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Neurocognitive Patterns, Symptom Clusters, and Premorbid Factors that Predict Protracted Recovery from Concussion in Females

Sarah Pulaski
Philadelphia College of Osteopathic Medicine, sarahpu@pcom.edu

Philadelphia College of Osteopathic Medicine

Department of Psychology

NEUROCOGNITIVE PATTERNS, SYMPTOM CLUSTERS, AND PREMORBID FACTORS THAT PREDICT PROTRACTED RECOVERY FROM CONCUSSION IN FEMALES

By Sarah Pulaski

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Dissertation Approval

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Committee Members' Signatures:

Donald P Masey, PsyD, Chairperson

Robert A DiTomasso, PhD, ABPP

Brian J Balin, PhD

Robert A DiTomasso, PhD, ABPP, Chair, Department of Psychology

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Abstract

Concussion is an increasingly diagnosed injury that affects individuals of all ages. Although the underlying cause is unknown, research has demonstrated that females who sustain a concussion experience longer recoveries. Existing research has documented a relationship between age, gender, post-concussive headache and mental health conditions, and recovery; however, limited research has investigated the relationship between premorbid clinical variables and recovery. Research on post-injury neurocognitive declines and recovery has also demonstrated varied findings. Moreover, dizziness has been identified as significantly predictive of prolonged recovery, but no studies have investigated the effect of premorbid headache conditions on the development of dizziness. The goals of this study were to determine whether (1) premorbid mental health conditions and/or premorbid headaches and post-concussive neurocognitive patterns of decline would predict longer recovery from concussion; (2) premorbid headaches would predict post-concussive dizziness; and (3) mental health conditions would predict post-injury affective symptoms in a group of females from a specialized outpatient concussion treatment facility (N=180). Results indicated that delay in initial post-injury evaluation was most predictive of a prolonged recovery and that premorbid mental health conditions positively predicted post-injury psychiatric symptoms. These direct positive relationships existed while controlling for age at injury, prior history of concussion, and mechanism of injury. This is one of the few studies to investigate the relationship between premorbid mental health conditions and recovery, and the only study to

investigate the relationship between premorbid headache conditions and (1) post-concussive dizziness and (2) prolonged recovery.

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Chapter One

Introduction

Statement of the Problem

Concussion affects approximately 5% of the total population in the United States (Fife & Kalra, 2015). Of the total traumatic brain injuries that occur annually, approximately 75%-90% are classified as concussion or mild traumatic brain injury. In the United States, across all levels of athletics, approximately 1.6 to 3.8 million sports- or recreation-related concussions occur annually; however, these figures only account for those athletes who lost consciousness following injury (Kontos et al., 2013). Loss of consciousness is assumed to occur in less than 10% of concussive injuries, suggesting that the actual rate of sports- and recreation-related concussions is approximately 10 times larger (Gulla, 2013). It is estimated that in high school athletics alone, approximately 136,000 concussions occur each year as a result of sports (Kontos et al., 2013). In the general population, as many as 1.5 million people sustain a traumatic brain injury annually, with at least 75% of the injuries classified as mild (U.S. Centers for Disease Control and Prevention, September 2003). The high prevalence rates of concussion result in substantial health care costs, with approximately $60 billion dollars paid in the total lifetime costs-of injury in the United States alone (Karr, Areshenkoff, & Garcia-Barrera, 2014).

A concussion is defined as a mild traumatic brain injury that results from an "impulsive force transmitted to the head resulting from a direct or indirect impact to the head, face, neck, or elsewhere" (Daneshvar, Nowinski, McKee, & Cantu, 2011, p. 3). According to the 2008 international symposia on Concussion in Sports (CIS), a

concussion results from a traumatic biomechanical force that causes a complex metabolic and pathophysiological process that affects the brain (McCrory et al., 2009). As a result of the growing awareness of concussions, the neuropsychological and medical community has gradually begun to view concussion as a transient change in neurocognitive and neurophysiological functioning (De Beaumont et al., 2013; De Beaumont, Beauchemin, Beaulieu, & Jolicoeur, 2013; De Beaumont, Brisson, Lassonde, & Jolicoeur, 2007; De Beaumont, Lassonde, Leclerc, & Theoret, 2007; Henry et al., 2011; Signoretti, Lazzarino, Tavazzi, & Vagnozzi, 2011; Tremblay et al., 2013).

Much of the research on concussion has focused on athletes or military personnel, although findings are also thought to apply to the general population. Specifically in regard to sports-related concussions, symptoms usually last less than 72 hours, and most injuries resolve within 7 to 10 days (Ellemberg, Henry, Macciocchi, Guskiewicz, & Broglio, 2009; McCrory et al., 2009). Moreover, although the duration of recovery can vary widely, most athletes (about 83%) fully recover and return to play within three weeks (Lau, Kontos, Collins, Mucha, & Lovell, 2011a). Approximately 50% of those athletes recover and return to play by one week post-injury. However, the remaining 17% of athletes who do not fully recover experience a protracted recovery, with symptoms persisting longer than three weeks (i.e., $\geq$ 21 days) and occasionally lasting several years in individuals with persistent concussive symptomatology (Lau et al., 2011a). In non-sport related concussions, the majority of individuals fully recover within the first three months following injury; however, as many as 33% of individuals may experience persistent symptoms (Leddy, Sandhu, Sodhi, Baker, & Willer, 2012). Although some progress has been made to predict which individuals are likely to suffer a

protracted recovery, more research is required to identify how premorbid factors predict recovery, as well as how specific post-concussive neurocognitive declines predict recovery (Lau et al., 2011a).

Post-concussive factors associated with protracted recovery. To date, most of the concussion research has examined the post-concussive factors that are associated with a protracted recovery. Acute post-concussive dizziness has been found to be the single greatest predictor for a protracted recovery among high-school football players (Lau et al., 2011b). Research from the migraine literature has also found that vertigo, dizziness, motion sensitivity, and other vestibular problems occur as part of some migraine presentations, perhaps as a result of a hypersensitivity to motion (Bisdorff, 2014; Calhoun, Ford, Pruitt, & Fisher, 2011). What triggers migraine is not fully understood; however, research has begun to elucidate the pathophysiological underpinnings during a migraine attack (Bhaskar, Saeidi, Borhani, & Amiri, 2013). Research on the pathophysiology of migraine in mouse models has indicated that migraine may be the result of cerebral hyperexcitability, increased glutamatergic neurotransmission, and among those with aura, greater susceptibility to cortical spreading depression (Ferrari, Klever, Terwindt, Ayata, & Van Den Maagdenberg, 2015). It has also been proposed that in those with migraine without aura, spreading depression may lead to activation of the trigeminovascular system, which is known to underlie the pain that is experienced in migraine headache (Ferrari et al., 2015). Specifically, research suggests that migraine results when a trigger leads to a period of increased blood flow that is followed by cortical spreading depression, which leads to changes in glial activity, subsequent neuronal activity, and further increase in blood flow (Bhaskar et al., 2013). Similarly,

during a concussive injury, a complex neurometabolic cascade occurs that ultimately results in cortical spreading depression that likely underlies the symptoms observed following a concussive injury (Giza & Hovda, 2001). This suggests that individuals with migraine might not only be at an increased risk for suffering post-concussive migraines and other headaches, but might also be at an increased risk for having vestibular involvement following a concussion. Additionally, athletes who present with post-concussive migraines, generalized headaches, and cognitive symptoms are found to generally have longer recovery times, with some estimates as high as 7.3 times longer than athletes without post-concussive migraines or other headaches (Harmon et al., 2013; Kontos et al., 2013; Lau et al., 2011b; Mihalik et al., 2013). Other research has also suggested that general post-concussive headaches are associated with a 2.6-fold increase in risk of prolonged recovery as compared to athletes who do not experience post-concussive headache symptoms (Kontos, Covassin, Elbin, & Parker, 2012). In the general population as well as among athletes, research has also documented the role of post-concussive mental health conditions and psychosocial distress in the development of prolonged recovery from concussion (Waldron-Perrine, et al., 2014). Finally, some research has suggested that a decline in neurocognitive performance may predict a protracted recovery from concussion; however, to date, few studies have examined the clinical significance of specific cognitive declines (e.g., reaction time, visual memory, verbal memory, etc.) regarding the ability to predict a protracted recovery. The *Immediate Post Concussion Assessment and Cognitive Testing* (*ImPACT*) battery is one of the most frequently used computerized batteries to assess for concussion clinically. Research has typically used the *Reliable Change Index* (*RCI*) on the ImPACT for a

variety of neurocognitive variables to determine the magnitude of change from baseline that exceeds the range of normal score variation (*Clinical Interpretation Manual for ImPACT 6.0*, 2007; Hinton-Bayre, 2012). If an individual demonstrates a change in test performance that falls outside the range of normal score variation, the ImPACT report denotes these changes in the test performance (*Clinical Interpretation Manual for ImPACT 6.0*). Given variable findings in the literature, further research is required to investigate whether declines in specific cognitive functions (e.g., reaction time) are more predictive of a protracted recovery (e.g., Carman et al., 2015; Karr et al., 2014).

In addition to the limited research that has been conducted investigating whether declines in specific cognitive functions predict patterns of recovery, limited research has been conducted examining the premorbid factors that predict a protracted recovery from concussion. Moreover, it is still unknown how premorbid factors are related to post-concussive symptom presentation. The few studies that have examined premorbid factors found female gender predicts a longer recovery (Harmon et al., 2013; King, 2014a; King, 2014b; Preiss-Farzanegan et al., 2009). Age has also been found to predict longer recovery from concussion, although patterns have varied depending on the population studied (Harmon et al., 2013; King 2014a; King 2014b; Preiss-Farzanegan et al., 2009). In sports-related injuries, younger age has been found to predict longer recovery, while among the general population, older age (> 40 years) has been associated with prolonged recovery (Harmon et al, 2013; King 2014a; King 2014b; Preiss-Farzanegan et al., 2009). When appropriately compared to males, female athletes tend to suffer a greater number of concussions (Harmon et al., 2013). Females across populations also tend to report and/or experience a greater number of severe concussion symptoms, and they tend to experience

a slower rate of recovery than their male counterparts (Harmon et al., 2013; King 2014a; King 2014b; Preiss-Farzanegan et al., 2009). Some studies have suggested that this trend may be a result of females' decreased head-neck segment mass, which may contribute to increased angular acceleration of the head following a traumatic blow, resulting in more significant biomechanical force and a more severe concussive injury (Tierney et al., 2005). It is also possible that estrogen and different levels of cerebral blood flow may account for the increased severity of symptoms and prolonged duration of recovery that is more likely to occur in female athletes (Esposito, Van Horn, Weinberger, & Berman, 1996; Wunderle et al., 2014). Although these trends are observed in females with concussion, these trends are not unique to concussive injuries, and research shows that females, across the lifespan, tend to demonstrate similar recovery characteristics across most injuries relative to males (e.g., Colvin & Lynn, 2010; Kempen, Sanderman, Scaf-Klomp, & Ormel, 2003; Lanese, Strauss, Leizman, & Rotondi, 1990). Despite these trends, there is still no definitive understanding of why females tend to suffer more severe concussion symptoms and prolonged patterns of recovery in comparison to males.

Premorbid factors associated with protracted recovery. Despite the growing knowledge of how premorbid demographic variables, like age and sex, relate to the risk of a protracted recovery, little research has investigated how premorbid clinical variables predict a prolonged recovery. For example, adjustment to one's injury status has been found to play a role in how one recovers from concussion (Ponsford et al., 2012). Preliminary research has demonstrated that mental health concerns, especially anxiety, may increase the likelihood for a protracted recovery (Ponsford et al., 2012). Specifically, research has found that concussed athletes demonstrate significantly higher

levels of somatic depression and anxiety between 2 and 14 days following injury, which has also been found to be associated with poorer performance on neurocognitive measures of visual memory and reaction time (Broshek & Freeman, 2005; Kontos et al., 2012). However, very few studies have examined whether premorbid mental health conditions are associated with a higher risk of post-concussive somatic reactive depression and/or anxiety among athletes or in the general population with concussion. Additionally, despite the growing awareness that post-concussive migraines, headaches, and dizziness all significantly predict a protracted recovery, no research has established whether a premorbid history of migraine or other headaches leads to an increased risk of developing the cognitive-fatigue-migraine concussion presentation (with exacerbated post-concussive migraines, headaches, and/or post-concussive dizziness).

Symptom clusters of concussion. Knowing if certain premorbid clinical variables are predictive of specific post-concussive symptom clusters may help to guide therapeutic interventions. Recent research has begun to differentiate the symptom clusters of concussion that tend to present together (Pardini et al., 2004; Kontos et al., 2012). Specifically, within 7 days of injury, symptoms begin to cluster into domains of (a) *Cognitive-Fatigue-Migraine,* (b) *Affective*, (c) *Somatic*, and (d) *Sleep*, although these clusters are somewhat blurred and overlap with one another (Kontos et al., 2012). In particular, during the first week of injury, the Cognitive-Fatigue-Migraine presentation has been found to generally consist of different vestibular, cognitive, sleep, and somatic symptoms including migraines, feeling slowed down, fatigue, mental fogginess, dizziness, and difficulty concentrating (Kontos et al., 2012). Following the first week post-injury, however, symptom presentation becomes more distinct and falls into the (a)

Somatic, (b) Cognitive, (c) Sleep, and (d) Emotionality domains (Pardini et al., 2004). These preliminary diagnostic classifications were an important development in the clinical management of concussions; however, identifying premorbid clinical variables and post-concussive factors that predict post-concussive symptom clusters that are associated with prolonged recovery (e.g., cognitive-fatigue-migraine) is also necessary. This knowledge will help clinicians to better inform concussed individuals about their prognosis, particularly in relation to their expected length of time away from play or other daily activities. By being able to inform individuals from the outset that they may have a more extended recovery, clinicians can help patients to realistically evaluate their trajectory for symptom improvement. Having the information to realistically help patients evaluate their trajectory for recovery may help to manage emotional complications that may result from unexpected protracted recovery by reducing stress and the likelihood for symptom exacerbation as a result of stress.

Consistent with the findings that somatic anxiety and depression are associated with worse performance on specific neurocognitive measures, a decline in neurocognitive functioning following injury has also been found to be associated with protracted recovery (Harmon et al., 2013). Research has demonstrated that reduced reaction time is a sensitive predictor of concussive injury in athletes (Collie, Makdissi, Maruff, Bennell, & McCrory, 2006; Eckner, Kutcher, Broglio, & Richardson, 2014; Eckner, Kutcher, Richardson, 2011; Iverson, Brooks, Collins, & Lovell, in press). Despite this knowledge, very little research has examined post-injury declines in specific cognitive domains (e.g., reaction time, visual memory, etc.) and whether they predict prolonged recovery in non-athletes. By using RCI models, it is possible to determine when an athlete demonstrates a

statistically significant change in test performance that falls outside the range of normal score variation; however, the clinical significance of the decline is not fully understood. RCI models rely on test-retest normative data that are obtained by assessing comparable controls on two separate occasions (Hinton-Bayre, 2012). Knowledge about the clinical significance of declines in specific cognitive domains would help to guide therapeutic interventions earlier in recovery.

