accessible and effective in symptom management and the acute diagnosis of concussion (Gioia, Schneider, Vaughan, Isquith, 2009). However, based on the subjective nature of self-reported symptoms during recovery, using these symptoms to dictate progression through graduated return to play guidelines may be challenging for both the sport community (i.e., coaches, organizations and players) and medical community. Youth athletes, with a high incentive to return to sport may not yet have the emotional or cognitive maturity to grasp the health implications of concussion. Recent findings showed that nearly 50% of high school athletes did not report their concussion to a health professional following injury (Register-Mihalik et al., 2013). The most common reasons for not reporting were that players: 1) did not think their injury was serious enough to warrant medical attention; 2) did not want to be withheld from competition; 3) lacked awareness about their probable concussion (Register-Mihalik et al., 2013). It is important to note that many youth concussion studies to date have illustrated that even beyond self-reported symptom resolution, certain neurocognitive sequelae persist, such as delayed working memory reaction time (Dziemianowicz et al., 2012; McCrea et al., 2005; Sinopoli et al., 2014). Effectively and safely timing physical and cognitive exertion
following injury may be a challenge when using self-report diagnostic tools as a standalone measure to evaluate concussion as it may not comprehensively assess recovery from injury. Thus, concussion management tools that rely on self-report of symptoms are often augmented by neuropsychological tests, which examine cognitive impairments post-concussion.

Neuropsychological assessments are utilized to detect changes in cognitive abilities post-concussion. Current guidelines for adult and youth participants measure neuropsychological indices at pre-injury (baseline) and then compare these measures to neuropsychological scores post-concussion (Reed et al., 2014). Post injury scores are examined to determine whether they return to baseline, and in the absence of baseline measure, these scores are compared to normative values (Cohen, Gioia, Atabaki, & Teach, 2009; Guskiewicz et al., 2004). Most commonly, executive function (EF) is disrupted post-concussion, and EF deficits are one of the most common cognitive consequences following concussion (Echemendia, Putukian, Mackin, Julian, & Shoss, 2001; Moser et al., 2007). Neuropsychological assessment however, is somewhat isolated since the evaluation of cognition is sequestered from motor and emotional domains, which are also affected by concussion (Halstead & Walker, 2010).

The clinical evaluation of cognition may not be a sufficient diagnostic tool to comprehensively capture the dynamic characteristics of performance within a real world environment (Huang & Mercer, 2001). Therefore, in managing concussion, an individual may appear to be recovered when performing an isolated cognitive task; however, impaired performance post-concussion may be observed when combining cognitive and motor tasks to mimic a real world environment. Dual task protocols are often used to augment the isolated nature of cognitive evaluations, within the clinical setting. However, cognitive testing may be prone to issues of subjectivity in the athletic population, as there may be an influence of the athlete’s motivation to return to play (Echemendia & Julian, 2001).

Although cognitive testing may be further along the spectrum of objectivity as compared to subjective self-report symptoms, cognitive testing coupled with neuroimaging is a further progression towards an objective diagnostic tool. Advances in functional neuroimaging have enhanced our understanding of concussion recovery in youth by revealing altered haemodynamic response mediated by physical and higher-order cognitive task demands during both the acute (Chen et al., 2008; Chen et al., 2007; Chen et al., 2004) and subacute (Gosselin et al., 2011;
phases of injury in adults. Studies observing both youth and adult participants have found neuropsychological differences post-concussion when combining cognitive and motor tasks, which would have otherwise gone undetected with an isolated cognitive test (Fait, McFadyen, Swaine, & Cantin, 2009; Sinopoli et al., 2014).

Functional imaging techniques may be effective in understanding neurophysiological nuances post-concussion (Chen et al., 2004); yet, the protocols can be lengthy, expensive and invasive. Neurophysiological parameters are emerging in the broader field of brain injury as an objective tool to govern recovery (Gall, Parkhouse, Goodman, 2004; Leddy, Kozlowski, Fung, Pendergast, Willer, 2007). More specifically, disturbances in the autonomic nervous system (ANS) function and its associated parasympathetic and sympathetic branches provide a potential window to explore the developing physiological landscape of a maturing youth. Utilizing physiological parameters as a measure of stress following concussive injury may be a clinically useful tool in the effective management of concussion.

Neurophysiological parameters, such as heart rate variability (HRV) may satisfy the need for a tool to effectively manage and observe physiological stress post-concussion. The investigation of physiological parameters such as heart rate variability may hold promise as an objective measure from which to monitor recovery in youth concussion and in promoting safe and optimal return to activity in all domains of life. The research presented in this thesis makes a significant contribution to understanding the utility of HRV as a neurophysiological measure of stress and recovery in youth athletes post-concussion.

1.5 Rationale

Novel methods of objective assessment for concussion are needed to augment the use of subjective self-report methods of diagnosis and management of concussion. Measures of heart rate variability may have the potential to objectively assess readiness to return to play and readiness to learn following concussion. Although current objective measures such as cognitive testing and neuroimaging can be effective, they can have inherent limitations. Self-report measures and cognitive testing can be influenced by subjective factors such as underreporting and motivation to return to play (Echemendia & Julian, 2001; Register-Mihalik et al., 2013). Heart rate variability may fill this gap as it may have the potential to objectively navigate the subjective influential factors of the youth athlete. Additionally, because HRV is non-invasive,
inexpensive, and accessible, it may be a useful tool to augment alternative objective methods such as fMRI and CT scans.

Further, long duration monitoring of HRV outside of a clinical setting, which was used in this study, is a novel approach to understanding the physiological stress an individual may encounter in their daily activities following concussion. Physiologic measures such as heart-rate variability may offer an innovative measure but little research has been done to understand this parameter especially in youth following concussion. This research is needed to: (1) determine the protocol and methodology necessary to conduct heart rate variability research among youth athletes with concussion; and, (2) generate preliminary observations to guide future researching in determining a marker of physiological stress post-concussion in the youth athlete population. The data presented in this thesis are aimed at contributing to a knowledge base of physiological markers of stress and brain recovery post-concussion.

1.6 Purpose and objectives

The objectives of this thesis aim to generate novel observations about the role of heart rate variability as an objective indicator for neurophysiological stress and recovery management following concussion in youth athletes. Further, the objectives are aimed at identifying the relationship between subjective post-concussion symptoms (PCS) and HRV measures in youth athletes. The specific objectives are to:

1. Determine a protocol for the assessment of heart rate variability among youth athletes.
2. Generate preliminary observations about the relationship between objective (HRV) and subjective (PCS) measures of neurophysiological stress following concussion across the recovery trajectory (immediately following injury and up to 6 months post-injury).

Hypothesis: HRV taken during resting states will demonstrate a moderate statistically significant negative correlation with PCS.

3. Generate preliminary observations about changes in heart rate variability measures, and if there is an observable change following concussion in youth athletes as compared to baseline measures.

Hypothesis: Adolescents with concussion will demonstrate lower HRV and higher PCS (indicating increased neurophysiological stress) when compared to baseline measures.
1.7 Thesis Organization

This thesis is divided into five chapters. Following this introductory chapter, Chapter 2 provides an overview of the literature related to the pathophysiology of concussion and the use of and rationale for HRV as a tool for concussion management. Chapter 3 presents methodology in the analysis of heart rate variability and the technical considerations in observing electrophysiological signals in TBI. Chapter 4 presents the results from investigation of the associations between HRV and post-concussion symptoms. Chapter 5 includes a general discussion regarding the results of the heart rate variability analysis, limitations in this research project, future directions and clinical considerations.
2 Literature Review

2.1 Overview

This chapter will outline the current definition of concussion and will provide an overview of the pathophysiological changes associated with the metabolic disruptions that occur following concussion specific to youth. Further, HRV will be discussed as a tool to measure pathophysiological changes following concussion in youth. Previous research utilizing HRV in brain injury will be discussed and the current literature base of HRV in concussion management will be outlined.

2.2 Concussion Definition

Understanding the complexity of brain injury has challenged academics for centuries. Hippocrates (460 BCE to 377 BCE) was one of the first to document several complex pathophysiological processes, including brain injury (Panourias, Skiadas, Sakas, & Marketos, 2005). In the 10th century, Persian physician Rhazes, documented the first clear separate acknowledgment of concussion (McCrory & Berkovic, 2001; Rhazes, 1548), and other scholars around that time identified that brain trauma could occur without injury to the skull (Goodrich, 1997). The documentation and definition of concussion has evolved over the history of medicine and is continually distinguished from other forms of brain injury as novel research emerges regarding concussion (Alexander, 1995; American Academy of Neurology, 1997; Kutner & Barth, 1998). The contemporary distinction of concussion is currently defined by the Concussion in Sport Group, an international expert panel on concussion research, as “a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces” (McCrory et al., 2013, p.90). The Concussion in Sport Group has established a consensus summarizing the thematic characteristics of concussion for consistency of identification, diagnosis and management: (McCrory et al., 2013)

1. Concussion may be caused by a direct blow to the head, face or neck or a blow elsewhere on the body with an “impulsive” force transmitted to the head.

2. Concussion typically results in the rapid onset of short-lived impairment of neurologic function that resolves spontaneously.
3. Concussion may result in neuropathological changes but the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury. No abnormality on standard structural neuroimaging studies is seen in concussion.

4. Concussion results in a graded set of clinical symptoms that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course. In a small percentage of cases, however, post-concussive symptoms may be prolonged.

2.3 Pathophysiology of Mild Traumatic Brain Injury

2.3.1 Ionic Shifts and Metabolic Changes

The detrimental consequences of concussion have been linked to pathophysiological changes that occur as a cascade of events in the brain, which disrupt brain metabolism and function (see figure 2.1) (Giza & Hovda, 2014). Following the immediate biomechanical injury of the brain during traumatic brain injury (TBI), neuronal membranes are affected and voltage dependent potassium (K⁺) channels open and increase extracellular K⁺ (Hubschmann & Kornhauser, 1983; Julian & Goldman, 1962; Katayama, Becker, Tamura & Hovda, 1990; Takahashi & Manaka, 1981). This increase in extracellular potassium leads to depolarization of the cell, which in turn causes a release of the excitatory amino acid (EAA) glutamate, which exacerbates the K⁺ efflux by activating (1) kainate, (2) N-methyl-D-aspartate (NMDA), and (3) D-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors (Katayama, Becker, Tamura, & Hovda, 1990). The extent of this relationship is related to the degree of the biomechanical injury to the brain. For example, in circumstances where the biomechanical force is inconsequential, glial cells in the brain take up excessive extracellular K⁺ (Ballanyi, Grafe, & ten Bruggencate, 1987; Kuffler, 1967; Paulson, Newman, 1987); but, in cases of greater magnitude, brain injury can further disrupt the mechanisms responsible for maintaining brain homeostasis. During brain injury, extracellular K⁺ increases depolarization of the cell, triggering further release of EAA (i.e., glutamate), opening of EAA receptor channels (NMDA, AMPA, kainate) and in turn continuing the efflux of extracellular K⁺ (D’Ambrosio, Maris, Grady, Winn, & Janigro, 1999; Astrup, Rehncrona, & Siesjo, 1980; Hansen, 1977; Hansen, 1978).
In addition to the ion efflux from the cell, there is an influx of calcium and sodium into the cell (Giza & Hovda, 2014). The increase in intracellular calcium may continue longer than the other ionic shifts that occur following biomechanical insult (Giza & Hovda, 2014; Yoshino, Hovda, Kawamata, Katayama, & Becker, 1991). The increase in intracellular calcium is accompanied by increased calcium in the mitochondria (Giza, & Hovda, 2014). This additional need for energy triggers glucose metabolism following concussion, which is often paired with impaired oxidative metabolism, which has been shown to be disrupted following brain trauma and in turn allows for another stimulus for increased glycolysis (Verweij, Muizelaar, & Lee, 1997; Xiong, Peterson, Verwij, Vinas, Muizelaar, Lee, 1998; Xiong, Peterson, Muizelaar, Lee, 1997).

