Exploring the effect of aerobic and balance exercise as an interventional strategy for post-concussion syndrome.

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Chapter 1 - Introduction

A concussion is a mild traumatic brain injury (mTBI) resulting from a force applied directly and/or indirectly to the head causing the brain to collide within the skull (McCrory et al., 2013). This injury affects an individual's ability to concentrate, make decisions, react to stimuli, and maintain balance and posture. In addition, this may also result in headaches, nausea, changes in mood, and numerous other symptoms (McCrory et al., 2013). Every concussion is unique and no two individuals who have sustained a concussion will present with the same symptomology. There are still significant gaps within the literature pertaining to concussion etiology, prevalence, diagnosis, management, rehabilitation, and return to play/work. Nonetheless, this body of literature has increased exponentially in recent years.

In approximately 80% of cases, concussions spontaneously resolve over a period of 7-10 days (Belanger, Barwick, Kip, Kretzmer, & Vanderploeg, 2013; Willer & Leddy, 2006). Subsequently, an estimated 20% of concussed individuals will experience lingering symptoms of concussions for weeks, months, and, in some cases, years. Consequently, these persisting symptoms may lead to difficulty with psychosocial adjustment, deterioration of quality of life, and/or decreased financial independence because of diminished performance or absence from work or school (Kleffelgaard, Roe, Soberg, & Bergland, 2012). The phenomenon of lingering symptoms past the typical acute recovery period of 7-10 days is referred to as post-concussion syndrome (PCS; American Psychological Association, 2013; World Health Organization, 1992). Studies of PCS have revealed that the normal neurophysiological processes of the brain are impaired as a result of the injury. Additionally, abnormalities in the white matter of the brain have been observed in individuals with PCS more than one year after the initial injury. Even

more troublesome is the fact that when these neurophysiological processes are impaired in youth, there is a risk that normal cognitive development may be altered, as a result (Shrey et al., 2011).

As of yet there is no effective treatment for acute concussion or PCS (Leddy et al., 2013; McCrory et al., 2013; Patterson & Holohan, 2012). Presently, rest is prescribed as the treatment of choice, but has only been shown to be effective in the acute stage of the injury (7-10 days). There is no reported effectiveness for rest for PCS that persists beyond this period (Moser at al., 2012). Recent evidence indicates that strategically controlled forms of exercise may create the ideal internal environment to restore impaired neurophysiological functions of the brain in order to rehabilitate an individual suffering from PCS and alleviate symptoms. The development of such an effective rehabilitation protocol for PCS would benefit children, adolescents, and adults alike by promoting quicker resolution of symptoms so that they can return to play, school, work, and life.

There appears to be a gap in the literature of investigations examining the impact of exercise-based treatment options to rehabilitate individuals with PCS. Evidence from other domains of neurological rehabilitation literature has reported promising improvements in cognitive functions and balance in response to exercise-based treatments. Exercise-based treatment of PCS warrants further exploration due to the current lack of an effective method of treatment.

Chapter 2 - Review of the Literature

The following literature review will provide a detailed rationale for utilizing aerobic exercise and balance training as an interventional rehabilitation strategy for PCS. As the proposed study involved exercise, the review presented will pertain to sports-related concussion and an athletic population.

Concussion

Definition and prevalence. The 2013 Canadian Community Health Survey reported that from 2009-2010, 29,000 concussions occurred in Canadians aged 12-19 years; and 60,000 concussions occurred in 20-64 year old Canadians. In total, 94,000 concussions affected individuals (58,000 males and 36,000 females) aged 12 years and older between 2009-2010 (Statistics Canada, 2013). Similarly, in the United States, it is estimated that between 1.6 and 3.8 million sport-related concussions occur each year (Covassin, Elbin, Harris, Parker, & Kontos, 2012). Historically, concussion has been a term used to describe a low-velocity injury causing the brain to shake around in the skull, resulting in clinical symptoms that "are not necessarily related to a pathological injury" of any one structure or function of the brain (McCrory et al., 2013, p. 250). This definition is problematic for researchers and clinicians as every concussion presents with unique clinical symptoms. The revised definition of concussion agreed upon at the 2012 Zurich Conference of Concussion in Sport is as follows:

> Concussion is a brain injury and is defined as a complex pathophysiological process affecting the brain, induced by biomechanical forces. Several common features that incorporate clinical, pathologic, and biomechanical injury constructs that may be utilised in defining the nature of a concussive head injury include:

1. Concussion may be caused either by a direct blow to the head, face, neck, or 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 neurological function that resolves spontaneously. However, in some cases, symptoms and signs may evolve over a number of minutes to hours.
3. Concussion may result in neuropathological changes, but the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury, and as such, no abnormality is seen on standard structural neuroimaging studies.
4. Concussion results in a graded set of clinical symptoms that may or may not involve loss of consciousness (LOC). Resolution of the clinical and cognitive symptoms typically follows a sequential course; however, it is important to note that in some cases it may be prolonged (McCrory et al., 2013).

The panel emphasized additionally, the separation of concussion and mTBI. A traumatic brain injury (TBI) is an injury that occurs after a sudden physical trauma induced by a mechanical force damages the brain (Oxford Dictionary of Sports Science and Medicine, n.d.). Traumatic brain injuries are classified as either closed or open TBI. In closed TBI, a trauma is experienced, but the skull is not compromised. Conversely, in an open TBI, the trauma is so great that the skull fractures, and may be accompanied by the risk of permanent injury and/or death. The severity of TBI can range from a mild concussion, to an extreme coma, or death (Dawodu, 2015). Mild traumatic brain injury accounts for 70-90% of TBI hospital admissions (Dean, Sato, Vieira, McNamara, & Sterr, 2015). Concussion and mTBI are sometimes used interchangeably. Although concussion is a subset of mTBI, all concussions are mTBIs, but not all mTBIs are concussions (Centers for Disease Control and Prevention, 2014; McCrory et al., 2013). For the

remainder of this document, the term concussion will be used in place of mTBI, while the term TBI will be used when referring to moderate to severe head injuries. The subsequent section of this document presents evidence regarding sport-related concussion estimates, and possible explanations for the variability amongst estimates.

Concussion in sport. In Canada, 37% of individuals aged 20-24 years participate in sport; the same can be said for 29% of those aged 25-34 years and 23% of 35-54 year olds (Statistics Canada, 2013). Additionally, the 2005 Canadian Health Survey reported that 52% of Canadians over the age of 12 years were consistently moderately active to regularly active (Statistics Canada, 2014). Billette and Janz (2011) reported that 25% of Canadians over the age of 12 years sustain an injury while exercising or participating in sport. Furthermore, concussions account for approximately 6% of all injuries for those aged 20 to 64 years (Statistics Canada, 2013, Appendix 3). As mentioned above, it is estimated that millions of sports-related concussions occur each year in the United States alone, but the range varies by approximately 2 million concussions per year. As a result, research has been conducted in an attempt to gain a better grasp of the true incidence of sports-related concussion. Delaney et al. (2002) collected 529 questionnaires from 328 Canadian university level football and 201 Canadian university level soccer players. They found that 12.4% of the soccer players recognized experiencing at least one sports-related concussion; despite the low recognition rate, 62.7% of the soccer players reported experiencing signs and symptoms of at least one sports-related concussion. For the football players, 16.5% within the same study recognized experiencing one sports-related concussion; however, similar to the soccer players, 70.4% of the football players reported experiencing concussion signs and symptoms. In 2001, football players were anonymously asked how many sports-related concussions they sustained in a season; the results revealed that 25% of

the football players indicated experiencing more than three sports-related concussions per season (Langburt, Cohen, Akhthar, O'Neill, & Lee, 2001). McCrea et al. (2004) conducted a retrospective and confidential survey of 1,532 American high school football players to uncover more evidence as to why there was such large discrepancies in the reporting of sports-related concussions. McCrea et al. discovered that in their sample, 15.3% of the football players reported one sports-related concussion during their current season. Of those same athletes, about half who sustained a sports-related concussion (47.3%) reported the occurrence to someone (McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004). Additionally in the same study, McCrea et al. (2004) reported that the three most common reasons for an athlete not to report a sports-related concussion included: "not thinking the injury was serious enough to need attention (66.4% of unreported sports-related concussion), motivation to not be withheld from competition (41.0%), and lack of awareness of probable sports-related concussion (36.1%)" (p. 15). The results of the McCrea et al. study revealed some indications as to why there are large discrepancies in the sports-related concussion estimates presented above, suggesting that there must be greater awareness and education before accurate estimates of sports-related concussion prevalence can be made.

Symptoms of concussion. A concussion is a highly variable injury from one person to the next. As a result, the presence of symptoms that are debilitating to one individual may not be present to the same degree in another individual who has also sustained a concussion. Symptoms of concussion can be generally stratified into four subgroups consisting of cognitive symptoms, somatic symptoms, affective disorders, or sleep disturbances. Table 1 summarizes the common symptoms reported within each subgroup (Herring, Cantu, Guskiewicz, Putukian, & Kibler,

2011). This high variability of symptomology makes concussion assessment, management, and rehabilitation challenging for researchers and clinicians.

Table 1.

Summary of common symptoms of concussion

Symptoms			
Cognitive	Somatic	Affective	Sleep Disturbances
Confusion	Headache	Emotional lability	Trouble falling asleep
Anterograde amnesia	Dizziness	Irritability	Sleeping more than usual
Retrograde amnesia	Balance disruption	Fatigue	Sleeping less than usual
Loss of Consciousness	Nausea/vomiting	Anxiety	
Disorientation	Visual disturbances	Sadness	
Feeling "in a fog" or "zoned out"	Phonophobia		
Vacant Stare			
Inability to focus			
Delayed motor and verbal response			
Slurred/incoherent speech			
Excessive drowsiness			

(Herring et al., 2011)

Lingering symptoms of concussion and post-concussion syndrome. While the majority of concussions (80-90%) spontaneously resolve within a 10 day period following the injury, 10-20% of individuals experience symptoms of concussion persisting past 10 days that may last for weeks, months, and in some cases greater than a year (Belanger et al., 2013; Willer & Leddy, 2006). The lingering and persistent symptoms of concussion are termed PCS. The mechanisms of acute concussion that account for the presentation of different symptoms from one concussion to another, spontaneous symptom resolution, and the true prevalence of acute concussion (recovery within 10 day period) remains unclear. Even less is understood of the mechanisms that underlie PCS that would explain why 10-20% of concussed individuals go on to

experience PCS. More specifically, there are conflicting results within the literature relating to symptom duration, the absence of objective neurological findings, the presentation of symptoms, and PCS etiology (Legome & Wu, 2014). This may be due in part to the lack of a gold standard and global definition for PCS (Baker, Freitas, & Leddy, 2012; Legome & Wu, 2014). The different definitions of PCS presented in the fourth edition of the *Diagnostic and Statistics Manual* (DSM IV) and that of the World Health Organization (WHO) result in further controversy regarding those individuals who do or do not have the condition. Table 2 summarizes these two definitions.

Table 2.

Comparison of DSM IV and WHO post-concussion syndrome criteria

Organization	Required Criteria	Three or More of These Symptoms
DSM IV	Cognitive deficits in attention or memory	- Fatigue - Sleep disturbance - Headache
WHO International Classifications of Diseases	Not applicable	- Dizziness - Irritability - Affective disturbance - Apathy - Personality change - Headache - Dizziness - Fatigue - Irritability - Insomnia - Concentration difficulty - Memory difficulty

(American Psychological Association, 2013; WHO, 1992)

Comparisons of the two definitions resulted in the discovery that the WHO's definition of PCS is six times more sensitive for diagnosing, or possibly over-diagnosing the condition than the DSM IV criteria (Boake et al., 2005). This discrepancy speaks to the importance of establishing an

agreed upon global definition for researchers and clinicians to conduct investigations of PCS using the same parameters. Time since injury is not included in either definition summarized in Table 2 as criteria of PCS diagnosis, causing confusion within the literature. As a consequence of the lack of an adequate definition of PCS, authors define PCS ranging from symptoms present for greater than one week after injury, to symptoms that persist for at least six months (Legome & Wu, 2014).

In addition to the lack of a global definition of PCS, there is also controversy related to the differential diagnosis of the condition. In 1988, Lishman suggested the first model for PCS differential diagnosis. Lishman (1988) proposed that in regards to PCS "organic factors are chiefly relevant in the earlier stages, whereas long-continued symptoms are perpetuated by secondary neurotic developments" (p. 460). Simply put, the initial symptoms following a concussion may be attributed to the result of disrupted neurophysiology. As weeks and months pass, there is a shifting balance wherein the lingering symptoms may be the result of underlying psychogenic causes. The symptoms of PCS include those already listed in Table 1 but the individual continues to experience these past the typical recovery time period of approximately 10 days (Makdissi, Cantu, Johnston, McCrory, & Meeuwisse, 2013). Some of the symptoms of PCS are similar to those seen in patients presenting with migraine, depression, or with other mental health disorders, attention deficit hyperactivity disorder (ADHD), learning disabilities, and sleep disorders. This makes it extremely difficult to differentiate between symptoms that continue to linger past 10 days directly due to concussion, versus symptoms that manifest as a result of an underlying secondary condition (Leddy et al., 2012). Silverberg and Iverson (2011) revisited Lishman's model to explain PCS symptoms, with the addition of further evidence. Their review reported that both neurophysiological and psychological factors may play a causal

role in PCS from the moment the concussion is sustained. With this information taken into account, Lishman's model may no longer accurately explain the symptomology of PCS (Silverberg & Iverson, 2011). More recently, new evidence has strengthened the notion that neurophysiological impairments do persist and contribute to PCS.

Dean et al. (2015) were the first to investigate signs of sustained structural changes of morphological and structural connectivity of the brain in a sample of subjects with PCS lasting more than a year after the concussion had occurred. The researchers utilized cortical thickness/volume analysis and voxel-based morphometry measured by magnetic resonance imaging to evaluate brain morphometry. Diffusion tensor imaging was also used in order to account for structural connectivity. The results of this study revealed damaged white matter and, to a lesser extent, grey matter. Additionally, those who reported more PCS symptoms appeared to have more damage to the grey and white matter than those who reported fewer symptoms. The authors stated that this was the first evidence of such morphological and structural connectivity alterations to the brain in subjects with PCS; suggesting a neurophysiological basis for lingering symptoms (Dean et al., 2015). This information added to the growing body of evidence pertaining to the mechanisms responsible for PCS. An understanding of these underlying mechanisms of PCS is necessary in order to develop a rehabilitation protocol for PCS which takes these mechanisms into account and effectively addresses each. Thus, the subsequent sections of this document provide greater detail regarding neurophysiological, psychogenic, and modifying factors in PCS.

Factors and modifiers influencing concussion outcomes. Due to the variability of symptoms experienced from one concussion to another, there is a growing body of literature regarding factors and modifiers that may affect concussion symptomology and recovery

outcomes. Table 3 summarizes numerous factors and modifiers that affect concussion outcomes and recovery (Harmon et al., 2013; McCrory et al., 2013). Having a history of previous concussion increases the probability of experiencing future concussion, in addition to extending the amount of time needed to return to typical functioning and symptom resolution (McCrory et al., 2013; Shrey et al., 2011). Depression, psychiatric illness, post-traumatic stress disorder (PTSD), and mood disorders have also been identified as both premorbid and comorbid factors affecting symptom reporting and recovery outcomes (Harmon et al., 2013; McCrory et al., 2013; Merrit & Arnett, 2014; Morgan et al., 2015; Waljas et al., 2015). Additionally, Morgan et al. (2015) reported that a family history of psychiatric illness, mood disorder, and/or migraine increased the likelihood of the development of lingering symptoms following a concussion. It can be difficult to diagnose an individual with PCS that is presenting with these findings, as these symptoms are not specific to concussion only and may be frequently reported by healthy adults and people suffering from chronic pain disorders, PTSD, and depression, with no history of concussion (Belanger et al., 2013; Waljas et al., 2015). These factors support the need for gold-standard diagnostic criteria for PCS in order to rule out premorbid/comorbid factors affecting symptom reporting. Conversely, Belanger et al. (2013) examined potential positive factors associated with a reduced risk of PCS such as self-efficacy, education, and symptom attributions. An individual suffering from PCS with negative symptom attributions subjectively perceives that all of his/her symptoms are directly related to concussion; whereas an individual with PCS who has positive symptom attributions may be able to identify another cause for why he/she may be experiencing a symptom aside from concussion.

Table 3.

Concussion factors and modifiers which impact concussion outcomes and recovery

Factors	Modifier
Symptoms	Number Duration (>10 days) Severity
Signs	Prolonged LOC (>1 minute) Amnesia
Sequelae	Concussive convulsions
Temporal	Frequency- repeated concussions over time Timing – injuries close together in time Recency – recent concussion or traumatic brain injury
Threshold	Repeated concussions occurring with progressively less impact force or slower recovery after each successive concussion
Age	Child and adolescent (<18 years old)
Comorbidities and Premorbidities	Migraine, depression, or other mental health disorders; ADHD, learning disabilities, and sleep disorders
Medication	Psychoactive drugs and anticoagulants
Behaviour	Dangerous style of play
Sport	High-risk activity, contact and collision sport, high sporting level

(McCrory et al., 2013)

The provision of educational material regarding concussion diagnosis, symptoms, normalization of symptoms, reassurance of positive expectation of recovery, and coping strategies have shown to reduce PCS severity in some instances (Belanger et al., 2013). Lastly, self-efficacy referred to a person's confidence in themselves to undergo change, complete tasks, and reach goals in regards to PCS recovery (Belanger et al., 2013). A hierarchal regression analysis was conducted to predict PCS severity and symptom resolution. First, demographic factors were entered (age,

sex, education, and time since the injury) and this accounted for 10.9% of the variance in post-concussion symptoms. Secondly, psychiatric distress was added to the regression model, and accounted for another 63.2% of the variance in post-concussion symptoms. Lastly, self-efficacy, PCS education, and attributions were collectively added to the model as a single positive factor. This combined factor accounted for an additional 21% of the variance, in comparison to the second model, for a total of 84.3% of variance accounted for (Belanger et al., 2013). In contrast, negative perceptions and symptom attributions following a concussion have been documented to be a strong predictor of PCS at six months (Hou et al., 2012). These negative symptom attributions may result in the appearance of persisting PCS when the individual may have actually recovered from PCS. An individual with negative attributions may perceive any headache, fatigue, dizziness, or memory lapse to be related to his/her concussion rather than a lack of sleep or stressful day.

Sex and age have also been reported to be two of the most common factors investigated regarding symptom reporting (Belanger et al., 2013; Kontos et al., 2012; Merrit & Arnett, 2014; Mounce et al., 2013). Several studies have reported that females have worse outcomes and higher reporting rates than males (Delaney, 2002; Gessel, 2007; Harmon et al., 2013; Kontos et al., 2012; McCrory et al., 2013; Merrit & Arnett, 2014; Reddy, Collins, & Gioia, 2008). Females have been documented to report a greater number of cognitive, affective, somatic, and sleep disturbance symptoms at baseline, as well as following injury that resulted in post-concussion in comparison to males (Kontos et al., 2012; Mounce et al., 2013). Contradictory findings have been reported due to different designs and methodologies among studies in addition to the use of different definitions of PCS. While some studies have reported that females experience greater neurocognitive decline following a concussion, others have reported inconsistent results relating

to neurocognitive decline in concussed females (Merrit & Arnett, 2014). Mounce et al. (2013) conducted a study on adults admitted to the emergency department following concussion and reported a significant interaction effect between sex and symptom reporting. Female participants consistently reported symptoms as more severe and debilitating than male participants. Although symptom reporting significantly differed between sexes, Waljas et al. (2015) reported that sex was not a significant predictor of PCS one month after the initial injury using WHO diagnostic criteria. Furthermore, a 2011 study showed that despite apparent sex differences for reporting symptoms, there appears to be no major sex difference in regards to symptom resolution and return to play (Frommer et al., 2011).

In addition to sex, age has also been identified as a factor related to lingering post-concussion symptoms. Concussion estimates peak during adolescence and young adulthood, when sport-related concussion are more common due to greater participation in competitive sport, recreation, and physical activity (PA; Langlois, Rutland-Brown, &Thomas, 2005). High school athletes reported more baseline cognitive and somatic symptoms in comparison to college students who reported a greater number of sleep disturbance symptoms (Kontos et al., 2012). While most concussions in adults (i.e., greater than 18 years of age) spontaneously resolve within 5-7 days after sustaining the injury, the same cannot be said for children and adolescents (Grady, 2010). Athletes in high school were found to have an average recovery time of 10-14 days (Grady, 2010). The current literature lacks a large body of information to explain this phenomenon; however, a theory is beginning to emerge describing why a longer average recovery time is seen in youth. A number of significant alterations to neurophysiology have been documented in animal as well as human studies and these changes have been shown to increase the brain's vulnerability to further injury in both young individuals and adults (Shrey, Griesbach,

& Giza, 2011). Following a concussion, changes in cerebral blood flow (CBF) have been well documented by numerous studies (Shrey et al., 2011). Decreased CBF may decrease nutrient and oxygen delivery to the brain; simultaneously, concentrations of neurotrophic factor known to regulate synaptic plasticity, and by extension memory formation, would also be decreased. The nature of these physiological processes and how concussion results in impairments to these mechanisms is discussed in further detail in the subsequent section.

Physiological Mechanisms of Concussion

Neurometabolic cascade of concussion. A concussion is a complex pathophysiological injury caused by biomechanical forces to the head, face, or neck (McCrory et al., 2013). Work by Giza and Hovda (2001) on animal models has led to the conclusion that concussion is not merely a structural brain injury but is, in fact, an acute metabolic injury resulting in changes to intra- and extra-cellular environments. The mechanical forces of a concussion may result in stretching of the neuronal cell membranes and axons leading to a disruption of the brain's ionic equilibrium and metabolism (Farkas, Lifshitz, & Povlishock, 2006). This metabolic injury is referred to as the neurometabolic cascade of concussion. The neurometabolic cascade causes an "abrupt, indiscriminant release of neurotransmitters and unchecked ionic fluxes to occur" (Giza & Hovda, 2001, p. 231). Following a concussion, this cascade occurs in children, adolescents, and adults alike.

The stretching of neuronal membranes and axons that occur due to concussion leads to a temporary ionic disequilibrium within the brain. This results in a drastic increase in extracellular potassium, causing an indiscriminate release of glutamate (an excitatory transmitter; Giza & Hovda, 2001; Shrey et al., 2011). Following this release, glutamate binds to the N-methyl-D-

aspartate (NMDA) receptor causing a build-up of intracellular calcium concentrations, which have been observed to cause dysfunction to mitochondrial respiration, and apoptosis (programmed cell death; Shrey et al., 2011).

Next, the ionic disequilibrium described above initiates an acute energy crisis within the brain. The adenosine-triphosphate (ATP) fueled sodium-potassium pump works excessively in an attempt to return ionic equilibrium; this process results in a hypermetabolism of glucose creating an imbalance between energy production and energy utilization, and a cellular energy crisis occurs (Giza & Hovda, 2001). This energy crisis is thought to make the brain increasingly more vulnerable to a second concussion as it is attempting to cope with the energy imbalance caused by the initial injury. The incidence of a second injury, prior to the full recovery from the initial concussion, may result in longer lasting impairment for the individual (Giza & Hovda, 2001). It is important to note that the pathophysiologic nature of concussion is far more complex than what is summarized above; this information is intended to provide a basic framework to understand the underlying physiology of such head injuries.

Concussion and youth. The knowledge that concussions are metabolic in nature (as opposed to structural) provides some insight as to why younger athletes experience longer recovery times than adults. The combination of metabolic factors related to puberty and the energy crisis that occurs as a result of concussion may be responsible for slower recovery in youth. The duration that typical metabolism is impaired within the brain is thought to be linked to the severity of the injury and worse recovery outcomes (Shrey et al., 2011). Within the literature, it is thought that the younger the athlete, the more prominent the impairments will be following concussion, and the longer these impairments will take to resolve in comparison to older athletes. This seemingly increased vulnerability is hypothesized to be linked to the fact that

the brain is undergoing development and/or the final stages of maturation during childhood and adolescence, respectively (Baillargeon, Lassonde, Leclerc, & Ellemberg, 2012; Shrey et al., 2011).

Baillargeon et al., (2012) examined if concussion during childhood, adolescence, or adulthood affected working memory following sports-related concussion equally, or if differences in working memory were present between developmental periods. Children (aged 9-12 years), adolescents (aged 13-16 years), and adults (greater than 18 years of age) who sustained a concussion were compared. It was expected that children would have more severe impairments than adolescents and adults, while adolescents would be more severe than adults. Interestingly, this study found that concussed children and adults performed similarly on outcome measures of working memory. Additionally, it was found that concussed adolescents had the greatest working memory impairment of the three groups (Baillargeon et al., 2012). The authors concluded that based on these findings, adolescents appeared to be the most vulnerable age group to experience atypical resolution of sports-concussion. It was hypothesized that this vulnerability was possibly the result of the disruption of typical brain functions following concussion compounded with the final stages of maturation (Baillargeon et al., 2012).

The physiological changes following concussion have been observed to increase the vulnerability of the brain to a second concussion in pediatric and adult athletes alike, especially if there is a force applied to the head within days of the initial injury (McCrory et al., 2013; Shrey et al., 2011). Furthermore, this increased vulnerability is especially of concern in youth as it may lead to a rare, but catastrophic phenomenon known as second-impact syndrome (SIS). There is much debate surrounding SIS; most evidence within the literature is in the form of case reports (Shrey et al., 2011). In the case of paediatric concussion, if a second impact is sustained prior to

the complete physiological resolution of the initial injury, catastrophic cerebral edema may occur within the skull (McCrory et al., 2013; Shrey et al., 2011). If intracranial pressure cannot be lowered by aspirating the fluid or decompressing the brain, SIS will result in an abrupt death. Some cases of SIS result in the affected athlete collapsing unexpectedly during practice or competition, soon followed by the absence of vital signs, and death (McCrory et al., 2013; Shrey et al., 2011).

Autonomic impairment following concussion. The autonomic nervous system is a division of the peripheral nervous system composed of the sympathetic and parasympathetic nervous systems. Wherein, the sympathetic nervous system controls the "flight or fight" reflex to prepare the body to deal with a stress or PA; conversely, the parasympathetic nervous system performs the opposite function relaxing the body after the stress or PA. As a whole, the autonomic nervous system is mainly responsible for the unconscious regulation of cardiac muscle, smooth muscle, and glands; more specifically controlling heart rate, respiration, blood pressure, and core body temperature (Autonomic Nervous System, 2007). A concussive injury has been reported to impair normal function of the autonomic nervous system, and may be an underlying factor for the development of PCS.

In 2004, Gall, Parkhouse, and Goodman recruited concussed junior level hockey players and were matched with non-concussed teammates, who most closely corresponded with their demographic characteristics. The purpose was to evaluate heart rate variability (HRV) following concussion using an electrocardiogram. At rest, no statistically significant differences of HRV were present between the two groups. However, when asked to perform a submaximal stationary bike exercise test within 72 hours of sustaining a concussion, nearly 50% of the concussed participants were unable to perform the exercise protocol due to the presence of symptoms (Gall

et al., 2004). On average, the concussed athletes were not able to perform the exercise test until the fifth day (+/-1.4 days) post-concussion. Within this study, the concussed athletes continued to present with abnormal HRV 10 days after their injury, suggesting that more time may be needed for full resolution and normalization of HRV. The authors suggested that this impaired function was due to an uncoupling between the autonomic and cardiovascular systems; wherein a desynchronization occurs between the cooperating systems. The injury may have disturbed the delicate balance between parasympathetic and sympathetic activity, resulting in abnormal HRV. In turn, recovery would require the resynchronization between both systems (Gall et al., 2004). Investigations following TBI have found that it may take up to six months for the autonomic and cardiovascular system to return to normal function. Although TBI is a more severe injury in comparison to concussion, it seems plausible that concussion may follow a similar resolution process as TBI, only on a shorter timeline (King, Lichtman, Seliger, Ehert, & Steinberg, 1997).

Junger et al. (1997) were one of the first groups to investigate impairments of cerebral blood flow (CBF) autoregulation following concussion, as opposed to TBI. Concussed individuals were demographically matched with healthy controls, in which 28% of concussed participants displayed severely impaired autoregulation following concussion. The impaired autoregulation of CBF in the concussed individuals was found to be a statistically significant observation when compared to the healthy controls. Under normal healthy conditions "CBF is tightly related to neuronal activity and cerebral glucose metabolism" (Giza & Hovda, 2001, p. 231). However, in instances of concussion, CBF may be reduced to 50% of normal function. As mentioned previously, studies investigating changes of CBF have been documented to increase the first day after injury, which is then followed by a significant reduction in CBF for many days afterwards (Shrey et al., 2011). An inquiry into the disruption of CBF in pediatric patients also

found that impaired autoregulation was observed in 42% of moderate to severe TBI, while 17% of those suffering mTBIs also experienced impaired autoregulation of CBF (Vavilala et al., 2004). Additionally, it has been reported that impaired CBF was associated with poor outcomes following mild, moderate, and severe TBI alike (Junger et al., 1997). During childhood and adolescence, youth are undergoing significant developmental changes in their brain and body as a whole; the physiological impairments following concussion may result in a disruption in the typical developmental processes and result in atypical development of the concussed child/adolescent (Shrey et al., 2011).

Cognitive impairment following concussion. As defined by the American Psychological Association, cognition consists of the processes of attending, remembering, and reasoning. Moreover, cognitive processes (also known as cognitive function) are higher mental functions and include perception, memory, language, problem solving, and abstract thinking (Gerrig & Zimbardo, 2002). The impairments to these higher mental processes following concussion have been thoroughly documented (Baillargeon et al., 2012; Broglio & Puetz, 2008; Ellemberg, Henry, Macciocchi, Guskiewicz, & Broglio 2009; Kleffelgaard et al., 2012; Majerskeet al., 2008; McCrory et al., 2013; Moore, Broglio, & Hillman, 2014; Moore, Hillman, & Broglio, 2014; Smits et al., 2009; Waljas et al., 2015). Specific mechanisms of concussion that cause these cognitive impairments, however, are still unclear. Levels of cognitive processing are typically measured in a clinical setting with neuropsychological (NP) test batteries for persons experiencing the effects of acute concussion and PCS alike (McCrory et al., 2013; Shrier, 2012). Traditionally NP testing has been administered in a paper-and-pencil format, however, this requires a significant amount of time to administer (2-3 hours), can be very expensive, and requires the involvement of a neuropsychologist to interpret the results (Harmon et al., 2013).

Recently, computerized NP tests have been developed to decrease the time of administration to 20-30 minutes, allow for the simultaneous administration to multiple individuals, and to not require a neuropsychologist for interpretation. These NP tests have been referred to as the cornerstone of acute concussion assessment and monitoring and are widely used. The computerized versions are utilized by many clubs and intercollegiate and professional sports leagues/teams to monitor their athletes (McCrory et al., 2013). Recommendations have been put in place to perform pre-season baseline assessments of athletes, in order to objectively identify cognitive impairments that may occur after an acute concussion (McCrory et al., 2013). Unfortunately, young athletes who are at the highest risk of concussion often do not have access to these computerized NP tests, as the tests are costly and do not fit within the small budgets of most school- or community-based youth sports teams/programs. In some cases, persons with PCS may present with no notable impairments as reported by computerized NP tests, despite subjectively reporting persistent symptoms (Baillargeon et al., 2012; Moore et al., 2014a; Moore et al., 2014b; Pontifex et al., 2009). More recently, electroencephalography (EEG) to monitor event-related potentials (ERPs) has been used as an alternative method to assess cognitive function in individuals with PCS (Baillargeon et al., 2012; Ellemberg et al., 2009; Moore et al., 2014a; Moore et al., 2014b; Pontifex et al., 2009). However, this alternative method of examining ERPs requires an EEG device as well as the ability of a trained individual to interpret the output of the EEG. Often EEG is available in hospitals, at universities, and research institutions, but are not often available in smaller clinical settings; thus, limiting the use of ERPs presently. Therefore, computerized NP test batteries serve as an accessible and interpretable method of assessing cognitive function in persons with PCS. In addition to cognitive

impairments secondary to concussion, diminished balance is a commonly reported symptom following concussion.