Based on the post-injury variables that are associated with prolonged recovery, and on the conceptualization of concussion as a metabolic crisis that exacerbates premorbid conditions, additional research is needed to examine which premorbid and post-injury clinical variables are associated with an increased risk of protracted recovery. Therefore, this study will address whether premorbid clinical variables, specifically a history of mental health conditions, migraines, and generalized headaches, predicts an exacerbation of similar post-concussive symptoms that are associated with a protracted recovery from concussion in females, as well as persistent concussion symptomatology. Additionally, by using an RCI for a computerized neurocognitive assessment, this study will attempt to define a pattern of neurocognitive decline that may be predictive of protracted recovery.

Chapter Two

Literature Review

Concussion

Concussion affects approximately five percent of the total population in the United States (Fife & Kalra, 2015). In the general population, as many as 1.5 million people sustain a traumatic brain injury, with at least 75% of the injuries classified as concussion; of those, a significant number are the result of sports- and recreation-related injuries (U.S. Centers for Disease Control and Prevention, September 2003). An estimated 44 million adolescents and 170 million adults in the United States participate in recreational and organized sports each year (Ma et al., 2012). Participation in both recreational and organized sports increases an individual's risk of suffering a sports-related concussion (Daneshvar, Nowinski, McKee, & Cantu, 2011). Consequently, the incidence of sports-related concussion is increasing as a greater number of people participate in athletics, with estimates ranging from 1.6 to 3.8 million in the United States annually; however, these figures do not account for those injuries that do not involve a loss of consciousness, suggesting that the actual rates of sports- and recreation-related concussion may be as much as 10 times these figures (U.S. Centers for Disease Control and Prevention, January 2013; Benson, Meeuwisse, Rizos, Kang, & Burke, 2011; Chrisman, Schiff, & Rivara, 2011; Covassin & Elbin, 2011; Daneshvar et al., 2011; d'Hemecourt, 2011; Giza et al., 2013; Harmon et al, 2013; Hunt & Asplund, 2010; Ma et al., 2012). In line with this trend toward increased participation in sports, female participation in athletics has also risen. More than 178,000 women participate on National Collegiate Athletic Association (NCAA) teams and an estimated 3,000,000

women participate in organized high school sports each year (National Federation of State High School Associations, 2008). Similarly, an increasing number of women are active members of the military, further increasing the rates of concussion among females.

Definition of Concussion

As a result of the growing awareness and prevalence of concussion, the definition of concussion has evolved over the past 30 to 40 years and is likely to continue to change as new research findings emerge (Lovell, 2009). At present, there is no universally accepted definition; however, several committees have put forth varying definitions of concussion (Lovell, 2009). The original definition of concussion, proposed in 1966 by the Committee on Head Injury Nomenclature of Neurologic Surgeons, has represented the most popular definition over the past 30 years (Lovell, 2009). According to the Committee on Head Injury Nomenclature of Neurologic Surgeons, a concussion is "a clinical syndrome characterized by the immediate and transient posttraumatic impairment of neural function, such as alteration of consciousness, disturbance of vision or equilibrium, etc., due to brain stem dysfunction" (Congress of Neurological Surgeons, as cited in Lovell, 2009, p. 96). This definition significantly emphasized the role of the brain stem and loss of consciousness in concussion, and underemphasized the role of other cortical and subcortical structures in the pathophysiology of concussion. As a result, more recently, other definitions of concussion have been proposed.

The most recent Zurich Consensus Statement on Concussion in Sport was issued in 2012 and defined concussion as a brain injury resulting from a "complex pathophysiological process affecting the brain, induced by biomechanical forces "from a direct blow to the face, head, neck, or elsewhere on the body, with an "impulsive" force

transmitted to the head (McCrory et al., 2013, p. 250). The 4th Zurich Consensus Statement further defined a concussion as an injury that typically results in the rapid onset of transient impairments in neurological functioning that typically resolve spontaneously. Concussion is a metabolic injury and results in a functional, rather than a structural, disturbance in brain functioning. Therefore, standard structural neuroimaging studies (e.g., MRI and CT) are normal in concussion (McCrory et al., 2013). Finally, concussion results in a set of clinical symptoms that may or may not involve the loss of consciousness, and resolution of these clinical symptoms often follows a sequential course, which, in some cases, may be prolonged. As the 4th Zurich Consensus Statement definition indicates, concussion is a brain injury that results from some type of impulsive force causing metabolic injury and transient symptomatology.

Biomechanics and Pathophysiology of Concussion

The metabolic injury of concussion occurs when an abrupt impulsive blow to the body or head causes the brain to move within the skull (Giza & Hovda, 2001). Such an impulsive hit results in the sudden acceleration and/or deceleration of the brain within the skull, resulting in the onset of linear (i.e., acceleration/deceleration) and/or rotational forces (Ommaya & Gennarelli, 1974). Rotational and linear head accelerations are thought to be the primary risk factors for concussive injury during an impact by causing strain patterns in brain tissue that may result in injury (Guskiewicz & Mihalik, 2011; Ommaya & Gennarelli, 1974).

It has been theorized that when an individual experiences an implosive hit that induces rotational or acceleration/deceleration forces, the result is an initial increase in hypermetabolism characterized by increased cellular demands (Giza & Hovda, 2001).

Specifically, a concussive injury result is an acute, mechanically induced, widespread neuronal excitation as a result of neuronal membrane depolarization (Shaw, 2002). Animal studies have demonstrated that during this period of neuronal excitation there is increased cerebral metabolism and increased cellular energy demands (Shaw, 2002). Specifically, Meyer and colleagues (1970) found an increase in oxygen consumption within the first 5 minutes following concussive injury (as cited in Shaw, 2002, p. 320), while other research has demonstrated increased glucose metabolic activity following concussive injury (Shaw, 2002; Yoshino, Hovda, Kawamata, Katayama, & Becker, 1991). Following this initial hypermetabolism, a several-day period of reduced cerebral metabolism occurs (Giza & Hovda, 2001). Although not yet fully understood, research suggests that rotational acceleration is the primary mechanism by which concussive injury occurs (Shaw; Ommaya & Gennarelli, 1974).

Immediately following an impulsive injury or a direct hit that causes acceleration-deceleration rotational/linear injury, a neurometabolic cascade begins to occur in the brain as a result of the sudden shearing and stretching of neurons (Marshall, 2012). Following injury, the dysregulation of ion channels in the cell membrane leads to an indiscriminant release of neurotransmitters and ionic fluxes, causing neuronal depolarization (Giza & Hovda, 2001). In response to this rapid depolarization, a widespread release of glutamate, an excitatory amino acid, occurs (Giza & Hovda, 2001). This widespread emission of glutamate causes a greater release of potassium and leads to the activation of N-methyl-d-aspartate (NMDA) receptors (Giza & Hovda, 2001). The activation of the NMDA receptors allows a rapid influx of calcium ions into the neurons, resulting in widespread neuronal excitation (Giza & Hovda, 2001). While it is possible

that this neuronal activation may yield many of the transient symptoms of concussion (e.g., vision problems, balance difficulties, confusion, etc.), this has not been demonstrated in the literature, and the underlying causes for these symptoms are not yet known (Giza & Hovda, 2001).

The large amount of calcium that flows into the cells following activation of the NMDA receptors negatively affects several other neuronal processes, including the functioning of mitochondria within the neurons and a disruption of neuronal connectivity. First, the large influx of calcium ions can damage neurofilaments and microtubules within the axon, resulting in a disruption of neural connectivity (Giza & Hovda, 2001). Second, the large influx of calcium ions overloads mitochondria, causing a disruption in neuronal energy production (Giza & Hovda, 2001). Mitochondrial calcium overload results in an uncoupling of oxidative phosphorylation within the electron transport chain, thereby reducing neuronal capacity for generating adenosine triphosphate (ATP) (Giza & Hovda, 2001). Additionally, mitochondrial calcium overload leads to the creation of reactive oxygen species (ROS), a potentially damaging substance, in the brain (Giza & Hovda, 2001). If the ROS buildup exceeds the cellular capacity to detoxify ROS from the neuron, oxidative stress, irreversible cell damage, and apoptosis may occur (Giza & Hovda, 2001). Following the temporary excitation phase that occurs as a result of a concussive impact, widespread neuronal suppression, also called "spreading depression" occurs, which is likely an explanation for the amnesia, emotional lability, fatigue, and cognitive deficits often observed in concussive injury (Giza & Hovda, 2001).

The result of this neurometabolic cascade is a reversible ion imbalance and possible neuronal or axonal damage (Giza & Hovda, 2001; Marshall, 2012). In order to

restore intra- and extracellular homeostasis, ATP dependent sodium-potassium pumps (NA^+/K^+ pumps) must return to maximal functioning. Following a concussion, however, disrupted mitochondrial functioning and uncoupled oxidative phosphorylation forces neurons to rely on less efficient anaerobic energy production. The post-concussive reliance on anaerobic energy production creates a substantial increase in the demand for glucose, resulting in the hypermetabolism of glucose. Unfortunately, this immediate demand for glucose is complicated by a reduction in cerebral blood flow that occurs after a concussive injury, creating a mismatch between the demand and availability for glucose. Thus, during the period of greatest ATP demands, there is a significant decrease in the production and availability of glucose, creating an energy crisis in the brain. The net result of a concussive injury is a neuronal ion imbalance, which causes cellular dysfunction, as well as an energy deficit resulting from decreased ATP production during a time when demand for ATP increases. This neuronal ion imbalance and resulting energy deficit lead to acute signs and subacute symptoms of concussive injuries.

Symptom Clusters and Acute Signs of Concussion

Individuals with concussive injuries can present with a variety of acute signs and subacute symptoms. Acute signs of concussion that may or may not be observed by staff or other individuals include posttraumatic/anterograde amnesia, retrograde amnesia, changes in personality or behavior, loss of consciousness, slowed response, clumsiness, confusion, or an appearance of being stunned or dazed (McCrory et al., 2009; McCory et al., 2013). The concussed individual may report immediate and/or delayed symptoms, which tend to cluster together. These symptoms clusters can be classified into the Cognitive-Fatigue-Migraine, Affective, Somatic, or Sleep subtypes, which may or may

not co-occur (Kontos et al., 2012; Marshall, 2012). The symptom clusters that fall into the Cognitive-Fatigue-Migraine subtype include confusion, retrograde or anterograde amnesia, disorientation, loss of consciousness, vacant stare, feeling "in a fog" or "zoned out," difficulty focusing, delayed motor and verbal responses, slurred speech, or drowsiness (McCrory et al., 2009; McCrory et al., 2013). The symptoms that are categorized in the Affective subtype include depression/sadness, fatigue, anxiety, irritability, or emotional lability (Khurana & Kaye, 2012; Marshall, 2012). The Somatic subtype includes headaches, balance difficulty, vertigo, dizziness, nausea/vomiting, phonophobia, photophobia, visual disturbance (e.g., diplopia), or fatigue (Khurana & Kaye, 2012; Marshall, 2012). Finally, the Sleep subtype includes trouble with initiating sleep, sleeping more than usual, or sleeping less than usual (Marshall, 2012). Refer to Table 1 for a summary of the items from the Post-Concussion Symptom Scale (PCSS) that load on each baseline and/or post-concussive symptom cluster. Each of these symptom clusters is often characterized by certain symptoms that may or may not be associated with certain patterns of recovery.

Patterns of Recovery/Protracted Recovery

A review of the concussion literature across populations reveals that the duration of recovery from concussion can vary widely. Concussion symptoms typically last less than 72 hours, and most concussive injuries spontaneously resolve in 7 to 10 days (Ellemberg et al., 2009; McCrory et al., 2009). The majority of athletes (about 83%) experience a resolution of their concussion symptoms within three weeks following injury, with 50% of these individuals returning to play by one week post-injury. The remaining 17% of athletes whose symptoms do not resolve within the first three weeks,

Table 1
PCSS Symptom Factors and Item Loadings on Baseline and Post-injury Symptom Clusters

Symptom Cluster	Baseline Symptom Factors	Post-Injury Symptom Factors
CFM	Sensitivity to light Sensitivity to noise Feeling slowed down Mentally foggy Difficulty concentrating Difficulty remembering Vision problems	Headache Dizziness Fatigue Drowsiness Sensitivity to light Sensitivity to noise Feeling slowed down Mentally foggy Difficulty concentrating Difficult remembering
Sleep	Fatigue Trouble falling asleep Sleeping less than usual Drowsiness	Trouble falling asleep Sleeping less than usual
Vestibular-Somatic	Headache Nausea Vomiting Balance Dizziness	Vomiting Numbness
Affective	Irritability Sadness Nervousness Feeling more emotional	Sadness Nervousness Feeling more emotional

Note. Items that cross-loaded onto multiple symptom clusters have been excluded; *CFM* = Cognitive-Fatigue-Migraine

experience a prolonged or protracted recovery, with symptoms persisting for greater than three weeks (i.e., $\geq$ 21 days), sometimes lasting a month or longer (Lau et al., 2011). Additionally, some athletes (approximately 10%) with protracted recovery experience *persistent post-concussive symptoms*, defined as the persistence of physical, psychological, behavioral, cognitive, and somatic symptoms at least 12 weeks or longer after the initial concussive injury (Willer & Leddy, 2006; Zemek, Osmond, Barrowman, et al., 2013). In contrast, the majority of individuals with non-sport related concussions fully recover within the first three months following injury; however, as many as 33% of

individuals may experience persistent symptoms (Leddy, Sandhu, Sodhi, Baker, & Willer, 2012). Factors that tend to be associated with a prolonged recovery from concussion include female sex, prior history of concussion, post-concussive dizziness, post-concussive migraine and other headache conditions, post-concussive mental health conditions, post-concussive decline in neurocognitive performance, and exhibiting a high number of concussion symptoms. Age has also been found to predict longer recovery, though the trends depend on the population studied (Harmon et al., 2013; Kontos et al., 2013; Lau et al., 2011b; Mihalik et al., 2013; Ponsford et al., 2012; Preiss-Farzanegan et al., 2009). Among those with sports- and recreation-related concussion, younger age tends to predict longer recovery; however, among those with non-sport related concussion, older age (> 40 years) is associated with longer recovery (King 2014a; King 2014b).

Post-concussion Syndrome.

Most individuals recover fully from concussions; however, a clinically significant minority experience *post-concussion syndrome*, one possible complication of concussive injury (Jotwani & Harmon, 2010). Post-concussion syndrome is defined by the World Health Organization as the persistence of any symptoms related to a concussion, including dizziness, headaches, fatigue, difficulty concentrating and performing mental tasks, irritability, insomnia, memory impairments, or reduced tolerance for stress (Jotwani & Harmon, 2012; Ma et al., 2012). Additionally, the *Diagnostic and Statistical Manual of Mental Disorders* defined post-concussion syndrome as the persistence of symptoms occurring three months or longer after injury (4th ed., *DSM-IV*; American

Psychiatric Association [APA], 1994; 4th ed., text rev.: *DSM-IV-TR*; American Psychiatric Association [APA], 2000; Ryan & Ward, 2003).