Following this initial phase of extracellular potassium ion efflux and calcium influx, energy requiring membrane pumps are utilized by the brain to restore ionic homeostasis (Giza & Hovda, 2014). However, an increase need for glucose metabolism is met with disrupted oxidative metabolism and increased dependency on glycolysis can lead to a mismatch between energy requirements and energy production within the cell (Bull, & Cummins, 1973; Mayevsky, Chance, 1974; Rosenthal, LaManna, Yamada, Younts, & Somjen, 1979). Increased glycolysis leads to an increase in lactate production, which has been observed after concussion (Nilsson, & Ponten, 1977; Yang, DeWitt, Becker, & Hayes, 1985; Meyer, Kondo, Nomura, Sakamoto, & Teraura, 1970; Nelson, Lowry, & Passonneau, 1966; Nilsson & Nordstrom, 1977). One of the metabolic disruptions that may occur due to brain trauma is the mismatch between lactate production due to glycolysis and disrupted lactate metabolism, leading to an increase in lactate accumulation (Gardiner, Smith, Kaggstrom, Shohami, & Siejo, 1982). Increased levels of lactate outside of the cell may result in neuronal dysfunction by inducing acidosis, membrane damage, altered blood brain barrier permeability, and cerebral edema (Kalimo, Rejmcrona, Soderfeldt, 1981; Kalimo, Rejmcrona, Soderfeldt, Olsson, & Siesjo, 1981; Meyers, 1979; Siemkowicz, & Hansen, 1978).

Following this period of potassium efflux, calcium influx and lactate accumulation is a period of neuronal suppression, termed spreading depression (Nicholson,& Kraig, 1981; Prince, Lux, & Neher, 1973; Van Harreveld, 1978; Somjen, & Giacchino, 1985). Spreading depression is characterized by depressed glucose metabolism, which can last up to four weeks post injury and can further the energy crisis that occurs due to the acute physiological reaction to biomechanical force (Bergsneider, 200). Overall, the change in ions inside and outside of the cell disrupts the
fine balance that occurs in the healthy brain and this disruption may have functional consequences post-concussion (Giza, & Hovda, 2014). Further, the *Spreading Depression*, furthers the energy crisis and stagnates the body’s inclination for homeostasis (Giza & Hovda, 2014). The pathophysiological changes that occur due to concussion may be amplified by the concurrent shift in cerebral blood flow (CBF) (Golding et al., 1999) and impaired cerebral autoregulation (Len & Neary, 2011).

### 2.3.2 Cerebral Blood Flow and Autonomic Regulation

Cerebral blood flow (CBF) changes following concussion vary as research shows differences in blood flow differ depending on the severity of the concussion and the timing along the recovery trajectory (Golding et al., 1999). Studies observing CBF following concussion have shown a decrease in CBF following injury and this decrease is relative to the severity of the injury (Golding et al., 1999; Grindel, 2003). However, this finding is controversial, as some studies do not show a difference in CBF after brain injury in persons over 30 years of age (Chan, Miller, & Dearden, 1992). Interestingly, studies performed in pediatric populations showed an increase in blood flow in the first day following mild TBI and a decrease in blood flow thereafter (Becelewski, & Pierzchala, 2003; Mandera, Larysz, & Wojtacha, 2002). A decrease in blood flow can further increase the energy crisis that occurs post-concussion due to the influx and efflux of ions and glutamate within the cells in the brain, which may be compounded by the alterations in blood flow (Shrey, Grisbach, & Giza, 2011). Beyond blood flow in the brain, it has been observed that the autonomic autoregulation of blood in the brain may be affected by concussion (Len & Neary, 2011; Leddy et al., 2007).

The cerebral autoregulation of blood and pressure in the brain is responsible for changes that occur in the brain, such as changes in systemic pressure (Len & Neary, 2011; Leddy et al., 2007; Rangel-Castill et al., 2008). Cerebral autoregulation is controlled by the autonomic nervous system, more specifically the sympathetic and parasympathetic nervous system (Len & Neary, 2011; Leddy et al., 2007). The autonomic nervous system (ANS) allows for adaptability of the brain and its systemic pressure by changing the diameter of blood vessels to change blood flow (Leddy et al., 2007; Gall et al., 2004). Some studies have examined cerebral autoregulation by observing heart rate variability and have found that the autonomic nervous systems role in
cerebral autoregulation was affected by traumatic brain injury up to 14 days post-concussion (Gall et al., 2004).

Figure 2.1: Pathophysiological changes induced by biomechanical forces. The pathophysiological changes that occur due to brain injury are the result of a cascade of events. Biomechanical insult ionic disequilibrium and metabolic disruptions, all in an environment of reduced blood flow and impaired autoregulation (Giza & Hovda, 2014).

2.4 Physiological Parameter: Heart Rate Variability

Heart rate variability (HRV) is a measure of the time intervals between heart beats, which may vary, due to factors such as: circadian cycle, stress, exercise, and respiration (Pecancha et al., 2013; Sztajzel, Jung, Sievert, & Beyes De Luna, 2008; Yilmaz et al., 2013). The sympathetic and parasympathetic nervous systems, two divisions of the autonomic nervous system, largely influence the time interval (R-R interval) between heart beats that are required for the body to
adapt to varying factors throughout the day (see figure 2.2) (Tran, Wijesuriya, Tarvainen, Karjalainen, & Craig, A, 2009; Armstrong, Kenny, Green, & Seely, 2011). These changes are facilitated by the neurohormonal influence of the ANS on the cardiac pacemaker, the sinoatrial (SA) node, which beats at a constant intrinsic rate of 100-120 beats per minute without the influence of the parasympathetic or sympathetic nerves (Malik & Camm, 2004). Due to key role the heart plays in adapting the body to different intrinsic and extrinsic cues, it is necessary that a physiological mechanism be in place to change the rate of the heart and blood flow throughout the body and the brain. Therefore, when necessary, the heart is slowed below its intrinsic pacemaker by the parasympathetic system, and by contrast, the heart rate is increased beyond its intrinsic rate by the sympathetic systems when necessary (Ernst, 2014). Changes in the influence of either autonomic system on the heart can be measured through analyzing heart rate variability.

Figure 2.2: Example of a QRS complex and RR Intervals

Understanding the influence of different branches of the autonomic nervous system on spectral components of HRV has facilitated the utility of HRV as an indirect measure of the autonomic nervous system and a potential indicator of physiological dysregulation associated with various health conditions. Akselrod et al. (1981) first discovered the association between spectral components of HRV and the different components of the autonomic nervous system. Three relevant spectral peaks associated with HRV and the ANS were identified: the VLF (very-low frequency) which contains frequencies below 0.04 Hz, LF (low frequency), which contain frequencies between 0.04 and 0.15 Hz, and Lastly, HF (high frequency) which contains frequencies between 0.15 and 0.4 Hz (Akselrod et al, 1981; Akselrod et al., 1985). The increasing sophistication of electrophysiology is continually evolving as is the understanding of the physiological origin of the hearts beat-to-beat variation and its association with phenomenon such as respiration rate, or autonomic control systems (Akselrod et al., 1981). Akselrod et al
(1981) used drugs for blocking the ANS and discovered that the parasympathetic system modulates the HF and LF spectral bands, and the sympathetic system modulates the LF spectral band, which has been corroborated in human and animal studies (Lewis et al., 2001; Akselrod et al., 1987).

The clinical utility of HRV as an indicator of the ANS has been explored in a variety of health conditions and many studies have been published on the use HRV as an effective and accessible tool (Ernst, 2014). Notably, Kleiger et al (1987) used HRV as a potential indicator to predict mortality after acute myocardial infarction, whereby higher measures of HRV were more favourable for recovery. The utility of HRV as a predictor of health outcomes has been explored by many disciplines and some researchers have even postulated that decreased variation between heart beats may predict an overall systemic issue and thus may be a risk factor for future disease or mortality (Pikkujamsa et al. 1999; Weber et al. 2010; Kaplan et al. 1991). Similar findings have been documented in multiple domains and literature has linked to changes in overall HRV to neurological disorders (Giubilei et al. 1998; Korpelainen et al. 1999), pain (Burton et al. 2009; Schubert et al. 1997), mental health disorders (Cohen et al., 1996; Thayer et al., 1996), and physical fitness (Sztajzel et al., 2008).

Changes in HRV may regulate according to an intrinsic homeostatic mechanism, but may become significantly lowered by stress, including that associated with the presence of tissue or cellular repair (Chen et al., 2011; Ng, Sundaram, Kadish, & Goldberger, 2009). Further, in a recent meta-analysis regarding emotional regulation and heart rate variability, Thayer et al (2012) propose that HRV may be a useful tool in understanding the physiological state of the brain. The assumption with all of these studies is that changes in HRV may reflect ineffective adaptation of the ANS to environmental cues or disruption of the balance of the two branches of the ANS on the heart.

Heart rate variability has been shown to be significantly associated with resting state brain activity (de Munck et al., 2008) such that increased heart rate variability has been linked to better cognitive and physical performance (Thayer, Hansen, Saus-Rose, Johansen, 2009). To date, heart rate variability research in the brain injury population has primarily been performed in populations with moderate to severe traumatic brain injury as an indicator of autonomic dysregulation and recovery from injury (King, Lichtman, Seliger, Ebert, & Steinberg, 1997;
Rapenne et al. 2001). Previous research has established HRV as a useful tool for evaluating stress capacity via autonomic dysfunction following severe traumatic brain injury in both adults (Su, Kuo, Kuo, Lai, & Chen, 2005) and children (Biswas, Scott, Sommerauer, Luckett, 2000). Changes in heart rate variability, specifically a decrease in variation, may reflect disturbed autonomic function following TBI due to neuropathophysiological changes associated with brain injury (Gall, Parkhouse, Goodman, 2004; Leddy, Kozlowski, Fung, Pendergast, Willer, 2007). This decrease in HRV is theorized to be due to an uncoupling of the neuroautonomic cardiovascular connection and normalization of autonomic balance and regulation is often associated with recovery (Baguley, Heriseanu, Felmingham, & Cameron, 2006). Although moderate to severe brain injury are distinct from concussion, and functional and structural changes may present differently, there is preliminary evidence to support the investigation of changes in HRV resulting from concussion similar to those found in other forms of brain injury (Abaji, Moore, Curnier, & Ellemberg, 2015; Gall et al., 2004; La Fountaine, Heffernan, Gossett, Bauman, & De Meersman, 2009).

Despite the initial support for the use of HRV in managing and diagnosing concussion, to date, there remains a paucity of literature regarding HRV and concussion, particularly in regards to the youth population. Research performed by Gall et al (2004) found that HRV measures among concussed male ice hockey players (N=14), with a mean age of 18 years (±0.4 years), showed no difference in HRV at rest compared to healthy controls. However, when the concussed individuals were dosed with the stress of exercise, changes in HRV parameters emerged compared to healthy controls (Gall et al., 2004). The authors observed a reduction in overall power and low and high frequency power (Gall et al., 2004), and theorized that the reduction in HRV resembled the uncoupling between the heart and the brain seen in the moderate to severe brain injury literature (Rapenne et al. 2001; King et al., 1997). Similar findings were observed in a study of concussed athletes (N=3) with an average age of 19 years old during an isometric hand grip test (IHGT) (La Fountaine, Heffernan, Gossett, Bauman, & De Meersman, 2009). Concussed athletes had reduced HRV measures at 48 hours post-injury as compared to their follow-up measures 2 weeks later when performing the IHGT (La Fountaine, Heffernan, Gossett, Bauman, & De Meersman, 2009). A preliminary study of college-aged athletes (N=10) also found a visible decrease in frequency domain measures at rest within 1 day post-concussion compared to pre-season baseline tests (Dobney, 2014). Although, changes in HRV may not be restricted to
the acute phases of concussion, as Abaji et al (2015) found modulations in HRV in college age athletes (N=12) at an average of 95 days post injury (±63 days). Modulations in HRV occurred during a hand grip test, and changes were not seen at rest when compared to matched controls (Abaji et al, 2015). Previous research highlights the potential of heart rate variability as a tool to observe physiological stress along the recovery trajectory, which can include both the acute and long-term physiological response to injury.