Balance impairment following concussion. The Oxford Dictionary of Sports Science and Medicine defines balance as: "the ability to maintain a stable and specific orientation in relation to the immediate environment" (Balance, 2007, p. 1), encompassing the ability to maintain static and dynamic balance. Specifically, "static balance is the ability to sustain a stationary position; alternatively dynamic balance is the ability to maintain equilibrium while moving" (Balance, 2007, p. 1). The maintenance of static and dynamic balance is achieved through the integration of reflexes within the eyes, semi-circular canals of the vestibular apparatus, skin pressure receptors, and muscle proprioceptors (Balance, 2007). Thus, a number of central and peripheral mechanisms are responsible for the integration of sensory feedback, and the resultant ability to balance (Ellemberg et al., 2009). Conversely, balance disturbance is the inability to stand with an upright posture within the limits of the base of support (Guskiewicz, 2011).

Headaches, dizziness, and balance disturbances are among the most commonly reported symptoms after a concussion; with 30% of concussed persons reporting abnormal balance and 75.6% reporting dizziness (Guskiewicz, 2011). Concussed individuals also present with balance disturbances on both low-tech clinical balance tools, as well as when using sophisticated force platform technologies (Ellemberg et al., 2009; Herring et al., 2011; McCrory et al., 2013). In most, but not all cases, balance impairments following concussion normalize within 3-10 days following the injury (Ellemberg et al., 2009). Although balance deficits appear to resolve quickly in the majority of cases, if the function and/or sensory integration of the visual or vestibular systems are impaired due to concussion, abnormalities in balance may persist for weeks or

months (Guskiewicz, 2001; McCrea et al., 2003). Two mechanisms have been proposed to explain diminished balancing ability; the first is that damage has occurred to the peripheral receptors within the skin and muscles themselves. The second proposed mechanism is the result of structural damage of the centralized processing structures of the cerebellum or vestibular apparatus, which results in reduced integration of sensory information (Alsalaheen et al., 2010; Guskiewicz, 2011). There is still limited evidence to definitively support or refute these proposed mechanisms of diminished balance, however. Vestibular rehabilitation has shown promise as an effective intervention for persons with persistent dizziness and/or balance impairments following concussion (Alsalaheen et al., 2010). Furthermore, Alsalaheen et al. (2010) reported that the implementation of gaze stabilization exercises, standing balance, and walking with balance challenges have produced significant improvements as observed by self-report and clinical balance performance measures. Vestibular rehabilitation appears to strengthen the diminished integration of sensory information following concussion. This evidence provides justification for vestibular rehabilitation exercises as a component of a possible rehabilitation protocol, to improve balance disturbances and dizziness in the PCS population.

Rest, Exercise, and Concussion

Initially following concussion, the vast majority of concussed persons will benefit from cognitive and physical rest for a period of 7-10 days; typically his/her symptoms will spontaneously resolve within this window (Moser et al., 2012). Generally, subjects are instructed to engage in cognitive and physical rest which includes (but is not limited to) no school or work, driving, screen time, chores, and physical exercise or activity that results in perspiration (Moser et al., 2012). This period of rest is hypothesized to allow the brain enough time to resolve the metabolic disruption resulting from the neurometabolic cascade of concussion. The reduction in

cognitive and PA allows for the reallocation of ATP in order to restore intra- and extracellular ionic concentrations and metabolic homeostasis. Exercise within this recommended period of rest has been observed to exacerbate symptoms (Gall et al., 2004; McCrory et al., 2013). Although the exact mechanism is still unclear, it appears that cognitive and/or physical demands during this period of rest may divert ATP needed to resolve the metabolic energy crisis; thus, increasing the metabolic demand while the state of the brain is incapable of meeting such demands (Shrey et al., 2011).

To date, there is no identified gold standard for rehabilitating the PCS patient; rest appears to be the general treatment of choice (Patterson, & Holohan, 2012; Sayegh, Sandford, & Carson, 2010). Treatment recommendations for PCS beyond the acute phase (i.e., 7-10 days after injury) have consisted of rest, education, neurocognitive rehabilitation, and anti-depressant medications with limited results (Fann, Uomoto, & Katon, 2000; Ho& Bennett, 1997; Sayegh et al., 2010). For those with lingering symptoms, a period of prolonged rest could possibly result in physical deconditioning, the development of PCS comorbidities, and/or socioeconomic stress (Moore et al., 2014b; Papa, Ramia, Edwards, Johnson, & Slobounov, 2015). Although exercise within the acute stage following concussion has been shown to be detrimental, exercise for those with PCS shows promise as a rehabilitation strategy (Majerske et al., 2008). A moderate level of exertion and activity for those with PCS has been associated with more favourable symptom reports and measures of neurocognitive performance when compared to low and high levels of exertion (Majerske et al., 2008). As outlined briefly above, vestibular rehabilitation exercises have been reported to be effective in improving self-report and clinical measures of persisting balance disruptions and dizziness (Alsalaheen et al., 2010). Moreover, well-established benefits of PA, specifically aerobic exercise, appear to be a possibly potent method of addressing a

number of physiological and cognitive impairments for persons with PCS; especially if administered in a controlled, structured, and individualized manner (Majerske et al., 2008).

Physical activity has been extensively documented to have profound benefits on overall health and well-being for persons of all ages (Canadian Society for Exercise Physiology; CSEP, 2013). These benefits include strengthening bones and muscles; improved academic performance; maintenance of healthy body weight; prevention, reduction, and management of chronic disease; reduced stress, as well as depression; and overall improved physical and mental health (CSEP, 2013). In addition, the body of literature pertaining to the positive effect of PA and exercise on the brain and cognitive function is rapidly accumulating. In 2009, van Praag published a review summarizing the profound benefits of exercise on brain function. Winter et al., (2007) found that faster reaction time and verbal learning were present in healthy college students following 12 weeks of aerobic training. Despite differing durations, intensity, time, and type, PA improved cognitive function overall (Hillman, Erickson, & Kramer, 2008). Additionally, PA promotes recovery from depression and has been shown to be as potent as serotonergic medications (Babyak et al., 2000). Research hypotheses and study designs investigating the effects of PA on the brain are often focused on improvements in neurogenesis (formation of new neurons), angiogenesis (formation of new blood vessels), and the increase in neurotrophins (van Praag, 2009).

Many of these benefits are in response to regular aerobic exercise, defined as exercise or PA of low to moderate intensity performed for a long duration (greater than10-15 minutes) that is repetitive and cyclical in nature (Aerobic Exercise, 2007). Aerobic exercise includes activities such as walking, jogging, swimming, cycling, or cross-country skiing (Aerobic Exercise, 2007). For individuals with PCS, aerobic exercise may facilitate the resolution of impaired autonomic

control (Phillips et al., 2014). Specifically, aerobic exercise has been documented to improve cerebral blood flow and nutrient delivery to the brain, which is impaired in some individuals with PCS (Phillips et al., 2014; Shrey et al., 2011). Healthy individuals who regularly engage in aerobic activity display reduced sympathetic activity at a sub-maximal intensity, compared to sedentary individuals exercising at the same intensity (Carter, Bannister, & Blaber, 2003). Furthermore, greater parasympathetic control has been observed in those who regularly participate in aerobic exercise (Carter et al., 2003). These effects on the autonomic nervous system in response to aerobic exercise, may improve HRV in those experiencing PCS. In healthy older adults, aerobic exercise has been reported to improve attention, processing speed, and memory (Smith et al., 2010). Additionally, Lee et al. (2014) reported preliminary evidence that aerobic exercise improved cognitive functions in a sample of healthy adolescents. This evidence supports a rationale for the potential utility of aerobic exercise for improving physiological, autonomic, and cognitive impairments in those with PCS if administered in a controlled and individualized manner. Of particular interest are the underlying mechanisms in which aerobic exercise improves cognitive function via improved neuroplasticity and neurotrophin delivery.

Neuroplasticity. It is estimated that the human brain consists of 120 billion neurons, which function to regulate vital organs, allow conscious thought, produce speech, and store memories (Houzel-Herculano, 2009). Neuroplasticity is the ability of neurons to alter the strength and efficacy of pre-existing synapses in addition to forming new synaptic connections (Synaptic Plasticity, 2004; Wells, 2002). Furthermore, “neuroplasticity includes changes in strength of mature synaptic connections, as well as the formation and elimination of synapses in adult and developing brains” (Wells, 2002, p 1.). This formation of new synapses can also be

extended to include the regeneration of synapses after a central nervous system (CNS) injury. Thus, neuroplasticity allows the brain to continuously store new information and adapt throughout life without the need to physically grow in size. Warriach and Kleim (2010) identified neuroplasticity as the biological substrate for neurorehabilitation. Following a concussion, changes in the brain may alter the process of synaptic plasticity, which may manifest as cognitive impairments (Shrey et al., 2011).

It is thought that plasticity and memory formation are modulated by a phenomenon referred to as long-term potentiation (LTP; Purves et al., 2001). Long-term potentiation has been thoroughly studied in the hippocampus of mammals, an area within the brain that is crucial in the formation and retrieval of some memories (Purves et al., 2001). Although LTP has primarily been studied within the hippocampus, it has also been noted in the cortex, amygdala, and cerebellum (Purves et al., 2001). The phenomenon of LTP is the result of a physiological response that occurs at the synaptic level as a result of stimulation and activity (Purves et al., 2001). This response is initiated following activity that causes an intense and high frequency stimulation of the presynaptic neuron leading to the release of the neurotransmitter glutamate (Lynch, 2004). The released glutamate binds to the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor allowing sodium ion channels to open and the entry of an influx of sodium within the post-synaptic neuron (Lynch, 2004). If the concentration of sodium is great enough in the post-synaptic neuron, an action potential is triggered and the electrical impulse can travel to the next neuron (Lynch, 2004). The phenomenon of LTP also involves the N-methyl-D-aspartate (NMDA) receptor of the post-synaptic neuron along with the paired calcium ion channel; however, when the neuron is at resting potential, this ion channel is blocked by magnesium ions (Lynch, 2004). These magnesium ions are dislodged from the

calcium ion channel if the post-synaptic neuron's membrane potential is depolarized, which has been shown to occur as a consequence of high-frequency stimulation (Lynch, 2004). The resultant increase of calcium concentration within the post-synaptic neuron initiates several additional complex physiological reactions that sustain synapse efficiency and LTP that are beyond the scope of this review (Lynch, 2004). Although LTP is not entirely understood, the literature provides evidence that LTP is an underlying physiological mechanism that affects neuroplasticity and memory formation in mammals. In contrast to LTP, long-term depression (LTD) is a neurological process wherein specific synapses are weakened and the efficiency of the synapse is decreased (Purves et al., 2001). This weakening of synapses during LTD prevents the possibility of synapses reaching maximum efficacy as a result of LTP, in turn causing encoding of new information to be difficult (Purves et al., 2001). This complementary interaction between LTP and LTD to reversibly affect synaptic efficiency provides further support for these phenomena impacting neuroplasticity. Athletes who have experienced a history of concussion have been observed to display an alteration of LTP/LTD-like plasticity (De Beaumont, Tremblay, Poirier, Lassonde, & Theoret, 2012). A concussive injury to the brain may alter the pathways responsible for the typical regulation of LTP and LTD. Impaired LTP and LTD appears to possibly explain cognitive impairments related to working memory and attention reported by individuals with PCS. Hence, tapping into the physiological processes which modulate LTP and LTD may decrease self-reported and clinical measures of cognitive impairment for persons with PCS.

Neurotrophins and brain-derived neurotrophic factor. Neurotrophins are a family of proteins that have been shown to have a profound impact on neurons and the CNS as a whole. This family of proteins have been shown to be involved in regulating neuronal survival,

development, function, and plasticity (Huang & Reichardt, 2001). These regulatory properties can be categorized as those that primarily aid in trophic support of adult neurons or involved in promoting activity-dependent plasticity (Hennigan, O'Callaghan, & Kelly, 2007). In mammals, four proteins have been identified as the members of the neurotrophin family including: nerve growth factor, brain-derived neurotrophic factor (BDNF), neurotrophin-3, and neurotrophin-4 (Huang & Reichardt, 2001). The impact of neurotrophins is the most popular area of interest for researchers investigating how exercise impacts the brain. Of the four neurotrophic factors, nerve growth factor and BDNF have been the most extensively researched. According to Hennigan et al. (2007), the known effects specific to BDNF demonstrate the potential as a non-pharmacological intervention to benefit impaired neurological function. Brain-derived neurotrophic factor can be collected in humans via blood serum or saliva samples. Measurement of BDNF from serum appears to be the most accurate and widely used method (Cho, Kim, Lee, Kim, & Yoon, 2014; Lee et al., 2014; Tapia-Arancibia, Aliaga, Silhol, & Arancibia, 2008; Whiteman et al., 2014). Despite the accuracy of serum BDNF, this method of collection is invasive in nature as it requires a phlebotomist to draw the sample intravenously. In contrast, the measurement of BDNF in saliva offers a less invasive technique.

Hennigan et al. (2007) have reported that BDNF plays the greatest role of the neurotrophin family in promoting LTP. Decreased levels of BDNF have been reported in neurodegenerative diseases such as Alzheimer's Disease (AD) and Huntington's Disease; and also in neuropsychiatric conditions such as depression and schizophrenia (Adachi, Numakawa, Richards, Nakajima, & Kunugi, 2014). Therefore, BDNF concentrations may affect symptom reports, as well as time elapsed until symptom resolution for those with PCS. Therefore, improving concentrations of BDNF in individuals with PCS may serve as a physiological

mechanism to create the internal environment necessary to facilitate the brain healing itself, in turn, possibly leading to the reduction or resolution of PCS symptoms. Brain-derived neurotrophic factor has been reported to display considerable variability between individuals due different collection and analysis methodologies, in addition to a number of non-technical factors. Non-technical factors affecting BDNF concentrations include age, PA, drinking, fasting, the time of sample collection, living in an urban environment, and smoking. Due to these factors serum BDNF concentrations in healthy subjects range from 12.2 +/- 2.4 to 64.1 +/- 13.1 nanograms/mL (Maffioletti, Zanardini, Gennarelli, & Bocchio-Chiavetto, 2014).

Aerobic exercise and brain-derived neurotrophic factor. Animal studies have been utilized to investigate the effect of aerobic exercise on BDNF concentrations and cognitive function in mice/rat models of concussion. Under normal conditions, it is proposed that exercise would increase BDNF concentrations (for review see Shrey et al., 2011) however, exercise within the acute concussion period actually led to decreased BDNF levels in mice (Griesbach, Gomez-Pinilla, & Hovda, 2004). When the administration of exercise to the concussed mice was delayed, increases in BDNF concentrations were observed and associated with improved hippocampal learning and memory (Griesbach et al., 2004). Additionally, rats with TBI also exhibited improved cognitive performance associated with increased BDNF concentrations following voluntary aerobic exercise (Griesbach et al., 2009). The relationship between BDNF, aerobic exercise, and concussion in humans has not been reported in the literature. However, investigations of healthy individuals report a number of associations between BDNF and aerobic exercise including: modulation of synaptic plasticity; maintenance of LTP; regulation of neuronal proliferation, survival, migration, and differentiation; and synapse formation and stabilization (Adachi et al., 2014; Griesbach et al., 2009; Phillips et al., 2014).

Effect of exercise and brain-derived neurotrophic factor on other neurological conditions. A recent study conducted by Koo et al. (2013) examined the neuroprotective effects of treadmill exercise in AD in mice. The researchers noted decreased BDNF in animals with AD. In turn, Koo et al. (2013) reported a similar rationale as outlined above as a possible treatment strategy for implementing exercise in order to improve BDNF for AD patients. The authors' use of treadmill exercise resulted in an upregulation of BDNF and associated improvements in learning and memory function in the mice with AD (Koo et al., 2013). These results are consistent with the previously reported findings, providing further support for the possible neuroplasticity through exercise-induced upregulation of BDNF. In addition, Phillips et al. (2014) stated that sustained PA enhanced immune function and anti-inflammatory processes within the body. This is a significant result of PA in relation to AD as chronic inflammation has been etiologically linked to cognitive impairment and neurodegenerative diseases, including AD (Phillips et al., 2014).

Mang, Campbell, Ross, and Boyd (2013) investigated the effect that aerobic exercise induced increased BDNF would have on neuroplasticity for motor rehabilitation in stroke survivors. The authors found that the effects of BDNF on the CNS as well as neural plasticity were key factors related to improvements observed in motor learning during stroke rehabilitation (Mang et al., 2013). Furthermore, Mang et al. suggested that in order to induce greater concentrations of BDNF, aerobic exercise should be performed four times per week, for greater than 30 minutes, at 70% of predicted heart rate maximum, and aerobic exercise should be combined with resistance exercises. Aerobic exercise was said to "prime the CNS for the neuroplastic change that underlies the desired behaviour change" (Mang et al., 2013, p. 1712). Cycling at a high intensity immediately prior to or following the practice of motor tasks

improved the participants' motor performance when tested for retention one and seven days after practicing (Mang et al., 2013). Other evidence indicates that lower intensity aerobic exercise performed daily produces lower concentration levels of acute BDNF, but greater concentrations of BDNF over the long-term (Ploughman et al., 2007; Shen et al., 2013; Shih, Yang, & Wang, 2013). Therefore, it appears as though lower to moderate exercise performed on a frequent basis will have the greatest prolonged effect on BDNF concentration levels. This study also cautioned that aerobic exercise alone did not result in improved neuroplasticity; rather, aerobic exercise created a more ideal neural environment which supported neuroplasticity (Mang et al., 2013). Since upregulation of BDNF via aerobic exercise resulted in promising outcomes in neurological conditions more severe than PCS, it appears plausible that a similar application tailored for PCS may be greatly beneficial.

Rehabilitation Strategies for Post-Concussion Syndrome

Standard rest care for post-concussion syndrome. As previously described, there is no identified gold standard for rehabilitating a patient with PCS; rest is the general treatment of choice (Patterson & Holohan, 2012; Sayegh, Sandford, & Carson, 2010). Cognitive and physical rest consisting of (but not limited to) no school or work, driving, screen time, chores, physical exercise, or activity that results in perspiration has been shown to be beneficial in the acute phase of approximately 1-10 days following concussion (Moser et al., 2012). The suggestion to continue to rest is commonly prescribed to those individuals with PCS due to the documented effectiveness of rest for acute concussion. However, some evidence suggests that this prescription is more detrimental than beneficial to persons with PCS (Moore et al., 2014b; Papa, Ramia, Edwards, Johnson, & Slobounov, 2015). Typically rest is prescribed in combination with educational material regarding concussion/PCS diagnosis, symptoms, normalization of

symptoms, reassurance of positive expectation of recovery, and PCS coping strategies (Belanger et al., 2013). For the remaining sections of this manuscript, standard rest care (SRC) will refer to the prescription of cognitive as well as physical rest, in combination with PCS educational material.

Exercise rehabilitation of post-concussion syndrome. Presently, it appears that Leddy et al. (2013) were the first and only group to investigate the possible application of aerobic exercise as an intervention strategy to improve brain functions for PCS. Participants consisted of females diagnosed with PCS who were randomly assigned to either an aerobic exercise or stretching group; additionally healthy controls were included as a third group. All participants completed a pre- and post-intervention functional magnetic resonance imaging (fMRI) to assess brain activation. Within this pilot study, the investigators administered a stationary bike exercise test to participants with PCS in order to determine at what heart rate and blood pressure each participant began to feel one or more symptoms of PCS (Leddy et al., 2013). Eighty percent of the recorded heart rate was calculated to determine the starting aerobic exercise intensity for the exercise intervention (Leddy et al., 2013). Participants were guided through aerobic exercise at a sub-symptom threshold intensity based on their heart rate. Prior to the treatment, the aerobic and stretching group displayed abnormal brain activation patterns compared to the healthy controls on fMRI, but the two groups did not differ from each other otherwise. Following treatment, a significant difference was observed between healthy controls and the stretching group. Notably, there was no significant difference reported between the healthy controls and the aerobic exercise group following the intervention, however the stretching group significantly differed from the exercise group. Furthermore, by the end of the intervention the aerobic exercise group were able to elevate their heart rate to their age predicted maximum; whereas, the stretching

group was unable to achieve this. Leddy et al. (2013) speculated that the aerobic exercise facilitated the restoration of CBF autoregulation, which was not observed in response to stretching.

The Fowler Kennedy PCS Management Guidelines (n.d.), cite Leddy et al.'s work, recommending aerobic exercise for 20-30 minutes with no increase in self-reported symptoms throughout the entire duration of exercise. Once 30 minutes without symptoms is achieved, the intensity may be increased. It is recommended to increase duration prior to increasing intensity with the end goal being 80-90% intensity for 20-30 minutes with no symptoms (Fowler Kennedy, n.d.; Leddy et al., 2013). Vestibular rehabilitation using balance exercises has also been reported to improve the symptoms of impaired balance for persons with PCS (Alsalaheen et al., 2010). No current standard program exists for balance exercise administration to the best of our knowledge for the concussion population. The Fowler Kennedy PCS Management Guidelines recommend balance exercises beginning in a two foot stance, on a firm level surface, and increasing the demand on the subject by progressing to a combination of one foot balance, soft/uneven surfaces, extremity movements, and with the integration of cognitive/visual challenge tasks (Fowler Kennedy, n.d.). While beneficial for determining balance exercise progressions, the guidelines do not provide information regarding the duration of balance exercises, number of repetitions or sets, or when to progress the subject to a more challenging exercise. These recommendations provide a framework to create a template of balance exercise progressions for rehabilitating balance in individuals with PCS. Aerobic and balance exercises display the potential utility as an effective rehabilitation strategy for improving symptom reports, clinical outcome measures, and symptom resolution times for persons with PCS.

Within the literature there is a lack of evidence that prolonged rest beyond the acute period of concussion would benefit individuals with PCS. Conversely, research has shown that forms of exercise have demonstrated effectiveness in improving neurological impairments in AD, stroke, and TBI in both human and animal models. Therefore, there is a need to evaluate the effectiveness of exercise programs tailored to address PCS in regards to symptom reports, clinical outcome measures, and symptom resolution times.

Purpose of the Research

Based on this rationale, the purpose of this study was to investigate the impact of a four week structured and supervised AEB program on cognitive function, balance, and saliva BDNF levels in a sample of 14-30 year old individuals diagnosed with PCS.

Research Questions

The following research questions were used to guide the purpose of this study:

1. Is there a difference between pre- and post-treatment on measures of resting heart rate and blood pressure values for individuals with PCS following a four-week AEB based program?
2. Is there a difference between pre- and post-treatment on measures of salivary-BDNF concentration levels for individuals with PCS following a four-week AEB based program?
3. Is there a difference between pre- and post-treatment Immediate Post-Concussion Assessment and Cognitive Testing tool (ImPACT) verbal memory, and visual memory, visual motor speed, reaction time composite scores for individuals with PCS following a four-week AEB based program?

4. Is there a difference between pre- and post-treatment AMTI force platform values of displacement in centre of pressure (COP) during the Balance Error Scoring System (BESS) for individuals with PCS following a four-week AEB based program?
5. Is there a difference between pre- and post-treatment Post-Concussion Symptom Scale (PCSS) scores for individuals with PCS following a four-week AEB based program?
6. What relationships are present between salivary-BDNF concentrations and PCSS score changes following a four-week AEB treatment, and what relationships are present between post-treatment values of salivary-BDNF concentration levels and PCSS scores.

Chapter 3 - Methods

Participants

After obtaining ethical approval from the Lakehead University Research Ethics Board, a one group pre-test post-test design was implemented. The effect of a supervised and progressive AEB retraining program was evaluated in 9 participants with PCS across 12 dependent variables. The dependent variables included: resting heart rate and resting blood pressure; ImPACT visual memory composite score, verbal memory composite score, visual motor speed composite score, and reaction time composite score; area of COP, velocity of COP, length of COP, and displacement of COP; PCSS scores; and salivary-BDNF concentrations.

Inclusion Criteria

Participants for the proposed study were included if they met the following criteria:

1) Males or females between the ages of 14 and 30 years;

2) Sustained a concussion in which the symptoms did not resolve within 10 days, and these symptoms persisted at least eight weeks after the initial injury;

3) Were diagnosed with PCS by a physician; and

4) Were cleared to begin exercising by his/her physician via their score on the Sport Concussion Assessment Tool (SCAT-3). After a minimum of eight weeks of persistent concussion symptoms from the initial injury, the supervising physician informed individuals with PCS of the current study if he/she had a SCAT-3 score greater than 20 and less than 90 (indicating persistent but not debilitating symptoms).

Exclusion Criteria

Conversely, participants were excluded if they:

1) Presented with headache pain that was associated with migraine headache;

2) Had been diagnosed with depression or other mental health disorders;

3) Had ADHD or any other learning disabilities or sleep disorders prior to sustaining the head injury resulting in PCS; and

4) Sustained a concussion but all of the symptoms had resolved in less than eight weeks.

Instrumentation and Outcome Measures

For this study, the following instruments and outcome measures were used:

Immediate post-concussion assessment and cognitive testing. The ImPACT (ImPACT; ImPACT Applications Inc., Pittsburgh, PA) battery is an established NP test measure used by researchers, clinicians, and numerous university and professional sports teams. Researchers and clinicians implement the ImPACT battery as a means to measure components of cognitive functioning including: attention, concentration, reaction time, memory, processing speed, decision making, problem solving, and response variability (www. impacttest.com, n.d.). Schatz, Pardini, Lovell, and Podell (2006) explored the sensitivity and specificity of the ImPACT battery when differentiating between concussed and non-concussed individuals and reported 82% sensitivity in correctly classifying concussed individuals, and 89% specificity for ruling out concussion in a healthy control group. Schatz revisited the psychometric properties of the ImPACT in 2010, evaluating the test-retest reliability of the ImPACT composite scores over two years. Schatz (2010) reported evidence of reliability for scores related to visual motor speed

using test-retest reliability (intra-class correlation (ICC) = .74), followed by the reaction time composite (ICC = .68), visual memory (ICC = .65), and, lastly, verbal memory (ICC = .46) scores. The ImPACT battery has evidence of construct validity as well when compared with traditional paper-and-pencil NP tests (Maerlender et al., 2010). Allen and Gfeller (2011) compared the ImPACT to traditional paper-and-pencil NP tests using a factorial analysis approach; the authors reported good overall evidence of concurrent validity with five factors explaining 69% of the variance in ImPACT scores. Another benefit of the ImPACT battery is the integration of the Post-Concussion Symptom Scale (PCSS) outcome measure, which is embedded within the test battery. These characteristics make the ImPACT battery a useful tool for researchers to assess concussion. As such, the ImPACT battery can be utilized as a quick means to measure constructs of cognitive function and to determine baseline measures. For the purpose of the proposed study, the ImPACT battery will be administered to PCS participants in order to measure cognitive function utilizing four composite scores (verbal memory, visual memory, visual motor speed, and reaction time) pre- and post-treatment.

Measures of balance. The BESS (University of North Carolina) is the current standard static (standing) balance assessment used for concussed athletes in sideline assessment (Brown et al., 2014; Iverson & Koehle, 2013). The BESS represents a simple balance assessment tool that is portable, requires little training, and allows for quick standing balance assessment. Moreover, the BESS is recommended as the static balance measure of choice for individuals with PCS (Fowler Kennedy reference, n.d.). The validity and reliability of simple standing balance assessment tools like the BESS has been called into question by some clinicians and researchers (Brown et al., 2014). Intra-tester reliability ranged from an ICC value of .50 to .98 for individual stances, while inter-tester reliability was reported to range from .44 to .96 for individual stances.

For the BESS total score, inter-tester reliability has been reported to range from .57 to .85. Therefore, the BESS reliability ranges from moderate (.50 -.75) to good (>.75). Criterion-related validity for the BESS was found to have statistically significant correlations ($p < .01$) for five of the six testing conditions, with the exception of double stance on firm ground (Brown et al., 2014.

Advance Mechanics Technologies Incorporated force plate and BIOSOFT software. The location of the COP during postural sway shifts in response to adjustments of force distribution needed to maintain balance. The COP is the "point at which an equivalent single force causes the same effect on a rigid body as a distributed force" (Robertson, Caldwell, Hamill, Kamen, & Whittlesey, 2004, p. 283). To account for varying levels of reliability, the BESS protocol was performed on top of an Advanced Mechanics Technologies Incorporated (AMTI) force platform in order to add a more reliable, valid and objective measure of postural sway during static balance. The AMTI force platform was used in this study to measure ground reaction forces that are generated during a body standing on the plate. Force platforms such as the AMTI force platform are widely used to quantify gait, balance, and other parameters of biomechanics. The AMTI force platform measures the ground reaction forces that are generated by a body standing or moving across the plate. The AMTI force plate is also capable of measuring torques about each axis and has six degrees of freedom, which includes three forces (f_z, f_x, and f_y) and three moments (M_z, M_x, and M_y). All of these measures are fed into an AMTI amplifier and converted to digital signals via an analog to digital converter. The information collected by the force platform is then uploaded into BIOSOFT computer software which allows the researcher to view and analyze data following collection. The BIOSOFT computer software calculates the x and y moments of postural sway which are used to compute the location of COP,

and produces graphical representations of this data. The coordinates of x and y COP points are calculated via the AMTI BIOSOFT software using Equations 1 and 2.

$$Y = M_X/F_Z \quad (1)$$

Where:
Y = position on the Y plane
M_X= torque in the X plane
Fz= Vertical force

$$X = M_Y/F_Z \quad (2)$$

X = position on the X plane
M_Y= torque in the Y plane
Fz= Vertical force

The COP during postural sway was recorded for the entire duration of each of the six 20 second BESS protocol trials. Moments and forces during postural sway in the vertical, anterior-posterior, and medial-lateral planes were measured and recorded. The displacement in postural sway and COP was displayed visually by the computer software using a 95% elliptical curve, which traced the displacement in COP point within a normal distribution and outliers throughout the duration of the trial. A summary report was produced by the software and the information was exported to Excel and SPSS in order to represent the COP displacement numerically.

Due to the subjective nature of BESS scoring, the BESS was used as a standard protocol to assess balance within this study; however, BESS scores were not recorded. Only COP area, COP velocity, total COP displacement, and COP length throughout each 20 second trial were recorded and used in the data analysis. The definitions for these specific measures of COP are as follows:

Centre of pressure area. The area of the COP was determined based on Heron's equation, and defined as the area included within the path of COP during the 20 second trial

(Kendig, 2000). Area of COP refers to the size of the 95% elliptical curve in cm^2 produced by the BIOSOFT computer software for each trial. The software calculated the area of COP based on the maximum deviation values of COP in the x and y directions throughout each 20 second trial. The most extreme values that fell outside of the 95% elliptical curve during each trial were not included in the calculation of COP area (cm^2).

Centre of pressure velocity. Velocity of the COP refers to the directional speed in cm/sec at which the COP deviated through the base of support throughout each 20 second trial. The average speed of directional changes in the COP throughout each 20 second trial was measured (cm/sec).