Several studies have found that specific concussion symptoms tend to predict longer duration of recovery from concussion and a higher likelihood of developing post-concussion syndrome. Specifically, athletes who present with four or more concussive symptoms, fogginess or fatigue, and headache that lasts longer than 60 hours tend to take longer to recover and report a longer duration of cognitive deficits (Harmon et al., 2013; Kontos et al., 2013; Lau et al., 2011b; Makdissi et al., 2010; Mihalik et al., 2013). Anxiety and depression have also been reported in more than a third of all patients with post-concussion syndrome, and in the general population, factors such as posttraumatic stress and pain have been found to be associated with longer recovery (King, 2014a; Dinan & Mobayed, 1992; Makdissi et al., 2010; McAllister & Arciniegas, 2002; Paniak et al., 2002). In sports- and recreation-related concussions, once symptoms have been present for more than 3 weeks, they often persist and may become resistant to treatment, while in the general population, most individuals recover within three months of injury (Leddy, Sandhu, Sodhi, Baker, & Willer, 2012; Makdissi et al.). Across populations, research has demonstrated that females, in particular, tend to experience and report a greater number of concussion symptoms (Fehr & Kuluz, 2014; Harmon et al., 2013; King 2014a; King 2014b). Additionally, research has also shown that females with concussion tend to experience slower recovery rates as compared to males with concussion (e.g., Harmon et al., 2013; Preiss-Farzanegan et al., 2009), suggesting that the persistence and severity of concussion symptomatology tends to differ depending on sex.

Concussion in Females

Concussion risk and symptom presentation appear to differ between males and females. In the case of athletics and non-sport related activities, when compared to males in equivalent sports or positions, females tend to suffer a greater number of concussions and experience and/or report a greater number of severe concussion symptoms (Harmon et al., 2013; Tsushima, Lum, & Geling, 2009). Females also tend to experience a slower rate of recovery than their male counterparts, with one recent study finding that female athletes took, on average, 22 days longer to recover than their male counterparts (Harmon et al., 2013; Preiss-Farzanegan et al., 2009). Although the underlying cause(s) for these differences are unknown, it is possible that these trends may result from anatomical differences between males and females, sociocultural factors, or a a combination of factors. Possible anatomical differences that may account for the higher rates of concussion in females include females' decreased head-neck segment mass, which may contribute to increased angular acceleration of the head following a traumatic blow, resulting in more significant biomechanical force and a more severe concussive injury (Tierney et al., 2005). It is also possible that estrogen, menstrual phase, and different levels of cerebral blood flow may account for the increased severity of symptoms and prolonged duration of recovery that is more likely to occur in female athletes (Esposito et al., 1996; Wunderle, Hoeger, Wasserman, & Bazarian, 2014). Sociocultural factors may also account for the different rates of concussion seen in males and females. In particular, society in the United States has tended to be more protective of females, as evidenced by restricting contact in sports as compared to parallel male sports (e.g., ice hockey, lacrosse) (Gessel, Fields, Collins, Dick, & Comstock, 2007). This tendency may

lead parents, clinicians, athletic trainers, and coaches to treat head injuries in females more seriously and may lead to a delayed return to play or daily activity (Gessel et al., 2007). Similarly, males are impacted by cultural forces that promote masculinity and strength, which may encourage males to underreport symptoms or avoid reporting their symptoms altogether (Gessel et al., 2007; McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004). Specifically a reluctance to report injury has been found in male high school football players. In particular, of players who had claimed to suffer a concussion, only 47.3% of players reported the injury (McCrea et al., 2004). In addition to the pressures that males may feel as a result of society's gender stereotypes, male athletes in particular may underreport injuries due to an unawareness of injury symptoms; unawareness of the significance of the injury; outside pressures (e.g., coaches, family members) to continue playing in spite of injury; a personal desire to continue playing; and the perception that reporting a concussion may have negative professional and financial consequences for the individual or team (Khurana & Kaye, 2012). Research examining sociocultural factors and the biomechanics of concussion has led to discoveries of trends that explain differences observed in the recovery from concussion between males and females; however, neuropsychological assessment has also served an important role in the clinical assessment and evaluation of concussion.

Role of Neurocognitive Assessment in the Evaluation of Concussion

The use of neuropsychological testing has been shown to have clinical value in the assessment and management of concussion. Research suggests that cognitive impairment following concussion may persist longer than subjective symptoms (Echemendia et al., 2013). Therefore, using neuropsychological testing in combination

with other clinical assessments may help to identify subtle cognitive impairments and may assist in documenting an individual's recovery from a concussive injury (Echemendia et al., 2013; McCrory et al., 2009). Most recently, the 4th Zurich Consensus Statement on Concussion in Sport recommended the use of neurocognitive testing in combination with other diagnostic information (McCrory et al., 2013).

During the 1980s, traditional paper-and-pencil neuropsychological testing was used to assess for cognitive deficits in concussed individuals (Echemendia et al.; Harmon et al., 2013). By the 1990s and 2000s, computerized neurocognitive testing was developed, providing an alternative to traditional paper-and-pencil neuropsychological testing in the assessment of concussion (Echemendia et al.; Harmon et al., 2013). Today, there are several computerized neurocognitive tests that are available for use in the assessment of concussion, including the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), Axon Sports, the Automated Neuropsychological Assessment Metrics (ANAM), and Headminder (Cernich, Reeves, Sun, & Bleiberg, 2007; Echemendia et al., 2013; Lovell, Collins, Podell, Powell, & Maroon, 2000; Reeves, Winter, Bleiberg, & Kane, 2007; Schatz, Pardini, Lovell, Collins, & Podell, 2006). The development and availability of these computerized neurocognitive assessments, their convenience of administration and efficiency, storage and synthesis of large amounts of data, and immediate availability of clinical reports has led computerized neurocognitive testing to become the norm in the evaluation of cognitive deficits from concussion (Echemendia et al., 2013). In the context of these general benefits of computerized neurocognitive assessments, some concern about parallel-forms reliability has arisen, specifically in regard to differences in the constructs assessed across various

computerized batteries (Allen & Gfeller, 2011). Moreover, concerns have been raised about the influence of other factors (e.g., sleep, recent physical activity, age, and sex) on performance on computerized neuropsychological tests (Majerske et al., 2008). Given these concerns, comprehensive paper-and-pencil testing is still helpful in the post-concussion management of complicated cases in which concussion symptoms persist (Echemendia et al, 2013; Harmon et al., 2012).

Prior to the start of the season, athletes often complete baseline neurocognitive testing. If an athlete sustains a concussion, the athlete completes a post-injury computerized neurocognitive assessment, and these post-injury scores are compared to the baseline scores to determine if any neurocognitive deficits are present (Echemendia et al., 2013). In theory, acquiring baseline scores and comparing these to post-injury scores are thought to improve the diagnostic accuracy of identifying a concussion by limiting the variance that is associated with potential pre-injury confounding variables (e.g., distraction during testing, age, sex, etc.; Echemendia et al., 2013). While baseline testing is becoming the norm in the assessment of sports-related concussions, this does not hold true for the management of concussion in the general population. Despite the theory that baseline testing improves diagnostic accuracy, research has found that acquiring baseline data is not necessary to identify cognitive decline, as the post-injury data from computerized testing has demonstrated strong sensitivity and strong specificity in comparisons of post-injury results to current test norms (Echemendia et al., 2012; Echemendia et al., 2013). Specifically, using post-injury data alone, the ImPACT Verbal Memory Composite has demonstrated 86% sensitivity and 95% specificity and the Visual-motor Processing Speed Composite has demonstrated 80% sensitivity and 97%

specificity in detecting neurocognitive decline (Echemendia et al., 2012). Thus, if baseline scores are not available, it is appropriate to compare post-injury scores to the applicable, well-developed normative data (Echemendia et al., 2013).

Prior studies have specifically examined the value of neurocognitive testing in identifying the presence of concussion and in identifying those individuals who may take longer to recover from their injury (e.g., Echemendia et al., 2012; Van Kampen et al., 2006). When either the symptom score or at least one neurocognitive test result is abnormal, most individuals (approximately 93%) are correctly classified as having a concussion (Van Kampen et al., 2006). In comparison, although individuals without a concussion may demonstrate one abnormal ImPACT score, none (0%) demonstrate both an elevated symptom score and an abnormal ImPACT result (Van Kampen et al., 2006). A previous study attempted to determine whether specific ImPACT composite scores could predict a longer recovery (defined in this study as two weeks or longer) in male high school football athletes (Lau, Collins, Lovell, 2011). Results of this study indicated that reduced scores on the visual memory or processing speed composites predicted a longer recovery (Lau et al., 2011). For the visual memory composite in particular, a score of 48 or less, a score of 46, and a score of 44.5, predicted longer recovery with 75%, 80%, and 85% specificity, respectively (Lau et al., 2011). For the processing speed composite, a score of 24.5 or less, a score of 23.46, and a score of 22.5, predicted a longer recovery with 75%, 80%, and 85% specificity, respectively (Lau et al., 2011). Another study examined whether specific composite scores on the ImPACT predicted recovery rates in athletes, but compared adolescents (13-16 year olds) to young adults (18-22 year olds) and included males and females (Zuckerman et al., 2012). Results from

this study indicated that adolescents generally required a longer average number of days to return to neurocognitive baseline, especially if the verbal memory, visual memory, and reaction time composites were decreased; however, scores on the processing speed composite were not significantly associated with a longer duration of recovery (Zuckerman et al, 2012.). It thus remains unclear which if any composite scores or individual neurocognitive subtests on the ImPACT predict a prolonged recovery. The growing awareness of the multifaceted nature of concussion (e.g., effects on neurocognition, mood, sleep, etc.) has also led to changes in state legislation to prevent early return-to-play and increased risk of subsequent injury.

Return-to-Play

In May 2009, Washington State passed the Zackery Lystedt Law (Washington House Bill 1824) to address the management of concussions in youth sports (Centers for Disease Control and Prevention, September 2013). The Zackery Lystedt Law was the first legislation to require the removal of the youth athlete from play and subsequent medical clearance for the athlete to return to play. Specifically, this law contained three essential elements: (a) all coaches, athletes, and parents must be informed about the dangers of concussions each year; (b) if concussion is suspected in a young athlete, that individual must be removed from play and is not permitted to return that same day; and (c) In the following days or weeks, a licensed health care professional must medically clear the young athlete before he or she is permitted to return to play (http://www.nflevolution.com/article/The-Zackery-Lystedt-Law?ref=270). Between 2009 and 2012, 42 additional states, as well as the District of Columbia, passed similar laws (Centers for Disease Control and Prevention, September 2013). By February 2014,

all 50 states and the District of Columbia had passed laws implementing the three basic tenets of the Zachery Lystedt Law (http://www.nflevolution.com/article/The-Zackery-Lystedt-Law?ref=270).

In 2012, the Third International Conference on Concussion in Sport (CIS) issued a consensus statement requiring that if an athlete is diagnosed with concussion, that athlete is not to return to play that same day (McCrory et al., 2009; McCrory et al., 2013). The only exception to this rule is in the case of some adult athletes (e.g., professionals), in which team physicians experienced in concussion management and with immediate access to sufficient resources enable a more rapid return-to-play evaluation. Even in these circumstances, the same management principles for concussion guidelines apply, involving full clinical and cognitive recovery before the athlete is permitted to return to play (McCrory et al., 2013).

Regardless of the cause of injury, all individuals who suffer a concussion are managed using a similar return-to-play or activity protocol. Table 2 presents a model of graded return-to-play protocol. This return-to-play strategy uses a stepwise progression, by which the individual should continue to advance to the next level of activity if asymptomatic at the current level (McCrory et al., 2013). According to this graduated return-to-play protocol, an individual who suffers a concussion begins at stage 1, which involves complete physical and cognitive rest for approximately 24 to 48 hours following injury, with the focus on recovery (Leddy & Willer, 2013; Marshall, 2012; McCrory et al., 2013).

The rationale for initial cognitive and physical rest is derived from research on human and animal models indicating that excessive or intense activity shortly after a

Table 2
UPMC's Graded Return-to-Play Protocol for Individuals Who Suffer a Concussion

Rehabilitation Stage	Functional Objective for Each Stage of Rehabilitation	Example Exercises	Purpose of Stage
Baseline (No Activity)	Complete cognitive and physical rest		Recovery
1.Light Aerobic Exercise	Intensity kept at 30-40% MPHR. 10-15 minutes light cardio exercise. No resistance training or impact activities. Light head movement/position change	Walking, swimming, stationary cycling, static balance activities, core exercises without head movements	Increase heart rate
2. Light to Moderate Aerobic Exercise	Intensity kept at 40-60% MPHR. 20-30 min. Low-intensity sport-specific activities, core exercises with head movements, low-level concentration activities	Low-intensity Sport-specific activities, core exercises with head movements	Increase heart rate with integration of limited head/body movement
3. Sport-Specific Exercise	Intensity kept at 60-80% MPHR. Integrate strength training and balance/proprioception. No contact activities	Sport-specific drills (e.g., skating in ice hockey, running drills in soccer)	Add movement
4. Non-Contact Training Drills	80% MPHR. Avoid contact activity, but resume aggressive training in all environments	Progression to more complex training drills (e.g., passing drills)	Exercise, coordination, cognitive load
5. Full Contact Practice	100% MPHR. Following medical clearance, athlete participates in normal training activities (with full contact)	Full physical training activities with contact	Restore confidence/allow coaching staff to assess functional skills
6. Return to Play	Return to normal game play		Return to play

Note. *MPHR* = Maximum Predicted Heart Rate

concussion prolongs recovery (Griesbach, Hovda, Molteni, Wu, & Gomez-Pinilla, 2004; Leddy & Willer, 2013; Majerske et al., 2008). Additionally, research found that there is a period shortly after a concussive injury when an individual is likely to experience worsening symptoms of concussion with cognitive or physical activity; during this time, the brain is more susceptible to repeat injury (Giza & Hovda, 2001). Stage 2 involves light aerobic activity with no resistance training (e.g., walking, swimming, stationary cycling), while keeping the intensity at less than 70% maximum predicted heart rate (MPHR; Marshall, 2012; McCrory et al., 2013). The goal of this stage is to increase the individual's heart rate. Recent research has supported Stage 2 of the graduated return-to-play protocol, demonstrating that it is safe for adults with concussive injuries to exercise up to 74% of their MPHR (Kozlowski et al., 2013). Additionally, while research demonstrates that excessive activity too soon after concussive injury is detrimental to recovery, research also suggested that too little activity impedes recovery (Majerske et al., 2008). Aerobic activity performed 14 to 21 days after concussion has been associated with an up-regulation of *Brain Derived Neurotrophic Factor (BDNF)* and improved cognitive performance (Griesbach et al., 2004). The intent for the third stage of the protocol is to add movement to the individual's physical activity, while excluding any head-impact activities (Marshall, 2012; McCrory et al., 2013). For athletes in particular, this involves initiation of sport-specific exercise (e.g., skating drills in ice hockey, running drills in soccer; Leddy & Willer, 2013; Marshall, McCrory et al., 2013; Willer & Leddy, 2006). Stage 4 involves more complex non-contact training that focuses on exercise, coordination, and cognition (e.g., passing drills in football and ice hockey), and the individual is able to begin progressive-resistance training (Leddy & Willer, 2013;

Marshall, 2012; McCrory et al.; Willer & Leddy, 2006). Following medical clearance, the individual is able to enter the fifth stage, which allows full contact practice in his or her respective sport or activity. For athletes, this involves participating in normal training activities with the goal of restoring the athlete's confidence and assessing functional skills by the coaching staff (Leddy & Willer, 2013; Marshall, 2012; McCrory et al., 2013; Willer & Leddy, 2006). Finally, in stage 6, the individual returns to normal game play or daily activity. Usually, each step is expected to take 24 hours to complete, so that the individual should complete the entire rehabilitation protocol in one week, once he or she are asymptomatic at rest and with challenging exercise (Leddy & Willer, 2013; Marshall, 2012; McCrory et al., 2013; Willer & Leddy, 2006). If any post-concussion symptoms occur while completing a level in the stepwise program, the individual is returned to the previous asymptomatic level, and he or she must try to progress to the next level after an additional 24-hour rest period (Leddy & Willer, 2013; Marshall, 2012; McCrory et al., 2013; Willer & Leddy, 2013). Although any post-concussion symptoms an individual has may be exacerbated while completing the stepwise program, migraines and other headache conditions in particular may recur during the return-to-play protocol. Despite this, research has demonstrated that using this type of gradual reintroduction of activity is beneficial to recovery from concussion (Kozlowski et al., 2013; Leddy et al., 2010; Leddy & Willer, 2013; Silverberg & Iverson, 2013). Specifically, the gradual reintroduction of aerobic exercise has been associated with reduced concussion symptoms, improved fitness, and reduced recovery time, in contrast to prolonged rest, which may lead to such secondary symptoms as reactive depression, physiological deconditioning, and fatigue (Leddy et al., 2010; Willer & Leddy, 2006). Even in those

individuals who proved slow to recover, low-level exercise may beneficial, provided that it does not result in a significant exacerbation of symptoms (McCrory et al., 2012). Researchers have hypothesized that individuals with refractory post-concussion symptoms experience a physiological disruption that consists of impaired cerebral autoregulation and altered autonomic function (Leddy et al., 2010). Progressive, subsymptomatic aerobic exercise has therefore been recommended for individuals with persistent concussive symptomatology, as exercise reduces sympathetic activity, increases parasympathetic activation, and improves cerebral blood flow (Leddy et al., 2010).