Due to the accessible nature of HRV, monitoring the change in this measure over time holds significant potential as an objective neurophysiological parameter that may help determine the rate of recovery and subsequently be used clinically to prescribe appropriately timed levels and intensity of activity following concussion (Thayer et al., 2009). Heart rate variability may provide support to currently used management tools, such as self-report measures and cognitive testing. Future research is needed to determine how monitoring the change in HRV at rest over time as a neurophysiological indicator of homeostatic disruption and recovery can be combined with other standard clinical assessment measures (i.e., the Post-Concussion Symptom Inventory, cognitive testing) to assist in the management of return to activity in children and youth following concussion.

2.5 Summary

Concussion has functional consequences among the pediatric population. Following biomechanical insult, there are pathophysiological changes associated with the metabolic disruptions that occur. Objectively measuring these pathophysiological changes is challenging and HRV may serve as an indicator of physiological stress post-concussion. Although studies have started to examine the effect that moderate to severe traumatic brain injuries have on heart rate variability, very few studies have focused on HRV in concussion, and even fewer have focused on concussion and youth populations. Understanding the unique physiological difference among youth compared to adult populations is important to determine whether a change in HRV is indicative of measures of function and recovery post-concussion.
Chapter 3

3.1 Overview

This thesis is a subset of a larger prospective longitudinal cohort study that is on-going. This chapter describes the recruitment of participants and the procedure in which data was collected. Further, the outcome measures used in the statistical analysis are described in detail. The analysis of the HRV signal using the RHRV program with the R Statistical program is outlined and explained. Lastly, this chapter describes the statistical methods used to analyze the relationship between HRV and self-reported symptoms of concussion, as well as, the relationship between HRV and concussion across the recovery trajectory.

3.2 Methods

3.2.1 Participants

The participant sample consisted of 29 healthy youth athletes, and was comprised of 21 females and 8 males with a mean age of 13.71 years (± 2.26) and 12.5 years (± 1.51) respectfully (see Chapter 4, for detailed demographic description). This convenience sample was recruited from 700 youth sport participants who completed pre-injury baseline testing in Ontario, Canada, between November 2013-November 2014 (see Appendix 2 for letters of support). The objective of the larger study was to evaluate the utility of HRV in the youth athlete population. The recruitment strategy of this larger study focused on youth sport teams across Ontario, thus all participants in this thesis were athletes, although this was not considered inclusion criteria.

General inclusion criteria:
1) Male or female, age 10-18 years;
2) Participants in the concussion group will have had a recent concussion (within 48 hours), diagnosed by their physician or by a physician at Holland Bloorview Kids Rehabilitation Hospital (Toronto, Ontario) according to 3rd International Consensus Statement on Concussion in Sport:
   i. A direct blow to the head, face, neck or elsewhere on the body with an impulsive force transmitted to the head;
   ii. Rapid onset of short lived impairment of neurologic function that resolves spontaneously;
iii. Neuropathological changes;
iv. A graded set of clinical symptoms that may or may not involve loss of consciousness;
v. No abnormality on standard structural neuroimaging studies (MRI, CT Scan) if this was included in patient’s diagnosis of concussion (McCrory et al., 2009).

Note: None of the participants in this study received standard neuroimaging such as a CT scan or MRI, as these protocols are not routinely administered as part of concussion assessment protocols.

Exclusion criteria:
1) Prior history of a cardiovascular or neurological condition;
2) Prior history of psychiatric disease or mental health conditions;
3) Currently taking medication that can influence heart rate or blood pressure

3.3 Procedure

The data presented in this study represents a subset of data being collected as part of a larger, prospective, longitudinal cohort study. The larger study includes assessments of neurocognition, balance, strength and agility in addition to post-concussion symptoms and HRV.

3.3.1 Pre-injury/Baseline Testing

All participants completed the same battery of assessments during the pre-injury/baseline testing. After obtaining informed consent, participants were asked to complete a demographic questionnaire (including medical/concussion, sport and education history), along with a baseline measure of post-concussion symptoms (using the PCSI). Participants were encouraged to ask questions if any information was unclear.

Participants were fitted with a heart rate strap and taught how to use the heart rate watch appropriately. Heart rate recording was obtained from a Polar RS800CX watch (RS800cx; Polar Electro, Kemple, Finland) and chest strap. The RS800CX watch has a 1 millisecond sampling resolution and an accuracy of ±0.5 seconds/day. The full technical specifications of the RS800CX watch and monitor can be found in Appendix 5. Participants in this thesis represent a subset of individuals from a larger ongoing study where the HRV protocol
changed during the study. Participants had either long duration recordings (N=9), short duration recordings (N=7), or received short duration recordings at baseline and long duration during all follow up recordings (N=13). Both short and long duration recording protocols occurred at the end of each testing session. The short duration recording protocol occurred for 15 minutes, which consisted of 10 minutes of lying down and 5 minutes of sitting. In the long duration recording protocol, HRV was collected during all participants’ daily activities following each testing session for a 24 hour period.

Participants who received the long duration recordings were provided with an activity log and asked to complete the log based on a 24-hour day. Instructions were provided with information on how to remove the strap/monitor and switch off the system.

3.3.2 Post-Injury/Follow-up Testing
After a diagnosis of concussion was obtained from a physician, participants were encouraged to return for follow-up testing soon after an injury (within 48 hours). Upon the first follow-up visit, research staff recorded injury details and any functional concerns using the Acute Concussion Evaluation (ACE) form. Participants were provided with post-concussion information, education and resources. Heart rate and post-concussion symptom data was collected weekly until all concussion symptoms had resolved. Participants were scheduled to repeat data collection at 1-week, 1-month, 3 months and 6 months post-concussion symptom resolution. However retention of recruitment for the post-symptom resolution time points was variable, which is discussed further in chapter 5 regarding the limitations of this thesis.

Demographic factors such as age, gender and concussion history were not included in the statistical analysis as there was not a sufficient sample size to retain statistical power. Thus to focus on the objective(s) of this thesis, and to ensure statistical power, the outcome measures used in this thesis were a subset of the outcome measures that were used in the larger cohort study. For this thesis, participants PCSI score, and HRV measures were the two outcome measures used to assess the relationship between concussion and neurophysiological stress.
3.4 Outcome Measures

3.4.1 Post-concussion Symptom Inventory (PCSI)

Self-report of concussion symptoms were assessed using the Post-Concussion Symptom Inventory (PCSI) at pre-injury and compared to post-injury scores (Gioia, Schneider, Vaughan, & Isquith, 2009). The total symptom score was calculated based on the sum of the ratings for each of the symptoms (Gioia et al, 2009). Two different versions of this test were used to account for the different ages of participants. The Post-Concussion Symptom Inventory for Children (PCSI-C) (Gioia, Janusz, Sady, Vaughn, Schneider, & Natale, 2012) was utilized for ages 8-12 years and contains items rated on a 3-point Likert scale assessing experiential presence of symptom(s), whereby, 0=not a problem, 1=A little, and 2=A lot. The Post-Concussion Symptom Inventory (PCSI) was utilized for ages 13-18, and employs a 6-point Likert scale, whereby participants report the presence or absence of commonly reported concussion symptoms as, 0= Not a problem, 3= Moderate problem and 6= Severe problem (Gioia, Schneider, Vaughan, Isquith, 2009).

PCSI outcome values were the total score on the test, and were compared to their baseline measures in analysis. The scores of the two age dependent versions of the PCSI were converted and weighted to match each other since each test differs in the length of items used and the types of scales for rating symptoms. This was accomplished by multiplying each item score on the PCSI for children by 3 to account for the different rating scales, and then the total score was multiplied by 1.83 to account for the different number of items in the inventory.

3.4.2 Heart Rate Variability

HRV measures were calculated for each subject using standard time and frequency domain parameters set out by the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology for both long duration (24 hour) recordings and 15-minute recordings at rest (Task Force, 1996). The RHRV package in the R Statistical Program was used to calculate heart rate variability.
The time-domain measures measure the variation in the heart rate over time by assessing the intervals between heartbeats over a continuous ECG recording. The HRV time-domain outcomes measures are summarized in table 3.2.

Table 3.1: Time-domain measures used in RHRV programs.

<table>
<thead>
<tr>
<th>Time Domain Measure</th>
<th>Units of Measurement</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td>ms</td>
<td>Standard deviation of the RR intervals in the recording</td>
</tr>
<tr>
<td>SDANN</td>
<td>ms</td>
<td>Standard deviation of the averages of the 5 minute RR intervals in a recording</td>
</tr>
<tr>
<td>pNN50</td>
<td>%</td>
<td>Proportion of NN intervals differing by more than 50 ms</td>
</tr>
</tbody>
</table>

Frequency domain measures are unique to this study protocol and were created using the RHRV package within the R statistical environment (see Appendix 1). All of the frequency domain measures that were created were calculated via 5 minute windows that occurred consecutively throughout the recording (see table 3.3). Max total HRV (0-0.4 Hz) is the signal throughout the recording that was highest for a single 5-minute window. Derived from this signal are the high frequency (0.15-0.4 Hz) and low frequency (0.04-0.15 Hz) measures within the 5-minute window that contained the highest total power. Lastly, two variables that were created were the maximum signal for both high frequency and low frequency throughout the recording, that is, which 5-minute window had the maximum high frequency signal (0.15-0.4 Hz) and which 5-minute window had the maximum low frequency window (0.04-0.15 Hz) throughout the recording (see Table 3.4)(Task Force, 1996).

Table 3.2: Frequency-domain measures used in RHRV programs.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units of Measurement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max Total HRV (0-0.4 Hz)</td>
<td>ms²</td>
<td>Maximum HRV signal per 5-minute window in total recording. Thought to be an indicator of the overall autonomic nervous system.</td>
</tr>
<tr>
<td>Max HRV HF (0.15-0.4 Hz)</td>
<td>ms²</td>
<td>High Frequency value at corresponding Maximum HRV signal per 5 minute window. Thought to be an indicator of the parasympathetic system.</td>
</tr>
<tr>
<td>Max HRV LF (0.04-0.15 Hz)</td>
<td>ms²</td>
<td>Low Frequency value at corresponding Maximum HRV signal 5 per minute window. Thought to be an indicator of the parasympathetic and sympathetic system.</td>
</tr>
<tr>
<td>Max HF (0.15-0.4 Hz)</td>
<td>ms²</td>
<td>Maximum High frequency signal per 5-minute window throughout recording. Thought to be an indicator of the parasympathetic system.</td>
</tr>
</tbody>
</table>
| Max LF  
(0.04-0.15 Hz) | ms²  | Maximum Low Frequency signal per 5 minute window throughout recording. Thought to be an indicator of the parasympathetic and sympathetic system. |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Max LF/Max HF</td>
<td>ms²</td>
<td>Ratio of the maximum LF and maximum HF, which is thought to be an indicator of the balance between the parasympathetic and sympathetic systems.</td>
</tr>
</tbody>
</table>

Computing heart rate variability using R is a step-wise and iterative approach, which is described in the following 5 steps. See appendix 1 for the full script that was used in the R statistical program to calculate HRV using the RHRV package.

1. Firstly, the RR intervals, or the time between successive R complexes is calculated using the RHRV package. Successive R-wave times are computed, where by the n-th RR interval is calculated; however, these time series are not equidistantly sampled, due to the variability of the heart (see Appendix 6 for raw data).

2. The time series is interpolated using the *InterprolatedNIHR* function within the RHRV program, which allows for evenly spaced heart rate values. This function allows for a uniformly sampled heart rate series, which is essential for calculating frequency domain measures (see Appendix 8 for raw data).

