2020

A Longitudinal Examination of Biomechanical Balance and Quantitative Multidomain Assessments During Recovery Following Sport-Related Concussion

Moira Kate Pyrhoda
University of Denver

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Abstract

Sport-related concussion is an inherent risk to athlete health in contact and collision sports. Both short- and long-term risks are associated with the injury. Short-term, athletes may develop post-concussion syndrome (PCS), the persistence of cognitive, physical, and emotional symptoms for weeks or months after injury. Athletes who return to play (RTP) prematurely are at increased risk for lower extremity injury and repeated concussion injuries. Long-term, history of multiple concussions have been linked to neurodegenerative diseases. Due to these risks, concussion assessments must be sensitive to the injury and useful in the diagnosis, recovery, and RTP phases of the injury.

Sideline clinical assessments for symptoms, balance, and neurocognition among other domains are utilized to meet the recommendation for a multidomain approach to concussion assessment. Particularly in balance testing, there is concern that standard observational sideline tests do not measure lasting balance deficits for more than three days post-injury. Biomechanical balance measures appear to longitudinally assess sensory integration capabilities of concussed athletes better than clinical observational scoring. This dissertation measured the sensitivity of biomechanical balance measures to concussion longitudinally in athletes up to 6 months post-injury, and in athletes reporting a history of concussion. Sensitive biomechanical balance measures were then assessed in multidomain logistic regression models to determine the most longitudinally sensitive combination of multidomain assessments to concussion.

A combined cohort of 186 National Collegiate Athletic Association (NCAA) Division I (DI) athletes at the University of Denver participated in this research. Each athlete participated in an extensive data collection, including instrumented standing and functional balance tasks, neurocognitive assessment, oculomotor assessment, vestibular-ocular assessment, a blood draw, and symptom scoring. Specific Aim 1 assessed the discriminative ability and sensitivity to concussion of linear measures of biomechanical balance in a comparison of non-concussed athletes to concussed athletes tracked longitudinally up to 6 months post-injury. Specific Aim 2 evaluated group differences between non-concussed athletes and those with a documented history of concussion more than 6 months post-injury of linear and nonlinear measures of biomechanical balance. Specific Aim 3 evaluated the longitudinally sensitive and discriminatory measures of biomechanical balance from Aim 1 in multidomain logistic regression models to determine the most longitudinally sensitive combination of multidomain assessments.

Together, these Specific Aims indicate that linear measures of COP velocity in standing balance discriminate well between non-concussed and acutely concussed athletes and are longitudinally sensitive to concussion up to 6 months post-injury. These measures also show deficits in athletes with a history of concussion, indicating a potential lack of vestibular and sensorimotor integration recovery leading to reduced neuromuscular functioning. Lastly, these measures on their own generate a model that is longitudinally sensitive to concussion and may aid in concussion recovery, rehabilitation, and RTP decision making.

Document Type

Dissertation

Degree Name

Ph.D.

Department
Engineering

First Advisor
Bradley S. Davidson

Second Advisor
Kim Gorgens

Third Advisor
Kevin Shelburne

Keywords
Post-concussion syndrome, Return to play, Assessment

Subject Categories
Biomechanics and Biotransport | Biomedical Engineering and Bioengineering | Engineering

A LONGITUDINAL EXAMINATION OF BIOMECHANICAL BALANCE AND QUANTITATIVE MULTIDOMAIN ASSESSMENTS DURING RECOVERY FOLLOWING SPORT-RELATED CONCUSSION

A Dissertation

Presented to

the Faculty of the Daniel Felix Ritchie School of Engineering and Computer Science

University of Denver

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

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by

Moira Kate Pryhoda

June 2020

Advisor: Bradley S. Davidson, PhD

Author: Moira Kate Pryhoda
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Degree Date: June 2020

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ACKNOWLEDGMENTS

I would like to thank my advisor, Dr. Bradley Davidson, for his unwavering support of and immeasurable role in my academic and professional growth over the past four years. Dr. Davidson is a constant source of insight and intellect while extending me the patience and freedom to learn and grow as a researcher. I would also like to thank my committee members. Dr. Kim Gorgens, your enthusiasm and support of my research has been instrumental in inspiring me to do great work. Dr. Kevin Shelburne, thank you for your constant mentorship, steady guidance, and valued perspective. Dr. Peter Laz, I am grateful to you for your prominent role in providing me with a solid academic foundation. Dr. Lotta Granholm-Bentley, your vision for the concussion study is extensive and exciting. Thank you for your guidance on the biological and theoretical aspects of concussion.

I would also like to thank Julie Campbell and her expert team of the athletic trainers, the DU NCAA coaches, and the participating athletes. This work would not be possible without your support and collaboration. Thank you for your extensive efforts in making this project a success. I sincerely hope this work has a positive impact on the health of your athletes.

Several research assistants and undergraduate students were the backbone of this work, assisting in athlete recruitment and data collections. Your countless hours of effort are deeply appreciated. Lastly, I would like to extend a heartfelt thank you to the D'Ambrosia family, without whom I would not be here. Thank you for your unnecessary yet steadfast support of me and my professional goals. I am forever grateful to you for introducing this coach to sport biomechanics.

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CHAPTER 1: INTRODUCTION

Up to 3.8 million sport-related concussions are diagnosed annually in the United States alone, and estimations suggest that only 50% of concussions are reported (Harmon *et al.* 2013). With a host of potential short-term physical, emotional, and psychological symptoms, together defined as post-concussion syndrome (PCS; Harmon *et al.*, 2013), a higher risk of lower extremity injury and repeated concussion after return to play (RTP; McCrea *et al.*, 2020; Herman *et al.*, 2017; Harada *et al.*, 2019), as well as links to long-term neurodegenerative diseases including chronic traumatic encephalopathy (CTE; Baugh *et al.*, 2012), concussive injury is an ongoing safety issue in athletics. The National Collegiate Athletic Association (NCAA) adopted its Concussion Policy and Legislation in 2010 (Buckley *et al.*, 2017), which recommends that athletes participate in a brain injury and concussion history survey, symptom evaluation, cognitive assessment, and balance evaluation before participation in a collegiate sport. These assessments must be both sensitive to the initial injury and in the recovery, rehabilitation, and RTP phases post-concussion.

Concussion is a complex injury, which may result in direct or indirect damage to the central or peripheral nervous system, including connections to the cerebellum, where unconscious movement information is processed. Here, we propose that biomechanical standing balance measures are sensitive indicators of concussion based on the theory that two of the three standing balance sensory inputs, the vestibular and proprioceptive systems, have direct inputs to the cerebellum, the pathways of which may be injured in concussion (McLeod & Hale, 2015, Hurtubise *et al.*, 2020, Hirad *et al.*, 2019). Healthy balance output relies on the normal functioning of at least two sensory systems (Goldberg 2000). Standing balance tasks typically include an eyes-closed portion, eliminating the visual system, which is the only sensory system used in balancing that does not have a direct input to the cerebellum. With this impairment, standing balance tasks may be useful in determining if the connections to the cerebellum are compromised, and if the vestibular and proprioceptive systems have deficits that prevent normal neuromuscular functioning and an accurate balance response.

The NCAA typically uses the Balance Error Scoring System (BESS) to evaluate standing balance, which is a series of six eyes-closed balance tasks consisting of three stances on both hard and foam surfaces. Evaluators count the number of pre-defined errors, up to 10, that occur during each 20-second stance. Learning effects are a concern with the BESS test (Mulligan *et al.*, 2013), and studies also show that the total BESS score is unreliable and lacks sensitivity to concussion (Finnoff *et al.*, 2009). Biomechanical balance measures may have more potential as sensitive indicators of concussion. Measures of standing balance are significantly different from non-concussed athletes acutely post-concussion (e.g. Powers *et al.*, 2014; Rochefort *et al.*, 2017; Thompson *et al.*, 2017; Wood *et al.*, 2019) and to documented history of concussion (e.g. Buckley *et al.*, 2016; De Beaumont *et al.*, 2011; Schmidt *et al.*, 2018; Sosnoff *et al.*, 2011).

The objective of this work is to establish biomechanical balance as a sensitive indicator of the short- and long-term deficits present in medically-diagnosed concussion to improve multidomain clinical concussion diagnosis, recovery, rehabilitation, and RTP protocols. Three specific aims accomplish this objective:

Specific Aim 1: Assess the discriminative ability and sensitivity to concussion of linear measures of biomechanical balance in a comparison of non-concussed athletes to concussed athletes tracked longitudinally up to 6 months post-injury.

Specific Aim 2: Evaluate group differences of linear and nonlinear measures of biomechanical balance between non-concussed athletes and those with a documented history of concussion more than 6 months post-injury.

Specific Aim 3: Evaluate the longitudinally sensitive and discriminatory measures of biomechanical balance (Aim 1) in multidomain logistic regression models to determine the most longitudinally sensitive combination of multidomain assessments.

1.1 Importance and Impact

Athlete health is paramount in the sports industry. Due to the emotional and competitive nature of high-level sports participation, athletes who underreport symptoms in favor of returning to play sooner, or coaches who may have difficulty objectively assessing a concussed athlete during gameplay may unintentionally influence subjective concussion diagnosis (Voss *et al.*, 2015). With the availability of quickly administered, objective, and longitudinally sensitive measures, athletes may have a higher chance of receiving a proper diagnosis. They may also enter recovery, rehabilitation, and RTP protocols faster, leading to fewer short- and long-term complications post-injury (McCrea *et al.*, 2020). Biomechanical measures of standing balance provide an opportunity for objective assessment (Horak & Mancini, 2013). Standing balance tests are quickly administered, at 30 seconds per task. Additionally, tools such as the Wii balance board are available to integrate biomechanical standing balance algorithms (Chang *et al.*, 2014) for clinical application. With the eventual creation of software that seamlessly integrates these biomechanical balance measures, coaches and athletic trainers will have the opportunity to quickly and objectively assess an athlete for concussion.

This dissertation is the first work to measure discriminative ability and sensitivity to concussion of linear measures of biomechanical standing balance. These methods help determine the clinical applicability of standing balance measures. This work is also the first to track concussed athletes up to 6 months post-concussion longitudinally. To date, most longitudinal studies terminate one to two months post-injury (e.g. Rochefort *et al.*, 2017; Parrington *et al.*, 2018), which limits the ability to track lasting balance deficits that may contribute to further injury, including lower extremity injury or repeated concussion. The use of logistic regression models in this work further assesses the applicability of biomechanical balance measures by examining the performance of balance within various multidomain assessment models. Clinical translation of data is crucial, and this work takes steps forward in applying standing balance research findings.

1.2 Dissertation Overview

Chapter 2 presents an overview of the current understanding of concussion in sports, including short- and long-term consequences. Mechanical and neuroanatomical theories and findings introduce the concept of using balance to fill the need for a sensitive indicator of concussion. **Chapter 3** provides a narrative review of clinical and biomechanical standing and functional balance assessments evaluated for use with concussion cohorts, and recommendations for the clinical application of the research findings. **Chapter 4** provides a detailed assessment of the methods used to obtain biomechanical balance measures and the statistics used to draw conclusions in the forthcoming experimental chapters. Using the foundational knowledge established in Chapters 2-4, Chapters 5-7 are experimental investigations. **Chapter 5** establishes discriminative and sensitive biomechanical standing balance measures in athletes tracked longitudinally up to 6 months post-concussion (**Specific Aim 1**). **Chapter 6** determines group differences of biomechanical standing balance measures between athletes with a reported history of concussion sport-matched to their teammates with no history of concussion (**Specific Aim 2**). **Chapter 7** evaluates the longitudinally sensitive and discriminatory measures of biomechanical balance from Chapter 5 in multidomain logistic regression models to determine the best performing combination of multidomain assessments (**Specific Aim 3**). **Chapter 8** provides conclusions of the main findings, limitations, and recommendations for future research. The appendices provide additional data and information. **Appendix A** provides calculated effect sizes for studies included in the narrative review. **Appendix B** and **Appendix C** include full sets of results for Aim 1 and Aim 2, respectively. **Appendix D** contains raw data for Aim 3. **Appendix E** provides the full data collection sheet, the script used for testing sessions, and scoring instructions.

CHAPTER 2: DEFINITION, REVIEW OF CONCUSSION IN SPORT AND SUPPORT FOR BALANCE AS A SENSITIVE INDICATOR OF CONCUSSION

2.1 Definition, demographics, and epidemiology

2.1.1 Traumatic brain injury

A traumatic brain injury (TBI) is defined as a change in brain function following a traumatic force (Menon *et al.*, 2010). This injury typically occurs when a sudden, external force is applied to the head directly, or indirectly through an impulse force traveling to the brain that disrupts structural characteristics of the brain and causes impairment of brain function (Kazl & Torres, 2019). The most common mechanism for acquiring a TBI is age-dependent; motor vehicle accidents and assaults are the most common mechanism between ages 15-65, and falls are the most common mechanism under 15 years of age and over 65 (CDC 2013). Estimations suggest that 5.3 million Americans are living with post-TBI disabilities (Langlois *et al.*, 2006). There is robust medical data that supports proper categorization and understanding of TBI. TBI results in neurological dysfunction, which is known to primarily be a structural brain injury, and standard structural neuroimaging commonly show abnormalities (Ling *et al.*, 2015).

2.1.2 Definition of concussion

Concussion is commonly defined as a mild TBI (mTBI; Giza *et al.* 2013; Broglio *et al.* 2014), although there is disagreement on whether this is the proper categorization (McCrory, 2001). The first attempt to clearly define concussion in 1997 described the injury as a trauma-induced change in mental status that may or may not include loss of consciousness (Pervez *et al.*, 2018). Current definitions are more robust than this first description, yet no consensus definition has been established. Definitions tend to describe a concussion as the resulting physiological brain injury after the application of a biomechanical force resulting in neurological impairments (Giza & Kutcher, 2014). In definitions describing concussion as an mTBI, clinical injury scores used to classify TBI, such as the Glasgow Coma Scale (GCS), are used. The GCS scores visual, verbal, and motor responses of the patient (Kazl & Torres, 2019; CDC. 2013). This is a subjective grading scale in which higher scores define a more responsive patient in each response category (CDC 2013). GCS scores for concussion are typically in the mild range (score of 13-15; Kazl & Torres 2019). Medical definitions may additionally include descriptions of structural imaging findings, a loss or change in consciousness, and the presence or absence of amnesia (Roozenbeek *et al.*, 2013).

The challenge in creating a single definition for concussion emerges from the various needs and uses of the definition. For example, sport sideline assessment and emergency room assessment may need different definitions based on the severity of injury typically encountered. Tools that are accessible for diagnosis and screening may differ across clinical applications as well. In TBI, a clinical interview is considered the gold standard, but this is not accessible outside of medical settings (Walker *et al.* 2015).

More recently, clarity in the definition of concussion specifically related to sport is emerging due to work to define the condition by both the American Medical Society and in periodically updated consensus statements provided by the working group at the International Conference on Concussion in Sport and the Concussion in Sport Group (CISG; McCrory *et al.*, 2017). These definitions together state that a concussion is a complex pathophysiological process resulting in disturbance of brain function induced by traumatic biomechanical forces as a blow directly to the head or neck, or a blow elsewhere on the body with an impulsive force transmitted to the head (Harmon *et al.*, 2013; McCrory *et al.*, 2017). Neurological impairment typically emerges and resolves rapidly, but clinical and cognitive symptoms can take minutes to hours to appear. Concussion recovery follows a sequential course that may or may not be prolonged depending on initial injury severity and progression of symptom resolution. Clinically, a concussion most often results in symptoms reflecting functional disturbance and axonal injury rather than structural brain damage, typically without visible lesions using standard neuroimaging (Ling, Hardy, and Zetterberg 2015).

This definition does not address the underlying mechanism of concussion, potential abnormalities, or give a method to index severity, nor does it define resulting injury to brain regions or networks (McCrory, 2001). Recommendations to enhance the current definition state that modifications should include the biomechanics of sustaining concussion, physiology, specific clinical symptoms and cognitive signs, neuroimaging findings, fluid biomarker results, and genetic factors (McCrory, 2001). A complete understanding and full definition of concussion is essential to create a clear path for diagnosis and injury recovery.

2.1.3 Epidemiology

Before discussing the mechanical and biological consequences of concussion, it is essential to highlight the short- and long-term effects of concussive injury and describe at-risk populations. In this text, the terms ‘concussion’ and ‘mTBI’ are used interchangeably, with the acknowledgment that more work is needed to understand if this is appropriate. The most well documented acute effect of concussion is post-concussion syndrome (PCS), the persistence of signs and symptoms for weeks or months post-concussion, which is exacerbated by many factors including repetitive mTBIs (Yang *et al.* 2015). PCS physiological symptoms can include headache, dizziness, insomnia, exercise intolerance, cognitive intolerance, fatigue, as well as noise and light sensitivity. Psychological symptoms, including depression, irritability, and anxiety, may also occur, as can cognitive problems such as memory loss, poor concentration, and reduced problem-solving skills (Harmon *et al.* 2013). The risk for developing PCS increases for athletes with a personal history of migraine, history of previous concussions, younger age, learning disabilities, or attention deficit hyperactivity disorder (ADHD) (Collins *et al.* 2014; Cottle *et al.* 2017). Acute concussion also increases the risk of lower extremity injury and second concussion after return to play (RTP; McCrea *et al.* 2020; Herman *et al.* 2017), which may be due to continued neuromuscular deficits past RTP time.

More evidence is emerging linking neurodegenerative disease to mTBI. A single event leading to moderate or severe TBI is related to an increased risk of chronic traumatic encephalopathy (CTE) and other neurodegenerative conditions, including Alzheimer's disease (AD; McKee *et al.*, 2016; Fleminger *et al.*, 2003). Although several sources conclude no connection between exposure to a single mTBI and incidence of neurodegenerative disease (Bigler, 2013; Carson, 2017; Guskiewicz *et al.*, 2005; McCrory *et al.*, 2013), studies suggest that repetitive mTBI without full recovery time between events could increase the risk (Guskiewicz *et al.* 2005). Additional factors impact the risk for long-term brain damage, including initial injury severity, age, number of concussions, and repeated subconcussive head impacts (Levin & Diaz-Arrastia, 2015). CTE is characterized by executive dysfunction, depression, memory impairment, and dementia, amongst other types of cognitive and affective dysfunctions (Baugh *et al.* 2012). In a recent *post mortem* study, investigators examined the brains of teenage athletes after mTBI and found evidence of CTE (Tagge *et al.* 2018), suggesting that the onset of pathology may be earlier than previously thought. Guskiewicz *et al.* (2005) documented earlier than typical onset of AD in a cohort of retired American football players. In that study, the football players who reported three or more mTBIs had five times greater mild cognitive impairment (MCI) diagnoses and three times greater reported memory problems compared to players who did not report a history of mTBIs. Firm evidence for the specific biological mechanisms for this increased risk after repetitive mTBI does not yet exist, although progress is being made to understand potential mechanisms (**Section 2.2**).

2.1.4 Demographics

Demographic studies have identified risk factors for sustaining sport-related concussions. There is a strong relationship between the type of sport played and risk of concussion (Mason, 2013), although concussion risk is not restricted to full-contact sports (Cantu, 1997). For males, the highest risk of sustaining concussion exists in American football, Australian rugby, and wrestling. Females are at the highest risk in soccer, lacrosse, field hockey, and basketball (Cantu, 1997; Esselman & Uomoto, 1995; Giza *et al.*, 2013b; McCrory *et al.*, 2017). Both genders are at risk in ice hockey (Simmons *et al.*, 2017). A high risk for concussions is also reported in athletes participating in lacrosse, although fewer studies on injury consequences in lacrosse have been conducted compared to other high impact sports (Foss *et al.*, 2017; Reynolds *et al.*, 2016). Athletes playing baseball, softball, volleyball, and gymnastics reportedly have a lower risk for sustaining concussions compared to other contact and collision sports (Giza *et al.* 2013a). Females have twice the risk as males for sustaining a concussion while playing sports with similar rules for both genders, such as soccer and basketball (Cantu, 1986), potentially due to differences in neck strength ("Concussion Classification: Historical Perspectives and Current Trends" 2008), hormonal cycles (LeBlanc 1999), or due to a higher reporting frequency in females.

Younger aged players have an increased risk of sustaining a concussion (Collins *et al.*, 2014; Giza *et al.*, 2013b). Sports participation accounts for 54% of the total reported cases of pediatric concussion (Anderson *et al.*, 2006). Risk of sustaining a second concussion increases in children with a previous concussion (Kazl & Torres, 2019). In older players, including high school, college, and professional levels, concussion risk is similar for all levels of play (Kontos *et al.* 2013). A lower socioeconomic status (Cantu, 2001), alcohol and drug use, and pre-existing psychiatric and cognitive disorders are all additional risk factors for concussion (McCrory *et al.* 2005).

2.2 Diagnosis and reporting

Due to our lack of understanding of the condition (Kazl & Torres, 2019) as well as the fact that acute signs and symptoms are variable and change rapidly, a concussion is one of the most complex injuries to diagnose and manage (McCrory *et al.* 2017), for which no single diagnostic test or marker currently exists (McCrory *et al.*, 2017). The Centers for Disease Control and Prevention (CDC) utilize International Classification of Diseases, Tenth Edition, Clinical Modification (ICD-10-CM) codes for diagnosing TBI. These codes have demonstrated high specificity (98%) but low sensitivity (46%) to concussion (Bazarian *et al.*, 2006), supporting the need to develop different diagnostic tools for mTBI. A multidomain approach to mTBI diagnosis, including clinical symptoms, cognitive testing, and physical performance, is now preferential (Giza & Kutcher, 2014). A conservative and gradual approach for return to play (RTP) is typically based on the resolution of symptoms with both rest and physical activity, as well as neurocognitive function returning to baseline (Kazl & Torres, 2019). An individualized introduction back to full sports-play is also proposed, accounting for factors that consider an athlete to be entirely symptom-free before RTP (Harmon *et al.* 2013). An excellent example of this multidomain approach is the Sport Concussion Assessment Tool – 5th Edition (SCAT5), which includes immediate, on-field assessment and introduces a six-step screening system:

athlete background, symptom evaluation, cognitive screening, neurological screening, delayed recall, and a final decision regarding RTP.

The National Collegiate Athletic Association (NCAA) adopted its Concussion Policy and Legislation in 2010 (Buckley *et al.*, 2017), which recommends that all athletes participate in a baseline brain injury/concussion history survey, symptom evaluation, cognitive assessment, and balance evaluation before participation in a collegiate sport. The team physician or athletic trainer is responsible for determining sport eligibility based on this evaluation.

Despite these guidelines, many competitive athletes do not report concussions and may not receive the clinical attention needed to avoid short- and long-term impairments. Many factors influence self-reporting of injury, including lifestyle factors, socioeconomic factors, and gender (Balasundaram *et al.*, 2016). Physician-observed games have a higher concussion rate (Echlin *et al.* 2012), strengthening the argument that self-reporting is not an accurate assessment of concussion rate in sport. In a survey of collegiate athletes at the end of their collegiate career, 34% had reported a concussion during their career, 11% recognized a concussion that went unreported, and 26% displayed symptoms characteristic of a concussion (Llewellyn *et al.*, 2014). In a study of football players, 53% of concussions went unreported during a full season (McCrea *et al.*, 2004). These statistics support evidence that athletes may recognize symptoms of concussion, but do not seek care (Harmon *et al.*, 2013; Llewellyn *et al.*, 2014; McCrea *et al.*, 2004; Meehan *et al.*, 2013). Therefore, an objective approach to concussion assessment may be beneficial.

2.3 Concussion theoretical perspectives

2.2.1 Neuroanatomical perspective

An understanding of neuroanatomy is essential in determining a course of action for diagnosis and treatment. This section provides a brief and simplified neuroanatomy overview of the pathways and brain regions that are relevant for concussion-related injuries.

The central nervous system (CNS) contains the cerebrum, cerebellum, brainstem, diencephalon (including the thalamus and hypothalamus), basal ganglia, and spinal cord (**Figure 2.1**). The cerebrum integrates complex sensory information as well as conscious movement information. The cerebellum regulates posture and coordination of movement. The brainstem is composed of the midbrain, pons, and medulla. It regulates primitive, unconscious functions, including breathing and heart rate, along with being an essential ascending and descending neural passageway. The basal ganglia are a group of nuclei involved in voluntary movement, eye movements, and cognition among other functions. The thalamus is a sensory relay and integrative center that connects the cerebral cortex, basal ganglia, and brainstem, among other structures. Sensory fibers that ascend through the brainstem synapse in the thalamus and are then relayed to the sensory area of the cerebral cortex. Descending motor fibers from the cortex pass to the brainstem. The spinal cord contains both central gray matter and peripheral white matter. The gray matter contains neuronal cell bodies and synapses, while the white matter contains ascending and descending fiber pathways. The ascending pathways relay sensory input information to the brain. The descending pathways relay motor instructions from the brain to the rest of the body (Goldberg 2000).

Three primary sensory systems provide input information from the body to the brain that are relevant to concussion; the visual, vestibular, and proprioceptive sensory systems. The visual pathway begins when light rays from the visual fields enter the eye and travel through the lens to the retina. From the retina, the information is transmitted through ganglion cells, which come together to form the optic nerves. The optic nerves extend to the optic chiasm, where some nerve fibers cross the midline to be processed further on the contralateral side of the brain, and the information continues along the optic tract to terminate in the thalamus. The lateral geniculate nuclei (LGN) of the thalamus receive visual information. Axons of the optic tract that are important for visual reflexes also extend to the superior colliculi, which resides in the midbrain. The optic tract axons synapse with cell bodies of the LGN in the thalamus. Visual information travels by optic radiations from the LGN to the primary visual cortex in the occipital lobe.

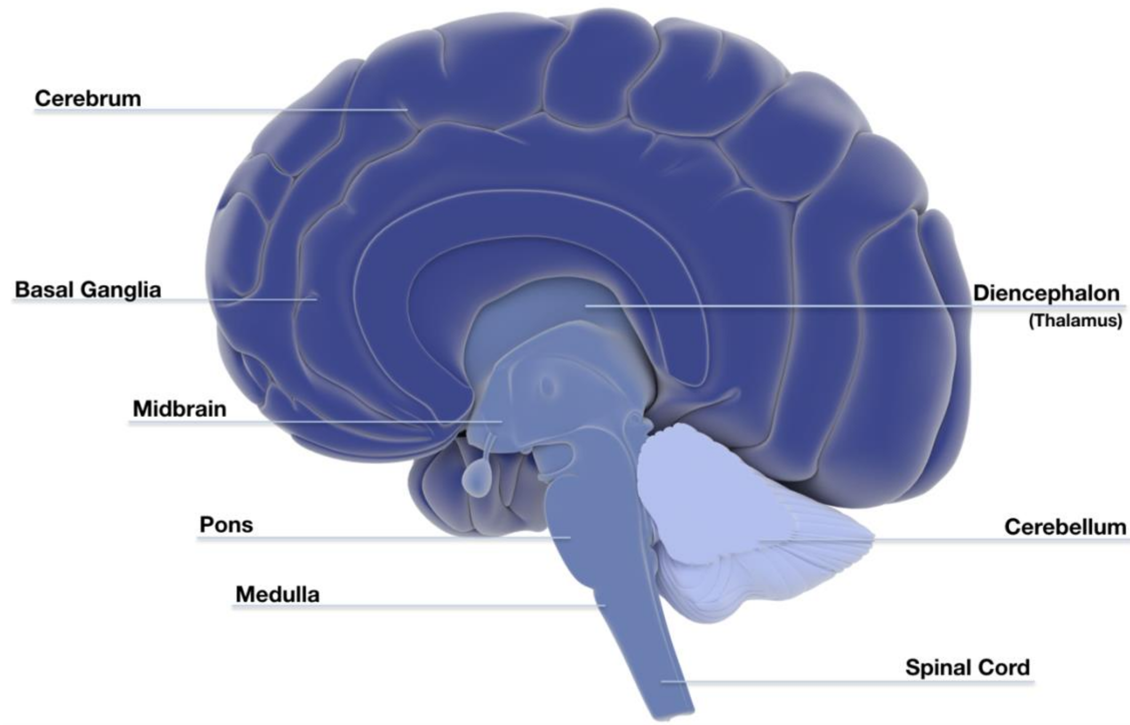

Figure 2.1. The basic locations of the main structures of the central nervous system.

The peripheral vestibular system contains three semicircular canals (anterior, posterior, and lateral) and two otolithic structures located in the inner ear. The semicircular canals, which detect angular acceleration of the head, are arranged approximately orthogonal to each other, each relating to a different plane of motion (pitch, yaw, and roll). These semicircular canals contain endolymph fluid and hair cells, which convert mechanical motion to electrical impulses. The two otolithic structures detect linear movement and the force of gravity exerted on the body. Information from each of these sensory structures is transmitted through the vestibulocochlear nerve (CN8) to the vestibular nerve ganglion and enters the brain at the brainstem level. Neural signals from vestibular nuclei at the brainstem make ascending connections, including to the oculomotor nuclei and the thalamus, make projections to the cerebellum, and make descending connections to the spinal cord. Motor responses to vestibular information include the vestibulo-ocular reflex (VOR), the vestibulospinal reflex (VSR), and the vestibulocollic reflex (VCR). The VOR is responsible for maintaining stable vision during head movements, the VSR stabilizes the body during standing balance to maintain the center of gravity within the base of support, and the VCR acts on the neck muscles to stabilize the head (McLeod & Hale, 2015). These networks are highly sensitive to injuries and play a significant role in identifying post-concussion brain health.

The proprioceptive sensory system has two components: a conscious and an unconscious component. The conscious component is responsible for the ability to understand limb positioning and create joint motion. This component enters the spinal cord and moves through the ascending pathways to terminate in the thalamus. The information is then relayed to the sensory area of the cerebrum. Once the cerebrum processes the information, it moves down the motor/corticospinal pathway through the brainstem to synapse in the anterior horn of the spinal cord before leaving the cord to generate a motor response. The unconscious component of proprioception enters the spinal cord and moves through the ascending spinocerebellar tract. The information is then relayed to the cerebellum. The brainstem connects to the cerebellum through the superior, middle, and inferior cerebellar peduncles, which connect the midbrain, pons, and medulla, respectively. The spinocerebellar pathway enters the cerebellum through the superior (midbrain) and inferior (medulla) peduncles. This component of proprioception is responsible for the ability to perform complex motions subconsciously without actively thinking about joint positioning and motion. (Goldberg 2000). The importance of these sensory pathways in concussive injury is described further in **Section 2.4.1**.

2.2.2 Mechanical perspective

Geometry and material properties of the skull and brain provide the basis for the traditional theory to explain the mechanism behind concussion (**Figure 2.2**). Inertial loading produces a centripetal progression of strains from the outer surfaces inwards towards the brainstem. With low inertial loading, shear strains extend only to the cortex. Higher inertial loading will reach the brainstem and may result in loss of consciousness (Ommaya & Gennarelli, 1974). Growing evidence suggests that this theory is not complete. Symptoms related to the brainstem have been reported in the absence of cortical symptoms (McCrory, 2001). Additionally, lack of consistency in structural neuroimaging results, even in patients with severe symptoms, support the hypothesis that concussion is mainly a functional physiologic dysfunction, rather than a structural lesion, and that both the cortex and the brainstem are equally crucial as anatomical focus points in both low and high inertial loading concussive events (McCrory, 2001).

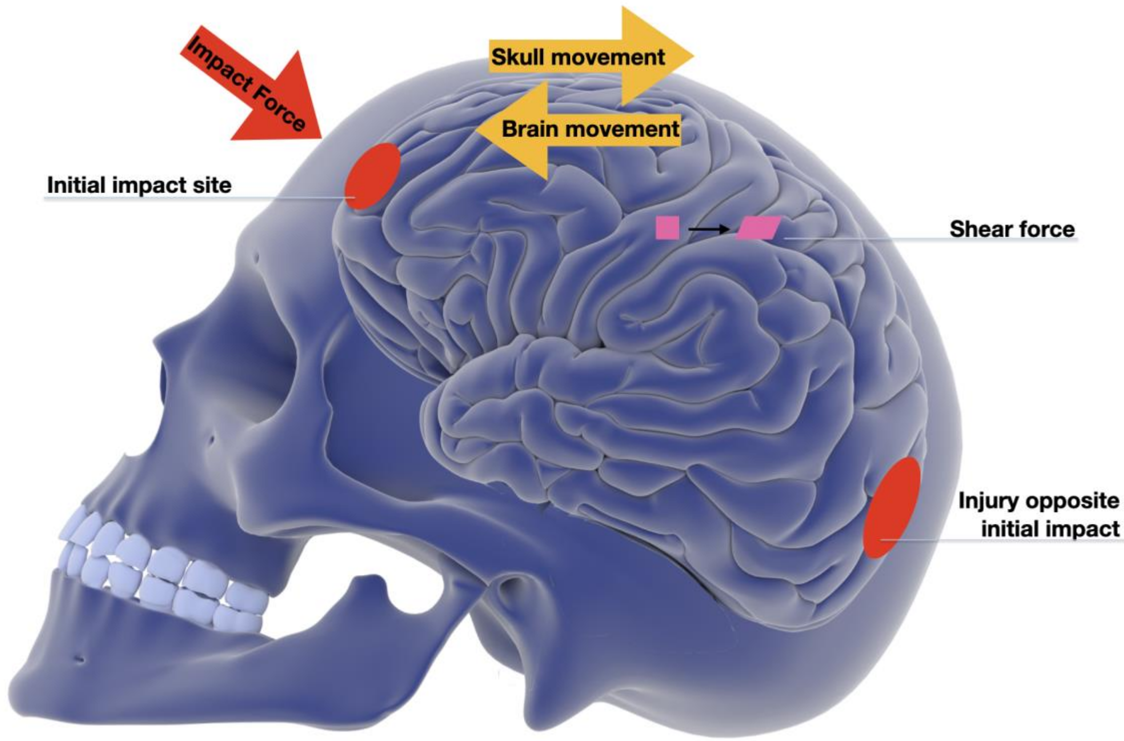

Figure 2.2. A simplified schematic demonstrating forces and injuries associated with concussion. The initial injury site on the brain corresponds with the location of the direct impact force on the skull. The skull moves with the impact force, while the brain initially stays in place, causing it to move towards the impact force with respect to the skull, resulting in shear forces between the skull and the brain. An injury opposite the initial injury site occurs due to continued brain movement within the skull. Adapted from Kleiven (2013).

Head acceleration studies provide support for multiple sites of simultaneous anatomical focus. In a potentially concussive blow to the skull, inertial loading includes both linear and rotational acceleration. Linear acceleration correlates to increased cranial pressure (Meaney & Smith, 2011) and rotational acceleration accounts for 78% of the variance in shear stress following an impact (Zhang *et al.*, 2004). While linear acceleration may result in the initial injury to specific points on the cerebrum, rotational acceleration may contribute to additional injury sites, such as the brainstem, which is highly sensitive to rotational loading due to a narrow anatomical structure.

Finite element analysis (FEA) modeling of concussion supports this theory, showing an ununiform distribution of stresses and strains through the brain due to brain geometry, tissue properties, and skull architecture (McIntosh *et al.*, 2014; Patton *et al.*, 2015). Due to this, anatomical areas have differing physiological and biochemical disturbances. FEA analysis has shown the highest concentration of strains in the brain following a concussion in the midbrain of the brainstem in both boxers and football players (Viano *et al.* 2005).

Biological approaches have supported these mechanical approaches to understanding the injury. A reduction in white matter integrity in many areas of the brain has been associated with concussion, including the midbrain (Hirad *et al.* 2019), the corticospinal tracts, and the corpus callosum (Henry *et al.* 2011). Damage to white matter tracts, which decreases neurotransmission, has been associated with the persistence of symptoms post-concussion (Hurtubise *et al.*, 2020). The number of damaged white matter tracts was correlated with reaction time (Niogi *et al.* 2008). Additionally, decreased white matter integrity along the frontoparietal-cerebellar tracts was associated with decreased performance on cognitive-motor integration tasks (Hurtubise *et al.*, 2020).

2.4 A call for objective clinical assessment of concussions

The lack of reporting and unclear diagnostic tools in concussion assessment create a need for higher sensitivity screening and diagnostics (Voss *et al.*, 2015), and the neuroanatomical and mechanical bases provide information to hypothesis which types of diagnostics might be effective. Most importantly, these specialized diagnostic tools need to identify long-term signs and symptoms of concussion in order to avoid the increased risk for neurodegenerative conditions later in life (Kazl & Torres, 2019). A non-invasive approach is preferential to assess incidence, acute recovery, and presentation of chronic difficulties in both symptomatic and asymptomatic cases (Hirad *et al.* 2019). This need may be addressed by balance measures (Echlin *et al.* 2012; Giza *et al.* 2013b), due to increasing evidence regarding the theories of brain dysfunction following a concussion.

2.4.1 Balance as a measure of concussive injury

This dissertation proposes that standing balance is a sensitive indicator of concussion based on the premise that connections to the cerebellum are compromised. In a healthy individual, inputs to standing balance are given by the visual, vestibular, and proprioceptive sensory systems pathways. When an athlete experiences a concussion, linear and rotational acceleration of the head cause applied and shear force injuries. Both types of damage result in direct impact injury and in indirect damage to the central and peripheral nervous system and sensory pathways. Direct injury may occur to vestibular organs, the vestibular nerve, or the brainstem, while indirect injury can affect the visual, motor, or ocular pathways with axonal hyper-stretching and demyelination injuries manifesting as decreased white matter integrity (McLeod and Hale 2015). These damages can lead to vestibular and sensorimotor deficits, causing reduced neuromuscular functioning (**Figure 2.3**).