Migraine and Other Headache Conditions

In the general population worldwide, migraines and other headache conditions are some of the most common complaints that practicing physicians treat. A review of 107 studies from six continents examined the global estimates of primary headache conditions and found that the reported prevalence was 11% for migraine, 42% for tension-type headache, and 3% for chronic daily headache (Buse et al., 2013). With few exceptions (e.g., cluster headache), it is well known that most primary headache conditions have a higher prevalence in females than in males, with migraine having the most pronounced difference in prevalence across sexes (Buse et al., 2013). Several large-scale epidemiological studies investigating migraine have found that the migraine occurs among females at approximately triple the rate among men, although this difference varies across the lifespan (Buse et al., 2013; Lipton, Diamond, Reed, Diamond, & Stewart, 2001; Lipton et al., 2013; Lipton, Stewart, Diamond, Diamond, & Reed, 2001; Stewart, Lipton, Celentano, & Reed, 1992). Additionally, females with migraine are

more likely to report experiencing more headaches per year, a longer duration of impairment, and more likely to report experiencing symptoms associated with migraine, including phonophobia, photophobia, nausea, vomiting, unilateral head pain (in adults), bilateral head pain (in adolescents), throbbing head pain, blurred vision, and/or visual aura (Buse et al., 2013; Lipton, Diamond et al., 2001; Lipton, Stewart et al., 2001; Lipton et al., 2013; Stewart, et al., 1992). There are many potential triggers of migraine, which include menstruation (i.e., menstrual migraine), sleep changes, stress, alcohol, weather changes, hunger, withdrawal from medications, etc. (Baldacci et al., 2012).

Definition of Migraine

Migraine is a disabling primary headache condition that affects many people worldwide, including athletes. Migraine can be classified into two major subtypes: *migraine without aura* and *migraine with aura* (Headache Classification Committee of the International Headache Society, 2013). These subtypes are not mutually exclusive and may co-occur in individuals (Dimberg & Burns, 2005; Headache Classification Committee of the International Headache Society, 2013). According to the International Classification of Headache Disorders, third edition (ICHD-III; 2013) distributed by the International Headache Society (IHS), migraine without aura is characterized by recurrent headaches with specific clinical features and symptoms (Dimberg & Burns, 2005; Headache Classification Committee of the International Headache Society, 2013). Diagnostic criteria for primary migraine without aura include at least five recurrent attacks, each lasting 4 to 72 hours if left untreated (Dimberg & Burns, 2005; Headache Classification Committee of the International Headache Society, 2013). The headache attacks must include at least two of these four characteristics: a pulsating quality,

unilateral location, moderate to severe pain, or aggravation of the headache by physical activity (Headache Classification Committee of the International Headache Society, 2013). Nausea and/or vomiting or photophobia and phonophobia must be present (Dimberg & Burns, 2005; Headache Classification Committee of the International Headache Society, 2013).

According to the ICHD-III criteria, migraine with aura is a primary headache condition chiefly characterized by the presence of transient focal neurological symptoms (i.e., aura) that may precede or coincide with the migraine headache (Dimberg & Burns, 2005; Headache Classification Committee of the International Headache Society, 2013). A migraine aura involves temporary focal neurological symptoms that typically develop gradually over 5-20 minutes and last for less than 60 minutes, usually occurring prior to the onset of a migraine headache, as defined by the ICHD-III criteria for migraine without aura (Dimberg & Burns, 2005; Headache Classification Committee of the International Headache Society, 2013). These temporary focal neurological symptoms may include visual disturbances (e.g., flickering lights or loss of vision), sensory symptoms (e.g., numbness or pins and needles), or speech disturbance (Headache Classification Committee of the International Headache Society, 2013).

Migraine and vestibular dysfunction. Vertigo is a common complaint among individuals with migraine. An estimated 38% of those with migraine also suffer from vertigo (Baker, Curtis, Trueblood, & Vangsnes, 2013). Several terms have been used to describe comorbid migraine and vertigo, including *vestibular migraine, migraine-associated dizziness, vertiginous migraine, migraine-related vestibulopathy, benign recurrent vertigo, and migraine-related vertigo* (Cherian, 2013). Those with comorbid

migraine and vertigo may be categorized as having either *migranious vertigo* or *migraine-associated vertigo* (Baker et al., 2013; Fasunla, Ibekwe, & Nwaorgu, 2012). Migrainous vertigo involves episodic vertigo that occurs simultaneously with other migraine symptoms (Baker et al., 2013; Cherian, 2013). Migraine-associated vertigo involves episodic vertigo in an individual with a history of migraine but does not require that the migraine and vertigo occur simultaneously (Baker et al., 2013; Cherian, 2013; Fasunla et al., 2012). Others research has further distinguished between definite migrainous vertigo and probable migrainous vertigo by adding the requirement that the vertiginous symptoms be triggered by typical migraine precipitants (Cherian, 2013).

Several prior studies have identified abnormal vestibular functioning in those individuals with vestibular migraine. *Vestibular-evoked myogenic potentials* (*VEMP*) is a test that measures the event-related potential of *sternocleidomastoid muscle relaxation* and is understood to be a test of *saccular (otolith) function* (Cherian, 2013). A prospective case-control study comparing individuals with migrainous vertigo to healthy controls found that those with migrainous vertigo demonstrated abnormal VEMP findings, suggesting that these individuals may have a lesion in the *sacculocollic pathway* (Hong, Kim, Park, & Lee, 2010). In another study, those with migrainous vertigo were compared to individuals with migraine without vertigo, as well as to healthy controls, on the Gaze Stabilization Pitch Test and an assessment of *functional gait* (Baker, et al., 2013). The Gaze Stabilization Pitch Test is an assessment of *vestibular ocular reflexes,* while the assessment of functional gate requires the use of both vestibular ocular reflexes and vestibular spinal reflexes (Baker et al., 2013). Findings from this study indicated that those with migrainous vertigo appeared to demonstrate a slower head movement on the

Gaze Stabilization Pitch Test and to perform poorly in the assessment of functional gait, in comparison to healthy controls and those with migraine without vertigo (Baker et al., 2013). These findings implied that those with migrainous vertigo experienced underlying differences in their vestibular ocular reflexes. Cumulatively, these studies supported the proposal that those suffering from migrainous vertigo possess abnormal vestibular functioning.

Definition of Tension-Type Headache

Tension-type headache is a headache condition that, like migraine, affects a large number of people worldwide. Similar to migraine, tension-type headache has three recognized subtypes: *infrequent episodic* tension-type headache, *frequent episodic* tension-type headache, and *chronic* tension-type headache (Headache Classification Committee of the International Headache Society, 2013). All of these tension-type headache conditions are characterized by similar headache attacks, which differ in frequency. Tension-type headache attacks must include at least two of the following four characteristics: a pressing or tightening and non-pulsating quality, bilateral location, mild or moderate intensity, or no aggravation by routine physical activity (e.g., climbing stairs or walking). In addition, the headache attacks must not be associated with nausea or vomiting and can only be associated with either photophobia or phonophobia (Headache Classification Committee of the International Headache Society, 2013). Infrequent episodic tension-type headache is characterized by at least ten episodes of headache occurring less than 12 days per year, each lasting between 30 minutes and one week (Headache Classification Committee of the International Headache Society, 2013). In order to meet criteria for frequent episodic tension-type headache, at least 10 episodes of

headache must occur over an average of one to 14 days per month for more than three months (i.e., $\geq$ 12 and < 168 days per year; Headache Classification Committee of the International Headache Society, 2013). Finally, chronic tension-type headache is characterized by headaches occurring at least 15 days per month on average for more than three months (Headache Classification Committee of the International Headache Society, 2014). Moreover, in chronic tension-type headache, the headache attacks last anywhere from hours to days, or are unremitting (Headache Classification Committee of the International Headache Society, 2013).

Depression

Like headache conditions, post-concussive mood disorders are also associated with a prolonged recovery from concussion. According to the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.), the term *depressive disorders* encompasses several conditions including *Disruptive Mood Dysregulation Disorder* (only diagnosed in individuals aged 6 to 18 years of age), *Major Depressive Disorder*, *Persistent Depressive Disorder* (i.e., *Dysthymia*), *Premenstrual Dysphoric Disorder*, *Substance/Medication-Induced Depressive Disorder*, *Depressive Disorder Due to Another Medical Condition, Other Specified Depressive Disorder,* and *Unspecified Depressive Disorder* (*Diagnostic and Statistical Manual of Mental Disorders,* 5th ed.: *DSM-5*; American Psychiatric Association [APA], 2013). Although Major Depressive Disorder represents the characteristic form of these conditions, the common feature of these depressive disorders is the persistence of a sad, irritable, or empty mood, associated with cognitive and somatic changes that significantly impede an individual's capacity to function (*DSM-5*; APA, 2013). Some of the somatic and cognitive changes that may result from these

depressive disorders include significant weight changes or changes in appetite, insomnia or hypersomnia, diminished ability to think or concentrate, feelings of worthlessness or guilt, psychomotor agitation or retardation, or recurrent thoughts of death, suicidal ideation, or suicidal attempts (*DSM-5*; APA, 2013).

According to the World Health Organization (2012), depression affects more than 350 million people worldwide. The Centers for Disease Control and Prevention (2012) estimates that one of every 10 adults in the United States reports suffering from symptoms of depression, while other estimates suggest that 17.7% of Americans experience such symptoms during their lifetime (Driessen & Hollon, 2010; Hammond, Gialloreto, Kubas, & Davis, 2013). Although the incidence of depression appears to peak in the 20s, depression can also affect younger children and older adults (*DSM-5*; APA, 2013). With the exception of Disruptive Mood Dysregulation Disorder, the prevalence of depressive disorders is more common in females than in males (*DSM-5*; APA, 2013).

Depression in Athletes

Although significant time and money have been devoted to treating the physical injuries of athletes, less extensive resources have been allotted to treating their associated psychological problems. Traditionally, athletes, their coaches and trainers, and the general public widely held the view that only those athletes who are mentally strong succeed (Markser, 2011). Recently, however, research has begun to investigate the prevalence of psychological disorders among athletes (e.g., Glick & Horsfall, 2005; Hammond et al., 2013; Mainwaring, Bisschop, Comper, Richards, & Hutchison, 2010). Despite stereotypes that athletes are immune to mental health concerns that may affect the general population, in fact athletes appeared to contend with a number of unique

challenges that may make them more susceptible to mental health concerns (Esfandiari, Broshek, & Freeman, 2011).

Athletes are at risk for depression, and it appears that they suffer from it at the same rate as the general population (Broshek & Freeman, 2005; Markser, 2011). Female athletes were at increased risk for experiencing depression, reporting a 1.32-fold increase in incidence of depressive symptoms compared to their male counterparts (Hammond et al., 2013). In addition, female athletes tend to report a greater number of depressive symptoms than male athletes (Hammond et al., 2013). Collegiate athletes in particular are at a high risk of experiencing depression, due to the combination of the typical stressors associated with this period in life and the commitment to competitive intercollegiate athletics (Yang et al., 2007). Furthermore, 40% to 50% of collegiate athletes sustain an athletic injury, which may or may not include concussion, that results in one or more incidents of time lost from participation in sports during their college years (Yang et al., 2007). Participating in athletic competitions and being part of a team are often core components of an athlete's identity, and the inability to participate in athletic competition often results in difficulties coping with the injury cognitively, behaviorally, and emotionally (Yang et al., 2007). As a result, these struggles often led athletes to experience decreased self-esteem and feelings of anger, anxiety, and/or depression (Yang et al., 2007). Depression in athletes may manifest somewhat differently than in the general population, with athletes exhibiting competition burnout, diminished strength or energy, and an increased number of injuries or illnesses (Broshek & Freeman, 2005). Although general participation in sports has been found to serve as a buffer against stress, student-athletes are required to balance the competing demands for

time of practice, class, study, competition, social activities, and travel, often resulting in reduced time for self-care (Esfandiari et al., 2011). In addition, as a result of participating in athletics, they may need to contend with unwanted attention that may result from the heightened visibility among their peers, and they may experience pressure from family members who are overinvolved in their athletic pursuits (Esfandiari et al., 2011). In addition to these social pressures and the risk of injury, athletes will often need to deal with issues related to playing time and conflicts with teammates or coaches (Esfandiari et al., 2011). As a result of this surfeit of competing demands, athletes are not only at risk of depression but also of other mental health concerns, such as anxiety and eating disorders.