3. Since the recording of HRV is susceptible to noise within the heart rate signal, it is filtered within the RHRV program using the *FilterNIHR* function, see Appendix 7 for visualization of non-interpolated data. Standard values are obtained by identifying minimum and maximum heart beats per minute. The default values of the RHRV program, which were implemented for this protocol, are assigned as a minimum of 25 beats per minute and a maximum of 200 beats per minute.

4. Time domain analysis is calculated via the *CreateTimeAnalysis* function within the RHRV program. With the *CreateTimeAnalysis* function, the RHRV program allows the specification of the window that will be used to calculate the RR intervals, which is set for the entire recording in this protocol.
5. The frequency analysis is created via the transformation of the signal using the Fast Fourier Transform method (FFT). Fast Fourier Transform is a non-parametric method for determining the power spectrum density of the HRV signal (Task Force, 1996). The `CalculatePowerBand` function in RHRV is used to calculate the power spectrum density of the RR intervals using FFT. The window size (300 seconds) and window shift (300 seconds) are defined in the R script outlined in Appendix 1. Window size is the length of time that the HRV signal is captured for the frequency analysis, which is measured in seconds. The window shift is the displacement of the window across the recording. In this protocol, multiple consecutive windows are observed throughout each recording to determine the frequency domain parameters. The frequency ranges used in this protocol were set to the standards outlined by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (see Table 3.2) (Task Force, 1996). The output for LF, HF and total power are visualized in Appendix 9 to 11 respectively.

<table>
<thead>
<tr>
<th>Value</th>
<th>ULF</th>
<th>VLF</th>
<th>LF</th>
<th>HF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minimum (Hz)</strong></td>
<td>0</td>
<td>0.003</td>
<td>0.04</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Maximum (Hz)</strong></td>
<td>0.003</td>
<td>0.04</td>
<td>0.15</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Ranges for heart rate variability set out by the European Task Force on Cardiology. The ranges are ultra low frequency (ULF), very low frequency (VLF), low frequency (LF), and high frequency (HF) (Task Force, 1996).

### 3.5 Statistical Analysis

#### 3.5.1 Overview

Heart rate variability was analyzed in regards to its relationship with self-reported symptoms of concussion across baseline and the recovery trajectory, as well as, the effect that concussion had on different measures of HRV over time. Analyzing the effect of concussion on heart rate variability measures was accomplished by using individual’s baseline measures as a benchmark for pre-injury status. Spearman correlations were used to observe the relationship between self-reported symptoms of concussion and different parameters of heart rate variability. Secondly,
the effect of concussion on measures of HRV across the recovery trajectory was analyzed using mixed-effect modeling. All statistical analyses were completed using R Statistical Program v. 3.2.0 and the threshold for statistical significance was set at $p \leq 0.05$ (R Development Core Team).

3.5.2 Heart Rate Variability and PCSI

Spearman correlations were used as a non-parametric method to evaluate the association between time and frequency domain measures of HRV and PCSI. As seen in Appendix 3, the Kernel Densities of each HRV measure showed a non-normal distribution of data, thus a non-parametric method of analysis was necessary. Participant’s baseline measures were grouped together to capture group characteristics before their concussion, and post-concussion groups were separated and grouped by days post injury between 0 and 21 days. Previous unpublished research by Dobney (2014), showed a decrease in HRV measures in college age athletes, within 48 hours of concussion, therefore, time was an important factor to account for in analysis. In order to capture the relationship between PCSI and HRV measures in the acute phase of concussion, data points between days 0 and 7 were grouped together. Each participant that completed the study protocol returned for their follow up appointments post-concussion at different times along their recovery trajectory. Due to the small sample size of this data set and variable follow up times, individuals were grouped between 0 and 7 days, rather than a narrower time frame, to ensure an adequate sample size for analysis. Further, since each participant had multiple follow up data points, groups A2 and A3 were created to ensure that data points did not overlap within different groups (see Table 3.5). Data points beyond 21 days post injury were not included in the correlation analyses because there was not a sufficient amount of data.

<table>
<thead>
<tr>
<th>Measures</th>
<th>Days Post Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>A0</td>
<td>Baseline</td>
</tr>
<tr>
<td>A1</td>
<td>0-7 days post injury</td>
</tr>
<tr>
<td>A2</td>
<td>8-14 days post injury</td>
</tr>
<tr>
<td>A3</td>
<td>15-21 days post injury</td>
</tr>
</tbody>
</table>
3.5.3 HRV Measures Across Time and Injury Status

Mixed-effect modeling was used to evaluate and describe the effect of concussion on measures of HRV across the recovery trajectory. Mixed effect modelling allows the user to define their variables as either fixed effects or random effects. Random variables may be defined as unobserved variables that may be unique to a certain context (Bates, 2010). Separate models were created for each dependent variable and each model was built with both fixed and random effects. Independent fixed effect variables included in the analysis were as follows: Post Concussion Symptom Inventory, days post injury, concussion status (yes/no), recording type (short duration/long duration)(see table 3.6). Each participants ID was used as a random effect, which allowed intra-individual observations of the effect of concussion on measures of HRV. All analyses were performed with the lme4 package within the statistical environment R (R Development Core Team).

A step-wise approach is required to determine the proper fit of the model to the data as outlined by the literature (Turner, 2015; Bates et al, 2014). Building a mixed model is an iterative approach, outlined in the following steps:

1. Building a null model that acts as a baseline that can be compared against all other models that are created (Hox, 2010). For the null model, no predictors are included in the model and only the dependent variable and a random intercept is included for the random effect (Kreft & Leeuw, 1998).

2. To create the most parsimonious model, each predictor is then added to the model using a stepwise and iterative approach. To establish the best fit model, the fit indexes of the deviance from each model are compared to the null model. The deviance is an indication of how well the model fits the data (Hox, 2010).

3. The difference between the deviance scores from each model is compared using chi-square statistic (Turner, 2015). The lower the deviance score, the better the fit of the model to the data (Hox, 2010).

All the models used in this thesis specified the same fixed effects and random effects for each dependent variable. Using a step-wise and iterative approach outlined above, each fixed effect
improved the deviance of the overall model. Using the degrees of freedom and the Chi-squared method, each of the fixed effects that were included, significantly improved the model.

**Table 3.5**: Variables used in the Mixed Effect Models.

<table>
<thead>
<tr>
<th>Dependent Variables</th>
<th>Fixed Effects</th>
<th>Random Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td>Days Post Injury</td>
<td>Participant ID (Participant’s Identification number)</td>
</tr>
<tr>
<td>SDANN</td>
<td>PCSI</td>
<td></td>
</tr>
<tr>
<td>pNN550</td>
<td>Concussion Status (yes/no)</td>
<td></td>
</tr>
<tr>
<td>HRV Index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max Total HRV</td>
<td>Recording Type (short duration/long duration)</td>
<td></td>
</tr>
<tr>
<td>Max HRV HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max HRV LF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max LF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4 Results

4.1 Overview

This chapter outlines the demographic characteristics of the concussed participants in this study. Descriptive statistics were generated for HRV measures at baseline and post injury. Further, significant results from the spearman correlations between PCSI and HRV measures elucidate the relationship between self-reported symptoms of concussion and heart rate variability. Mixed model analysis of both time-domain and frequency domain HRV measures is summarized in respect to the relationship of these measures along the recovery trajectory.

4.2 Demographic Information

Participants consisted of 29 healthy youth athletes, including 21 females and 8 males with a mean age of 13.71 years (± 2.26 years) and 12.5 years (± 1.51 years) respectfully. The average age of participants was 13.38 years (±2.13 years) at baseline. The average height and weight of participants was 156.57 centimeters (cm) (±13.36 (cm)) and 50.83 kilograms (kg) (±8.75 (kg)) respectfully.

The mechanism of injury of each participant was documented, as well as the type of activity the individual was participating in while they sustained their concussion. In our sample of 29 youth, 21 of the concussions were sport related, 3 injuries were non-sport related, and details surrounding 5 of the injuries were not documented by the research team. The majority of the sport related injuries were sustained during ice hockey.

Lastly, co-morbidities were documented for each participant in the study. Of the 29 participants, 2 participants reported receiving speech therapy; only 1 participant reported receiving special education. Of the 29 concussed participants, 13 reported having sustained at least one previous concussion.

4.3 Post Concussion Symptom Inventory

The scores from the PCSI for each concussed participant were graphed across number of days post-injury for each follow-up session (see figure 4.1). Visual analysis of the PCSI data shows an initial increase in PCSI scores post-concussion, followed by a decrease in PCSI scores as days post injury increase along the recovery trajectory (see figure 4.1). Statistical analysis of the PCSI
data showed a negative correlation between PCSI scores at follow up one (between 0-7 days post-concussion) and days post injury within follow up one \((r=-0.44, P=0.03)\), suggesting that PCSI scores decrease as days post injury increase within 7 days of the injury. Visual analysis shows similar trends when males and females are graphed separately, suggesting an increase in PCSI scores following concussion, followed by a decrease in scores along the recovery trajectory.

Participants’ baseline measures were categorized as A0, and post-injury groups were separated by days post-injury between 0 and 21 days post injury (see table 3.5). Data points beyond 21 days post injury were not included in the correlation analyses because there was not a sufficient amount of data.

**Figure 4.1** Post-concussion Symptom Inventory Score for all concussed participants. A0 through A3 using a box plot to depict the data. Outliers are illustrated in this box plot via small dots outside of the plot’s data range.
4.4 Heart Rate Variability Measures

4.4.1 Descriptive Statistics

Box plots were generated for each time-domain and frequency domain heart rate variability measure. With respect to the time-domain measures, SDNN, SDANN, and HRV Index all show a visible increase in the group median of heart rate variability post-concussion, as indicated by a thick black line in figures 4.2 to 4.5 below. For the time-domain measures that showed a visible increase in group medians, there was also a visible increase in the interquartile range of each score, suggesting a larger group dispersion of the data post-concussion as compared to ranges at baseline (see appendix 3 for Kernel Distribution of HRV measures).

Figure 4.2: SDNN and Test point. This figure is a visualization of SDNN across the trajectory of time. A0 is baseline, A1 is 0-7 day post injury, A2 is 8-14 days post injury, and A3 is 15-21 days post injury.
Figure 4.3: SDANN and Test point. This figure is a visualization of SDANN across the trajectory of time. A0 is baseline, A1 is 0-7 day post injury, A2 is 8-14 days post injury, and A3 is 15-21 days post injury.

Figure 4.4: pNN50 and Test point. This figure is a visualization of pNN50 across the trajectory of time. A0 is baseline, A1 is 0-7 day post injury, A2 is 8-14 days post injury, and A3 is 15-21 days post injury.
Figure 4.5: HRV Index and Test point. This figure is a visualization of HRV Index across the trajectory of time. A0 is baseline, A1 is 0-7 day post injury, A2 is 8-14 days post injury, and A3 is 15-21 days post injury.

Several frequency domain HRV measures showed a visible increase in group medians from baseline to follow up post-concussion, as indicated by the thick black line in figures 4.6 to 4.10. Similar to time domain HRV measures, several frequency domain measures showed a visible increase in interquartile range, suggesting a larger dispersion of the data post-concussion as compared to baseline scores (see figures 4.6-4.10).
Figure 4.6: Max HRV HF and Test point. This figure is a visualization of Max HRV HF across the trajectory of time. A0 is baseline, A1 is 0-7 day post injury, A2 is 8-14 days post injury, and A3 is 15-21 days post injury.

Figure 4.7: Max HRV LF and Test point. This figure is a visualization of Max HRV LF across the trajectory of time. A0 is baseline, A1 is 0-7 day post injury, A2 is 8-14 days post injury, and A3 is 15-21 days post injury.
Figure 4.8: Max HF and Test point. This figure is a visualization of Max HF across the trajectory of time. A0 is baseline, A1 is 0-7 day post injury, A2 is 8-14 days post injury, and A3 is 15-21 days post injury.