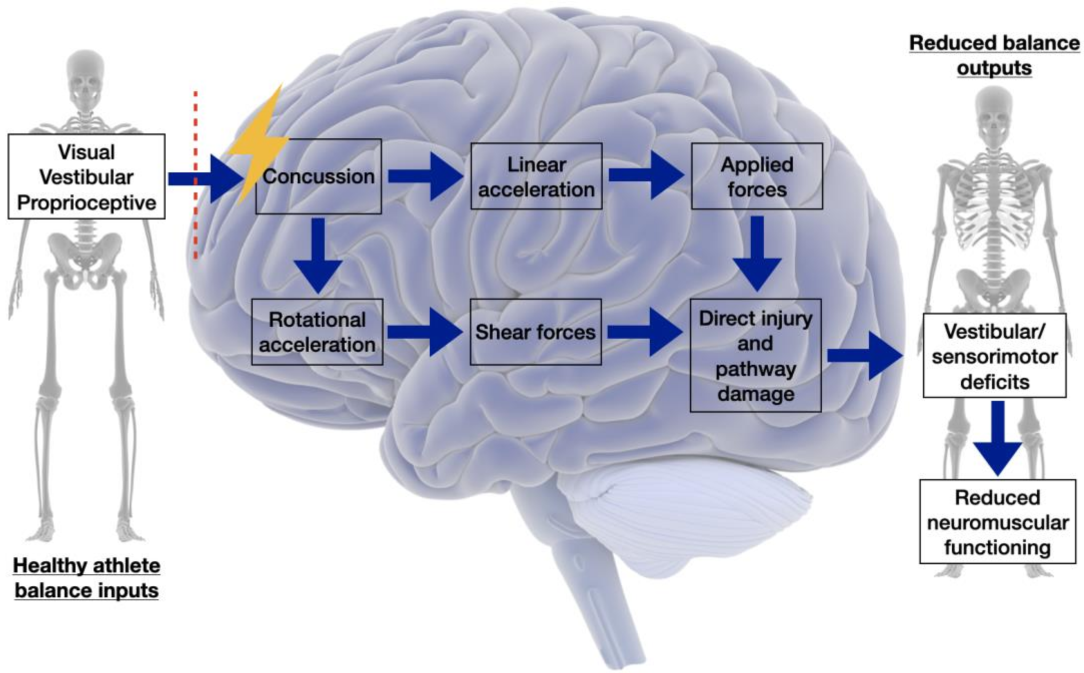

Figure 2.3. A flow chart depicting a combined neuroanatomical and mechanical concussive injury theory. Sensory pathways used in healthy balance are affected by concussion. During a concussion, the head undergoes linear acceleration, leading to applied forces on the brain and rotational acceleration, leading to shear forces on the brain. Both types of forces lead to direct impact injuries and damage to sensory pathways. This can lead to vestibular and sensorimotor deficits which reduces the neuromuscular functioning necessary for balance.

The sway associated with standing balance is a form of unconscious movement that is processed in the cerebellum. Both the vestibular and proprioceptive systems have pathways directly to the cerebellum. The vestibular system makes projections to the cerebellum through the ascending neural signals from vestibular nuclei in the brainstem. The unconscious component of the proprioceptive system is relayed through the spinocerebellar tract to the cerebellum. As standing balance tasks are typically performed with the eyes closed, these tests eliminate the sensory system that does not enter the cerebellum and may be useful in determining whether connections to the cerebellum have been damaged, and if the vestibular and proprioceptive systems are functioning normally to output an accurate balance response. A limitation of this theory is that if a concussive event does not affect the connections of the vestibular or proprioceptive pathways, changes in standing balance may not occur. However, the connections of the brain are complex and intertwined, and standing balance may be affected indirectly when other parts of the brain are injured.

An example of a clinical standing balance is the Romberg test, an examination of neurological function during balance. The Romberg test is positive if the patient sways during standing balance with the eyes closed but does not sway when eyes are open. A positive Romberg indicates either proprioceptive or vestibular deficits due to the lack of visual information in the eyes-closed condition. If either the vestibular or proprioceptive sensory system has a deficit, the patient will sway in the eyes-closed condition. In concussion, balance impairments most likely due to the inability to resolve sensory conflict from unstable surfaces or inaccurate visual information. When sensory systems were isolated, concussed patients had increased impairments with inaccurate proprioceptive information, indicating that concussion may be an injury affecting the vestibular system (McLeod and Hale 2015).

Apart from the hypothesis that balance may be a sensitive indicator of concussion, balance is an ideal example of a clinically useful biomarker because it is inexpensive, non-invasive, can be simple to use, and has the potential to be scientifically tested (Horak and Mancini 2013). Sensitive metrics of balance are available to clinicians outside a scientific laboratory (Horak and Mancini 2013). Objective measures of balance should be associated to specific pathophysiological markers from imaging or blood (Horak and Mancini 2013), and also to patient improvements including reduction of falls, lower extremity injuries, and susceptibility to a second concussion (Melzer *et al.*, 2010; Norris *et al.*, 2005) to create a case for such a biomarker. The best objective balance biomarker will aid in risk assessment before symptoms appear (Horak and Mancini 2013). To provide proof of concept for a balance biomarker, large and longitudinal cohorts should be examined to assess sensitivity, specificity, and validity (Horak and Mancini 2013). The lack of neuroimaging in this study limits the ability to test for standing balance as a biomarker for concussion directly. While this research determines the discriminative ability and sensitivity of standing balance to concussion, future work should consider establishing associations between neuroimaging and biomechanical balance.

CHAPTER 3: A REVIEW OF STANDING AND FUNCTIONAL CLINICAL AND BIOMECHANICAL BALANCE MEASUREMENT IN SPORT-RELATED CONCUSSION ASSESSMENT

3.1 Abstract

Lack of reporting and unclear diagnostic tools for sport-related concussion creates a need for the design of objective screening tools. Standing and functional biomechanical balance measures may fill this need and add sensitivity to multidomain concussion assessment. This narrative review discusses standing and functional balance theory, relevant literature on balance deficits post-concussion, and explores avenues for expansion into clinically relevant diagnostics. Clinical balance measures, such as Balance Error Scoring System (BESS) error scores, are found to show group differences between concussed and healthy athletes in the acute period post-concussion. However, these differences are not apparent as recovery progresses. Biomechanical balance measures may provide more sophisticated analysis, with measures such as center of pressure (COP) velocity and approximate entropy (ApEn) in the anterior-posterior (AP) direction in quiet stance and gait velocity displaying group differences past the acute period. Proposed next steps include providing evidence for balance as a biomarker through associations to pathophysiological markers and patient improvements, measuring the sensitivity of balance measures to concussion, creation of cutoff scores that distinguish between healthy

and concussed athletes, design of clinically accessible balance measurement devices for sideline concussion assessment, and the evaluation of rehabilitation methods for recovery of movement patterns.

3.2 Introduction to balance measurement in sport-related concussion

Concussion is one of the most complex injuries to diagnose and manage (McCrory *et al.,* 2017) due to our lack of understanding of the condition as well as acute signs and symptoms that are variable and change rapidly (Harmon *et al.*, 2013). A multidomain management approach including clinical symptoms, cognitive testing, and physical performance is preferred (Giza & Kutcher, 2014), yet unclear and subjective diagnostic tools within those domains create a need for higher sensitivity screening and diagnostics (Voss *et al.*, 2015b). Many competitive athletes do not report concussions, limiting the applicability of subjective and self-reporting diagnostic methods. For example, 53% of concussions went unreported during a full football season (McCrea *et al.* 2004), supporting evidence that athletes may recognize symptoms of concussion, but fail to report and do not seek care (Llewellyn *et al.*, 2014; Meehan *et al.*, 2013; McCrea *et al.*, 2004; Harmon *et al.*, 2013). Objective screening and diagnostic tools may fill the need created by athlete underreporting and subjective diagnostics. Balance is noted as potentially useful avenue to address this need (Echlin *et al.*, 2012; Giza *et al.*, 2013b).

Balance in human movement is maintained through relationships between the center of gravity (COG, alternatively the center of mass; COM) vector and the base of support (BOS; Pollock *et al.*, 2000). Sensory information delivered to the central nervous system (CNS) via the visual, proprioceptive, and vestibular sensory systems is processed to create calculated postural responses. This narrative review is an examination of the fundamental current knowledge on balance deficits post-concussion to open a discussion on the most essential next steps in the field. Balance tasks are grouped into *Standing Balance* (static balance) or *Functional Balance* (dynamic balance). During a standing balance task, the objective is to maintain a standing posture and remain as still as possible. During a functional balance task, the balancer prevents falling while executing a functional task such as walking, running, turning, or picking up an object. These standing and functional balance tasks are measured by *Clinical Methods* and *Research Methods*. Efforts to make biomechanical balance testing clinically accessible are highlighted.

3.3 Standing balance

3.3.1 Theoretical perspective

Standing, or static, balance is a state of static equilibrium in which there are no external forces on the body, and internal forces in the body have a resultant force of zero. The COM, BOS, and center of pressure (COP) interrelate to maintain balance (**Figure 3.1**). The COM is the resultant force vector of the individual body segmental center of mass vectors and is where the force of gravity acts on the body. The BOS in standing balance is defined as the area underneath the feet that is in contact with the ground. The ground reaction force (GRF) acts against the force of gravity underneath the feet. The COP is the resultant force vector of the individual ground reaction force vectors. Standing balance is maintained by keeping the COM within the BOS. The COP measures the net neuromuscular response needed to control the COM (Winter *et al.*, 1996). In perfect balance, the COP is directly below the COM, although this is not typically the case, since there is inherent sway associated with standing balance. During this sway, if the COM is within the BOS, balance is maintained. The COM is maintained within the BOS through ankle control and hip control. The use of ankle control in quiet stance is dominant in healthy populations. This corrects for small perturbations in the COM by using ankle plantar and dorsiflexors to keep the COM within the BOS. When ankle control is ineffective, hip control using hip abductors and adductors is employed for larger perturbations of the COM. When both ankle and hip control fail, a step is necessary to regain balance before a fall occurs (Winter *et al.*, 1996).

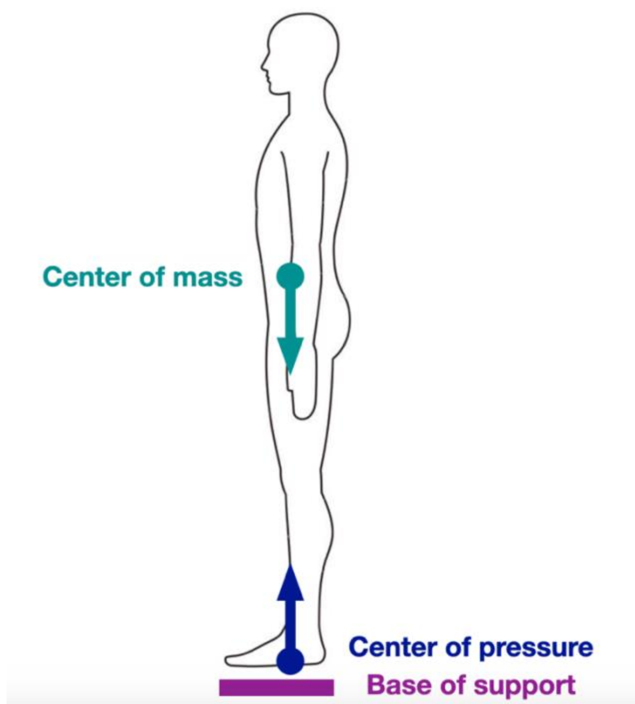

Figure 3.1. Illustration of center of mass (COM), center of pressure (COP), and base of support (BOS) locations when standing. The COM is the location of the resultant force of gravity, the COP is the resultant force of all individual COP vectors acting against the foot, and the BOS is the area underneath the feet in contact with the ground.

There are three main stances typically employed during standing balance tasks; the double-leg stance, single-leg stance, and tandem stance (e.g. Balance Error Scoring System; BESS). In the double-leg stance, participants stand with feet together or pelvis-width apart. In the single-leg stance, the participant lifts one leg off the ground, typically the dominant leg, with a 45º flexion of the knee. The tandem stance is a heel-to-toe stance where the participant places the non-dominant foot directly behind the dominant foot. The foot placement in these stances change the dominant control planes (**Figure 3.2**). In the double-leg stance, hip control is dominant in the ML component of the COP, and ankle control is dominant in the AP component of the COP. In the tandem stance, this relationship is the opposite where ankle control is dominant in the ML component of the COP, and hip control is dominant in the AP component of the COP. Control dominance was determined using separate data for the left and right foot across two force platforms (Winter *et al.*, 1996). This method does not allow for the same analysis for the single-leg stance, although ankle and hip corrective action increase in the frontal plane during sensory impaired (eyes-closed and on foam) single-leg stances relative to a single-leg, eyes-open stance on a firm surface, potentially suggesting that a mixed strategy where both hip and ankle control are utilized in both planes is in effect (Riemann *et al.*, 2003).

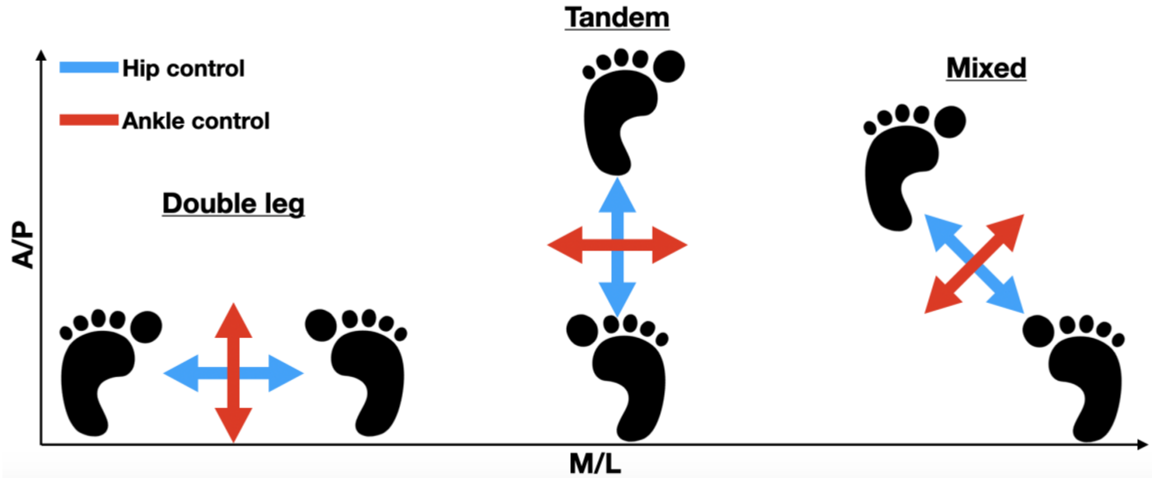

Figure 3.2. Ankle and hip control strategies and corresponding balance planes in three stances. In the double-leg stance, mediolateral (ML) balance is under hip control and anterior-posterior (AP) balance is under ankle control. In the tandem stance, this relationship is the opposite where ML balance is under ankle control and AP balance is under hip control. In a mixed 45º stance, balance along both planes has contributions from both ankle and hip control (Winter *et al.* 1996).

The surface type and visual field used in standing balance tasks add additional factors to consider. From a neuroanatomical standpoint, standing balance is maintained when two of the three sensory systems (visual, vestibular, and proprioceptive) are functional (Goldberg, 2000). While a solid, flat surface is most common for balance testing, tests may also call for the use of foam (e.g. BESS) or sway-referenced surfaces (e.g. Sensory Organization Test; SOT). In both cases, the input to the proprioceptive system is compromised, and the balancer must rely on accurate information from the vestibular and visual systems. The visual field is the second component that can be changed, and this is typically done through the use of an eyes-closed task (e.g. BESS) or introducing moving screens or objects into the visual field (e.g. SOT). These changes compromise the input information from the visual system, and the balancer must rely on the proprioceptive and vestibular systems to maintain balance. When both the surface and visual field are compromised, such as in an eyes-closed standing balance task on foam, the vestibular system provides the only accurate sensory information. In this case, the balancer will have trouble maintaining a healthy balance response due to the impairment of two of the three sensory systems. Neurological injury, such as concussion, may cause direct or indirect injury to the sensory systems, which can further complicate balance ability in some populations.

3.3.1 Clinical measures of standing balance

The Romberg test was developed to identify deficits of the vestibular and proprioceptive sensory systems (Murray *et al.*, 2014b). Two quiet stances (eyes-open and eyes-closed) with the feet together are performed. The Romberg test is positive if the balancer does not have difficulty in the eyes-open condition, but sways in the eyes-closed condition. A positive Romberg suggests a vestibular or proprioceptive deficit (Goldberg, 2000). This is a highly subjective test (Jacobson *et al.*, 2011), and the sensitivity and specificity of the Romberg test to concussion are not robust at 0.55 and 0.77, respectively (Murray *et al.*, 2014b).

The Clinical Test of Sensory Integration in Balance (CTSIB; Shumway-Cook and Horak, 1986) was created to increase sensitivity to vestibular deficits. The original CTSIB protocol includes six standing balance tasks that block or obscure sensory input information with the placement of a dome over the patient's head or by standing on foam (Shumway-Cook & Horak, 1986; Guskiewicz, 2011). A modified CTSIB has been created that utilizes a force platform to increase the objectivity of the test (Cohen *et al.*, 1993). In both the original and modified protocol, balance is measured on a scale from 1-4, with a 4 indicating a participant at risk for falling. Utilizing the CTSIB, concussed athletes had decreased stability <3 days post-concussion (Guskiewicz *et al.*, 1997). Reliability, sensitivity, and specificity are not established in concussed athlete populations for the CTSIB.

The Balance Error Scoring System (BESS, University of North Carolina-Chapel Hill) was designed specifically for sport-related concussion and is the most commonly used tool for sideline concussion balance testing (Guskiewicz, 2011). The BESS is a series of three eyes-closed balance tasks; the single-leg stance, double-leg stance, and tandem stance, each performed on a firm surface and foam (**Figure 3.3**).

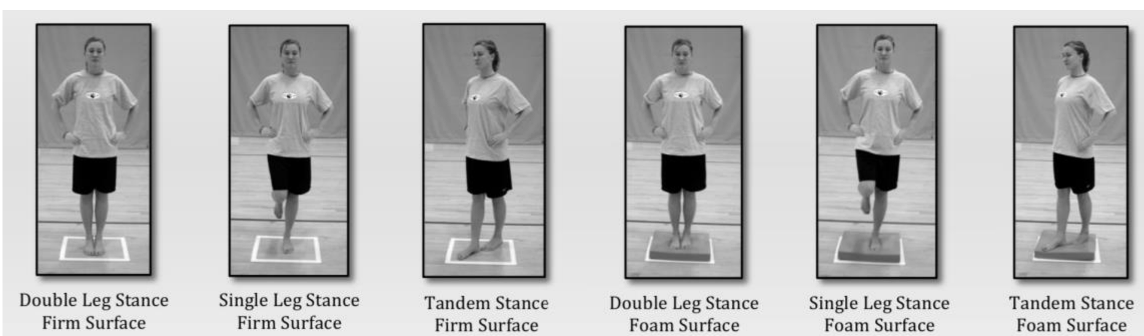

Figure 3.3. The six stances of the Balance Error Scoring System (BESS, University of North Carolina-Chapel Hill). The eyes are closed for 20 seconds in all six stances, while the scorer counts the number of pre-defined errors.

The scorer counts the number of errors the balancer incurs, up to 10, during the 20-second balance trial. Errors include taking a step, opening the eyes, taking the hands off the hips, flexion or abduction of the hip, lifting the forefoot or heel off of the testing surface, and remaining out of the testing stance for greater than five seconds. Concussed athletes tend to have decreased postural stability, concluded from a higher number of errors, acutely post-concussion compared to error scores of non-concussed athletes (Guskiewicz *et al.*, 2001; McCrea *et al.*, 2003; Nelson *et al.*, 2016). BESS error scores resolve at a maximum of 5 days post-concussion (McCrea *et al.*, 2003; Nelson *et al.*, 2016). With longitudinal utilization, the BESS has learning effects up to 60 days post-concussion (Mcleod *et al.*, 2004; Mulligan *et al.*, 2013). Substantial changes in scores (9.4 points, interrater or 7.3 points, intrarater) are necessary before attributing changes in balance to the balancer rather than the scorer, exhibiting the lack of sensitivity of this test (Finnoff *et al.* 2009). Methods to increase the sensitivity of the BESS have been developed. Removal of double stance tasks and scoring three trials of each the single-leg and tandem tasks provided higher sensitivity (modified BESS; Hunt *et al.*, 2009) as did taking the mean score from 3 subsequent administrations of the full BESS protocol (Broglio *et al.*, 2009). The total BESS has low to moderate reliability (0.57-0.74; McCrea *et al.*, 2005; Finnoff *et al.*, 2009), high specificity (0.96), and low sensitivity (0.34) to concussion (Lanska & Goetz, 2000). The sensitivity of the BESS drops to 0.07 at 1 week post-concussion (McCrea *et al.*, 2005).

The Sensory Organization Test (SOT) uses dynamic force platforms to increase the objectivity of standing balance tests. There are six conditions of the SOT, involving three visual conditions (eyes-open, eyes-closed, sway referenced) and two surfaces (fixed, sway referenced; **Figure 3.4**) in which the participant balances for 20 seconds. In the sway referenced conditions, the visual field or surface move anterior-posteriorly in response to the patient's COP. The six conditions of the SOT are used to calculate four composite scores on a 100-point rating scale: composite balance, somatosensory ratio, vestibular ratio, and visual ratio (Guskiewicz *et al.*, 2005). Lahat *et al.* (1996) identified impaired balance on the SOT in children within 36 hours of concussion. Concussed athletes have decreased postural control, as determined through lower SOT composite scores, up to 5 days post-concussion compared to non-concussed athletes (Guskiewicz *et al.*, 2001; Riemann *et al.*, 1999), similar to the BESS. Reliability, sensitivity, and specificity have not been established for the SOT in concussed athlete populations. While the SOT is the most objective clinical assessment available, it is costly and not portable, limiting broad application (Kelly *et al.*, 2014).

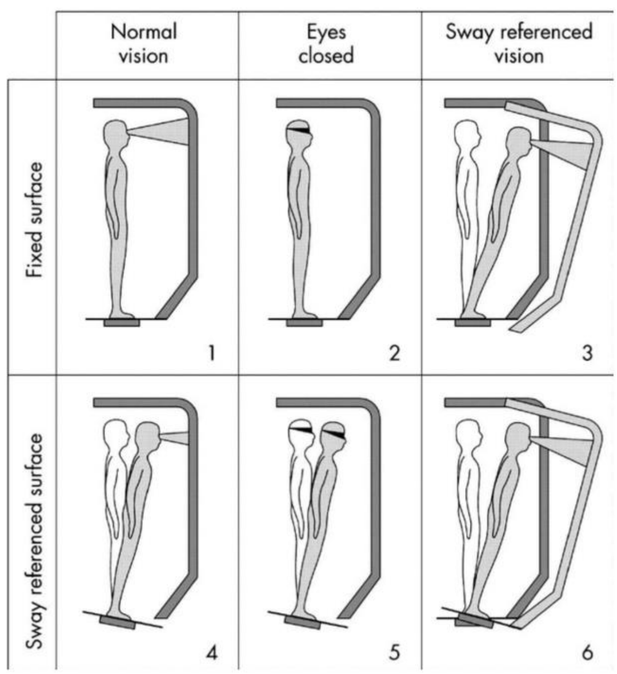

Figure 3.4. The six conditions of the Sensory Organization Test (SOT; NeuroCom International, Inc.)

In a comparison of BESS, SOT, and CTSIB, Murray *et al.* (2014a) reported that none of these balance test batteries were capable of measuring concussion-related balance dysfunction greater than three days after the injury. Therefore, these clinical methods may not have the sensitivity needed to measure sensorimotor deficits that may cause further injury at return to play (RTP).

3.3.2 Research methods of standing balance

Instrumented biomechanical balance techniques identify lasting deficits, in disagreement with the quick recovery of clinical balance measures (Rochefort *et al.*, 2017). Standing balance is frequently assessed biomechanically using force platforms to measure COP, an indicator of the neuromuscular control mechanism used to maintain balance (Winter *et al.* 1996). Standard linear measures of the COP include displacement (total, ML, AP), displacement area commonly reported as the 95% confidence ellipse area, and average velocity (total, ML, AP; Duarte & Freitas, 2010; King *et al.*, 2017). Concussed football players showed greater COP AP displacement in eyes-closed quiet stance immediately after injury with an improvement of function before RTP (Powers *et al.*, 2014). Although the athletes in Powers *et al.* (2014) improved displacement before RTP, athletes with history of concussion had increased COP AP displacement (De Beaumont *et al.*, 2011) and COP ML displacement (Degani *et al.*, 2017). Increased COP sway area has also been reported in athletes with history of concussion in both eyes-open and eyes-closed quiet stance conditions (Degani *et al.*, 2017; Thompson *et al.*, 2005). COP AP velocity continued to be elevated during eyes-closed quiet stance in concussed football players at

RTP (Powers *et al.*, 2014). These deficits may indicate poor sensorimotor integration in athletes post-concussion (Powers *et al.*, 2014).

Nonlinear measures of the COP provide information about the regularity and complexity of COP signals. Approximate entropy (ApEn) is a measure of the logarithmic likelihood of time series patterns reappearing. In these calculations, the pattern length and similarity factor (how similar patterns must be to be considered a match) are specified. The similarity factor is typically set to a percentage (10-20%) of the standard deviation of COP displacement (Sosnoff *et al.*, 2011). The output of ApEn indicates the regularity of the signal, with values near 0 indicating highly regular signals, and values near 2 indicating irregular signals. Signals with high ApEn are thought to indicate complexity in the balance strategy. In populations with postural control deficits, ApEn typically decreases, potentially indicating a loss of complexity (Pincus, 1991). Gao *et al.* (2011) found that approximate entropy can identify impaired postural control acutely post-concussion when linear measures of the COP have recovered. Cavanaugh *et al.* (2005) found more regular ApEn in both the AP and ML direction in athletes within 48 hours of concussion. In the same cohort, ApEn in the ML direction remained lower up to 96 hours post-concussion (Cavanaugh *et al.*, 2006). Sosnoff *et al.* (2011) did not detect significant changes between athletes with and without a history of concussion, but found that for athletes with concussion history, ApEn in the AP direction became more irregular, and ApEn in the ML direction became more regular as stance difficulty increased on the sensory organization test (SOT). In athletes with a history of multiple concussions at least nine months prior, De Beaumont *et al.* (2011) found more regular ApEn in the AP direction.

Sample entropy is less reliant on data length, behaves more consistently, and discriminates between groups better than ApEn (Montesinos *et al.*, 2018). A study of former football players with a history of multiple diagnosed concussions showed more regular sample entropy in the ML direction during condition 5 of the SOT, the sway-referenced surface eyes-closed balance task, when compared to age, height, and sport-matched athletes with no history of concussion (Schmidt *et al.*, 2018). The deficits apparent in nonlinear measures of the COP further indicate that balance does not recover acutely post-concussion, and standing balance measures may be useful in concussion protocols.

3.3.3 Clinically available biomechanical standing balance instrumentation

Commercially available instruments, such as the Wii Balance Board, provide an opportunity to biomechanically measure standing balance in the clinic. Chang *et al.* (2014) found COP pathlength on a Wii balance board to be more accurate than BESS error scores, indicating that biomechanical balance measured in clinical devices is a promising technique. While the sensitivity of the Wii balance board to sway is lower than traditional force platforms, it is high enough to use in clinical practice (Leach *et al.*, 2014), showing high within device (0.94) reliability and between device (0.89) reliability in comparison to a laboratory-grade force platform (Clark *et al.*, 2010). Athletes 1 month post-concussion had a larger ellipse area during eyes-open, eyes-closed, and dual-task conditions, and higher COP ML velocity during a dual-task condition compared to a control group (Rochefort *et al.*, 2017). Murray *et al.* (2014) used the WiiFit soccer game paired with a monocular eye-tracking device to measure gaze deviation during balance tasks and found that patients with concussions had a higher number of gaze deviations than non-concussed patients.

Wearable devices, including inertial measurement units (IMU's), can also be useful for balance data collection. An IMU placed on the L5 vertebrae during BESS firm surface trials measuring root mean square (RMS) mean acceleration of ML and AP sway had higher sensitivity to concussion than BESS error scoring (King *et al.*, 2014). Accelerometer and gyroscope data from an iPad placed on the sacrum increased the sensitivity of double-leg stance measurements and increased test-retest reliability compared to BESS error scores (Simon *et al.*, 2017).

3.4 Functional balance

3.4.1 Theoretical perspectives

Functional, or dynamic, balance is the maintenance of equilibrium during functional tasks such as walking. In the clinical setting, gait tasks are typically measured spatiotemporally. In a biomechanical setting, functional balance is assessed using a motion capture system to derive kinematic and kinetic data. Functional balance tasks require CNS feedback and control mechanisms similar to full sports play, potentially making them useful as concussion recovery progresses. Unlike standing balance, the COM can leave the BOS in functional balance tasks without leading to a fall as the body translates and rotates in all three planes of motion. While there are many interesting types of movements in which the goal is to maintain balance, this text focuses mainly on forward gait, a simple and well understood functional balance task.

In normal gait, the COM leaves the BOS during single-leg stance phases (Woollacott & Tang, 1997). There are four basic tasks during gait: (1) progress towards the destination through continuous movement generation, (2) maintaining equilibrium during forward progression, (3) adaptability to changes in environment or subsequent tasks, and (4) initiation and termination of movement (Woollacott & Tang, 1997). Patla *et al.* (1993) describes two balance mechanisms for equilibrium maintenance; a proactive control mechanism and a reactive control mechanism. The proactive control mechanism is in effect before the balancer identifies a threat to stability, and the reactive control mechanism initiates when the balancer encounters a trip, slip, or other balance error that could lead to a fall. The proactive control mechanism activates muscles or initiates joint torques to reduce biomechanical threats to balance during walking, and detects potential environmental hazards and makes adjustments before the hazard (Woollacott & Tang, 1997). The visual sensory system is vital in detecting threats to balance in the proactive control mechanism. The reactive control mechanism uses the vestibular and proprioceptive sensory systems to determine the severity of the threat to balance and to initiate an appropriate response to the threat (Patla *et al.*, 1993).

3.4.2 Clinical methods of functional balance

Generally, clinical methods for assessing functional balance rely on spatiotemporal measures during the phases of the gait cycle. In single-task gait, a slower gait speed has been documented in the acute period post-concussion (Howell *et al.*, 2013; Lee *et al.*, 2013). Slower gait speed continues up to 3 months post-concussion (Buckley *et al.*, 2016;

Howell *et al.*, 2017b), but appears to recover by one year after the injury (Fino, 2016). Dual-task gait is also slower in concussed subjects up to 60 days post-concussion, and appears to resolve by one year post-injury as with single-task gait (Fino, 2016; Howell *et al.*, 2017b). Tandem gait was also found to be slower in the acute period, including during a dual-task (Howell *et al.*, 2017). Stride length is shorter for concussed subjects compared to controls acutely and up to 14 days, but appears to recover by 28 days post-injury (Parker *et al.*, 2006). Athletes more than 3 months post-concussion had increased double-leg support time, and decreased step length, step length variability, and step velocity (Buckley *et al.*, 2016). Stride time, length, and width appear to recover by one year post-injury (Fino *et al.*, 2016). Obstacle crossing studies show slower gait and smaller stride width post-concussion but these measures appear to recover after the acute period (Fino *et al.*, 2018). The slower gait, smaller step and stride length, and increased double-support time indicate a conservative gait strategy post-concussion, with some measures showing continued impairment months after the injury.

3.4.3 Research methods of functional balance

Varied biomechanical techniques have been assessed for functional balance in concussed populations. The conservative gait strategy commonly reported in clinical findings has been demonstrated using biomechanical techniques by increased stability of the COM in the frontal plane during single-task gait (Parker *et al.,* 2005) and less separation between the COM and COP in concussed subjects (Parker *et al.*, 2006). In dual-task gait, larger COM ML deviations in dual-task gait have been found for concussed subjects compared to controls (Catena *et al.* 2007; Parker *et al.*, 2007), and sway area and sway velocity remain higher up to 28 days post-concussion (Parker *et al.*, 2006), indicating that the ability to maintain a conservative gait strategy may be diminished with divided attention.

3.4.4 Clinically available biomechanical functional balance instrumentation

There is continued work on the development of commercially-viable objective measures of functional balance. While using accelerometers on the lumbar spine during dual-task walking, Howell *et al.* (2015) found significantly lower peak ML acceleration during the gait cycle among concussed patients for the first two months post-concussion, agreeing with previous studies reporting a conservative gait strategy (Howell *et al.*, 2013; Lee *et al.*, 2013; Parker *et al.* 2006). Johnston *et al.* (2019) found that rugby players who went on to sustain a concussion during the season had higher sample entropy, indicating increased signal irregularity, in the anterior reach of the Y balance test, as measured from an inertial sensor on the lumbar spine. Concussed individuals also exhibited decreased trunk local dynamic stability and increased stride time variability during dual-task walking compared to matched controls in a study using accelerometers placed on the trunk and head. (Fino, 2016). At 30 days post-concussion, athletes also had increased variability of the COM in the ML direction when approaching obstacles (Baker & Cinelli, 2014). These deficits indicate diminished control of gait stability and are encouraging methods to portably measure biomechanical measures of gait.

3.5 Recommendations for future directions

Clinical standing balance methods such as the BESS, SOT, and CTSIB are sensitive to concussion acutely, but lose sensitivity as soon as three days post-concussion (Murray *et al.*, 2014b). Clinical functional balance tasks fare better in terms of longitudinal sensitivity with spatiotemporal measures indicating deficits up to 3 months post-concussion (e.g. Buckley *et al.*, 2016)**.** Biomechanical balance in both standing and functional tasks appear to distinguish between healthy and concussed athletes well. For example, COP AP velocity and ApEn during quiet stance show group differences past RTP (Powers *et al.*, 2014; De Beaumont *et al.*, 2011), indicating poor sensorimotor integration. Measures of gait such as lower separation of the COM and COP in concussed subjects indicate a conservative gait strategy (Parker *et al.*, 2006). These continued deficits provide evidence that objective measures of biomechanical balance could offer a strong addition to the multidomain assessment of concussion, and work should continue into portable and clinically assessible methods to measure these deficits.

More work is needed to understand the sensitivity of balance assessment to concussion. The majority of studies focus on the significance of group differences between healthy and concussed athletes. Johnston *et al.*, (2019) appears to be the first study to determine sensitivity and specificity of a biomechanical balance test (sample entropy as measured from an inertial sensor during the Y balance test) and use this information to determine a preliminary cutoff score that determines athletes at risk for sustaining a concussion. This method is a clinically relevant application that has implications for athlete monitoring procedures and potential preventative vestibular and sensorimotor rehabilitation. Work should continue to determine the sensitivity and possible cutoff scores of biomechanical balance variables that have shown significant differences between healthy and concussed athletes. Ideally, cutoff scores could prospectively determine athletes at risk for concussion and aid in objective measurement during the concussion diagnosis and recovery process. Objective measurement may, in turn, lower the known risk of repeated concussion and post-concussion lower-extremity injuries (McCrea *et al.*, 2020; Herman *et al.*, 2017), which are thought to be due to continued neuromuscular deficits past RTP.

Ideally, biomechanical balance can also be used as a biomarker for concussion. While biomechanical balance is an ideal example of a clinically useful biomarker because it is inexpensive, non-invasive, can be simple to use, and has the potential to be scientifically tested (Horak & Mancini, 2013), the specific measures must be proven to fit the criteria for a biomarker through association to pathophysiological markers from imaging or blood (Horak & Mancini, 2013), and to patient improvements including reduction of falls, lower extremity injuries, and repeated concussion (Melzer *et al.*, 2010; Norris *et al.*, 2005).

If biomechanical balance variables are validated as biomarkers for concussion, the next proposed step is clinical translation. A device or application that is available and accessible for front-line providers, including athletic trainers, coaches, and athletes, is a vital step in translating academic knowledge into a useful outcome for individual athlete health. Vestibular and sensorimotor rehabilitation options should also be assessed for the ability to assist athletes in developing safe movement patterns. In a case study, Prangley *et* *al.* (2017) found that a 4-week protocol of vestibular training exercises increased balance control in individuals with post-concussion syndrome (PCS), indicating that rehabilitation may be useful for recovery of sensory integration. These steps are important both for athletes found to be at risk for sustaining a concussion, and for athletes in recovery post-concussion.

Finally, more data is needed on individual case study athletes. While group trends are an important first step in understanding the significance and sensitivity of various balance measures to concussion, the concussion recovery process is complex and multifaced, and must be assessed individually for each athlete due to differences in injury severity and varying demands of particular sports. Determining the true applicability of sensitive balance measures and rehabilitation techniques will lie in robust and high-volume individual case study analysis.