Anxiety

The category of *anxiety disorders* contains a number of conditions including *Selective Mutism, Separation Anxiety Disorder*, *Specific Phobia, Social Anxiety Disorder* (i.e., *Social Phobia*), *Panic Disorder, Agoraphobia, Generalized Anxiety Disorder*, *Substance/Medication-Induced Anxiety Disorder, Anxiety Disorder Due to Another Medical Condition*, *Other Specified Anxiety Disorder*, and *Unspecified Anxiety Disorder* (*DSM-5*; APA, 2013). Although now considered a trauma- and stressor-related disorder rather than an anxiety disorder under the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed., 2013) the core features of *Post-Traumatic Stress Disorder (PTSD)* also include significant levels of anxiety in response to exposure to actual or threatened death, such as from a perceived significant or traumatic event that causes injury (*DSM-5*; APA, 2013). The characteristic features of these anxiety disorders are persistent and excessive fear and anxiety, as well as behavioral disturbances (*DSM-5*; APA, 2013). Fear

and anxiety are highly comorbid, but the situations that tend to evoke these conditions differ. Fear is defined as the emotional response to a perceived imminent threat, but anxiety involves the anticipation of a future threat (*DSM-5*; APA, 2013). The experience of fear is associated with the autonomic arousal that is required for fight or flight, thoughts of immediate danger, and escape behaviors. In contrast, anxiety is associated with vigilance and muscle tension in anticipation of a future threat and involves cautious or avoidant behaviors (*DSM-5*; APA, 2013).

Anxiety disorders are the most common form of mental illness in the general population, affecting approximately 40 million adults in the United States (aged 18 and older; Centers for Disease Control and Prevention, 2011). According to the Centers for Disease Control and Prevention (2011), the estimated lifetime prevalence of any anxiety disorder is greater than 15%, while the annual prevalence is greater than 10%. Similar to the majority of depressive disorders, most anxiety disorders tend to be more prevalent in females than in males (Centers for Disease Control and Prevention, 2011; *DSM-5*; APA, 2013).

Anxiety in Athletes

Anxiety disorders have been studied in sport psychology literature and have been found to be highly comorbid with depressive disorders and common in both male and female athletes (Markser, 2011; Masten, Tusak, & Faganel, 2006). Anxiety associated with performance or competition has been found to predict the duration and quality of one's experiences in sports and other achievement domains (e.g., academics, business, and music; Grossbard, Smith, Smoll, & Cumming, 2009). Specifically, high levels of anxiety tend to be associated with poor performance in sports, as well as reduced

enjoyment of and participation in athletics (Grossbard et al., 2009). Intercollegiate student athletes tend to perceive stronger family pressure to succeed athletically, as compared to their non-athlete and intramural athletic peers (Broshek & Freeman, 2005). Moreover, a study of college students found that social anxiety may generalize to competitive sports, indicating that socially anxious intercollegiate athletes may experience increased evaluation anxiety, especially if they have trouble meeting their own expectations or the expectations of their family (Broshek & Freeman, 2005; Norton, Burns, Hope, & Bauer, 2000).

Mental Illness and Concussion

Although research has often focused on the neurocognitive effects of concussion, clinical evidence suggests that there is a relationship between concussion and emotional sequelae. Among non-athletes with mild traumatic brain injuries, emotional disturbances have been identified immediately following injury (Dikmen, McLean, & Temkin, 1986; King, 2014a; Mainwaring et al., 2010). The incidence of depression among those with traumatic brain injury (TBI) has been estimated to be 6% in mild TBI and 77% in more severe cases of TBI (Jorge & Robinson, 2003). Similarly, research has found that athletes with concussive injuries often demonstrate acutely elevated depressive and anxiety symptoms that have been found to be strongly associated with a prolonged recovery from concussion and post-concussion syndrome (Garden & Sullivan, 2010; King & Kirwilliam, 2011; Mainwaring et al., 2004; Ponsford et al., 2012). Additionally, research has revealed a high correlation between depression symptom scores and symptoms of anxiety in intercollegiate student athletes (Yang et al., 2007). Consistent with these findings, *functional magnetic resonance imaging (fMRI)* studies have found

that among concussed male athletes with depressive symptoms, there is reduced cerebral activity in the *dorsolateral prefrontal cortex* and increased activity in the *anterior cingulate* and *medial orbito-frontal cortices*, patterns of neural activity that are typically found in individuals with Major Depressive Disorder (Chen, Johnston, Petrides, & Ptito, 2008). Moreover, in athletes with concussion, elevated symptoms of depression have been found to be associated with decreased neurocognitive performance, specifically in the domains of visual memory and reaction time (Covassin, Elbin, Larson, & Kontos 2012; Kontos, Covassin, Elbin, & Parker, 2012). Similarly, elevated anxiety symptoms post-concussion have been found to strongly predict continuing post-concussive symptoms at three months post-injury (Ponsford et al., 2012). As such, post-concussive mental health conditions, such as anxiety and depression, tend to be related to continuing post-concussive symptoms.

Relationship between Recovery from Concussion, Headaches, and Mental Health Conditions

Of the symptoms that may present with a concussive injury, headache is the most commonly reported, occurring in approximately 70% of athletes (Lovell, 2009). Although the exact prevalence of post-concussive headache is unknown, it is recognized that a high number of individuals who sustain non-sport related concussions experience post-concussive headache (King 2014a; King 2014b). Among athletes, those who present with the Cognitive-Fatigue-Migraine cluster, specifically with symptoms of post-concussive migraines, probable migraines, generalized headaches (e.g., tension-type headaches), and cognitive symptoms, have been found to generally have longer recovery times (Lau et al., 2011b). Early research on sports-related concussion has suggested that

post-concussive migraine is associated with a significantly greater risk of protracted recovery, with some estimates as high as 7.3 times greater than athletes without post-concussive migraines or other headaches (Harmon et al., 2013; Kontos et al., 2013; Mihalik et al., 2013). In addition, research has suggested that athletes with post-concussive migraine report significantly higher rates of post-concussive sleep, cognitive, somatic, and emotional symptoms (Kontos et al., 2013). Other research has also suggested that general post-concussive headaches are associated with a 2.6-fold increase in risk of prolonged recovery as compared to athletes who do not experience post-concussive headache symptoms (Kontos et al., 2012). While the exact figures for non-sport related injury are unknown, it is unclear whether a premorbid history of migraine and other headache conditions complicates or prolongs the recovery from a concussive injury; however, research findings suggest that post-concussive headache with headache, photophobia, nausea, phonophobia, increased reported symptoms for two weeks following concussion, and concurrent reductions in verbal and visual memory and reaction time, is related to a prolonged recovery from concussion (Kontos et al., 2013).

In the sports-related concussion literature, one study found that post-concussive dizziness was the single greatest predictor of a prolonged recovery in male high school football players (Lau et al., 2011). Although it is unknown if this pattern generalizes for females with concussion, these results suggest the possibility that the Cognitive-Fatigue-Migraine subtype is prone to lead to a more prolonged recovery from concussion. Research from studies on migraines and other headache conditions has found that vertigo, dizziness, motion sensitivity, and other vestibular problems occur as part of some migraine presentations. Moreover, the pathophysiology of migraine is similar to that of

concussion in that both result in *initial cerebral hyperexcitability*, characterized by increased blood flow, followed by spreading cortical depression (Bhaskar et al., 2013; Ferrari et al, 2015; Giza & Hovda, 2001). This suggests that those with a premorbid migraine or other headache condition may be more inclined to present with vestibular dysfunction and the Cognitive-Fatigue-Migraine subtype, post-concussively (Calhoun, Ford, Pruitt, & Fisher, 2011). Consequently, it is possible that individuals with premorbid migraine and other headache conditions might not only be at an increased risk for suffering from post-concussive migraines and other headaches, but might also be at increased risk of vestibular involvement following a concussion.

Early research examining the relationship between mental health conditions and recovery from concussion has found that those who experience post-concussive symptoms of anxiety and depression tend to experience prolonged recovery times. Although the rates are unknown for those with concussion in the general population, research investigating sports-related concussions has found that concussed athletes demonstrate significantly higher levels of somatic depression and anxiety between 2 and 14 days following injury, which has also been found to be associated with poorer performance on specific neurocognitive measures, as well as a continuation of post-concussive symptoms (Broshek & Freeman, 2005; Kontos et al., 2012; Ponsford et al., 2012).

Purpose of the Study

The purpose of this archival, regression-model study was to identify if specific premorbid clinical variables predicted an exacerbation of similar post-concussive symptom clusters that are associated with a protracted recovery in females with concussion. Specifically, this study sought to determine if a premorbid clinical history of migraines and/or generalized headaches was associated with an increased risk of developing post-concussive migraines and/or generalized headaches; if a premorbid history of mental health/psychiatric conditions was associated with an increased risk of post-concussive psychiatric symptoms; and if a premorbid history of migraines and/or generalized headaches was predictive of post-concussive dizziness. In addition, using the Reliable Change Index (RCI), this study attempted to define a pattern of neurocognitive decline in specific cognitive domains (e.g., *reaction time, visual memory, verbal memory*, etc.) following post-concussive injury that was predictive of protracted recovery (*Clinical Interpretation Manual for ImPACT 6.0*, 2007).

To address these questions, the study examined premorbid and post-injury reports of migraine and other headache conditions, dizziness, psychiatric history, and neurocognitive performance. These reports were obtained through archival data that was collected through the Sports Medicine Concussion Program at the University of Pittsburgh Medical Center (UPMC). The population consisted of 180 cases of concussion in females. Data included results from a computerized neurocognitive assessment (i.e., Immediate post-concussion Assessment and Cognitive Testing; ImPACT), medical records, and symptom self-reports from the Post Concussion Symptom Scale (PCSS) contained within the ImPACT.

Chapter Three

Hypotheses

The goal of the current study was to explore whether premorbid clinical variables, specifically a history of mental health conditions and/or premorbid headaches, and post-concussive neurocognitive patterns of decline, predict a prolonged recovery from concussion. Therefore, the following hypotheses were proposed:

1. A premorbid history of migraines, probable migraines, and tension-type headaches, defined as occurring in patients who reported a headache condition that was diagnosed and independently treated by a physician, in addition to younger age, history of prior concussions, mechanism of injury, and longer delay before initial evaluation, will predict a protracted recovery from concussion, defined as recovery from concussion occurring 21 days or longer after initial injury (H_1).
2. A premorbid history of migraines, probable migraines, and tension-type headaches, defined as occurring in patients who reported a headache condition that was diagnosed and independently treated by a physician, in addition to younger age, history of prior concussions, mechanism of injury, and longer delay before initial evaluation, will predict post-concussive dizziness, defined as a greater change in the items that relate to dizziness on the PCSS between the initial and final post-injury evaluations (i.e., more significant dizziness symptoms at initial evaluation post-injury) (H_2).
3. A premorbid history of anxiety and depression, defined as occurring in patients who reported a mental health condition that was diagnosed and

independently treated by a psychologist or physician, in addition to younger age, history of prior concussions, mechanism of injury, and longer delay before initial evaluation, will predict post-concussive Affective symptomatology, defined by a greater change in the Affective symptom cluster scores on the PCSS between the initial and final post-injury evaluations (i.e., more significant affective symptoms at initial evaluation post-injury) (H_3).

4. Post-concussive Affective symptomatology, post-concussive Cognitive-Fatigue-Migraine symptomatology, younger age, history of prior concussions, mechanism of injury, longer delay before initial evaluation, and post-concussive declines in visual-motor processing speed, reaction time, and visual memory, all defined as a greater change in scores between the initial and final post-injury evaluations, will be associated with a protracted recovery from concussion, defined as recovery from concussion occurring 21 days or longer after initial injury (i.e., more significant impairments in these domains at initial evaluation post-injury) (H_4).

Chapter Four

Method

Design and Design Justification

An archival regression model was used to examine whether premorbid mental health conditions (i.e., anxiety and depression), premorbid headache conditions (i.e., pre-injury diagnosis of migraine, probable migraine, and tension-type headache), and post-concussive neurocognitive declines predicted a protracted recovery from concussion in females. This design was selected in order to identify how these premorbid factors predicted recovery in females with concussion. Concussion was operationalized as the clinical definition provided by the 4th Zurich Consensus Statement from 2012, which defines concussion as a brain injury resulting from a "complex pathophysiological process affecting the brain, induced by biomechanical forces" from a direct blow to the face, head, neck, or elsewhere on the body, with an "impulsive" force transmitted to the head (McCrory et al., 2013, p. 250). The 4th Zurich Consensus Statement further defines concussion as a metabolic injury that (1) results in the rapid onset of transient impairments in neurological functioning that typically resolve spontaneously, (2) results in a functional, rather than a structural, disturbance in brain functioning, and (3) results in a set of clinical symptoms that often resolve in a sequential course, which occasionally may be prolonged.

Recovery from concussion for student athletes was operationally defined as occurring when an individual had successfully cleared all levels of the graded *Exertion Program* and had been cleared by the healthcare professional (i.e., neuropsychologist or physician) for a complete return to full-contact sports and full academic activities without

accommodations. For non-athletes, recovery was operationally defined as occurring when an individual had successfully cleared all levels of the graded Exertion Program and had been cleared by the healthcare professional (i.e., neuropsychologist or physician) for a complete return to daily activities and work. For all individuals, full recovery was defined as the date that a medical professional (i.e., neuropsychologist or physician) had cleared them to return to all normal daily activities. Protracted recovery was defined as recovery occurring 21 days or longer after concussion. Persistent symptomatology was defined as ongoing concussion symptoms (e.g., somatic, cognitive, sleep, physical, and psychological) continuing for 12 weeks or longer after initial injury. Recovery from concussion was examined by evaluating the average duration of recovery (in days). A continuous variable was formed to examine the severity of prolonged concussion as compared to those who experienced expected rates of recovery. Premorbid headache conditions (including migraine, probable migraine, and tension-type headache) were operationalized as occurring in patients who reported in the clinical interview and the Demographic section of the ImPACT a headache condition that was diagnosed and independently treated by a physician. Premorbid mental health conditions (including anxiety and depression) were operationalized as occurring in patients who reported in the clinical interview and the Demographic section of the ImPACT a mental health condition that was diagnosed and independently treated by a psychologist or physician. Post-concussive Affective symptomatology was defined as a greater change in the Affective symptom cluster scores on the PCSS between the initial and final post-injury evaluations, reflecting greater Affective symptomatology immediately post-concussion. Post-concussive Cognitive-Fatigue-Migraine (CFM) symptomatology was defined as a greater

change in the CFM cluster score on the PCSS between the initial and final post-injury evaluations, reflecting more significant CFM symptoms at immediately post-injury. Post-concussive neurocognitive decline was operationalized as a reduced score on any of the ImPACT Composite Scales immediately post-injury (as measured by the Reliable Change Index, RCI) compared to final post-injury performance (Van Kampen, Lovell, Pardini, Collins, & Fu, 2006). Table 3 presents the established RCI scores for determining decline in relation to composite scores.

Table 3
Group Means and Reliable Change Index (RCI) Scores for Each ImPACT Composite Score

ImPACT Composite	Concussed Group Baseline (mean and S.D.)	Concussed Group Follow-Up (mean and S.D.)	RCI Value (.80 CI)
Verbal Memory	85.7 (8.9)	76.0 (14.4)	8.75
Visual Memory	74.0 (12.8)	64.3 (13.8)	13.55
Reaction Time	0.57 (0.08)	0.64 (0.13)	0.06
Processing Speed	36.0 (6.8)	32.7 (8.6)	4.98
Symptom Report	6.8 (9.6)	25.6 (19.9)	9.18

Note. Deviations from the expected means that fall outside of the *RCI* scores are considered abnormal. Adapted from Van Kampen, Lovell, Pardini, Collins, & Fu, 2006.