Figure 4.9: Max LF and Test point. This figure is a visualization of Max LF across the trajectory of time. A0 is baseline, A1 is 0-7 day post injury, A2 is 8-14 days post injury, and A3 is 15-21 days post injury.
4.4.2 Heart Rate Variability and Post-Concussion Symptom Inventory Scores

Spearman correlations were used to observe the relationship between measures of heart rate variability and post-concussion symptom inventory scores. At baseline, there were positive correlations between PCSI and pNN50 ($r_s=0.41$, $P=0.04$), and Max HRV LF ($r_s=0.42$, $P=0.02$), whereby higher scores of self-reported symptoms on the PCSI were associated with higher scores of pNN50 and Max HRV LF.

At follow up one (0-7 days post-concussion), there were positive correlations between PCSI and SDNN ($r_s=0.60$, $P=0.001$), HRV Index ($r_s=0.41$, $P=0.04$), Max Total HRV ($r_s=0.63$, $P=0.001$), and Max LF ($r_s=0.47$, $P=0.03$) whereby higher scores of self-reported symptoms were associated with higher values of these HRV measures. At follow up two (8-14 days post-concussion), there were positive correlations between PCSI and SDNN ($r_s=0.74$, $P=0.01$), Max HRV HF ($r_s=0.78$, $P=0.001$),
$P=0.003$), and Max HRV LF ($r_s=0.81$, $P=0.004$), whereby higher scores of self-reported symptoms were associated with higher values of these HRV measures. There were no significant associations between PCSI and HRV measures at follow up three (15-21 days post-concussion).

**Table 4.1:** Significant associations between measures of HRV and PCSI at corresponding time points.

<table>
<thead>
<tr>
<th>Relationship Between Post Concussion Symptom Inventory Scores and HRV Measures</th>
<th>Baseline</th>
<th>A1 (0-7 days post injury)</th>
<th>A2 (8-14 days post injury)</th>
<th>A3 (15-21 days post injury)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pNN50 ($r_s=0.41$; $P=0.04$)</td>
<td>SDNN ($r_s=0.60$; $P=0.00$)</td>
<td>SDNN ($r_s=0.74$; $P=0.01$)</td>
<td>No significant correlations</td>
<td></td>
</tr>
<tr>
<td>Max HRV LF ($r_s=0.42$; $P=0.02$)</td>
<td>HRV Index ($r_s=0.41$; $P=0.04$)</td>
<td>Max HRV HF ($r_s=0.78$; $P=0.00$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max Total HRV ($r_s=0.63$; $P=0.00$)</td>
<td>Max HRV LF ($r_s=0.81$; $P=0.00$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max LF ($r_s=0.47$; $P=0.03$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: **Denotes a strong relationship between variables, and * denotes a moderate relationship between variables.

### 4.4.3 Mixed Model Analysis

Mixed model analysis was used to evaluate the effect of concussion on different measures of heart rate variability across time. Baseline measures were used as a benchmark of HRV values pre-injury and these values were compared to HRV values post-concussion, while accounting for days post injury, concussion status, PCSI score, and recording type. Participant ID was used as a random effect, but is not included in the main effects discussed below. Both time and frequency domain measures are analyzed to describe the effect of concussion, the effect of time, and presence or absence of self-reported concussion symptoms. Appendix 4 illustrates the residuals of each mixed model, which were used to test the assumptions of homoscedasticity, linearity, and distribution of residuals for each model.
4.4.3.1 SDNN
Results of the mixed modeling analysis revealed significant effects of days post injury, PCSI and the interaction between PCSI and days post injury on SDNN. Days post injury had a significant main effect on SDNN ($B=0.211$, $CI\ [0.14, 0.40]$, $SE=0.09$, $t=2.37$, $p=.002$), whereby a higher SDNN was found with increasing days post injury (see Figure 4.3). Concussion status was not significant in predicting SDNN. Thus, it did not matter whether an athlete was injured, but rather, how far along they were in time post injury. PCSI also had a main effect on SDNN ($B=0.965$, $CI\ [0.49, 1.60]$, $SE=0.26$, $t=3.68$, $p=.000$), whereby a higher SDNN was found with higher self-reports of post-concussion symptoms when compared to those who had fewer self-reported symptoms (see Figure 4.2). Recording type was not found to be significant in this model. A significant interaction between days post injury and SDNN was also found ($B=-0.01$, $CI\ [-0.02, -0.005]$, $SE=0.01$, $t=-2.88$, $p=.005$).

4.4.3.2 SDANN
Results of the mixed modeling analysis revealed significant effects of days post injury, PCSI and the interaction between PCSI and days post injury on SDANN. Days post injury had a significant main effect on SDANN ($B=0.20$, $CI\ [0.14, 0.43]$, $SE=0.10$, $t=1.20$, $p=.05$), whereby a higher SDANN was found with increasing days post injury (see Figure 4.5). Concussion status was not significant in predicting SDANN. Thus, it did not matter whether an athlete was injured, but rather, how far along they were in time post injury. PCSI also had a main effect on SDANN ($B=0.79$, $CI\ [0.20, 1.42]$, $SE=0.30$, $t=2.67$, $p=.01$), whereby a higher SDANN was found with higher self-reports of post-concussion symptoms when compared to those who had fewer self-reported symptoms (see Figure 4.4). These results were still robust after controlling for a significant recording type ($B=21.37$, $CI\ [7.79, 40.46]$, $SE=9.10$, $t=2.35$, $p=.02$), whereby those who completed the long duration recording protocol were found to have a higher SDANN when compared to participants who completed the short duration recording protocol. A significant interaction between days post injury and SDANN was also found ($B=-0.02$, $CI\ [-0.03, -0.004]$, $SE=0.01$, $t=-2.37$, $p=.02$).
4.4.3.3 pNN50
Results of the mixed modeling analysis revealed significant effects of PCSI and the interaction between PCSI and days post injury on pNN50. PCSI had a main effect on pNN50 ($B= 0.25$, $CI [0.102, 0.59]$, $SE=0.11$, $t= 2.23$, $p=.03$), whereby a higher pNN50 was found with higher self-reports of post-concussion symptoms when compared to those who had fewer self-reported symptoms (see Figure 4.6). Concussion status was not significant in predicting pNN50. These results showed an effect of recording type ($B=-10.87$, $CI [-14.50, -1.57]$, $SE=3.81$, $t=-2.85$, $p=.006$), whereby those who completed the short duration recording protocol were found to have a higher pNN50 when compared to participants who completed the long duration recording protocol. A significant interaction between days post injury and pNN50 was also found ($B= -0.01$, $CI [-0.01, -0.001]$, $SE=0.002$, $t=-2.70$, $p=.01$).

4.4.3.4 HRV Index
Results of the mixed modeling analysis revealed significant effects of days post injury, PCSI and the interaction between PCSI and days post injury on HRV Index. Days post injury had a significant main effect on HRV Index ($B= 0.06$, $CI [0.001, 0.11]$, $SE=0.02$, $t= 2.37$, $p=.02$), whereby a higher HRV Index score was found with increasing days post injury (see Figure 4.8). Concussion status was not significant in predicting HRV Index. Thus, it did not matter whether an athlete was injured, but rather, how far along they were in time post injury. PCSI also had a main effect on HRV Index ($B= 0.32$, $CI [0.16, 0.48]$, $SE=0.07$, $t= 4.43$, $p=.00$), whereby a higher HRV Index was found with higher self-reports of post-concussion symptoms when compared to those who had fewer self-reported symptoms (see Figure 4.7). These results showed an effect of recording type ($B=5.60$, $CI [2.12, 10.53]$, $SE=2.46$, $t=-2.28$, $p=.03$), whereby those who completed the long duration recording protocol were found to have a higher HRV Index when compared to participants who completed the short duration recording protocol. A significant interaction between days post injury and HRV Index was also found ($B=-0.004$, $CI [-0.01, -0.001]$, $SE=0.002$, $t=-2.92$, $p=.004$).

4.4.3.5 Max Total HRV
Results of the mixed modeling analysis revealed days post injury, PCSI, and concussion status were not significant in predicting total score on max total HRV. However, there was a significant effect of recording type ($B=11472.7821$, $CI [3.92, 33.42]$, $SE=3533.45$, $t= 3.27$, $p=.003$),
whereby those who completed the long duration recording protocol were found to have a higher max total HRV score when compared to participants who completed the short duration recording protocol.

### 4.4.3.6 Max HRV HF

Results of the mixed modeling analysis revealed significant effects of days post injury, PCSI and the interaction between PCSI and days post injury on Max HRV HF. Days post injury had a significant main effect on Max HRV HF \((B= 5.60, CI \[0.40, 10.29\], \ SE=2.35, t= 2.39, p=.01)\), whereby a higher Max HRV HF score was found with increasing days post injury (see Figure 4.10). Concussion status was not significant in predicting Max HRV HF. Thus, it did not matter whether an athlete was injured, but rather, how far along they were in time post injury. PCSI also had a main effect on Max HRV HF \((B= 22.86, CI \[8.18, 36.47\], \ SE=6.83, t= 3.34, p=.002)\), whereby a higher Max HRV HF score was found with higher self-reports of post-concussion symptoms when compared to those who had fewer self-reported symptoms (see Figure 4.9). A significant interaction between days post injury and Max HRV HF was also found \((B= -0.40, CI \[-0.74, -0.12\], \ SE=0.15, t=-2.70, p=.00)\).

### 4.4.3.7 Max HRV LF

The results of the mixed modelling analysis indicate that there were no main effects on max HRF LF. Days post injury, PCSI, recording type and concussion status were not significant in predicting total score on max HRV LF \((p>0.05)\).

### 4.4.3.7 Max HF

The results of the mixed modelling analysis indicate that only PCSI had a main effect on max HF. Days post injury, PCSI, recording type and concussion status were not significant in predicting total score on max HF. PCSI also had a main effect on max HF \((B=25.51, CI \[5.91, 49.13\], \ SE=9.94, t= 2.57, p=.01)\), whereby a higher max HF score was found with higher self-reports of post-concussion symptoms when compared to those who had fewer self-reported symptoms (see Figure 4.11).

### 4.4.3.8 Max LF

The results of the mixed modelling analysis indicate that there were no main effects on max LF. Days post injury; PCSI, recording type and concussion status were not significant in predicting
4.4.3.9 LF/HF Ratio

The results of the mixed modelling analysis indicate that there was only an interaction between days post injury and PCSI on the LF/HF ratio. Days post injury, PCSI, recording type and concussion status were not significant in predicting total score on LF/HF ratio. A significant interaction between days post injury and LF/HF ratio was also found ($B= 0.00$, $SE=0.00$, $t= -2.14 \ p=.04$).

4.5 Summary

This chapter discusses the results of the heart rate variability analysis in regards to several different objectives. Firstly, the correlations between PCSI scores and HRV measures illustrated the relationship that is present between measures of self-reported symptoms and HRV. The positive correlations between different HRV variables and PCSI at baseline, follow up one (0-7 days post-concussion) and follow up two (8-14 days post-concussion) elucidate that higher rates of HRV are associated with higher scores of PCSI at these time points.

Table 4.2: Summary table of the main effects in the mixed model analysis with + used as positive significant main effects and – used as negative significant main effects. Grey boxes in the table are variables with no significant main effect in the model.