Total centre of pressure displacement. Displacement of the COP referred to the overall total deviation of the COP from the base of support during each 20 second trial measured in cm. Maximum and minimum values of COP displacement in x and y directions were measured. These values were exported to Excel. Displacement in the x and y directions were calculated by subtracting the minimum displacement value from the maximum displacement value for both the x and y directions, respectively (cm). Equation 3 was used to calculate the total displacement for each trial.

$$\text{Cumulative displacement} = \sqrt{x\ displacement^2 + y\ displacement^2} \quad (3)$$

Centre of pressure length. The length of COP was defined as the resultant length of the path of COP in the x and y directions throughout each 20 second trial measured in cm (Winter, 2009). The AMTI force plate software produced a visual representation of the path of COP as a single continuous line throughout the trial. When this data was uploaded into the BIOSOFT computer software, the total length the COP travelled during each trial was calculated (cm).

Post-concussion symptom scale. The PCSS was administered for participants to self-report his/her symptoms and is embedded within the ImPACT test battery. The PCSS is a 22-item scale that was initially developed in the 1980s and led to the development of other similar scales (Leddy et al., 2012; Lovell et al., 2006). Subsequently, many outcome measures and scales have been developed in an attempt to record and grade concussion symptoms, as well as symptom severity. There is currently, however, no agreed upon gold standard to assess concussion symptoms and their severity (McCrory et al., 2013). In many cases, the development of concussion scales has not been matched with detailed investigations into their reliability and validity (Eckner & Kutcher, 2010). In 2006, Lovell et al. examined the reliability of the PCSS in a sample of 1,746 high school and university student athletes, including 260 concussed athletes and found that there was no difference in self-reported symptoms between high school and university student athletes. However, a significant difference in self-reported symptoms was found between males and females in both samples, with females reporting a greater number of symptoms than males. Additionally, the PCSS has a reported high Cronbach's alpha value of internal consistency ranging from .88 to .94 for non-concussed and .93 for the concussed student athletes. Lastly, the PCSS has been adopted by the National Football League, National Hockey League, and numerous colleges and universities (Lovell et al., 2006). The PCSS is used to record self-reported symptoms that a concussed individual has experienced over a 24 hour period. Symptoms are recorded across 22 items, each measured with a Likert scale from 0 (no symptoms) to 6 (severe symptoms). This allows for researchers and clinicians to monitor the concussed individual's progress towards symptom resolution.

Sport Concussion Assessment Tool. The SCAT-3 (Appendix E) is the third version of the SCAT and was developed by a group of sport-related concussion experts at the 4th

International Consensus meeting on Concussion in Sport held in Zurich, Switzerland in November 2012 (McCrory et al., 2013). The SCAT-3 is a standardized tool used for evaluating injured athletes, aged 13 years or older, for concussion. The performance on the SCAT-3 assists medical professionals in determining whether or not the athlete is ready to begin a stepwise program to return to play (RTP). The SCAT-3 consists of the compilation of eight individual assessments/examinations that have each been proven to be reliable and valid in isolation (Guskiewicz, 2003; Maddocks, Dicker, & Saling, 1995; McCrea, 2001; McCrory et al., 2013; Schneiders, Sullivan, Gray, Hammond-Tooke, & McCrory, 2010a; Schneiders et al., 2010b). The SCAT-3 is intended for use as a streamlined method of sideline and clinical assessment of concussion, but is not meant to replace comprehensive NP testing that would be more sensitive to subtle deficits undetectable by the SCAT-3 (McCrory et al., 2013).

Procedures

Recruitment. All participants for the study were referred from the Lakehead University Concussion Clinic. The SCAT-3 was administered by the physician to assist in determining whether or not the athlete was ready to begin a stepwise program to RTP. The physician determined if the potential participant with PCS was cleared to begin engaging in light PA. Individuals who met the inclusion criteria were identified and informed of the study by the referring physician. Prospective participants gave his/her consent to the physician to share his/her contact information with the student researcher in order to receive more detailed information about the study. Once contact was made over the telephone or via email, the participant was scheduled for the initial assessment at which time an information letter detailing what would be required of them in order to participate was provided (refer to Appendix B for a copy of the information letter). Next, participants over the age of 18 provided informed consent

to participate within the study (refer to Appendix C for a copy of the consent form). Participants under the age of 18 completed the assent form (Appendix D) and afterwards the legal guardians or parents of potential participants under the age of 18 provided informed consent for the child to participate in the study (Appendix C).

Data Collection

Upon receiving informed consent, the data collection process consisted of three distinct components: 1) Initial (pre-treatment) assessment; 2) Four week AEB program and concussion education (Appendix G); and 3) Post-treatment assessment.

Collection of salivary-BDNF. The data collection process and initial assessment began at the Northern Ontario School of Medicine (NOSM) whereby a saliva sample was provided by the participant. The saliva sample was collected by the student researcher to obtain salivary BDNF concentrations prior to beginning the intervention. Participants were instructed to refrain from brushing his/her teeth, smoking, and consuming food or drink within two hours of the sample collection. Additionally, participants were instructed to withhold from consuming any alcohol within 12 hours of the collection. Evidence indicates that both serum and saliva BDNF concentration levels were greatest in the morning and declined throughout the day (Tirassa et al., 2012). To control for this, salivary-BDNF samples were collected between 8:00-9:00 a.m. to minimize any effect of diurnal variation. The student researcher passively collected approximately 2 mL of unstimulated whole resting saliva into a 2 mL microcentrifuge tube and then placed on ice. All samples were coded by the student researcher and passed to the research assistant following collection. The microcentrifuge tubes containing participant salivary samples were centrifuged at 4000 rpm for 15 minutes at 4°C to remove cellular debris; afterwards the salivary samples were aliquoted into 1.5 mL microcentrifuge tubes and protease inhibitor

cocktail was added to a final dilution of 1:100 after centrifugation. All samples were stored at -80°C in a freezer within the NOSM laboratory until the sample analysis was completed. During the post-treatment assessment, a second saliva sample was collected and treated in the same manner. Once a pre- and post-treatment saliva sample was collected for all participants, the frozen samples were thawed, and centrifuged for a second time to remove any remaining cellular debris. All samples were acidified with 1M hydrochloric acid to release any BDNF that may be complexed to other proteins, then re-neutralized with 1M sodium hydroxide and diluted for assay purposes. Lastly, the total protein concentrations of BDNF were measured in picograms per millilitre (pg/mL) utilizing an enzyme-linked immunosorbent assay (ELISA) technique described by Mandel, Ozdener, and Utermohlen (2011). The ELISA technique was completed by project member Sarah Niccoli, a trained research assistant and laboratory technician at NOSM.

A sandwich ELISA technique was used to quantifiy salivary-BDNF measurement, following the protocol put forward by Mandel et al. (2011). A 96-well microwell plate (NuncMaxisorp; VWR, West Chester, PA) was incubated at 4^{o}C overnight containing 100 µL of monoclonal mouse anti-human BDNF (clone 35928.11; Millipore, Etobicoke, ON), diluted to 1 µg/mL in filter-sterilized phosphate buffered saline (PBS) at a pH of 7.4. The 96-well plate was manually soaked and washed three times for one minute with Tris buffered saline (TBS) + 5% tween (TBST), and blocked with 300 µL of 3% bovine serum albumin-(BSA) in PBST for 2.5 hours at room temperature. Next, samples were acidified to a pH of 3.0 for 20 minutes using 1M of HCl; after 20 minutes the samples were neutralized with 1M NaOH and diluted in a 1% BSA buffer in PBST to a ratio of 1:4. Samples were compared to standards diluted in the same buffer as the samples, ranging from 15.63 to 500 pg/mL using a full-length, homodimeric recombinant BDNF (Peprotech, Rocky Hill, NJ). The plate was washed five times and 100 µL of

sample/standard was added to all wells. At this point the plate was incubated at room temperature for two hours with agitation, and subsequently washed five more times. After this, 100 µL of polyclonal chicken anti-human BDNF (2.5 µg/mL; Promega, Madison, WI) was added to the plate for 2.5 hours, and the plate was washed five times again; another one hour incubation took place after the addition of 100 µL of anti-chicken IgY-HRP (1 µg/mL; Promega) to each well. Following this last incubation, the plate was washed a final five times, after which 100 µL of room temperature Pierce 1- Step Ultra TMB solution (Pierce Biotechnology, Rockford, IL) was added to each well for 15 minutes. Afterwards, 1M HCl was added to stop the reaction, and the assay was read at 450 nanometres (nm). The amount of BDNF (pg/mL) was calculated using the regression equation provided with the standards (Mandel et al., 2011). During the ELISA procedure, salivary-BDNF duplicate samples for each participant were also analyzed. These duplicates were used to ensure the difference between the duplicated salivary-BDNF samples was low, in order to ensure intra-sample reliability. The average salivary-BDNF concentration level of the two duplicates was used for calculations and comparisons.

Following the saliva collection, the rest of the initial assessment took place in the multi-purpose laboratory (SB-1028) in the Lakehead University Sanders Building. Within the Sanders Building, physiological measures of resting heart rate (beats per minute; bpm) and resting blood pressure (millimeters of mercury; mmHg) were recorded using a heart rate monitor, stethoscope and sphygmomanometer. Participant age (years), height (cm), and weight (kg) was also recorded during the initial assessment. Next, participants completed the ImPACT battery. The computerized NP ImPACT battery assessed domains of cognitive function including: attention span, working memory, sustained and selective attention time, response variability, non-verbal problem solving, and reaction time. The ImPACT battery required approximately 25 minutes to

complete on a computer and consisted of a demographic profile, current concussion symptoms and conditions questionnaire, baseline and post-injury neurocognitive tests, and a graphic display of the test scores. A total of six composite scores were computed after the completion of ImPACT. For the purpose of this study only the reaction time, visual motor speed, visual memory, and verbal memory composite scores were recorded and analyzed. The ImPACT battery was completed on a laptop computer in a quiet area free from noise and distractions within the multi-purpose laboratory (SB-1028).

Balance testing. Lastly, participants had his/her static balance assessed utilizing the BESS protocol and was completed on an AMTI force platform. The BESS protocol was comprised of three testing positions: 1) Double leg stance (DS) with the feet touching (side by side), and their hands on his/her hips with their eyes closed; 2) Single leg stance (SL), standing on the non-dominant leg with their hands on his/her hips, and their eyes closed; and 3) Tandem stance (TS), standing with the toes of the non-dominant foot touching the heel of the dominant foot, their hands on his/her hips, and their eyes closed (Figure 1). Testing consisted of one trial in each of the described positions on a firm surface, followed by one trial in each testing position standing on a foam pad, for a total of six trials lasting 20 seconds each.

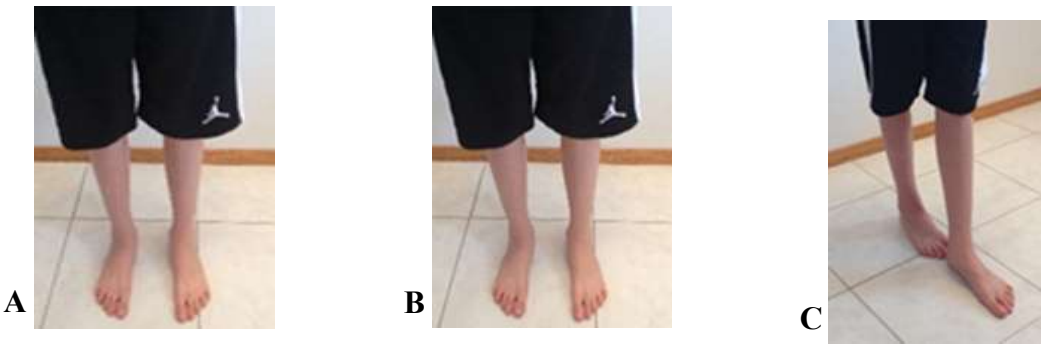

Figure 1. Double leg stance (A); single leg stance (B); and tandem stance (C).

The BESS protocol was completed on an AMTI force platform (connected to a desktop computer) to measure the amount of displacement in the participant's COP during each of the six 20 second testing trials. Area, velocity, displacement, and length values of COP were recorded and extracted for pre- and post-treatment statistical comparisons.

The initial assessment concluded after the completion of the balance assessment. At this point, participants scheduled a time for his/her first exercise session. When all exercise sessions concluded, participants completed the post-treatment assessment conducted in the exact same manner as the initial assessment.

Supervised and progressive AEB training program. Participants attended 12 one hour AEB training sessions over the course of four weeks (three sessions per week). All sessions were completed within the Lakehead University Sanders Building. The 12 sessions began with a warm-up followed by, stationary cycling, balance training, and then a cool down guided under the supervision of the student researcher. During the exercise sessions, participants were also provided with concussion educational material (Appendix G) to better understand his/her PCS. During the exercise sessions participants and guardians were encouraged to ask the supervising researcher questions regarding the educational material to clarify his/her understanding. Intensity for the aerobic exercise component on the stationary bike was individualized for each participant based on his/her resting heart rate. The Karvonen formula was used to calculate each AEB group participant's exercise intensity, based on his/her heart rate reserve (HRR). This value was used as the starting point to monitor intensity at the onset of the four week AEB training program.

The Karvonen formula (Equation 4) calculates exercise intensity as follows:

Target Exercise Heart Rate = ((220 – Age - Resting Heart Rate) × % Intensity) (4)
+ Resting Heart Rate (Karvonen Method, 2007).

The resting heart rate used in the calculation was the resting heart rate the participant presented with at the beginning of each session after wearing a heart rate monitor (Polar FT2 HR Monitor, Polar, Inc, Kempele, Finland) for two minutes in a relaxed seated position. The 2012 Concussion Consensus guidelines recommend a stepwise progression of PA following concussion before returning to sport or activity (McCrory et al., 2013). However, these guidelines do not recommend a specific starting intensity to begin this stepwise progression program. Leddy et al. (2011) developed and validated a graded treadmill test in order to determine at what heart rate intensity PCS symptoms are exacerbated, and used this information to tailor a stepwise progression program. However, the intent of this study was to avoid symptom exacerbation altogether, if possible. The CSEP guidelines for aerobic exercise state that exercising at 20% of HRR is classified as light intensity, which has been deemed safe for de-conditioned individuals, older adults, and those with chronic disease (CSEP, 2012). Thus, 20% of HRR was used and represented a logical, safe, and conservative exercise intensity to begin introducing exercise to participants with PCS. All components of the exercise sessions were supervised and facilitated by the student researcher, who is a Certified Personal Trainer through the CSEP. Scheduling of the exercise sessions was self-selected by the participant to best fit his/her schedule. Participants were required to attend three sessions over seven day period, for a total of 12 sessions within the four weeks. Participants had the option to choose to withdraw from any session or the study at any time. The time commitment for each session was approximately 40-60 minutes (i.e., sessions

towards the beginning of the structured exercise program lasted approximately 40 minutes and sessions later in the intervention were 60 minutes in length).

The AEB intervention sessions began with 5 minutes of cycling on a stationary cycle ergometer (Monark 828E Ergometer, Monark Exercise, Vansbro, Sweden) as a warm-up. Prior to cycling, the seat and handle bar height was adjusted by the student researcher until the participant was seated comfortably. During the warm-up, the speed was self-selected by the participant; with the instruction to gradually raise his/her HR to 20% of HRR. Heart rate was monitored and measured by a HR monitor worn by the participant. Every two minute interval the researcher would check the participant's heart rate to ensure he/she was at the desired HR intensity. Participants were advised to bring water with them and to hydrate whenever he/she felt necessary. Once the participant raised his/her HR to 20% of HRR he/she engaged in aerobic exercise in the form of stationary cycling. While on the bike, participants kept his/her water within arm's reach and hydrated at his/her own discretion. During the first exercise session, participants cycled at an intensity of 20% of HRR for 20 minutes. Aerobic exercise intensity and duration was increased by 10% and 5 minutes respectively every week. Therefore, by session six participants had progressed to a HR representing 30% of HRR for 25 minutes; and by session 12, 35 minutes of cycling at a HR 50% of HRR. See Appendix H for an illustration of the exercise progression template. If the participant noted an exacerbation of any one of his/her concussion symptoms, he/she was instructed to stop cycling, and no further exercise was administered on the same day. The HR which his/her symptoms were exacerbated at would be recorded. If this were to occur, the intensity of the aerobic exercise component during the next exercise session was adjusted based on the HR recorded at symptom exacerbation. If symptom exacerbation occurred while exercising at 20% of HRR, the exercise intensity was modified to resting HR plus 20% of

the HR recorded at symptom exacerbation. For example, if a 20 year old participant with a resting HR of 70 bpm experienced symptom exacerbation at a HR of 96 bpm (20% HRR), his/her intensity was modified (96 bpm x 20% + 70 bpm) to 89 bpm based on their HR at symptom exacerbation. This way, if symptom exacerbation occurred, exercise intensity was individualized to the participant's current symptom exacerbation threshold.

Upon completion of the aerobic exercise component, participants were given a 5 minute rest period and water break. Afterwards, the focus of the exercise session shifted to balance training. Balance training exercises utilized the same three positions that were tested with the BESS protocol: 1) DS, 2) SL, and 3) TS standing (Appendix I). Balance training exercises were administered throughout the 12 sessions in the same order; DS was performed first, followed by SL, and TS third. Balancing on the non-dominant leg was performed first in both the single leg and tandem two-foot stance conditions (non-dominant foot at the back of the TS position). Participants had a one minute rest period between each of the different balance training positions. Participants completed three sets for each of the three stances. During weeks one and two of the intervention (sessions 1-6), participants maintained his/her balance in each of the positions for 15 seconds; which increased to 20 seconds in weeks three and four. The surface the participant stood on while balancing and whether his/her eyes were open or closed was also manipulated in addition to increasing the duration for which he/she balanced. During week one of the exercise program, participants balanced on the hard and firm surface of the laboratory floor with his/her eyes open; during week two, the eyes were still open but he/she balanced on a soft, low-density foam surface that was placed on the floor; during week three, the eyes were closed and the participant balanced on the firm floor; and lastly, during week four, the eyes were closed in combination with standing on the soft, low-density foam surface. If the participant was

not able to maintain his/her balance for the entire duration of the exercise, they were allowed to try again to gain his/her balance until he/she achieved the desired duration of maintaining the position. The student researcher logged the heart rate intensity the participant completed his/her aerobic exercise at for each session. Additionally, the duration of the aerobic and balance exercises were logged (Appendix J). After the participant completed the balance training exercise, he/she was guided by the student researcher through a cool-down consisting of light stretching of major muscle groups (Appendix K).

After completing the four-week program, all participants completed a post-treatment assessment in the same manner as described previously for the initial assessment with each of the subsequent steps for data collection completed for the post-treatment measures.

Data Analysis

Statistical analysis was completed using IBM SPSS 20. Descriptive statistics were calculated in order to provide the mean and standard deviations for the variables of interest. Statistical significance was examined using Paired Sample T-Test procedures for changes in pre- to post-treatment measures for each of the dependent variables including: resting HR, resting BP, salivary-BDNF levels, verbal memory, visual memory, visual motor speed, reaction time, area of COP, velocity of COP, length of COP, displacement of COP, and PCSS scores. A Bonferroni correction was applied to the measures of COP to minimize type I error. The level of statistical significance was set at $\alpha < .05$ for all tests. Pearson Product Moment Correlation Coefficients (PCC) were also performed to assess the relationship between BDNF and PCSS scores. The PCC was also used to assess the relationship between the change in salivary-BDNF level pre- and post-treatment and change in PCSS scores; the relationship between change in salivary-BDNF

concentration and post-treatment PCSS score; and the relationship between post-treatment salivary-BDNF concentration and post-treatment PCSS score. Change was calculated by subtracting the post-treatment from the pre-treatment measures for salivary-BDNF concentrations and PCSS scores.

Chapter 4 – Results

The results of this study provide evidence that a supervised and progressive AEB retraining program may assist with the recovery and rehabilitation process for patients with PCS.

Demographics

Nine participants with PCS were recruited into the study. The demographic findings and characteristics of the participants with PCS are presented in Table 4. A mean of 99.88 days (SD ± 79.95) elapsed from the date of participant's initial concussion, before being recruited into the study. Participant's required a mean of 36.78 (SD ± 11.85) days to complete the study.

Table 4**.**

Participant demographics

	Mean	Standard Deviation	Minimum	Maximum
Age (years)	16.33	2.55	14	21
Education (years)	10.00	1.58	8	12
Height (cm)	169.67	11.95	154	188
Weight (kg)	69.33	25.30	53	132
Time Since Concussion (days)	99.88	79.95	51	291
Time in Intervention (days)	36.78	11.85	20	60

Descriptive and inferential statistical analysis techniques were used to help address each of the guiding research questions:

Question 1. Is there a difference between pre- and post-treatment on measures of resting heart rate and blood pressure values for individuals with PCS following a four-week AEB based program?

There was no statistically significant difference between pre-treatment resting HR (M = 68.11, SD ± 2.99) and post-treatment resting HR values (M = 66.56, SD ± 2.10), $t(8) = 0.84$, p = .43, 95% CI [-2.71, 5.82]. There was no statistically significant difference between pre-treatment resting systolic BP (M = 110.89, SD ± 1.87) and post-treatment resting systolic BP (M = 110.78, SD ± 2.093), $t(8) = 0.09$, p = .93, 95% CI [-2.73, 2.95]. Additionally, there was no statistically significant difference in pre-treatment resting diastolic BP (M = 70.11, SD ± 2.42) and post-treatment resting diastolic BP (M = 71.22, SD ± 2.01), $t(8) = 0.42$, p = .42, 95% CI [-4.10, 1.88].

Question 2. Is there a difference between pre- and post-treatment salivary-BDNF concentration levels for individuals with PCS following a four-week AEB based program?

There was no statistically significant difference in pre-treatment salivary-BDNF concentrations (M = 226.01, SD ± 69.63) compared to post-treatment salivary-BDNF concentrations (M = 209.33, SD ± 44.37), $t(8) = 0.29$, p = .78, 95% CI [-115.46, 148.82]. Figure 2 illustrates the individual changes in BDNF concentrations for pre- and post-treatment values.

Individual changes in salivary-BDNF concentration levels were quite variable across the nine participants. Participants one, five, and six all entered the study with very low levels of salivary-BDNF compared to the other six participants. While both participants one and five experienced modest changes in salivary-BDNF concentrations post-treatment, participant six experienced a seven fold increase from pre-treatment levels (52.70 pg/mL) to post-treatment levels (389.86 pg/mL). Participant two displayed very little change in salivary-BDNF concentration from pre-treatment levels (155.53 pg/mL) to post-treatment levels (150.65 pg/mL).

While participants three (223.57 pg/mL to 147.90 pg/mL), four (699.86 pg/mL to 400.84 pg/mL), seven (390.47 pg/mL to 333.10 pg/mL), and nine (250.42 pg/mL to 107.93 pg/mL) demonstrated declines in salivary-BDNF levels from pre-treatment to post-treatment. Participants one (56.97 pg/mL to 80.77 pg/mL), six (52.70 pg/mL to 389.86 pg/mL), and eight (139.05 pg/mL to 215.64 pg/mL) demonstrated increases in salivary-BDNF post-treatment.

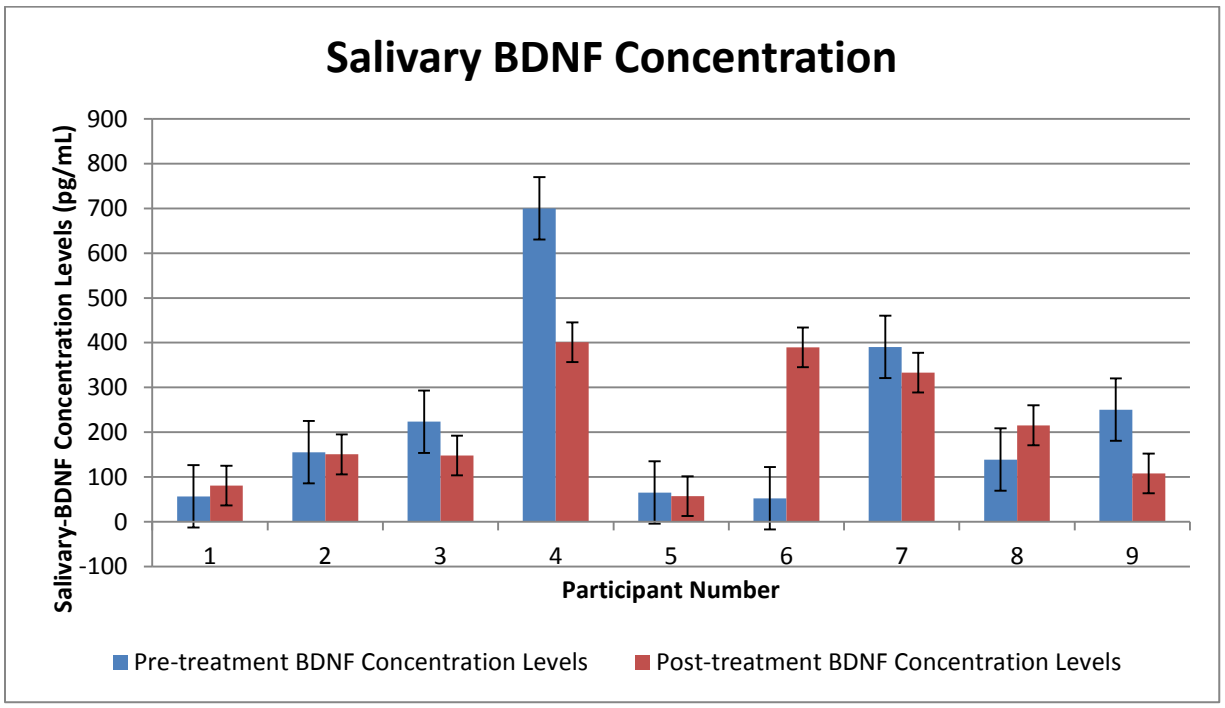

Figure 2. Individual changes in salivary-BDNF concentration levels.

Question 3. Is there a difference between pre- and post-treatment Immediate Post-Concussion Assessment and Cognitive Testing tool (ImPACT) composite scores (verbal memory, and visual memory, visual motor speed, reaction time) for individuals with PCS following a four-week AEB based program?

Verbal Memory

There was no statistically significant difference in pre-treatment verbal memory (M = 75.56, SD ± 21.20) and post-treatment verbal memory (M = 80.00, SD ± 21.72) scores measured with the ImPACT test battery, $t(8) = -1.68$, $p = .13$, 95% CI [-10.54, 1.65]. Figure 3 illustrates the individual changes in verbal memory for each participant.

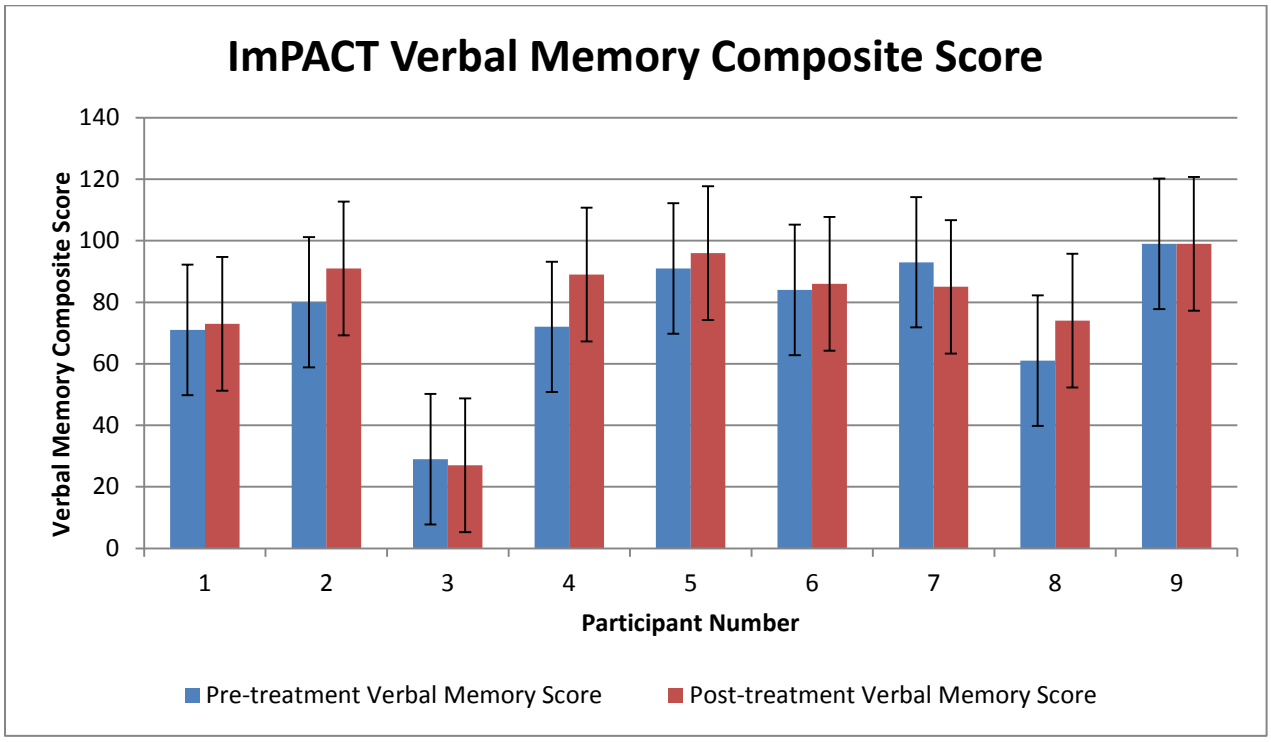

Figure 3. Individual changes in ImPACT verbal memory composite score.

Individual changes in verbal memory varied across the nine participants. Participants one (71 to 73), five (91 to 96), and six (84 to 86) exhibited very modest improvements in verbal memory following the AEB treatment. Participants two (80 to 91), four (72 to 89), and eight (61 to 74) also exhibited improvements in verbal memory, but to a greater extent than the

improvements observed in participants one, five, and six. Participants three (29 to 27) and seven (93 to 85) were the only participants who exhibited a decrease in verbal memory following the AEB treatment program. Participant nine exhibited no change (99 to 99) in verbal memory following the AEB treatment program. Overall, six of the nine participants demonstrated improvements in verbal memory scores following the AEB treatment, whereas three of nine participants displayed a decrease or no change in verbal memory.

Visual Memory

There was no statistically significant difference in pre-treatment visual memory (M = 63.22, SD ± 18.59) and post-treatment visual memory (M = 70.44, SD ± 18.37) scores measured with the ImPACT test battery, $t(8) = -1.73$, $p = .12$, 95% CI [-16.87, 2.42]. Figure 4 illustrates the individual changes in visual memory for each participant.