Participants

Archival data was gathered from the charts of 180 females who ranged in age from 9 to 62 ($M = 20.57$, SD = 11.57), who were evaluated and treated for a concussion at the Sports Concussion Program at the University of Pittsburgh Medical Center (UPMC). Concussions were the result of sports-related injuries ($N = 102$), falls ($N = 27$), motor vehicle accidents ($N = 32$), blows to the head ($N = 14$), or assaults ($N = 5$). The Sports Medicine Concussion Program at UPMC is a specialty care medical clinic located in Pittsburgh, Pennsylvania. Table 4 describes a summary of the mechanisms of injury in the current sample.

Table 4
Mechanisms of Injury and the Frequency of Occurrence in the Current Sample

Mechanism of Injury	Frequency (*N*)
Sports-Related Injury	102
Fall	27
Motor Vehicle Accident	32
Bump or Blow to the Head	14
Assault	5

Note. Total $N = 180$.

The current study used an exempt, deidentified, medical records protocol that was approved by the University of Pittsburgh and Philadelphia College of Osteopathic Medicine institutional review boards. Demographic data provided by UPMC included age at injury. Clinical data provided by UPMC included premorbid headache conditions, premorbid mental health conditions, mechanism and type of injury, reaction time, visual-motor reaction time, visual memory, dizziness, post-concussive headache symptoms, post-concussive affective symptoms, days until initial evaluation, and total recovery time in days. Table 5 provides additional clinical information that characterized the current sample.

Table 5
Descriptive Statistics of Clinical Variables of Patient Sample

Clinical Variables	Mean (SD)
Age at Injury	20.57 (11.57)
Number of Prior Concussions (*N*=178)	0.78 (1.46)
Time to Initial Evaluation in Days (*N*=179)	69.32 (170.50)
Total Recovery Time in Days (*N*=153)	203.4 (260.80)
Post-concussive Reaction Time (*N*=166)	0.48 (0.24)
Post-concussive Visual Memory (*N*=166)	38.99 (15.51)
Post-concussive Visual-Motor Reaction Time (*N*=166)	36.99 (8.71)
Post-concussive Dizziness (*N*=167)	3.68 (1.73)

Note. Total $N = 180$; Patients were excluded due to missing data or scores greater than 3 standard deviations above the mean.

Inclusion and Exclusion Criteria

Inclusion criteria consisted of female gender, a diagnosis of one or more concussion(s), undergoing ImPACT testing, and range of age between 5 and 90 years old. Exclusion criteria consisted of male gender, age outside of the preselected range, not undergoing ImPACT testing, pre-existing learning disorders and/or *Attention Deficit/Hyperactivity Disorder (ADHD),* and a documented history of moderate to severe traumatic brain injury (TBI), as defined by structural brain changes identified on clinical imaging (i.e., MRI and CT Scan). Individuals with ADHD and learning disorders were excluded from the sample, because prior research has documented reduced performance at baseline evaluation that requires different norms, as well as a longer recovery from injury in these populations (e.g., Elbin et al., 2013; Sussman & Mautner, 2014).

Recruitment

Medical professionals and athletic trainers referred participants to the Sports Concussion Program at UPMC for re-evaluation/second opinion and for further treatment for concussion management. As this was an archival sample, the data were already available.

Measures

Immediate post-concussion Assessment and Cognitive Testing (ImPACT). ImPACT (version 2.1) is a computerized neuropsychological test battery that is used to assist in evaluating and managing concussion (Lovell, Collins, Podell, Powell, & Maroon, 2000; Schatz, Pardini, Lovell, Collins, & Podell, 2006). The battery consists of three sections that include demographic data, neuropsychological testing, and self-reported symptom data as measured by the PCSS. The demographic section obtains

information on relevant medical, psychological, sports, and history of concussion. The neuropsychological testing section contained within ImPACT (version 2.1) consists of six neuropsychological tests, including *Word Memory, Design Memory, Xs and Os, Symbol Match, Color Match*, and *Three-Letter Memory* (Schatz et al., 2006). Each of these tests is intended to assess different domains of cognitive functioning (Schatz et al, 2006). These neuropsychological tests specifically measure the following: (a) Word Memory (verbal recognition memory, learning and retention), (b) Design Memory (spatial recognition memory, learning and retention), (c) Xs and Os (visual working memory and cognitive speed), (d) Symbol Match (memory and visual-motor speed), (e) Color Match (impulse inhibition and visual-motor speed), and (f) Three-Letter Memory (verbal working memory and cognitive speed). From these six tests, four composite scores are generated, including Verbal Memory, Visual Memory, Reaction Time, and Visual-Motor Speed (Schatz et al., 2006). Tables 6 and 7 provide a summary of the neuropsychological tests and composite scores obtained from ImPACT.

Among high school and college athletes, the online version of ImPACT (version 2.1) has demonstrated excellent sensitivity (91.4%) and moderate specificity (69.1%) (Schatz & Sandel, 2013).

Table 6
The ImPACT (Version 2.1) Neuropsychological Test Battery and the Different Domains of Cognitive Functioning Assessed by Each Test

Test Name	Cognitive Domain Assessed
Word Memory	Verbal recognition memory
Design Memory	Spatial recognition memory
Xs and Os	Cognitive speed and visual working memory
Symbol Match	Memory and visual-motor speed
Color Match	Visual-motor speed and impulse inhibition
Three-Letter Memory	Cognitive speed and verbal working memory

Note. Adapted from Lovell (2009).

Table 7
Composite Scores Obtained on the ImPACT (Version 2.1) and the Corresponding Contributing Scores from the Neuropsychological Tests

Composite Scores	Contributing Scores
Verbal Memory	Word Memory (learning and delayed) Symbol Match Memory Score Three-Letter Memory Score
Visual Memory	Design Memory (learning and delayed) Xs and Os Percent Correct
Reaction Time	Xs and Os (average counted correct reaction time) Symbol Match (average weighted reaction time for correct responses) Color Match (average reaction time for correct responses)
Visual-Motor Processing Speed	Xs and Os (average correct distractors) Symbol Match (average correct responses) Three-Letter Memory (number of correctly counted numbers)
Impulse Control	Xs and Os (number of incorrect distractors) Color Match (number of errors)

Note. Adapted from Lovell (2009).

The *positive likelihood ratio* (*PLR*, the ratio between the probability of detecting a positive test result when a concussion is present and the probability of a positive test result in the absence of a concussion) is 2.95:1, suggesting a high likelihood of correctly detecting a concussion when a concussion is present. The *negative likelihood ratio* (*NLR*, the ratio between the probability of a negative finding in the presence of a concussion and the probability of a negative test result in the absence of a concussion) is 0.12:1, suggesting that 12% of the time, ImPACT correctly classifies an individual without a concussion (a NLR less than 0.2 is considered useful for ruling out a clinical condition) (Schatz & Sandel, 2013). Test-retest reliability, as measured by an intra-class correlation coefficient (ICC), for ImPACT (version 2.1) is high (ICC is greater than 0.3) in all domain scores (Verbal Memory: ICC = .459; Visual Memory: ICC = .653; Processing Speed: ICC = .742; Reaction Time: ICC = .676) (Schatz, 2009).

Post-Concussion Symptom Scale (PCSS). The third and final section of ImPACT consists of the PCSS. The PSS is a 22-item self-report inventory that is used to document and track concussion symptoms (ImPACT Applications, Inc., 2007; Lovell & Collins, 1998). The scale asks the athlete to rate each symptom on a 7-point Likert scale from 0 (*no symptoms*) to 6 (*severe symptoms*), based on the athlete's current experience. Total scores range from 0 to 132, and higher total scores indicate greater total symptoms (ImPACT Applications, Inc., 2007).

A factor analysis conducted on the PCSS found that the symptoms reported on the PCSS are organized into four clusters: *Migraine, Cognitive, Sleep,* and *Neuropsychiatric* (Lau, Collins, & Lovell, 2011). Internal consistency for the PCSS is moderate to high (α = .75 to .94) and test-retest reliability is adequate (r = .80; ImPACT Applications, Inc., 2007).

Procedure

An athletic trainer, athletic director, primary care physician, or other medical professional referred all individuals to the Sports Medicine Concussion Program at UPMC for evaluation and treatment of a sports-related concussion. Once admitted to the Sports Medicine Concussion Program at UPMC, all individuals underwent an initial clinical interview by a neuropsychologist, initial neurocognitive testing (ImPACT, 2007), and patient feedback. Based on the findings from the clinical interview and neurocognitive testing, length of recovery, and symptom presentation, participants in the *prolonged recovery group* were referred for additional services, including physical therapy, vestibular therapy, a comprehensive neuropsychological evaluation, and/or follow-up neurocognitive testing via ImPACT. The decision to return an athlete to play

was made by the staff neuropsychologist. Determination of return to play was based on the individual's performance on ImPACT, report of symptoms on the PCSS, and exacerbation of concussive symptomatology during physical exercise and cognitive exertion (e.g., tasks requiring mental/cognitive effort).

Chapter Five

Results

The purpose of the current study was to investigate whether premorbid clinical variables, specifically a history of mental health conditions and/or premorbid headaches and post-concussive neurocognitive patterns of decline, predicted prolonged recovery from concussion in females. An a priori power analysis revealed that 120 participants were required for the regression analyses to obtain 80% power in detecting a medium-sized effect, when employing a 0.05 criterion of statistical significance. The number of participants exceeded the required minimum sample size. All statistical analyses were performed using the Statistical Package for Social Sciences, version 22 (SPSS 22; IBM Inc., https://www14.software.ibm.com) with alpha set at $p < 0.05$ (two-tailed). Across analyses, the tolerance test indicated that the assumption of little or no multicollinearity had been violated (Tolerance = .000). Specifically, sports-related injuries were strongly correlated with injuries resulting from motor vehicle accidents, falls, and blows to the head; therefore, sports-related injury was automatically excluded from the regression models to meet the assumption of multicollinearity. Otherwise, the data were normally distributed and assumptions for logistic and bivariate regressions were met.

Descriptive analyses were conducted to examine the rates of improvement between the initial and final post-injury evaluations in post-concussive clinical and neurocognitive symptoms. Table 8 provides a summary of the rates of change between the initial post-injury evaluation and the final evaluation prior to discharge.

Table 8
Rate of Change in Clinical Variables Between Initial and Final Post-injury Evaluations

Variable	Mean (S.D.)
Visual Memory Change	-13.01 (15.51)
Reaction Time Change	.09 (.24)
Visual-Motor Speed Change	-7.88 (8.71)
Cognitive-Fatigue-Migraine Symptom Change	16.75 (13.73)
Affective Symptom Change	2.86 (4.36)

Hypothesis 1

A logistic regression was used to identify which predictors best explained the amount of variance in the development of prolonged recovery from concussion, as specified in hypothesis 1. It was hypothesized that a premorbid history of migraines, probable migraines, and tension-type headaches would predict a more protracted recovery from concussion, to a greater extent than younger age, prior number of concussions, mechanism of injury, and longer delay to initial evaluation. Results from the logistic regression revealed that the overall model explained 18% of the variance (R^2 = .18, $F(8,140) = 3.86$, $p < .000$). It was found that time to first evaluation was significantly positively predictive of longer recovery (β = .96, $p < .001$), such that those who waited longer to undergo an initial evaluation for concussion took longer to fully recover. Contrary to the predictions outlined in hypothesis 1, a premorbid history of headaches was not significantly predictive of prolonged recovery (β = -49.48, p = .21). Table 9 provides a summary of the regression analysis associated with hypothesis 1.

Hypothesis 2

A simple regression was used to identify whether a premorbid history of migraines, probable migraines, and tension-type headaches would predict post-concussive dizziness as specified in hypothesis 2 to a greater degree than younger age,

prior number of concussions, and mechanism of injury. Results from the simple regression analysis

Table 9
Regression Analysis Summary Predicting Recovery Time in Hypothesis 1

Variable	B	S.E.B	T
Premorbid Headache Conditions	-49.48	38.82	-1.28
Age at Injury	.24	1.90	.12
Number Prior Concussions	-2.10	13.38	-.16
Mechanism of Injury – MVA	7.82	55.42	.14
Mechanism of Injury – Fall	-18.72	54.91	-.34
Mechanism of Injury – Blow to head	-107.02	78.47	
Mechanism of Injury - Assault	-73.73	143.92	-.51
Time to First Evaluation	.96	.19	5.00*

Note. $R^2 = .18$ ($N = 148$, $p < .001$); *$p < .001$

failed to support hypothesis 2. Specifically, results revealed that the overall model explained only 3% of the variance ($R^2 = .03$, $F(8,153) = .61$, $p = .77$), and none of the variables in the model were significantly predictive of post-concussive dizziness, as defined as higher change in score on items related to dizziness between the first and last post-injury evaluations. Table 10 provides a summary of the regression analysis for hypothesis 2.

Table 10
Regression Analysis Summary Predicting Post-concussive Dizziness in Hypothesis 2

Variable	B	S.E.B	T
Premorbid Headache Conditions	-.04	.29	-.14
Age at Injury	.00	.01	.19
Number Prior Concussions	.00	.10	.03
Mechanism of Injury – MVA	.63	.42	1.45
Mechanism of Injury – Fall	.36	.42	.85
Mechanism of Injury – Blow to Head	.43	.54	.79
Mechanism of Injury – Assault	.13	1.11	.11
Time to First Evaluation	.00	.00	-1.42

Note. $R^2 = .03$ ($N = 161$, $p = .77$)

Hypothesis 3

A simple regression was used to identify which predictors best explained the amount of variance in the development of post-concussive affective symptomatology as specified in hypothesis 3. In specific, it was hypothesized that a premorbid mental health history would significantly predict post-concussive affective symptomatology to a greater extent than younger age, prior number of concussions, mechanism of injury, and longer delay before initial evaluation. Results from the simple regression supported hypothesis 3. In particular, results revealed that the overall model explained 10% of the variance (R^2 = .10, $F(8,154) = 2.06$, $p < .05$). A premorbid history of anxiety and/or depression proved to be significantly positively predictive of post-concussive affective symptomatology, defined as a higher change in score in affective symptoms between first and last post-injury evaluations ($\beta = 2.66$, $p = .002$). Table 11 shows the summary of the regression analysis for hypothesis 3.

Table 11
Regression Analysis Summary for Predicting Post-concussive Affective Symptomatology in Hypothesis 3

Variable	B	S.E.B	t
Premorbid Mental Health History	2.66	.83	3.21*
Age at Injury	.00	.03	.01
Number Prior Concussions	.03	.24	.11
Mechanism of Injury – MVA	1.43	1.00	1.44
Mechanism of Injury – Fall	1.33	1.01	1.32
Mechanism of Injury – Blow to Head	.47	1.30	.36
Mechanism of Injury – Assault	.06	2.66	.02
Time to First Evaluation	.00	.00	-1.60

Note. $R^2 = .10$ ($N = 162$, $p < .05$); $*p < .01$

Hypothesis 4

A logistic multiple regression was used to identify those factors that best predicted a prolonged recovery from concussion that were identified in hypothesis 4. It

was hypothesized that post-concussive Affective symptomatology, post-concussive Cognitive-Fatigue-Migraine symptomatology, and post-concussive declines in Visual-motor Processing Speed, Reaction Time, and Visual Memory would significantly predict prolonged recovery to a greater extent than younger age, prior number of concussions, mechanism of injury, and delay to initial evaluation. Results from the logistic regression revealed that the overall model explained 24% of the variance ($R^2 = .24$, $F(12,132) = 3.40$, $p < .001$). Time between injury and first evaluation emerged as significantly positively predictive of longer recovery time ($\beta = .46$, $p < .001$), indicating that those who longest deferred an initial post-injury evaluation were more likely to experience a more prolonged recovery; however, contrary to the expected results, none of the post-injury symptoms or neurocognitive declines were significantly predict longer recovery times. Table 12 provides the regression analysis summary for hypothesis 4.