CHAPTER 4: DETAILED METHODS AND SINGLE ATHLETE DATA EXAMPLES

4.1 Introduction

The objective of this dissertation is to increase the clinical relevance of biomechanical balance measures through measuring the discriminative ability and sensitivity of balance measures and applying balance measures to models of multidomain concussion assessments. Each athlete participated in a multidomain evaluation in the Human Dynamics Laboratory at DU that consisted of instrumented standing and functional balance tasks, neurocognitive assessment, oculomotor assessment, vestibular-ocular assessment, a blood draw, and symptom tracking. Standing balance is arguably more appropriate for clinical use than functional balance due to the portability of sensitive devices (e.g. Wii balance board) and the ability to integrate biomechanical balance algorithms into software that first responders, including coaches and athletic trainers, can use. Therefore, while both standing and functional balance were assessed in the concussion study protocol, this dissertation will focus only on standing balance moving forward. Additionally, the vestibular-ocular assessment and blood biomarker results are not included in this analysis. This chapter outlines the methods used to assess Aims 1-3, and includes single athlete data examples to provide an introduction to the experimental chapters.

Each concussed athlete was evaluated at four timepoints post-concussion: <3 days, 1 week, 1 month, and 6 months. Symptom tracking was only assessed at two timepoints post-concussion: <3 days, and 1 week, as further symptom tracking post-concussion is not routinely collected in the National Collegiate Athletic Association (NCAA) protocol. Healthy athletes without concussion history and athletes reporting a history of concussion were evaluated at a single time point while not actively in season for their sport.

In **Aim 1**, linear measures of the COP for each standing balance task were evaluated for healthy athletes without concussion history at a single timepoint and at the four post-concussion timepoints for athletes sustaining a concussion. The measures from concussed athletes were 1) compared to the sport-matched non-concussed athlete group at each timepoint and 2) used to determine diagnostic thresholds based on sensitivity and specificity.

In **Aim 2**, linear and nonlinear measures of the COP for each standing balance task were evaluated for healthy athletes without concussion history and athletes reporting history of concussion at a single timepoint. The measures from the concussed athletes were 1) compared to the sport-matched non-concussed athlete group to assess group differences that may indicate lasting deficits.

In **Aim 3**, the discriminative and sensitive standing balance measures from Aim 1, neurocognitive testing composite scores, task completion times and error counts from the oculomotor test, and total symptom score were evaluated for healthy athletes without concussion history at a single timepoint and for athletes sustaining a concussion at the four post-concussion timepoints. The measures from concussed athletes were 1) compared to the sport-matched non-concussed group at each time point and 2) used to determine the most longitudinally sensitive logistic regression model of multidomain concussion assessments.

4.2 Participants

Detailed explanations of participants for each of the three aims are available in the individual experimental chapters (Aim 1: Chapter 5, Aim 2: Chapter 6, Aim 3: Chapter 7). A combined cohort of 186 NCAA Division I (DI) athletes at the University of Denver participated in these Aims. **Aim 1 and 3** evaluated healthy athletes without concussion history at a single timepoint and athletes who sustained a concussion at four post-concussion timepoints. **Aim 2** evaluated healthy athletes without concussion history and athletes reporting history of concussion each at a single timepoint.

4.3 Standing balance apparatus

Standing balance data were collected using two force platforms (40cm x 70 cm) embedded side by side in the laboratory flooring (Bertec Corp), which measured ground reaction forces at 1000 Hz. The Airex Balance Pad (Airex AG, Sins, Switzerland) was used for tasks requiring a foam surface. The balance pad fit within the dimensions of each force platform and is consistent with foam used in the sports medicine facility by the National Collegiate Athletic Association (NCAA) Division I (DI) athletes at the University of Denver.

4.4 Procedure

Standing balance tasks included all stances from the BESS test (University of North Carolina, Chapel Hill, NC) performed with a single foot on force platforms. The BESS protocol consists of three eyes-closed standing balance stances (single-leg stance, double-leg stance, and tandem stance) performed for 20 seconds on two surfaces (hard surface and foam surface). For this study, BESS tasks were performed for 30 seconds on the force platform, and the first 5 seconds and last 5 seconds of trial data were removed as to capture only balance rather than movement into or out of the stance position. The double-leg and tandem stances were performed with each foot on a separate force platform and separate foam balance pad while maintaining consistency with BESS protocol instructions for stance positioning. Results from the standing balance tasks are evaluated in **Aims 1-3**.

In the same testing session as balance testing, each athlete completed the King-Devick (KD) test administered by the session tester, and the computerized Immediate Post-concussion Assessment and Cognitive Testing (ImPACT) assessment. The KD test is a portable, sideline oculomotor examination in which athletes read a series of numbers as fast and with the least amount of errors as possible. Task completion time and error count are recorded for each of the three tests that are sequentially harder. The ImPACT consists of 8 tasks: immediate word recall, delayed word recall, immediate design recall, delayed design recall, symbol-matching, 3-letter recall, X's and O's test, and color-matching. Results from these tasks are grouped into five score categories: verbal memory, visual memory, visual motor speed, reaction time, and impulse control. Symptom scoring was collected pre-season (baseline) and post-concussion daily until symptoms resolved by NCAA D1 athletic trainers at the University of Denver. Athletes rated a series of 22 symptoms individually on a scale from 0-6. All individual symptom scores were summed for a total symptom score. Results from all multidomain tasks are evaluated in **Aim 3**.

4.5 Balance data processing

Linear measures of the COP, including ellipse area and average COP velocity (Total, ML, AP), and nonlinear measures of the COP, including sample entropy (ML, AP), were calculated for all BESS trials using customized Matlab code. **Aim 1** evaluates linear measures of the COP, and **Aim 2** evaluates both linear and nonlinear measures. The following process outlines variable calculation from the raw data.

<u>Step 1: Filtering</u>

All data were filtered using a 4th order low-pass Butterworth filter with a 5 Hz cutoff (**Equations 1 and 2**; **Figure 4.1**; Carpenter *et al.*, 2010) in Matlab. The sampling rate of the force platforms was 1000 Hz.

$$[b, a] = butter\left(4, \frac{cutoff}{\frac{sample\_rate}{2}}, 'low'\right) \tag{1}$$

$$filtered\_data = filtfilt(b, a, data) \tag{2}$$

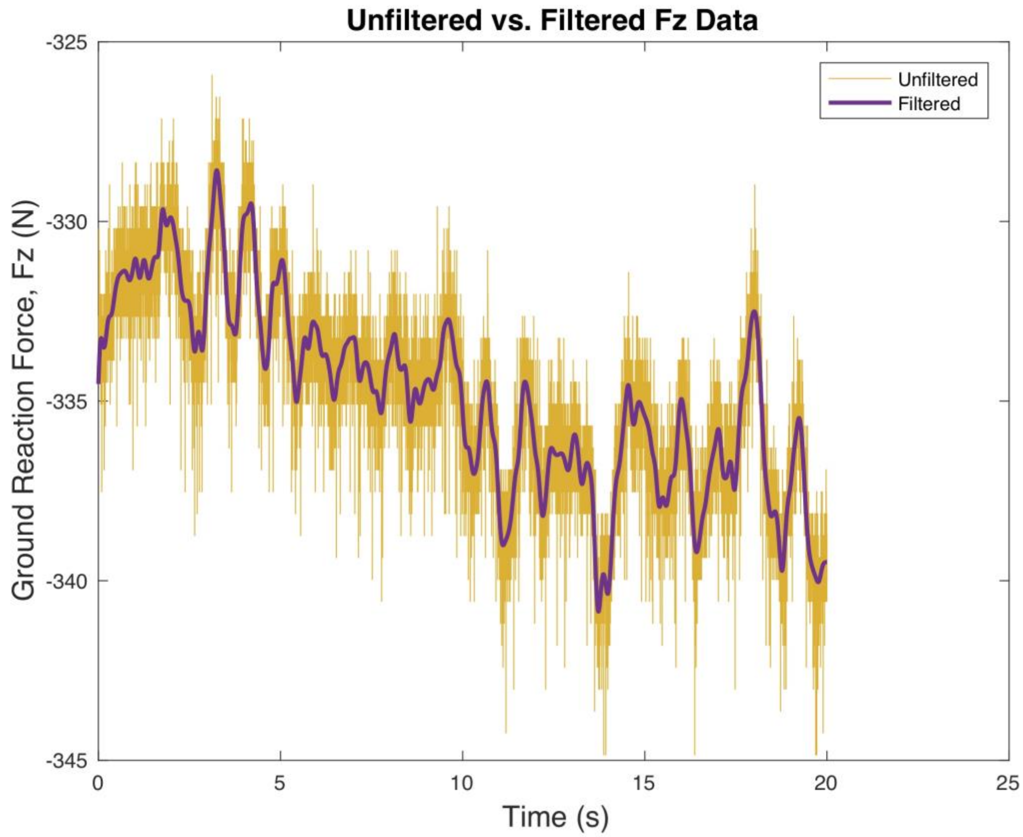

Figure 4.1. A visual representation of the 4th order low-pass Butterworth filter. This example shows ground reaction force data in the Fz direction before and after the filter was applied. The data is from a single force platform during a double-leg stance task where weight is spread across two force platforms.

Step 2: Transformation of double-leg stance and tandem stance forces and moments

Due to the different orientations and separate coordinate systems of the force platforms, force platform data for double-leg and tandem stances in which the athlete is standing on two force platforms were transformed to the same coordinate system. The double-leg stance transformation process is detailed below as an example (**Figure 4.2**).

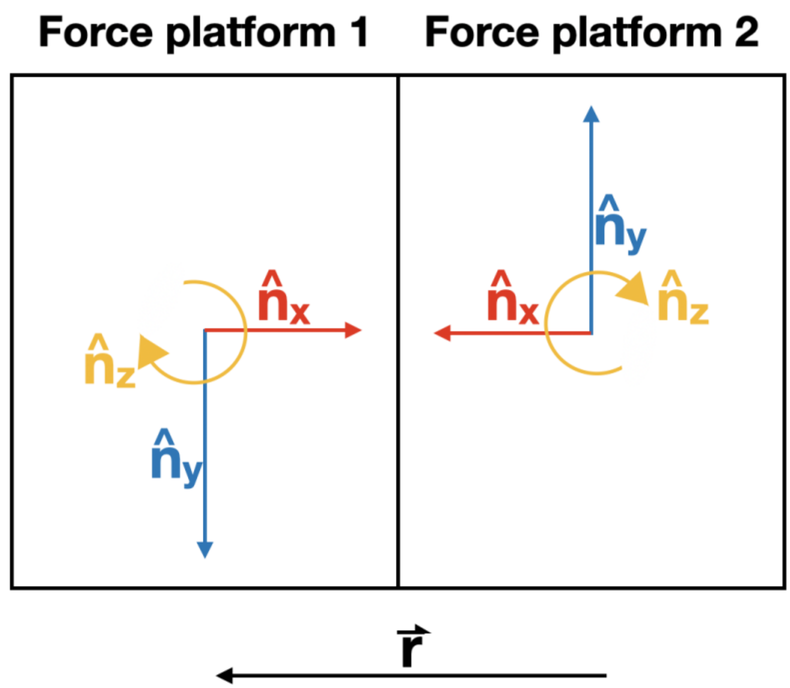

Figure 4.2. The orientation and individual coordinate systems of the two force platforms in the Human Dynamics Laboratory at the University of Denver utilized for the double-leg and tandem stance tasks.

In this transformation, the axes of the local coordinate system of force platform 2 (FP2) are rotated and translated to the local coordinate system of force platform 1 (FP1). The transformation matrix is the 3-dimensional matrix consisting of the direction cosines of the coordinate axes. In general form (**Equation 3**):

$$[T] = \begin{bmatrix} \cos\theta_{11} & \cos\theta_{12} & \cos\theta_{13} \\ \cos\theta_{21} & \cos\theta_{22} & \cos\theta_{23} \\ \cos\theta_{31} & \cos\theta_{32} & \cos\theta_{33} \end{bmatrix} \quad (3)$$

For this specific case, both the x- and y-axes are rotated by 180º (**Equation 4**). The z-axis of FP2 is not rotated with respect to FP1:

$$[T] = \begin{bmatrix} -1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \tag{4}$$

Using this transformation matrix, the measured forces from FP2 are transformed into the local coordinate system of FP1 (**Equation 5**, where superscript '1' denotes measured values from FP2 and superscript '2' denotes transformed values of FP2):

$$\begin{bmatrix} F_x^2 \\ F_y^2 \\ F_z^2 \end{bmatrix} = \begin{bmatrix} -1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \cdot \begin{Bmatrix} F_x^1 \\ F_y^1 \\ F_z^1 \end{Bmatrix} \tag{5}$$

The measured moments from FP2 are transformed into the local coordinate system of FP1 by **Equation 6**:

$$\begin{Bmatrix} M_x^2 \\ M_y^2 \\ M_z^2 \end{Bmatrix} = \begin{bmatrix} -1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \cdot \begin{Bmatrix} M_x^1 \\ M_y^1 \\ M_z^1 \end{Bmatrix} + \vec{r} \times \begin{Bmatrix} F_x^2 \\ F_y^2 \\ F_z^2 \end{Bmatrix} \tag{6}$$

Where $\vec{r}$ is a vector describing the displacement (in mm) of the origin of FP2 with respect to FP1 (**Equation 7**):

$$\begin{Bmatrix} M_x^2 \\ M_y^2 \\ M_z^2 \end{Bmatrix} = \begin{bmatrix} -1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \cdot \begin{Bmatrix} M_x^1 \\ M_y^1 \\ M_z^1 \end{Bmatrix} + \begin{bmatrix} -400 \\ 0 \\ 0 \end{bmatrix} \times \begin{Bmatrix} F_x^2 \\ F_y^2 \\ F_z^2 \end{Bmatrix} \tag{7}$$

<u>Step 3: Cutting trial length for trials with BESS errors</u>

During the single-leg and tandem stances, many athletes were unable to complete the full 30 seconds without performing an error. Consistent with the BESS protocol, athletes were instructed to return to the testing position as quickly as possible following an error. To account for these errors, we used a method similar to that of Riemann *et al.* (1999). In this method, the trial was cut to the longest length of time a subject could maintain 90% bodyweight on the force platform, and any trial that contained less than five seconds was excluded from analysis and replaced with an imputed value from trials meeting the trial length constraint (**Figure 4.3**).

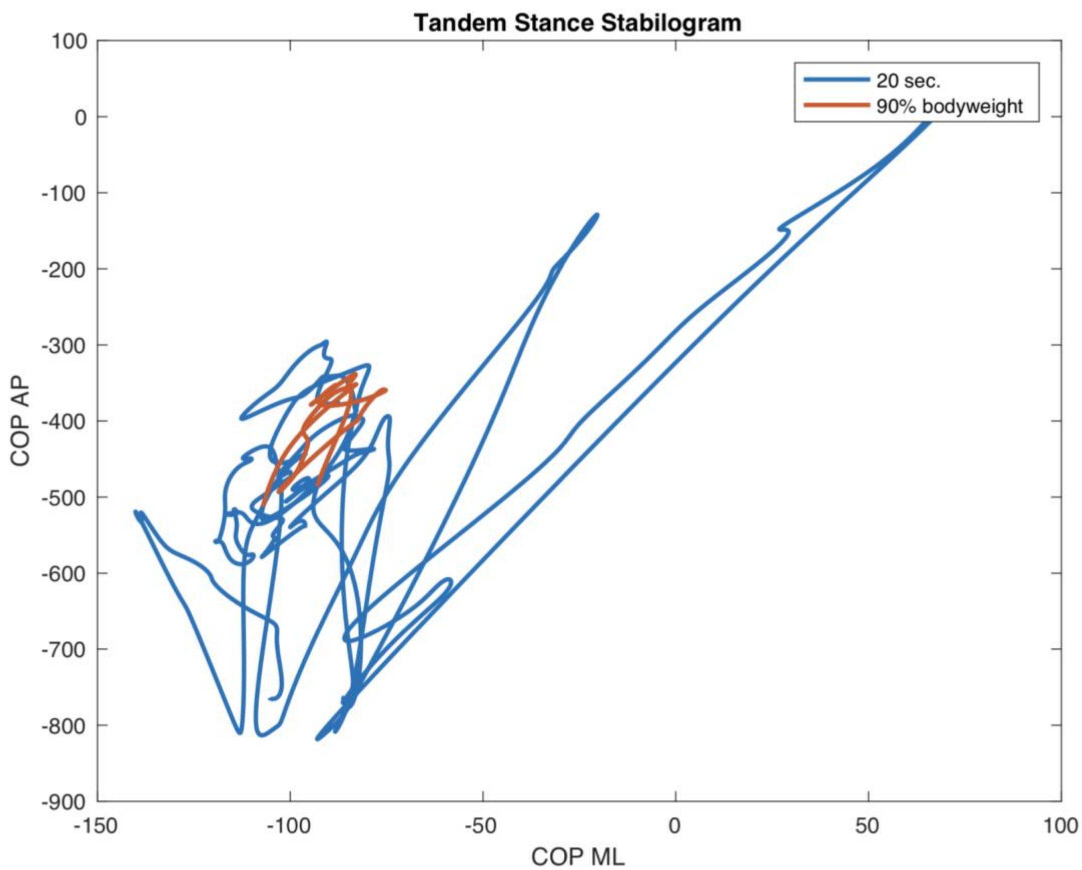

Figure 4.3. An example of a COP stabilogram for the tandem stance illustrating both the stabilogram for the entire trial and the stabilogram cut to the longest path in which the athlete was able to maintain 90% body weight over the force platform. While it is common to detrend stabilogram data, this is not performed in this case as to allow visualization of the 90% bodyweight path directly over that of the entire trial. It is clear that the athlete had step or sway errors in the full trial due to the large displacements of the COP. These errors are omitted in the 90% bodyweight trial.

Step 4: Calculating center of pressure (COP)

COP along the x- and y-axes for FP1 (**Equations 8 and 9**) and FP2 (**Equations 10 and 11**) was calculated using the transformed force and moment data and accounting for the height of the lab flooring (hlab = 10 mm) and the height of the foam when applicable (hfoam = 65 mm):

$$COP_x^1 = ((-(hlab + hfoam) * F_x^1) - M_y^1)/F_z^1 \tag{8}$$

$$COP_y^1 = ((-(hlab + hfoam) * F_y^1) - M_x^1)/F_z^1 \tag{9}$$

$$COP_x^2 = ((-(hlab + hfoam) * F_x^2) - M_y^2)/F_z^2 \tag{10}$$

$$COP_y^2 = ((-(hlab + hfoam) * F_y^2) - M_x^2)/F_z^2 \tag{11}$$

Composite COP for the x- and y-axis is then calculated as (**Equation 12 and 13**):

$$COP_x = (F_z^1 * COP_x^1 + F_z^2 * COP_x^2)/(F_z^1 + F_z^2) \tag{12}$$

$$COP_y = (F_z^1 * COP_y^1 + F_z^2 * COP_y^2)/(F_z^1 + F_z^2) \tag{13}$$

Step 5: Calculating ellipse area and COP velocity

Ellipse area is calculated as the 95% confidence area of the COP position vector during the length of the trial. In general form (**Equation 14**):

$$Ellipse\ Area = 2 * \pi * F_{0.05[2,n-2]}(\sigma_{ML}^2 * \sigma_{AP}^2 - \sigma_{ML,AP}^2) \tag{14}$$

Where F is the F statistic at the 95% confidence level with n data points, σ_{ML} and σ_{AP} are the standard deviations of the ML and AP axes, respectively, and $\sigma_{ML,AP}$ is the covariance. For a large sample size, $F_{0.05[2,\infty]} = 3.00$ (Prieto & Myklebust, 1993). The standard deviations are calculated in **Equations 15 and 16** where i is the i_{th} value of the COP position vector ($COP_x = x_i$ and $COP_y = y_i$), and μ is the mean of the COP position vector:

$$\sigma_{ML} = \sqrt{\frac{\sum(x_i - \mu_x)}{n}} \tag{15}$$

$$\sigma_{AP} = \sqrt{\frac{\sum(y_i - \mu_y)}{n}} \tag{16}$$

The covariance is calculated as (**Equation 17)**:

$$\sigma_{ML,AP} = \frac{1}{n} * \sum(x_i - \mu_x)(y_i - \mu_y) \tag{17}$$

And the ellipse area accounting for the F statistic becomes (**Equation 18**):

$$Ellipse\ Area = 2 * \pi * 3\sqrt{{\sigma_{ML}}^2 * {\sigma_{AP}}^2 - {\sigma_{ML,AP}}^2} \tag{18}$$

Average COP velocity is calculated as the mean pathlength scaled by trial time. Pathlength is calculated as **(Equation 19**):

$$pathlength = \sum_{i=1}^{n} \sqrt{(x_{i+1} - x_i)^2 + (y_{i+1} - y_i)^2} \tag{19}$$

And the mean COP velocity is calculated as (**Equation 20**):

$$COP\ velocity = mean\left(\frac{pathlength}{trial\_time}\right) \tag{20}$$

COP velocity for the ML and AP axes are calculated by only accounting for the pathlength along the respective axis (**Equations 21 and 22**):

$$pathlength_{ML} = \sum_{i=1}^{n} \sqrt{(x_{i+1} - x_i)^2} \tag{21}$$

$$pathlength_{AP} = \sum_{i=1}^{n} \sqrt{(y_{i+1} - y_i)^2} \tag{22}$$

Step 6: Calculating sample entropy

Sample entropy (SampEn) measures the regularity of a time series, in this case, the COP ML or COP AP time series, and is a refinement of the approximate entropy (ApEn) technique (Yentes *et al.* 2013). ApEn generates a unitless number from 0 and 2 in which 0 denotes a perfectly regular time series, and 2 denotes an entirely random time series. The ApEn algorithm has a bias towards regularity due to counting each subseries as matching itself. SampEn does not count subseries self-matches, is more independent of data length, and shows high statistical validity (Groome *et al.* 1999). SampEn is calculated with four parameters m, r, τ, and n where m is subseries length, r is the similarity tolerance, τ is the sampling frequency, and n is data length. For these calculations, $m = 5$, r was set to 10% of the standard deviation (Sosnoff *et al.*, 2011), and τ was set to 10 Hz by data resampling at every 100th data point (Caccese *et al.*, 2016).

Assume a time series data length of n with a constant time interval τ, and a template vector with length m. SampEn is calculated as (**Equation 23**):

$$SampEn = -\log\frac{A}{B} \tag{23}$$

Where A is a distance function with the number of template vector pairs having $d[x_{m+1}(i), x_{m+1}(j)] < r$ and B is a distance function with the number of template vector pairs having $d[x_m(i), x_m(j)] < r$.

Step 7: Data exclusion procedure

The missing data slots in trials where the athlete could not maintain 90% body weight over the force platform for at least five seconds were assigned a random value (Hot-deck Imputation Method; Yan, 2011) sampled from existing trials of the timepoint. This replacement method provides a conservative estimate of balance performance in the concussed cohort because the value from the excluded trials, if measurable, would have shown a more substantial balance impairment than the replacement value.

4.6 Statistical analysis

4.6.1 Aim 1

Cohen's *d* effect size—with a 95% confidence interval—was calculated to compare the non-concussed group to post-concussion athletes at each timepoint. Groups were considered statistically different when the effect size was greater than 0.5 (moderate) and the 95% confidence interval did not cross or include zero. Cohen's *d* effect size (**Equation 24**) is calculated by subtracting the mean of the non-concussed, healthy athlete population (μ_{HA}) from the mean of the post-concussion population (μ_{PC}) scaled by the pooled standard deviation, *s*. This calculation is completed for each post-concussion timepoint separately.

$$d = \frac{\mu_{PC} - \mu_{HA}}{s} \tag{24}$$

Pooled standard deviation is calculated by (**Equation 25**):

$$s = \sqrt{\frac{(n_{PC}-1)\sigma_{PC}^2 + (n_{HA}-1)\sigma_{HA}^2}{n_{PC}+n_{HA}-2}} \tag{25}$$

For those results with moderate or higher effect sizes between non-concussed cohort and <3 days post-concussion, a linear mixed-effects model (**Equation 26**) was applied (R Foundation for Statistical Computing, Vienna, Austria) with the fixed effect of timepoint (non-concussed athlete, <3 days, 1 week, 1 month, and 6 months post-concussion) and the random effect of subject (Bates *et al.*, 2015, Kuznetsova *et al.*, 2017):

$$Variable \sim Days + (1|Subject) + \varepsilon \tag{26}$$

Models were fit with the restricted maximum likelihood (REML) algorithm and *p*-values for each post-concussion timepoint were calculated with the Kenward-Roger first-order approximation to maintain Type I error rate to 0.05 for the model fit (Luke 2017).

For each variable with moderate or large effects between the non-concussed athlete and <3 days timepoint, a receiver operating characteristic (ROC) curve was developed using the healthy athlete timepoint as non-concussed and the <3 days timepoint as concussed. Using only the data corresponding to the first post-concussion timepoint ensures that the curve is truly based on athletes that do and do not have the condition. To create a ROC curve, results for a single balance measure are numerically ranked with an indication of the presence or absence of the condition. For each ranked data point, the false positive rate (1 – specificity) and true positive rate (sensitivity) are calculated. The area under the ROC curve (AUROC) is calculated using the trapezoid method (**Equation 27**):

$$AUROC = \sum_{i=1}^{n} \frac{(x_i - x_{i-1}) * (y_i - y_{i-1})}{2} \tag{27}$$

The AUROC is commonly used as a measure of discriminative ability between conditions. An AUROC approaching 1 is considered excellent in terms of discriminative ability (**Table 4.1**).

Table 4.1. Discriminative ability classifications of AUROC ranges.

AUROC	CLASSIFICATION
0.90-1.0	Excellent
0.80-0.90	Good
0.70-0.80	Fair
0.60-0.70	Poor
0.50-0.60	Fail

For balance measures with fair or higher discriminative ability, the Youden Index (YI; *J*) was calculated for each data point (**Equation 28**):

$$J = Sensitivity + Specificity - 1 \tag{28}$$

For results with $J > 0.5$, the data point corresponding to the maximum YI was chosen as a cutoff value that is clinically useful to specify the incidence of concussion (Habibzadeh *et al.*, 2016). Sensitivity and specificity (**Equations 29 and 30**) are reported for results with an AUROC > 0.7 and YI > 0.5. In the following equations, true positive (TP) is the number of athletes at a post-concussion timepoint with a balance measure value that indicates the condition (above the threshold), true negative (TN) is the number of non-concussed athlete balance measure values that do not indicate the condition (below the threshold), false positive (FP) is the number of non-concussed athlete values that indicate the condition (above the threshold), and false negative (FN) is the number of athletes at a post-concussion timepoint with balance measure values that do not indicate the condition (below the threshold).

$$Sensitivity = \frac{TP}{TP+FN} \tag{29}$$

$$Specificity = \frac{TN}{TN+FP} \tag{30}$$

4.6.2 Aim 2

Aim 2 presents a simple statistical comparison of athletes with no history of concussion and athletes with concussion history. Due to non-normal distributions and unpaired data, *p*-values were calculated using the Wilcoxon rank-sum test with a null hypothesis that the medians of the populations are equal at a significance level of 0.05. In this test, the values from both groups are ordered and ranks are assigned. Rank observations from each group are summed (R_1 and R_2) and U is calculated as (**Equation 31**):

$$U = \min{(R_1, R_2)} \tag{31}$$

The null hypothesis is rejected if the probability of observing a value of U or lower is less than or equal to α=0.05 (**Equation 32**):

$$P(value \geq U) \leq \alpha \tag{32}$$

Following this, Rosenthal's r effect size was calculated for measures with $p \leq 0.05$ (**Equation 33**):

$$r = \frac{Z}{\sqrt{n}} \tag{33}$$

Where Z is the standardized Z-score and n is the total number of observations of both groups combined.

4.6.3 Aim 3

Cohen's d effect size (**Equation 24**)—with a 95% confidence interval—was reported to compare the non-concussed group to post-concussion athletes for each measure at each timepoint. A linear mixed-effects model was applied (R Core Team, 2019) with the fixed effect of timepoint (non-concussed athlete, <3 days, 1 week, 1 month, and 6 months post-concussion) and the random effect of subject (**Equation 26**; Bates *et al.* 2015; Kuznetsova *et al.*, 2017).

A receiver operating characteristic (ROC) curve was developed using the non-concussed athlete timepoint and the <3 days timepoint for each variable in each domain test, as in Aim 1. The measure with the highest AUROC from each domain was chosen for further analysis, with the exception of the balance domain, for which both measures were included.

The measures with the highest AUROC from each domain were used to form logistic regression models to determine the most longitudinally sensitive combination of objective multidomain tests. Logistical regression models were run in R using the generalized linear model (glm) function for all individual domains and multidomain combinations (see **Chapter 7**). The dependent, or target, variable was the probability that the athlete has or does not have a concussion at each post-concussion timepoint. A code example for a multidomain model is shown in **Equation 34**, where *Class* is the classification of non-concussed or concussed for an athlete:

$$glm(Class \sim Reaction\_time + COP\_velocity + Total\_symptoms \qquad (34)$$

The models were formed based on the non-concussed and acute (<3 days) timepoints and applied to all four post-concussion timepoints. This approach mirrors that used for the AUROC calculation to ensure that the models are based on athletes that do and do not have the condition. Due to class bias present in the sample, the data were resampled in equal proportions. 75% of the <3 days timepoint data were sampled for model training data, and the same number of data points were sampled from the non-concussed data for equal proportions. The remaining data at both timepoints were used as test data to statistically measure the performance of the model. A model cutoff score corresponding to the maximum Youden Index (**Equation 28**) was used to determine sensitivity and specificity (**Equations 29 and 30**).

4.7 Single-athlete data examples

In the following examples, data from one athlete is visualized pre- and post-concussion (non-concussed athlete and <3 days timepoint; **Aims 1 and 3**) or data from an athlete with a history of concussion is compared to a sport-matched athlete without a history of concussion (**Aim 2**). These examples are not meant to present findings; rather, they serve as a single-athlete case analysis to introduce the methods and measures presented in this dissertation.

4.7.1 Aim 1

In the single-athlete case analysis for **Aim 1**, data from the tandem stance on foam stance during the healthy athlete and <3 days timepoints are used to illustrate the COP measures. COP ML and AP are calculated as described in Step 4 of **Section 4.5**, after trials were cut to include only the longest continuous time where 90% body weight was over the force platform. The athlete maintains 90% body weight over the force platform for a notably lower time post-concussion compared to the non-concussed athlete timepoint (**Figures 4.4 and 4.5**). In the tandem stance, the ML component of the COP is under ankle control while the AP component of the COP is under hip control (see **Chapter 3**). The athlete was having considerable trouble maintaining ankle control post-concussion based on the large displacements of the COP ML data. Ankle extensors receive input from the lateral vestibulospinal tract, which can be damaged following vestibular injury such as in concussion. Damage to the lateral vestibulospinal tract is believed to cause greater COP displacement along the places associated with ankle torque (Powers *et al.*, 2014), which is supported in these data. Hip control appeared to be more successful at keeping the center of mass within the base of support, as COP AP displacements post-concussion are small in comparison to the non-concussed, healthy athlete data.

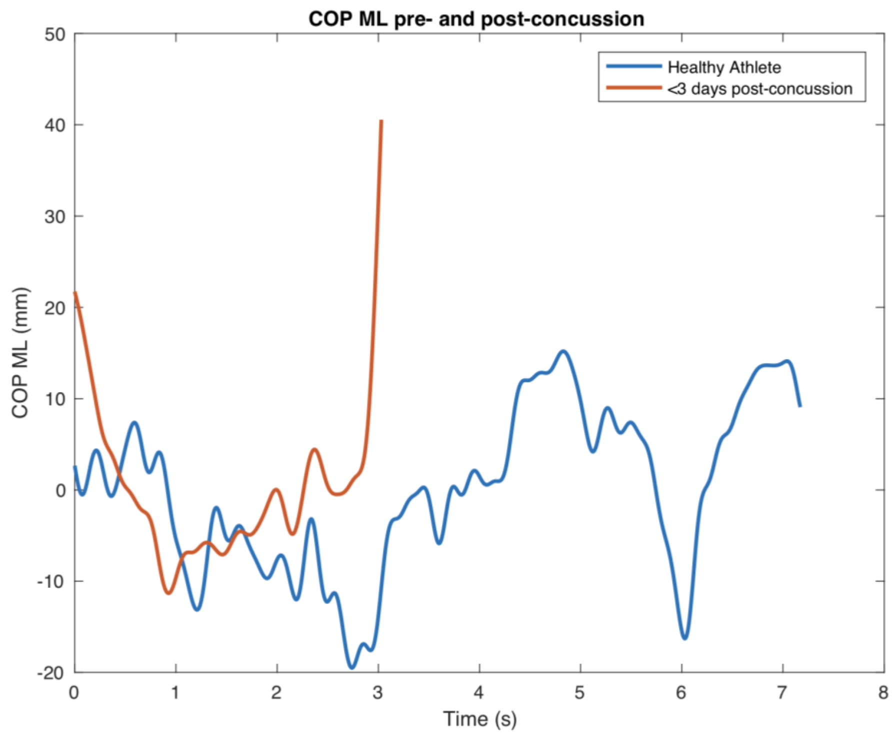

Figure 4.4. COP ML displacement over trial time for the non-concussed and <3 days post-concussion timepoints for a single athlete. The athlete maintains 90% body weight over the force platform for a shorter time post-concussion, and has trouble maintaining ankle control.

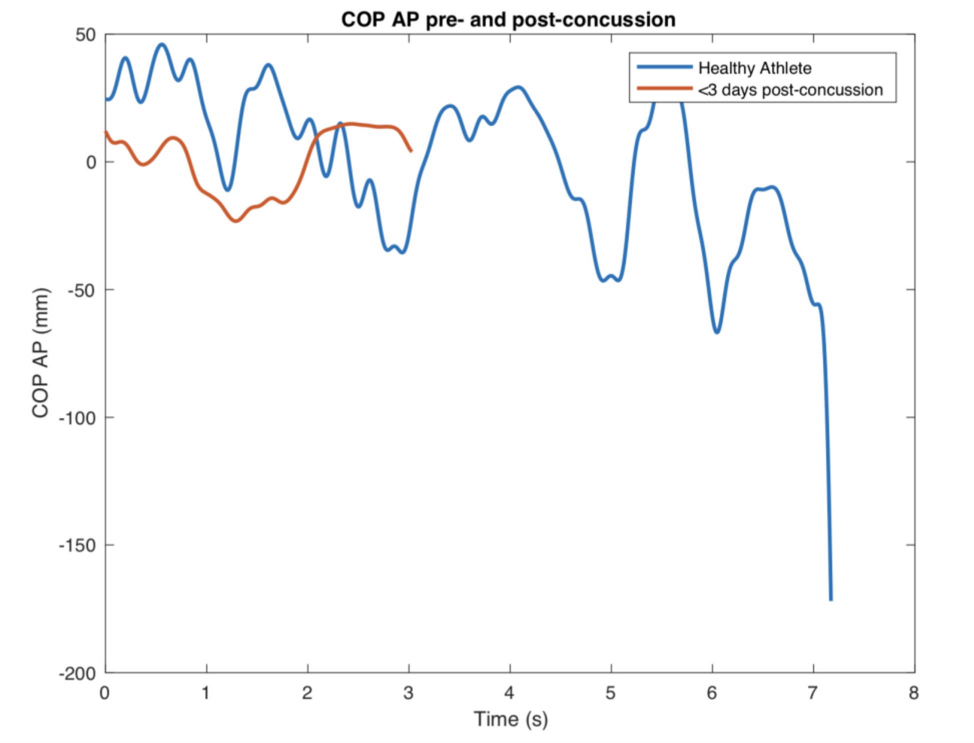

Figure 4.5. COP AP displacement over trial time for the non-concussed and <3 days post-concussion timepoints for a single athlete. While the athlete maintains 90% body weight over the force platform for a shorter time post-concussion during this period, hip control appears dominant.

COP stabilograms pre- and post-concussion illustrate that at both timepoints, the athlete was having difficulty maintaining the tandem stance on foam, as indicated by the deviations from the main stability area (**Figure 4.6**). The ellipse area is smaller post-concussion, demonstrating that balance moves to a conservative strategy post-concussion (**Figures 4.7 and 4.8**, see **Chapters 3 and 5**). In this case, the conservative strategy appears to be controlled by the increased success of hip control, demonstrated by a smaller COP AP displacement post-concussion.