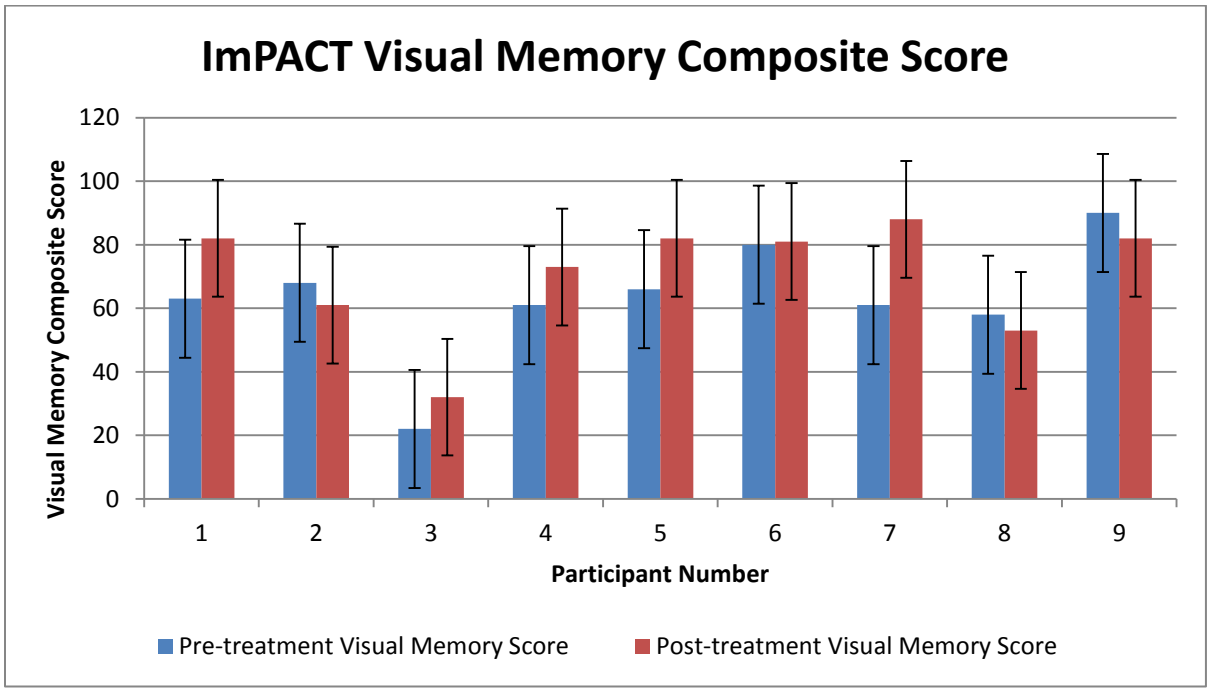

Figure 4. Individuals changes in ImPACT visual memory composite score.

Individual changes in visual memory varied across the nine participants. Participants one (63 to 82), three (22 to 32), four (61 to 73), five (66 to 82), and seven (61 to 88) displayed notable improvement in visual memory scores following the AEB treatment program. Participant six (80 to 81) also exhibited improvement; however the change was very modest. Participants two (68 to 61), eight (58 to 53), and nine (90 to 82) exhibited declines in visual memory following the AEB treatment program. Similar to verbal memory, six of the nine participants demonstrated improvements in visual memory scores following the AEB treatment, whereas three participants were observed to have reduced visual memory scores following treatment.

Visual Motor Speed

There was a statistically significant improvement between pre-treatment visual motor speed (M = 29.62, SD ± 7.85) and post-treatment (M = 34.15, SD ± 8.60) visual motor speed scores, measured with the ImPACT test battery, $t(8) = -2.56$, p = .03, 95% CI [-8.60, -0.45], $d = -0.55$. Figure 5 illustrates individual changes in visual motor speed for each participant.

Individual changes in visual motor speed varied across the nine participants. Participant one (19.60 to 25.10), two (29.83 to 37.40), four (36.25 to 39.13), five (29.63 to 38.72), six (35.08 to 45.70), and nine (25.88 to 35.92) exhibited improved visual motor speed following the AEB treatment program. Participant three displayed no change (16.7 to 16.7) in visual motor speed following the AEB treatment program. Participant seven displayed a very modest decrease (32.7 to 31.8) in visual motor speed, while participant eight exhibited a greater decrease (40.92 to 36.85) in visual motor speed following the AEB treatment program. Six of the nine participants demonstrated improvements in visual motor speed following the AEB treatment program,

whereas three participants exhibited no change or declines in visual motor speed following treatment.

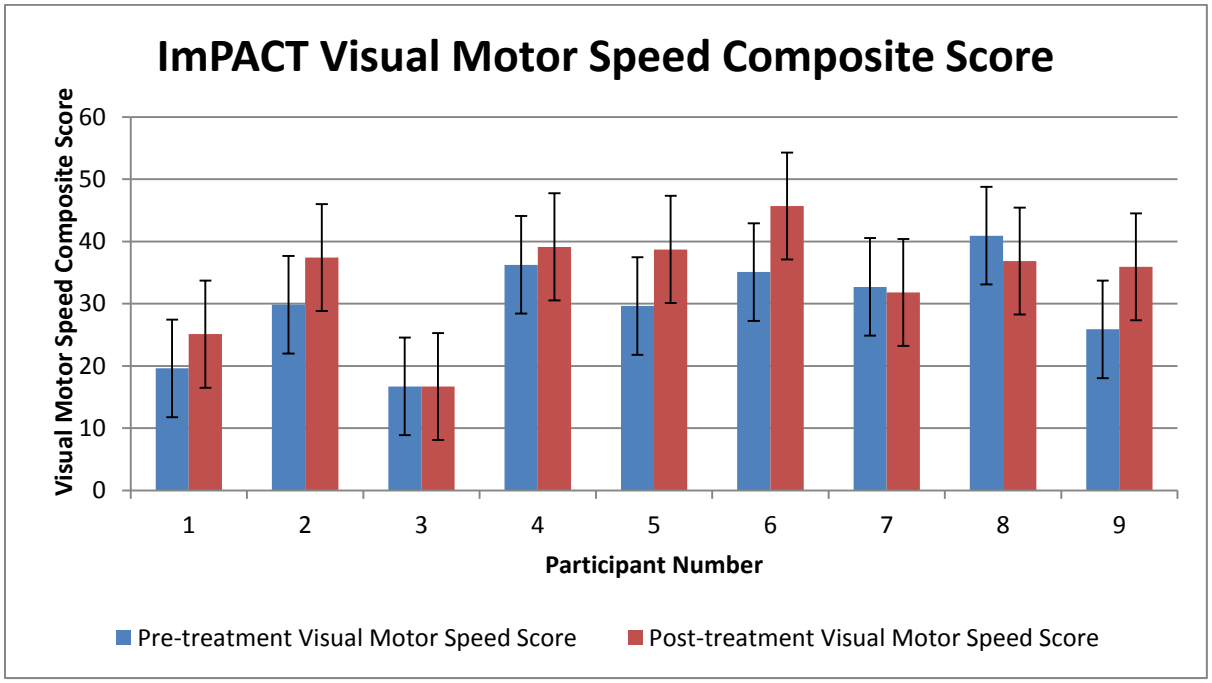

Figure 5. Individual changes in ImPACT visual motor speed composite score.

Reaction Time

There was no statistically significant change in pre-treatment reaction time (M = 0.71, SD ± .25) and post-treatment reaction time (M = 0.72, SD ± .26) measured with the ImPACT battery, $t(8) = -0.16$, p = .88, 95% CI [-0.05, 0.05]. Figure 6 illustrates individual changes in reaction time for each participant.

Very modest individual changes in reaction time were observed across the nine participants following the AEB treatment program. Participants one (0.80 to 0.74 sec), two (0.69 to 0.67 sec), and four (0.57 to 0.52 sec) exhibited modest decreases in reaction time after the AEB treatment program. Participants three (1.35 to 1.37 sec), seven (0.6 to 0.62 sec), eight (0.55 to 0.61 sec), and nine (0.64 to 0.66 sec) displayed small increases in reaction time following the

AEB treatment program. Participant five (0.6 to 0.72 sec) and six (0.61 to 0.53 sec) were observed to have the greatest changes in reaction time following the AEB program. Overall, seven of the nine participants were observed to have very small changes in reaction time of approximately 0.05 seconds following the AEB program.

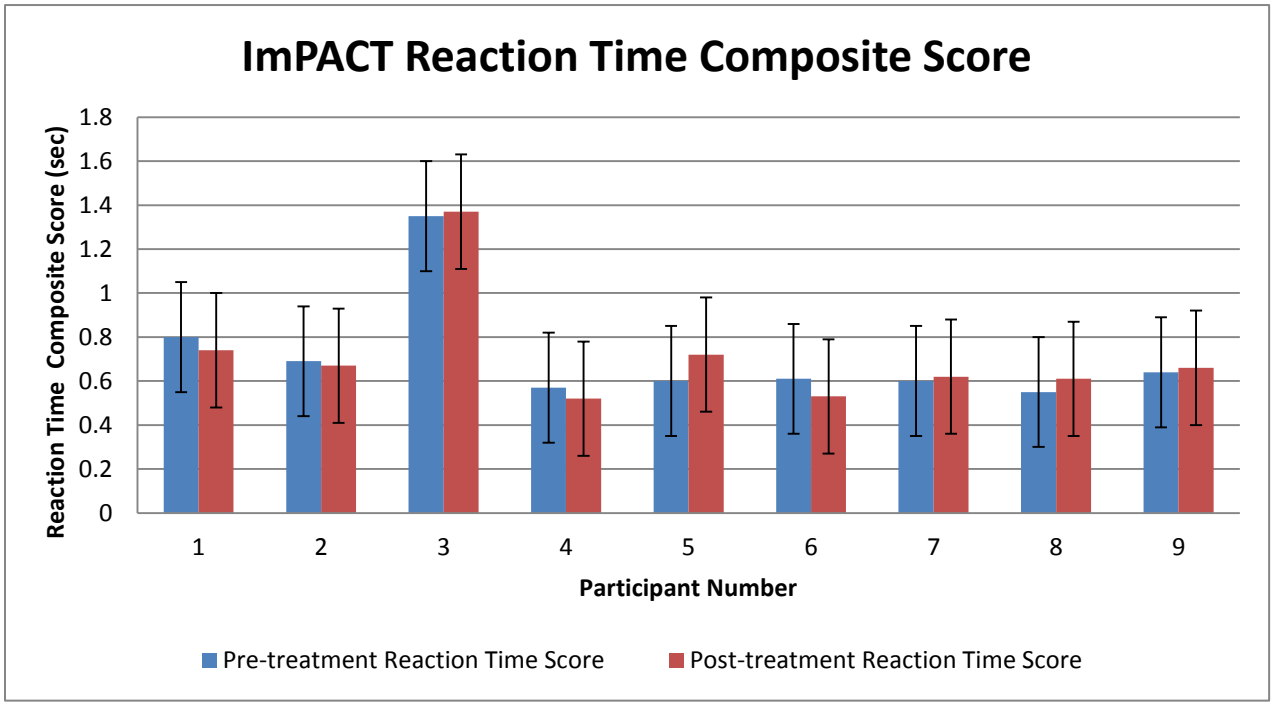

Figure 6. Individual changes in ImPACT reaction time composite score.

Question 4. Is there a difference between pre- and post-treatment AMTI force platform values of displacement in centre of pressure (COP) during the Balance Error Scoring System (BESS) for individuals with PCS following a four-week AEB based program?

Area of Centre of Pressure

There was no statistically significant difference in the area of COP in five out of six BESS conditions. There was no significant change in DS ($t(8) = -1.20$, $p = .26$, 95% CI [-1.69, 0.53]), SL ($t(8) = 0.59$, $p = .57$, 95% CI [-1.69, 2.85]), or TS ($t(8) = -0.90$, $p = .40$, 95% CI [-

1.09, 0.48]) on a firm surface. Additionally, there was no statistically significant difference in DS ($t(8) = 2.08$, p = .07, 95% CI [-0.14, 2.84) and SL ($t(8) = 1.10$, p = .30, 95% CI [-0.71, 2.01]) on a foam surface. However, there was a statistically decrease in the area of COP during TS on a foam surface, $t(8) = 2.464$, p = .04, 95% CI [0.31, 9.43] $d = 1.22$. Although, after applying a post hoc Bonferroni correction the change in DS foam area of COP was not significant at the adjusted alpha value of p = 0.0125. Pre- and post-treatment area of COP descriptive statistics and Paired Sample T-Test results are presented in Table 5.

Table 5.

Area of COP pre-/post-treatment change

Balance Condition	Pre-Treatment Mean (±SD)	Post-Treatment Mean (±SD)	Paired Samples T-Test
DS Firm	0.59 (±.41)	1.17 (±1.80)	$t(8) = -1.20$, p = .26
SL Firm	2.47 (±2.47)	1.89 (±1.20)	$t(8) = 0.59$, p = .57
TS Firm	1.06 (±.73)	1.37 (±1.26)	$t(8) = -0.90$, p = .40
DS Foam	3.11 (±2.23)	1.76 (±1.53)	$t(8) = 2.08$, p = .07
SL Foam	3.62 (±1.52)	2.96 (±2.29)	$t(8) = 1.10$, p = .30
TS Foam	7.55 (±5.34)	2.68 (±1.80)	$t(8) = 2.464$, p = .04*

* indicates significant changes following the exercise program

Velocity of Centre of Pressure

There was no statistically significant differences in participant pre- and post-treatment velocity of COP values during DS ($t(8) = -0.86$, p = .41, 95% CI [-0.28, 0.13]), SL ($t(8) = 0.73$, p = .48, 95% CI [-0.27, 0.52]), and TS ($t(8) = -0.74$, p = .48, 95% CI [-0.42, 0.22]) on a firm surface. There was no statistically significant differences in velocity of COP during TS on a foam ($t(8) = 1.73$, p = .12, 95% CI [-0.23, 1.62]). There was statistically significant decreases in pre- and post-treatment velocity of COP in both DS ($t(8) = 4.06$, p = .004, 95% CI [0.22, 0.79], *d*

= 0.88) and SL ($t(8) = 3.80$, p = .005, 95% CI [0.23, 0.94], $d = 0.66$) on a foam surface. Pre- and post-treatment descriptive statistics for the velocity of COP and Paired Sample T-Tests results are presented in Table 6.

Table 6.

Velocity of COP pre-/post-treatment change

Balance Condition	Pre-Treatment Mean (±SD)	Post-Treatment Mean (±SD)	Paired Samples T-Test
DS Firm	0.78 (±.20)	0.85 (±.44)	$t(8) = -0.86$, p = .41
SL Firm	2.15 (±.56)	2.03 (±.72)	$t(8) = 0.73$, p = .48
TS Firm	1.61 (±.88)	1.71 (±.80)	$t(8) = -0.74$, p = .48
DS Foam	1.88 (±.69)	1.37 (±.44)	$t(8) = 4.06$, p = .004*
SL Foam	3.00 (±.88)	2.41 (±.89)	$t(8) = 3.80$, p = .005*
TS Foam	2.98 (±1.20)	2.29 (±.94)	$t(8) = 1.73$, p = .12

* indicates significant changes following the exercise program

Length of Centre of Pressure

There was no statistically significant differences in participant pre- and post-treatment length of COP values during DS ($t(8) = -0.86$, p = .41, 95% CI [-5.61, 2.55]), SL ($t(8) = 0.73$, p = .48, 95% CI [-5.43, 10.49]), and TS ($t(8) = -0.74$, p = .48, 95% CI -8.39, 4.31]) on a firm surface. There was also no statistically significant difference in TS on a foam surface ($t(8) = 1.73$, p = .12, 95% CI [-4.65, 32.41]). There was a significant decrease in pre- and post-treatment length of COP in both DS ($t(8) = 4.06$, p = .004, 95% CI [4.34, 15.80], $d = 0.87$) and SL ($t(8) = 3.80$, p = .005, 95% CI [4.62, 18.87], $d = 0.66$) on a foam surface. Following post hoc Bonferroni corrections these changes remained significant at an adjusted alpha value of p = 0.0125. Pre- and post-treatment length of COP descriptive statistics and Paired Sample T-Tests results are presented in Table 7.

Table 7.

Length of COP pre-/post-treatment change

Balance Condition	Pre-Treatment Mean (±SD)	Post-Treatment Mean (±SD)	Paired Samples T-Test
DS Firm	15.53 (±3.97)	17.06 (±8.81)	$t(8) = -0.87$, p = .41
SL Firm	43.05 (±11.25)	40.52 (±14.40)	$t(8) = 0.73$, p = .48
TS Firm	32.12 (±17.62)	34.16 (±16.04)	$t(8) = -0.74$, p = .48
DS Foam	37.51 (±13.79)	27.44 (±8.84)	$t(8) = 4.06$, p = .004*
SL Foam	59.97 (±17.68)	48.22 (±17.78)	$t(8) = 3.80$, p = .005*
TS Foam	59.69 (±24.03)	45.81 (18.82)	$t(8) = 1.73$, p = .12

* indicates significant changes following the exercise program

Total Displacement of Centre of Pressure

There were no statistically significant changes in pre-treatment and post-treatment total displacement of COP in five out of the six BESS conditions. There was no statistically significant differences in DS ($t(8) = -1.30$, p = .23, 95% CI [-0.52, 0.15]), SL ($t(8) = 0.96$, p = .36, 95% CI [-0.83, 2.03]), and TS ($t(8) = -0.43$, p = .68, 95% CI [-0.84, 0.58]) on a firm surface. Furthermore, there was no statistically significant differences in SL ($t(8) = 0.65$, p = .54, 95% CI [-0.85, 1.51]) and TS ($t(8) = 2.07$, p = .07, 95% CI [-0.20, 3.71]) on a foam surface. There was a statistically significant decrease between pre-treatment and post-treatment total displacement of COP for DS on a foam surface, $t(8) = 3.93$, p = .004, 95% CI [0.32, 1.22], $d = 1.17$. Following post hoc Bonferroni correction this change remained significant at an adjusted alpha value of p = 0.0125. Pre- and post-treatment displacement of COP descriptive statistics and Paired-Samples T-Tests results are presented in Table 8.

Table. 8

Total displacement of COP pre-/post-treatment change

Balance Condition	Pre-Treatment Mean (±SD)	Post-Treatment Mean (±SD)	Paired Samples T-Test
DS Firm	1.30 (±.43)	1.49 (±.77)	$t(8) = -1.30$, p = .23
SL Firm	3.12 (±1.39)	2.52 (.97)	$t(8) = 0.96$, p = .36
TS Firm	1.89 (±.73)	2.03 (±1.07)	$t(8) = -0.43$, p = .68
DS Foam	2.80 (±.74)	2.03 (±.56)	$t(8) = 3.93$, p = .004*
SL Foam	3.59 (±.47)	3.26 (±1.63)	$t(8) = 0.65$, p = .54
TS Foam	4.75 (±2.20)	3.00 (±1.29)	$t(8) = 2.07$, p = .07

* indicates significant changes following the exercise program

Question 5. Is there a difference in pre- and post-treatment Post-Concussion Symptom Scale (PCSS) scores for individuals with PCS following a four-week AEB based program?

There was a statistically significant improvement in the PCSS scores post-treatment (M = 18.00, SD ± 30.09) compared to pre-treatment (M = 33.11, SD ± 23.17), $t(8) = 3.37$, p = .01, 95% CI [4.77, 25.45], $d = 0.56$. Figure 7 illustrates the individual changes in PCSS scores for each participant.

Eight out of the nine participants demonstrated a mean reduction of 15.11 (SD ± 13.45) on the PCSS score post-treatment compared to pre-treatment scores. Only participant three reported an increase from pre-treatment PCSS score (78) to post-treatment PCSS score (91). Participant seven had the greatest reduction in PCSS score from pre-treatment (45) to post-treatment (8). Conversely, participant five had the smallest reduction in PCSS score from pre-treatment (9) to post-treatment (3).

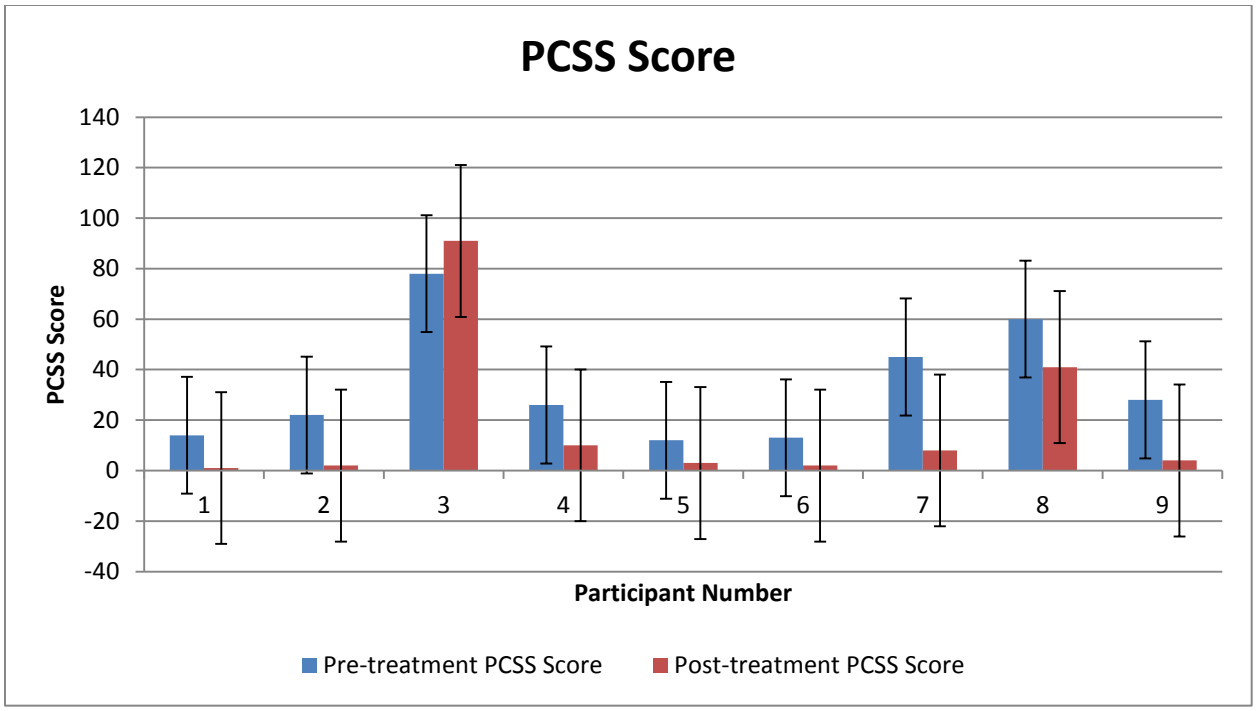

Figure 7. Individual changes in PCSS scores.

Question 6. What relationships are present between salivary-BDNF concentrations and PCSS score changes following a four-week AEB treatment, and what relationships are present between post-treatment values of salivary-BDNF concentration levels and PCSS scores?

No significant relationship was detected between change in BDNF concentrations (M = 16.78, SD ± 171.91) and PCSS change score (M = 15.11, SD ± 13.45) , $r(9) = .10$, $p = .81$ (Figure 8). There was no significant relationship between changes in BDNF concentration (M = 16.78, SD ± 171.91) and post-treatment PCSS scores (M = 18.00, SD ± 30.09), $r(9) = -.11$, $p = .79$ (Figure 9). Lastly, no significant relationship was detected between post-treatment BDNF concentrations (M = 209.33, SD ± 133.12) and post-treatment PCSS scores (M = 18.00, SD ± 30.09), $r(9) = -.10$, $p = .80$ (Figure 10).

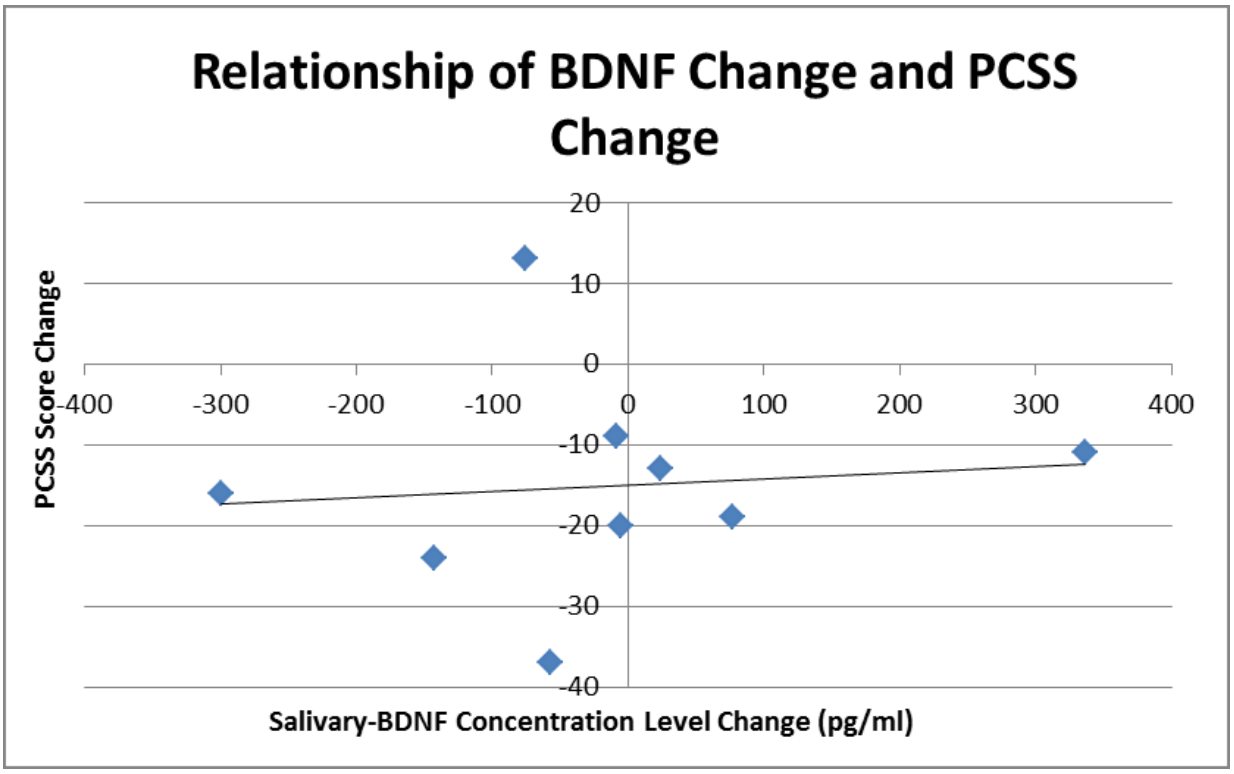

Figure 8. Relationship of salivary-BDNF concentration level change (pg/mL) and PCSS score change.

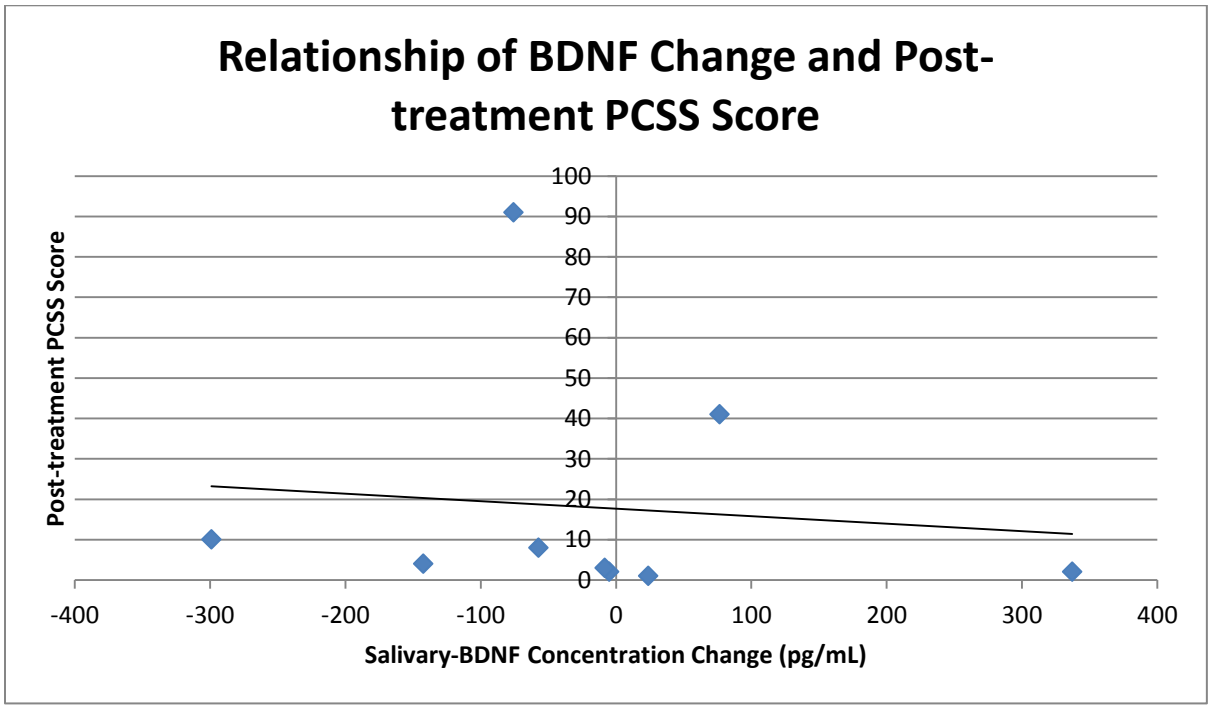

Figure 9. Relationship of salivary-BDNF concentration level change (pg/mL) and post-treatment PCSS score.

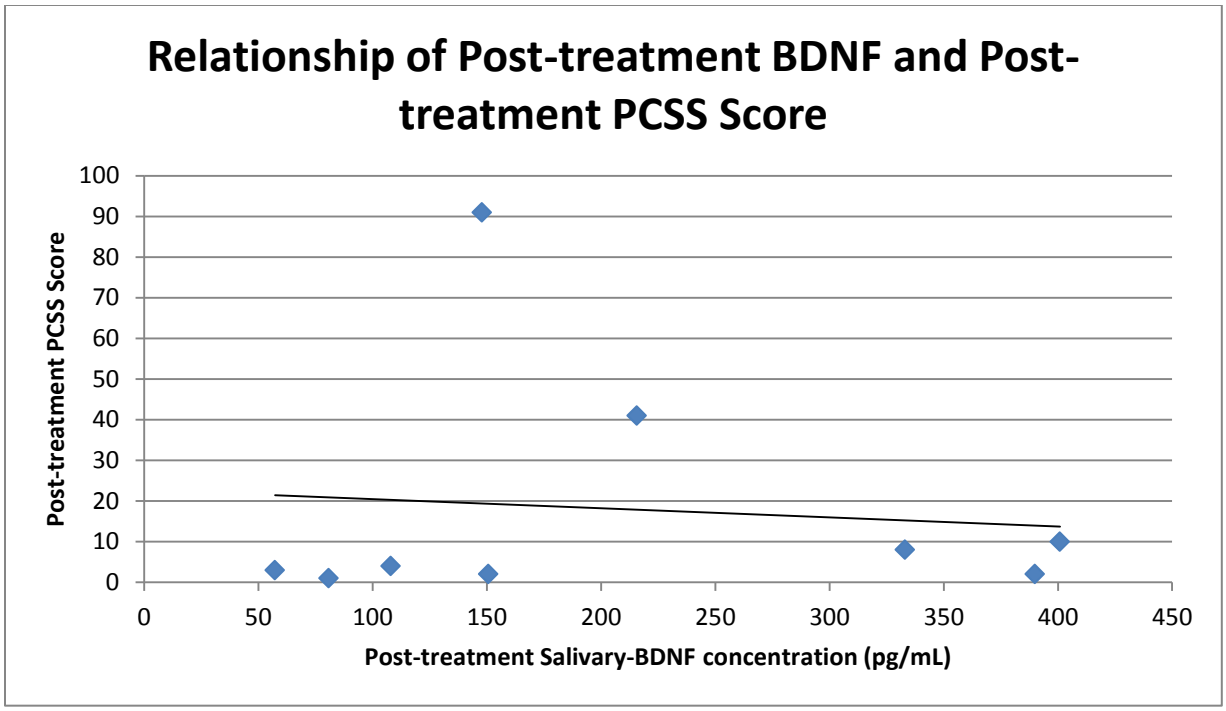

Figure 10. Relationship of post-treatment salivary-BDNF concentration level (pg/mL) and post-treatment PCSS score.