<table>
<thead>
<tr>
<th>HRV Variable</th>
<th>PCSI</th>
<th>Days Post Injury</th>
<th>Concussion Status</th>
<th>Recording Type</th>
<th>Days Post Injury and PCSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDANN</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pNN50</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>HRV Index</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Max Total HRV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max HRV HF</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Max HRV LF</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max HF</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max LF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF/HF Ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The relationship between PCSI and HRV was similar when examining the mixed model analysis. The effect of self-reported symptoms on HRV was a prevalent factor among several different
HRV measures. Moreover, days post injury had a significant main effect on several different HRV measures. The significant main effects of each model are summarized in Table 4.3 Interestingly, concussion status did not have an effect on any of the time or frequency domain measures examined in this protocol, even when days post injury showed a significant effect. These findings suggest a relationship between HRV and PCSI across the recovery trajectory which may be mediated by days post injury. Further analysis is needed to elucidate the relationships between these variables.
Chapter 5

5.1 Overview

This thesis aimed to generate preliminary observations about the feasibility of collecting heart rate variability as a measure of physiological stress following concussion in the youth athlete population. Three objectives were created to accomplish this task. Firstly, this thesis aimed to determine a protocol for the assessment of heart rate variability among youth athletes. Second, this thesis aimed to generate preliminary observations about the relationship between objective (HRV) and subjective (PCSI) measures of physiological stress across the recovery trajectory of concussion. Lastly, this thesis aimed to generate preliminary observations regarding an observable change following concussion in youth athletes as compared to baseline measures.

5.2 Summary of Results

Preliminary observations about the relationship between HRV and subjective measures of post-concussion symptoms illustrate the potential utility of HRV in observing physiological stress following concussion in the youth population. At the onset of this study, it was hypothesized that higher reported symptoms of concussions would negatively correlate with lower scores of heart rate variability; however, the final results of this thesis contradicted that assumption.

Findings from the mixed model analysis suggest an increase in HRV along the recovery trajectory (across days post injury). Mixed effect models revealed that higher measures of self-reported symptoms had a relationship with heart rate variability and indicated an interaction between days post-injury and PCSI scores such that the relationship between HRV and PCSI scores varied depending on the number of days post-concussion.

The positive association between heart rate variability measures and self-reported concussion symptoms at rest is interesting because it may contradict previous research examining HRV in concussed athletes (Gall et al 2004; La Fountaine et al, 2009). Interestingly, these studies observed an overall decrease in HRV following concussion; however, these changes were seen when individuals were asymptomatic and while dosed with physiological stressors (see Table 5.1). Previous research did not observe changes in HRV following concussion while individuals were at rest (Abaji et al, 2014; Gall et al, 2004; La Fountaine et al, 2009). The decrease in HRV
observed in previous brain injury studies is theorized to be due to a disruption of the autonomic nervous system caused by the brain injury (Baguley, Heriseanu, Felmingham, & Cameron, 2006).

Table 5.1: Summary of previous research regarding HRV and concussion.

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Days Post Injury</th>
<th>Recording Protocol</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gall et al., 2004</td>
<td>14 Concussed (Male); 14 Controls (Male)</td>
<td>1.8 (±2 days)</td>
<td>5 Minutes asymptomatic at rest; 5 minutes during low to moderate exercise</td>
<td>Decrease in Mean RR interval and Decrease in LF and HF power during exercise, compared to controls.</td>
</tr>
<tr>
<td>La Fountaine et al., 2009</td>
<td>3 Concussed (1 female; 2 male); matched controls</td>
<td>48 hours; 2 weeks</td>
<td>5 minutes at rest; 3 minutes Isometric hand grip contraction (IHGT)</td>
<td>No significant change at rest; decrease in heart rate complexity at 48 hrs during IHGT.</td>
</tr>
<tr>
<td>Abaji et al., 2014</td>
<td>12 concussed (male); 12 matched controls</td>
<td>95 (±63 days post injury)</td>
<td>5 minutes at rest; 3 minutes Isometric hand grip contraction (IHGT)</td>
<td>No significant change at rest; increase in LF. Increases in LF/HF ratio during IHGT.</td>
</tr>
</tbody>
</table>

LF: low frequency; HF: high frequency; mTBI: traumatic brain injury.

Interpreting the change in HRV measures observed in this thesis is challenging based on its’ complexity and dynamic physiological characteristics. Understanding the personal characteristics of each athlete could help explain the influences that each individual has on changes in HRV.

For example, HRV may be affected by a multitude of factors throughout daily activity including: stress (Berston & Cacioppo, 2004), physical activity (Perini & Veicsteinas, 2003), circadian rhythm (Viola et al, 2002), sleep (Busek et al, 2005), or a pathophysiology such as brain injury (Gall et al, 2004; King et al, 1997; La Fountaine et al, 2009; Rapenne et al 2001). The findings in this thesis may contradict previous research due to the fact that the concussions documented in this research were not severe enough to elicit an observable cardioautonomic disruption beyond changes in HRV due to contextual factors such as increased rest with time off from school and sports as part of the management protocol. Moreover, if increases in HRV in association with
post-concussion symptoms were rooted in the pathophysiology of the concussion, a stepwise upward trend of HRV following injury would be expected rather than increasing values over time, which were observed in the mixed model analysis. Thus, increases in HRV in conjunction with self-reported symptoms- observed in this thesis- may be due to the combined influence of contextual changes associated with concussion such as decreased physical activity, stress, or other factors that would disrupt physiological homeostasis post-concussion rather than the pathophysiology of concussion itself.

Understanding the relationship between post-concussion symptoms and HRV is challenging, since it was hypothesized at the onset of this thesis that higher reports of symptoms would equate to pathological changes in autonomic functioning and thus decreases in HRV. However, changes in HRV observed in this study may be a result of observing the contextual and environmental changes that are associated with increased rest and inactivity following a concussion. Rest was prescribed in the acute stages of recovery until symptoms resolved following a concussion. The increase in HRV associated with self-reported symptoms that were observed may be due to rest alone and may not have been elicited by the pathophysiology of concussion, which has been reported in more moderate to severe brain injury literature (Goldstein, Toweill, Susanna, Sonnenthal, Kimberly, 1998; Korpelainen, Huikuri, Sotaniemi, Myllyla, 1996; King, Lichtman, Seliger, Ehert, Steinberg, 1997). Nonetheless, there is a dynamic interplay between the effect of concussion on measures of HRV due to the pathophysiology of the injury, and alternatively, the changes in HRV that may be induced by the occupational changes related to the injury.

Using these data as a preliminary observation of changes that may occur in HRV following concussion is important in understanding the physiological stress that each athlete may endure as they progress through their stages of recovery. Disentangling the etiology of each participant’s symptoms following concussion is challenging as symptoms can sometimes be idiopathic; however, changes in HRV may hold promise for establishing the presence of physiological stress following concussion regardless of its etiology.

The clinical implications of this research highlight the potential of HRV in the management of physiological stress post-concussion. The long duration protocol in this study was conducted in a real world setting, which captures the importance of creating a measure of recovery that can
capture the youth athlete while performing their activities of daily living. Although the long duration protocol did not occur within a controlled clinical setting, the protocol allowed for the observation of HRV while participants were at rest overnight and also during their daily activities. The findings suggest that a trend still exists in HRV post–concussion regardless of the potential influence of undocumented factors in the long duration protocol. More research is needed to determine the reasons for increases in HRV; however, these preliminary data are valuable to clinicians and researchers as it indicates that higher levels of HRV may not always equate to healthier physiological outcomes.

5.3 Limitations

When interpreting the changes in HRV observed in this study, the potential influence of sex, history of previous concussion and recovery protocol should be taken into consideration. The majority of the sample was female and therefore males were under-represented. Some research has suggested that ovarian hormones during the menstrual cycle may have an effect on measures of HRV (Sato et al., 1995), although the effect of sex on HRV in youth athletes in understudied. Previous research by Hedelin et al. (2000) suggests sex differences in junior athletes following training sessions. Even though there were not differences in resting heart rate, female athletes had higher levels of parasympathetic activity, as indicated by HF power (Hedlin et al, 2000). Beyond the influence of sex on HRV, previous research has documented that females (ages 12-26 years) may report more symptoms at baseline and were 43% more likely than males to report any symptom associated with concussion (Brown et al., 2015). The differential symptom reporting between males and females, coupled with the potential sex differences in HRV adds complexity to the relationship between PCSI and HRV observed in this thesis.

Moreover, 13 of the 29 participants in this thesis had a history of at least one previous concussion. Individuals with multiple concussions may respond physiologically different to subsequent concussions when compared to individuals who have never sustained a concussion. Also, a previous concussion may effect how an individual manages their injury as compared to those who have not experienced a concussion. Factors such as previous concussion and sex may influence and mediate the relationship between PCSI and HRV, yet their contributory power is difficult to ascertain due to a small sample size and lack of statistical power.
Additionally, upon commencing follow-up testing, participants received a consistent and detailed recovery protocol that included appropriate rest and activity restrictions. In particular, the increase in HRV associated with self-reported symptoms that were observed may be due to the number and severity of symptoms predating increased rest and may not have been elicited by the pathophysiology of concussion, which has been reported in more moderate to severe brain injury literature (Goldstein, Toweill, Susanna, Sonnenthal, Kimberly, 1998; King, Lichtman, Seliger, Ehert, Steinberg, 1997; Korpelainen, Huikuri, Sotaniemi, Myllyla, 1996).

Due to the change in the protocol for the larger study from which this thesis was developed, both short duration (15 minute protocol) and long duration (≤24 hour protocol) recordings were utilized in the analysis of HRV in concussed individuals. Previous research has shown strong correlations between short term and long term spectral indices (Bigger, 1993) and 5 min recordings and 24 h recordings were found to be equally appropriate for observing time-domain HRV variables (Mazzeo et al, 2011). Nonetheless, recording type was used as a covariate in the mixed model analysis and results indicated an effect of recording type on certain time and frequency domain HRV measures. This means that HRV measures that had a main effect of PCSI and also a main effect of recording type were predisposed to the influence of recording protocol in relation to changes observed in association with PCSI.

Additionally, there may have been limitations in the statistical analysis of this thesis. More specifically, the linear aspect of mixed models may not have effectively captured the intra-individual variance in HRV across time points. The relationship between days post injury, PCSI and HRV may not have been best described by a linear relationship. Thus HRV at discrete points in time may have been masked by the influence of many data points over the recovery trajectory. For example, the interaction between days post injury and PCSI on different measures of HRV in the mixed model analysis may allude to a relationship between these variables at discrete points in time across the recovery trajectory that is currently unknown.

Lastly, a control group was not used in this analysis and consequently this did not allow for the calculation of an effect size for the mixed model analysis. Further, a lack of normative values for HRV in healthy youth athletes did not allow for the values of individuals to be referenced against healthy, or “normal” HRV values. Thus, it is unknown whether the baseline values of each participant could be considered a health benchmark for comparison. For example, a low HRV
value at baseline may indicate physiological stress before the injury due to overtraining (Mourot et al, 2004) or physical exertion (Perini & Veicsteinas, 2003), and thus increases in HRV may occur as the injured individual is prescribed rest following their concussion. Therefore, the lack of a control group, coupled with the lack of normative values adds complexity to inferring whether the changes observed in this thesis are due to concussion and as a result these findings should be interpreted conservatively.

5.4 Future Directions

Future research is needed to determine whether changes in HRV are due to pathophysiological changes induced by the biomechanical injury itself rather than confounding factors associated with HRV. Documenting factors that may influence HRV is important in order to separate the influential effect of concussion on the different measures of heart rate variability following injury. Future research should document activity levels using objective measures such as actigraphy to further understand the relationship between PCSI and HRV. Furthermore, an objective measures of activity, such as actigraphy, may be useful in documenting sleep/wake patterns of participants as heart rate variability has been shown to be affected by sleep and circadian cycle (Busek et al, 2005; Tobaldini et al, 2013). Beyond documenting activity via actigraphy, future studies should aim to observe HRV along the recovery trajectory via long duration recording protocol while documenting return to play (McCrory et al., 2009, 2013) and return to school activity (Zemek, Duval, Dematteo, et al., 2014). Observing the response in HRV to different physical and cognitive protocols is important in understanding potential changes in HRV that may be influenced by cognitive or physical demands following concussion.