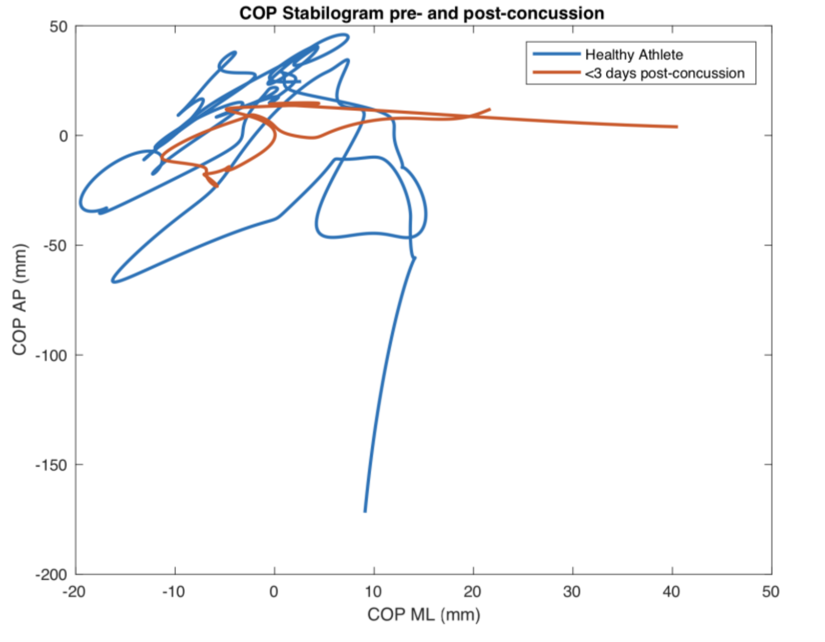

Figure 4.6. COP stabilogram for the non-concussed and <3 days post-concussion timepoints for a single athlete. The deviations from the main stability area indicate that the athlete was having trouble maintaining the stance at both timepoints.

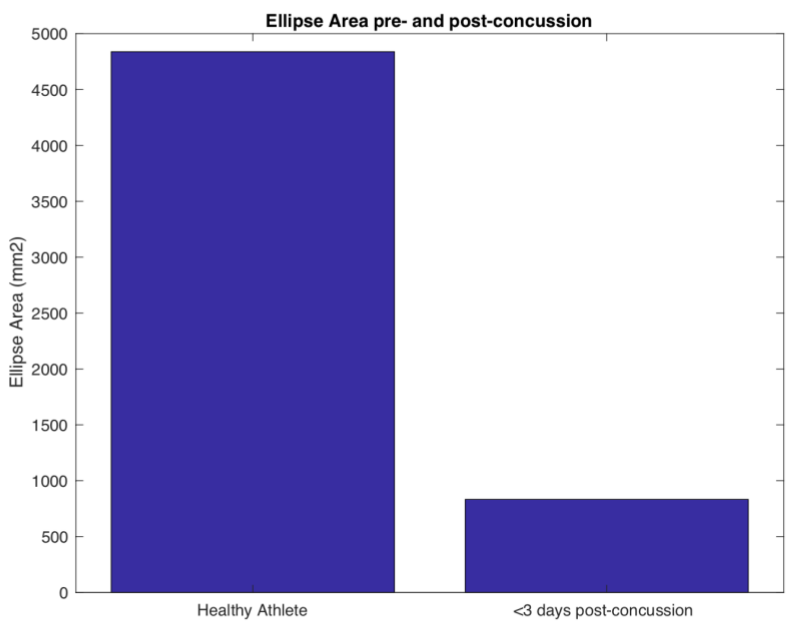

Figure 4.7. Ellipse area for the non-concussed and <3 days post-concussion timepoints for a single athlete. Ellipse area decreases post-concussion for this athlete, an indication of a more conservative strategy in this balance stance.

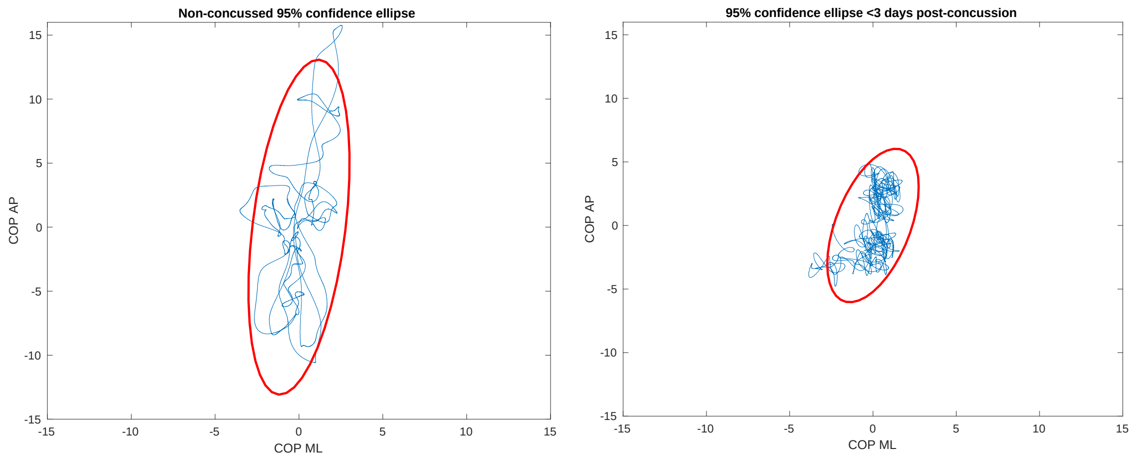

Figure 4.8. The 95% confidence ellipse plotted on a stabilogram for the non-concussed and <3 days post-concussion timepoints for a single athlete. The 95% confidence ellipse is notably smaller acutely after the injury, confirming a conservative balancing strategy.

Total, ML, and AP mean COP velocity decrease post-concussion for this athlete, further indicating the use of a conservative strategy post-concussion (**Figure 4.9**).

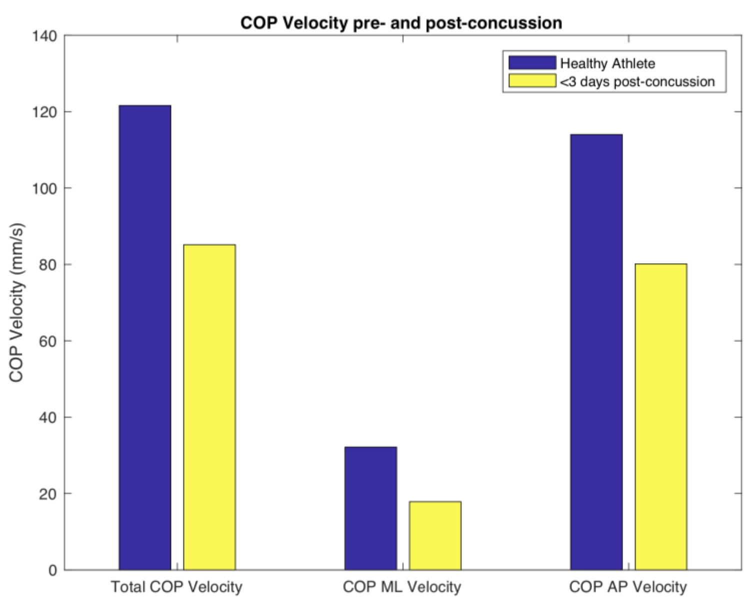

Figure 4.9. COP velocity (total, ML, AP) for the non-concussed and <3 days post-concussion timepoints for a single athlete. All measures decrease post-concussion for this athlete, indicating a more conservative strategy during the tandem stance on foam.

4.7.2 Aim 2

One athlete with a history of repeated concussion and one sport-matched non-concussed, healthy athlete are shown for the additional variables of sample entropy in the ML and AP directions in the double-leg stance on a hard surface. Both the ML and AP components of sample entropy are higher in the athlete reporting a history of concussion (**Figure 4.10**), indicating more irregular movement patterns post-concussion in the COP data series (see **Chapters 3 and 6**).

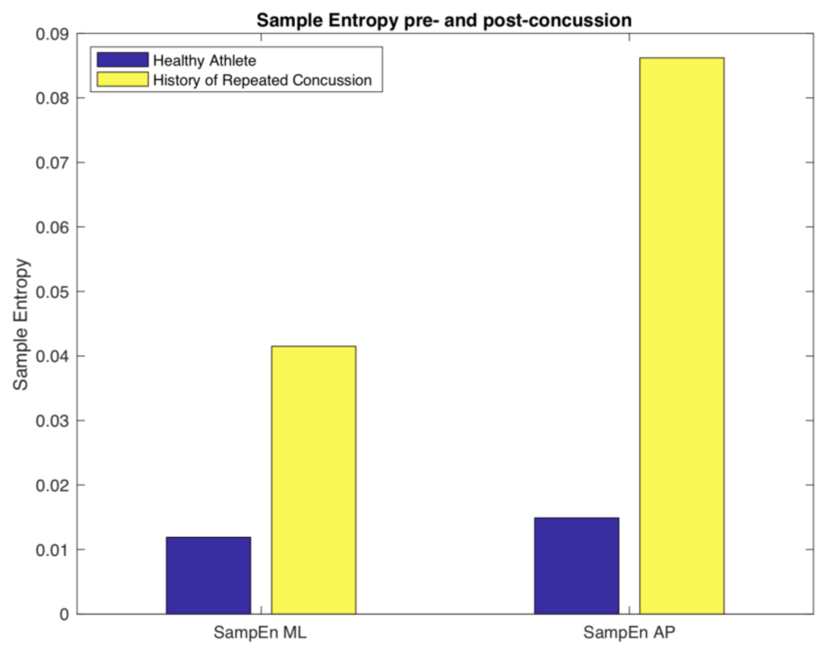

Figure 4.10. Sample entropy (ML, AP) is higher for a male hockey player with a history of repeated concussion relative to a male hockey player without a history of concussion, indicating more random COP movement patterns post-concussion.

4.7.3 Aim 3

The data from each of the multidomain tests are illustrated for the non-concussed athlete and <3 days timepoints, using the same athlete as the Aim 1 example. The memory composite scores do not appear sensitive to concussion for this athlete (**Figure 4.11**). The concussion did not impact the verbal memory score, and the visual memory score increases post-concussion, where a higher score indicates better memory function. Visual motor speed (VMS) also appears insensitive to concussion (**Figure 4.12**). VMS increases for this athlete post-concussion, where a higher VMS composite score indicates better performance. Reaction time was not affected by concussion, indicating that reaction time was not sensitive to concussion for this athlete (**Figure 4.13**). The impulse control composite score is the sum of errors over the different phases of testing. This athlete committed more errors post-concussion than at the non-concussed timepoint (**Figure 4.14**). This athlete reported no symptoms at the non-concussed timepoint. Post-concussion, this athlete reported a total symptom score of 8, indicating that the total symptom score is sensitive to concussion acutely (**Figure 4.15**). Task completion time for all three King-Devick (KD) tasks increases for this athlete post-concussion, indicating the potential sensitivity of this oculomotor task to concussion (**Figure 4.16**).

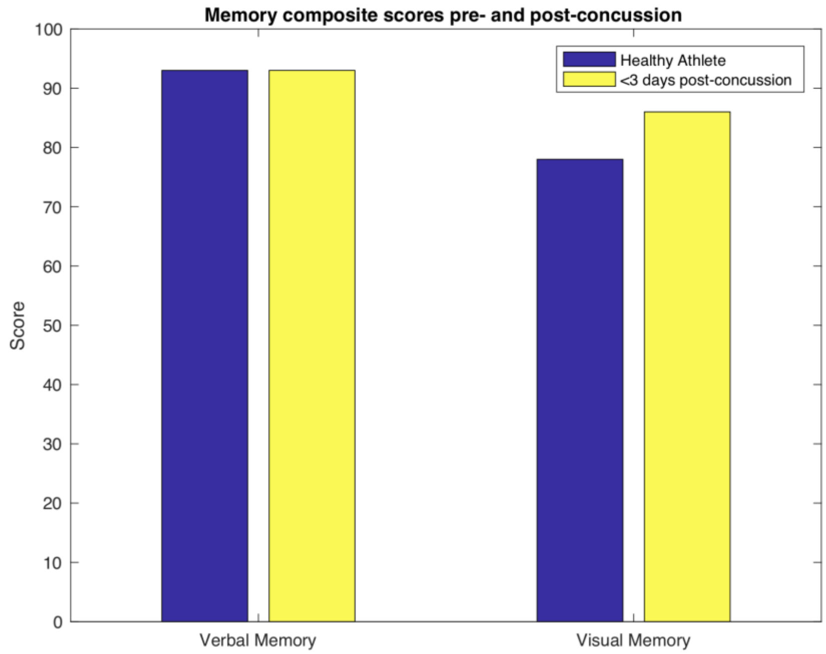

Figure 4.11. Verbal and visual memory composite scores for the non-concussed and <3 days post-concussion timepoints for a single athlete. The verbal memory composite score was not affected by concussion, and the visual memory score increased post-concussion, indicating that these memory composite scores are not sensitive to concussion for this athlete.

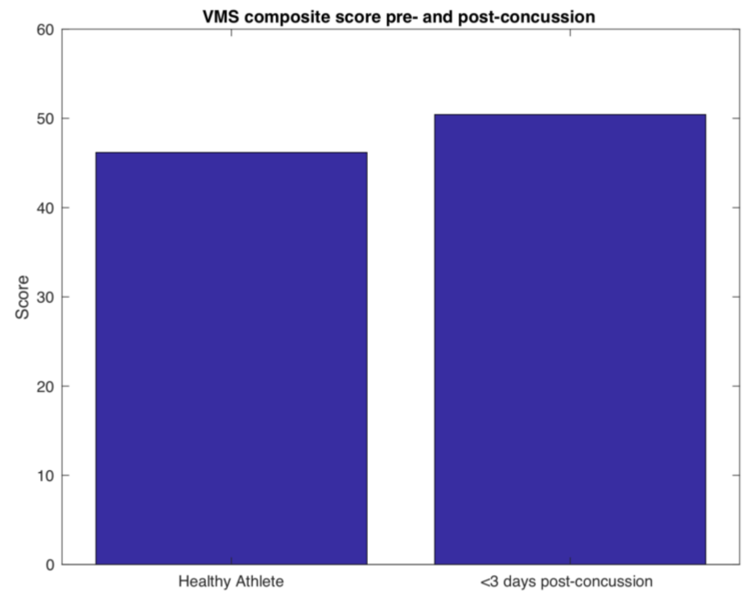

Figure 4.12. VMS composite score for the non-concussed and <3 days post-concussion timepoints for a single athlete. The score increases post-concussion for this athlete, indicating that this composite score is not sensitive to concussion.

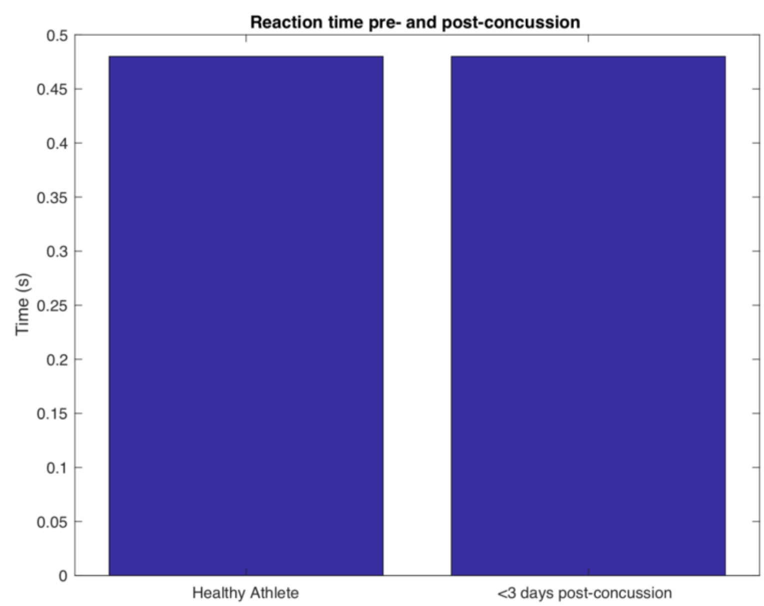

Figure 4.13. Reaction time for the non-concussed and <3 days post-concussion timepoints for a single athlete. This composite score was not affected by concussion for this athlete.

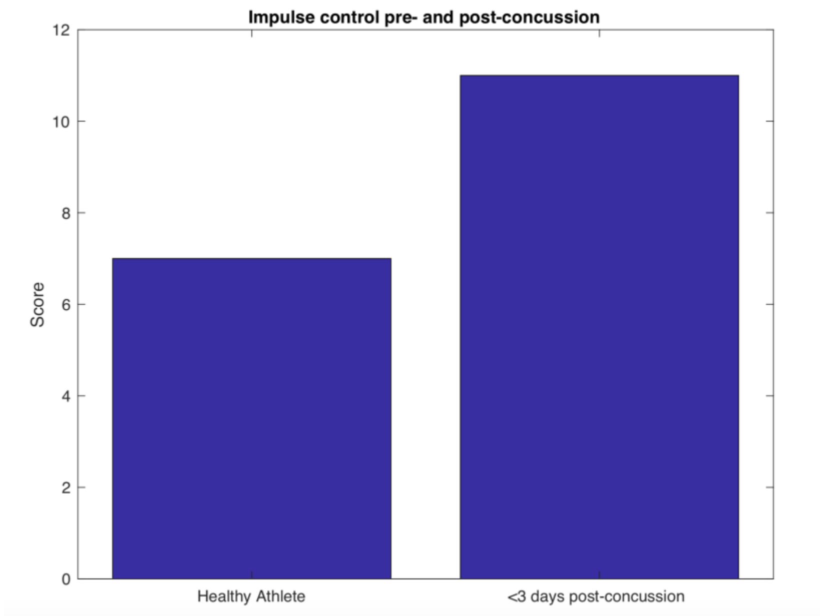

Figure 4.14. Impulse control composite score for the non-concussed and <3 days post-concussion timepoints for a single athlete. This athlete committed more errors during ImPACT testing post-concussion than at the healthy athlete timepoint.

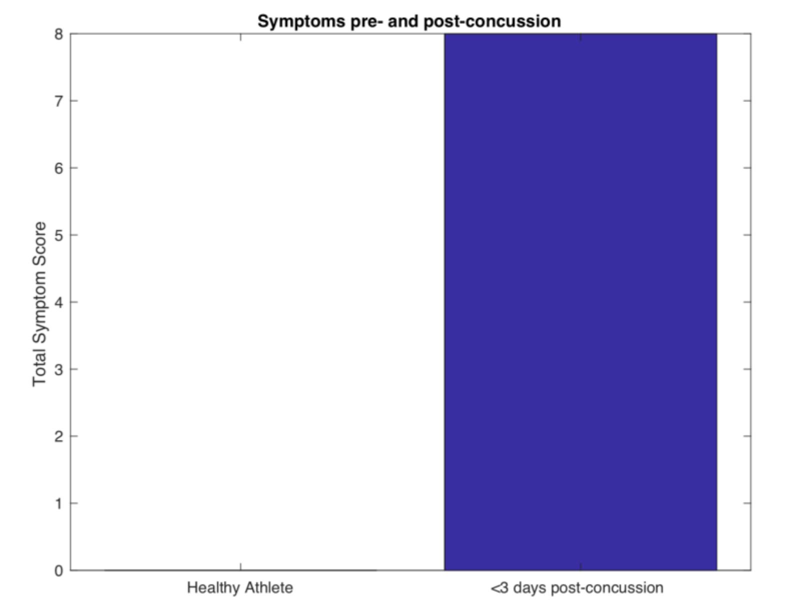

Figure 4.15. Total symptom score for the non-concussed and <3 days post-concussion timepoints for a single athlete. This score is sensitive to concussion acutely for this athlete.

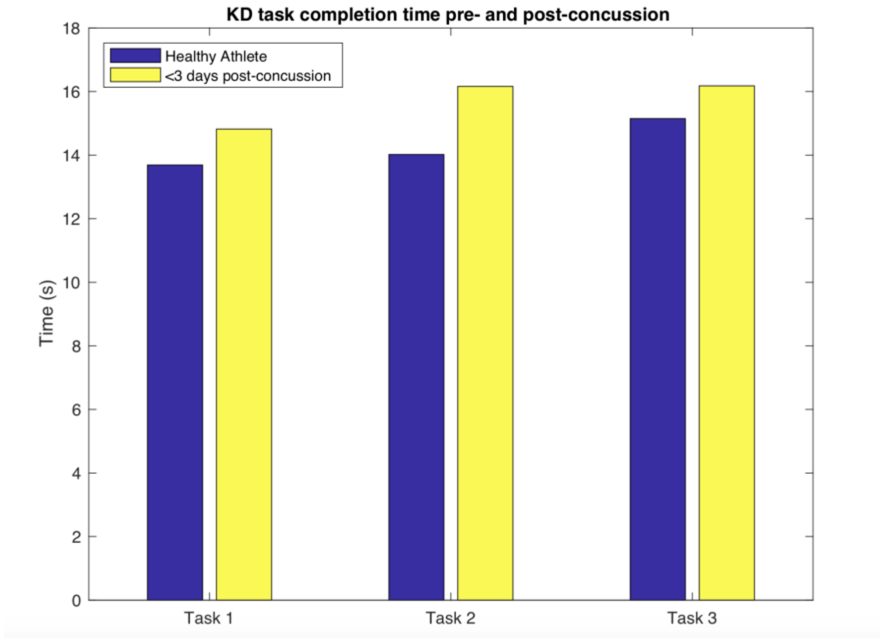

Figure 4.16. Task completion times in the three King-Devick (KD) tasks for the non-concussed and <3 days post-concussion timepoints for a single athlete. All three task completion times increase for this athlete post-concussion.

CHAPTER 5: ACUTE DEFICITS – LINEAR MEASURES OF BIOMECHANICAL STANDING BALANCE ASSESSED LONGITUDINALLY IN ATHLETES POST-CONCUSSION

5.1 Abstract

Sport-related concussion return to play (RTP) decisions are primarily based on the resolution of self-reported symptoms and neurocognitive function. Some evaluators also incorporate balance; however, an objective approach to balance that can detect effects beyond the acute condition is warranted. The purpose of this study (**Aim 1**) is to examine linear measures of biomechanical balance up to 6 months post-concussion, and to develop preliminary diagnostic thresholds useful for RTP. Each concussed athlete participated in instrumented standing balance tasks at four timepoints post-concussion. The measures from concussed athletes were compared to the sport-matched non-concussed athlete group at each timepoint. Center of pressure (COP) mediolateral (ML) velocity in double-leg stance on a hard surface discriminated between non-concussed and concussed athletes. COP anterior-posterior (AP) velocity in tandem stance on foam showed sensitivity to concussion. Nine of 15 athletes at 6 months post-concussion did not recover to within the proposed COP ML velocity threshold in a double-leg stance on a hard surface. Five of 7

athletes at 6 months post-concussion did not recover to within the COP AP velocity threshold in the tandem stance on foam. This lack of recovery potentially indicates vestibular and sensorimotor impairments past the typical period of RTP.

5.2 Introduction

Concussions are an ongoing safety issue in athletics. Up to 3.8 million sport-related concussions are diagnosed annually in the United States, and an estimated 50% of concussions go unreported (Harmon *et al.* 2013). Immediately following concussion, athletes can experience a host of clinical indicators such as reduced cognitive function, physical symptoms, emotional changes, and sleep disturbances. Conventionally, clinical symptoms (e.g. headache, dizziness, nausea) are reported by the athlete at the time of the injury and are tracked following a concussion, and after these symptoms resolve, the concussed athlete moves into a structured protocol for return to play (RTP). If the symptoms do not resolve within multiple weeks or months, the athlete is diagnosed with post-concussion syndrome (PCS; Asken *et al.*, 2017; Harmon *et al.*, 2013).

Although typically employed by most National Collegiate Athletic Association (NCAA) teams, evaluating readiness for RTP using self-reported clinical symptoms may be inadequate. Balasundaram *et al.* (2016) found that post-concussion symptom self-reporting was influenced by several factors, including alcohol consumption, mental fatigue, anxiety, and depression. Many researchers have concluded that best practice for concussion evaluation and RTP should embrace a multidomain approach, including assessments such as clinical symptoms, cognitive testing, and physical performance testing

(Lempke *et al.*, 2020). In fact, guidelines for managing concussion endorse multidomain baseline assessment for post-injury comparison (Casey *et al.*, 2016). Specifically, the NCAA's Diagnosis and Management of Sport-Related Concussion Best Practices Interassociation Consensus Document (NCAA Sport Science Institute, 2016) recommends that every athlete should have a baseline and post-injury assessment that includes self-report symptom evaluation, cognitive assessment, and balance evaluation.

According to Kazl & Torres (2019), an ideal approach for managing RTP is conservative and gradual, and is based on two items: 1) Resolution of symptoms with both rest and exertion and 2) Neurocognitive function returning to baseline. A gradual and individualized introduction back to full sports-play is also recommended, accounting for factors such as symptom, cognitive, and neurological screening resolution that consider an athlete to be symptom-free before RTP (Bazarian *et al.* 2006). The Sport Concussion Assessment Tool – 5th Edition (SCAT5) is the recommended standard from the Concussion in Sport Group (Echemendia *et al.* 2017) which includes immediate, on-field assessment and introduces a six-step screening system: athlete background, symptom evaluation, cognitive testing, neurological evaluation, delayed recall, and final decision.

Despite the clinical and academic focus on concussion assessment protocols and tools, most lack quantitative objectivity, which raises suspicion of their ability to measure readiness for RTP following a concussion. For example, the SCAT5, the recommended standard, relies on subjective qualitative measures such as self-reported symptoms and subjective quantitative measures such as observed balance errors. While reliability is not published for the SCAT5, an earlier version of the SCAT, the SCAT3, reports practice effects at a retest interval of 7 days and low reliability (Pearson's r=0.63, 0.49, 0.66, and 0.57 for symptoms, standardized assessment of concussion, full Balance Error Scoring System (BESS), and modified BESS, respectively; Chin *et al.*, 2016). In addition, competitive athletes are hesitant to report concussions and may not receive the clinical attention needed to avoid short- and long-term impairments. In a study of football players, 53% of concussions went unreported during a full season (Michael McCrea *et al.* 2004). These findings support past evidence that athletes may recognize symptoms of concussion, but do not seek medical care (Harmon *et al.*, 2013; Llewellyn *et al.*, 2014; McCrea *et al.*, 2004; Meehan *et al.*, 2013).

Balance measurement is a domain that has the potential to produce objective measurements of concussion; however, the current clinical implementation fails to demonstrate adequate sensitivity to concussion. The most common balance assessment used for concussed athletes is the Balance Error Scoring System (BESS), which is subjectively scored by counting the number of pre-defined errors that an athlete incurs during a series of 3 eyes-closed balance stances each performed on a hard surface and a foam pad. Learning effects, reliability, and sensitivity to concussion are a concern with the BESS test. Mulligan *et al.* (2013) found learning effects present until at least four weeks post-concussion, and McLeod *et al.* (2004) found learning effects up to 60 days post-concussion in a longitudinal study. Finnoff *et al.* (2009) reported that the total BESS score was found to be unreliable, and substantial changes in scores are necessary (9.4 points, interrater or 7.3 points, intrarater) before attributing changes to the athlete rather than the administrator. Murray *et al.* (2014) also found that BESS scores are unable to detect balance changes in an acute concussion cohort past the third recovery day, potentially due to the known learning effects.

Several investigators are considering biomechanically-based measures of balance as an objective tool to assess concussion in the acute period immediately following an injury and up to a month after the event. In studies evaluating acutely concussed athletes, linear measures of standing (static) balance, such as the 95% confidence ellipse that captures COP excursion (ellipse area) and the mean velocity of the resultant force vector under the foot (center of pressure velocity), are common. A recent meta-analysis found a significantly larger ellipse area in subjects two weeks post-concussion (Wood *et al.*, 2019). A larger ellipse area was also found during a double-leg eyes-closed task in subjects at 1-month post-concussion (Rochefort *et al.*, 2017). Concussed football players displayed a higher center of pressure (COP) anterior-posterior (AP) displacement acutely post-concussion compared to their non-concussed teammates (Powers *et al.*, 2014). While COP AP displacement decreased before RTP (an average of 26±15 days post-concussion) and was not significantly different from controls, average COP AP velocity remained elevated at RTP compared to controls in this cohort.

Most research on concussion metrics fails to follow the athlete beyond RTP, despite the increased risk for lower extremity injury and repeated concussion in athletes cleared for play (McCrea *et al.*, 2020; Herman *et al.*, 2017). The purpose of this study is to develop diagnostic thresholds of linear biomechanical balance measures for athletes, including acutely post-concussion and up to 6 months following injury. We develop these thresholds using data from a prospective cohort of NCAA Division I (DI) athletes post-concussion and a reference cohort without concussion history. To our knowledge, this is the first investigation to track objective measures of biomechanical balance at an interval of this length after RTP.

5.3 Methods

Each athlete participated in a balance testing session in the Human Dynamics Laboratory at the University of Denver that consisted of instrumented standing balance tasks. These tasks were part of an extensive comprehensive data collection that also included instrumented functional balance tasks, a neurocognitive assessment, a vestibulo-ocular assessment, and a blood draw. Each concussed athlete was evaluated at four timepoints post-concussion: <3 days, 1 week, 1 month, and 6 months. Each athlete without concussion history was evaluated at a single timepoint while not actively in season for their sport. We calculated linear measures of the COP for each standing balance task. The measures from concussed athletes were 1) compared to the sport-matched non-concussed group at each timepoint and 2) used to determined diagnostic thresholds based on sensitivity and specificity. This study was approved by the University of Denver IRB (Protocol 854307).

5.3.1 Participants

NCAA D1 athletes from the University of Denver (n=117) represented by basketball (8 females, 6 males), diving (1 female, 2 males), gymnastics (8 females), hockey (9 males), lacrosse (20 females, 16 males), soccer (11 females, 12 males), swimming (8 females, 9 males), and volleyball (7 females) participated in this study (**Table 5.1**). Twenty-five athletes sustained medically diagnosed concussion during this 3-year study. Three athletes sustained two concussions during this time and were re-enrolled separately for each concussion. While the original goal was to obtain baseline data for all eligible athletes and assess athlete recovery individually post-concussion, only five athletes who sustained concussion participated in baseline testing. Therefore, sport-matched data (n=92) from athletes with no reported history of concussion were used as a non-concussed athlete reference.

Table 5.1. Number of athletes in the non-concussed and post-concussion cohorts by sport and gender.

SPORT	NON-CONCUSSED FEMALE	NON-CONCUSSED MALE	CONCUSSED FEMALE	CONCUSSED MALE
BASKETBALL	2	6	2	0
DIVING	1	1	0	1
GYMNASTICS	6	0	3	0
HOCKEY	0	6	0	3
LACROSSE	15	12	7	4
SOCCER	8	12	3	0
SWIMMING	8	9	0	1
VOLLEYBALL	6	0	1	0

Concussed athletes (n=25) were asked to participate in 4 timepoints post-concussion: <3 days, 1 week, 1 month, and 6 months. Each timepoint was voluntary and required separate informed consent. Therefore, the number of athletes that participated in each timepoint varied as follows: <3 days (n=16), 1 week (n=19), 1 month (n=13), and 6 months (n=15). Only three athletes participated in all four timepoints.

5.3.2 Apparatus

Data were collected using two force platforms (40cm x 70 cm, Bertec Corp) embedded side by side in the laboratory flooring, which measured ground reaction forces at 1000 Hz. An Airex Balance Pad (Airex AG, Sins, Switzerland) was used for standing balance tasks requiring a foam surface. This balance pad fits within the dimensions of each force platform and is consistent with foam used in the sports medicine facility by the NCAA Division I athletes at the University of Denver.

5.3.3 Procedure

Standing balance tasks included all stances from the BESS test (University of North Carolina, Chapel Hill, NC) performed with one foot placed on each of the force platforms. The BESS protocol consists of three standing balance stances (single-leg stance, double-leg stance, and tandem stance) performed for 20 seconds with eyes closed both on a hard surface and on a foam surface. For this study, BESS tasks were performed for 30 seconds on the force platform. The first 5 seconds and last 5 seconds of trial data were removed to isolate balance rather than movement into or out of the stance position. Each of the three tasks was performed both on the force platform and a foam balance pad placed on the force platform, consistent with the BESS protocol. The single-leg stance was performed on a single force platform and a single foam balance pad. The double-leg and tandem stances were performed with each foot on a separate force platform and separate foam balance pad while maintaining consistency with BESS protocol instructions for stance positioning.

5.3.4 Data processing

All data were filtered using a 4th order low-pass Butterworth filter with a 5 Hz cutoff (Carpenter *et al.*, 2010). Using custom code (MATLAB 2017a, MathWorks, Inc., Cambridge, MA), ellipse area and average COP velocity (Total, ML, AP) were calculated for all BESS trials. During the single-leg and tandem stances, many athletes were unable to complete the full 30 seconds without performing an error. Consistent with the BESS protocol, athletes were instructed to return to the testing position as quickly as possible following an error. To account for these errors, we used a method similar to that of Riemann *et al.* (1999). In this method, the trial window was cut to the longest time a subject could maintain 90% bodyweight on the force platform (**Table 5.2)**, and any trial that did not contain greater than 5 seconds of continuous data was excluded from analysis (**Table 5.3**). Data from excluded trials were replaced with a random value (Hot-deck Imputation Method; Yan, 2011) sampled from existing trials of the same timepoint. This method provides a conservative estimate of balance performance in the concussed cohort because the value from the excluded trials, if measurable, would have shown a more substantial balance impairment than the replacement value.

Table 5.2. Mean and range of trial time in seconds for which athletes included in the analysis maintained 90% bodyweight over the force platform at each timepoint for the single-leg and tandem stances.

	SINGLE-LEG		TANDEM	
	Hard	**Foam**	**Hard**	**Foam**
NON-CONCUSSED	16.9 [6.1-20]	9.9 [5-20]	11 [5-20]	9.1 [5.1-20]
<3 DAYS	15.8 [5.3-20]	10.6 [5.3-20]	8.4[5.1-15.5]	6.4 [5.1-9]
1 WEEK	18 [7.8-20]	11 [5.3-20]	11.2 [5.5-20]	11.6 [6.5-19.9]
1 MONTH	18.6 [8-20]	10.2 [5.6-16.4]	11.9 [6.5-18.5]	10.3 [7-16.5]
6 MONTHS	17.9 [11.7-20]	11.4 [6.2-20]	11.8 [5.4-20]	8.4 [5.2-14.8]

Table 5.3. Number of athletes at each timepoint unable to maintain 90% body weight over the force platform for the single-leg and tandem stance tasks. The total number of athletes for each timepoint were as follows: non-concussed: n=117, <3 days: n=16, 1 week: n=19, 1 month: n=13, and 6 months: n=15.

	SINGLE-LEG		TANDEM	
	Hard	**Foam**	**Hard**	**Foam**
NON-CONCUSSED	3	29	15	48
<3 DAYS	1	2	2	10
1 WEEK	1	3	3	11
1 MONTH	0	2	3	6
6 MONTHS	0	2	1	8

5.3.5 Statistical analysis

Cohen's *d* effect size—with a 95% confidence interval—was calculated to compare the non-concussed athlete group to post-concussion athletes at each timepoint. Groups were considered statistically different when the effect size was greater than 0.5 (moderate), and the 95% confidence interval did not cross or include zero. Because the purpose of this study was to determine which measures were sensitive to concussion, only variables that were statistically different with at minimum a moderate effect size (d>0.50) from the non-concussed athlete cohort to the <3 days post-concussion timepoint—with confidence intervals that did not cross zero—were evaluated. For those results with moderate or greater effect sizes between non-concussed athlete and <3 days post-concussion, a linear mixed-effects model was applied (R Foundation for Statistical Computing, Vienna, Austria) with the fixed effect of timepoint (non-concussed athlete, <3 days, 1 week, 1 month, and 6 months post-concussion) and the random effect of subject (Bates *et al.*, 2015; Kuznetsova *et al.*, 2017). Models were fit with the restricted maximum likelihood (REML) algorithm, and p-values for each post-concussion timepoint were calculated with the Kenward-Roger first-order approximation to maintain Type I error rate to 0.05 for the model fit (Luke 2017). Results are reported as (Cohen's d effect size [Confidence interval], p-value) for each post-concussion timepoint.

For each variable with moderate or large effects between the non-concussed athlete cohort and <3 days timepoint, a receiver operating characteristic (ROC) curve was developed using the non-concussed athlete timepoint to indicate those who do not have the condition and the <3 days timepoint to indicate those who have the condition. Using only the data corresponding to the first post-concussion timepoint ensures that the curve is based on athletes that do and do not have the condition. An area under the ROC curve (AUROC) approaching 1 is considered excellent in terms of discriminative ability (**Table 5.4**). For results with fair or higher discriminative ability, the Youden Index (YI; J) was calculated for each data point. The YI is a performance metric that maximizes both sensitivity and specificity, which are inversely related in diagnostic tests with numeric data. For results with a $J > 0.5$, the data point corresponding to the maximum YI was chosen as a threshold that is clinically useful to specify the incidence of concussion (Habibzadeh *et al.*, 2016).

Sensitivity and specificity were also calculated for results with an AUROC > 0.7 and J > 0.5.

Table 5.4. Commonly reported classification system for the discriminative ability of the area under the receiver operating characteristic (AUROC) curve.

AUROC	CLASSIFICATION
0.90-1.0	Excellent
0.80-0.90	Good
0.70-0.80	Fair
0.60-0.70	Poor
0.50-0.60	Fail

5.4 Results

Three linear balance metrics: COP ML velocity in the double-leg stance on a hard surface, and total COP velocity and COP AP velocity in the tandem stance on foam, had moderate or larger effect sizes at all post-concussion timepoints, fair or higher AUROC, and J > 0.5. Sensitivities for each post-concussion timepoint were high for both total and AP COP velocity in the tandem stance on foam, and relatively low for COP ML velocity in the double-leg stance on a hard surface. Clinical thresholds were calculated for these three metrics and applied to a case study where the threshold was useful in one of the four post-concussion data points for COP ML velocity in the double-leg stance on a hard surface, and all four post-concussion data points for total and AP COP velocity in the tandem stance on foam.