Table 12
Regression Analysis Summary Predicting Recovery Time for Hypothesis 4

Variable	β	S.E.B	t
Post-concussive Affective Symptoms	3.52	5.39	.65
Post-concussive CFM Symptoms	-2.71	1.84	-1.48
Age at Injury	-.14	2.11	-.06
Number Prior Concussions	9.26	14.37	.64
Mechanism of Injury – MVA	-35.34	62.13	-.57
Mechanism of Injury – Fall	-29.50	62.48	-.47
Mechanism of Injury – Blow to Head	-112.77	85.78	-1.32
Mechanism of Injury – Assault	-36.03	156.84	-.23
Time to First Evaluation	.46	.12	3.81*
Post-concussive Visual-Motor Reaction Time	-5.99	4.03	-1.49
Post-concussive Reaction Time	198.67	128.81	1.49
Post-concussive Visual Memory	-1.31	1.62	-.81

Note. *CFM* = Cognitive-Fatigue-Migraine; $R^2 = .24$ ($N = 144$), $p < .001$) *$p < .001$

Additional Analyses

Initial post-injury Scores

Due to concern that the use of post-injury score change may have masked statistical results, the same analyses were conducted using only the scores from initial post-injury evaluations. Across these additional analyses, the tolerance test indicated that the assumption of little or no multicollinearity was not supported (Tolerance = .000), as sports-related injuries were strongly correlated with injuries resulting from motor vehicle accidents, falls, and impacts to the head. As with the previously described analyses, sports-related injury was therefore excluded from the regression models to meet the assumption of multicollinearity. Otherwise, data were normally distributed, and assumptions for logistic and bivariate regressions were supported.

Findings from these analyses revealed similar results. Results for hypothesis 1 were unchanged; there were no post-injury scores included in the logistic regression. Therefore, consistent with results obtained by using post-injury change scores and revealed that the overall model explained 18% of the variance ($R^2 = .18$, $F(8,140) = 3.86$, $p < .001$), with only time until first evaluation significantly positively predicting longer recovery ($\beta = .96$, $p < .001$). Table 13 provides the regression analysis summary associated with hypothesis 1 using initial post-injury values.

In the new analyses, hypothesis 2 predicted that premorbid headache conditions would, to a greater extent than age at injury, mechanism of injury, and time until first evaluation, significantly predict post-concussive dizziness at the initial post-injury evaluation. Results indicated that the overall model reached statistical significance and explained 11% of the variance ($R^2 = .11$, $F(8,153) = 2.24$, $p < .05$). Specifically, injuries

Table 13
Regression Analysis Summary Predicting Recovery Time in Hypothesis 1 Using Initial Post-injury Scores

Variable	β	S.E.B	t
Premorbid Headache Conditions	-49.48	38.82	-1.28
Age at Injury	.24	1.90	.12
Number of Prior Concussions	-2.10	13.38	-.16
Mechanism of Injury – MVA	7.82	55.42	.14
Mechanism of Injury – Fall	-18.72	54.91	-.34
Mechanism of Injury – Blow to Head	-107.02	78.47	-1.36
Mechanism of Injury - Assault	-73.73	143.92	-.51
Time to First Evaluation	.96	.19	5.00*

Note. $R^2 = .18$ (N=148, $p < .001$); *$p < .001$

resulting from motor vehicle accidents significantly predicted post-concussive dizziness (β = .85, p = .44),and age at injury approached significance (β = .03, p = .57); however, contrary to the hypothesis, premorbid headache conditions were not significantly predictive of post-concussive dizziness (β = .12, p = .68). Table 14 provides the regression analysis summary associated with hypothesis 2 derived from initial post-injury values.

Table 14
Regression Analysis Summary Predicting Recovery Time in Hypothesis 2 Using Initial Post-injury Scores

Variable	B	S.E.B	t
Premorbid Headache Conditions	.12	.29	.41
Age at Injury	.03	.01	1.92
Number of Prior Concussions	-.06	.10	-.60
Mechanism of Injury – MVA	.85	.42	2.03*
Mechanism of Injury – Fall	.34	.42	.82
Mechanism of Injury – Blow to Head	.89	.54	1.65
Mechanism of Injury - Assault	.84	1.10	.76
Time to First Evaluation	.00	.00	-.89

Notes. $R^2 = .11$ (N=161, $p = .03$); *$p < .05$

Hypothesis 3 predicted that premorbid mental health conditions would significantly predict post-concussive affective symptomatology to a greater extent than

age, mechanism of injury, and time until initial evaluation. With the new analysis, results demonstrated that the overall model explained 26% of the variance ($R^2 = .26$, $F(8,154) = 6.86$, $p < .001$), with premorbid mental health conditions ($\beta = 3.70$, $p < .001$) and age at injury ($\beta = .12$, $p = .002$) proving significantly positively predictive of post-concussive affective symptomatology at initial post-injury evaluation. Additionally, the analysis revealed that motor vehicle accidents approached significance for predicting initial post-concussive affective symptoms ($\beta = 2.18$, $p = .051$). Table 15 provides the regression analysis summary associated with hypothesis 3 using initial post-injury values.

Table 15
Regression Analysis Summary Predicting Recovery Time in Hypothesis 3 Using Initial Post-injury Scores

Variable	β	S.E.B	t
Premorbid Mental Health History	3.70	.92	4.02**
Age at Injury	.12	.04	3.23*
Number of Prior Concussions	-.29	.27	-1.08
Mechanism of Injury – MVA	2.18	1.12	1.97
Mechanism of Injury – Fall	1.18	1.12	1.05
Mechanism of Injury – Blow to Head	1.05	1.45	.73
Mechanism of Injury - Assault	5.20	2.96	1.76
Time to First Evaluation	.00	.00	-1.73

Note. $R^2 = .26$ (N=162, $p < .001$); *$p < .01$; **$p < .001$

The goal for hypothesis 4 was to identify which pre-morbid characteristics, post-injury symptoms, and post-injury neurocognitive declines best predicted a prolonged recovery from concussion. When using all initial post-injury scores, the model for hypothesis 4 was found to significantly explain 18% of the variance ($R^2 = .18$, $F(12,132) = 2.40$, $p = .008$). Specifically, initial post-injury declines in reaction time ($\beta = 283.05$, $p < .05$) and longer delays to initial evaluation ($\beta = .46$, $p < .001$) were significantly predictive of longer recovery. Table 16 provides the regression analysis summary associated with hypothesis 4 using initial post-injury values.

Table 16
Regression Analysis Summary Predicting Recovery Time in Hypothesis 4 Using Initial Post-injury Scores

Variable	β	S.E.B	t
Post-concussive Affective Symptoms	3.28	5.47	.60
Post-concussive CFM Symptoms	-.30	1.99	-.15
Age at Injury	-2.07	2.28	-.90
Number of Prior Concussions	7.12	15.40	.46
Mechanism of Injury – MVA	-26.25	65.54	-.40
Mechanism of Injury – Fall	-23.89	65.76	-.36
Mechanism of Injury – Blow to Head	-101.20	92.08	-1.10
Mechanism of Injury - Assault	-37.54	165.99	-.23
Time to First Evaluation	.46	.12	3.74**
Post-concussive Visual-Motor Reaction Time	-1.66	3.71	-.45
Post-concussive Reaction Time	283.05	134.17	2.11*
Post-concussive Visual Memory	.97	1.71	.57

Note. *CFM* = Cognitive-Fatigue-Migraine; $R^2 = .18$ ($N = 144$, $p < .01$); *$p < .05$; **$p < .001$

Limited Sample and Increased Specificity

Although the initial analyses were conducted with larger ranges in age and time until initial evaluation, results from these analyses indicated that premorbid and post-injury factors were significantly predictive of prolonged recovery. As a result, specific analyses were conducted with a more limited age range to identify premorbid factors, post-concussive symptoms, and neurocognitive declines that significantly predicted injury recovery in a sample of individuals that was most represented in past concussion research.

At present, the current literature on concussion primarily includes studies of individuals who are 22 years of age or younger, due to the convenient availability of this population on college campuses in which sports-related concussion is studied. Moreover, the ImPACT is not currently normed for individuals below 10 years of age (ImPACT Applications, Inc., 2007). Additionally, the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.: *DSM-IV-TR*; APA, 2000) defines Post-concussion Syndrome

as occurring when symptoms persist for longer than 90 days (or three months). Therefore, additional analyses were conducted with a more limited age range of 10 to 22 years, excluding individuals who had waited longer than 90 days to undergo initial post-injury evaluation (Total N = 123; $M = 15.20$, SD = 2.20). Concussions were the result of sports-related injuries ($N = 88$), falls ($N = 16$), motor vehicle accidents ($N = 11$), impactsto the head ($N = 7$), or assault ($N = 1$). Moreover, because of the multicollinearity identified for sports-related concussions, the analyses were re-run with mechanism of injury excluded as a covariate. For exploratory purposes, hypothesis 4 was divided into premorbid factors, post-concussive symptoms, and post-concussive neurocognitive declines to predict duration of recovery with additional post-concussive symptoms (i.e., vestibular and sleep) and neurocognitive declines (i.e., verbal memory) entered as covariates. Results of these exploratory analyses follow.

Hypothesis 1

A logistic regression was used to identify which predictors best explained the amount of variance in the development of prolonged recovery from concussion as specified in hypothesis 1. It was hypothesized that a premorbid history of migraines, probable migraines, and tension-type headaches would predict a more protracted recovery from concussion to a greater extent than younger age, history of prior concussions, and longer delay to initial evaluation. Results from the logistic regression analysis failed to support hypothesis 1. The overall model explained only 5% of the variance ($R^2 = .06$, $F(4,109) = 1.78$, $p = .14$), and only delay to initial evaluation was correlated with longer recovery time ($\beta = 1.49$, $p = .05$), suggesting that those who waited longer to undergo an initial evaluation for concussion took longer to fully recover.

Contrary to the predictions outlined in hypothesis 1, a premorbid history of headaches did not significantly predict prolonged recovery ($\beta = -42.28$, $p = .18$). Table 17 provides the regression analysis summary associated with hypothesis 1 using a limited age range, limited time between injury and initial post-injury, and exclusion of mechanism of injury.

Table 17
Additional Regression Analysis Summary Predicting Recovery Time in Hypothesis 1 Using a Limited Age Range, Reduced Time (in Days) between Injury and Post-Injury Evaluation, and Exclusion of Mechanism of Injury as a Predictor

Variable	β	S.E.B	t
Premorbid Headache Conditions	-42.28	31.22	-1.35
Age at Injury	10.27	7.07	-.35
Number of Prior Concussions	9.37	15.56	.66
Time to First Evaluation	1.49	.76	1.95*

Note. $R^2 = .06$ *(*$N = 113$*)*; $p = .14$; $^*p = .05$

Hypothesis 2

A simple regression analysis was used to identify whether a premorbid history of migraines, probable migraines, and tension-type headaches would predict post-concussive dizziness as specified in hypothesis 2 to a greater extent than younger age, prior history of concussion, and longer delay until initial evaluation. Results from the simple regression analysis failed to support hypothesis 2. Specifically, results revealed that the overall model explained only 4% of the variance ($R^2 = .04$, $F(4,115) = 1.25$, $p = .29$), and none of the variables in the model significantly predicted post-concussive dizziness. Table 18 provides the regression analysis summary for hypothesis 2 using a limited age range, limited time between injury and initial post-injury, and exclusion of mechanism of injury.

Table 18
Additional Regression Analysis Summary Predicting Post-concussive Dizziness in Hypothesis 2 Using a Limited Age Range, Reduced Time (in Days) between Injury and Post-Injury Evaluation, and Exclusion of Mechanism of Injury as a Predictor

Variable	β	S.E.B	t
Premorbid Headache Conditions	-.05	.33	-.13
Age at Injury	.10	.08	1.35
Number of Prior Concussions	-.27	.17	-1.63
Time to First Evaluation	-.01	.01	-1.35

Note. $R^2 = .04$ ($N = 119$, $p = .29$)

Hypothesis 3

A simple regression was used to identify which predictors best explained the amount of variance in the development of post-concussive affective symptomatology as specified in hypothesis 3. It was specifically hypothesized that a premorbid mental health history would significantly predict post-concussive affective symptomatology to a greater extent than younger age, history of concussion, and longer delay before initial evaluation. Results from the simple regression supported hypothesis 3. Specifically, results revealed that the overall model explained 19% of the variance ($R^2 = .19$, $F(4,114) = 6.88$, $p < .001$). It was found that premorbid history of anxiety and/or depression was significantly positively predictive of post-concussive affective symptomatology ($\beta = 5.11$, $p < .001$). Table 19 provides the regression analysis summary associated with hypothesis 3 using a limited age range, limited time between injury and initial post-injury, and exclusion of mechanism of injury.

Hypothesis 4

Three logistic multiple regressions and two paired-sample t-tests were used to identify the premorbid, post-injury, and neurocognitive factors that best predicted a prolonged recovery from concussion as identified in hypothesis 4. Paired-sample t-tests

Table 19
Additional Regression Analysis Summary for Predicting Post-concussive Affective Symptomatology in Hypothesis 3 Using a Limited Age Range, Reduced Time (in Days) between Injury and Post-Injury Evaluation, and Exclusion of Mechanism of Injury as a Predictor

Variable	β	S.E.B	t
Premorbid Mental Health History	5.11	1.07	4.78*
Age at Injury	.16	.18	.85
Number of Prior Concussions	-.43	.40	-1.07
Time to First Evaluation	.01	.02	.71

Note. $R^2 = .19$ ($N = 118$); $p < .001$; *$p < .001$

were conducted to compare premorbid mental health conditions and post-concussive Affective symptoms, as well as premorbid headache conditions and post-concussive Cognitive-Fatigue-Migraine symptoms. Results of the first paired-samples t-test indicated that there was a significant difference between those individuals with premorbid mental health conditions ($M = .15$, $SD = .36$) and subsequent post-concussive Affective symptomatology ($M = 2.98$, $SD = 4.35$; $t = -7.34$, $p < .001$). Results of the second paired-samples t-test indicated that there was a significant difference in those individuals with premorbid headache conditions ($M = .32$, $SD = .47$) and subsequent post-injury Cognitive-Fatigue-Migraine symptoms ($M = 20.83$, $SD = 13.70$; $t = -16.44$, $p < .001$).