Chapter 5 – Discussion

The purpose of this study was to investigate the impact of a four week structured and supervised AEB program on cognitive function, balance, and saliva BDNF levels in a sample of 14-30 year old individuals diagnosed with PCS. The results of this study add to the currently limited body of literature regarding the use of exercise as a treatment strategy for improving lingering symptoms of concussion observed in PCS. The subsequent sections will expand and discuss the results of this study in greater detail.

Question 1. Is there a difference in pre- and post-treatment resting heart rate and blood pressure values for individuals with PCS following a four-week AEB based program?

No statistically significant changes in resting heart rate or blood pressure were observed in response to the AEB program. Aside from experiencing PCS, all participants were healthy high school and university aged individuals who regularly participated in PA and/or sport prior to his/her concussion which resulted in PCS. Regular PA is strongly associated with optimal blood pressure and heart rate (CSEP, 2013). Due to the nine participants regular involvement and history of participating in PA, it was expected that signs of physical deconditioning, due to weeks or months of SRC, would have been observed in the form of elevated resting heart rate and blood pressure values. This was not the case within the current sample of individuals with PCS. All blood pressure and heart rate values recorded both before and after AEB treatment fell within the normal healthy ranges described by the CSEP (2013); although it is important to note that this study only measured heart rate and blood pressure at rest. Similar findings have also been reported by Gall et al. (2004) who found that at rest there was no difference in HRV between acutely concussed hockey players and matched non-concussed teammates. During a

submaximal stationary bike exercise test, however, significant differences in HRV were observed between the acutely concussed and non-concussed hockey players. Abnormal HRV continued to persist 10 days after the initial injury (Gall et al., 2004). Although this study examined HRV in the acute stage of concussion (7-10 days post injury), these notable abnormalities in the concussed individuals may explain the continued symptoms and changes sometimes observed in in the PCS stage of concussion. It is hypothesized that HRV abnormalities are a result of the disruption between the synchronization of the autonomic and the cardiovascular systems. In a study on TBI, it was reported that the normalization of the function of the autonomic and cardiovascular systems may take up to six months following injury (King et al., 1997). With the mean number of days post-concussion for the participants in the present study being 99.88 days, the normalization described may not have been completed yet contributing to some of the ongoing complaints. The lack of change in resting HR observed in the present study in combination with the results reported by Gall et al. and King et al. warrant the further study of HRV rather than resting HR in response to an AEB treatment program for individuals with PCS.

Question 2. Is there a difference in pre- and post-treatment salivary-BDNF concentration levels for individuals with PCS following a four-week AEB based program?

Concentrations of salivary-BDNF were not found to significantly increase in response to the four week AEB treatment program at the group level. Three participants had notable increases in salivary-BDNF in response to the program. Two participants displayed little to no change in concentration levels, and four participants exhibited declines in salivary-BDNF concentrations following the AEB treatment program. It was hypothesized that salivary-BDNF concentration levels might be low before beginning the AEB treatment, and that four-weeks of

aerobic exercise might result in an increase in salivary-BDNF concentrations. In a previous pilot study by McGeown, Sanzo, Zerpa, Lees, and, Niccoli (2016), a four-week AEB program in a sample of university aged, healthy, and physically active individuals (n=10) resulted in an increase in mean salivary-BDNF concentration levels from 548.98 pg/mL (pre-treatment) to 796.17 pg/mL (post-treatment) after the completion of the AEB program. These findings of increased salivary-BDNF levels in healthy and regularly physically active individuals provided a rationale for the implementation of AEB treatment for individuals with PCS. If BDNF concentrations significantly improved in healthy individuals, then it was hypothesized lower levels of salivary-BDNF concentrations would be observed and greater improvements in salivary-BDNF were expected following treatment for PCS. Furthermore, low levels of BDNF have been reported in neurodegenerative diseases such as AD, and Huntington's Disease, as well in neuropsychiatric conditions such as depression and schizophrenia when compared to healthy controls (Adachi et al., 2014). The low salivary-BDNF concentration findings of this study for individuals with PCS are in agreement with the reported results within the literature regarding other neurodegenerative/neuropsychiatric conditions prior to administrating an aerobic exercise program. The PCS group mean salivary-BDNF concentration level before the four-week AEB treatment program was 226.01 pg/mL was observed to not significantly decrease following the four-week AEB treatment program to a group mean of 209.33 pg/mL. Due to a small sample size more evidence is required to evaluate the impact of exercise-based treatment of PCS and related changes in salivary-BDNF concentration levels. The PCS group displayed an average salivary-BDNF concentration level less than half of what was reported in a healthy sample before the AEB program. Following the AEB program the PCS group salivary-BDNF concentrations were nearly one quarter of the concentration levels reported in healthy individuals (McGeown et al.,

2016). These improvements in symptoms and functionality in neurodegenerative and neuropsychiatric conditions have been hypothesized and reported to be facilitated as a result of increased BDNF concentrations (Griesbach et al., 2009; Koo et al., 2013; Mang et al., 2013; Ploughman et al., 2005; Quaney et al., 2009; Shen et al., 2013; Shih et al., 2011; van Praag, 2009). Interestingly, the administration of aerobic exercise for AD, stroke, TBI, and depression has been documented to improve symptoms and function (Griesbach et al., 2009; Koo et al., 2013; Ploughman et al., 2005; Quaney et al., 2009; Shen et al., 2013; Shih et al., 2011). Koo et al. (2013) reported improvements in AD following three months of aerobic exercise treatment performed five days per week in mice. Seven days of treadmill walking initiated four days after ischemic stroke in mice was associated within improvements in cognitive function and motor learning (Ploughman et al., 2005). Quaney et al. (2009) reported that three sessions per week at 70% of HR maximum for 45 minutes was associated with motor learning outcomes following stroke in humans. In rat models of TBI 14 days of low to moderate intensity aerobic exercise, beginning 24 hours after TBI, was associated with improved synaptic plasticity and cognitive functions (Shen et al., 2013; Shih et al., 2011). However, Griesbach et al. (2004) report disruption in BDNF and other plasticity related proteins in rats if exercise is administered too soon after TBI. Conversely, Griesbach et al. (2009) reported five days aerobic treadmill exercise administered after 14 days of rest following TBI was associated with improvements in BDNF and synaptic plasticity. These studies share the same limitation in that the only the effect of exercise on increased BDNF was measured, rather than the amount of time necessary to reach maximum neurological recovery in response to heightened BDNF concentrations due to exercise.

A number of possible explanations may account for the lack of increase in salivary-BDNF concentration reported in this study which is in disagreement with other neurological

investigations of aerobic exercise and BDNF. Recently, Ellis et al. (2015) proposed three post-concussion disorders (PCDs) of PCS that may explain the underlying cause for persistent PCS. Physiologic PCD is "characterized by persistent concussion symptoms and impairments caused by continued alterations in global cerebral metabolism" (Ellis et al., 2015, p. 240). Vestibulo-ocular PCD is "characterized by persistent concussion symptoms and impairments caused by dysfunction of the vestibulo-ocular system" (Ellis et al., 2015, p. 242). Cervicogenic PCD is "characterized by persistent concussion symptoms and impairments caused by dysfunction of the cervical spine somatosensory system" Ellis et al., 2015, p. 244). The authors explain differential diagnosis of the three PCDs can be achieved using a clinical history, physical examination, and treadmill testing. A Balke treadmill protocol can be used to bring participants with PCS to the point of symptom exacerbation or exhaustion (Leddy et al., 2011). If individuals with PCS experienced symptom exacerbation prior to exhaustion he/she were deemed to have physiologic PCD. Conversely, if individuals with PCS were capable of performing the Balke protocol to exhaustion with no symptom exacerbation he/she were deemed to have vestibulo-ocular or cervicogenic PCD. Differentiating between vestibulo-ocular and cervicogenic PCD would then rely upon findings of the clinical history and physical examination (Ellis et al., 2015). Furthermore, the authors indicated that physiologic PCD would benefit the most from an aerobic exercise-based treatment, whereas vestibulo-ocular and cervicogenic PCDs would benefit mostly from individualized treatment protocols to address specific symptoms of PCS (Ellis et al., 2015). Participants recruited within the current study were not stratified into PCD sub-groups of PCS. In retrospect, had a larger sample been recruited and if participants were grouped based on respective PCDs, different results may have been observed in response to the AEB treatment. Those participants with physiologic PCD may have depicted greater improvements in BDNF

concentrations, cognitive functions, and symptoms of PCS. In contrast, individuals with one of the other PCD may have depicted no improvements following the AEB treatment due to the lack of individualization. Further investigation is warranted to determine the effect exercise-based treatment may have on the different PCDs of PCS. In addition to PCDs, the AEB treatment program design may not have been administered for the ideal length of time at an appropriate intensity and frequency.

The intent of the AEB treatment program was to have all participants complete 12 exercise sessions over the span of four weeks (three sessions per week, in approximately 28 days). The mean number of days to complete the AEB program was 36.78 (± 11.85), with a minimum of 20 and a maximum of 60 days. This variability and wide range was increased with the availability of some participants. Interestingly, participant six completed the AEB treatment in 20 days and exhibited the greatest improvement in salivary-BDNF levels. In contrast, participant five required 60 days to complete the AEB program and exhibited the lowest concentration of salivary-BDNF levels post-treatment program. These findings suggest that the frequency of sessions in a given period of time and the overall length could possibly have an effect on salivary-BDNF levels in individuals with PCS. Twelve exercise sessions administered over an average of five weeks may not have provided the necessary frequency of exercise or duration of treatment to result in an improvement in BDNF concentration levels. Although in healthy individuals twelve AEB program sessions over a four-week period (requiring a mean of 30 days to complete) resulted in increased salivary-BDNF concentration levels the same frequency and length of the program may not suffice for the concussed population and this would seem reasonable due to the delays in recovery in other aspects of the injury (McGeown et al., 2016). For individuals with PCS further exploration is necessary to determine the ideal number of

weeks and frequency of therapeutic exercise required to improve salivary-BDNF concentration levels.

Within the literature there is a lack of information regarding ideal initial aerobic exercise intensity for a stepwise exercise progression program for patients with PCS. This study used an initial exercise intensity of 20% HRR. According to the CSEP guidelines, utilizing 20% of HRR is considered light PA and is deemed safe for de-conditioned individuals, older adults, and those with chronic disease. In order to avoid symptom exacerbation this conservative exercise intensity appeared to be a logical intensity as a starting point to begin a stepwise program for individuals with PCS. However, during the first week of the AEB program when participants performed stationary cycling at 20% of HRR, participants subjectively reported that the intensity felt far too easy. Furthermore, participants subjectively reported that it was challenging to keep his/her heart rate low enough to maintain 20% of HRR during stationary biking. The researcher supervising the exercise sessions had to routinely remind participants to not exceed his/her target heart rate during the first week of the AEB treatment program. While valuable to report that 20% of HRR appears to be too conservative to begin a stepwise exercise program for PCS. Notably, no participants experienced symptom exacerbation during the aerobic exercise component of the 12 AEB treatment sessions; this may have also had an effect on overall BDNF findings in such a short period of time. In studies investigating the utility of aerobic exercise to improve BDNF concentrations following stroke, concluding recommendations state that moderate intensity exercise appears to have the greatest effect of upregulating BDNF concentration levels associated with improved neurological function (Austin, Ploughman, Glynn, & Corbett, 2014; Ploughman et al., 2005; Quaney et al., 2009; Shih et al., 2011). Quaney et al. (2009) reported improvements in motor learning following eight weeks of moderate aerobic exercise performed

three times per week. Koo et al. (2013) presented similar recommendations for the implementation of moderate aerobic exercise program (performed five days per week for three months) to improve impaired neurological function observed in AD via the upregulation of BDNF concentration levels. Five to seven days of moderate aerobic exercise has also been reported to be effective at increasing BDNF concentrations and associated improvements in neurological function following TBI in mice (Griesbach et al., 2009). When making comparisons between human and rodent studies of neurological interventions caution should be used as findings in rodents may not directly transfer to human physiology and neurology. However, these rodent studies are useful to refer to due to the limited breadth of studies within the literature including human participants. Conversely, acute bouts of high intensity forms of stationary cycling or running have been reported to induce the greatest improvements in BDNF concentrations in the short term in young healthy individuals; these improvements were associated with improved learning and hippocampal-dependent memory (Griffin et al., 2011; Winter et al., 2007). Similar findings have been reported regarding increases in BDNF concentrations following high intensity aerobic exercise in stroke, which was associated with improved motor learning and performance (Mang et al., 2013). However, high intensity forms of aerobic exercise may not have the same results in the concussed population as this intensity of exercise may exacerbate symptoms and possibly delay or hinder PCS recovery. The associated improvements reported in neurological function in healthy individuals and neurological conditions and disorders other than PCS suggest that further research is required to explore the optimal exercise intensity to use; possibly, light to moderate intensity exercise being the most appropriate target levels, however more exploration is required to insure no aggravation of symptoms occurs in this patient population.

The findings of this study suggest that a greater body of literature is necessary to determine the ideal frequency, intensity, and length of therapeutic aerobic exercise treatment necessary to induce increased BDNF concentrations in PCS. Future studies should begin aerobic exercise at an initial intensity greater than 20% of HRR, as long as symptoms are not exacerbated. Additionally, our results suggest that a higher frequency and/or a longer duration of AEB treatment sessions may induce greater improvements in salivary-BDNF concentration levels. Avoiding symptom exacerbation, however, must always be the goal when administrating aerobic exercise to individuals with PCS.

Question 3. Is there a difference in pre- and post-treatment Immediate Post-Concussion Assessment and Cognitive Testing tool (ImPACT) composite scores (verbal memory, and visual memory, visual motor speed, reaction time) for individuals with PCS following a four-week AEB based program?

Investigations have revealed that normal neurophysiological processes of the brain are impaired as a result of an acute concussion, and these impairments continue to persist for individuals with PCS (Dean et al., 2015; Leddy et al., 2013; Messe et al., 2013; Moore et al., 2014b; Pontifex et al., 2009; Smits et al., 2009). Dean et al. (2015) reported damage to white and grey matter cells within the brain in individuals with PCS, also noting greater damage to white matter than grey matter. White and grey matter cells form the neuroelectric connective network within the CNS, allowing for the efficient conduction of sensory information and motor responses throughout the nervous system (White Matter, 2007; Grey Matter, 2007). Individuals with PCS who report a higher number of symptoms were also reported to have greater damage to white and grey matter (Dean et al., 2015). Impaired function of neuroelectric connectivity has also been reported in several other studies of PCS utilizing EEG to assess ERPs during

functional cognitive tasks (Messe et al., 2013; Moore et al., 2014b; Pontifex et al., 2009). Furthermore, studies assessing impaired cognitive function in PCS using fMRI have reported abnormal brain activation patterns during working memory, selective attention, and math processing tasks (Leddy et al., 2013; Smits et al., 2009). To date, Leddy et al. (2013) appear to be the only other group within the literature to investigate the effect of an exercise-based treatment program on a measure of cognitive function in PCS. The design for the Leddy et al. study placed four participants with PCS in an aerobic exercise group; four participants with PCS in a placebo stretching group; and four healthy non-concussed matched controls were also included within the study. All participants completed a math processing task during fMRI at the onset of the study, followed by either a 12 week aerobic exercise, or a 12 week low-intensity stretching program. Healthy controls did not participate in either program. Following the 12 weeks, a second math processing task was conducted for all participants using fMRI. Before treatment, the aerobic and stretching group displayed abnormal brain activation patterns compared to the healthy controls on fMRI, but the two groups did not differ from each other. Following treatment, a significant difference was observed between healthy controls and the stretching group. Notably, there was no significant difference reported between the healthy controls and the aerobic exercise group following the intervention, however the stretching group significantly differed from the exercise group. Furthermore, by the end of the intervention the aerobic exercise group were able to elevate their heart rate to their age predicted maximum; whereas, the stretching group was unable to achieve this (Leddy et al., 2013). The findings of the Leddy et al. study suggest that a therapeutic effect of aerobic exercise to normalize atypical brain activation patterns in PCS to typical patterns of healthy non-concussed individuals may have occurred. The ImPACT battery was used to assess changes to verbal memory, visual memory,

visual motor speed, and reaction time in response to a four-week AEB treatment program within this study. Statistically significant differences were not detected for verbal memory, visual memory, or reaction time in response to the AEB treatment program but a significant improvement in visual motor speed was observed post-treatment. Visual motor speed can be defined as the evaluation of visual processing, learning, memory, and visual-motor response speed (ImPACT, n.d.). Six of the nine participants had large increases in visual motor speed following the AEB treatment program. One participant was observed to have no change, and only one participant had a very minor decrease (<1 correct response) in visual motor speed following the AEB program. It would appear that following four-weeks of AEB treatment participants with PCS experienced improvements in recognition, processing, and response speed during the ImPACT battery. Conversely, the results of the present study are not in agreement with the findings reported by Leddy et al., but the disparity in results may be explained by a number of factors.

The absence of verbal and visual memory improvements may be attributed to the variable BDNF concentration level response to treatment, wherein higher levels of BDNF are thought to facilitate improved performance on memory tasks. Therefore the higher performance on visual motor speed observed within the current study may not be related to BDNF concentration levels. Leddy et al. (2013) reported improved activation patterns within the brain during a math processing task following an exercise treatment program. Future investigations should use fMRI or EEG to measure brain activation patterns before and after exercise-based treatment. Changes in activation patterning may be related to improved visual motor speed results post-treatment. Caution must be used when interpreting the results due to the small sample size and further investigation is warranted to examine the impact of exercise on these variables.

The ImPACT was used to assess cognitive function for this study as it is a widely used clinical measure for assessing concussion. The ImPACT is generally intended to be used to collect baseline values of cognitive function. Following an acute concussion, the ImPACT battery can be administrated again to assess the magnitude of cognitive impairment due to concussion. During recovery from concussion, the ImPACT battery can be re-administered multiple times to monitor improvements in cognitive function. The absence of significant changes to verbal memory, visual memory, and reaction time may be due to a number of possibilities including the lack of effectiveness of the AEB treatment program in its current format, length, and progressive structure to improve these cognitive functions. In contrast, the ImPACT battery may lack the requisite sensitivity to detect more subtle deficits and/or changes in cognitive function in individuals with PCS (Pontifex et al., 2009). Although not represented by the ImPACT battery results, towards the end of the four-week AEB treatment program, participants and guardians subjectively reported improved cognitive function during daily tasks. Participants subjectively reported feeling as though their forgetfulness had decreased and it was easier to focus attention on daily tasks that had given them notable difficulty prior to joining the study.

These subjective reports from participants and guardians suggest some improvement in cognition in response to the AEB treatment program. The ImPACT battery may lack the necessary sensitivity to detect more subtle cognitive deficits in PCS as compared to drastic changes in cognition following acute concussion. Pontifex et al. (2009) evaluated the sensitivity to detect long-term cognitive impairments following concussion using ERPs, measured by EEG, during cognitive tasks in contrast to the ImPACT battery composite scores. The results of the study concluded that there appeared to be a lack of long-term cognitive impairments following

concussion using the ImPACT battery. However, EEG revealed notable deficits in neuroelectric measures of cognitive control, as well as deficits in performance during cognitive tasks. The findings reported by Pontifex et al. in combination with the results of this study suggest that future investigations of PCS should compare or consider the use of an alternate method of assessing cognitive function other than the ImPACT test battery. Functional magnetic resonance imaging and/or EEG to measure ERPs during cognitive tasks would provide a more robust assessment of cognitive impairments during the recovery from PCS as well as may be more sensitive to small changes noted in these impairments following treatment.

Aside from the possible limited sensitivity of the ImPACT battery for assessing PCS, the lack of significant changes in salivary-BDNF concentrations may also account for the absence of significant improvements in verbal and visual memory as measured by the ImPACT battery. Exercise-induced increases in BDNF concentration levels have been reported to facilitate mechanisms of neuroplasticity, which in turn facilitate improved hippocampal learning and memory (Griffin et al., 2011; Shrey et al., 2011; Winter et al., 2007). The lack of salivary-BDNF concentration levels observed at the group level could explain the lack of statistically significant changes in verbal memory, visual memory, and reaction time at the group level in response to the AEB treatment program. The rational for improvements in variables of cognitive function in response to exercise relied upon the upregulation of BDNF concentrations and the associated improvements in neuroplasticity. It is possible that if the AEB treatment program sessions were administered more frequently, at moderate intensity, for longer than four-weeks, higher salivary-BDNF concentration levels may have been observed. These higher concentrations may have facilitated greater improvements in verbal memory, visual memory, and reaction time as measured by the ImPACT battery. Improvements in these variables were observed at the

individual level on a participant by participant basis; future designs, however, should incorporate the use of a control group receiving no intervention to determine if these individual changes occurred due to the intervention or simply due to the effect of time.

Insignificant changes in verbal memory, visual memory, and reaction time as measured by the ImPACT battery may also be explained by the variable nature of concussion. Symptoms and impairments observed following concussion are unique. Two concussions caused by the same mode of injury (i.e., hit against the boards in hockey) are likely to present with completely different signs and symptoms (McCrory et al., 2013). Severity of symptoms depends on a large number of factors. Some notable factors include the age, sex, magnitude of impact, the area of the brain affected, and history of previous concussions (McCrory et al., 2013). Additionally, the underlying PCD(s) that may be causing persistent PCS symptoms need to be considered (Ellis et al., 2015). Physiologic PCD may exhibit a greater improvement in cognitive functions following AEB treatment due to improved glucose metabolism, and possible increased in BDNF concentrations. Vestibulo-ocular or cervicogenic PCDs may not illustrate improved cognitive function following AEB treatment since the respective underlying mechanisms of each PCD would not be addressed. Improvements or lack of improvements observed following the four-week AEB treatment program may be a result of whether or not the treatment addressed the PCD and symptoms individuals with PCS continue to suffer from. Due to the lack of improvement in three of four variables of cognitive function measured by the ImPACT battery within this study, it appears that treatment programs should be developed in an individualized manner to address PCD(s) and symptoms of PCS specific to the individual. Exercise-based treatment would be expected to benefit those with physiologic PCD the most due to improved glucose metabolism and possible improvements in BDNF levels in response to exercise. Whereas vestibulo-ocular

PCD may respond the best to an individualized program including retraining of the ocular reflexes and vestibular system; and cervicogenic PCD may respond to individualized treatment of the cervical spine and related systems (Ellis et al., 2015).

Question 4. Is there a difference in pre- and post-treatment AMTI force platform values of displacement in centre of pressure (COP) during the Balance Error Scoring System (BESS) for individuals with PCS following a four-week AEB based program?

The BESS protocol was utilized within this study as a standardized measure to assess balance for individuals with PCS. The BESS protocol is the standard static (standing) balance assessment used for assessment of acute concussion (Brown et al., 2014; Iverson & Koehle, 2013). The BESS protocol has also been recommended as the static balance measure of choice for individuals with PCS (Fowler Kennedy reference, n.d.). However, the validity and reliability of the BESS protocol has been called into question by some clinicians and researchers due to the subjective nature of scoring BESS protocol performance (Brown et al., 2014). To account for this, the BESS protocol was performed on an AMTI force platform to acquire more accurate and standardized measures of COP displacement during the BESS protocol trials. Four measures of COP displacement were extracted from the force platform data including: COP area, COP velocity, COP length, and total displacement of COP. There was no significant change detected in static balance performance during DS, SL, or TS for any of the measures of COP when performed on a firm surface. Alternatively, there was variability in the significant changes observed during DS, SL, or TS when performed on a foam surface. Area of COP was found to be significantly reduced during TS on a foam surface but not under any other condition. Velocity and length of COP was significantly reduced in both DS and SL performed on a foam surface. Total displacement of COP was significantly reduced in DS on a foam surface but not under any

other condition. These results suggest that the treatment program did have some effect on improving static balance for individuals suffering from PCS. However, these changes were not consistently observed across area, velocity, length, and total displacement of COP during the BESS protocol. These results suggest improvements in balance that would carry over to functional tasks of daily living, and sport-related skills. Improvements observed in TS on a foam surface following the AEB treatment may suggest greater control while ambulating on soft or even terrains. Improved balance during DS on a foam surface may indicate greater control of balance during prolonged periods of standing at school, work, or during daily/sport-related activities. In a sporting context, improvements in SL balance on a firm surface may have the most clinical relevance. Sports such as hockey expose the athlete to many instances when he/she will have to maintain his/her balance on one leg dynamically and statically. Improved balance in SL on a foam surface may carry over to RTP in sports that often demand the athlete to be able to control him-/herself on one leg. Furthermore, better balance in an unstable position such as SL may lower re-injury risk by reducing the chance of a fall wherein another concussion may occur.

Similar findings were also found with the prescription of an AEB program using the same progressions of balance exercises in a sample of healthy controls; the area and velocity of COP performance was also improved during four out of six BESS trial conditions and positions (McGeown et al., 2016). Improved area and velocity of COP values were reported during the SL and TS positions on a firm surface, as well as DS and SL stance positions on a foam surface (McGeown et al., 2016). Since balance progressions in a four-week AEB program improved static balance in healthy individuals with no balance impairments, greater improvements in static balance were expected in a sample of individuals suffering from PCS. Impairments in balance observed in PCS are speculated to be a result of deficits in sensory integration due to the initial

concussion (Alsalaheen et al., 2010). Improvements in balance were observed in healthy individuals with no balance issues to a greater extent than the improvements in balance observed in PCS following a four-week AEB treatment program. Within this study balance exercises were progressed once per week (three weekly sessions total) and this may not have allowed the necessary amount of time and practice for adaptation of sensory integration to occur.

Two participants in particular could not maintain static balance for greater than five seconds during SL or TS with eyes closed on a foam surface during the fourth week of the AEB treatment program. These same two participants each experienced symptom exacerbation one time during week three of the AEB treatment. The researcher noticed that participants had begun to hold his/her breath during these more challenging balance exercises. The researcher then routinely reminded participants to breathe throughout the balance exercises and this successfully prevented any further symptom exacerbation during balance exercises. To eliminate the risk of a fall, the balance exercises were regressed for these participants wherein they performed exercises with their eyes closed on a firm surface as was administered in week three of the AEB program. These participants may have had a greater benefit in response to the AEB program if the balance portion of the treatment was individualized to his/her balancing abilities, and progressed accordingly over the following weeks. This may have allowed these participants with greater balance challenges to begin treatment at an easier progression than what appeared appropriate for the rest of the group. Future studies should investigate the ideal amount of time, and appropriate difficulty of balance exercise progressions to induce a greater improvement in static balance for those suffering with PCS. Clinically it appears that balance exercises should be challenging enough that the individual with PCS must focus in order to maintain static balance, but easy enough that the individual can maintain his/her balance for 15-20 seconds at a time. Once the

individual with PCS can perform a balance exercise for 20 seconds or more with ease for multiple trials, progression of time may be appropriate. If the exercise is progressed too quickly or is too challenging for the individual, the improvements in static balance for those with PCS may be limited and be too challenging.

Question 5. Is there a difference in pre- and post-treatment Post-Concussion Symptom Scale (PCSS) scores for individuals with PCS following a four-week AEB based program?

Significant improvements in PCSS scores were found following the four-week AEB treatment program. This finding suggests a beneficial effect of the progressive treatment in reducing some of the symptoms in this sample associated with PCS. Exercise administered too soon following acute concussion has been documented to exacerbate symptoms and worsen outcomes of concussion (Gall et al., 2004; Griesbach et al., 2004; McCrory et al., 2013). The results of this study are in agreement with the findings of improvement in symptoms of PCS following exercise-based treatment reported by Leddy et al. (2013). Participants within this study had been receiving SRC since he/she suffered the initial concussion that developed into PCS. Symptoms of PCS continued to persist despite engaging in SRC. For 80-90% of concussions symptoms spontaneously resolve within a period of 7-10 days when SRC is administered (Belanger et al., 2013; McCrory et al., 2013; Moser et al., 2012; Willer & Leddy, 2006). However, there is no documented benefit of prolonged SRC beyond this 7-10 day period (Moser et al., 2012). Due to the evidence that acute exercise may worsen symptoms of concussion in some individuals, the administration of exercise-based treatment for PCS has been widely avoided in favour on more conservative treatment. Leddy et al. (2013) were able to demonstrate improved brain activation patterns using fMRI and an ability to reach age-predicted heart rate maximum during exercise following an exercise-based treatment in the sample with PCS. These

improvements were not reported in a control sample with PCS receiving a placebo stretching protocol to mimic SRC. While the current study did not have a control group receiving no AEB treatment, significant improvements in PCSS scores were still achieved after participants had been prescribed prolonged SRC of varying lengths. The most clinically relevant finding of this study is that, despite notable differences in methodology, both Leddy et al. and our results concur and elicited improvements in symptoms of PCS. Yet more investigation is required to reveal what underlying mechanisms of PCS are affected and improved by exercise-based treatments. As evidence grows regarding PCDs more effective exercise-based treatment options can be developed in order to address these underlying factors of PCS.

While the four-week AEB treatment program appears to have improved underlying physiological impairments contributing to PCS, there may be a psychological component to consider as well. Both neurophysiological and psychological factors play a causal role in the development of PCS from the instant the acute concussion occurs (Silverberg & Iverson, 2011). Participant's subjectively reported feeling relieved when he/she were informed of the study, citing that he/she was willing to try any treatment that may improve his/her PCS other than rest. Belanger et al. (2013) suggested that if an individual suffering from PCS is confident that he/she will improve, then this positive outlook may impact the rehabilitation process and outcome and the individual would likely recover from his/her PCS. Whereas an individual with PCS with low confidence or a negative outlook may not recover or experience a delayed recovery. Furthermore, if an individual with PCS negatively attributes headache, difficulty concentrating, or other concussion-like symptoms directly to his/her concussion, then they are at greater risk for persistent PCS symptoms (Belanger et al., 2013). Conversely, if an individual with PCS can positively attribute headache or difficulty concentrating to the lack of sleep or a stressful day,

these positive attributions were associated with reduced risk of persistent PCS symptoms (Belanger et al., 2013). How an individual with PCS perceives his/her symptoms appears to be a notable contributor to the outcomes of PCS recovery. There appears to be no evidence examining these perceptions of PCS and how they may or may not be changed in response to an exercise-based treatment.

It is possible that in the present study, the four-week AEB treatment program may have affected underlying psychological factors contributing to PCS. Offering a treatment option other than SRC may have led participants to attribute concussion-like symptoms to another cause, and/or led to participants having an increased confidence that he/she would actually recover from PCS. However, an outcome measure used to assess psychological factors related to PCS was not administered within this study so possible changes in these contributing psychological factors were undetected. Future studies examining the effect of an exercise-based treatment for PCS should collect data pertaining to psychological factors of PCS in addition to physiological and cognitive factors.

Question 6. What relationships are present between salivary-BDNF concentrations and PCSS score changes following a four-week AEB treatment, and what relationships are present between post-treatment values of salivary-BDNF concentration levels and PCSS scores?

It was hypothesized that the AEB treatment program administered to individuals with PCS was expected to improve concentration levels of salivary-BDNF. These expected increases in BDNF were hypothesized to result in improved cognition and a reduction in PCSS scores following the four-weeks AEB intervention. However, these expected changes were not

observed within this study. A significant relationship between changes in salivary-BDNF concentration levels and changes in PCSS scores were not detected in this sample of individuals with PCS following treatment. Additionally, a significant relationship was not detected between changes in salivary-BDNF concentration levels and post-treatment PCSS scores. Finally, no significant correlation was detected between post-treatment salivary-BDNF concentration levels and post-treatment PCSS scores. A significant reduction in PCSS scores were observed following treatment despite the lack of significant changes in salivary-BDNF concentration levels. Had the four-week AEB treatment program been administered more frequently, at a higher exercise intensity, for a longer period of time greater improvements in salivary-BDNF concentrations may have been observed as discussed above. It is possible that if salivary-BDNF concentrations were increased more effectively then a different effect on cognitive factors of PCS may have occurred due to increased neuroplasticity. If greater improvements in cognitive factors occurred this may have been reflected in lower scores for cognitive factors included within the PCSS. Therefore, relationships between salivary-BDNF concentrations and PCSS scores may have been observed.