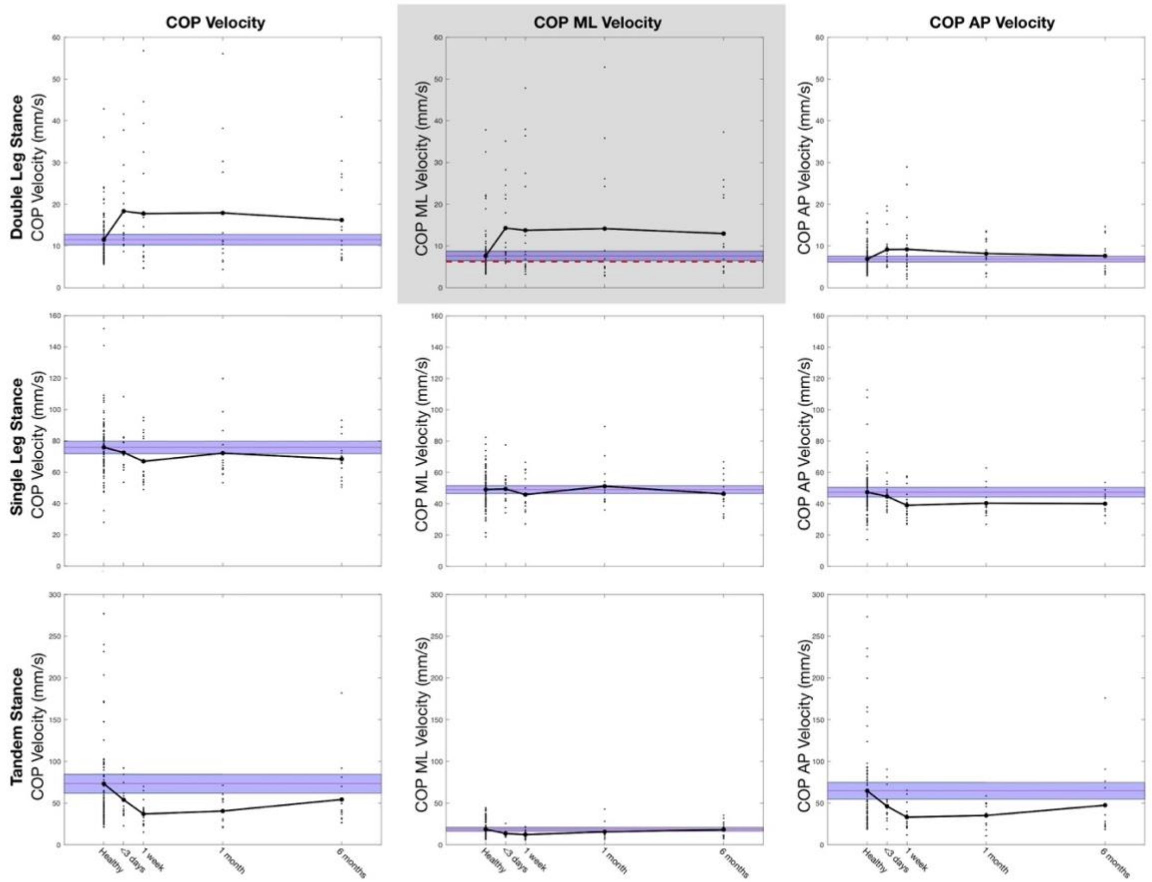

Figure 5.1. COP velocity (total, ML, AP) in mm/s for the stances on a hard surface for each of the five timepoints: non-concussed (healthy) athlete, <3 days, 1 week, 1 month, and 6 months. The connected dots are the means for each timepoint. The small dots are each of the individual athlete data points. The solid red line extrapolates the mean of the non-concussed athlete group across the graph area. The purple area indicates the 95% confidence interval of the non-concussed athlete mean. COP ML velocity in the double-leg stance was found to discriminate well between concussed and non-concussed athletes. The red dashed line (middle-top graph of COP ML velocity) indicates the proposed clinical threshold value.

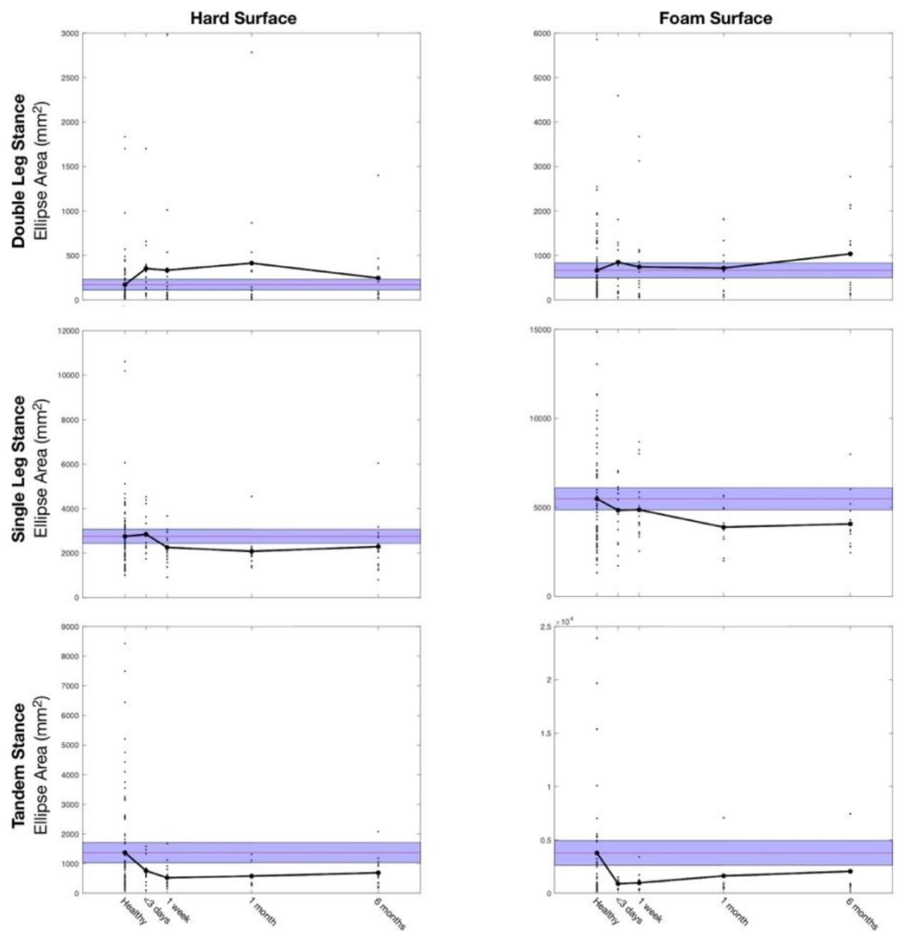

Figure 5.2. Ellipse area (mm2) for the six stances for each of the five timepoints: non-concussed (healthy) athlete, <3 days, 1 week, 1 month, and 6 months. The connected dots are the means for each timepoint. The small dots are each of the individual athlete data points. The solid red line extrapolates the mean of the non-concussed athlete group across the graph area. The purple area indicates the 95% confidence interval of the non-concussed athlete mean.

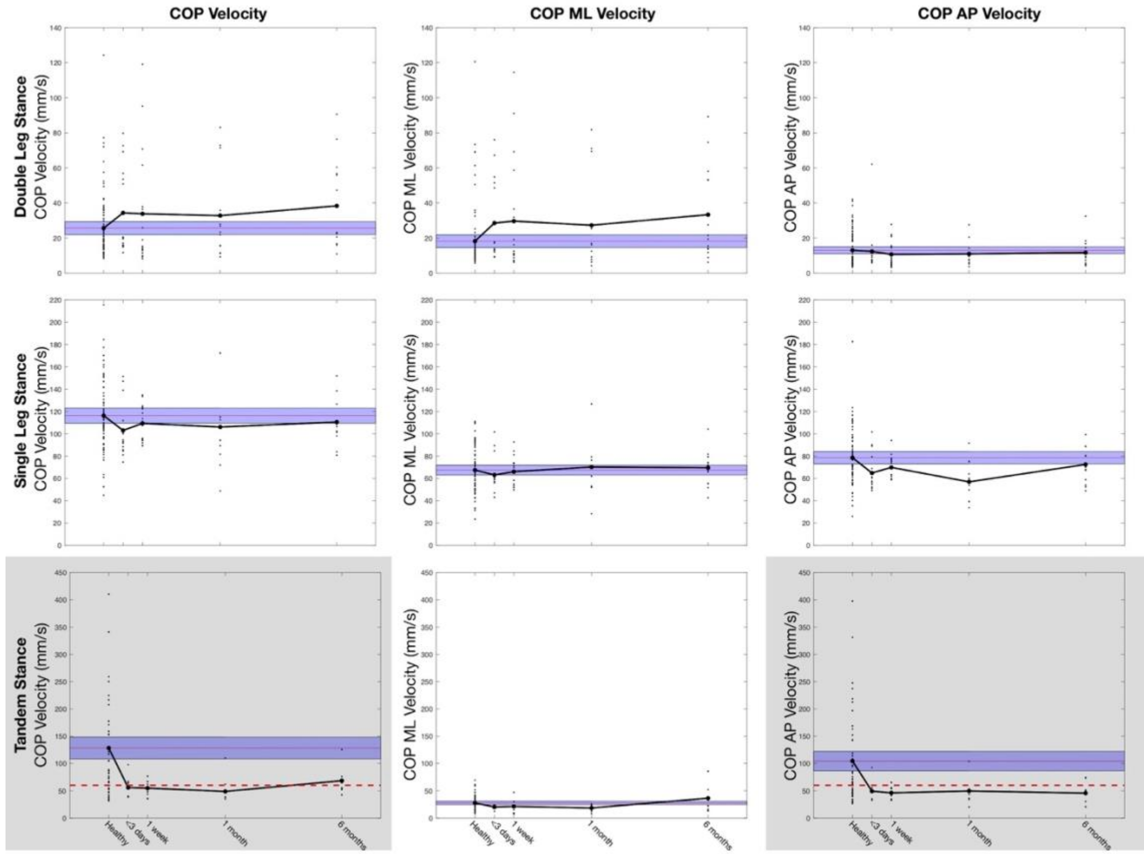

Figure 5.3. COP velocity (total, ML, AP) in mm/s for the stances on a foam surface for each of the five timepoints: non-concussed (healthy) athlete, <3 days, 1 week, 1 month, and 6 months. The connected dots are the means for each timepoint. The small dots are each of the individual athlete data points. The solid red line extrapolates the mean of the non-concussed athlete group across the graph area. The purple area indicates the 95% confidence interval of the non-concussed athlete mean. Total COP velocity and COP AP velocity in the tandem stance were found to be sensitive to concussion at all four post-concussion timepoints. The red dashed line (bottom left and right graphs of COP total and AP velocity) indicates the proposed clinical threshold value.

5.4.1 Effect sizes of linear balance measures

Results that demonstrated a moderate or large effect size between non-concussed athletes and athletes <3 days post-concussion are reported here, and full effect size results are available for all variables in **Appendix B: Tables B.1-B.3**. Ellipse area was larger, and total, ML, and AP COP velocity were higher post-concussion during the double-leg stance on a hard surface (**Figures 5.1 and 5.2**). Ellipse area was larger with a moderate effect within 3 days (*d*=0.60) and at 1 month (*d*=*0*.65), but not at 1 week (*d*=0.43) or 6 months (*d*=0.26) (**Table 5.5**). Total COP velocity had a large effect within 3 days (*d*=1.00), a moderate effect at 1 week (*d*=0.75), a large effect at 1 month (*d*=0.82), and a moderate effect at 6 months (*d*=0.68). COP ML velocity had a large effect within 3 days (*d*=1.06), 1 week (*d*=0.81), 1 month (*d*=0.87), and 6 months (*d*=0.82) post-concussion. COP AP velocity was significantly higher post-concussion with a moderate effect within 3 days (*d*=0.63), and at 1 week (*d*=0.55), but not at 1 month (*d*=0.38) or 6 months (*d*=0.22).

In the foam tasks (**Figures 5.2 and 5.3**), COP ML velocity was higher with a moderate effect post-concussion during the double-leg stance on foam <3 days with a moderate effect (*d*=0.57), 1 week (*d*=0.56), and a large effect at 6 months (*d*=0.80), but not at the 1 month timepoint (*d*=0.48). In the tandem stance on foam, ellipse area was lower with a moderate effect within 3 days (*d*=0.56) and 1 week post-concussion (*d*=0.55), but not 1 month (*d*=0.40) and 6 months post-concussion (*d*=0.32). Total COP velocity was lower with a large effect <3 days (*d*=0.81), 1 week (*d*=0.83), 1 month (*d*=0.87), and a moderate effect size at 6 months (*d*=0.66). COP AP velocity was lower with a moderate effect size within 3 days (d=0.69), 1 week (d=0.74), 1 month (d=0.67), and 6 months (d=0.73).

Table 5.5. 95% confidence interval of the effect size and *p*-value reported for all balance measures with an effect size of 0.5 or greater at the <3 days post-concussion timepoint.

STANCE	SURFACE	BALANCE MEASURE	TIMEPOINT	EFFECT SIZE (*D*)	CONFIDENCE INTERVAL	*P*-VALUE
DOUBLE-LEG	Hard	Ellipse area	<3 days	0.6	[0.06, 1.14]	0.99
			1 week	0.43	[-0.07, 0.93]	0.086
			1 month	0.65	[0.06, 1.24]	0.086
			6 months	0.26	[-0.29, 0.81]	0.158
		Total COP velocity	<3 days	1	[0.45, 1.55]	0.081
			1 week	0.75	[0.24, 1.26]	**0.011**
			1 month	0.82	[0.22, 1.42]	**0.023**
			6 months	0.68	[0.12, 1.24]	**0.04**
		COP ML velocity	<3 days	1.06	[0.50, 1.62]	0.074
			1 week	0.81	[0.30, 1.32]	**0.009**
			1 month	0.87	[0.27, 1.47]	**0.014**
			6 months	0.82	[0.26, 1.38]	**0.017**
		COP AP velocity	<3 days	0.63	[0.09, 1.17]	**0.0116**
			1 week	0.55	[0.05, 1.05]	**0.035**
			1 month	0.38	[-0.21, 0.97]	0.28
			6 months	0.22	[-0.33, 0.77]	0.433
	Foam	COP ML velocity	<3 days	0.57	[0.03, 1.11]	0.183
			1 week	0.56	[0.06, 1.06]	**0.048**
			1 month	0.48	[-0.11, 1.07]	0.115
			6 months	0.8	[0.22, 1.38]	**0.014**
TANDEM	Foam	Ellipse area	<3 days	0.56	[0.02, 1.10]	**0.005**
			1 week	0.55	[0.05, 1.05]	**0.002**
			1 month	0.4	[-0.19, 0.99]	**0.015**
			6 months	0.32	[-0.23, 0.87]	0.074
		Total COP velocity	<3 days	0.81	[0.26, 1.36]	**0**
			1 week	0.83	[0.34, 1.34]	**0**
			1 month	0.87	[0.27, 1.47]	**0**
			6 months	0.66	[0.10, 1.22]	**0.012**
		COP AP velocity	<3 days	0.69	[0.14, 1.24]	**0**
			1 week	0.74	[0.23, 1.25]	**0**
			1 month	0.67	[0.08, 1.26]	**0**
			6 months	0.73	[0.17, 1.29]	**0**

5.4.2 Discriminative ability and clinical thresholds

COP ML velocity in the double-leg stance on foam was categorized as poor for discriminative ability (area under the receiver operating characteristic curve; AUROC=0.65). In the double-leg stance on a hard surface, ellipse area and COP velocity had fair discriminative ability (AUROC=0.74, 0.76, respectively), COP ML velocity had good discriminative ability (AUROC=0.81), and COP AP velocity had poor discriminative ability (AUROC=0.68). For the tandem stance on foam, ellipse area had poor discriminative ability (AUROC=0.66), and COP velocity and COP AP velocity had fair discriminative ability (AUROC=0.76, 0.72, respectively). Maximum YI was calculated for all variables with fair or higher discriminative ability. Maximum YI's for ellipse area, COP velocity, and COP ML velocity in the double-leg stance on a hard surface were J=0.42, 0.48, 0.50, respectively. In the tandem stance on foam, maximum YI for COP velocity and COP AP velocity were J=0.59 and 0.57, respectively. Sensitivity for each post-concussion timepoint and clinical thresholds were determined for results with $J > 0.5$. Sensitivities were low for each timepoint for COP ML velocity in the double-leg stance on a hard surface, and high for each timepoint for both total COP velocity and COP AP velocity in the tandem stance on foam (**Table 5.6**). The clinical threshold for COP ML velocity in the double-leg stance on a hard surface was 6.2 mm/s. In the tandem stance on foam, clinical thresholds were 67.0 mm/s for COP velocity, and 60.0 mm/s for COP AP velocity.

Table 5.6. Sensitivity and specificity reported for balance measures with an area under the receiver operating characteristic (AUROC) curve > 0.7 and a Youden Index (YI) > 0.5.

		DOUBLE-LEG	TANDEM	
		Hard Surface	**Foam Surface**	
	Timepoint	**COP ML Velocity**	**COP Velocity**	**COP AP Velocity**
SENSITIVITY	<3 days	0.50	1.00	0.94
	1 week	0.37	1.00	1.00
	1 month	0.38	0.92	0.85
	Six months	0.53	0.87	1.00
SPECIFICITY	Non-concussed	0.78	0.43	0.38

5.5 Discussion

This investigation expands on previous work (e.g. Powers *et* al., 2014) to show that biomechanical measures of standing balance are sensitive to the presence of concussion several months after return to play (RTP) and introduces quantitative thresholds with potential clinical application. The double-leg stance on a hard surface and tandem stance on foam surface are the most sensitive stances for detecting the effects of concussion using COP velocity. The COP ML velocity during the double-leg stance discriminates between concussed and non-concussed athletes better than other linear measures of balance. Total COP velocity and COP AP velocity during the tandem stance on foam are sensitive to injury at all four post-concussion timepoints. We also assessed the ability to use ellipse area, a popular displacement-based COP measure, and found its ability to discriminate between athletes with satisfactory sensitivity and specificity weak, and not useful for determining reliable cutoffs.

5.5.1 Linear balance measures and thresholds

A key finding in this study is that even 6 months following concussion, balance measures did not recover. Nine of 15 athletes for COP ML velocity in the double-leg stance on a hard surface and 5 of 7 athletes for COP AP velocity in the tandem stance on foam did not recover to within the proposed thresholds, although all athletes were cleared for RTP using standard methods. While total COP velocity in the tandem stance on foam was also found to be sensitive to concussion, this sensitivity is based mainly on the dominance of the AP component, and therefore only COP AP velocity for this stance is discussed further. With typical RTP times of 7-10 days for collegiate athletes (Collins *et al.* 1999; Guskiewicz *et al.* 2003; Pellman *et al.* 2006), these results indicate that many athletes have unresolved concussion-related vestibular and sensorimotor impairments at RTP. This is supported by evidence that athletes are more susceptible to lower extremity injury following concussion (Herman *et al.* 2017).

The maximum YI was used to determine the clinical thresholds, which were found to be 6.2 mm/s for COP ML velocity in the double-leg stance on a hard surface and 60.0 mm/s for COP AP velocity in the tandem stance on foam. For COP ML velocity in the double-leg stance on a hard surface, the reported clinical threshold falls below the mean of the non-concussed athlete data (top-middle, **Figure 5.1**). This is most likely due to the right-tailed distribution of the non-concussed athlete data and will result in false positives for non-concussed athletes. The COP AP velocity in the tandem stance on foam also shows a right-tailed distribution in the non-concussed athlete data. In this case, however, the distribution results in a clinical threshold that is between the mean of the non-concussed athlete data and the means of the post-concussion data because a lower COP AP velocity indicates impairment in this stance (bottom-right, **Figure 5.3**). This metric will result in fewer false positives for non-concussed athletes than COP ML velocity in the double-leg stance on a hard surface.

Due to a low number of post-concussion athletes participating in the baseline collection before their season, a sport-matched non-concussed athlete population was used for comparison to the post-concussion cohort. The sport-matching and large data size of the non-concussed athlete group allow for robust comparison to the post-concussion cohort, although this approach does not provide direct evidence for how useful the proposed thresholds are for single athlete pre- and post-concussion diagnosis. One athlete during the study participated in all five timepoints: non-concussed athlete, <3 days, 1 week, 1 month, and 6 months. To visualize the potential clinical diagnostic application of this technique, and with the understanding that these trends may be purely coincidental, this athlete's data for COP ML velocity in the double-leg stance on a hard surface and COP AP velocity in the tandem stance on foam were plotted with the threshold (**Figure 5.4**). For COP ML velocity in the double-leg stance on a hard surface, the athlete's non-concussed data and three of the four post-concussion timepoints are lower than the threshold and the <3 days timepoint is on the threshold, indicating that this threshold is not useful for this particular athlete. In the tandem stance on foam for COP AP velocity, the athlete's non-concussed velocity is higher than the threshold, and all four post-concussion timepoints are lower than the threshold, indicating that this measure is sensitive to concussion up to 6 months post-concussion for this athlete.

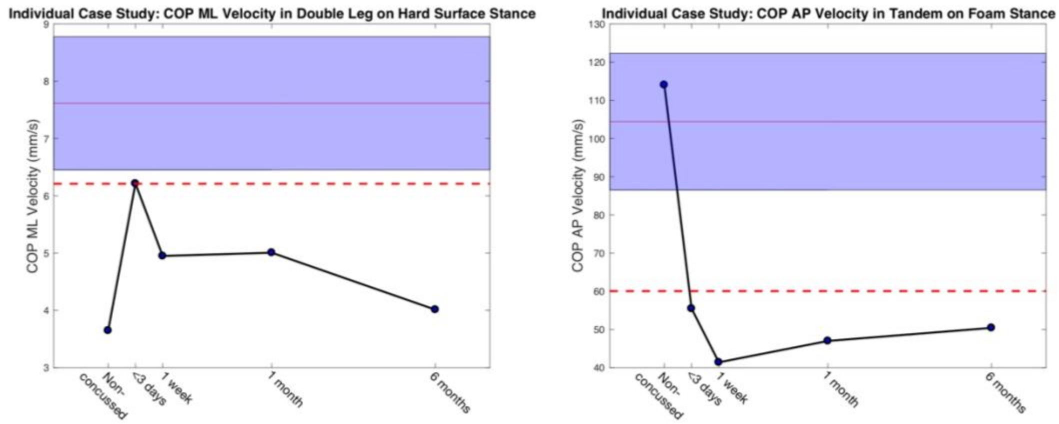

Figure 5.4. COP ML velocity in the double-leg stance on a hard surface and COP AP velocity in the tandem stance on foam for the case study athlete. The connected dots are the individual data points for each of the five timepoints: non-concussed athlete, <3 days, 1 week, 1 month, and 6 months. The red dashed line indicates the threshold value. The threshold value was sensitive to concussion at the <3 days timepoint for COP ML velocity in the double-leg stance on a hard surface, and for all four post-concussion timepoints for COP AP velocity in the tandem stance on foam.

Because these COP measures are sensitive to concussion, comparison to clinical thresholds may prove to be a useful addition to RTP decision making. Despite management guidelines suggesting multidomain assessment and decision-making, typically only self-reported symptom scores are tracked for recovery before starting RTP protocol. For example, 87% of athletic trainers will return an asymptomatic athlete to play based on self-reported symptoms, even if neurocognitive scores have not returned to baseline (Covassin *et al.* 2009). The addition of a sensitive and clinically accessible balance test could guide RTP decision making by providing insight on lasting vestibular and sensorimotor deficits. Note, however, that the balance thresholds reported here are only a starting point in the design of robust clinically valuable thresholds. It will be necessary, as the measures are used, to associate threshold scores with other clinically meaningful, adverse outcomes such as lower extremity injuries post-concussion or incidence of a second concussion. Additionally, for maximum usefulness, clinical threshold scores should be developed based on specific populations and continuously updated with new data to increase power.

5.5.2 Balance mechanisms to explain COP outcomes

An important feature of the COP velocity measures collected during standing balance is that these are traditional measures in biomechanical analyses, easily collected, repeatable, and comparisons to other investigations are readily available. Our data in the non-concussed cohort for ellipse area and COP velocity closely match the findings in a similar cohort tested for all 6 BESS stances (Caccese *et al.*, 2016). Also, our data from athletes immediately following concussion for these measures on a double-leg stance on a hard surface—the most frequent stance tested in the literature—align well with the trends and means of two other investigations (Powers *et al.*, 2014; Rochefort *et al.*, 2017).

Our results show differences in the COP ML component of velocity in the double-leg stance and the COP AP component of velocity in the tandem stance between non-concussed and concussed athletes, indicating that concussed athletes shift to the use of hip control. Winter *et al.* (1996) explain these mechanisms based on foot position where in the double-leg stance, the ML component of COP is under hip control, while the AP component is under ankle control. In the tandem stance, this relationship is opposite, with the ML component under ankle control and the AP component under hip control (Winter *et al.* 1996). In general, the use of ankle control in quiet stance is dominant in healthy reference populations. Ankle control corrects for small perturbations in the center of gravity by using ankle plantar and dorsiflexors to keep the center of gravity within the base of support. When ankle control is ineffective, and larger perturbations of the center of mass occur, hip control using abductors and adductors is employed. Since the feet are narrow in both of these stances as prescribed by the BESS test, athletes may be even more inclined to use hip control rather than ankle control.

5.5.3 Clinical implementations and future work

Of the six balance tasks in the BESS test, the double-leg stance on a hard surface is the only stance that does not include 'learned' behavior. The single-leg stance, tandem stance, and all stances on foam require the athlete to modify their standard standing balance strategy. As the athlete learns these new stances, learning effects may also occur, which are well documented in studies measuring the sensitivity of clinical BESS error scores (Mulligan *et al.*, 2013; McLeod *et al.*, 2004). Since the double-leg stance on a hard surface does not require a new learned standing balance strategy, it may be the most direct measure of standing balance during concussion recovery.

In contrast to the double-leg stances, COP AP velocity in the tandem stance on foam decreases post-concussion. The tandem stance and the foam surface are both alterations to typical standing balance. Dynamic balance measures in concussed cohorts typically rely on a gait task, where many studies have shown a conservative gait strategy being used post-concussion (Chen & Chou, 2010; Buckley *et al.*, 2016). Due to the changes the tandem stance on foam introduces to typical standing balance, it may operate more similarly to a dynamic balance task, where conservative movement strategies are preferred.

While the absence of a learning effect is important when determining a balance test useful for tracking concussion recovery over time, sensitivities for each timepoint indicate that the COP ML velocity in the double-leg stance on a hard surface is only between 37-53% sensitive for each post-concussion timepoint in this cohort. In contrast, COP AP velocity in the tandem stance on foam is between 85-100% sensitive for each post-concussion timepoint. That being said, all athletes were able to complete the double-leg stance task, while approximately half were able to complete the tandem stance on foam task with the constraints of 90% body weight over the force platform for five or greater seconds in both non-concussed and post-concussion athletes. While these results are promising, more individual case study work is needed to see which of these stances are useful for clinicians. Future studies should consider the usefulness of the foam pad as a balance perturbation mechanism, particularly for inclusion in vestibular or sensorimotor rehabilitation, and the role this may play in reintegrating the sensory systems post-concussion.

5.5.4 Limitations

The original goal of the study was to capture pre-season baseline data for all eligible athletes and assess athlete recovery individually at four post-concussion timepoints. Due to only five athletes who sustained concussion participating in pre-season baseline testing, sport-matched data from athletes with no reported history of concussion were used as a non-concussed athlete reference. The number of athletes in the sport-matched data was much higher than the number of athletes in the post-concussion group, and there was also difficulty in maintaining athlete interest to participate in all four timepoints post-concussion. These limitations caused inconsistency and large fluctuations in the number of athletes tested at each timepoint, which may affect the validity of the results, and could be the cause for some measures showing significance at counterintuitive timepoints. These difficulties with data collection limit the clinical impact of this study, and future work should create a more robust cohort, and more directly monitor individual athletes.

5.6 Conclusions

COP ML velocity in double-leg stance on a hard surface discriminated between non-concussed and concussed athletes at the <3 days timepoint, while COP AP velocity in tandem stance on foam was sensitive to concussion at all four post-concussion timepoints. More than half of the concussed athletes did not recover within the proposed COP velocity thresholds in either stance at 6 months post-concussion. These results potentially indicate continued vestibular and sensorimotor impairments and have implications for RTP protocols and the possible benefit of rehabilitation methods for concussion recovery.

CHAPTER 6: CHRONIC DEFICITS – LINEAR AND NONLINEAR MEASURES OF BIOMECHANICAL STANDING BALANCE IN HIGH-VELOCITY ATHLETES WITH REPORTED HISTORY OF CONCUSSION

6.1 Abstract

Concussion is linked to an increased risk of secondary injury after return to play (RTP), including lower extremity injury and repeated concussion. Athletes typically RTP within 7-10 days after symptoms resolve, despite the indication of continued impairment of the central or peripheral nervous system. The purpose of this study is to survey 24 biomechanical balance measures to evaluate group differences between athletes with and without a history of concussion. Each athlete participated in a single session of instrumented standing balance tasks. The measures from the athletes with a history of concussion were compared to sport-matched non-concussed athletes. Four measures were significantly different between groups: center of pressure (COP) mediolateral (ML) velocity in the single-leg stance on foam, and ellipse area, COP ML velocity, and COP anterior-posterior (AP) velocity in the tandem stance on foam. These group differences indicate continued vestibular or sensorimotor impairment affecting neuromuscular functioning, and these balance measures may be useful to track recovery, identify athletes that may benefit from rehabilitation, and lower the risk of further injury at RTP.

6.2 Introduction

Sport-related concussions can lead to physical, psychological, and emotional symptoms. These deficits are tracked in the acute phase after injury, which typically lasts 7-10 days, due to immediate concerns regarding readiness for return to play (RTP; Harmon *et al.* 2013). The Centers for Disease Control and Prevention (CDC) recommend a six-step RTP progression, only moving to the next step when the athlete does not report symptoms at the current step: (1) return to regular, academic activities, (2) light aerobic activity, (3) moderate activity, (4) heavy, non-contact activity, (5) practice and full contact, and (6) return to competition (CDC 2019). Deficits are not typically tracked long-term since recovery from concussion is most commonly based on the resolution of symptoms, which generally resolve in the acute phase.

One year after concussion, some patients still experience unresolved symptoms of post-concussion syndrome, such as headache, dizziness, and nausea (PCS; Røe *et al.*, 2009). It has been suggested that vestibular or sensorimotor-targeted rehabilitation could help patients experiencing chronic PCS to improve balance through resolution of sensory integration deficits (Peterka *et al.* 2011). Wade *et al.* (1997) observed increased walking speed, stride length, and step length during a rehabilitation period for inpatient brain injury patients, indicating that rehabilitation can assist in the recovery of balance post-injury. It is possible that rehabilitation could have a similar effect on concussed patients.

Concussion has been linked to a higher risk of lower extremity injuries and repeated concussion after RTP (McCrea *et al.*, 2020; Herman *et al.*, 2017; Harada *et al.*, 2019). The association of concussion to repeated concussion and lower extremity injury may be due to continuing neuromuscular deficits post-concussion after RTP (Harada *et al.* 2019). This theory is supported by McCrea *et al.* (2020), who report that a longer recovery time before RTP was linked to a lower incidence of repeated concussion. The ability to suspend RTP in athletic populations is challenging. Harmon *et al.* (2013) suggested that athletes are not forthcoming about symptoms, potentially downplaying the effects of concussion. Relying solely on self-reported symptoms may, therefore, result in the belief that full recovery from concussion has occurred and in premature RTP (Van Kampen 2006). For these reasons, self-reported symptom scores should be used in tandem with more objective tests during concussion management. While symptom scores must recover, it is also essential that objective measures of neuromuscular functioning return to baseline before RTP.

Standing balance tasks provide measures of postural stability that may deliver objective measures of sensorimotor integration deficits following concussion. Sensorimotor integration deficits directly affect neuromuscular functioning since a lower capability of the central nervous system (CNS) to integrate stimuli causes lower subconscious activation of motor actions, including those for joint motion and loading. Three sensory input systems contribute to standing balance; the visual, vestibular, and proprioceptive sensory systems. Two of the three sensory input systems must be functional to maintain balance to maintain healthy balance (Goldberg 2000). The surface type and visual field used in standing balance tasks can be modified to induce a deficit in one of the sensory systems. For example, the Balance Error Scoring System (BESS) calls for eyes to remain closed in all tasks, and the use of a foam surface in some tasks. In these tasks, the input information from the visual system is lost, and proprioceptive input is compromised, so the balancer must rely on the vestibular system to maintain balance. As a result, the balancer may have difficulty maintaining a healthy balance response due to the impairment of two of the three sensory systems. Sensory input may be further compromised due to neurological injury, such as concussion, which complicates balance ability through injury to the central or peripheral nervous system.

The study of balance measures past RTP time is underdeveloped, but existing investigations indicate that objective biomechanical measures of standing balance may exhibit longitudinal sensitivity to concussion. For example, COP AP velocity remains higher in the eyes-closed quiet stance at RTP in concussed football players (Powers *et al.*, 2014). A study of former football players with a history of two or more diagnosed concussions showed more regular sample entropy in the ML direction during condition 5 of the SOT, a sway-referenced surface eyes-closed balance task, when compared to age, height, and sport-matched athletes with no history of concussion (Schmidt *et al.* 2018).

The purpose of this study is to survey a series of 24 standard biomechanical standing balance measures and determine which are significantly different between athletes without a history of concussion and athletes at least 6 months post-concussion. This investigation is the largest assessment (n=42) of linear measures of standing balance (e.g. ellipse area, COP velocity), and second-largest study of nonlinear measures of standing balance (e.g. approximate entropy; Sosnoff *et al.*, 2011), in current athletes reporting a history of concussion to date. We develop this analysis based on a retrospective cohort of National Collegiate Athletic Association Division I (NCAA DI) athletes with and without a history of concussion. An objective balance test would give front line providers more information regarding the injury, allow utilization of sensorimotor and vestibular training to increase postural stability and neuromuscular functioning, and potentially lower the risk of lower extremity injury or repeated concussion after RTP.

6.3 Methods

Each athlete participated in an balance testing session in the Human Dynamics Laboratory at the University of Denver that consisted of instrumented standing balance tasks. This testing session was part of a larger comprehensive dataset that included instrumented functional balance tasks, neurocognitive assessment, vestibular-ocular assessment, and a blood draw. Each athlete self-reported history of concussion, including how many concussions had been sustained and time since the last concussion. Each athlete, regardless of concussion history, was evaluated at a single timepoint while not actively in season for their sport. Linear and nonlinear measures of the COP were calculated for each standing balance task. The measures for the athletes reporting a history of concussion at least 6 months from the session date were compared to sport-matched athletes reporting no history of concussion (non-concussed athlete group). This study was approved by the University of Denver IRB (Protocol 854307).

6.3.1 Participants

NCAA D1 athletes from the University of Denver (n=88) participating in high-velocity sports represented by basketball (6 females, six males), gymnastics (2 females), hockey (11 males), lacrosse (18 females, 14 males), skiing (8 females, 2 males), soccer (9 females, 9 males), and volleyball (3 females) participated in this study (**Table 6.1)**. Of these participants, 42 athletes reported a history of concussion, and 46 athletes reported no history of concussion. Of athletes reporting a history of concussion, 26 reported one previous concussion, and 16 reported two or more previous concussions. All athletes in the history of concussion group sustained their concussion at least 6 months from the testing date.

Table 6.1. The number of National Collegiate Athletic Association (NCAA) Division I (DI) athletes that participated in this study by group (non-concussed, concussed), gender, and sport.

SPORT	NON-CONCUSSED FEMALE	NON-CONCUSSED MALE	CONCUSSED FEMALE	CONCUSSED MALE
BASKETBALL	2	3	4	3
GYMNASTICS	1	0	1	0
HOCKEY	0	6	0	5
LACROSSE	10	8	8	6
SKIING	4	1	4	1
SOCCER	5	5	4	4
VOLLEYBALL	1	0	2	0
TOTALS	23	23	23	19

6.3.2 Apparatus

Two force platforms (40cm x 70 cm) embedded side by side in the laboratory flooring (Bertec Corp), which measured ground reaction forces at 1000 Hz were used to collect data. The Airex Balance Pad (Airex AG, Sins, Switzerland) was used for standing balance tasks requiring a foam surface. This balance pad is consistent with foam used in the sports medicine facility by the NCAA Division I athletes at DU and fit within the dimensions of each force platform.