Beyond documenting factors such as activity and rest in association with HRV, factors such as food intake may be useful to observe following concussion. Although short term changes in HRV have not been observed following the ingestion of meals (Ambarish et al, 2005), high carbohydrate and high fat nutrition revealed an increase in LF/HF ratio (Millis et al, 2009). Other drugs such as caffeine have been shown to increase HRV in both diabetic patients and in controls (Richardson et al, 2004). Documenting factors that influence HRV and that are pertinent to the youth athlete population is important in understanding the influence that the concussion itself may have on HRV.
Further, previous research by Gall et al (2004), used exercise as a method of eliciting a difference in HRV measures when compared to controls. Reductions in HRV were only seen when the concussed individuals were dosed with physical activity. Similarly, changes in HRV indices have been found during a hand grip test following concussion in asymptomatic athletes (Abaji et al., 2014; La Fountaine et al., 2009). As compared to the protocol used in this study, future research in the pediatric population may find that an orthostatic test or physical activity intervention may illicit different physiological responses as compared to measuring HRV in individuals at rest. The challenge when employing a physiological stressor protocol (such as physical activity) to evaluate an autonomic disruption following injury is that these tests are often performed when participants are asymptomatic. Therefore, eliciting a physiological response post-concussion may be difficult while athletes are still experiencing symptoms. Observing participants at rest, throughout a 24 hour period, may hold the most promise for understanding the effect that concussion may have on youth athletes who are still symptomatic.

Beyond future methodological directions, statistical analysis of HRV is complex and warrants further research. Using an individual’s baseline as a benchmark of physiological disruption following injury may hold the most potential to observe changes in stress following injury as normative trends for healthy youth heart rate variability values do not yet exist. Previous work has documented high inter-individual variation in HRV (Nunan, Sandercock, & Brodie, 2010). Linear regression models may not accurately elucidate the effect that each individual has on the regression line. For example, the basic regression equation \(Y_i=B_0+B_1X_i+e_i\) links individual differences in X to individual differences in Y but does not account for the effect of individual differences in this relationship (as represented by \(\beta_0\) and \(\beta_1\)). Capturing intra-individual differences between baseline and follow-up HRV measures is challenging as the mean difference may not be satisfactory to define change. Using each participant as a random effect in the mixed model analysis in this study allowed for a more accurate comparison between baseline and post-concussion measures. Utilizing each participant as a random effect to capture intra-individual differences is important as little research has been performed in the youth sport population to determine how to assess a healthy HRV score at baseline. Future research may aim to use visual analysis to supplement inferential analysis in observing trends among single subjects in order to comprehensively observe intra-individual changes in HRV along the recovery trajectory following concussion.
5.5 Conclusion

This thesis pilot tested a protocol for data collection and analysis of HRV in a subset of youth recovering from concussion. Moreover, this research revealed the methodological nature of different recording protocols for capturing long duration and short duration HRV values in youth athletes at baseline and following concussion. This thesis has proven critical to the success of future research as it revealed a need to collect long duration recordings and to consider the role of mediating factors such as sex and age during the recruitment of appropriate control subjects. Furthermore, this thesis revealed a significant relationship between an objective biomarker of stress (HRV) and the self-report of perceived post-concussion symptoms (PCSI). Observing the relationship between HRV and PCSI speaks to the feasibility of observing HRV as a measure of physiological stress post-concussion. Further research is needed to understand these preliminary observations of heart rate variability and its relationship with days post injury and self-reported symptoms of concussion.
6 References


Neuropsychological evaluation in the diagnosis and management of sports-related concussion


Reed, N., Murphy, J., Dick, T., Mah, K., Paniccia, M., Verweel, L., & Keightley, M. A multi-modal approach to assessing recovery in youth athletes following concussion. *Journal of Visualized Experiments.* Accepted April 3, 2014 (In Press)


Neuroscience and Biobehavioral Reviews, 36, 747–756.


Appendix 1: RHRV Script

####HRV Program

```r
> library(RHRV)

> library(lubridate)

> library(TTR)

> options("digits.secs"=5)

####Enter window size and shift

> subjectID <- 1

> window.size <- 300

> window.shift <- 300

> file.name <- "File route"

####Get start time and date

> x <- scan(file.name, skip=4,nmax=2, what=list(""))

> x.frame<-as.data.frame(x)

> date<-ymd(substr(x.frame[1,],6,14))

> date<-format(date, "%d/%m/%Y")

> starttime<-substr(x.frame[2,],11,20)
```
```r
> DateTime <- paste(date, starttime)
> date1 <- dmy_hms(DateTime)

#####input RR

> RR.input <- scan(file.name, skip=78)
> RR <- as.data.frame(RR.input)
> write(RR.input, file="testing.txt", ncolumns=1)

#####New HRV Data list

> HRV.data = CreateHRVData()
> HRV.data = SetVerbose(HRV.data, TRUE)
> HRV.data <- LoadBeatRR(HRV.data, "testing.txt", RecordPath="C:/Users/brainfit3/Desktop/HRV/RHRV/", scale = 0.001, datetime = DateTime)
> HRV.data = BuildNIHR(HRV.data)
> HRV.data = FilterNIHR(HRV.data)
> HRV.data = InterpolateNIHR(HRV.data, freqhr = 4)
> PlotHR(HRV.data)
> HRV.data = CreateTimeAnalysis(HRV.data, size = window.size, interval = 7.8125)
> HRV.data = CreateFreqAnalysis(HRV.data)
> HRV.data = SetVerbose(HRV.data, TRUE)
> HRV.data = CalculatePowerBand(HRV.data, indexFreqAnalysis = 1, size = window.size, shift = window.shift, type = "fourier")
```
> ULFmin = 0, ULFmax = 0.003, VLFmin = 0.003, VLFmax = 0.04,
> LFmin = 0.04, LFmax = 0.15, HFmin = 0.15, HFmax = 0.4

> PlotPowerBand(HRV.data, indexFreqAnalysis = 1, ymax = 5000, ymaxratio =
> 10, hr = TRUE, normalized = TRUE)

> fgh <- HRV.data["Beat"]

> fgh <- as.data.frame(fgh)

> names(fgh)

> fgh$Time[1]

> fgh$Time <- as.duration(fgh$Time)

> fgh$Time <- fgh$Time + date1

> par(mfrow = c(5, 1))

> plot(fgh$Time, fgh$RR, type = "l", ylab = "R-R interval(s)", xlab = "Time of Day")

> plot(fgh$Time, fgh$niHR, type = "l", ylab = "niHR (bpm)", xlab = "Time of Day")

> abc <- HRV.data["FreqAnalysis"]

> HRVTotal <- abc[[1]]$ULF + abc[[1]]$VLF + abc[[1]]$LF + abc[[1]]$HF

> HRVLF <- abc[[1]]$LF

> HRVHF <- abc[[1]]$HF

#### Set time vector

> start.time.FFT <- window.size/2
> end.time.FFT <- start.time.FFT + (length(HRVTotal) - 1) * window.size

> FFT.length <- seq(start.time.FFT, end.time.FFT, window.shift)

> FFT.time <- as.duration(FFT.length) + date1

> plot(FFT.time, HRVTotal, type="l", xlim = c(min(fgh$Time), max(fgh$Time)),

> ylab = "Total HRV", xlab = "Time of Day")

> plot(FFT.time, HRVLF, type="l", xlim = c(min(fgh$Time), max(fgh$Time)),

> ylab = "LF HRV", xlab = "Time of Day")

> plot(FFT.time, HRVHF, type="l", xlim = c(min(fgh$Time), max(fgh$Time)),

> ylab = "HF HRV", xlab = "Time of Day")

#### Find highest Total HRV period

> max.line <- which.max(HRVTotal)

> max.HRVTotal.time <- ymd_hms(FFT.time[max.line])

> max.HRVTotal <- HRVTotal[max.line]

> max.HRVLF <- HRVLF[max.line]

> max.HRVHF <- HRVHF[max.line]

#### Find highest LF period

> max.line.LF <- which.max(HRVLF)

> max.HRVLF.time <- ymd_hms(FFT.time[max.line.LF])

> max.HRVLF.only <- HRVLF[max.line.LF]
### Find highest HF period

```r
> max.line.HF <- which.max(HRVHF)

> max.HRVHF.time <- ymd_hms(FFT.time[max.line.HF])

> max.HRVHF.only <- HRVF[max.line.HF]

> max.HRVTotal.time

> max.HRVTotal

> max.HRVLF

> max.HRVHF

> max.HRVLF.time

> max.HRVLF.only

> max.HRVHF.time

> max.HRVHF.only
```
Appendix 2: Consent Forms and Information Letters

Information Letter and Consent Forms for Participation in:
‘NeuroCare’ as Innovation in Intervention: A neurophysiological approach to determine readiness for return to activity

Dear youth,

My name is Michelle Keightley. I am part of a research team at the Holland Bloorview Kids Rehabilitation Hospital that is studying Sports-Related Concussion in Children and Youth. Before agreeing to take part in this study, it is important that you understand how you will be involved.

What is the study about?

We want to learn more about recovery from sports-related concussion in children and youth. Specifically, we want to know how youth athletes feel after a concussion. Things like headaches, feeling sick to their stomach or feeling more tired than normal. We want to know if these feelings affect performance on brain and body fitness tests. This information can help create return-to-activity (school, sport etc.) guidelines specific to youth athletes.

We also want to learn more about whether the brain and body are ready to increase activity after a concussion by measuring heart rate. We will use this new approach alongside other measures of concussion recovery. These include measures of symptoms, balance, thinking, strength, and brain function. We will use a special camera to let us see how the brain works. We hope that this new approach can tell us more about when young athletes are ready to return to activity after a concussion. We are not sure this new approach works. That is why we are doing this study.

What will happen during the study?

We will ask you to take part in up to 2 different parts

A. Brain and Body Fitness Testing and Long Duration Heart Rate Monitoring

B. Functional Magnetic Resonance Imaging (MRI) of the Brain

We would like to invite you to participate in the first part of this study. If you are contacted again to participate in part 2 of our study (MRI), we will ask for your permission again. We will ask for your email when you come for the testing in case we need to contact you again. We want to learn more about how youth athletes recover after a concussion. In order to participate you must show me that you understand what you will have to do in this study and what the risks and benefits to being in the study are. If you can not do this, then you cannot take part in the study. A researcher will also meet with you to review everything in this letter. You can decide then if you want to take part.

How many people will participate in this study?
There will be different numbers of participants completing the different aspects of this study. Male and female athletes between the ages of 10-18 years have been invited to take part in this study.

A. Brain and Body Fitness Testing/ Long Duration Heart Rate Monitoring: Up to 1400 athletes will take part in this study. A member of the research team within the BrainFit Lab at Holland Bloorview Kids Rehabilitation Hospital (150 Kilgour Rd., Toronto) will complete brain and body fitness tests with you. These tests will take approximately 1-2 hours to complete. These tests will measure your brain health, cognitive/thinking performance, balance performance, strength performance and heart rate. When you come in for testing, we will ask for your email address just in case we have to contact you again.

- These tests will be completed at baseline (or at the start of the sport/school year before an injury happens).
- You will be asked to wear a heart rate monitor for 24 consecutive hours. The heart rate monitor involves wearing a watch and a chest strap. The monitor does not hurt and all testing takes place on the outside of the body. While wearing the heart rate monitor you may do all the things you normally do in a day including while you sleep. However, activities that might get the monitor wet (swimming, bathing etc.) cannot be done.
- Heart rate monitoring will involve athletes who get and do not get injuries. You will complete an activity log to track what you do during the 24 hours that you wear the heart rate monitor. This activity log will take approximately 5 minutes to complete. We will show you how to fill in this log.

If you experience a concussion during your sport season, you will do these same tests again immediately following injury (within 48 hours). Each time we will take 1-2 hours at Holland Bloorview. You will also do the same tests weekly until post-concussion symptoms have gone away. Then you will do the tests 4 more times: 1-week, 1 month, 3 months and 6 months after post-concussion symptoms have gone away.