Despite the lack of changes in salivary-BDNF concentration levels, significant improvement in PCSS scores were still observed. An alternative explanation for these findings is that there may in fact be no relationship between BDNF concentrations and symptoms of PCS. The changes observed in PCSS scores in this study may be due to an effect on other physiological mechanisms and/or psychological factors in response to AEB treatment that were not measured within this study. Although it is important to reiterate that the individuals with PCS within this study were observed to have post-treatment salivary-BDNF concentration levels approximately one quarter of the concentration levels observed in healthy individuals following

four-weeks of a similar AEB program. Therefore, suggesting lingering impairments in salivary-BDNF regulation, and by extension possible persistence of PCS. To our knowledge, this is the first study to examine concentration levels of BDNF in a sample of individuals with PCS who have received an exercise-based treatment. Further exploration is required to determine the true impact an exercise-based treatment program has on concentration levels of salivary-BDNF for individuals suffering from PCS before conclusions regarding the presence or absence of relationships can be made. Furthermore, different findings may have been observed if plasma-BDNF concentration levels were examined as opposed to salivary-BDNF levels.

Chapter 6 – Conclusion

The purpose of the study was to investigate the impact of a four week structured and supervised aerobic and balance exercise program on cognitive function, balance, and saliva BDNF levels in individuals diagnosed with PCS. Findings of this study suggest that the AEB treatment improved reports of PCS symptoms in addition to some improvements in measures of static balance during the BESS protocol (area of COP: TS foam; velocity of COP: DS and SL foam; length of COP: DS and SL foam; and total displacement of COP: DS foam) and cognitive function during the ImPACT battery (visual motor speed). Salivary-BDNF concentration levels were not significantly changed in response to the four-week AEB program. However, this may be due to a number of factors and requires further investigation. Exercise-based treatment strategies may be found to be more effective at alleviating symptoms of PCS than SRC as the body of literature continues to grow. The preliminary evidence reported in the current study is clinically relevant as our findings suggest exercise-based treatments may improve PCS outcomes in a more favourable manner than SRC.

Limitations

A number of limitations were present in the study and the interpretation of the results must take into consideration these limitations. First, a small pool of individuals with PCS was recruited for the current study. Secondly, there was not a large enough sample to recruit a control group of individuals with PCS. The lack of a control group may have an effect on the internal validity within the current study. Without a control group, outliers within the sample of individuals with PCS may have impacted the effect the AEB treatment had on dependent variables. Had a larger sample been recruited, then the effectiveness of the AEB program could

have been contrasted against individuals with PCS receiving only SRC treatment. Direct comparisons between the treatment group and the control group may have more clearly illustrated any changes in symptoms of PCS, cognitive function, balance, and salivary-BDNF levels. Due to a small sample size, a delimitation of this study was that it was not possible to stratify participants with PCS into one of the three recently proposed PCS subgroups: physiologic, vestibulo-ocular, or cervicogenic (Ellis, Leddy, & Willer, 2015). It is possible that individuals with a predominantly physiological cause for his/her PCS symptoms may benefit the most from an exercise program focused on cardiovascular and balance retraining, via restoring normal physiological functions. Whereas individuals with a predominantly vestibulo-ocular or cervicogenic causes may require an individualized treatment program with a different focus on the underlying vestibulo-ocular or cervicogenic contributors. Thirdly, the ImPACT battery was used to assess cognitive functions before and after the AEB treatment program. The ImPACT is an affordable and widely used tool for assessing cognitive function; however, the ImPACT is predominantly intended to be used for establishing baseline cognitive performance in individuals who have not been concussed, and to assess the changes in cognitive function from baseline after an acute concussion. It is possible that changes in cognitive function may have occurred in response to the intervention but the ImPACT may have lacked the necessary sensitivity to detect these changes. Lastly, both underlying physiological and psychological factors contribute to the development of PCS (Silverberg & Iverson, 2011). This study only assessed the effect of the AEB program on physiological and cognitive factors of PCS. Had a psychological assessment, tool, or questionnaire been included in the design of this study a more comprehensive depiction of the effectiveness of the AEB program on PCS would have been possible and this impact from a psychological perspective may have added to the clinical utility of interpreting the findings.

Future Directions and Recommendations

Future studies should investigate the administration of a similar supervised exercise program for individuals with PCS with a larger sample size. In order to allow for a control group as well as to stratify participants into physiological, vestibulo-ocular, and cervicogenic subgroups of PCS. The starting aerobic exercise intensity of 20% HRR within this study may have been too conservative as a starting point for participants with PCS. This intensity did not exacerbate symptoms of PCS, but participants also subjectively reported that the intensity was so conservative that it was difficult to keep his/her HR that low while performing stationary cycling. Conversely, starting at a low intensity may be a good option to insure that symptom provocation does not occur resulting in a setback for the patient. A more conservative starting point with a longer duration lasting eight to twelve weeks with varied exercise including cardiovascular conditioning, balance retraining, vestibular or ocular exercises, and exercises addressing cervical spine range of motion or strength issues might be more appropriate. More research is needed to determine the ideal dosage including the frequency, intensity, time, and type of exercise that would be most effective at eliciting improvements in individuals with PCS. Future studies should also consider integrating alternative techniques to measure cognitive functions for individuals with PCS. Electroencephalography technology used to measure ERPs during cognitive tasks and/or fMRI during cognitive tasks may provide more information on the cognitive functions and communication within the brain while recovering from PCS. Concentrations of BDNF could also be measured and compared between salivary and plasma BDNF values to determine if a shared or different effect is seen in response to exercise. Lastly, quantitative measurement of psychological factors of PCS should be further investigated in

combination with physiological factors of PCS; in order to illustrate the effectiveness of a supervised exercise program in regards to changes in both contributing factors of PCS.

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Appendix A
Directed Study

Pilot Study

Introduction

Concussion is an injury defined as a complex pathophysiological process affecting the brain induced by forces causing linear, rotational, and angular movements of the brain, or a combination thereof (McCrory et al., 2013). In 2013 the Canadian Community Health Survey reported that 94,000 concussions affected Canadians (58,000 males and 36,000 females) aged 12 years and older between 2009 and 2010 (Statistics Canada, 2013). Symptoms of concussion are highly variable, and no two concussions are alike, even if sustained by the same individual (McCrory et al., 2013). Due to the variable nature of concussion, symptoms are generally stratified into one of four categories: 1) somatic (physical symptoms); 2) cognitive (thinking and processing symptoms); 3) affective (emotional symptoms); or 4) sleep disturbances (Herring, Cantu, Guskiewicz, Putukian, & Kibler, 2011). Most individuals who sustain a concussion recover in less than two weeks but 10-20% experience lingering symptoms of concussion beyond two weeks. These enduring and persistent symptoms beyond two weeks are diagnosed and labelled as post-concussion syndrome (PCS). Neuropsychological (NP) testing has been stated to be the cornerstone of concussion assessment and management (McCrory et al., 2013). These NP tests allow researchers and clinicians to objectively and quantitatively evaluate deficits of cognitive function following concussion. Computerized NP batteries have been developed in order to reduce cost and ease the process of assessment and administration. These computerized formats take 20-30 minutes to complete, and several can be administered at once if multiple computers are available (Maerlender et al., 2010). The Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) battery appears to be one of the most commonly used computerized NP testing programs used in the case of baseline testing for many patients, sport teams, and athletes but not as commonly used in the presence of chronic symptoms due to PCS.

It is unclear if computerized NP test batteries such as the ImPACT demonstrate the necessary sensitivity to detect deficits that may be more subtle in PCS than acute concussion. Currently, there is also a lack of a gold standard and agreement on the definition of PCS (Baker, Freitas, & Leddy, 2012; Legome & Wu, 2014). This presents a significant challenge for researchers and clinicians to assess, monitor, and rehabilitate PCS, as the condition is not consistently operationalized within the literature. Furthermore, little is known about the underlying mechanisms that result in persistent symptoms progressing from an acute concussion to PCS.

It is hypothesized that the initial concussive injuries may interrupt the delicate synchronization of certain physiological pathways, which fails to resynchronize and result in persistent symptoms. As a result, impaired cognitive function and the ability to maintain balance may last for weeks or months following concussion if the function or sensory integration of the visual and/or vestibular systems is disrupted (Guskiewicz, 2001; McCrea et al., 2003). Also, damaged white matter cells within the brain have been reported in PCS patients with greater damage being associated with more severe symptoms (Dean et al., 2015). Lastly, following concussion, impaired autonomic function has been documented in the form of abnormal heart rate variability and cerebral blood flow (Gall, Parkhouse, & Goodman, 2004; Junger et al., 1997; Shrey, Greisbach, & Giza, 2011; Vavilala et al., 2004). These underlying impairments are especially worrisome when present in young developing neurological systems as these impairments may disrupt the typical developmental processes and result in atypical development with possible resultant long term ramifications on the individual (Shrey et al., 2011).

The vast majority of concussed patients often benefit from cognitive and physical rest during the acute (initial 7-10 day) phase of the concussion (Moser, Glatts, & Schatz, 2012). Generally, patients are instructed to engage in cognitive and physical rest which includes no

school or work, driving, screen time, chores, physical exercise, or activity that results in perspiration (Moser et al., 2012). This period of rest is hypothesized to allow the body to di-vert necessary energy stores to resolving the metabolic disturbances documented to occur following the neurometabolic cascade of concussion (Giza & Hovda, 2001; Shrey et al., 2011). Exercise during this acute phase following concussion has been observed to exacerbate the symptoms of concussion (Gall et al., 2004; McCrory et al., 2013). There is, however, no specific method of progressing rehabilitation in PCS patients following the acute period and rest is generally continued as the prescribed treatment and standard of care (Moser et al., 2012; Patterson & Holohan, 2012; Sayegh, Sandford, & Carson, 2010). Typically, rest is often prescribed as the treatment of choice because it is conservative and can be used in combination with education, reassurance of positive expectations of recovery, and suggested coping strategies (Belanger, Barwick, Kip, Kretzmer, & Vanderploeg, 2013). However, there is limited evidence that extended rest, beyond 7-10 days, will benefit those with PCS positively. An extended period of cognitive and physical rest beyond the first 7-10 days may result in improvement in some cases or, conversely, increased physical, psychological, and/or social stress in the form of physical deconditioning, hyperawareness of the symptoms, or loss of productivity at work or school (Kleffelgaard, Roe, Soberg, & Bergland, 2012; Moore, Hillman, & Broglio, 2014; Papa, Ramia, Edwards, Johnson, & Slobounov, 2015).

Early evidence now suggests the benefits of an active exercise program for those experiencing PCS due to the growing link within the literature regarding exercise and neuroplasticity and the ability of neurons to alter the strength and efficacy of pre-existing synapses in addition to forming new synaptic connections (Wells, 2002). Aerobic exercise has also been reported to increase concentrations of neurotrophic factors and biological markers

within the body which aid in the regulation of neuronal survival, development, function, and plasticity (Huang & Reichardt, 2001). Brain-derived neurotrophic factor (BDNF) is one of the identified neurotrophic factors of interest, and the reported effects specific to BDNF demonstrate its potential as a non-pharmacological assist to benefit impaired neurological function (Hennigan, O'Callaghan, & Kelly, 2007). Exercise has been documented to be one way to increase BDNF levels and has been correlated with improvements in neurological functions such as learning and memory, and in altering an individual's mood (Griffin et al., 2011; Erickson et al., 2013; Shih et al., 2013). Increased concentrations of BDNF through the administration of aerobic exercise has also been reported to improve cognitive function and memory in Alzheimer's Disease, stroke, and animal models of concussion (Koo et al., 2013; Mang, Campbell, Ross, & Boyd, 2013; Shrey et al., 2011).

To date, it appears that Leddy et al. (2013) were the first and only group to investigate the possible application of aerobic exercise in human subjects as an intervention strategy for PCS. Leddy and colleagues had participants with PCS perform an exercise protocol in order to determine the heart rate intensity in which participant symptoms were exacerbated. Afterwards, an individualized stationary bike aerobic exercise program was developed for each participant tailored to his/her recorded symptom exacerbation threshold. Participants were provided with instructions and exercise intensities below his/her symptom threshold. Brain activation was then measured using fMRI before and after the exercise program. At the baseline assessment, participants in the biking group were no different in terms of brain activation patterns than a control group of participants with PCS assigned to a stretching only group. The brain activation patterns observed in both PCS groups were significantly different, however, than the activation patterns seen in a group of healthy non-concussed individuals. After the completion of the

exercise program, the PCS biking group displayed improved activation patterns that were the same as the healthy individuals, whereas the PCS stretching group remained significantly different. Furthermore, participants in the PCS biking group were able to elevate his/her heart rate to their theoretical maximum without experiencing any symptom exacerbation, while the stretching group was unable to do so (Leddy et al., 2013). These results highlight the need for further investigation into the utility of exercise to rehabilitate patients that have persistent concussion symptoms. Similarly, based on the evidence within other areas of the literature, it appears that BDNF may be a biomarker of interest to monitor change in brain health at the time of baseline or initial assessment or following the implementation of rehabilitation programs. Supervised and controlled exercises may promote improvements to stimulate/regulate mechanisms of neuroplasticity. In turn, this may provide a stimulus to facilitate the internal physiological environment for the brain to heal itself via plasticity. More research, however, is required on the feasibility of implementing the assessment of this biomarker in combination with other clinical evaluative tools and the effect that exercise may have on such variables. Therefore, the purpose of this pilot study was to investigate the effects of a supervised and structured four week aerobic exercise and balance exercise program on resting heart rate, blood pressure, cognitive function, balance, and salivary-BDNF concentrations in a sample of normal healthy individuals.

Methods

Subjects. Ten healthy participants absent of any debilitating injury or condition that would prevent them from exercising were recruited for the pilot study. Participants ranged in age be-tween 20 and 29 years and all participants were regularly physically active for 150 minutes or more on a weekly basis prior to entering the study (see Table 1). Potential participants were

excluded from the study if he/she were not within the age range, was recovering from an injury or condition preventing them from exercise, or did not regularly participate in 150 minutes or more of physical activity per week.

Table 1.

Participant characteristics and demographic information

Sex	3 females; 7 males
Age (years)	M=22.90; SD=2.28
Height (cm)	M=171.20; SD=6.91
Body Mass (Kg)	M=74.94; SD=12.29

Procedures. After obtaining ethical approval from the academic institution, prospective participants were recruited using convenience sampling. Informed consent was obtained from prospective participants and afterwards an initial screening assessment was completed in which age, height, and body mass was measured and recorded. Prior to collecting the saliva sample, participants were instructed to refrain from brushing his/her teeth, smoking, and consuming food or drink within two hours of the sample collection and avoiding the consumption of any alcohol 12 hours prior to collection. Samples of salivary-BDNF were collected in the morning between 8:00-9:00 a.m. to minimize the effect of any diurnal variation. The pre-treatment data collection began by obtaining a 2mL saliva sample to assess BDNF concentrations. Participants passively drooled into a microcentrifuge tube to provide the sample, which was then put on ice. A modified methodology from Mandel et al. was followed for processing. Briefly, samples were centrifuged in a precooled centrifuge at 4000 rpm for 15 minutes. Supernatant was then aliquoted into tubes to which protease inhibitor cocktail was added to a final dilution of 1:100. These saliva samples were then frozen and stored at -80°C.

Next, participants completed a neurocognitive assessment using the computerized ImPACT battery. The ImPACT was used to assess verbal memory, visual memory, reaction time, and the visual motor speed of participants. Schatz, Pardini, Lovell, and Podell (2006) explored the sensitivity and specificity of the ImPACT battery when classifying concussed and non-concussed individuals and reported 82% sensitivity to correctly classifying concussed individuals, and 89% specificity for ruling out concussion in a healthy control group. Schatz revisited the psychometric properties of the ImPACT in 2010, evaluating the test-retest reliability of the ImPACT composite scores over two years. Schatz (2010) reported that the visual motor speed composite demonstrated the best test-retest reliability (intra-class correlation, ICC, = 0.74), followed by the reaction time composite (ICC= 0.68), visual memory (ICC= 0.65), and, lastly, verbal memory (ICC= 0.46). The ImPACT battery has demonstrated good construct validity as well when compared with traditional paper-and-pencil NP tests (Maerlender et al., 2010). Lastly, Allen and Gfeller (2011) compared the ImPACT to traditional paper-and-pencil NP tests using a factor analysis approach; the authors reported good overall concurrent validity with five factors explaining 69% of the variance in ImPACT scores.

After the ImPACT battery was completed, participants were asked to perform the Balance Error Scoring System (BESS) protocol on an AMTI force platform (see Figure 1). The AMTI force plate has 6 degrees of freedom, recording 3 forces (fz, fx, fy) and 3 moments (Mz, Mx, My). All these measures are fed into an AMTI amplifier and converted to digitals signals via an analog to digital converter. The in-formation is fed into BIOSOFT computer software through an USB port. The computer software uses the concepts of moments to compute COP. That is, the pressure points in the x and y directions along the base of support. Participants stood in a DS position with the feet touching (side by side), hands on his/her iliac crests with their eyes closed;

SL position standing on the non-dominant leg with his/her hands on their iliac crests and their eyes closed; and TS position standing with the toes of the non-dominant foot touching the heel of the dominant foot, hands on his/her iliac crests, and their eyes closed. The BESS protocol was completed on an AM-TI force platform and values of displacement in centre of pressure (COP) during each of the six trials were recorded. Displacement in the COP was assessed by measuring both the average velocity of the COP, in addition to the area of COP throughout the duration of the BESS trials. The location of the COP will shift in response to postural adjustments made to maintain balance; these shifts are referred to as displacement in the COP. The displacement in COP is displayed visually by the computer software using a 95% elliptical curve, which traces the displacement in COP point within a normal distribution and outliers throughout the duration of the trial. A summary report is produced by the software and the information can be exported to Excel or SPSS in order to represent the COP displacement numerically. The displacement was recorded and compared pre- and post-treatment.

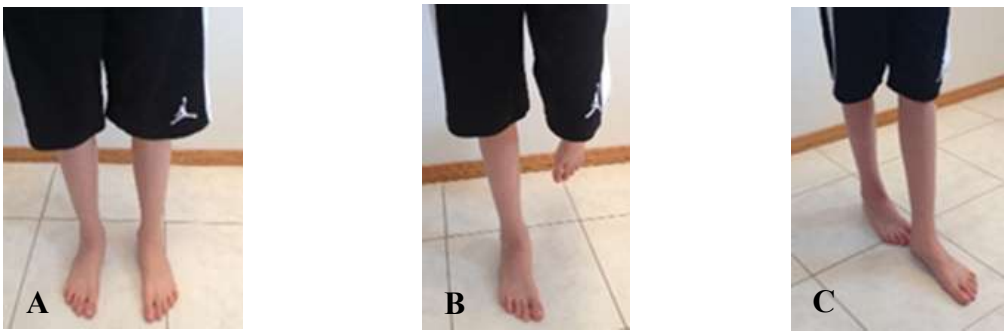

Figure 1. Double leg stance (A); Single Leg Stance (B); and Tandem Stance (C).

After the initial assessment measures were completed, all participants then attended 12 supervised exercise sessions over a four week period (three times per week); each session required approximately 40-60 minutes. Throughout the exercise sessions, participants wore a

heart rate monitor that was used to maintain the intensity of the exercise at a given target exercise heart rate for each supervised session. Sessions began with a five minute warm-up on a cycle ergometer at a self-selected speed and resistance until he/she reached their respective target HR. The Karvonen formula, Target Exercise Heart Rate = ((220-Age-Resting Heart Rate)×%Intensity)+Resting Heart Rate, was used to individualize and calculate exercise intensity for each participant based on his/her heart rate reserve (HRR; Karvonen Method, 2007). The first exercise session target intensity was 40% of HRR, for a total of 25 minutes (including a five minute warm-up). Throughout the 12 exercise sessions, the intensity and duration of stationary cycling was progressed following a predetermined exercise progression template. Intensity was increased by 5% of HRR in sessions 3, 5, 7, 9, and 11; additionally, the duration of aerobic exercise was increased by five minutes at the beginning of each new week. Therefore, for session one, aerobic exercise was performed at 40% of HRR for a total of 25 minutes, whereas by session 12, participants cycled for 40 minutes at an intensity of 65% of HRR.

After completing the cycling component of each session, participants rested for five minutes. Afterwards, they were asked to complete three sets of balance exercises in DS, SL, and TS positions on both legs. Balance exercises also followed a predetermined exercise progression template. In order to modify intensity over the four weeks, participants completed the exercises with their eyes open or closed, and exercises were performed on a firm tile surface, or low density foam surface. In weeks one and two, the balance exercises were performed for trials of 15 seconds, and subsequently progressed to 20 seconds per trial in weeks three and four. In week one, balance trials were performed with eyes open on a firm surface; for week two with eyes open on a foam surface; for week three with eyes closed on a firm surface; and for week four with eyes closed on a foam surface. Therefore, for session one, participants performed each

balancing condition for 15 seconds with eyes open on a firm surface and by session 12, trials were performed for 20 seconds on a low density foam surface with his/her eyes closed. After completing 12 exercise sessions, participants were re-examined following the same protocol described previously for the initial baseline assessments. Individual saliva samples were stored until samples were collected from all of the participants. A sandwich ELISA technique was then used to optimize salivary-BDNF measurement, following the protocol described by Mandel, Ozdener, and Utermohlen (2011). A 96-well microtiter plate (Nunc Maxisorp; VWR, West Chester, PA) was incubated at 4oC overnight containing 100 µl of monoclonal mouse anti-human BDNF (clone 35928.11; Millipore, Etobicoke, ON), diluted to 1 µg/ml in filter-sterilized phosphate buffered saline (PBS) at a pH of 7.4. The 96-well plate was manually washed three times, soaking for one minute between each time, with tri-buffered saline (TBS) plus 5% tween (TBST), and blocked with 300 µl of 3% bovine serum albumin (BSA) in 0.05% PBST for 2.5 hours at room temperature. Next, samples were acidified to a pH of 3.0 for 20 minutes using 1M of HCl; after 20 minutes, the samples were neutralized with 1M NaOH and diluted in a 1% BSA buffer in PBST to a ratio of 1:4. Samples were compared to standards diluted in the same buffer as the samples, ranging from 15.63 to 500 pg/ml using a full-length, homodimeric recombinant BDNF (Peprotech, Rocky Hill, NJ). The plate was washed five times and 100 µl of sample/standard was added to all wells in duplicate. At this point, the plate was incubated at room temperature for two hours with agitation, and subsequently washed five more times. After this, 100 µl of poly-clonal chicken anti-human BDNF (2.5 µg/ml; Promega, Madison, WI) was added to the plate for 2.5 hours, and the plate was washed five times again; another one hour incubation took place after the addition of 100 µl of anti-chicken IgY-HRP (1 µg/ml; Promega) to each well. Following this last incubation, the plate was washed a final five times, after which

100 µl of room temperature Pierce 1- Step Ultra TMB solution (Pierce Biotechnology, Rockford, IL) was added to each well for 15 minutes. Afterwards, 100 µl 1M HCl was added to stop the reaction, and the assay was read at 450 nanometres (nm). The amount of BDNF (pg/ml) was calculated using the regression equation provided with the standards (Mandel et al., 2011).

Data Analysis. Descriptive statistics were used to compare the mean and standard deviations for individual ImPACT battery and BESS protocol scores and salivary-BDNF values. Data analysis was completed using IBM SPSS 20 to evaluate any change that occurred following the exercise program. Changes observed in the dependent variables were assessed for statistical significance using Paired Samples t-Tests, with an alpha level of .05. The analysis evaluated the effect of the exercise program on the dependent variables (resting heart rate; resting blood pressure; ImPACT verbal memory, visual memory, visual motor speed, and reaction time scores; salivary-BDNF concentration; and BESS total score, COP displacement, and average velocity of COP) comparing pre- and post-treatment scores and values.

Results

There were no significant differences in resting heart rate ($t(9) = 2.08$, $p = .07$), resting systolic blood pressure ($t(9) = .67$, $p = .52$), or resting diastolic blood pressure ($t(9) = .71$, $p = .49$). Additionally, there were no significant changes in cognitive functions of verbal memory ($t(9) = -.27$, $p = .79$), visual memory ($t(9) = .60$, $p = .56$), or visual motor speed ($t(9) = 1.26$, $p = .24$) scores with ImPACT testing. Notably, there was a statistically significant increase in reaction time ($t(9) = -2.47$, $p = .04$) after the exercise program while performing cognitive tasks (see Table 2). The mean reaction time for participants before the exercise program was .53 +/- .05 seconds per response, whereas after the program this increased to .59 +/- .09 seconds per response (see Figure 2).

Table. 2

Descriptive Statistics for ImPACT Composite Scores

ImPACT Battery Components	Pre-Exercise Program	Post-Exercise Program
Verbal Memory (% correct)	85.500 (±10.341)	86.600 (±8.733)
Visual Memory (% correct)	74.300 (±11.245)	72.400 (±12.057)
Visual Motor Speed (# of correct responses)	43.800 (±6.369)	42.422 (±6.925)
Reaction Time (seconds)	.528 (±.054)	.586 (±.090)*

* indicates significant changes following the exercise program

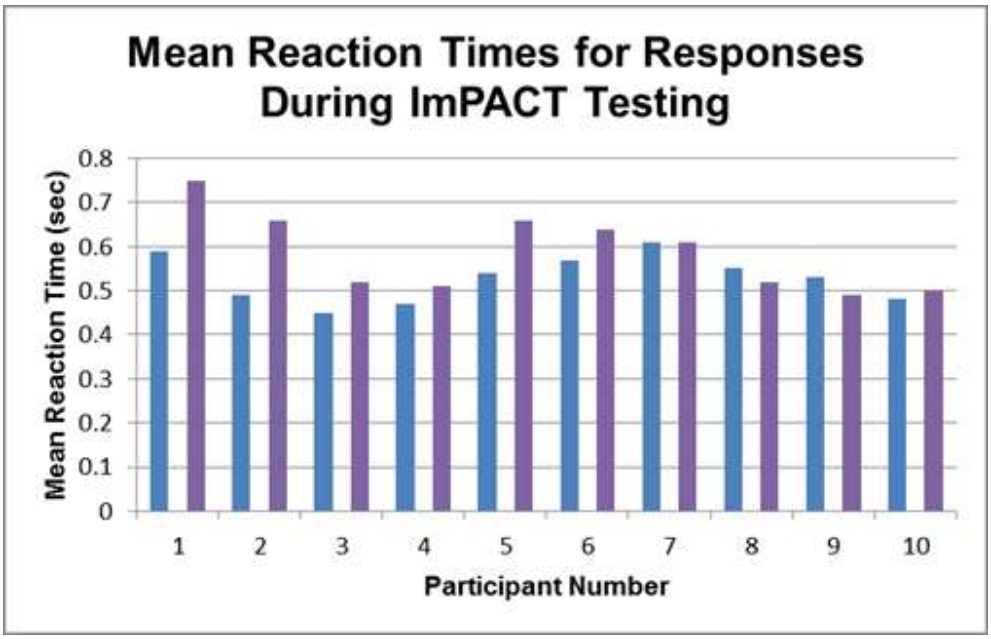

Figure 2. Changes observed in mean reaction time (sec) during the ImPACT test battery. pre-treatment mean reaction times; - post-treatment mean reaction times.

Salivary BDNF concentrations were observed to significantly increase in response to the exercise program ($t(9) = -1.809$, $p = .05$). Saliva sample mean BDNF concentration levels at baseline pre-treatment were 137.25 +/- 88.07 pg/ml, while the mean concentration post-treatment was 199.04 +/- 80.13 pg/ml (see Figure 3).

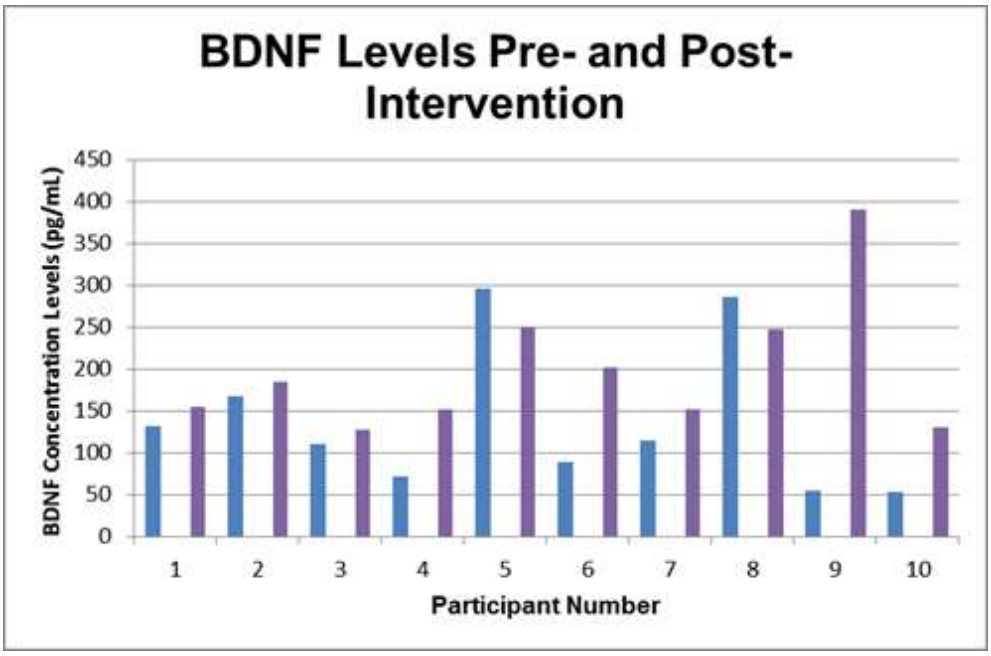

Figure 3. Changes observed in the BDNF concentration levels (pg/mL). - BDNF levels pre-treatment; - BDNF levels post- intervention.

The BESS total score was significantly reduced ($t(9) = 5.76$, $p = .0001$; see Figure 4). A number of significant differences in measures of balance were observed post-treatment (see Table 3). Analysis revealed significant reductions in the average velocity of COP during double foam stance ($t(9) = 4.69$, $p = .001$); single leg firm stance ($t(9) = 3.09$, $p = .01$); single leg foam stance ($t(9) = 2.65$, $p = .03$); and tandem firm stance ($t(9) = 2.36$, $p = .04$) when performing the BESS protocol. Furthermore, statistically significant reductions in the area of the COP were observed during the double foam stance ($t(9) = 4.47$, $p = .002$); single leg firm stance ($t(9) = 2.28$, $p = .04$); single leg foam stance ($t(9) = 3.00$, $p = .015$); and tandem firm stance ($t(9) = 2.49$, $p = .04$) during the BESS protocol.

Table 3.

Descriptive statistics for average velocity of COP (cm/sec) and average area of displacement of COP (cm^2) during the BESS protocol.