6.3.3 Procedure

Standing balance tasks included all stances from the BESS test (University of North Carolina, Chapel Hill, NC). The BESS protocol consists of three standing balance stances (single-leg stance, double-leg stance, and tandem stance) performed for 20 seconds with the eyes closed both on a hard surface and on a foam surface. For this study, BESS tasks were performed for 30 seconds on the force platform, and the first 5 seconds and last 5 seconds of trial data were removed as to capture only balance rather than movement into or out of the stance position. Each of the three tasks was performed directly on the force platform and a foam balance pad placed on the force platform. The single-leg stance was performed on a single force platform and a single foam balance pad. The double-leg and tandem stances were performed with each foot on a separate force platform and separate foam balance pad while using BESS protocol instructions for stance positioning.

6.3.4 Data processing

All data were filtered using a 4th order low-pass Butterworth filter with a 5 Hz cutoff (Carpenter *et al.*, 2010). Using customized Matlab (2017a, MathWorks, Inc., Cambridge, MA) code, linear measures of the COP, including ellipse area and average COP velocity (Total, ML, AP), and nonlinear measures of the COP, including sample entropy (ML, AP), were calculated for all BESS trials. For sample entropy, the length of the pattern m was set to 2, the pattern similarity factor r was set to 20% of the standard deviation, and the sampling frequency τ was set to 10 Hz by data resampling at every 100th data point (Caccese *et al.*, 2016). During the single-leg and tandem stances, many athletes were unable to complete the full 30 seconds without performing an error. Consistent with the BESS protocol, athletes were instructed to return to the testing position as quickly as possible following an error. To account for these errors, we used a method similar to that of Riemann *et al.* (1999). In this method, the trial was cut to the longest length of time a subject could maintain 90% bodyweight on the force platform (**Table 6.2**), and any trial that did not contain greater than 5 seconds was excluded from analysis (**Table 6.3**). The missing data slots were assigned a random value (Hot-deck Imputation Method; Yan, 2011) sampled from existing trials of the same group. This replacement method provides a conservative estimate of balance performance in the concussed cohort because the value from the excluded trials, if measurable, would have shown a more substantial balance impairment than the replacement value.

Table 6.2. Mean and range of trial time in seconds for which athletes included in the analysis maintained 90% body weight over the force platform in both groups for the single-leg and tandem stances.

	SINGLE-LEG		**TANDEM**	
	Hard	Foam	Hard	Foam
NO CONCUSSION	17.3 [6.1-20]	10.4 [5.1-20]	11 [5-20]	7.9 [5.1-12.8]
CONCUSSION	18.1 [7.7-20]	8.8 [5.2-18.1]	11 [5.2-20]	7.7 [5.1-18.7]

Table 6.3. Number of athletes in both groups unable to maintain 90% body weight over the force platform for the single-leg and tandem stance tasks. The total number of athletes for each group was as follows: non-concussed: n=46, concussed: n=42.

	SINGLE-LEG		**TANDEM**	
	Hard	Foam	Hard	Foam
NO CONCUSSION	2	13	6	29
CONCUSSION	1	16	10	27

6.3.5 Statistical analysis

Due to non-normal distributions and unpaired data, *p*-values were calculated using the Wilcoxon rank-sum test, which tests the null hypothesis that the medians of the populations are equal at a significance level of 0.05. Rosenthal's *r* effect size was calculated for statistically significant measures to compare the non-concussed athlete group to the concussion history group (Rosenthal & Rubin, 1991; Tomczak & Tomczak, 2014). Results are reported as (*p*-value; Rosenthal's *r* effect size).

6.4 Results

Statistically significant differences between the non-concussed and history of concussion group were found for linear balance measures. Four of 24 variables rejected the null hypothesis of equal medians between non-concussed athletes and athletes with a history of concussion in the Wilcoxon rank-sum test. Results that had a statistically significant *p*-value are reported here, and full results are available for all variables in **Appendix C, Tables C.1-C.3**. The single-leg stance and tandem stance on foam were the most sensitive stances for detecting the effects of concussion using linear balance measures. In the tandem stance on foam, ellipse area was smaller for athletes with a history of concussion ($p<0.01$; $r=0.38$; **Figure 6.1; Table 6.4**). COP ML velocity was lower for athletes with history of concussion in both the single-leg ($p<0.01$; $r=0.38$; **Figure 6.2**) and tandem ($p<0.01$; $r=0.33$; **Figure 6.3**) stances on foam. COP AP velocity was lower for athletes with a history of concussion in the tandem stance on foam ($p<0.01$; $r=0.31$; **Figure 6.4**). COP velocity measures in the stances on a hard surface and the double-leg stance tasks were not found to be statistically significant. Nonlinear measures of concussion (sample entropy in the ML and AP directions) were not statistically significant between groups.

Table 6.4. Stances and balance measures with statistically significant *p*-values. Rosenthal's *r* effect size was calculated for the statistically significant measures.

STANCE	SURFACE	BALANCE MEASURE	*P*-VALUE	EFFECT SIZE (*R*)
SINGLE-LEG	Foam	COP ML Velocity	0.0003	0.38
TANDEM	Foam	Ellipse Area	0.0003	0.38
		COP ML Velocity	0.002	0.33
		COP AP Velocity	0.0035	0.31

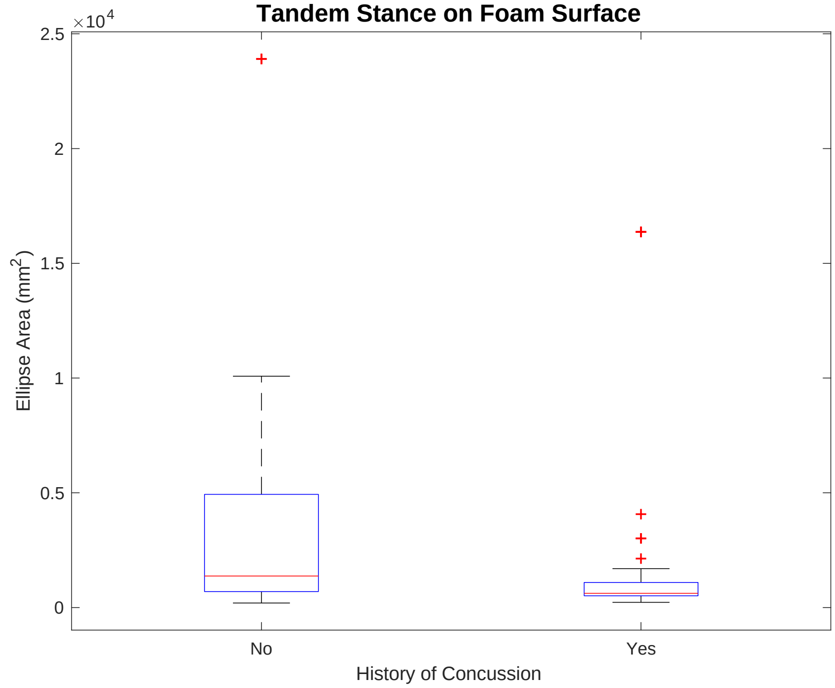

Figure 6.1. Ellipse area is smaller for athletes with a history of concussion in the tandem stance on foam ($p<0.01$; $r=0.38$).

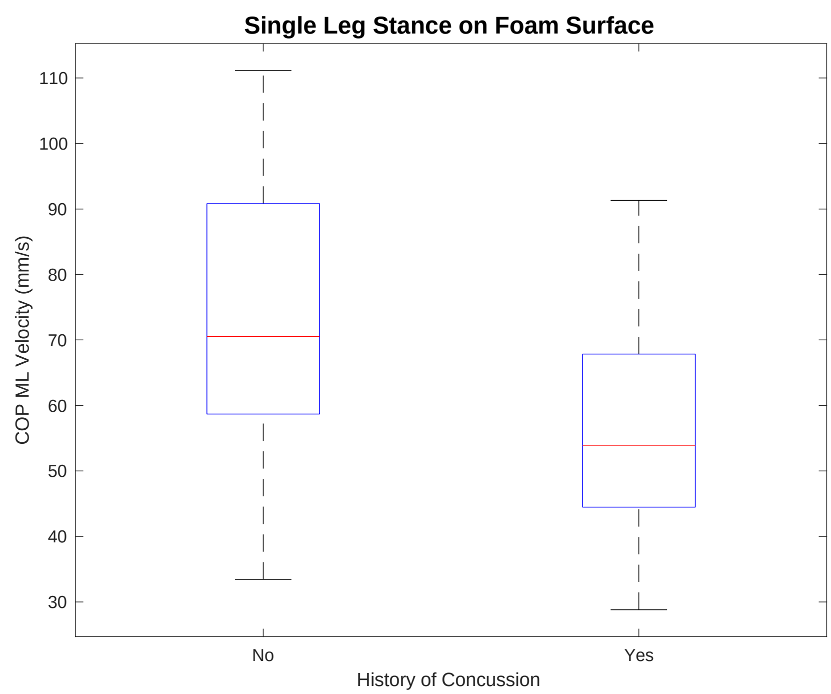

Figure 6.2. COP ML velocity is lower for athletes with a history of concussion in the single-leg stance on foam ($p<0.01$; $r=0.38$).

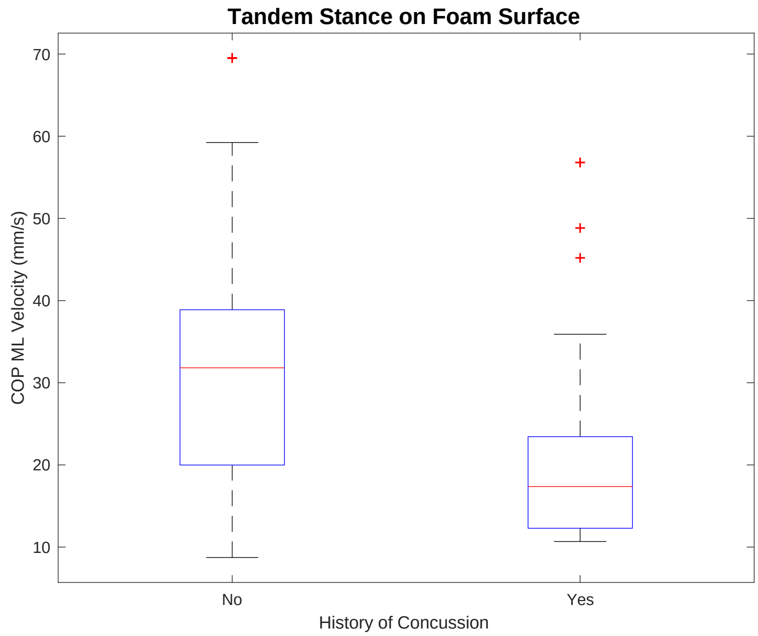

Figure 6.3. COP ML velocity is lower for athletes with a history of concussion in the tandem stance on foam (p<0.01; r=0.33).

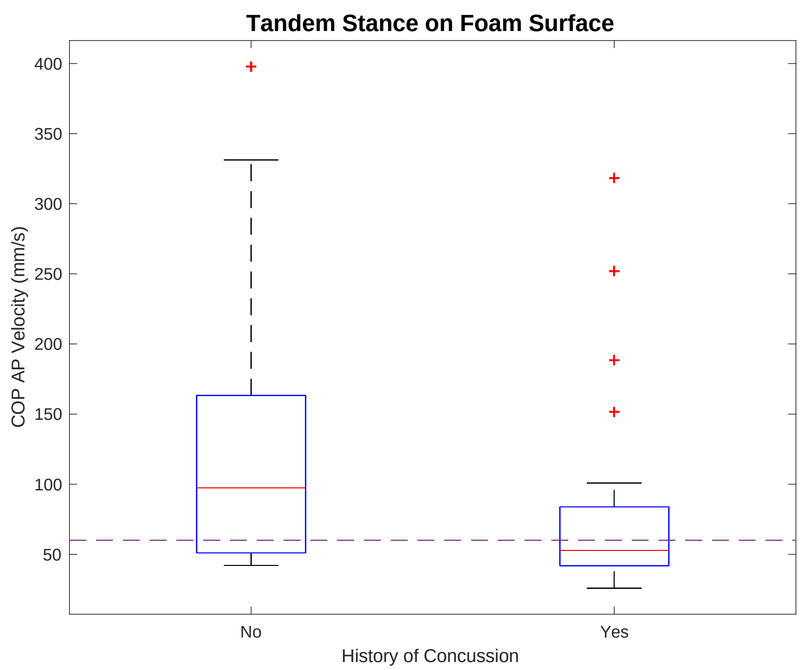

Figure 6.4. COP AP velocity is lower for athletes with a history of concussion in the tandem stance on foam (p<0.01; r=0.31). The median of the history of concussion group is below the threshold (denoted by a dashed line) reported for this stance in Chapter 5, indicating potential continued impairment.

6.5 Discussion

This study surveyed 24 standard biomechanical standing balance measures to determine measures that were statistically significant between athletes without a history of concussion and athletes at least 6 months post-concussion. Linear measures of the COP in two stances performed on foam, the single-leg and tandem stances, had significant differences between athletes who did and did not report a history of concussion. None of the stances on a hard surface and the nonlinear measures in any stance showed significant differences.

6.5.1 A common balance measure

Aim 1 in **Chapter 5** showed that linear measures of the COP, specifically COP velocity, are sensitive in the acute phase and up to 6 months post-concussion. COP AP velocity in the tandem stance on foam is a measure that was common between the acute and long-term studies. Chapter 5 also reported clinical thresholds that were useful in distinguishing between non-concussed and post-concussion cohorts. The reported clinical threshold for COP AP velocity in the tandem stance on foam (60 mm/s) appears to distinguish between the medians of the retrospective cohorts, as the median of the history of concussion cohort remains below the reported threshold, while the median of the non-concussed athlete group is above the reported threshold (**Figure 6.4**). Sensitivity and specificity are 0.55 and 0.72, respectively, when this threshold is applied to the history of concussion cohort. Sensitivity and specificity are not high for this cohort using this threshold, indicating that some athletes may recover in terms of sensory integration capabilities, yet others are experiencing chronic neuromuscular deficits.

6.5.2 Mechanisms to explain balance outcomes

The significant differences between athlete groups on the eyes-closed on foam tasks are most likely due to the decreased sensory input information available to the athlete and the faster stabilization mechanisms necessary when standing on foam (Riemann *et al.*, 2003). In these stances, the input from the proprioceptive system becomes unreliable, and the visual system has no input information, so the athlete must further rely on the vestibular system to maintain balance. Additionally, the foam surface requires faster joint stabilization mechanisms compared to firm surfaces. Even 6 months post-concussion, although some sensorimotor integration may have recovered, neuromuscular functioning may not return to baseline. The lack of sensory input information combined with absence of full sensorimotor integration recovery likely allows for the observation of discrete balance deficits in these stances. The double-leg stance increases proprioceptive input in comparison to the other stances. This stance may not be sensitive to a history of concussion due to the added sensory input information, allowing for greater sensorimotor integration compared to the other stances, which in turn, can process an appropriate balance strategy.

COP velocity was lower in both the single-leg and tandem stance on foam and ellipse area in the tandem stance on foam was smaller for athletes with a history of concussion. While a lower COP velocity and smaller ellipse area are not typically reported post-concussion, few studies report comparisons of linear balance measures on foam stances of the BESS, instead opting to analyze a quiet stance. **Chapter 5** found decreased COP velocity in the tandem stance on foam up to 6 months post-concussion. While COP velocity in the single-leg stance was not found sensitive to concussion at 6 months post-injury in this study, learning effects associated with repetitive BESS testing or the large fluctuations in participant numbers at each post-concussion timepoint may have affected the sensitivity of this task. Due to the challenges associated with increased stance complexity, more narrow BOS, and decreased proprioceptive input on the foam surface in these stances, these tasks may be producing a conservative strategy similar to the well documented conservative gait strategy reported post-concussion (T. a. Buckley *et al.* 2015).

There are two methods used to maintain the center of mass (COM) within the base of support (BOS) that may produce this lower velocity; the use of ankle control and hip control. The use of ankle control corrects for small perturbations in the COM by using ankle plantar and dorsiflexors to keep the COM within the BOS, and is dominant in healthy populations. When ankle control is ineffective, hip control using abductors and adductors is employed for larger perturbations of the COM (Winter *et al.* 1996). In the double-leg stance, the use of hip control is dominant in the ML component of the COP, and the use of ankle control is dominant in the AP component of the COP. In the tandem stance, this relationship is opposite where the use of ankle control is dominant in the ML component of the COP, and the use of hip control is dominant in the AP component of the COP. Although control dominance has not been explicitly evaluated for the single-leg stance, Riemann *et al.* (2003) found that ankle and hip corrective action increase in the frontal plane during both a single-leg stance with eyes closed and a single-leg stance on foam relative to a firm surface single-leg, eyes-open stance, potentially suggesting that a mixed strategy where both hip and ankle control are utilized in both planes is in effect. Both COP AP velocity and COP ML velocity were significantly different between groups in the tandem stance on foam, indicating that both ankle and hip control are important contributors to maintaining balance in the concussed population. Additionally, COP ML velocity was lower in the history of concussion group for the single-leg stance. If the single-leg stance does use a mixed strategy in both planes, this is further confirmation that both the use of ankle and hip control are advantageous post-concussion.

Sample entropy was not found to be significantly different between athlete groups, matching the findings of Sosnoff *et al.* (2011), but not those of De Beaumont *et al.* (2011) or Schmidt *et al.* (2018), who found lower ApEn in the AP direction and sample entropy in the ML direction, respectively. A change in entropy is related to the regularity of the COP signal, with a higher sample entropy indicating irregularity. A lower entropy post-concussion is typically explained using the loss-of-complexity hypothesis of aging and disease (Lipsitz & Goldberger, 1992). Both of the studies reporting group differences had small group sample sizes ($n \leq 21$), while Sosnoff *et al.* (2011) reported a larger cohort (n=62 concussed participants). These nonlinear measures are relatively new, and small sample sizes may result in an inflated effect size (Halsey *et al.* 2015). More work is needed to determine what group differences of nonlinear measures, if any, are significant for concussion.

6.5.3 Clinical implementations and future work

The clinical focus for athletes is to RTP safely, and there are currently no objective measures that are sensitive to further injury risk. RTP is typically based on self-reported symptoms, and athletes may underreport symptoms (Harmon *et al.* 2013), highlighting the need for objective measures. Even when symptoms are resolved, there are increased rates of lower extremity injury and repeated concussion after RTP (McCrea *et al.*, 2020; Herman *et al.*, 2017; Harada *et al.*, 2019). The balance measures reported here that have statistically significant group differences between athletes with and without a history of concussion may be useful to track vestibular and sensorimotor deficits after symptoms have resolved in the acute period.

Concussion results in injury to the peripheral or central nervous system, and these chronic balance deficits are an indication of continued direct or indirect injury to regions such as the vestibular organs, the brainstem, or motor pathways. Sensorimotor or vestibular rehabilitation may provide an avenue towards recovery. In a case study, Prangley *et al.* (2017) found that four weeks of vestibular training exercises increased balance control in individuals with PCS. With more work on the benefits of vestibular rehabilitation in athletes with lasting balance deficits, the use of rehabilitation used together with objective balance tracking may provide a method to decrease recovery time and reduce further injury after RTP.

6.5.4 Limitations

The stances with significant group differences – the singe-leg and tandem stances on foam – were stances that many athletes could not maintain 90% bodyweight over the force platform for at least five seconds. The inability to meet this constraint was found in both groups of athletes, indicating that it is not related to concussion. Further work is needed to determine measures that can be universally completed by all athletes. Additionally, all measures have small effect sizes. This result may mean that the balance deficits in athletes with a history of concussion may not be significant enough to demonstrate differences on the individual athlete level.

6.6 Conclusions

COP ML velocity in both the single-leg stance on foam and tandem stance on foam, and ellipse area and COP AP velocity in the tandem stance on foam were significantly lower in athletes with history of concussion compared to sport-matched non-concussed athletes. Lower COP velocity in concussed athletes matches the findings in **Chapter 5**, indicating that athletes with a history of concussion continue to apply a conservative movement strategy and may have balance impairments related to lasting sensory integration deficits. These balance measures may be useful to track recovery of neuromuscular functioning, identify athletes that may benefit from vestibular or sensorimotor rehabilitation, and lower the risk of further injury at RTP.

CHAPTER 7: SENSITIVITY OF MULTIDOMAIN LOGISTIC REGRESSION MODELS UP TO SIX MONTHS POST-CONCUSSION

7.1 Abstract

Guidelines recommending a multidomain approach to concussion assessment are not widely practiced, and protocols tend to rely on subjective and self-reported measures. There is a need for objective and sensitive assessment measures due to the risk of secondary injury after return to play (RTP), including lower extremity injury and repeated concussion, when subjective measures have resolved. The purpose of this study is to determine which weighted combination of objective concussion assessment measures has the greatest longitudinal sensitivity to concussion for athletes up to 6 months post-concussion using logistic regression models. Each concussed athlete participated in a multidomain assessment at four timepoints post-concussion. The measures from concussed athletes were compared to the sport-matched non-concussed athlete group at each timepoint. The most sensitive multidomain model was a combination of two balance measures: COP ML velocity in the double-leg stance on a hard surface, and COP AP velocity in the tandem stance on foam. Total symptom score results indicate excellent sensitivity <3 days post-concussion, but sensitivity quickly decreased to very poor at 6 months while the two-stance balance estimates indicated stable sensitivity across timepoints (0.86-1.0). These results provide a basis for understanding risk of secondary injury after RTP, and have implications

for assessment protocols and potential usefulness of sensorimotor or vestibular rehabilitation to assist with concussion recovery.

7.2 Introduction

Sport-related concussion management practices currently rely on a diverse set of published guidelines (King *et al.*, 2014). The most recent guidelines suggest a multidomain assessment which can include symptom evaluation, neurocognitive functioning, physical performance, and general disposition (Echemendia *et al.*, 2017). Athletic trainers are commonly the first responders to a concussion incident. A recent survey found that only 53% of athletic trainers employed a minimum of a 3-domain concussion assessment battery (Lempke *et al.*, 2020). The most common free-standing domains reportedly used for assessment included a symptom assessment scale (87% of respondents), balance assessment (85%), and computerized neurocognitive testing (60%). Only 45% of respondents reported use of an oculomotor assessment. When surveyed on the domains assessed for return-to-play (RTP), 61% of respondents used neurocognitive testing, 58% used symptom assessment, and 58% used balance testing. Only 29% reportedly used oculomotor assessment. Covassin *et al.* (2009) also reported that 87% of athletic trainers would return an asymptomatic athlete to play based on self-reported symptoms even if neurocognitive scores have not returned to baseline. The lack of multidomain concussion assessment use, as well as the variation in assessment and RTP protocols, likely means that current concussion diagnosis and RTP procedures lack sensitivity to the injury.

Even when multidomain assessments are utilized, questions remain about the sensitivity and objectivity of common sideline testing tools (Harmon *et al.*, 2013). In the three most common domains used by athletic trainers; symptom evaluation, balance, and neurocognitive testing, the Sport Concussion Assessment Tool (SCAT) was the most commonly used symptom evaluation assessment, the Balance Error Scoring System (BESS) the most common balance assessment, and the Immediate Post-Concussion Assessment and Cognitive Test (ImPACT) the most common neurocognitive assessment (Lempke *et al.*, 2020). Objectivity is obtained using quantitative measurement techniques, which of these most common assessments, only ImPACT provides.

The most recent version of the SCAT, the SCAT5, is a six-step screening tool including athlete background, symptom evaluation, cognitive screening, neurological screening, delayed recall, and final decision. 81.1% of athletic trainers use the included symptom checklist in the SCAT in concussion assessment protocols (Lempke *et al.*, 2020). Post-concussion symptom self-reporting is influenced by factors including alcohol consumption, mental fatigue, anxiety, and depression (Balasundaram *et al.*, 2016). In addition to those factors, Harmon *et al.* (2013) suggested that athletes are also not forthcoming about symptoms, potentially downplaying concussion, which may lead to RTP before full recovery (Van Kampen, 2006).

ImPACT is one of several commonly used commercial computerized cognitive assessment batteries. 83.5% of athletic trainers report using ImPACT as the preferred neurocognitive concussion assessment tool (Lempke *et al.*, 2020). The reliability and validity of the ImPACT battery has been well-established acutely post-concussion. In a cohort of high school athletes tested within 72 hours of concussion, ImPACT was found to have 81.9% sensitivity and 89.4% specificity to concussion (Schatz *et al.*, 2006). ImPACT generates five composite scores: Verbal Memory, Visual Memory, Processing Speed, Reaction Time, and Impulse Control. Each composite score has been individually assessed for sensitivity to concussion. Of these composite scores, visual memory and reaction time have been found to be the most sensitive to cognitive changes following concussion (Majerske *et al.*, 2008).

The oculomotor system is an important but often neglected domain in concussion management. The King-Devick (KD) test is a frequently used concussion screening tool that focuses on timed saccadic eye movements. The KD test has 86% sensitivity and 90% specificity to concussion (Galetta *et al.*, 2015). A comparison of baseline, post-concussion, and post-season KD test scores showed poorer scores post-mTBI and improvement post-season with high test-retest reliability (Leong *et al.*, 2015). When the KD test was used after games, it was sensitive to undetected mTBIs (King *et al.*, 2015). The addition of the KD test to a concussion battery may therefore increase sensitivity of a multidomain battery.

The Balance Error Scoring System (BESS) is an observational diagnostic tool frequently used post-concussion. Here, clinicians count the number of pre-defined errors, up to 10, on single-leg, double-leg, and tandem stance tasks on firm and foam surfaces with the eyes closed during a 20-second balancing task. The BESS is the most commonly used balance metric for sideline concussion diagnosis despite concerns about the lack of sensitivity (Finnoff *et al.*, 2009) and potential learning effects (Mcleod *et al.*, 2004; Mulligan *et al.*, 2013). For that reason, instrumented biomechanical techniques may add diagnostic accuracy for the assessment of long-term injuries. Center of pressure (COP) measures including displacement and average velocity (King *et al.*, 2017) have shown significance in concussed cohorts. For example, in one study, concussed football players showed greater COP AP displacement immediately after injury with an improvement of function before RTP, but COP AP velocity continued to be elevated at the time of RTP (Powers *et al.*, 2014). This deficit may be due to injury to the pathways of the central or peripheral nervous system, resulting in lower resolution information from the sensory systems associated with balance. In the same study, total symptom score was elevated acutely post-concussion (34.89±22.08), and essentially resolved (1.22±1.92) at RTP, strengthening the argument that objective measures may be necessary to track lasting deficits.

While many domains have been assessed individually, there is a lack of research assessing the sensitivity of objective multidomain assessment models. The purpose of this study is to evaluate multidomain concussion assessments using logistic regression models to explore which combination of measures has the greatest longitudinal sensitivity to concussion for athletes up to 6 months post-concussion. This analysis is developed based on a prospective cohort of National Collegiate Athletic Association Division I (NCAA DI) athletes post-concussion and a reference cohort of non-concussed athletes with no history of concussion. To our knowledge, this is the first study to create such models and measure the sensitivity of multidomain concussion assessments longitudinally up to 6 months post-concussion.

7.3 Methods

Each athlete participated in a multidomain assessment in the Human Dynamics Laboratory at the University of Denver that consisted of instrumented standing balance tasks, a neurocognitive assessment, and an oculomotor assessment. These tasks were part of an extensive comprehensive data collection that also included instrumented functional balance tasks, a vestibular-ocular assessment, and a blood draw. Separately, each athlete participated in symptom tracking with their sport-specific athletic trainer. Each concussed athlete was evaluated for standing balance, neurocognitive testing, and oculomotor testing at four timepoints post-concussion: <3 days, 1 week, 1 month, and 6 months. Symptom tracking was evaluated at two timepoints post-concussion: <3 days, and 1 week. Symptom tracking was overseen by the athletic department and was not completed at the 1 month and 6 month timepoints, in accordance with NCAA protocol. Each athlete without concussion history was evaluated at a single timepoint while not actively in season for their sport. Linear measures of the COP (ellipse area, COP velocity) for each standing balance task (BESS), composite scores generated by neurocognitive testing (ImPACT), task completion times and error counts in the oculomotor test (KD), and ImPACT post-concussion symptom scale (PCSS) total symptom score were evaluated. The measures from concussed athletes were 1) compared to the sport-matched non-concussed group at each timepoint and 2) used to create logistic regression multidomain models to determine the most sensitive and specific longitudinal model. This study was approved by the University of Denver IRB (Protocol 854307).

7.3.1 Participants

NCAA D1 athletes from the University of Denver (n=117) participated in baseline testing. Twenty-seven athletes sustained medically diagnosed concussion during this 3-year study. Three athletes sustained two concussions during this time and were re-enrolled separately for each concussion. While the original goal was to obtain baseline data for all eligible athletes and assess athlete recovery individually post-concussion, only five athletes who sustained concussion had participated in baseline testing. Therefore, sport-matched baseline data (n=117) from athletes with no reported history of concussion were used as a reference cohort.

Concussed athletes (n=27) were asked to participate in four tests at each of four timepoints post-concussion: <3 days, 1 week, 1 month, and 6 months. Each timepoint and test was voluntary and required re-consenting. The number of athletes that participated in each timepoint and test therefore varied and is reported in **Table 7.1**.

Table 7.1. Number of athletes participating in each multidomain test at each timepoint.

TIMEPOINT	BALANCE	OCULOMOTOR	NEUROCOGNITIVE	SYMPTOM REPORTING
NON-CONCUSSED	92	109	73	75
<3 DAYS	16	17	15	20
1 WEEK	19	19	15	21
1 MONTH	13	14	12	0
SIX MONTHS	15	15	10	0

7.3.2 Apparatus

Balance data were collected using two force platforms (40cm x 70 cm) embedded side by side in the laboratory flooring (Bertec Corp), which measured ground reaction forces at 1000 Hz. The Airex Balance Pad (Airex AG, Sins, Switzerland) was used for standing balance tasks requiring a foam surface. This balance pad fit within the dimensions of each force platform, and is the foam used in the sports medicine facility by the NCAA Division I athletes at DU.

7.3.3 Procedure

Standing balance tasks included all stances from the BESS test (University of North Carolina, Chapel Hill, NC) performed on force platforms. The BESS protocol consists of three standing balance stances (single-leg stance, double-leg stance, and tandem stance) performed for 20 seconds with eyes closed both on a hard surface and on a foam surface. BESS tasks were performed for a total of 30 seconds on the force platform, and the first 5 seconds and last 5 seconds of trial data were removed as to capture only continuous balance rather than movement into or out of the stance position. Each of the three tasks were performed both on the force platform and a foam balance pad placed on the force platform, consistent with the BESS protocol. The single-leg stance was performed on a single force platform and a single foam balance pad. The double-leg and tandem stances were performed with each foot on a separate force platform and separate foam balance pad while maintaining BESS protocol instructions for stance positioning.

In the same testing session as balance testing, each athlete completed the KD test administered by the session tester and the computerized ImPACT assessment. The KD test is a portable, sideline oculomotor test in which athletes read a series of numbers as fast as possible and with the least number of errors. Task completion time and error count are recorded for each of the three sequentially harder tests. The Immediate Post-Concussion Assessment and Cognitive Test (ImPACT; Lovell *et al.*, 2000) consists of 8 tasks: immediate word recall, delayed word recall, immediate design recall, delayed design recall, symbol-matching, 3-letter recall, X's and O's test, and color-matching. Results from these tasks are grouped into five composite scores: verbal memory, visual memory, visual motor speed, reaction time, and impulse control. Symptom scoring was collected pre-season (baseline) and post-concussion daily until symptoms resolved (12.52 ± 15.35 days) by the NCAA D1 athletic trainers at the University of Denver using the ImPACT post-concussion symptom scale (PCSS). Athletes rated a series of 22 symptoms individually on a scale from 0-6. All individual symptom scores were summed for a total symptom score with a possible range of 0-132.

7.3.4 Balance data processing

All data were filtered using a 4th order low-pass Butterworth filter with a 5 Hz cutoff (Carpenter *et al.*, 2010). Using customized Matlab (2017a, MathWorks, Inc., Cambridge, MA) code, ellipse area and average COP velocity (Total, ML, AP) were calculated for all BESS trials. During the single-leg and tandem stances, many athletes were unable to complete the full 30 seconds without performing an error. Consistent with the BESS protocol, athletes were instructed to return to the testing position as quickly as possible following an error. To account for these errors, we used a method similar to Riemann *et al.* (1999), where the trial was cut to the longest length of time a subject could maintain 90% bodyweight on the force platform, and any trial that contained less than 5 seconds was excluded from analysis (**Table 7.2**). The missing data slots were assigned a random value (Hot-deck Imputation Method; Yan, 2011) sampled from existing trials of the same cohort and timepoint. This replacement method provides a conservative estimate of balance performance in the concussed cohort because the value from the excluded trials, if measurable, would have shown a larger balance impairment than the imputed value. **Chapter 5** previously reported that COP ML velocity in the double-leg stance on a hard surface discriminated well between non-concussed and concussed athletes at the <3 days timepoint, and COP AP velocity in the tandem stance on foam was sensitive to concussion at all four post-concussion timepoints. These two measures are therefore chosen for continued exploration in this assessment.

Table 7.2. Number of athletes at each timepoint unable to maintain 90% body weight over the force platform for the single-leg and tandem stance tasks. The total number of athletes for each timepoint were as follows: non-concussed: n=117, <3 days: n=16, 1 week: n=19, 1 month: n=13, and 6 months: n=14.

	SINGLE-LEG		TANDEM	
	Hard	**Foam**	**Hard**	**Foam**
NON-CONCUSSED	3	29	15	48
<3 DAYS	1	2	2	10
1 WEEK	1	3	3	11
1 MONTH	0	2	3	6
SIX MONTHS	0	2	1	8

7.3.5 Statistical analysis

Cohen's *d* effect size—with a 95% confidence interval—was calculated to compare the non-concussed group to post-concussion athletes for each measure at each timepoint. Results are reported as (Cohen's *d* effect size [Confidence interval]) for each post-concussion timepoint.

A receiver operating characteristic (ROC) curve was assessed using the non-concussed athlete timepoint and the <3 days timepoint for each variable in each domain test. Using only the data corresponding to the first (<3 days) post-concussion timepoint, rather than all four post-concussion timepoints, ensures that the curve is truly based on athletes that do and do not have the condition. An area under the ROC curve (AUROC) approaching one is considered excellent in terms of discriminative ability (**Table 7.3**). The measure with the highest AUROC from each domain was chosen for further analysis, with the exception of the balance domain, for which both measures were included due to both demonstrating fair or better discriminative ability.

Table 7.3. Commonly reported classification system for the discriminative ability of the area under the receiver operating characteristic (AUROC) curve.

AUROC	CLASSIFICATION
0.90-1.0	Excellent
0.80-0.90	Good
0.70-0.80	Fair
0.60-0.70	Poor
0.50-0.60	Fail

The measures with the highest AUROC from each domain were utilized to form logistic regression models to determine the most longitudinally sensitive combination of objective multidomain tests. Using only the measures with the highest AUROC ensures that models tested are those that will have the highest discriminative ability available from the multidomain tests. Logistic regression models were run for all individual domains and multidomain combinations to explain the relationship between the presence of concussion binary variable to the multidomain test independent variables (**Figure 7.1**). The dependent, or target, variable was the probability that the athlete has or does not have a concussion at each post-concussion timepoint. The models were constructed based on the non-concussed and <3 days timepoints and applied to all four post-concussion timepoints. This approach mirrors that used for the AUROC calculation to ensure that the models are based on athletes that do and do not have the condition. Due to class bias present in the sample, the data were resampled in equal proportions. 75% of the <3 days timepoint data were sampled for model training data, and an equal number of data points were sampled from the non-concussed data for equal proportions. The remaining data at both timepoints were used as test data to statistically measure the performance of the model. A model cutoff score corresponding to the maximum Youden Index was used, and sensitivity and specificity of the model at this cutoff score are reported (**Appendix C**).

$$
\boxed{\begin{array}{l}
y = RXN + KD + SS + DH \\
y = RXN + KD + SS + TF \\
y = SS + DH \\
y = SS + TF \\
y = RXN + KD + DH + TF \\
y = RXN + KD + DH \\
y = RXN + KD + TF \\
y = DH + TF
\end{array}}
$$

Figure 7.1. List of multidomain logistic regression models assessed for longitudinal sensitivity to concussion. RXN: ImPACT reaction time composite score, SS: total symptom score, KD: task completion time for the second KD test, DH: COP ML velocity in the double-leg stance on a hard surface, TF: COP AP velocity in the tandem stance on foam.

7.4 Results

The measures with the highest AUROC from each domain were: the reaction time composite score from the ImPACT neurocognitive assessment, task completion time from the second test in the KD oculomotor assessment, total symptom score from the ImPACT PCSS, and COP ML velocity in the double-leg stance on a hard surface. The most longitudinally sensitive single-domain assessment was COP AP velocity in the tandem stance on foam. A multidomain assessment of the two balance measures combined provided the highest longitudinal sensitivity up to 6 months post-concussion.

7.4.1 Discriminative ability and effect sizes of multidomain concussion assessments

The measure from each domain with the highest area under the receiver operating characteristic curve (AUROC) is reported here, and full AUROC results are available for all measures in **Table 7.4**. The reaction time composite score from ImPACT had the highest discriminative ability of all the composite scores (AUROC=0.57), although it still ranks as a fail in terms of discriminative ability. The task completion time for the second number reading task in the King-Devick (KD) had the highest AUROC of all task completion times and error scores with poor discriminative ability (AUROC=0.68). Total symptom score had good discriminative ability (AUROC=0.89), as did COP ML velocity in the double-leg stance on a hard surface (AUROC=0.81). COP AP velocity in the tandem stance on foam had fair discriminative ability (AUROC=0.72).