- If you experience a concussion during your sport season, we may ask that you bring a friend (who has not recently had a concussion) and who is the same age and gender as you to participate in the same brain and body tests that you do following your injury. You will get an information sheet to give to your friend and they can decide then if they want to participate.
- If you get an orthopaedic injury (e.g., broken arm, sprained ankle etc.), instead you may be invited to do these same tests again immediately following the injury (within 48 hours). You will do the same number of tests as the athletes who get a concussion. It will also take 1-2 hours at Holland Bloorview.
- If you get both a concussion and an orthopedic injury, you can only be in one follow-up group.
- Remember it is possible that your ability to return to competitive sports will be delayed after a concussion; but this will only happen if you don’t feel well enough to play, not because you are participating in this study.

Even if you don’t get a concussion or orthopedic injury, we may contact you to do these other tests. We will only contact you if you match the age and sex of another participant who has a concussion. You can decide then if you want to do them.
- Brain and body fitness testing will also include recording your history of concussions and other history of medical conditions you may have had. Also, we will be collecting information on age, height, weight, sport(s) played, playing position and level of play. This information will be used to find out if some participant characteristics are more related to performance on brain and body fitness tests than others. Collecting this information will take approximately 10 minutes.

If you have questions concerning the Brain and Body Fitness Testing portion of this study, please call Michelle at 416.425.6220 ext 6651 or Nick at 416-425-6220 x3861.

B. Functional Magnetic Resonance Imaging of the Brain: Up to 75 athletes who did the brain and body fitness testing will do this part of the study. A member of the research team at the Toronto Western Hospital (399 Bathurst St., Toronto) will complete brain imaging with you using a MRI machine. This testing will take approximately 1½ hours to complete. The MRI machine is a powerful magnet that looks like a big doughnut, and you will lie down on a bed with your head and shoulders in the “doughnut hole”. We will put some pillows around your head to keep it from moving and then ask you to stay very still while we scan your brain to get the pictures. Some of the brain scans will take pictures of the brain’s structure and some others will take pictures of the brain’s activity. During the brain activity scans, you will be asked to perform a computer task. This computer task will ask you to press a button in response to pictures and words that you see. You will see a series of pictures or words. You will then see a second series of pictures or words. During this second series of pictures or words, you will be asked to press one button if you saw the picture or word in the first series and another button if you did not see the picture or word in the first series.

- If you experience a concussion during your sport season, you will be asked to complete two brain scans. The first will be completed within 48-72 hours of the concussion and the second will be completed within 1 week after concussion symptoms have resolved.
- If you experience an orthopaedic injury (e.g., broken arm, sprained ankle etc.), you may be asked to complete two brain scans after your injury. The first will be completed within 48-72 hours of the concussion (experienced by another participant in the study) and the second will be completed within 1 week after their concussion symptoms have resolved.

Additionally, we will have an equal number of athletes who have not been injured (no concussion or orthopaedic injury) complete the same number of brain scans. If this is you, you will only be invited to do the MRI scan if you match another athlete that is the same age and sex as you.

If you have questions concerning the Functional Magnetic Resonance Imaging of the Brain portion of this study, can call Karen Davis at 416.603.5662.

Are there any risks to doing the study?

A. Brain and Body Fitness Testing/Long-Duration Heart Rate Monitoring: There is the possibility that some of the testing and questions may be fatiguing, stressful or produce unpleasant feelings. You will be able to stop or take a break at any time if you feel too uncomfortable. You do not need to answer questions that you do not want to answer or that make you feel uncomfortable. We will tell you what questions need to be answered or tests that need to be done to stay in the study.
There are no known risks with long duration heart rate monitoring. You may experience some discomfort and frustration while wearing the heart rate monitor for the 24 hour period. At any time, you can stop doing this part. You can remove the monitor at any time and no one will mind.

C. Long Duration Heart Rate Monitoring: There are no known risks with long duration heart rate monitoring. You may experience some discomfort and frustration while wearing the heart rate monitor for the 24 hour period. At any time, you can stop doing this part. You can remove the monitor at any time and no one will mind.

Are there any benefits to doing this study?

We hope to better understand recovery in young athletes following concussion. This study could help other children and youth like you who have experienced concussions in the future.

Payment or Reimbursement

Some aspects of this study will include reimbursement for participation:

A. Brain and Body Fitness Testing/Long-Duration Heart Rate Monitoring:

You will be given a $10 gift card from Tim Horton's for wearing the heart rate monitor for the 24 hour period. If the testing session is not completed for any reason, and you drop out during the testing session, you will still receive the gift card.

Control participants (no injury or orthopaedic injury) who complete additional brain and body fitness testing (in addition to baseline/pre-injury testing) will be reimbursed $40 per additional testing session. If the testing session is not completed for any reason, you will still receive the full reimbursement.

B. Functional Magnetic Resonance Imaging of the Brain:

You will be given a $40 gift card from SportChek per brain imaging session. If the testing session is not completed for any reason, you will still receive the gift card.

Will anyone know what you say?

All the information we collect about you will be kept private. Rather than use your name on study papers, a randomly assigned identification number will be used. No one but the study staff will know that it was you who was in the study.

We will not make public anything that might identify you, unless required by law. For example, we have a legal duty to report suspected child abuse and potential harm to self or others. If the results of the study are published, your name will not be used. All data collected will be combined to form one large data set. As a result, individual sport teams and participants will not be identified. We must keep the research data we collect for 7 years as required by Holland Bloorview.

We will keep all of your information in a locked cabinet the BrainFit lab. Only the researchers who are directly involved in this study will have access to your information. All of your
information that is kept on the computers in the lab will be protected by a special password that only the researchers know.

Because we are asking your whole team to participate, there is a chance that your teammates might know that you are participating in this study. They also might know if you get a concussion or an orthopaedic injury.

You do not give up legal rights due to research-related harm.

There is a possibility that our findings will be commercialized and you will have no ownership rights over the information. It is possible that a company or Holland Bloorview may get money from the sale of certain products in the future.

**Do I have to do this?**

If you decide not to take part in this study, that is okay. If you decide to take part, but then at any time during the study you no longer want to participate, that is okay. This will not affect your involvement with your sport team or your treatment at Holland Bloorview Kids Rehabilitation Hospital.

**What if I have questions?**

Please ask me to explain anything you don’t understand before signing the consent forms. My phone number is 416.425.6220 ext 6651 or Nick Reed (researcher at Holland Bloorview) at 416.425.6220 ext 3861. If you leave a message, I or a member of the research team, will return your call within 48 hours.

If you have any questions about your rights as a research participant, please contact the Holland Bloorview Research Ethics Board at 416-425-6220 ext. 3507.

Thank you for thinking about helping us with this project.

Yours truly,

Michelle Keightley, Ph.D., C.Psych.
Clinician Scientist
BrainFit Lab, Bloorview Research Institute
150 Kilgour Rd., Toronto, ON, M4G 1R8
mkeightley@hollandbloorview.ca
416.425.6220 ext 6651
CONSENT FORM #1

BLOORVIEW RESEARCH INSTITUTE

‘NeuroCare’ as Innovation in Intervention: A neurophysiological approach to determine readiness for return to activity

RE: Participating in the ‘Brain and Body Fitness Testing and Long Duration Heart Rate Monitoring’ portion of this study

Please complete this form below and after discussing it with your family, please return it to the researcher. You will receive a signed copy of this form.

______________________________ explained this study to me. I have read the attached Information Letter and understand what this study is about.

I understand that I may drop out of the study at any time.

I agree to participate.

______________________________  ______________________  __________
Youth’s Name (please print)       Signature              Date

I support my child’s decision to take part in this research study.

______________________________  ______________________  __________
Parent’s Name (please print)      Signature              Date

I have explained this study to the above participant and have answered all their questions.

______________________________  ______________________  __________
Name of Person Obtaining Consent  Signature              Date
Appendix 3: Kernel Density Plots for HRV Measures

3.1 Kernel Density SDNN

3.2 Kernel Density SDANN
3.3 Kernel Density pNN50

Kernel Density of pNN50

3.4 Kernel Density of HRV Index

Kernel Density of HRV Index
3.5 Kernal Density of Max Total HRV

![Kernel Density of Max Total HRV](image)

N = 102  Bandwidth = 3058

3.6 Kernal Density of Max High Frequency

![Kernel Density of Max High Frequency](image)

N = 102  Bandwidth = 253.6
3.7 Kernal Density of Max HRV HF

Kernel Density of Max HRV HF

3.8 Kernal Density of Max HRV LF

Kernel Density of Max HRV LF
3.9 Kernal Density of Max LF
Appendix 4: Assumptions of Linear Mixed Models

4.1 SDNN

Fitted Values and Residuals Values of SDNN

Residuals of Mixed Model for SDNN
Residuals of the SDNN Mixed Model

Q-Q Plot of Residuals SDNN
4.2 SDANN

Fitted Values and Residuals Values of SDANN

Residuals of Mixed Model for SDANN
Residuals of the SDANN Mixed Model

Q-Q Plot of Residuals SDANN
4.3 pNN50

Fitted Values and Residuals Values of pNN50

Residuals of Mixed Model for pNN50
Residuals of the pNN50 Mixed Model

Q-Q Plot of Residuals pNN50
4.4 HRV Index
4.5 Max Total HRV
4.6 Max HRV HF

Fitted Values and Residuals Values of Max HRV HF

Residuals of Mixed Model for Max HRV HF
4.7 Max HRV LF

Fitted Values and Residuals Values of Max HRV LF

Residuals of Mixed Model for Max HRV LF
Residuals of the Max HRV LF Mixed Model

Q-Q Plot of Residuals Max HRV LF
4.8 Max HF

Fitted Values and Residuals Values of Max HF

Residuals of Mixed Model for Max HF
Residuals of the Max HF Mixed Model

Q-Q Plot of Residuals Max HF
4.9 Max LF

**Fitted Values and Residuals Values of Max LF**

**Residuals of Mixed Model for Max LF**
Residuals of the Max LF Mixed Model

Q-Q Plot of Residuals Max LF
4.10 LF HF Ratio

Fitted Values and Residuals Values of LF/HF Ratio

Residuals of Mixed Model for LF/HF Ratio
# Appendix 5: Technical Specifications of RS800CX

## Technical Specifications RS800CX

<table>
<thead>
<tr>
<th>Watch</th>
<th>RS800CX</th>
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<tbody>
<tr>
<td>Battery Life</td>
<td>Average 1 year (1h/day, 7 days/week)</td>
</tr>
<tr>
<td>Battery Type</td>
<td>CR2032</td>
</tr>
<tr>
<td>Battery Sealing Ring</td>
<td>O-Ring 20.0 x 1.1, material: Silicone</td>
</tr>
<tr>
<td>Operating Temperature</td>
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</tr>
<tr>
<td>Wrist band and buckle material</td>
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<tr>
<td>Watch Accuracy</td>
<td>Better than ± 0.5 seconds/day at 25°C/77°F</td>
</tr>
<tr>
<td>Accuracy of heart rate monitor</td>
<td>± 1% or 1 bpm, whichever larger. Definition applies in stable conditions</td>
</tr>
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</tr>
<tr>
<td>Maximum time</td>
<td>99 h 59 mins 59 s</td>
</tr>
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<td>RR Recording</td>
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<table>
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<tr>
<td>Connector Material</td>
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</tr>
<tr>
<td>Strap Material</td>
<td>38% Polyamine, 29% Polyurethane, 20% Elastane, 13% Polyester</td>
</tr>
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</table>
Appendix 6: RR Intervals
Appendix 7: Non-Interpolated Heart Rate
Appendix 8: RR Interpolated Heart Rate

Interpolated instantaneous heart rate

![Heart rate graph](image-url)
Appendix 9: LF Power

![Graph showing LF Power over time]

- Y-axis: LF HRV
- X-axis: Time of Day
- Data points indicate fluctuations in LF HRV throughout the day.
Appendix 10: HF Power

![Graph showing HF Power over time](image-url)
Appendix 11: Total Power

![Graph showing Total Power over time]

- X-axis: Time of Day
- Y-axis: Total HRV
- Graph shows fluctuations in Total HRV throughout the day, with peaks around 18:00 and 19:30.