	COP Velocity(cm/sec)		COP Displacement Area (cm2)	
BESS Protocol Trial	**Pre- Exercise**	**Post- Exercise**	**Pre- Exercise**	**Post- Exercise**
DS Firm Surface	.62±.14	.65±.10	.29±.13	.42±.23
SL Firm Surface	2.30±.59	1.77±.34*	2.07± 1.63	1.38 ±.99*
TS Firm Surface	1.78±.58	1.30±.19*	1.71±1.41	.61±.26*
DS Foam Surface	1.76±.47	1.24±.18*	2.04±.84	1.16±.40*
SL Foam Surface	4.73±2.78	2.92±.98*	9.32±5.84*	3.99±2.54*
TS Foam Surface	3.08±1.41	2.25±.61	5.63±4.64	2.82±1.64

* indicates significant changes following the exercise program

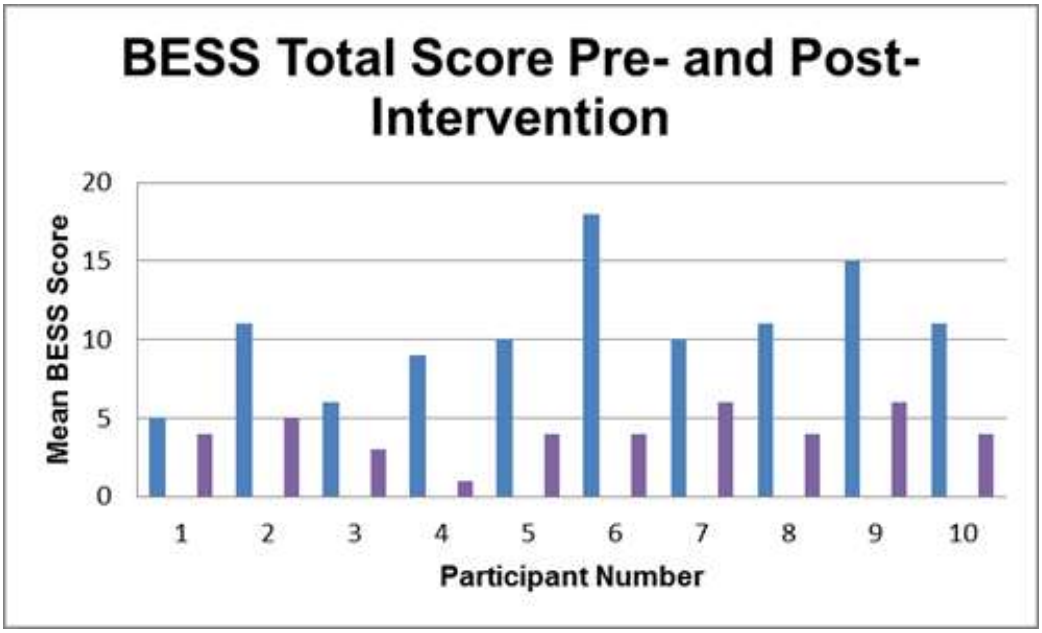

Figure 4. Changes observed in the BESS protocol total score. – pre-treatment BESS score; - post-treatment BESS score.

Discussion

The purpose of this pilot study was to investigate the effects of a supervised and structured four week aerobic and balance exercise program on resting heart rate, blood pressure, cognitive function, and balance in a healthy sample of individuals as a preliminary study for proof of concept to be later applied to a PCS population. While minimal to modest changes were initially hypothesized to be observed following the exercise program in this population, several distinct results were found. No significant changes in resting heart rate, resting systolic, or diastolic blood pressure were found. This result was not unexpected due to the healthy, physically active sample recruited for the exercise program. Regular physical activity is associated with optimal blood pressure and heart rate (Canadian Society of Exercise Physiology [CSEP], 2013). Activity strengthens the heart and vessels, in addition to improving the control of the autonomic nervous system's regulation of heart rate and blood pressure (CSEP, 2013). If an

individual experiencing PCS was prescribed a period of cognitive and physical rest for weeks or months, this may result in physical deconditioning, which may impair the regulation of heart rate and blood pressure. Less than ideal regulation of heart rate and blood pressure has been hypothesized as a reason why individuals with PCS continue to present with symptoms long after the typical recovery period of 7-10 days (Gall et al., 2004). Therefore, the prescription of this exercise program may result in different findings in the future application to a patient population in which heart rate and blood pressure are impaired.

No significant differences were observed in verbal memory, visual memory, or visual motor speed with ImPACT testing, however, reaction time significantly increased when completing the ImPACT battery. The increased reaction time may be explained by a learning effect and the fact that participants consciously took more time to react to the stimuli in order to avoid incorrect responses during the post-treatment test session. However, it is notable that although reaction time increased, the delay in reaction time was very small (.06 seconds). Even though participants were slower to respond to the tasks, responses and scores were no better than those measured pre-exercise.

Concentrations of salivary BDNF were significantly in-creased in response to the four week exercise program. This was a particularly interesting finding as BDNF has been reported to demonstrate the potential as a non-pharmacological intervention to benefit impaired neurological function (Hennigan et al., 2007). Furthermore, BDNF has been documented as a major factor in the regulation of neuroplasticity; the ability of the brain to undergo changes in strength of mature synaptic connections, as well as the formation of synapses in adult and developing brains (Hennigan et al., 2007; Wells, 2002). The phenomenon of neuroplasticity also extends to the regeneration of synapses following an injury to the CNS, such as is the case with a

concussion. Aerobic exercise has been observed to be an effective method of increasing BDNF concentrations (Hennigan et al., 2007; Koo et al., 2013; Mang et al., 2013; van Praag, 2009).

The prescription of aerobic exercise to healthy adoles-cents and college students has been observed to result in improved cognitive function, faster reaction times, and verbal learning (Lee et al., 2014; van Praag, 2009). These findings were not replicated within the current study; how-ever, this may be attributed to the fact that the ImPACT battery has been designed to assess cognitive function in concussed individuals and not necessarily normal healthy controls. Therefore, the ImPACT may lack adequate sensitivity to detect more subtle changes in a healthy population.

In animal models of Alzheimer's Disease, voluntary treadmill exercise upregulated BDNF concentrations and was associated with improvements of learning and memory function (Koo et al., 2013). Similarly, in animal models of concussion, voluntary treadmill exercise resulted in increased BDNF levels, associated with improved learning, memory, and overall cognitive performance (Mang et al., 2013). The findings of the current study support these findings in that aerobic exercise and balance retraining resulted in increased salivary BDNF. However, the timing and administration of exercise may be crucial for the prescribing clinician, as aerobic exercise prescribed within the acute phase of concussion (initial 7-10 days after injury) may result in increased symptoms and possibly decreased BDNF concentrations. Conversely, delayed administration of aerobic exercise following the acute phase resulted in upregulation of BDNF associated with improved cognitive function in mice (Shrey et al., 2011). Leddy et al. (2013) appeared to be the only group to date to administer aerobic exercise to a sample of human participants with PCS. While the authors did not measure BDNF concentration levels within their study, they did report that the prescription of aerobic exercise improved

cognitive impairments associated with PCS. Prior to the completion of the exercise program, participants with PCS were observed to have significantly different patterns of brain activation during cognitive tasks, as measured by fMRI when compared to healthy controls. Following the aerobic exercise program, participants with PCS improved, exhibiting similar brain activation patterns during cognitive tasks as the healthy controls (Leddy et al., 2013).

The structure and administration of the exercise protocol within the current study elicited significant increases in salivary BDNF, despite all of the participants being healthy and regularly physically active individuals. Therefore, it seems plausible that in a sample of individuals with PCS a similar exercise program may increase BDNF concentrations, facilitate neuroplasticity, and by extension, lead to PCS symptom reduction. The findings of the present study warrant further investigation on the effect of aerobic exercise on BDNF concentration and cognitive function in individuals with PCS.

Significant reductions in the BESS total scores were also observed in the current study. The BESS protocol is a widely used clinical tool for the assessment of static balance following concussion, with established normative data collected from healthy, post-secondary aged individuals (Iverson, & Koehle, 2013). Based on the improvements observed in the BESS scores of the healthy individuals in response to the exercise program in the current study, it seems plausible that concussed individuals experiencing balance impairments may also benefit from a similar exercise program. Significant reductions in the average velocity of the COP and the area of COP were also observed in four of the six BESS trials. These findings in a healthy population provide evidence that further exploration of a balance retraining program similar to the one administered in the current study may be applied in a subsequent study and possibly aid in improving balance deficits in participants with PCS.

Since the exercise program elicited improvements in individuals with no underlying conditions of impaired balance, it seems plausible, that similar or greater improvements may be observed in a sample of patients with PCS. Balance deficits associated with PCS are hypothesized to be the result of diminished sensory integration due to the initial concussive injury (Alsalaheen et al., 2010). Therefore, a progressive exercise program may foster improvements in impaired integration of sensory information by challenging the neuromuscular system to adapt to new demands and, by extension, result in greater ability to maintain balance.

The limitations of the current study include the fact that the ImPACT battery was used to measure cognitive functions of healthy participants. The ImPACT is designed to detect deficits in cognitive function in concussed individuals with notable impairments. It is possible that subtle changes in cognitive function may have occurred, which the ImPACT lacked the requisite sensitivity to detect. Second, due to a small sample size, the statistical power of the results from this study was low. Replication of this aerobic and balance exercise program with a larger sample size and control group may reveal different trends within the data undetected within the present study. Lastly, this pilot study only examined healthy individuals who were regularly physically active prior to entering the study. Different results may be found if replicated with a sample of PCS or sedentary individuals. Future studies should investigate the impact of a similar, supervised aerobic exercise and balance retraining program for individuals with PCS, as long as exercise is administered below symptom threshold. If exercise is a possible viable option for PCS rehabilitation, more research regarding the ideal frequency, intensity, time, and type of exercise will have to be investigated. In addition, further investigation into the role BDNF plays as a biomarker in the severity of PCS symptoms, as well as rehabilitation in other neurological impairment is warranted. Furthermore, exercise has been reported to act as a potent as

serotonergic mediator promoting recovery from depression (van Praag, 2009). If exercise and BDNF display positive relationships with improving outcomes and certain symptoms then future studies exploring the effect of exercise on BDNF concentrations in individuals with depression or with other neurological impairments is warranted

Conclusion

The current pilot study supported the feasibility of a supervised four week aerobic and balance exercise program and demonstrated that the administration of such a program to a sample of healthy, physically active individuals resulted in improvements in salivary-BDNF concentrations, static balance, average velocity, and area of COP measures. Further research is required to explore the application of supervised exercise programs in the concussion population or individuals with other neurological impairments.

Appendix B
Information Letter

Lakehead UNIVERSITY

School of Kinesiology
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kinesiology@lakeheadu.ca

Dear Potential Participant,

You are being invited to participate in the following research project. The project is being conducted by me, Josh McGeown, a Master's of Science in Kinesiology student at Lakehead University under the supervision of Dr. Paolo Sanzo, Assistant Professor in the School of Kinesiology at Lakehead University. The title of the study is "Exploring the effect of aerobic and balance exercise in comparison to standard rest care as interventional strategies for post-concussion syndrome". The purpose of the proposed study will be to investigate and compare the impact of four-weeks of structured and supervised aerobic and balance exercise (AEB) program versus four weeks of standard rest care (SRC) on impaired cognitive function, balance, and saliva protein levels in a sample of 14-30 year old athletes diagnosed with post-concussion syndrome (PCS).

Participation in this study requires that you are male or female between the ages of 14 and 30 years. You have been diagnosed with a concussion by your supervising physician, and the symptoms of your concussion have not resolved within a minimum of eight weeks to a maximum of two years after the injury. In addition you must be absent of an injury or condition, other than concussion, that prevents you from exercising, including a lower limb injury within six months prior to referral to the study. Your supervising physician has identified you meet inclusion criteria for this study, and informed the research team. The treatment you receive from your supervising physician will in no way be affected by your decision to participate or not participate within this study. Prior to participation, you will be required to sign a consent form. If you are under the age of 18 you will be required to provide assent and have a guardian complete an informed consent form for you. At this point the primary researcher will randomly assign you to either a SRC program or an AEB program. Participation in this study includes an initial assessment, adhering to a treatment program for the period of four-weeks, followed by a final assessment. The initial assessment will begin at the Northern Ontario School of Medicine. During this time you will be required to provide a saliva sample at the Northern Ontario School of medicine; between 8:00 and 9:00 a.m. to control for any variability. You will be instructed to withhold from brushing your teeth, smoking, and consuming food or drink two hours prior to the assessment day. Additionally, you will be asked to avoid consuming any alcohol and/or exercising within 12 hours of the assessment. It will take approximately 10 minutes to provide this small saliva sample in order to determine concentrations of BDNF, a protein in the body known to benefit brain function. The student researcher will passively collect two millilitres of saliva into a small tube that will then be frozen until the completion of the study. All BDNF samples will be discarded into a biohazardous material disposal as per Lakehead University Biological Safety Manual after the study has been completed. The remainder of the initial assessment will take place in room SB-1028 of the

Lakehead University Sanders Building; beginning with measuring your resting values of heart rate and blood pressure. Next, you will complete a 25 minute computerized assessment of your attention, memory, reaction time, impulse control, and problem solving ability using the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) battery. This computer based test will be completed on a laptop in SB-1028. Lastly, you will complete a balance assessment requiring you to stand in three different positions: feet together, single leg, and heel to toe. During the balance assessment you will complete all three stances with your eyes closed on a firm surface and all three stances on a soft foam surface (also with eyes closed) for 20 seconds per stance. The student researcher will instruct, administer, and record all components of the initial assessment; approximately 60 minutes of your time will be required for the initial assessment.

If you are randomly assigned to the SRC program you will be instructed to engage in cognitive and physical rest to the best of your ability for the span of four weeks. You will be provided with educational material detailing what cognitive and physical rest consists of. Additionally, this information package will include material about diagnosis, symptoms, activities that may worsen symptoms, normalization of symptoms, reassurance of positive expectation of recovery, and coping strategies to try and decrease your symptoms. You will also be provided with a log book. In this log book you will be given instructions to record any activities you do over the span of the four weeks that does not qualify as cognitive or physical rest. You will be instructed to describe the activity, the duration the activity was performed, and if it triggered any of your symptoms. Standard rest care has typically been the conservative treatment option of choice prescribed by health care professionals to deal with short term and long term symptoms following a concussion. After you have completed four-weeks in the SRC program, the AEB program will be offered to you if you choose to take it.

If you are randomly assigned to the AEB program, upon completion of the initial assessment you will schedule a time for the first exercise session. You will also be provided with the same log book and educational material as the SRC program. The AEB program requires you to attend three, one hour long supervised exercise sessions per week, for four consecutive weeks, for a total of 12 sessions. During these exercise sessions you will be guided through a five minute warm-up, followed by 20-35 minutes of cycling on a stationary bike, and concluding with exercises designed to improve balance. These balance exercises will require you to perform the same three stances as in the balance assessment that have been modified to make them slightly more challenging by altering the duration, surface you stand on, and whether your eyes are open or closed. Throughout these exercise sessions you will be supervised by the student researcher who is a Canadian Society of Exercise Physiology certified personal trainer. All testing will take place in the multi-purpose laboratory (SB-1028) in the Sanders Building at Lakehead University. The specific protocol for the

stationary cycling and balance exercises will be controlled by the student researcher; every three sessions the intensity of cycling and difficulty of the balance exercises will be slightly increased by the student researcher to provide a greater challenge. The goal of all exercise sessions is to remain below your symptom threshold, meaning exercising at a level that will not reproduce your symptoms. Should your symptoms be brought on at any point during the exercise sessions, the session will end for that day. The following session your exercise intensity will be individualized based on the heart rate at which your symptoms were triggered at. This way, the exercise intensity is individualized to your specific symptom threshold. After completing all 12 exercise sessions, you will complete a final assessment consisting of the same measurements and tests completed during the initial assessment. This session will once again require approximately one hour of your time.

The full extent of potential benefits to participants within this study are unknown at this time. The intent of this study is to gain information about whether there are any benefits of an exercise-based program versus a rest-based program, or vice versa. It is the hope of the research team that participation will help alleviate symptoms a result of either a SRC or AEB program. However, it is also possible that your symptoms will remain the same or worsen. By participating in this study you will be benefitting future patients with PCS. Information gained from this study will add to the body of literature available regarding rehabilitation strategies of PCS. This information may guide future research in order to develop a safe an effective method to rehabilitate PCS. Therefore, by participating within the study you may benefit yourself as well as future individuals experiencing the same lingering symptoms following concussion as you have.

The full extent of potential risks for participation in this study are unknown, a component of this study is to determine what the risks of exercise/rest might be. Within the AEB program it is possible that your symptoms may be triggered during or after the session due to exercise. This risk is minimized by individualizing your exercise intensity based on your age and resting heart rate. If your symptoms are exacerbated by exercise you will be instructed by the student researcher to stop exercising for the rest of the session. The symptoms and severity of symptoms will be recorded in addition to the intensity at which your symptoms were brought on. The following session you would exercise at a further individualized intensity based on the heart rate that was recorded when your symptoms were brought on. Another risk could be sustaining a soft tissue strain during the completion of the exercises. This risk will be minimized by including a warm-up prior to cycling on the stationary bike and having the exercises supervised and progressed by the student researcher. In addition, there is a risk of falling during the balance training exercises. To minimize this risk, all balance training will be completed on a clean and flat surface, and the student researcher will serve as a spotter to ensure that no falls happen. All participants will be

supervised and guided through the two assessments and 12 exercise sessions by the primary student researcher, Josh McGeown (HBK), a Certified Personal Trainer through the Canadian Society for Exercise Physiology. Through this certification the student researcher is qualified to supervise exercise, as well as trained to administer proper spotting techniques during balancing exercises. Potential risks within the SRC program may include physical deconditioning due to rest. Additionally, if you do not adhere to the assigned rest recommendations it is possible you may experience an onset of symptoms due to activity. This will be accounted for by providing you coping strategies in the educational material provided to you at the beginning of the study.

Participation in this study is completely voluntary; you have the right to withdraw at any time. All information that you provide will be strictly confidential and you have the right to decline answering any questions. Your name will not be used in the study; rather you will be assigned an anonymous participant number. Only the student researcher, Josh McGeown, and his supervisor, Dr. Paolo Sanzo, will have access to the recorded data and personal information. All information will be securely stored in Dr. Paolo Sanzo's office at Lakehead University for a period of five years.

The results from this study may be presented in a paper, oral presentation, and/or poster presentation format as part of the course requirements for completing the Master's of Science in Kinesiology program. As well, the abstract may be submitted for consideration for conference presentation and/or publication in an academic journal. Full anonymity and confidentiality will be observed during the course of the research, in the final report, and in the presentation of the results. You will not be identified in any way as you will have been assigned an anonymous participant number. If requested, you will be provided with a copy of your results upon the completion of the study.

If you have any questions or would like to participate in the study please contact me at jpmcgeow@lakeheadu.ca or at 807-631-4000. You may also contact my supervisor, Dr. Paolo Sanzo, at psanzo@lakeheadu.ca or 807-343-8647 should you have any questions or concerns. This research has been approved by the Lakehead University Research Ethics Board. If you have any questions related to the ethics of the research and would like to speak to someone outside of the research team, please contact Sue Wright at the Lakehead University Research Ethics Board at swright@lakeheadu.ca or 807-343-8283.

Thank you for your cooperation.

Sincerely,
Josh McGeown
HBK, MScKine (candidate)
Lakehead University

Appendix C
Consent Form

Lakehead UNIVERSITY

School of Kinesiology
t: (807) 343-8544
f: (807) 343-8944
kinesiology@lakeheadu.ca

I, , agree to participate in a study entitled "Exploring the effect of aerobic and balance exercise in comparison to standard rest care as interventional strategies for post-concussion syndrome". The study is being conducted by Josh McGeown, a Master's of Science in Kinesiology student at Lakehead University, and supervised by Dr. Paolo Sanzo, Assistant Professor in the School of Kinesiology at Lakehead University in partial fulfillment of the requirements to complete a Master's of Science in Kinesiology degree.

I have read and understand the recruitment letter. I understand that participation in this study requires concussed individuals, whose symptoms have not resolved within eight weeks to two years of the injury. I am between the ages of 14 and 30 years, and I am absent of an injury or condition other than concussion that prevents me from exercising. I understand by choosing to participate the treatment I receive from my supervising physician will not be affected in any way. I understand that as part of this study I will complete an initial assessment requiring about one hour, and afterwards I will be randomly assigned to one of two treatment programs. If I am assigned to the standard rest care (SRC) program I understand I am instructed to mentally and physically rest to the best of my ability for a period of four weeks. I understand that rest means avoiding any mental or physical exertion that brings on my symptoms. I understand part of my role will be to keep a log of any activities that do not qualify as rest, as defined by the information package provided to me. If I am randomly assigned to the aerobic and balance exercise (AEB) program I understand I will have to attend 12 exercise sessions that are 40-60 minutes each, completed over the span of four weeks. After four weeks in my program I understand that the study concludes with a 60 minute post-intervention assessment. I understand that I will be provided with the same information package and log book as the SRC program. I understand that the assessments and exercise sessions will be held within the Northern Ontario School of Medicine and the Lakehead University Sanders Building multi-purpose lab (SB-1028).

I understand that during both assessments I will have to provide a saliva sample to determine the effect of rest or exercise on a protein called brain-derived neurotrophic factor (BDNF), which is well known to benefit brain health. I understand that this data collection will be non-invasive, that my saliva will be frozen and stored in a locked laboratory until data is collected from all participants within the study. Once the saliva has been analyzed, I understand that it will be discarded as per the Lakehead University Biological Safety Manual Guidelines.

I understand that the full extent of potential risks for participation are unknown at this time and that part of the goal of this study is to identify what the possible risks of exercise or rest could be. I understand that within the AEB program it is possible that my symptoms may be exacerbated during or after the session due to exercise. I understand this risk will be minimized by individualizing my exercise intensity based on my age and resting heart rate. I understand if my symptoms are exacerbated by exercise I will be instructed by the student researcher to stop exercising for the rest of the session. My symptoms and severity of symptoms will be recorded as well as the intensity at which my symptoms were triggered. I understand that the following session my exercise intensity would be further individualized based on the heart rate that was

Lakehead UNIVERSITY

recorded when my symptoms were brought on. I understand a risk could be sustaining a soft tissue strain during the completion of the exercises. I understand I will complete a warm-up prior to cycling to minimize this risk, and all exercise will be progressed and supervised by the student researcher. I understand there is a risk of falling during the balance training exercises. To minimize this risk, all of my balance training will be completed on a clean and flat surface, and the student researcher will serve as a spotter to ensure that I do not fall. I understand I will be supervised and guided through the two assessments and 12 exercise sessions by the primary student researcher, Josh McGeown (HBK), a Certified Personal Trainer through the Canadian Society for Exercise Physiology. I understand through this certification the student researcher is qualified to supervise exercise, as well as trained to administer proper spotting techniques during balancing exercises. I understand potential risks within the SRC program may include physical deconditioning due to rest. Additionally, I understand if I do not adhere to the assigned rest recommendations it is possible I may experience an onset of symptoms due to activity. I understand I will be provided with coping strategies in the educational material provided to me at the beginning of the study to account for this.

I understand the full extent of potential benefits to participating in this study are unknown at this time. I understand the goal of this study is to gain information about are there are any benefits of an exercise-based program versus a rest-based program, or vice versa. I understand it is the hope of the research team that participation will help alleviate my symptoms as a result of either a SRC or AEB program. However, I understand it is also possible that my symptoms will remain the same or worsen. I understand by participating in this study I will be benefit future patients with PCS. I understand that the information gained from this study will guide future research in order to develop a safe an effective method to rehabilitate PCS.

I understand that my participation in this study is voluntary and that I may withdraw at any time. I also understand that my identity will remain anonymous and all data will be kept strictly confidential. Only Josh McGeown and Dr. Paolo Sanzo will have access to this data. No identifiable characteristics will be used in the final report, or in the presentation of the results. The data will be securely stored in the office of Dr. Paolo Sanzo for a period of five years.

I understand that I will be provided with a copy of my results at the completion of the study, if requested.

_____ _____

Participant Signature Date

_____ _____

Witness Date

If you wish to receive a copy of your results upon completion of the study please provide a phone number or email address so you can be contacted.

_____

Appendix D
Assent Form

Lakehead UNIVERSITY

School of Kinesiology
t: (807) 343-8544
f: (807) 343-8944
kinesiology@lakeheadu.ca

I, , agree to take part in a study titled "Exploring the effect of aerobic and balance exercise in comparison to standard rest care as interventional strategies for post-concussion syndrome". The study is being carried out by Josh McGeown, a Master's of Science in Kinesiology student at Lakehead University, and supervised by Dr. Paolo Sanzo, Assistant Professor in the School of Kinesiology at Lakehead University in partial fulfillment of the requirements to complete a Master's of Science in Kinesiology degree.

I have read and understand the recruitment letter. I understand that participation in this study requires concussed people, whose symptoms have not gone away within eight weeks to two years of the injury. I am between the ages of 14 and 30 years, and I do not have another injury or condition other than concussion, that prevents me from exercising. I understand by choosing to participate the treatment I receive from my supervising doctor will not be affected in any way. I understand that as part of this study I will complete an initial assessment requiring about one hour, and afterwards I will be randomly assigned to one of two treatment programs. If I am assigned to the standard rest care (SRC) program I understand I am instructed to rest to the best of my ability for a period of four weeks. I understand that rest means avoiding any mental or physical exertion that brings on my symptoms. I understand part of my role will be to keep a log of any activities that do not qualify as rest, as defined in the information package given to me. If I am randomly assigned to the aerobic and balance exercise (AEB) program I understand participation includes 12 exercise sessions that are 40-60 minutes each, over the span of four weeks. After four weeks in my program I understand that the study ends with a one hour post-intervention assessment. I understand that I will be provided with the same information package and log book as the SRC program. I understand that the assessments and exercise sessions will be held within the Northern Ontario School of Medicine and the Lakehead University Sanders Building multi-purpose lab (SB-1028).

I understand that during both assessments I will have to provide a saliva sample to find out the impact of rest or exercise on a protein called brain-derived neurotrophic factor (BDNF), which is well known to benefit brain health. I understand that this data collection will not be invasive at all, and that my saliva will be frozen and stored in a locked laboratory until data is collected from all participants within the study. Once the saliva has been analyzed, I understand that it will be disposed of as per the Lakehead University Biological Safety Manual Guidelines.

I understand that the all of the potential risks for participation are unknown at this time and that part of the goal of this study is to identify what the possible risks of exercise or rest could be. I understand that within the AEB program it is possible that my symptoms may be triggered during or after the session due to exercise. I understand this risk will be minimized by individualizing my exercise intensity based on my age and resting heart rate. I understand if my symptoms are triggered by exercise I will be instructed by the student researcher to stop exercising for the rest of the session. My symptoms and severity of symptoms will be recorded as well as the intensity at which my symptoms were triggered. I understand that the following session my exercise intensity would be further individualized based on the heart rate that was

Lakehead UNIVERSITY

recorded when my symptoms were brought on. I understand a risk could be sustaining a soft tissue strain during the completion of the exercises. I understand I will complete a warm-up prior to cycling to minimize this risk, and all exercise will be progressed and supervised by the student researcher. I understand there is a risk of falling during the balance training exercises. To minimize this risk, all of my balance training will be completed on a clean and flat surface, and the student researcher will serve as a spotter to ensure that I do not fall. I understand I will be supervised and guided through the two assessments and 12 exercise sessions by the primary student researcher, Josh McGeown (HBK), a Certified Personal Trainer through the Canadian Society for Exercise Physiology. I understand through this certification the student researcher is qualified to supervise exercise, as well as trained to administer proper spotting techniques during balancing exercises. I understand potential risks within the SRC program may include physical deconditioning due to rest. Additionally, I understand if I do not adhere to the assigned rest recommendations it is possible I may experience an onset of symptoms due to activity. I understand I will be accounted provided with coping strategies in the educational material provided to me at the beginning of the study to account for this.

I understand the full extent of potential benefits to participating in this study are unknown at this time. I understand the goal of this study is to gain information about are there are any benefits of an exercise-based program versus a rest-based program, or vice versa. I understand it is the hope of the research team that participation will help alleviate my symptoms as a result of either a SRC or AEB program. However, I understand it is also possible that my symptoms will remain the same or worsen. I understand by participating in this study I will be benefit future patients with PCS. I understand that the information gained from this study will guide future research in order to develop a safe an effective method to rehabilitate PCS.

I understand that my participation in this study is voluntary and that I may choose to leave the study at any time. I also understand that my identity will remain anonymous and all data will be kept strictly confidential. Only Josh McGeown and Dr. Paolo Sanzo will have access to my information. No characteristics that could identify will be used in the final report, or in the presentation of the results. The data will be securely stored in the office of Dr. Paolo Sanzo for a period of five years.I understand that I will be provided with a copy of my results at the completion of the study, if requested.

_____	_____
Participant Signature	Date
_____	_____
Legal Guardian Signature	Date
_____	_____
Witness	Date

If you wish to receive a copy of your results upon completion of the study please provide a phone number or email address so you can be contacted._____

Appendix E
Example of SCAT-3

SCAT3™

Sport Concussion Assessment Tool – 3rd Edition

For use by medical professionals only

Name | Date/Time of Injury: | Date of Assessment: | Examiner:

What is the SCAT3?[1]

The SCAT3 is a standardized tool for evaluating injured athletes for concussion and can be used in athletes aged from 13 years and older. It supersedes the original SCAT and the SCAT2 published in 2005 and 2009, respectively[2]. For younger persons, ages 12 and under, please use the Child SCAT3. The SCAT3 is designed for use by medical professionals. If you are not qualified, please use the Sport Concussion Recognition Tool[1]. Preseason baseline testing with the SCAT3 can be helpful for interpreting post-injury test scores.

Specific instructions for use of the SCAT3 are provided on page 3. If you are not familiar with the SCAT3, please read through these instructions carefully. This tool may be freely copied in its current form for distribution to individuals, teams, groups and organizations. Any revision or any reproduction in a digital form requires approval by the Concussion in Sport Group.

NOTE: The diagnosis of a concussion is a clinical judgment, ideally made by a medical professional. The SCAT3 should not be used solely to make, or exclude, the diagnosis of concussion in the absence of clinical judgement. An athlete may have a concussion even if their SCAT3 is "normal".

What is a concussion?

A concussion is a disturbance in brain function caused by a direct or indirect force to the head. It results in a variety of non-specific signs and/or symptoms (some examples listed below) and most often does not involve loss of consciousness. Concussion should be suspected in the presence of **any one or more** of the following:

- Symptoms (e.g., headache), or
- Physical signs (e.g., unsteadiness), or
- Impaired brain function (e.g. confusion) or
- Abnormal behaviour (e.g., change in personality).

SIDELINE ASSESSMENT

Indications for Emergency Management

NOTE: A hit to the head can sometimes be associated with a more serious brain injury. Any of the following warrants consideration of activating emergency procedures and urgent transportation to the nearest hospital:

- Glasgow Coma score less than 15
- Deteriorating mental status
- Potential spinal injury
- Progressive, worsening symptoms or new neurologic signs

Potential signs of concussion?

If any of the following signs are observed after a direct or indirect blow to the head, the athlete should stop participation, be evaluated by a medical professional and **should not be permitted to return to sport the same day** if a concussion is suspected.

Any loss of consciousness?	Y	N
"If so, how long?"		
Balance or motor incoordination (stumbles, slow/laboured movements, etc.)?	Y	N
Disorientation or confusion (inability to respond appropriately to questions)?	Y	N
Loss of memory:	Y	N
"If so, how long?"		
"Before or after the injury?"		
Blank or vacant look:	Y	N
Visible facial injury in combination with any of the above:	Y	N

1 Glasgow coma scale (GCS)

Best eye response (E)	
No eye opening	1
Eye opening in response to pain	2
Eye opening to speech	3
Eyes opening spontaneously	4
Best verbal response (V)	
No verbal response	1
Incomprehensible sounds	2
Inappropriate words	3
Confused	4
Oriented	5
Best motor response (M)	
No motor response	1
Extension to pain	2
Abnormal flexion to pain	3
Flexion/Withdrawal to pain	4
Localizes to pain	5
Obeys commands	6
Glasgow Coma score (E + V + M)	of 15

GCS should be recorded for all athletes in case of subsequent deterioration.