Table 7.4. Area under the receiver operating characteristic curve (AUROC) for all measures assessed from each domain test. The measure with the highest AUROC from each domain was chosen for further assessment with the exception of the balance domain where both measures were assessed.

TEST	VARIABLE	AUROC
IMPACT	Verbal Memory	0.45
	Visual Memory	0.44
	Visual Motor Speed	0.49
	Reaction Time	**0.57**
	Impulse Control	0.53
KING-DEVICK	Test 1 Time	0.66
	Test 1 Errors	0.15
	Test 2 Time	**0.68**
	Test 2 Errors	0.1
	Test 3 Time	0.65
	Test 3 Errors	0.05
SYMPTOMS	Total Symptom Score	**0.89**
BALANCE	Double-leg Stance on Hard Surface: COP ML Velocity	**0.81**
	Tandem Stance on Foam Surface: COP AP Velocity	0.72

Effect sizes for the measures with the highest AUROC for each respective domain are reported here, and full effect size results are available in **Table 7.5** and **Table 7.6**. Reaction time had a small effect at all 4 post-concussion timepoints (d=0.29, -0.22, -0.29, 0.29, respectively). Reaction time was longer at <3 days and 6 months post-concussion and shorter at 1 week and 1 month. Task completion time for the second number reading task in the KD was longer with a large effect at <3 days (*d*=0.85), and a moderate effect at 1 week and 1 month (*d*=0.50, 0.50). Task completion time was shorter with a small effect 6 months post-concussion (*d*=-0.26). Total symptom score was higher with a large effect at <3 days (*d*=1.21) and with a small effect at 1 week (*d*=0.25). COP ML velocity in the double-leg stance on a hard surface was higher with a large effect within 3 days (*d*=1.06), 1 week (*d*=0.81), 1 month (*d*=0.87), and 6 months (*d*=0.82) post-concussion. COP AP velocity in the tandem stance on foam was lower with a moderate effect at all four post-concussion timepoints (*d*=0.69, 0.74, 0.67, 0.73, respectively).

Table 7.5. Mean, standard deviation, and effect size for all multidomain measures assessed for all timepoints.

		Symptoms	**ImPACT**					**Balance**		**KD**					
	Timepoint	Total Symptom Score	Verbal Memory	Visual Memory	Visual Motor Speed	Reaction Time	Impulse Control	DH	TF	Task Time 1	Error Score 1	Task Time 2	Error Score 2	Task Time 3	Error Score 3
μ	Baseline	2.75	88.56	78.34	41.83	0.57	5.55	7.62	104.42	13.53	0.23	13.54	0.18	14.92	0.23
	<3 days	10.70	89.87	79.93	42.57	0.60	6.20	14.28	49.27	15.03	0.18	15.65	0.12	17.30	0.06
	1 week	4.48	91.40	81.93	45.90	0.56	4.93	13.74	46.13	14.67	0.05	14.74	0.00	16.83	0.16
	1 month	N/A	93.42	83.42	44.04	0.55	5.42	14.14	49.60	13.52	0.21	13.43	0.07	14.12	0.21
	6 months	N/A	97.70	87.20	45.66	0.60	4.50	12.96	45.61	12.47	0.13	12.97	0.07	13.75	0.27
σ	Baseline	6.42	8.96	12.45	6.90	0.07	3.81	5.61	86.40	2.04	0.59	2.21	0.47	2.75	0.52
	<3 days	7.26	8.16	13.24	5.37	0.07	3.08	9.27	16.27	3.14	0.39	3.82	0.33	5.24	0.24
	1 week	8.25	8.94	9.82	5.94	0.07	4.62	13.84	12.16	3.86	0.23	3.33	0.00	6.29	0.37
	1 month	N/A	4.32	9.27	6.41	0.08	4.03	15.81	26.36	2.06	0.58	1.89	0.27	2.05	0.43
	6 months	N/A	2.31	9.55	5.46	0.09	2.72	10.52	18.61	1.30	0.35	1.58	0.26	2.11	0.80
d	<3 days	**1.21**	0.15	0.13	0.11	0.29	0.18	**1.06**	**-0.69**	**0.68**	-0.09	**0.85**	-0.14	**0.75**	-0.35
	1 week	0.25	0.32	0.30	**0.60**	-0.22	-0.16	**0.81**	**-0.74**	0.48	-0.32	**0.50**	-0.42	**0.56**	-0.14
	1 month	N/A	0.56	0.42	0.32	-0.29	-0.03	**0.87**	**-0.67**	0.48	-0.32	**0.50**	-0.42	**0.56**	-0.14
	6 months	N/A	**1.08**	**0.73**	**0.57**	0.29	-0.28	**0.82**	**-0.73**	**-0.53**	-0.17	-0.26	-0.26	-0.44	0.07

Table 7.6. Effect sizes with confidence interval for the measures assessed in logistic regression models. DH: COP ML velocity in the double leg stance on a hard surface, and TF: COP AP velocity in the tandem stance on foam.

MEASURE	TIMEPOINT	EFFECT SIZE (*D*)	CONFIDENCE INTERVAL
REACTION TIME	<3 days	0.29	[-0.27, 0.85]
	1 week	-0.22	[-0.34, 0.78]
	1 month	-0.29	[-0.32, 0.90]
	6 months	0.29	[-0.37, 0.95]
TASK COMPLETION TIME	<3 days	0.85	[0.33, 1.37]
	1 week	0.50	[0.01, 0.99]
	1 month	0.50	[-0.06, 1.06]
	6 months	0.26	[-0.28, 0.80]
TOTAL SYMPTOM SCORE	<3 days	1.21	[0.69, 1.73]
	1 week	0.25	[-0.24, 0.74]
	1 month	N/A	N/A
	6 months	N/A	N/A
DH	<3 days	1.06	[0.51, 1.61]
	1 week	0.81	[0.30, 1.32]
	1 month	0.87	[0.28, 1.46]
	6 months	0.82	[0.26, 1.38]
TF	<3 days	0.69	[0.15, 1.23]
	1 week	0.74	[0.24, 1.24]
	1 month	0.67	[0.08, 1.26]
	6 months	0.73	[0.18, 1.28]

7.4.2 Logistic regression model sensitivity

Logistic regression models were run for individual domain measures including reaction time (RXN), task completion time for the KD second number reading task (KD), total symptom score (SS), and both balance variables; COP ML velocity in the double-leg stance on a hard surface (DH) and COP AP velocity in the tandem stance on foam (TF; **Table 7.7**). Multidomain logistic regression models were run for various combinations of domains (**Figure 7.1)**. The specificity rate was consistent for each model across all four post-concussion timepoints (**Table 7.7**). Therefore, model performance is evaluated based on longitudinal sensitivity.

TF is the most longitudinally sensitive single-domain model with sensitivities of 1.0, 0.71, 1.0, and 1.0 for each respective post-concussion timepoint (**Figure 7.2, Table 7.8**). Within three days post-concussion, SS is also highly sensitive (1.0), followed by DH (0.86), RXN (0.71), and KD (0.57). At 1 week post-concussion, TF and DH are the most sensitive (0.71), followed by RXN (0.57), SS, and KD (0.43). One month post-concussion, TF remains highly sensitive (1.0) while other measures continue to lose sensitivity (RXN=0.50, DH=0.25, KD=0.25), and sensitivity of SS falls to zero since no data exists for this SS at timepoints longer than 1 week post-concussion. Six months post-concussion, TF continues to have high sensitivity (1.0), and RXN is more sensitive than at other timepoints (0.75). All other domain measures continue to lose sensitivity (DH=0.25, KD=0.0, SS=0.0).

In the multidomain models, a combination of the two balance measures (y=DH+TF) appears to be the most longitudinally sensitive to concussion with sensitivities of 1.0, 0.86, 1.0, and 1.0 for each respective post-concussion timepoint (**Figure 7.3, Table 7.8**). Within three days post-concussion, y=SS+DH and y=SS+TF also have high sensitivity (1.0), followed by y=RXN+KD+SS+DH and y=RXN+KD+SS+TF (0.86), and then by y=RXN+KD+DH and y=RXN+KD+TF (0.71). One week post-concussion, the most sensitive multidomain model is y=DH+TF (0.86) followed by y=RXN+KD+SS+DH (0.71), y=RXN+KD+TF, y=RXN+KD+DH+TF, and y=SS+DH (0.57), then by y=SS+TF and y=RXN+KD+SS+TF (0.29), and finally y=RXN+KD+SS+DH (0.14). One month post-concussion, y=DH+TF is the most sensitive model (1.0) followed by y=RXN+KD+DH+TF and y=RXN+KD+TF (0.75), then by y=RXN+KD+DH (0.25). All other models fall to zero sensitivity. Six months post-concussion, y=DH+TF is the most sensitive model (1.0) followed by y=RXN+KD+DH+TF, y=RXN+KD+DH, and y=RXN+KD+TF (0.75), then by y=RXN+KD+SS+TF (0.5). All other models have zero sensitivity at this timepoint.

Table 7.7. Logistic regression models, equations, and *p*-values for all measures in the equation. RXN: ImPACT reaction time composite score, SS: total symptom score, KD: task completion time for the second KD test, DH: COP ML velocity in the double-leg stance on a hard surface, TF: COP AP velocity in the tandem stance on foam. *P*-values indicating significance (p>0.05) denote measures that are heavily weighted in the model equation.

MODEL	EQUATION	*P*-VALUES (LISTED IN ORDER RESPECTIVE TO THE MODEL EQUATION)
$\boldsymbol{y = RXN}$	$y = -9.79 + 17.2RXN$	p=0.02, 0.02
$\boldsymbol{y = SS}$	$y = -3.43 + 0.74SS$	p=0.0, 0.0
$\boldsymbol{y = KD}$	$y = -2.81 + 0.19KD$	p=0.17, 0.17
$\boldsymbol{y = DH}$	$y = -0.93 + 0.08DH$	p=0.12, 0.08
$\boldsymbol{y = TF}$	$y = 3.24 - 0.05TF$	p=0.01, 0.01
$\boldsymbol{y = RXN + KD + SS + DH}$	$y = -14.73 + 6.49RXN + 0.73SS + 0.44KD + 0.11DH$	p=0.12, 0.61, 0.007, 0.40, 0.17
$\boldsymbol{y = RXN + KD + SS + TF}$	$y = -798.26 + 765.58RXN + 51.22SS + 63.81KD - 17.29TF$	p=0.99, 0.99, 0.99, 0.99, 0.99
$\boldsymbol{y = SS + DH}$	$y = -4.33 + 0.73SS + 0.08DH$	p=0.01, 0.0, 0.24
$\boldsymbol{y = SS + TF}$	$y = 1.93 + 0.70SS - 0.11TF$	p=0.47, 0.01, 0.13
$\boldsymbol{y = RXN + KD + DH + TF}$	$y = -10.16 + 18.5RXN + 0.24KD + 0.02DH - 0.06TF$	p=0.10, 0.09, 0.36, 0.75, 0.02
$\boldsymbol{y = DH + TF}$	$y = 2.63 + 0.04DH - 0.05TF$	p=0.05, 0.43, 0.01
$\boldsymbol{y = RXN + KD + DH}$	$y = -10.25 + 16.55RXN - 0.004KD + 0.07DH$	p=0.02, 0.03, 0.98, 0.13
$\boldsymbol{y = RXN + KD + TF}$	$y = -10.2 + 18.81RXN + 0.25KD - 0.06TF$	p=0.11, 0.09, 0.32, 0.01

Table 7.8. Sensitivity and specificity for each logistic regression model at each post-concussion timepoint. RXN: ImPACT reaction time composite score, SS: total symptom score, KD: task completion time for the second KD test, DH: COP ML velocity in the double-leg stance on a hard surface, TF: COP AP velocity in the tandem stance on foam.

	<3 DAYS		**1 WEEK**		**1 MONTH**		**6 MONTHS**	
MODEL	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Y=RXN	0.714	0.51	0.57	0.5	0.5	0.53	0.75	0.52
Y=SS	1	0.73	0.43	0.74	0	0.75	0	0.76
Y=KD	0.57	0.87	0.43	0.89	0.25	0.89	0	0.89
Y=DH	0.86	0.68	0.71	0.68	0.25	0.67	0.25	0.67
Y=TF	1	0.64	0.71	0.65	1	0.64	1	0.64
Y=RXN+KD+SS+DH	0.86	0.81	0.14	0.82	0	0.85	0	0.85
Y=RXN+KD+SS+TF	0.86	0.82	0.29	0.83	0	0.85	0.5	0.85
Y=SS+DH	1	0.77	0.57	0.78	0	0.79	0	0.8
Y=SS+TF	1	0.92	0.29	0.92	0	0.92	0	0.92
Y=RXN+KD+DH+TF	0.86	0.71	0.57	0.72	0.75	0.71	0.75	0.7
Y=DH+TF	1	0.62	0.86	0.63	1	0.62	1	0.62
Y=RXN+KD+DH	0.71	0.52	0.71	0.52	0.25	0.52	0.75	0.52
Y=RXN+KD+TF	0.71	0.76	0.57	0.77	0.75	0.75	0.75	0.75

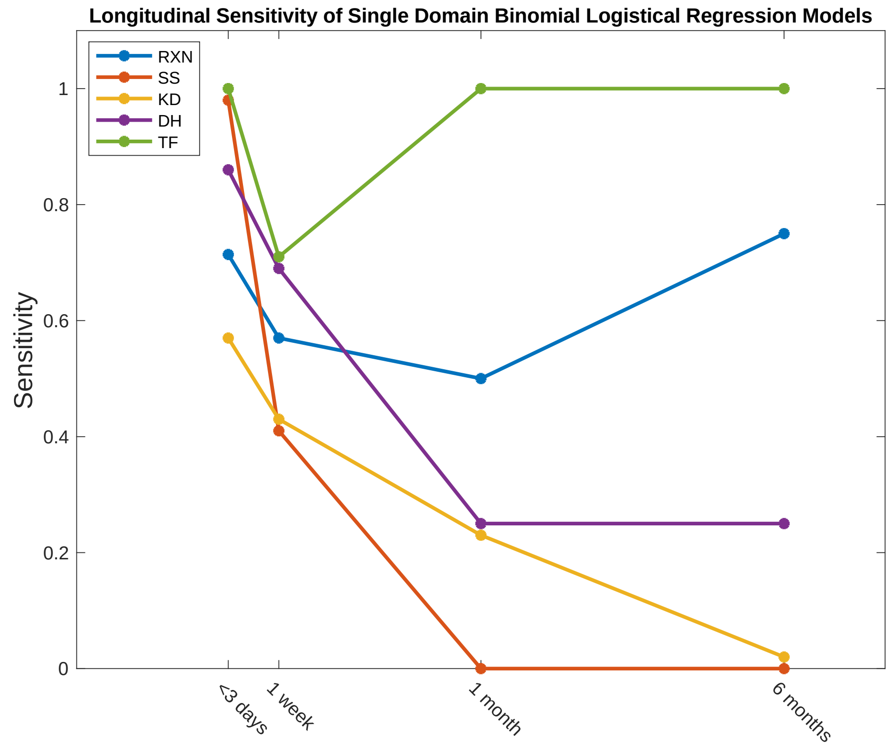

Figure 7.2. Longitudinal sensitivity of the single-domain logistic regression models. RXN: ImPACT reaction time composite score, SS: total symptom score, KD: task completion time for the second KD test, DH: COP ML velocity in the double-leg stance on a hard surface, TF: COP AP velocity in the tandem stance on foam. TF appears to maintain longitudinal sensitivity.

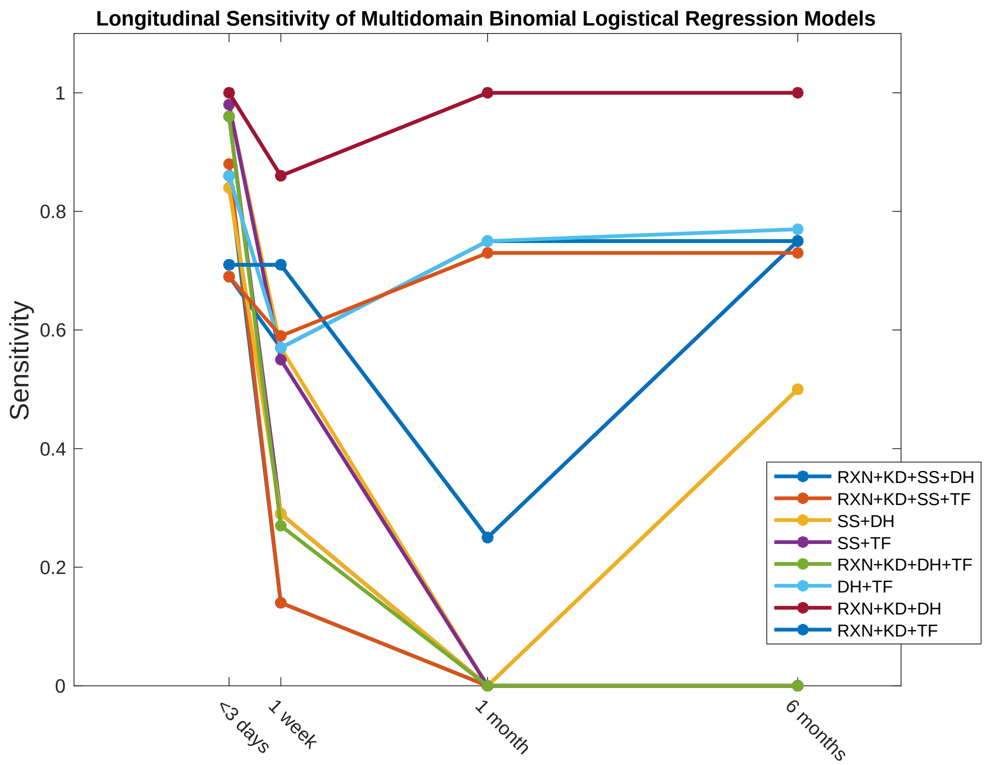

Figure 7.3. Longitudinal sensitivity of the multi-domain logistic regression models. RXN: ImPACT reaction time composite score, SS: total symptom score, KD: task completion time for the second KD test, DH: COP ML velocity in the double-leg stance on a hard surface, TF: COP AP velocity in the tandem stance on foam. DH+TF appears to maintain longitudinal sensitivity.

7.5 Discussion

This study determined the longitudinal sensitivity of multidomain logistic regression models for athletes up to 6 months post-concussion. A model of two balance measures: COP ML velocity in the double-leg stance on a hard surface, and COP AP velocity in the tandem stance on foam, was the most longitudinally sensitive model. Total symptom score was sensitive acutely post-concussion but recovered quickly. Balance measures have the potential to identify lasting sensorimotor deficits when other measures have returned to baseline.

7.5.1 Discriminative ability and effect sizes

The discriminative ability of all measures in each domain was assessed using the non-concussed cohort and the <3 days post-concussion timepoint. All ImPACT composite scores ranked as a fail in terms of discriminative ability, with reaction time ranking as the measure with the highest discriminative ability. The task completion times and error scores for the KD either ranked as a fail or had poor discriminative ability with the task completion time for the second number reading task ranking as the highest discriminative ability. COP AP velocity in the tandem stance on foam had fair discriminative ability while total symptom score and COP ML velocity in the double-leg stance on a hard surface had good discriminative ability. Together, this indicates that ImPACT composite scores and KD measures do not discriminate well between concussed and non-concussed athletes and therefore may have limited usefulness in concussion protocols. Total symptom score and balance measures, however, do discriminate well between concussed and non-concussed athletes and may provide multidomain models with more sensitivity to concussion than ImPACT and KD measures.

The measures with the highest discriminative ability from the neurocognitive and oculomotor domains (ImPACT reaction time and KD task completion time for the second test, respectively), total symptom score, and both balance measures were further assessed using effect size to determine the magnitude of change at each post-concussion timepoint relative to the non-concussed population. Reaction time had small effect sizes at all four post-concussion timepoints, and additionally, the direction of change varied, giving further confirmation that this measure is not useful for concussion diagnosis and recovery tracking.

Although the task completion time for the second KD task had poor discriminative ability, task completion time was longer with a moderate effect up to 1 month post-concussion. Total symptom score had a large effect <3 days post-concussion, but a small effect 1 week post-concussion, indicating that while this measure initially demonstrates group differences between the non-concussed population and athletes post-concussion, symptoms resolve quickly. Concussion has been linked to a higher risk of lower extremity injuries and repeated concussion after RTP (McCrea *et al.*, 2020; Herman *et al.*, 2017; Harada *et al.*, 2019), indicating continued sensorimotor deficits after symptoms resolve. COP ML velocity in the double-leg stance on a hard surface was higher with a large effect and COP AP velocity in the tandem stance on foam was lower with a moderate effect at all four post-concussion timepoints, indicating that these balance measures may be useful in longitudinal evaluations to identify lasting sensorimotor deficits.

7.5.2 Single and multidomain logistic regression models

The single-domain model for COP AP velocity in the tandem stance on foam is the most longitudinally sensitive of the single-domain models. All other single-domain models lose sensitivity over time except the model for reaction time, which has decreased sensitivity at 1 week and 1 month post-concussion relative to the <3 days timepoint, and increased sensitivity 6 months post-concussion. As discussed previously, the discriminative ability of reaction time is poor, and effect sizes show an inconsistent direction of change over the four post-concussion timepoints from the non-concussed cohort. In models of clinical concussion diagnostic tools, Broglio *et al.* (2019) also found that neurocognitive testing was not useful in an optimized assessment battery. The reaction time model may reflect random variability over time, rather than sensitivity to concussion. The lost sensitivity in the other single-domain models is a result of many of the athletes recovering back to baseline levels in these tests.

In the multidomain models used in this study, a combination of the two balance variables had high sensitivity at all four post-concussion timepoints. These objective measures may provide clinicians with detailed information on the sensorimotor integration functioning for athletes as recovery progresses. In turn, this may allow athletes with persistent balance deficits to receive vestibular or sensorimotor targeted rehabilitation to improve neuromuscular functioning and decrease the likelihood of lower extremity injury and repeated concussion, two injuries common at RTP post-concussion (Harada *et al.*, 2019; Herman *et al.*, 2017; McCrea *et al.*, 2020).

The models that included total symptom score as an independent variable quickly lost sensitivity due to total symptom score being heavily weighted in the model. The reported *p*-values for the y-intercept and each independent variable in the models are a test of significance with the null hypothesis that the independent variable does not have a significant effect on the dependent variable. In this case, the null hypothesis is that each independent domain measure does not have a significant effect on the likelihood that the athlete is in either the non-concussed population or the post-concussion population. In the models including total symptom score, the symptom score independent variable tends to reject the null hypothesis while the other independent variables do not. In these cases, the models are heavily weighted on total symptom score, and with quick resolution of symptoms post-concussion, these models fail in terms of longitudinal sensitivity since long-term sensitivity of these models would rely on athletes remaining symptomatic. The models not including total symptom score tend to fair better longitudinally, since the weighting of the model is based on objective outcomes that can be measured consistently over time.

7.5.3 Clinical implementations and future work

Development of quantitative assessment tools, such as the multidomain models presented, has the potential to improve concussion diagnosis and treatment. These findings suggest that symptom evaluation is an essential measure for concussion diagnosis and acute treatment, but that multidomain objective measures may prove more useful during recovery for their continued sensitivity to the physical and cognitive effects of concussion. The finding that symptom evaluation is particularly useful acutely post-concussion is helpful for concussion diagnosis scenarios in which athletic trainers and coaches are required to make fast evaluations and decisions during practice and gameplay. Subjective symptom scoring, while not without its drawbacks, is a quick and sensitive tool that is easily administered in sideline evaluations. While symptom scoring may be useful in this application, the model results suggest that it is not useful during recovery and RTP decisions post-concussion. In these cases, objective measures, particularly biomechanical measures of balance, could be more useful to critically examine lasting sensorimotor deficits.

7.5.4 Limitations

Despite the high longitudinal sensitivity of the two-stance balance model to concussion, there are limitations associated with the tandem stance on foam. While all athletes could complete the double-leg stance task, only approximately half were able to complete the tandem stance on foam task with the constraints of 90% body weight over the force platform for five or greater seconds in both non-concussed and post-concussion athletes, indicating that it is not related to concussion, but to the difficult nature of the task. Individual case study work may be helpful to determine if the tandem stance on foam is universally useful. Additionally, future work on instrumentation should prioritize measures that are capable of including data from all individuals, such as the double-leg stance where athletes have less sway and are less prone to steps during the balancing task.

The comparison of a non-concussed athlete cohort to the post-concussion cohort is an additional limitation. While the original goal was to collect pre-season baseline data for all athletes, only five athletes who sustained concussion participated in baseline testing. There was also difficulty in maintaining athlete interest to participate in all four post-concussion timepoints. Longitudinal monitoring of individual athletes will add to the clinical usefulness of these findings.

7.6 Conclusions

A logistic regression model of two biomechanical balance variables was the most longitudinally sensitive to concussion. Total symptom score was the most sensitive measure <3 days post-concussion, but lost sensitivity as soon as 1 week. Neurocognitive and oculomotor testing, while more longitudinally sensitive, did not appear to contribute heavily to the models and lost sensitivity over time. Biomechanical balance, specifically COP AP velocity in the tandem stance on foam, maintained longitudinal sensitivity. The use of a balance model may be a valuable and objective measure to identify athletes with lasting sensorimotor deficits.

CHAPTER 8: CONCLUSIONS AND RECOMMENDATIONS

The Specific Aims presented in this dissertation provide evidence that linear measures of the COP discriminate well between non-concussed and concussed athletes, are longitudinally sensitive up to 6 months post-concussion, and show statistically significant group differences in athletes with and without a history of concussion. Further, these measures generate a logistic regression model that is longitudinally sensitive to concussion and may aid in concussion rehabilitation and RTP decisions.

8.1 Conclusions of Specific Aims

In **Chapter 5**, two measures of biomechanical standing balance were found useful to differentiate between non-concussed and concussed athletes. COP ML velocity in double-leg stance on a hard surface discriminated between non-concussed and concussed athletes at the <3 days timepoint, while COP AP velocity in tandem stance on foam was sensitive to concussion at all four post-concussion timepoints. Preliminary quantitative thresholds were introduced for diagnostic and recovery applications, and a key finding was that these balance measures did not recover to within these thresholds even 6 months following concussion in more than half of the athletes. Both the ML component of the COP in the double-leg stance and the AP component of the COP in tandem stance are under hip control. These results indicate that concussed athletes shift to the use of hip control, as this strategy is utilized in standing balance when ankle control fails. COP ML velocity in the double-leg stance on a hard surface increased post-concussion, while COP AP velocity in the tandem stance on foam decreased post-concussion. Increased sway is typically reported post-concussion in quiet stance, matching the findings in this dissertation and indicating that athletes have difficulty regulating small balance perturbations. The decrease in sway during the tandem stance on foam may be due to differences in proprioception relative to quiet stance, causing the athletes to adopt conservative movement, similar to the conservative gait strategy typical of functional balance tasks. Together, these results indicate continued vestibular and sensorimotor impairments, and have implications for rehabilitation and RTP protocols.

Chapter 6 found that linear measures of the COP were useful in differentiating between non-concussed athletes and those with a documented history of concussion. COP ML velocity in both the single-leg stance on foam and tandem stance on foam, and ellipse area and COP AP velocity in the tandem stance on foam were significantly different between groups. Both of these tasks lose visual information with the eyes-closed nature of the task and have decreased proprioceptive information while standing on the foam pad. This lack of sensory input information and heavy reliance on the vestibular system likely allows for the observation of discrete balance deficits. Both COP AP velocity and COP ML velocity were lower post-concussion in the tandem stance on foam, indicating that both ankle and hip control are essential contributors to maintaining balance in athletes with history of concussion. COP ML velocity was lower post-concussion in the single-leg stance, which possibly uses a mix of ankle and hip control in both planes, as further confirmation that both ankle and hip control strategies are important long-term post-concussion. In both stances, COP velocity measures decreased post-concussion, matching the findings in Chapter 5, indicating that athletes with a history of concussion continue to apply a conservative movement strategy and may have lasting balance impairments.

In **Chapter 7**, multidomain concussion assessment measures, including those from the ImPACT neurocognitive test, the KD oculomotor test, total symptom score from the ImPACT PCSS, and the discriminatory and sensitive biomechanical balance measures from Chapter 5, were assessed for their contributions to logistic regression models. A key finding was that a model including both COP ML velocity in the double-leg stance on a hard surface and COP AP velocity in the tandem stance on foam was found to be the most longitudinally sensitive to concussion of all models assessed. ImPACT composite scores and KD measures had poor discriminative ability, indicating that they may have limited usefulness in concussion protocols. Balance measures and total symptom scores were found to discriminate well between non-concussed athletes and athletes <3 days post-concussion. Models including total symptom scores were weighted heavily on this measure. Due to quick resolution of symptoms post-concussion, these models had high sensitivity at the <3 days timepoint post-concussion, but lost sensitivity as recovery progressed. The models suggest that symptom evaluation is an essential measure for concussion diagnosis, but may not be useful in recovery protocols. For recovery applications and RTP decisions, objective measures, such as the longitudinally sensitive model of biomechanical balance, may be useful to identify continued vestibular and sensorimotor deficits.

8.2 Summary of limitations

There are several limitations in this work that should be considered. While measures of biomechanical balance were found to discriminate well between non-concussed and concussed athletes and were sensitive longitudinally post-concussion, this does not prove balance to be a biomarker for concussion. To create a case for a biomarker, biomechanical balance measures should be associated to pathophysiological markers from imaging or blood (Horak & Mancini, 2013), and also to patient improvements including lower risk of lower extremity injuries and repeated concussion (Melzer *et al.*, 2010; Norris *et al.*, 2005). This study does not attempt to provide proof of concept through either of these methods.

The original goal of the study was to track concussed athletes pre- and post-concussion. Due to only five athletes who sustained concussion participating in pre-season baseline testing, sport-matched data from athletes with no reported history of concussion were used as a non-concussed athlete reference. While this comparison is useful for identifying potential post-concussion deficits, concussive injury is complex and affects each athlete differently. The sport-matching and large data size of the non-concussed athlete group allow for robust comparison to the post-concussion cohort, although this approach does not provide direct evidence for usefulness of the proposed thresholds for single athlete pre- and post-concussion application. Post-concussion, there was also difficulty in maintaining athlete interest to participate in all four timepoints. Similar to the limitation regarding tracking athletes pre- and post-concussion, this limitation dampens our ability to measure post-concussion recovery on an individual scale.

Some stances with significant group differences, including the single-leg stance on foam in athletes with a history of concussion and the tandem stance on foam both post-concussion and athletes with a history of concussion were stances that many athletes could not maintain 90% bodyweight over the force platform for at least five seconds. The inability to meet this constraint was found in both non-concussed and concussed athletes, indicating that it is not related to concussion, but does limit the ability for universal application of these measures to all athletes.

In the multidomain logistic regression models, symptom scores were not evaluated at the one-month and six-month timepoints. Due to this, the models including symptom scoring quickly lost sensitivity. These models may be more longitudinally sensitive with this data. However, these models showed severely decreased sensitivity at the one-week timepoint compared to <3 days, indicating that symptoms resolve quickly, and are not longitudinally sensitive to concussion.

8.3 Recommendations for future work

The first recommendation for future work is to provide robust evidence that balance is an indicator of pathophysiological dysfunction post-concussion, which is best completed in a cohort of athletes participating in both a pre-season baseline test and post-concussion testing. Post-concussion testing, at a minimum, should include a timepoint <3 days post-concussion to ensure that pathophysiological and balance changes are indicative of concussive injury. Pathophysiological markers can include imaging or blood and should be associated to biomechanical measures of standing balance to prove that balance can be used as a surrogate for these pathophysiologic changes. A robust study may consider tracking lower extremity injuries and incidence of repeated concussion during the season to compare outcomes of athletes who do and do not sustain a concussion.

For maximum clinical applicability, biomechanical balance measures must be tracked in individual athletes pre- and post-concussion. Due to the complexity and differing levels of severity of the injury, individual athletes recover at varying rates. Systematic recording of injury severity, potentially through the use of multidomain tools, and consistent tracking of individuals post-concussion will provide more concrete proof of the sensitivity of biomechanical balance measures to concussion.

Further work is needed to determine biomechanical balance measures that can be universally completed by all athletes. While linear measures of the COP appear to be useful, many athletes cannot maintain body weight over the force platform for the duration of the trial during foam stances. Further work into determining the sensitivity of nonlinear measures of the COP to concussion during quiet stance may provide an avenue for a measure that can be completed by all athletes. Additionally, determining the sensitivity of gait tasks to concussion may provide clinical applications of the conservative gait strategy typically reported post-concussion.

Finally, while determining sensitivity and discriminative ability of biomechanical balance measures to concussion is a crucial first step in clinical translation of the research, the study of how vestibular and sensorimotor rehabilitation methods may contribute to concussion recovery could provide further clinical application. Rehabilitation methods focused on recovering the sensory pathways injured during concussion may be useful, either to decrease the time needed to recover balance post-concussion, or to reduce the risk of lower extremity injury and repeated concussion at RTP through increased neuromuscular functioning capabilities.

In summary, this work provides evidence to establish biomechanical balance as a sensitive indicator of the short-and long-term deficits in medically-diagnosed concussion. These lasting deficits potentially indicate continued impairment of the sensory pathways related to standing balance post-concussion. This work steps towards clinical translation of biomechanical balance measures in concussion assessment by determining linear measures of the COP that are 1) discriminative and longitudinal sensitive to acute concussion, 2) able to differentiate between athletes with and without a history of concussion, and 3) useful in longitudinally sensitive multidomain assessment models.

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APPENDIX A: NARRATIVE REVIEW EFFECT SIZES

Table A.1. Effect sizes are calculated for studies reported in the narrative review that explicitly compare concussed athletes to non-concussed athletes, and report both mean and standard deviation. In the cohort column, acute denotes recently concussed athletes before or at return to play and chronic denotes athletes with history of concussion. The arrow direction in the results column denotes the direction of significant change for concussed athletes relative to non-concussed athletes.

AUTHOR, YEAR	MEASURE	COHORT	RESULTS	EFFECT SIZE
GUSKIEWICZ, 1997	CTSIB	Acute	↑ CTSIB Score	0.82
GUSKIEWICZ, 2001	BESS	Acute	↑ BESS error score	0.66
MCCREA, 2003		Acute	↑ BESS error score	2.45
NELSON, 2016		Acute	↑ BESS error score	1.27
GUSKIEWICZ, 2001	SOT	Acute	↓ SOT composite scores	0.94
POWERS, 2014	COP	Acute	↑ COP AP velocity	7.6
DE BEAUMONT, 2011		Chronic	↑ COP AP displacement	0.06
DEGANI, 2017		Chronic	↑ COP ML displacement	1.63
THOMPSON, 2005		Chronic	↑ Ellipse area	0.48
SCHMIDT, 2018		Chronic	↓ ML SampEn	1.6
DE BEAUMONT, 2011		Chronic	↓ AP ApEn	0.26
HOWELL, 2013	Single-task gait	Acute	↓ Gait velocity	0.45
PARKER, 2006		Acute	↓ Gait velocity	0.01
FINO, 2016	Dual-task gait	Chronic	↓ Gait velocity	0.2
PARKER, 2006		Chronic	↓ Gait velocity	0.05
PARKER, 2007		Chronic	↓ Gait velocity	0.02

APPENDIX B: AIM 1 DATA TABLES

Table B.1. Mean, standard deviation, and effect size for linear biomechanical balance measures during double-leg stance tasks for all timepoints. Ellipse area is reported in mm^2 and COP velocity measures are reported in mm/s. Effect sizes with $d > 0.5$ are bolded.

		Double-leg Stance							
		Hard Surface				Foam Surface			
	Timepoint	Ellipse Area	COP Velocity	COP ML Velocity	COP AP Velocity	Ellipse Area	COP Velocity	COP ML Velocity	COP AP Velocity
Mean	Non-concussed	171	11.5	7.6	6.9	665	25.7	18.2	13.0
	<3 days	353	18.3	14.3	9.1	849	34.4	28.6	12.4
	1 week	334	17.7	13.7	9.2	742	33.8	29.7	10.7
	1 month	414	17.9	14.1	8.2	715	32.8	27.3	11.0
	6 months	246	16.2	13.0	7.6	1036	38.3	33.4	11.7
Standard Deviation	Non-concussed	284	6.1	5.6	3.4	799	17.8	17.3	9.5
	<3 days	405	10.3	9.3	4.7	1129	24.6	22.8	13.6
	1 week	686	15.2	13.8	7.2	1015	31.4	31.4	7.4
	1 month	754	15.5	15.8	3.8	621	25.8	27.6	6.7
	6 months	350	10.8	10.5	3.8	930	25.8	27.0	7.5
Effect Size	<3 days	**0.60**	**1.00**	**1.06**	**0.63**	0.22	0.46	**0.57**	-0.07
	1 week	0.43	**0.75**	**0.81**	**0.55**	0.09	0.40	**0.56**	-0.26
	1 month	**0.65**	**0.82**	**0.87**	0.38	0.06	0.38	0.48	-0.23
	6 months	0.26	**0.68**	**0.82**	0.22	0.45	**0.66**	**0.80**	-0.15

Table B.2. Mean, standard deviation, and effect size for linear biomechanical balance measures during single-leg stance tasks for all timepoints. Ellipse area is reported in mm^2 and COP velocity measures are reported in mm/s. Effect sizes with $d > 0.5$ are bolded.

		Single-leg Stance							
		Hard Surface				Foam Surface			
	Timepoint	Ellipse Area	COP Velocity	COP ML Velocity	COP AP Velocity	Ellipse Area	COP Velocity	COP ML Velocity	COP AP Velocity
Mean	Non-concussed	2750	75.8	49.0	47.3	5479	116.3	67.5	78.6
	<3 days	2844	72.4	49.4	44.6	4839	103.1	63.2	64.9
	1 week	2255	66.8	45.8	39.0	4863	109.3	66.0	69.9
	1 month	2075	72.1	51.1	40.3	3885	106.1	70.2	56.9
	6 months	2289	68.3	46.2	40.0	4067	110.6	69.6	72.5
Standard Deviation	Non-concussed	1527	19.2	12.1	15.0	2982	32.6	21.2	26.5
	<3 days	902	13.4	10.3	7.3	1669	23.5	16.0	16.5
	1 week	762	15.3	12.3	9.2	1762	16.2	12.6	9.1
	1 month	796	19.0	14.7	10.0	1311	34.9	28.4	17.0
	6 months	1245	12.9	11.0	7.5	1474	22.8	14.8	15.1
Effect Size	<3 days	0.06	-0.18	0.03	-0.19	-0.23	-0.42	-0.21	**-0.54**
	1 week	-0.35	-0.48	-0.27	**-0.59**	-0.22	-0.23	-0.07	-0.35
	1 month	-0.46	-0.19	0.17	-0.49	**-0.56**	-0.31	0.13	**-0.85**
	6 months	-0.31	-0.41	-0.23	**-0.52**	**-0.50**	-0.18	0.10	-0.24

Table B.3. Mean, standard deviation, and effect size for linear biomechanical balance measures during tandem stance tasks for all timepoints. Ellipse area is reported in mm^2 and COP velocity measures are reported in mm/s. Effect sizes with $d > 0.5$ are bolded.

		Tandem Stance							
		Hard Surface				Foam Surface			
	Timepoint	Ellipse Area	COP Velocity	COP ML Velocity	COP AP Velocity	Ellipse Area	COP Velocity	COP ML Velocity	COP AP Velocity
Mean	Non-concussed	1373	73.3	18.6	64.7	3783	128.3	27.6	104.4
	<3 days	761	54.0	13.6	46.2	897	55.9	20.2	49.3
	1 week	525	37.0	12.3	33.1	982	54.8	21.2	46.1
	1 month	582	40.5	15.6	35.1	1634	48.8	18.4	49.6
	6 months	692	54.3	18.2	47.4	2059	68.5	36.4	45.6
Standard Deviation	Non-concussed	1639	54.7	10.8	48.6	5598	96.5	15.2	86.4
	<3 days	405	21.5	4.1	20.0	445	15.6	3.1	16.3
	1 week	393	14.1	4.6	13.9	766	15.9	12.2	12.2
	1 month	364	16.5	9.7	16.6	2417	20.2	7.1	26.4
	6 months	517	40.7	9.9	42.2	2790	25.5	27.6	18.6
Effect Size	<3 days	-0.40	-0.38	-0.50	-0.41	**-0.56**	**-0.81**	**-0.53**	**-0.69**
	1 week	**-0.56**	**-0.72**	**-0.63**	**-0.71**	**-0.55**	**-0.83**	-0.44	**-0.74**
	1 month	**-0.51**	**-0.63**	-0.29	**-0.64**	-0.40	**-0.87**	**-0.64**	**-0.67**
	6 months	-0.44	-0.36	-0.04	-0.36	-0.32	**-0.66**	**0.50**	**-0.73**

APPENDIX C: AIM 2 DATA TABLES

Table C.1. Median, standard deviation, and *p*-value for linear and nonlinear biomechanical balance measures during single-leg stance tasks for athletes with and without a history of concussion. Ellipse area is reported in mm2, COP velocity measures are reported in mm/s, and sample entropy measures are unitless.

		Single-leg Stance											
		Hard Surface						Foam Surface					
	Timepoint	Ellipse Area	COP Velocity	COP ML Velocity	COP AP Velocity	Sample Entropy ML	Sample Entropy AP	Ellipse Area	COP Velocity	COP ML Velocity	COP AP Velocity	Sample Entropy ML	Sample Entropy AP
Median	No concussion	2624.44	77.15	52.00	45.45	1.38	1.24	5173.40	115.95	70.52	74.75	1.33	1.13
	Concussion	2695.48	75.77	53.93	42.74	1.34	1.16	3994.58	103.37	53.93	76.43	1.10	1.13
Standard Deviation	No concussion	1464.77	14.83	9.81	12.93	0.32	0.33	3523.88	27.30	20.15	21.40	0.55	0.34
	Concussion	1026.97	17.94	12.28	12.26	0.31	0.27	3920.43	25.53	16.55	24.85	0.44	0.32
***p*-value**	Concussion	0.64	0.85	0.43	0.43	0.95	0.49	0.30	0.07	**0.0003**	0.86	0.14	0.54

Table C.2. Median, standard deviation, and *p*-value for linear and nonlinear biomechanical balance measures during tandem stance tasks for athletes with and without a history of concussion. Ellipse area is reported in mm^2, COP velocity measures are reported in mm/s, and sample entropy measures are unitless.

		Tandem Stance											
		Hard Surface						Foam Surface					
	Timepoint	Ellipse Area	COP Velocity	COP ML Velocity	COP AP Velocity	Sample Entropy ML	Sample Entropy AP	Ellipse Area	COP Velocity	COP ML Velocity	COP AP Velocity	Sample Entropy ML	Sample Entropy AP
Median	No concussion	594.67	48.13	14.21	43.24	1.35	0.92	1372.59	71.35	31.81	97.27	1.20	1.13
	Concussion	524.34	48.72	14.51	41.89	1.25	0.92	619.96	70.38	17.37	52.76	1.26	1.27
Standard Deviation	No concussion	1017.18	48.11	9.33	58.25	0.41	0.30	5163.37	77.56	15.26	92.62	0.34	0.30
	Concussion	1644.37	28.85	8.54	30.61	0.37	0.34	4098.26	87.17	12.39	71.18	0.43	0.30
***p*-value**	Concussion	0.93	0.82	0.83	0.74	0.25	0.92	**0.0003**	0.65	**0.002**	**0.0035**	0.37	0.60

Table C.3. Median, standard deviation, and *p*-value for linear and nonlinear biomechanical balance measures during double-leg stance tasks for athletes with and without a history of concussion. Ellipse area is reported in mm^2, COP velocity measures are reported in mm/s, and sample entropy measures are unitless.

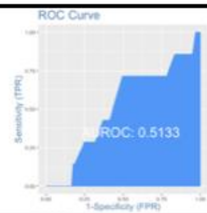
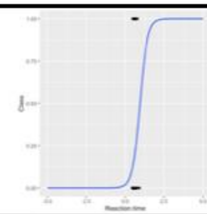
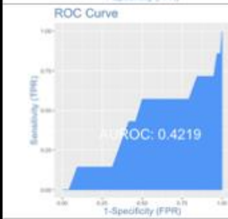
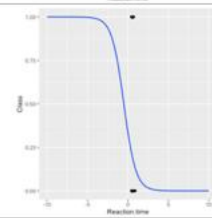
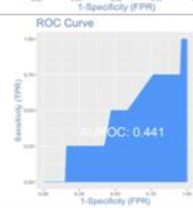
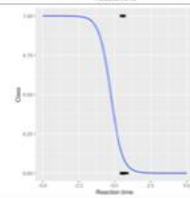
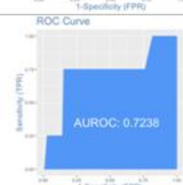
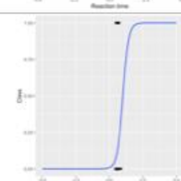
		Double-leg Stance											
		Hard Surface						Foam Surface					
	Timepoint	Ellipse Area	COP Velocity	COP ML Velocity	COP AP Velocity	Sample Entropy ML	Sample Entropy AP	Ellipse Area	COP Velocity	COP ML Velocity	COP AP Velocity	Sample Entropy ML	Sample Entropy AP
Median	No concussion	78.93	10.21	5.89	5.92	0.96	0.78	299.12	20.79	13.27	8.95	0.82	0.83
	Concussion	57.53	9.02	5.63	5.76	0.89	0.91	243.84	18.40	12.45	7.48	0.76	0.90
Standard Deviation	No concussion	200.14	8.62	8.39	3.52	0.31	0.31	946.32	21.95	21.69	9.55	0.18	0.28
	Concussion	1045.63	9.33	7.52	3.72	0.28	0.35	661.44	12.35	11.20	8.39	0.19	0.25
***p*-value**	Concussion	0.27	0.14	0.15	0.28	0.74	0.24	0.69	0.34	0.23	0.42	0.10	0.70

APPENDIX D: AIM 3 RAW DATA

This appendix provides the raw receiver operating characteristic (ROC) curves, area under the ROC (AUROC) results, logistic regression curves, sensitivity, and specificity for each of the four post-concussion timepoints for single-domain and multidomain logistic regression models. The cutoff is the model cutoff score calculated by the Youden Index that provides maximum model sensitivity and specificity between the non-concussed athlete and <3 days post-concussion timepoints.

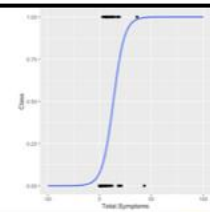
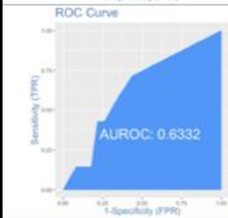
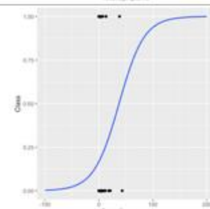
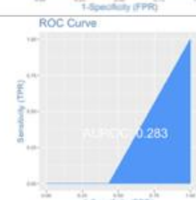
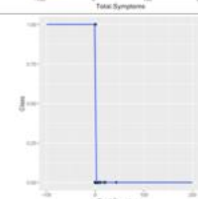
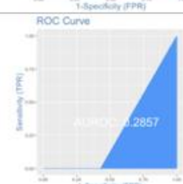
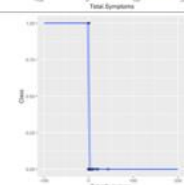
y=RXN

Cutoff = .496

	ROC	Regression	Sensitivity	Specificity
<3 days			0.714	0.51
1 week			0.57	0.5
1 month			0.5	0.53
6 months			0.75	0.52

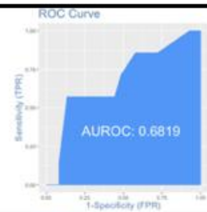
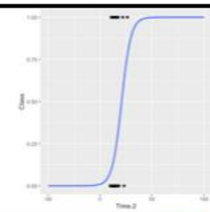
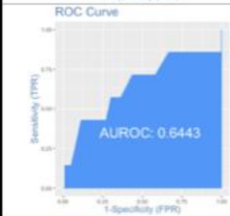
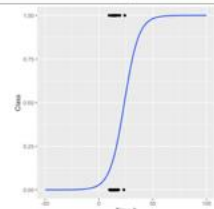
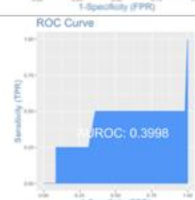
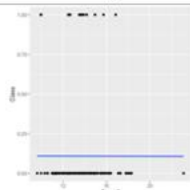
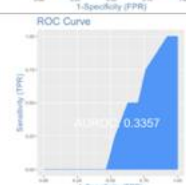
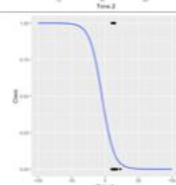
y=SS

Cutoff = .219

	ROC	Regression	Sensitivity	Specificity
<3 days			1	0.73
1 week			0.43	0.74
1 month			0	0.75
6 months			0	0.76

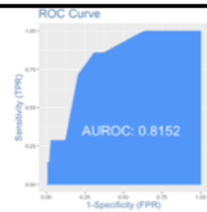
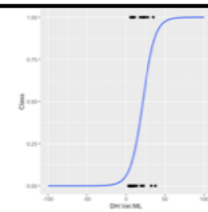
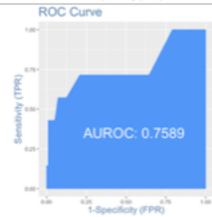
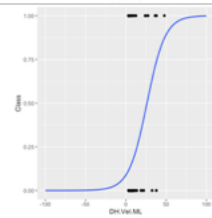
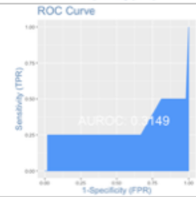
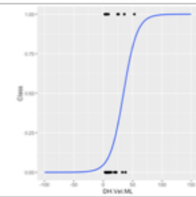
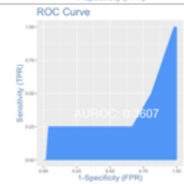
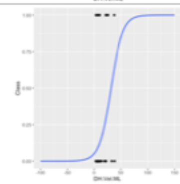
y=KD

Cutoff = .574

	ROC	Regression	Sensitivity	Specificity
<3 days			0.57	0.87
1 week			0.43	0.89
1 month			0.25	0.89
6 months			0	0.89

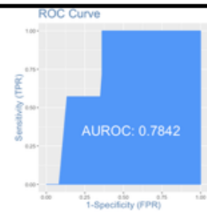
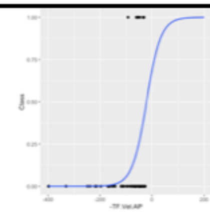
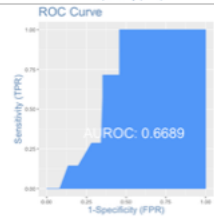
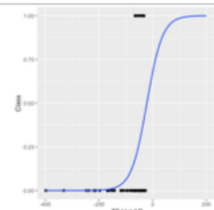
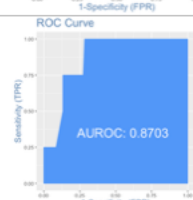
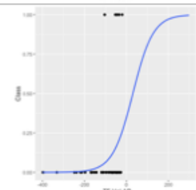
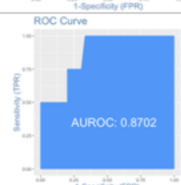
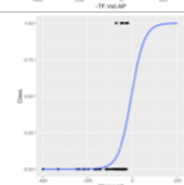
y=DH

Cutoff = .418

	ROC	Regression	Sensitivity	Specificity
<3 days			0.86	0.68
1 week			0.71	0.68
1 month			0.25	0.67
6 months			0.25	0.67

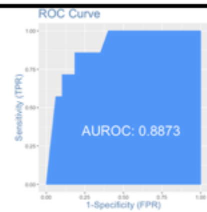
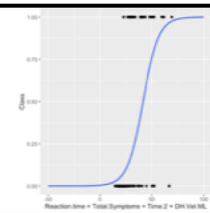
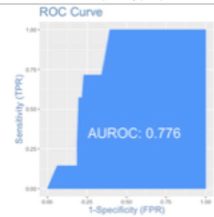
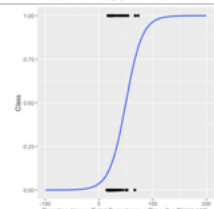
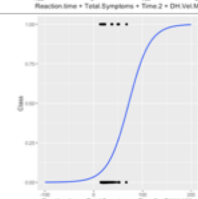
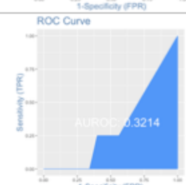
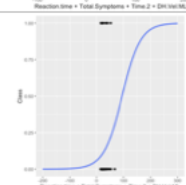
y=TF

Cutoff = .559

	ROC	Regression	Sensitivity	Specificity
<3 days			1	0.64
1 week			0.71	0.65
1 month			1	0.64
6 months			1	0.64

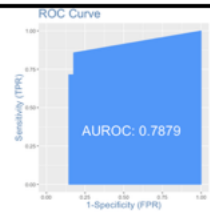
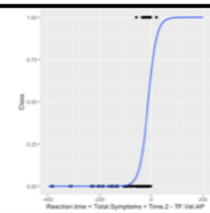
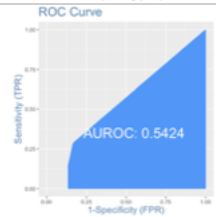
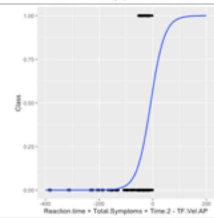
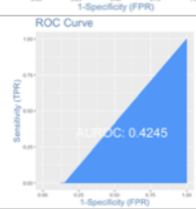
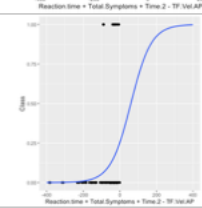
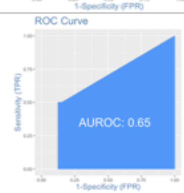
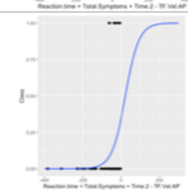
y=RXN+KD+SS+DH

Cutoff = .359

	ROC	Regression	Sensitivity	Specificity
<3 days			0.86	0.81
1 week			0.14	0.82
1 month			0	0.85
6 months			0	0.85

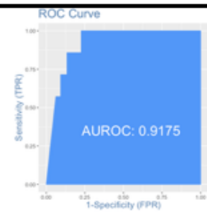
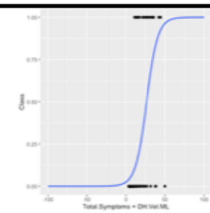
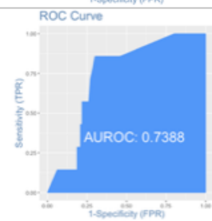
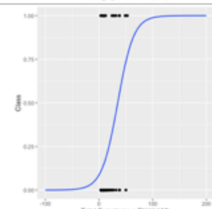
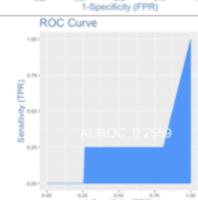
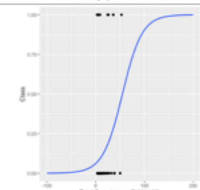
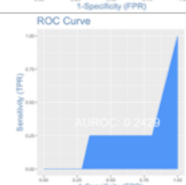
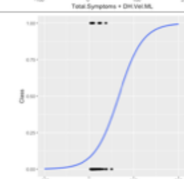
y=RXN+KD+SS+TF

Cutoff = .67

	ROC	Regression	Sensitivity	Specificity
<3 days			0.86	0.82
1 week			0.29	0.83
1 month			0	0.85
6 months			0.5	0.85

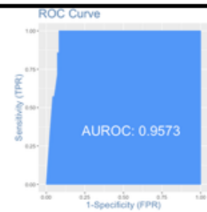
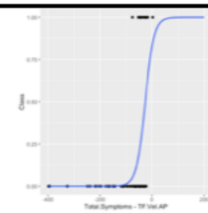
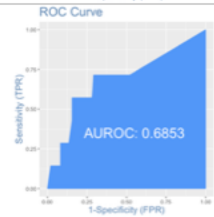
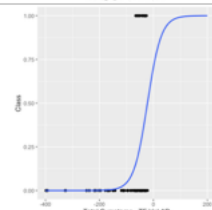
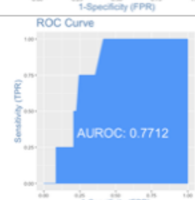
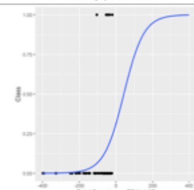
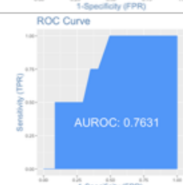
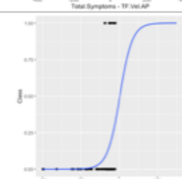
y=SS+DH

Cutoff = .179

	ROC	Regression	Sensitivity	Specificity
<3 days			1	0.77
1 week			0.57	0.78
1 month			0	0.79
6 months			0	0.8

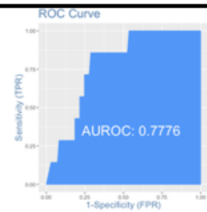
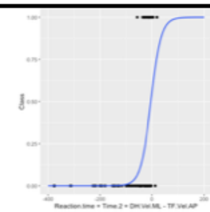
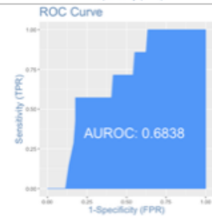
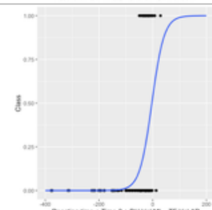
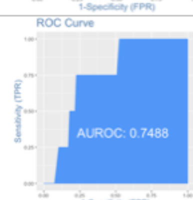
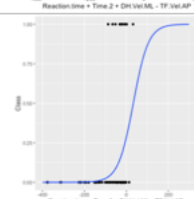
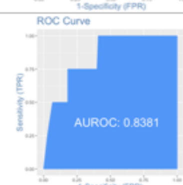
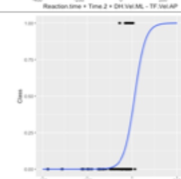
y=SS+TF

Cutoff = .63

	ROC	Regression	Sensitivity	Specificity
<3 days			1	0.92
1 week			0.29	0.92
1 month			0	0.92
6 months			0	0.92

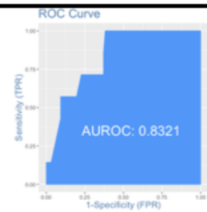
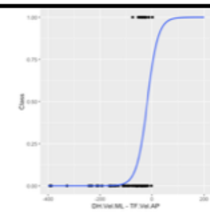
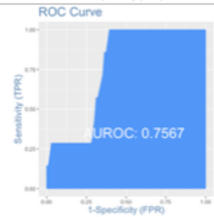
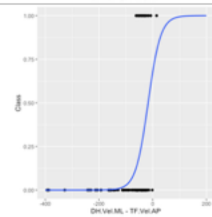
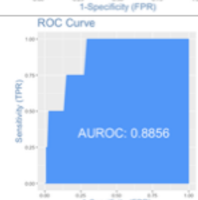
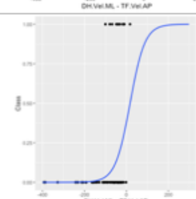
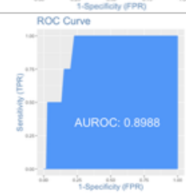
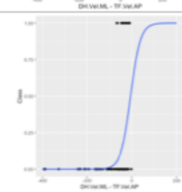
y=RXN+KD+DH+TF

Cutoff = .58

	ROC	Regression	Sensitivity	Specificity
<3 days			0.86	0.71
1 week			0.57	0.72
1 month			0.75	0.71
6 months			0.75	0.7

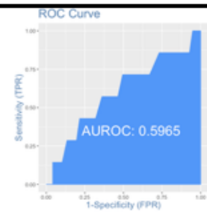
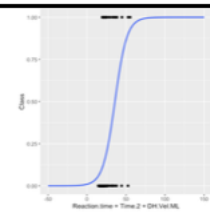
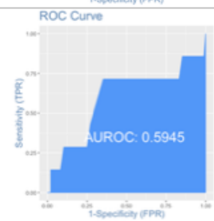
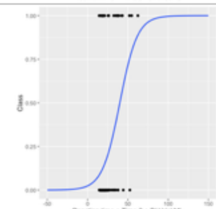
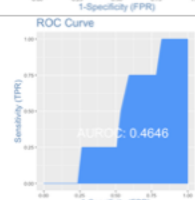
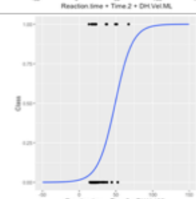
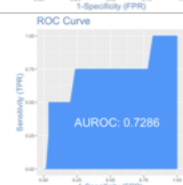
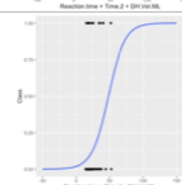
y=DH+TF

Cutoff = .523

	ROC	Regression	Sensitivity	Specificity
<3 days			1	0.62
1 week			0.86	0.63
1 month			1	0.62
6 months			1	0.62

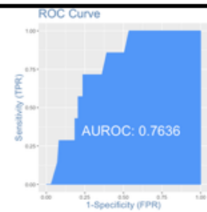
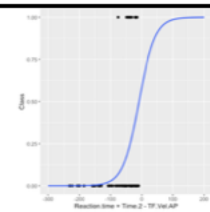
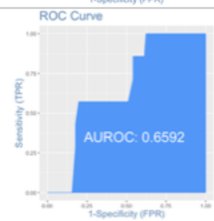
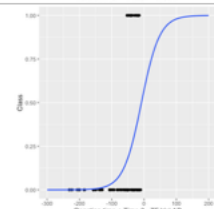
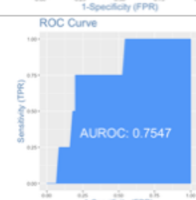
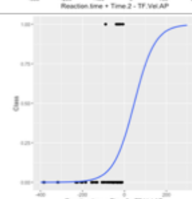
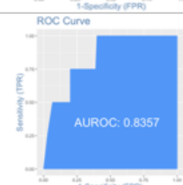
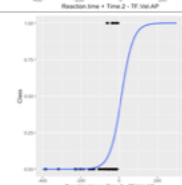
y=RXN+KD+DH

Cutoff = .432

	ROC	Regression	Sensitivity	Specificity
<3 days			0.71	0.52
1 week			0.71	0.52
1 month			0.25	0.52
6 months			0.75	0.52

y=RXN+KD+TF

Cutoff = .68

	ROC	Regression	Sensitivity	Specificity
<3 days			0.71	0.76
1 week			0.57	0.77
1 month			0.75	0.75
6 months			0.75	0.75

APPENDIX E: DATA COLLECTION DOCUMENTS

DU CONCUSSION BIOMARKER STUDY: BALANCE TESTING PROTOCOL

Scoring Sheet

GUID: ______________________

Session:

A Baseline **B** Acute PC **C** 1 week PC **D** 1 month PC **E** 6 month PC

Date: _______________________

Administrator(s): ________________________________ ___________________________________

00. Anthropometrics

- Handedness: _____________________
- Dominant foot: ___________________
- Height: __________________________
- Weight: __________________________

☐ **Put on marker set and double check with concussion marker skeleton**

#	Task	Additional Metric	BEST Score
00	Anthropometric stance		
	Dynamic calibration		
	Sitting lean: left, laterality		
	Sitting lean: left, verticality		
	Sitting lean: right, laterality		
	Sitting lean: right, verticality		
	L leg, eyes OPEN, hard surface	BESS:	
	R leg, eyes OPEN, hard surface	BESS:	
	Non dom leg, eyes CLOSED, hard surface	BESS:	
	Non dom leg, eyes OPEN, foam	BESS:	
	Non dom leg, eyes CLOSED, foam	BESS:	
	Double stance, eyes OPEN, hard surface	BESS:	
	Double stance, eyes CLOSED, hard surface	BESS:	
	Double stance, eyes OPEN, foam surface	BESS:	

	Double stance, eyes CLOSED, foam surface	BESS:	
	Tandem, eyes OPEN, hard surface	BESS:	
	Tandem, eyes CLOSED, hard surface	BESS:	
	Tandem, eyes OPEN, foam	BESS:	
	Tandem, eyes CLOSED, foam	BESS:	
	Gait	Time (sec):	
	Walk with head turns		
	Walk with pivot turn		
	GU&G (simple)	Time (sec):	
	GU&G (dual task)	Time (sec):	
	Alternate stair touching	Time (sec):	
	Sit on floor and stand	Time:	

Concussion Symptom Inventory (Check either absent or present)

Symptom	Absent	Present
Headache		
Nausea		
Balance problems/Dizziness		
Fatigue		
Drowsiness		
Feeling like "in a fog"		
Difficulty concentrating		
Difficulty remembering		
Sensitivity to light		
Sensitivity to noise		
Blurred vision		
Feeling slowed down		

VOMS

	Headache	Dizziness	Nausea	Fatigue	Fogginess	Comments
Baseline Symptoms						
Smooth pursuit						
Saccades (horizontal)						
Saccades (vertical)						
Near point convergence						Cm Cm cm
VOR horizontal						
VOR vertical						

Visual motion sensitivity						

King Devick

Trial	Time (to hundredth of a second)	Errors
1		
2		
3		

- ☐ Complete **ImPACT** (PC or Control Participants only)
- ☐ Complete **ANAM**
- ☐ **Pay** participant, fill our payment log and have participant initial payment log

Balance Testing Instructions

And Balance Scoring Instructions

1. **Anthropometric stance:** Stand with one foot on either force plate, shoulder width apart, with arms by your sides and palms facing forward. Hold this pose for 10 seconds. I will tell you when to relax.
2. **Dynamic calibration:** Start in the same position as the last pose. When I say 'switch', you will lift your arms bent to shoulder height. When I say 'switch' again, you will walk forward. (Note to tester: each pose is 3 seconds long.)
3. **Sitting vertically and lateral lean:** Sit on the chair and cross your arms over your chest. Close your eyes and lean as far to the right as possible and then return to vertical. Pause for 1 seconds, and then repeat on your left side. It's okay to lift your buttocks or feet.

Laterality		Verticality	
(3)	Maximum lean, subject moves upper shoulders beyond body midline, very stable	(3)	Realigns to vertical with very SMALL or no OVERSHOOT
(2)	Moderate lean, subject's upper shoulder approaches body midline or some instability	(2)	Significantly Over- or undershoots but eventually realigns to vertical
(1)	Very little lean, or significant instability	(1)	Failure to realign to vertical
(0)	No lean or falls (exceeds limits)	(0)	Falls with the eyes close

The next series of tasks are standing balance tasks. They are 30 seconds each.

4. **Single leg stance (eyes open):** Look straight ahead and put your hands on your hips. Bend your right leg behind you without letting it touch your left leg. Hold this position 30 seconds. (Repeat for left)
5. **Single leg stance (eyes closed):** Standing on your non-dominant leg, repeat the last test with your eyes closed. (Repeat with eyes open on foam and eyes closed on foam)
6. **Double leg stance:** Stand with your eyes open, feet together and hands on your hips. (Repeat for eyes closed, eyes open on foam and eyes closed on foam)
7. **Tandem stance:** Place one foot in front of the other touching toe to heel. Your dominant leg should be in front and eyes are open. Get your heel and toe as close as possible while keeping your feet on separate force plates. (Repeat for eyes closed, eyes open on foam and eyes closed on foam)

The BESS Score for All Stances: Count errors for a maximum of 10 during the first 20 seconds. Errors include:

- Moving hands off hips
- Opening eyes during eyes closed task
- Step, stumble, fall
- Abduction or flexion of the hip beyond 30 degrees
- Lifting forefoot or heel off the testing surface
- Remaining out of testing position for greater than 5 seconds

The BEST Score for Single and Tandem Stance:
(3) 30s stable
(2) 30s unstable
(1) < 30s
(0) Unable

The next series of tasks are walking tasks. You will start from the yellow line each time.

8. **Gait – Level Surface:** Walk at your normal pace from the first yellow line through the second yellow line.

(3) Normal: walks 20 ft., good speed (≤ 5.5 sec), no evidence of imbalance.
(2) Mild: 20 ft., slower speed (>5.5 sec), no evidence of imbalance.
(1) Moderate: walks 20 ft., evidence of imbalance (wide-base, lateral trunk motion, inconsistent step path) – at any preferred speed.
(0) Severe: cannot walk 20 ft. without assistance, or severe gait deviations OR severe imbalance

9. **Walk with head turns:** Beginning at the line, walk at your normal pace. When I say "right", turn your head to the right while continuing to walk forward. When I say "left", turn your head to the left.

(3) Normal: performs head turns with no change in gait speed and good balance
(2) Mild: performs head turns smoothly with reduction in gait speed,
(1) Moderate: performs head turns with imbalance
(0) Severe: performs head turns with reduced speed AND imbalance AND/OR will not move head within available range while walking.

10. **Walk with pivot turns:** Again beginning at the line, walk at your normal pace. When you reach the middle two force plates, turn 180 degrees with the least number of steps possible, then stop with one foot on either force plate.

(3) Normal: Turns with feet close, FAST (< 3 steps) with good balance.
(2) Mild: Turns with feet close SLOW (>4 steps) with good balance
(1) Moderate: Turns with feet close at any speed with mild signs of imbalance
(0) Severe: Cannot turn with feet close at any speed and significant imbalance.

11. **Timed Get Up and Go:** Sit on the chair with your back against the chair. When I say "go", you are going to stand up and walk as fast as you can around the cone and come back to sit in the chair.

(3) Normal: Fast (<11 sec with good balance)
(2) Mild: Slow (>11 sec with good balance)
(1) Moderate: Fast (<11 sec) with imbalance
(0) Severe: Slow (>11 sec) AND imbalance

12. **Timed Get Up and Go with Dual Task:** Pick a number from 70-100. (Have them tell you what the number is). You are going to start counting from your number backwards by 3's. When I say "go", you are going to continue counting

while standing up and walking around the cone as fast as you can and come sit back in the chair.

(3) Normal: No noticeable change between sitting and standing in the rate or accuracy of backwards counting and no change in gait speed.
(2) Mild: Noticeable slowing, hesitation or errors in counting backwards OR slow walking (10%) in dual task
(1) Moderate: Affects on BOTH the cognitive task AND slow walking (>10%) in dual task.
(0) Severe: Can't count backward while walking or stops walking while talking

13. **Alternate stair touching:** Complete this test as fast as possible while staying in control and without jumping. Alternating between feet, touch your feet to the top of the stair 8 times.

(3) Normal: Stands independently and safely and completes 8 steps in < 10 seconds
(2) Completes 8 steps (10-20 seconds) AND/OR show instability such as inconsistent foot placement, excessive trunk motion, hesitation or arhythmical
(1) Completes < 8 steps – without minimal assistance (i.e. assistive device) OR > 20 sec for 8 steps
(0) Completes < 8 steps, even with assistive devise

14. **Sit on floor and stand up:** Please sit on the floor and stand back up. You may use your hands or the chair for assistance if needed.

(3) Normal: Independently sits on the floor and stands up
(2) Mild: Uses a chair to sit on floor OR to stand up
(1) Moderate: Uses a chair to sit on floor AND to stand up
(0) Severe: Cannot sit on floor or stand up, even with a chair, or refuses

Concussion Symptom Inventory Instructions

"I am going to ask you a series of symptoms, and I want you to tell me if they are absent or present."

VOMS Testing Instructions

Place 2 chairs 3 feet apart.

"I am going to ask you a series of symptoms again, and this time, I want you to rank them 0-10 with 0 being not present at all, and 10 being the worst you can imagine. Then, we will complete eye tracking tests, and I'll ask you to rank your symptoms again."

1. **Smooth pursuit**: For this task, keep your head steady and follow the pen with your eyes. (Start pen in front of subject. Move pen right, left, up, down, back to center)
2. **Saccades (horizontal)**: Now my hands will be out to the side (Place hands far apart horizontally with two fingers up). Keep your head steady, and move your eyes back and forth between my hands as fast as possible. (Count eye movements, they are done after 10 each side.)
3. **Saccades (vertical)**: This is the same thing, except now move your eyes up and down (Place hands far apart vertically with two fingers up). (Count eye movements, they are done after 10 each side.)
4. **Near point convergence**: This time you hold the pen. Start with it at arms distance away from your face and slowly bring it towards your face until you see double or it gets blurry. I'm going to measure that distance. (Use tape measure to measure from pen to tip of nose, repeat test 3x.)
5. **VOR horizontal**: This task is to the beat of a metronome. This time you keep your eyes focused on the pen, and move your head back and forth to the beat of the metronome. (Set metronome to 180 bpm, set pen in front of subject.) (Count head movements, they are done after 10 each side.)
6. **VOR vertical**: This is the same thing, except now move your head up and down. (Count eye movements, they are done after 10 each side.)
7. **Visual motion sensitivity**: This is the last task in this series. I'll have you stand up and face the wall. Place your thumb in front of your face and focus on it. You'll keep focusing on it and move your body all the way to the right, and all the way to the left to the beat of the metronome. (Set metronome to 50 bpm.) (Count body movements, they are done after 5 each side.)

KD Testing Instructions

"This is a number reading test. You will read the numbers like you would normally read a page, left to right and top to bottom. Read the numbers as fast as you can trying not to make any errors."

ImPACT Testing Instructions (For PC participants only)

"ImPACT is a computerized neurocognitive test that you've completed before in Sports Med. It should take about 20-30 minutes."

ANAM Testing Instructions

"ANAM is a group of tasks that measure your thinking abilities. Each task will give you instructions about what you will see and how you should answer. If you have questions at any time, please let the examiner know. You will be asked to solve some problems and then respond as quickly as you can. Once completed, your responses will be saved on the tablet. There is no pass/fail on this test, so just try your best. Remember to always try your best."