2 Maddocks Score[3]

"I am going to ask you a few questions, please listen carefully and give your best effort."

Modified Maddocks questions (1 point for each correct answer)

What venue are we at today?	0	1
Which half is it now?	0	1
Who scored last in this match?	0	1
What team did you play last week/game?	0	1
Did your team win the last game?	0	1
Maddocks score		of 5

Maddocks score is validated for sideline diagnosis of concussion only and is not used for serial testing.

Notes: Mechanism of Injury ("tell me what happened"?):

Any athlete with a suspected concussion should be REMOVED FROM PLAY, medically assessed, monitored for deterioration (i.e., should not be left alone) and should not drive a motor vehicle until cleared to do so by a medical professional. No athlete diagnosed with concussion should be returned to sports participation on the day of Injury.

BACKGROUND

Name: _____ Date: _____

Examiner: _____

Sport/team/school: _____ Date/time of injury: _____

Age: _____ Gender: ☐ M ☐ F

Years of education completed: _____

Dominant hand: ☐ right ☐ left ☐ neither

How many concussions do you think you have had in the past? _____

When was the most recent concussion? _____

How long was your recovery from the most recent concussion? _____

Have you ever been hospitalized or had medical imaging done for a head injury? ☐ Y ☐ N

Have you ever been diagnosed with headaches or migraines? ☐ Y ☐ N

Do you have a learning disability, dyslexia, ADD/ADHD? ☐ Y ☐ N

Have you ever been diagnosed with depression, anxiety or other psychiatric disorder? ☐ Y ☐ N

Has anyone in your family ever been diagnosed with any of these problems? ☐ Y ☐ N

Are you on any medications? If yes, please list: ☐ Y ☐ N

SCAT3 to be done in resting state. Best done 10 or more minutes post excercise.

SYMPTOM EVALUATION

3 How do you feel?

"You should score yourself on the following symptoms, based on how you feel now".

	none	mild		moderate		severe	
Headache	0	1	2	3	4	5	6
"Pressure in head"	0	1	2	3	4	5	6
Neck Pain	0	1	2	3	4	5	6
Nausea or vomiting	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Blurred vision	0	1	2	3	4	5	6
Balance problems	0	1	2	3	4	5	6
Sensitivity to light	0	1	2	3	4	5	6
Sensitivity to noise	0	1	2	3	4	5	6
Feeling slowed down	0	1	2	3	4	5	6
Feeling like "in a fog"	0	1	2	3	4	5	6
"Don't feel right"	0	1	2	3	4	5	6
Difficulty concentrating	0	1	2	3	4	5	6
Difficulty remembering	0	1	2	3	4	5	6
Fatigue or low energy	0	1	2	3	4	5	6
Confusion	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
Trouble falling asleep	0	1	2	3	4	5	6
More emotional	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6
Nervous or Anxious	0	1	2	3	4	5	6

Total number of symptoms (Maximum possible 22) _____

Symptom severity score (Maximum possible 132) _____

Do the symptoms get worse with physical activity? ☐ Y ☐ N

Do the symptoms get worse with mental activity? ☐ Y ☐ N

☐ self rated ☐ self rated and clinician monitored

☐ clinician interview ☐ self rated with parent input

Overall rating: If you know the athlete well prior to the injury, how different is the athlete acting compared to his/her usual self?

Please circle one response:

no different | very different | unsure | N/A

Scoring on the SCAT3 should not be used as a stand-alone method to diagnose concussion, measure recovery or make decisions about an athlete's readiness to return to competition after concussion. Since signs and symptoms may evolve over time, it is important to consider repeat evaluation in the acute assessment of concussion.

COGNITIVE & PHYSICAL EVALUATION

4 Cognitive assessment

Standardized Assessment of Concussion (SAC)[4]

Orientation (1 point for each correct answer)

What month is it?	0	1
What is the date today?	0	1
What is the day of the week?	0	1
What year is it?	0	1
What time is it right now? (within 1 hour)	0	1
Orientation score		of 5

Immediate memory

List	Trial 1		Trial 2		Trial 3		Alternative word list		
elbow	0	1	0	1	0	1	candle	baby	finger
apple	0	1	0	1	0	1	paper	monkey	penny
carpet	0	1	0	1	0	1	sugar	perfume	blanket
saddle	0	1	0	1	0	1	sandwich	sunset	lemon
bubble	0	1	0	1	0	1	wagon	iron	insect
Total									

Immediate memory score total of 15

Concentration: Digits Backward

List	Trial 1		Alternative digit list		
4-9-3	0	1	6-2-9	5-2-6	4-1-5
3-8-1-4	0	1	3-2-7-9	1-7-9-5	4-9-6-8
6-2-9-7-1	0	1	1-5-2-8-6	3-8-5-2-7	6-1-8-4-3
7-1-8-4-6-2	0	1	5-3-9-1-4-8	8-3-1-9-6-4	7-2-4-8-5-6
Total of 4					

Concentration: Month in Reverse Order (1 pt. for entire sequence correct)

Dec-Nov-Oct-Sept-Aug-Jul-Jun-May-Apr-Mar-Feb-Jan	0	1
Concentration score		of 5

5 Neck Examination:

Range of motion Tenderness Upper and lower limb sensation & strength

Findings: _____

6 Balance examination

Do one or both of the following tests.

Footwear (shoes, barefoot, braces, tape, etc.) _____

Modified Balance Error Scoring System (BESS) testing[5]

Which foot was tested (i.e. which is the **non-dominant** foot) ☐ Left ☐ Right

Testing surface (hard floor, field, etc.) _____

Condition

Double leg stance:	Errors
Single leg stance (non-dominant foot):	Errors
Tandem stance (non-dominant foot at back):	Errors

And / Or

Tandem gait[6,7]

Time (best of 4 trials): _____ seconds

7 Coordination examination

Upper limb coordination

Which arm was tested: ☐ Left ☐ Right

Coordination score of 1

8 SAC Delayed Recall[4]

Delayed recall score of 5

INSTRUCTIONS

Words in *Italics* throughout the SCAT3 are the instructions given to the athlete by the tester.

Symptom Scale

"You should score yourself on the following symptoms, based on how you feel now".

To be completed by the athlete. In situations where the symptom scale is being completed after exercise, it should still be done in a resting state, at least 10 minutes post exercise.

For total number of symptoms, maximum possible is 22.

For Symptom severity score, add all scores in table, maximum possible is 22 x 6 = 132.

SAC[4]

Immediate Memory

"I am going to test your memory. I will read you a list of words and when I am done, repeat back as many words as you can remember, in any order."

Trials 2 & 3:

"I am going to repeat the same list again. Repeat back as many words as you can remember in any order, even if you said the word before."

Complete all 3 trials regardless of score on trial 1 & 2. Read the words at a rate of one per second. **Score 1 pt. for each correct response.** Total score equals sum across all 3 trials. Do not inform the athlete that delayed recall will be tested.

Concentration

Digits backward

"I am going to read you a string of numbers and when I am done, you repeat them back to me backwards, in reverse order of how I read them to you. For example, if I say 7-1-9, you would say 9-1-7."

If correct, go to next string length. If incorrect, read trial 2. **One point possible for each string length.** Stop after incorrect on both trials. The digits should be read at the rate of one per second.

Months in reverse order

"Now tell me the months of the year in reverse order. Start with the last month and go backward. So you'll say December, November … Go ahead"

1 pt. for entire sequence correct

Delayed Recall

The delayed recall should be performed after completion of the Balance and Coordination Examination.

"Do you remember that list of words I read a few times earlier? Tell me as many words from the list as you can remember in any order."

Score 1 pt. for each correct response

Balance Examination

Modified Balance Error Scoring System (BESS) testing[5]

This balance testing is based on a modified version of the Balance Error Scoring System (BESS)[5]. A stopwatch or watch with a second hand is required for this testing.

"I am now going to test your balance. Please take your shoes off, roll up your pant legs above ankle (if applicable), and remove any ankle taping (if applicable). This test will consist of three twenty second tests with different stances."

(a) Double leg stance:

"The first stance is standing with your feet together with your hands on your hips and with your eyes closed. You should try to maintain stability in that position for 20 seconds. I will be counting the number of times you move out of this position. I will start timing when you are set and have closed your eyes."

(b) Single leg stance:

"If you were to kick a ball, which foot would you use? [This will be the dominant foot] Now stand on your non-dominant foot. The dominant leg should be held in approximately 30 degrees of hip flexion and 45 degrees of knee flexion. Again, you should try to maintain stability for 20 seconds with your hands on your hips and your eyes closed. I will be counting the number of times you move out of this position. If you stumble out of this position, open your eyes and return to the start position and continue balancing. I will start timing when you are set and have closed your eyes."

(c) Tandem stance:

"Now stand heel-to-toe with your non-dominant foot in back. Your weight should be evenly distributed across both feet. Again, you should try to maintain stability for 20 seconds with your hands on your hips and your eyes closed. I will be counting the number of times you move out of this position. If you stumble out of this position, open your eyes and return to the start position and continue balancing. I will start timing when you are set and have closed your eyes."

Balance testing – types of errors

1. Hands lifted off iliac crest
2. Opening eyes
3. Step, stumble, or fall
4. Moving hip into > 30 degrees abduction
5. Lifting forefoot or heel
6. Remaining out of test position > 5 sec

Each of the 20-second trials is scored by counting the errors, or deviations from the proper stance, accumulated by the athlete. The examiner will begin counting errors only after the individual has assumed the proper start position. **The modified BESS is calculated by adding one error point for each error during the three 20-second tests. The maximum total number of errors for any single condition is 10.** If a athlete commits multiple errors simultaneously, only one error is recorded but the athlete should quickly return to the testing position, and counting should resume once subject is set. Subjects that are unable to maintain the testing procedure for a minimum of **five seconds** at the start are assigned the highest possible score, ten, for that testing condition.

OPTION: For further assessment, the same 3 stances can be performed on a surface of medium density foam (e.g., approximately 50 cm x 40 cm x 6 cm).

Tandem Gait[6,7]

Participants are instructed to stand with their feet together behind a starting line (the test is best done with footwear removed). Then, they walk in a forward direction as quickly and as accurately as possible along a 38mm wide (sports tape), 3 meter line with an alternate foot heel-to-toe gait ensuring that they approximate their heel and toe on each step. Once they cross the end of the 3m line, they turn 180 degrees and return to the starting point using the same gait. A total of 4 trials are done and the best time is retained. Athletes should complete the test in 14 seconds. Athletes fail the test if they step off the line, have a separation between their heel and toe, or if they touch or grab the examiner or an object. In this case, the time is not recorded and the trial repeated, if appropriate.

Coordination Examination

Upper limb coordination

Finger-to-nose (FTN) task:

"I am going to test your coordination now. Please sit comfortably on the chair with your eyes open and your arm (either right or left) outstretched (shoulder flexed to 90 degrees and elbow and fingers extended), pointing in front of you. When I give a start signal, I would like you to perform five successive finger to nose repetitions using your index finger to touch the tip of the nose, and then return to the starting position, as quickly and as accurately as possible."

Scoring: 5 correct repetitions in < 4 seconds = 1

Note for testers: Athletes fail the test if they do not touch their nose, do not fully extend their elbow or do not perform five repetitions. **Failure should be scored as 0.**

References & Footnotes

1. This tool has been developed by a group of international experts at the 4th International Consensus meeting on Concussion in Sport held in Zurich, Switzerland in November 2012. The full details of the conference outcomes and the authors of the tool are published in The BJSM Injury Prevention and Health Protection, 2013, Volume 47, Issue 5. The outcome paper will also be simultaneously co-published in other leading biomedical journals with the copyright held by the Concussion in Sport Group, to allow unrestricted distribution, providing no alterations are made.

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ATHLETE INFORMATION

Any athlete suspected of having a concussion should be removed from play, and then seek medical evaluation.

Signs to watch for

Problems could arise over the first 24–48 hours. The athlete should not be left alone and must go to a hospital at once if they:

- Have a headache that gets worse
- Are very drowsy or can't be awakened
- Can't recognize people or places
- Have repeated vomiting
- Behave unusually or seem confused; are very irritable
- Have seizures (arms and legs jerk uncontrollably)
- Have weak or numb arms or legs
- Are unsteady on their feet; have slurred speech

Remember, it is better to be safe.
Consult your doctor after a suspected concussion.

Return to play

Athletes should not be returned to play the same day of injury.
When returning athletes to play, they should be **medically cleared and then follow a stepwise supervised program,** with stages of progression.

For example:

Rehabilitation stage	Functional exercise at each stage of rehabilitation	Objective of each stage
No activity	Physical and cognitive rest	Recovery
Light aerobic exercise	Walking, swimming or stationary cycling keeping intensity, 70 % maximum predicted heart rate. No resistance training	Increase heart rate
Sport-specific exercise	Skating drills in ice hockey, running drills in soccer. No head impact activities	Add movement
Non-contact training drills	Progression to more complex training drills, eg passing drills in football and ice hockey. May start progressive resistance training	Exercise, coordination, and cognitive load
Full contact practice	Following medical clearance participate in normal training activities	Restore confidence and assess functional skills by coaching staff
Return to play	Normal game play	

There should be at least 24 hours (or longer) for each stage and if symptoms recur the athlete should rest until they resolve once again and then resume the program at the previous asymptomatic stage. Resistance training should only be added in the later stages.

If the athlete is symptomatic for more than 10 days, then consultation by a medical practitioner who is expert in the management of concussion, is recommended.

Medical clearance should be given before return to play.

Scoring Summary:

Test Domain	Score		
	Date: _____	Date: _____	Date: _____
Number of Symptoms of 22			
Symptom Severity Score of 132			
Orientation of 5			
Immediate Memory of 15			
Concentration of 5			
Delayed Recall of 5			
SAC Total			
BESS (total errors)			
Tandem Gait (seconds)			
Coordination of 1			

Notes:

Appendix F
Example Log Book

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Activity Log Book

Date	Describe the Activity	Duration of Activity	Symptoms brought on (try to be specific) or N/A if no symptoms	Symptom Severity from 0-6 (0 = no symptom, 6= as bad as it gets)

Appendix G
Standard Rest Care Educational Material

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Concussion.

A concussion is a complex physiological injury to the brain caused by direct or indirect force applied to the head. This force may occur as a result of 1) a direct blow to the head with a firm surface, piece of equipment, or body part; 2) an indirect blow causing a whiplash or; 3) a blow from a projectile object, such as a hockey puck.

These forces cause the brain to violently collide with the inside of the skull; the brain has a similar consistency to Jell-O, this collision causes the brain to deform against the skull. This deformation results in the bending and tearing of a number of individual brain cells. The symptoms experienced afterwards are the result of disrupted normal brain function due to these bent and torn brain cells. These tears cause a sudden release of chemicals which turns into an energy crisis within the brain. The brain needs more energy to try and repair itself, but is incapable of producing this energy due to the concussion. This makes a concussion more complicated than a structural injury like a broken bone or strained muscle.

Symptoms.

Symptoms of concussion are highly variable, no two concussion are alike. The type, amount, and direction of force in combination with the section of the head the force was applied to will impact the symptoms experienced. Symptoms are typically grouped into one of four categories: 1) Mental; 2) Physical; 3) Emotional and; 4) Sleep Disturbances. Specific symptoms for each category are listed in the table below. Symptoms may appear immediately, minutes, hours, days or weeks after the initial incident.

Summary of Common Symptoms of Concussion			
Symptoms			
Mental	Physical	Emotional	Sleep Disturbances
Confusion	Headache	Emotional lability	Trouble falling asleep
Anterograde amnesia	Dizziness	Irritability	Sleeping more than usual
Retrograde amnesia	Balance disruption	Fatigue	Sleeping less than usual
Loss of Consciousness	Nausea/vomiting	Anxiety	
Disorientation	Visual disturbances	Sadness	
Feeling "in a fog" or "zoned out"	Phonophobia		
Vacant Stare			
Inability to focus			
Delayed motor and verbal response			
Slurred/incoherent speech			
Excessive Drowsiness			

Post-Concussion Syndrome.

Under typical circumstances symptoms of concussion will resolve on their own within 7-10 days. About 20% of people who experience a concussion will experience lingering symptoms for weeks or months, this extended presence of symptoms is termed post-concussion syndrome (PCS). The reason why 20% of concussed people experience PCS is unknown, but researchers and experts suggest that normal functions of the brain, such as the ability to precisely control heart rate and blood pressure, are functionally impaired.

The primary forms of treatment of PCS have traditionally included rest and education. It is thought that rest allows the brain the opportunity to gradually heal itself without interrupting the healing process with activity or exertion that may bring on or worsen symptoms. Therefore rest has been promoted as a cornerstone for concussion management. Symptoms of PCS include any of those symptoms listed in the table above that remain beyond the typical healing period of 7-10 days.

Activities that may worsen symptoms.

As already mentioned, every concussion is unique. That being said activities that worsen symptoms will also be unique to each individual. Usually

activities that will worsen symptoms will fall into one of two categories, either cognitive (to do with mental tasks, thinking, learning, remembering, working, etc.) or physically demanding activities. Below is a list of common cognitive and physical tasks that may bring on, or worsen your symptoms.

Cognitive – School related activities such as homework, presentations and projects; work-related activities; driving; reading of things other than minor directions or instructions; significant reductions in screen time including: computer usage, video games, texting, television watching including visually intense movies/programs or athletic games; intense sensory stimulation such as loud noises or bright lights; excessive conversation or deep thought

Physical – Physical chores around the house like shovelling snow or taking out a heavy garbage bag; aerobic exercise; weight lifting; participation in sport; or any physical activity that results in sweating

As a general rule, any activity that makes you feel worse in any way should be avoided. These activities can be recorded in your log book. Listening to your body, and adjusting your activities accordingly is the best way to avoid worsening your symptoms.

Normalization of symptoms and positive expectations.

In most cases PCS will resolve within 3-6 months after experiencing the initial concussion. In more rare situations PCS may persist longer than 6 months, and in especially rare cases persist for greater than one year. In these minority of cases there are usually underlying factors that contribute to the long recovery.

Some research has shown that people with PCS may attribute all symptoms they are experiencing to PCS. For example, someone with PCS may be experiencing a headache and drowsiness and automatically attribute these symptoms to PCS because perceive these symptoms are related to the concussion they experienced. This person may have had a poor night's sleep the night before, and had a stressful day at work which may explain the drowsiness and headache. Negative expectations that all symptoms experienced must be a result of PCS has been associated with worse symptom outcomes, compared to individuals who have positive expectations that they are getting better and attributing symptoms to another logical cause. A positive mindset and understanding that you will get better as time passes may improve your day-to-day symptoms, as well as the length of time your PCS lasts for.

Coping strategies.

Rest and education have been shown by some studies to be effective at improving concussion symptoms. This document is put together to educate you about the need to know information about concussion and PCS so you can be

more aware of what is happening to your brain following concussion and how to address it.

In order to give your brain the best chance to heal itself it is advised that you take part in cognitive and physical rest to the best of your ability for four weeks. Coping strategies during this period of rest include:

- ***Cognitive and physical rest:*** avoiding, limiting or modifying any of the activities listed above or that you experience that may worsen your symptoms.
- ***Planning your day:*** You may notice a specific time of day when you feel the worst. Planning your daily schedule ahead of time to include times to rest, take a nap, or take some time to yourself to give your brain a chance to rest and to avoid over stimulation.
- ***Positive expectations and mindset:*** be honest with yourself and if any symptoms you are feeling are due to PCS or could it possibly be caused by a different reason
- ***Gradually trying to increase your activity:*** As you begin to feel improvement try to gradually increase your cognitive and physical activity levels. You do not want to bring on your symptoms, if you try increasing your activity and you trigger your symptoms then lay off because this is your body telling you that your brain is not ready for what you are asking it to do. Trying to push through symptoms will not benefit you, and may actually delay your recovery in the long run.
- ***Ongoing adjustments:*** You may experience different symptoms and severity of symptoms day to day. Adjust your activity and rest levels accordingly in order for you to feel as comfortable and symptom free as possible. Adhering to cognitive and physical rest should result in your symptoms progressively being decreased.

Appendix H
Exercise Progressions Template

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Week 1	Session 1 **Aerobic Exercise** *Intensity:*20% Target Heart Rate *Duration:*20 min **Balance Training** *Duration:*15 sec *Surface:* Firm *Eyes:* Open	Session 2 **Aerobic Exercise** *Intensity:*20% Target Heart Rate *Duration:*20 min **Balance Training** *Duration:*15 sec *Surface:* Firm *Eyes:* Open	Session 3 **Aerobic Exercise** *Intensity:* 20% Target Heart Rate *Duration:*20 min **Balance Training** *Duration:*15 sec *Surface:* Firm *Eyes:* Open
Week 2	Session 4 **Aerobic Exercise** *Intensity:*30% Target Heart Rate *Duration:* 25 min **Balance Training** *Duration:*15 sec *Surface:* Foam *Eyes:* Open	Session 5 **Aerobic Exercise** *Intensity:*30% Target Heart Rate *Duration:*25 min **Balance Training** *Duration:*15 sec *Surface:* Foam *Eyes:* Open	Session 6 **Aerobic Exercise** *Intensity:* 30% Target Heart Rate *Duration:* 25 min **Balance Training** *Duration:*15 sec *Surface:* Foam *Eyes:* Open
Week 3	Session 7 **Aerobic Exercise** *Intensity:* 40% Target Heart Rate *Duration:* 30 min **Balance Training** *Duration:* 20 sec *Surface:* Firm *Eyes:* Closed	Session 8 **Aerobic Exercise** *Intensity:* 40% Target Heart Rate *Duration:* 30 min **Balance Training** *Duration:* 20 sec *Surface:* Firm *Eyes:* Closed	Session 9 **Aerobic Exercise** *Intensity:* 40% Target Heart Rate *Duration:* 30 min **Balance Training** *Duration:* 20 sec *Surface:* Firm *Eyes:* Closed
Week 4	Session 10 **Aerobic Exercise** *Intensity:* 50% Target Heart Rate *Duration:* 35 min **Balance Training** *Duration:* 20 sec *Surface:* Foam *Eyes:* Closed	Session 11 **Aerobic Exercise** *Intensity:*50% Target Heart Rate *Duration:*35 min **Balance Training** *Duration:* 20 sec *Surface:* Foam *Eyes:* Closed	Session 12 **Aerobic Exercise** *Intensity:* 50% Target Heart Rate *Duration:*35 min **Balance Training** *Duration:* 20 sec *Surface:* Foam *Eyes:* Closed

*** If a participant experiences symptom exacerbation during any of the sessions the heart rate at which symptoms were brought on will be recorded. Subsequent sessions afterwards will have exercise intensity adjusted individually based on symptom threshold. For example, if symptoms exacerbation occurred during session 5 at a heart rate of 115 bpm, the following session exercise intensity would be adjusted to resting heart rate + 30% of the symptom threshold heart rate. This way exercise intensity should remain below the participant's symptom threshold.***

Appendix I
BESS Protocol

Balance Error Scoring System (BESS)

Developed by researchers and clinicians at the University of North Carolina's Sports Medicine Research Laboratory, Chapel Hill, NC 27599-8700

The Balance Error Scoring System provides a portable, cost-effective, and objective method of assessing static postural stability. In the absence of expensive, sophisticated postural stability assessment tools, the BESS can be used to assess the effects of mild head injury on static postural stability. Information obtained from this clinical balance tool can be used to assist clinicians in making return to play decisions following mild head injury.

The BESS can be performed in nearly any environment and takes approximately 10 minutes to conduct.

Materials

1) Testing surfaces
   -two testing surfaces are need to complete the BESS test: floor/ground and foam pad.

   1a) Floor/Ground: Any level surface is appropriate.

   1b) Foam Pad (Power Systems Airex Balance Pad 81000)
   Address = PO Box 31709 Knoxville, TN 37930 tel = 1-800-321-6975
   Web Address = www.power-systems.com

   Dimensions: Length: 10"
   Width: 10"
   Height: 2.5"

   The purpose of the foam pad is to create an unstable surface and a more challenging balance task, which varies by body weight. It has been hypothesized that as body weight increases the foam will deform to a greater degree around the foot. The heavier the person the more the foam will deform. As the foam deforms around the foot, there is an increase in support on the lateral surfaces of the foot. The increased contact area between the foot and foam has also been theorized to increase the tactile sense of the foot, also helping to increase postural stability. The increase in tactile sense will cause additional sensory information to be sent to the CNS. As the brain processes this information it can make better decisions when responding to the unstable foam surface.

2) Stop watch
   -necessary for timing the subjects during the 6, twenty second trials

3) An assistant to act as a spotter
   -the spotter is necessary to assist the subject should they become unstable and begin to fall. The spotter's attention is especially important during the foam surface.

4) BESS Testing Protocol
   -these instructions should be read to the subject during administration of the BESS

5) BESS Score Card

(the Testing Protocol and a sample Score Card are located at the end of this document)

BESS Test Administration

1) Before administering the BESS, the following materials should be present:
   -foam pad
   -stop watch
   -spotter
   -BESS Testing Protocol
   -BESS Score Card
2) Before testing, instruct the individual to remove shoes and any ankle taping if necessary. Socks may be worn if desired.
3) Read the instructions to the subject as they are written in the BESS Testing Protocol.
4) Record errors on the BESS Score Card as they are described below.

Scoring the BESS

Each of the twenty-second trials is scored by counting the errors, or deviations from the proper stance, accumulated by the subject. The examiner will begin counting errors only after the individual has assumed the proper testing position.

Errors: An error is credited to the subject when any of the following occur:

- moving the hands off of the iliac crests
- opening the eyes
- step stumble or fall
- abduction or flexion of the hip beyond 30°
- lifting the forefoot or heel off of the testing surface
- remaining out of the proper testing position for greater than 5 seconds

-The maximum total number of errors for any single condition is 10.

Normal Scores for Each Possible Testing Surface

	Firm Surface	Foam Surface	
Double Leg Stance	.009 ± .12	.33 ± .90	
Single Leg Stance	2.45 ± 2.33	5.06 ± 2.80	
Tandem Stance	.91 ± 1.36	3.26 ± 2.62	
Surface Total	3.37 ± 3.10	8.65 ± 5.13	
BESS Total Score			12.03 ± 7.34

Maximum Number of Errors Possible for Each Testing Surface

	Firm Surface	Foam Surface
Double Leg Stance	10	10
Single Leg Stance	10	10
Tandem Stance	10	10
Surface Total	30	30

-if a subject commits multiple errors simultaneously, only one error is recorded. For example, if an individual steps or stumbles, opens their eyes, and removes their hands from their hips simultaneously, then they are credited with only **one error**.
-subjects that are unable to maintain the testing procedure for a minimum of **five seconds** are assigned the highest possible score, ten, for that testing condition.

FIRM / GROUND TESTING POSITIONS

Double leg stance: Standing on a firm surface with feet side by side (touching), hands on the hips and eyes closed

Single leg stance: Standing on a firm surface on the non-dominant foot (defined below), the hip is flexed to approximately 30° and knee flexed to approximately 45°. Hands are on the hips and eyes closed.

Non-Dominant Leg: The non-dominant leg is defined as the opposite leg of the preferred kicking leg

Tandem Stance: Standing heel to toe on a firm surface with the non-dominate foot (defined above) in the back. Heel of the dominant foot should be touching the toe of the non-dominant foot. Hands are on the hips and their eyes are closed.

FOAM TESTING POSITIONS

Double leg stance: Standing on a foam surface with feet side by side (touching), with hands on the hips and eyes closed

Single leg stance: Standing on a foam surface on the non-dominant foot (defined below), with hip flexed to approximately 30° and knee flexed to approximately 45°. Hands are on the hips and eyes closed.

Non-Dominant Leg: The non-dominant leg is defined as the leg opposite of the preferred kicking leg

Tandem Stance: Standing heel to toe on a foam surface with the non-dominant foot (defined above) in the back. Heel of the dominant foo should be touching the toe of the non-dominant foot. Hands are on th hips and their eyes are closed.

WARNING: Trained personnel should always be present when administering the BESS protocol. Improper use of the foam could result in injury to the test subject.

Script for the BESS Testing Protocol

Direction to the subject: *I am now going to test your balance.*

Please take your shoes off, roll up your pant legs above ankle (if applicable), and remove any ankle taping (if applicable).

This test will consist of 6 - twenty second tests with three different stances on two different surfaces. I will describe the stances as we go along.

DOUBLE LEG STANCE:

Direction to the subject: *The first stance is standing with your feet together like this* [administrator demonstrates two-legged stance]

You will be standing with your hands on your hips with your eyes closed. You should try to maintain stability in that position for entire 20 seconds. I will be counting the number of times you move out of this position. For example: if you take your hands off your hips, open your eyes, take a step, lift your toes or your heels. If you do move out of the testing stance, simply open your eyes, regain your balance, get back into the testing position as quickly as possible, and close your eyes again.

There will be a person positioned by you to help you get into the testing stance and to help if you lose your balance.

Direction to the spotter: *You are to assist the subject if they fall during the test and to help them get back into the position.*

Direction to the subject: *Put your feet together, put your hands on your hips and when you close your eyes the testing time will begin*

[Start timer when subject closes their eyes]

SINGLE LEG STANCE:

Direction to subject: *If you were to kick a ball, which foot would you use?* [This will be the **dominant** foot]

*Now stand on your **non-dominant** foot.*

[Before continuing the test assess the position of the dominant leg as such: the dominant leg should be held in approximately 30 degrees of hip flexion and 45 degrees of knee flexion]

Again, you should try to maintain stability for 20 seconds with your eyes closed. I will be counting the number of times you move out of this position.

Place your hands on your hips. When you close your eyes the testing time will begin.

[Start timer when subject closes their eyes]

Direction to the spotter: *You are to assist the subject if they fall during the test and to help them get back into the position.*

TANDEM STANCE:

Directions to the subject: *Now stand heel-to-toe with your* **non-dominant** *foot in back. Your weight should be evenly distributed across both feet.*

Again, you should try to maintain stability for 20 seconds with your eyes closed. I will be counting the number of times you move out of this position.

Place your hands on your hips. When you close your eyes the testing time will begin.

[Start timer when subject closes their eyes]

Direction to the spotter: *You are to assist the subject if they fall during the test and to help them get back into the position.*

*** **Repeat each set of instructions for the foam pad**

Score Card

Balance Error Scoring System (BESS)
(Guskiewicz)

Balance Error Scoring System – Types of Errors
1. Hands lifted off iliac crest 2. Opening eyes 3. Step, stumble, or fall 4. Moving hip into > 30 degrees abduction 5. Lifting forefoot or heel 6. Remaining out of test position >5 sec
The BESS is calculated by adding one error point for each error during the 6 20-second tests.

SCORE CARD: (# errors)	FIRM Surface	FOAM Surface
Double Leg Stance (feet together)		
Single Leg Stance (non-dominant foot)		
Tandem Stance (non-dom foot in back)		
Total Scores:		

BESS TOTAL:

Which **foot** was tested: ☐ Left ☐ Right
(i.e. which is the **non-dominant** foot)

Appendix J
Exercise Session Record Log

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Date	Session Number	Heart Rate Intensity	Aerobic Exercise Duration	Balance Duration	Comments

Appendix K
Cool Down Stretches

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Thoracic Spine Stretch *

Hamstring Stretch *

Glute Stretch *

Hip Flexor Stretch *

Lat Stretch *

Chest Stretch *

Quadriceps Stretch *

(Images adapted from Google Images)