The first regression model investigated how premorbid variables, specifically premorbid mental health conditions and premorbid headache conditions, predicted duration of recovery to a greater extent than age at injury and history of concussion. Results from this logistic multiple regression revealed that premorbid injury variables were not significantly predictive of injury recovery, explaining only 3% of the variance ($R^2 = .03$, $F(4,109) = .81$, $p = .52$).

The second regression model examined how post-injury clinical variables, specifically post-injury Cognitive-Fatigue-Migraine symptoms and post-injury Affective symptoms, predicted duration of recovery to a greater extent than post-injury Vestibular symptoms, post-injury Sleep symptoms, and delay before initial evaluation. Results from this logistic multiple regression revealed that the overall model significantly predicted recovery and explained 16% of the variance ($R^2 = .16$, $F(5,107) = 3.91$, $p = .003$). In this model, delay to first evaluation ($\beta = 1.91$, $p < .05$) and post-concussive Cognitive-Fatigue-Migraine symptoms ($\beta = 3.08$, $p < .05$) significantly positively predicted longer recovery.

The final logistic multiple regression attempted to determine how post-injury neurocognitive declines, specifically visual memory, reaction time, and visual-motor - processing speed predicted duration of recovery to a greater extent than verbal memory. Results from this regression analysis failed to support the hypothesis that post-injury neurocognitive declines would predict recovery. Specifically, results revealed that the overall model explained only 3% of the variance ($R^2 = .03$, $F(4,108) = .78$, $p = .54$), and none of the variables in the model were significantly predictive of recovery. Table 20 provides the regression analysis summary for hypothesis 4, broken into pre-injury variables, post-injury symptoms, and post-injury neurocognitive declines using a limited age range, limited time between injury and initial post-injury, and exclusion of mechanism of injury.

Table 20

Additional Regression Analysis Summary Predicting Recovery Time for Hypothesis 4 Using a Limited Age Range, Reduced Time (in Days) between Injury and Post-Injury Evaluation, and Exclusion of Mechanism of Injury as a Predictor

Variable	β	S.E.B	t
Premorbid Factors Predicting Recovery			
Age at Injury	-2.41	7.39	-.33
Number of Prior Concussions	10.99	16.04	.69
Premorbid Mental Health History	8.91	42.59	.21
Premorbid Headache History	-51.44	31.43	-1.64
Post-injury Factors Predicting Recovery			
Time to First Evaluation	1.91	.75	2.57*
Post-injury CFM Symptoms	3.08	1.38	2.23*
Post-injury Affective Symptoms	-3.81	4.04	-.94
Post-injury Sleep Symptoms	8.21	5.28	1.56
Post-injury Vestibular Symptoms	1.89	12.50	.15
Neurocognitive Factors Predicting Recovery			
Verbal Memory Initial Post-injury	1.56	1.36	1.15
Visual Memory Initial Post-injury	-.33	1.32	-.25
Visual-motor Processing Speed Initial post-injury	-.83	2.54	-.33
Reaction Time Initial Post-injury	122.76	111.48	1.10

Note. *CFM* = Cognitive-Fatigue-Migraine; Premorbid Factors: $R^2 = .03$, ($N = 113$, $p = .52$); Post-injury Factors: $R^2 = .16$; ($N = 112$, $p = .003$); Neurocognitive Factors: $R^2 = .03$; ($N = 112$, $p = .54$); *$p < .05$

Chapter Six

Discussion

The primary goal of this study was to examine whether premorbid clinical variables, specifically, a history of mental health conditions and/or premorbid headaches, and post-concussive neurocognitive patterns of decline, would predict a prolonged recovery from concussion in females. Moreover, the study sought to investigate whether premorbid mental health conditions were related to post-concussive affective symptoms. This was the first study to examine whether a premorbid history of headache conditions predicts a higher likelihood of post-concussive dizziness, as well as whether a premorbid history of headache conditions predicts a higher likelihood of prolonged recovery.

The conceptual framework and methods that guided this study were influenced by the current research on concussions, the limited understanding of how pre-injury clinical variables affect post-concussive symptomatology and recovery, and the increased frequency of concussions in females. Regardless of the population, there is a clinically significant minority of people who experience a prolonged recovery from concussion, with females demonstrating longer recoveries relative to their male counterparts. Those individuals who experience a protracted recovery from concussion report ongoing symptoms of fatigue, irritability, social withdrawal, and depression, often resulting in significant frustration related to ongoing symptomatology, inability to participate in typical daily activities, reduced independence, loss of income, reduced social involvement, and difficulties meeting academic or work requirements (Rees & Bellon, 2007). The identification of premorbid clinical and demographic variables, in addition to post-concussive symptomatology and neurocognitive decline, is therefore an important

step to identifying those that might be at risk for a longer and more complicated recovery. If premorbid and post-concussive factors are identified that predict prolonged recovery, then expectations for recovery can be explained and appropriate treatment recommendations may be provided earlier in the course of treatment.

Current results failed to provide support for the hypothesis that a premorbid history of migraine and headache conditions would positively predict protracted recovery from concussion, while controlling for age, number of prior concussions, mechanism of injury, and delay before initial evaluation. Although this overall model significantly predicted protracted recovery from concussion, a premorbid migraine or headache history did not significantly predict longer recovery; rather, elapsed time before initial evaluation significantly predicted longer recovery. This indicates that when a concussion is suspected, it is of the utmost importance to undergo evaluation as soon as possible after the occurrence of a possible injury. Current results also failed to support the prediction that a premorbid history of migraine and headache conditions would predict post-concussive dizziness. Moreover, results lacked support for any significant predictive relationship between post-concussive dizziness and age, history of concussion, or delay before evaluation.

As hypothesized, a premorbid history of mental health concerns significantly and positively predicted post-concussive Affective symptomatology, corroborated by patients on the PCSS. This provided additional support for findings documented in the existing literature about the relationship between premorbid mental health conditions (specifically anxiety) and prolonged recovery from concussion.

Last, the hypothesis that post-concussive Affective symptomatology, post-concussive Cognitive-Fatigue-Migraine symptomatology, and post-concussive declines in visual-motor processing speed, reaction time, and visual memory would predict prolonged recovery to a greater extent than younger age, prior history of concussions, mechanism of injury, and delay before initial evaluation was only partially supported. Although the overall model was found to significantly predict prolonged recovery, only delay before initial evaluation and post-concussive decline in reaction time explained a significant amount of the variance in prolonged recovery. These findings provided further support for the importance of early evaluation following potential concussive injury and the importance of considering declines in reaction times.

Clinical Implications of Findings

Results from the current study highlighted the importance of early evaluation in the treatment and management of concussion. Results also provided support for the existing literature that has demonstrated that reduced reaction time is a sensitive measure of concussive injury, and that premorbid mental health conditions are associated with prolonged recovery.

The most notable findings of the current study related to time to post-injury evaluation. Delayed evaluation demonstrated a significant and positive relationship with prolonged recovery, suggesting that early identification and evaluation of concussion is related to injury recovery. Although the explanation for this current finding is not known, early identification and evaluation of concussion allows for prompt implementation of more targeted treatments and interventions, such as vestibular or vision therapy, that can help to mediate post-concussive recovery.

Results also affirmed the existing research base that has documented a relationship between premorbid mental health conditions and prolonged recovery. Existing research has documented elevations in anxiety and depression levels immediately after concussive injury, and adjustment to injury status and the influence of anxiety on recovery have been found to be especially predictive of longer recovery (Garden & Sullivan, 2010; King & Kirwilliam, 2011; Mainwaring et al., 2004; Ponsford et al., 2012). Adding to the existing literature on the relationship between mental health and concussion recovery, the current study demonstrated that premorbid mental health concerns are significantly predictive of post-concussive affective symptoms. Past research has already documented that post-concussive affective symptoms are related to a longer recovery from concussion. Although the study was unable to determine the exact underlying reasons for the relationship between post-concussive mental health concerns and recovery, it is likely those with post-concussive Affective symptomatology (especially anxiety) experience significantly greater rates of somatization and a greater sensitivity to physical sensations. In regard to the current study, its results provided evidence of a relationship between premorbid and post-concussive Affective symptomatology. It remains to be determined whether this relationship is a function of the metabolic crisis that occurs in the brain following concussive injury, or if it is the result of pre-existing sensitivity or heightened awareness of bodily sensations, which would increase an individual's sensitivity to the subtle neurocognitive, emotional, and somatic symptoms following injury.

Results from the additional analyses also indicated that post-injury Cognitive-Fatigue-Migraine symptoms are significantly predictive of prolonged recovery, which is

consistent with prior research on the relationship between post-concussive migraine and recovery (Kontos et al., 2013). While the underlying cause for this relationship is not yet known, the pathophysiology of both migraines and concussion may account for this relationship. Specifically, research on concussion and migraine indicate that the pathophysiology in both involves a degree of initial neuronal hyperexcitability characterized by increased blood flow, followed by a period of neuronal spreading depression (Bhaskar et al., 2013; Ferrari et al., 2015; Giza & Hovda, 2001; Shaw, 2002). This similar pathophysiology suggests that in the event of a concussive injury in people with a premorbid history of migraines, there may be a compounded pathophysiological effect that results in the worsening of migraine conditions post-concussively.

Finally, the current study added support to the current knowledge base that reaction time is a sensitive measure of concussive injury, but did not support the clinical utility of reduced visual or verbal memory in the prediction of longer recovery. Prior research had demonstrated that shortly after concussive injury, individuals tend to demonstrate reduced cognitive performance across two or more domains, including visual memory, reaction time, and verbal memory (Iverson et al., in press). While reaction time has consistently been demonstrated to be a very sensitive measure of concussive injury (Collie et al., 2006; Eckner et al., 2011; Eckner et al., 2014), the current sample consisted primarily of people who waited longer before an initial assessment after injury. Reaction time has traditionally taken longer to recover after injury, especially in individuals with a history of prior concussions, so it is possible that current findings are also the result of the clinical variables in the current sample (Covassin, Stearne, & Elbin, 2008). Moreover, prior research has demonstrated a positive relationship between

somatic depression and anxiety following injury and reduced performance on neurocognitive measures of reaction time (Broshek & Freeman, 2005; Kontos et al., 2012). Therefore, given the long delays before initial evaluation in the current sample, it is possible that the reductions in other cognitive domains had already resolved by the time of initial evaluation, leaving a discrepancy between reaction time following injury and reaction time following recovery.

Establishing that premorbid mental health conditions and post-concussive reaction time declines are significantly predictive of a protracted recovery from concussion has several potential clinical implications. This knowledge helps to predict which females, based on premorbid clinical variables and post-concussive neurocognitive decline, are at risk for a more prolonged recovery from concussion and so helps to guide therapeutic interventions. This knowledge may aid clinicians in informing concussed individuals about their prognosis, specifically as it relates to their expected length of time away from play or daily activities. By informing individuals from the outset that they are at risk of a more prolonged recovery, clinicians help them to realistically evaluate their trajectory for symptom improvement. By helping individuals to evaluate their trajectory for recovery realistically, clinicians can help manage post-concussive emotional complications that may result from unexpected protracted recovery by reducing stress and the likelihood of symptom exacerbation caused by it. Moreover, by informing concussion victims that those with anxiety may be at more risk of a longer recovery, clinicians can provide early education to patients about the relationship between their emotional and mental health states and perception of symptoms. By helping to initially identify which individuals are at risk for having a more prolonged recovery and what types of early interventions they

may require, the current stud informs the management of concussion in clinical practice, by athletic directors, school policies, and return-to-play or activity protocols for high school and collegiate athletes, professional athletes, and individuals in the general population.

Limitations of Current Study

There are several limitations to the current study. First, in an effort to reduce variability and control for gender differences, the sample consisted of females across the lifespan. Most of the literature on concussion, however, has focused on individuals with sports-related injuries who are younger than 22 years of age. The older individuals who are included in the current sample may have experienced prolonged recovery due to external factors (e.g., secondary gains as a result of Workman's Compensation), complicating the understanding of current results. In addition, the current sample included two individuals who were younger than 10 years of age at the time of their injury. It is unknown, however, if the results from their neurocognitive evaluations were valid, because ImPACT has not yet been normed on individuals younger than 10. In an effort to address these concerns, additional analyses were conducted with a more limited age range (10-22 years) that has been more widely studied in the concussion literature. Moreover, the current sample consisted only of females. As a result of physiological differences between males and females, the findings from this study are applicable only to females and cannot be extrapolated to males. Second, the investigator used an existing data set and did not collect the data directly from the participants. Therefore, there were limited opportunities for behavioral observations during assessment and interview. In addition, because the investigator used an already existing data set, it was unknown if any

participants were currently on medication management for premorbid mental health or headache conditions at the time that they sustained a concussion. Given that such knowledge was lacking, it is unclear how the management of these conditions might have influenced how these premorbid mental health and headache conditions predicted post-concussive symptom presentation or duration of recovery. Third, in the current sample, there was significant variability in the time elapsed before initial post-injury evaluation, which likely masked the effects of other clinical variables on injury recovery. To address these concerns, subsequent analyses were conducted after excluding individuals who had met criteria for post-concussion syndrome before they underwent an initial post-injury evaluation. Fourth, the current analyses did not include verbal memory, post-concussive sleep symptoms, or post-concussive vestibular symptoms as covariates in the analyses, making it difficult to ascertain what effect these variables had on recovery. To account for the possibility that these additional variables might have impacted recovery, they were included as covariates in additional analyses. Last, the current investigation used a continuous variable to define the number of days between injury and initial post-injury evaluation. Although delay before initial evaluation and duration of recovery were significantly positively correlated, it is unknown if there is a specific timeframe in which injured individuals should seek evaluation before their risk for longer recovery is increased.

Future Directions

As previously mentioned, this study sought to establish a predictive relationship between premorbid functioning, specifically mental health and headache conditions, and post-concussive neurocognitive decline and prolonged recovery from concussion in

females. First and foremost, as the findings from this study cannot be generalized to males, future research should examine whether these predictive relationships are similar in males across the lifespan. Second, replication of this study is warranted. Third, although the current analyses did not demonstrate a predictive relationship between premorbid headaches/migraine conditions and recovery, it is unknown if these results truly indicate that premorbid migraine or headache conditions are clinically unrelated to post-injury recovery. The current ICHD-III diagnostic criteria for migraine are quite stringent and require recurrent headache symptomatology; however, these strict criteria are intended more for research than for use in clinical practice. Although neurologists tend to diagnose migraine, the majority of patients with headaches typically present first to their primary care physicians. Primary care physicians tend to diagnose patients with tension-type headaches rather than migraine, as patients in clinical practice typically do not meet the stringent ICHD-III criteria for migraine; as a result, migraine and probable migraine are underdiagnosed in the general population (Ozge, Aydinlar, Tasdelen, 2014). Therefore, it is possible that the current results are reflective of inaccurate diagnoses and underdiagnosis of migraine conditions. Future concussion research should evaluate these findings in individuals who meet both stringent and general migraine and probable migraine criteria, and who are diagnosed and remain in the care of a neurologist. Fourth, the current study only controlled for the days before initial post-injury evaluation, but did not determine a timeframe in which evaluation should occur in order to reduce the risk of longer recovery. Current guidelines for the management of concussion suggest that early evaluation is imperative for the treatment of concussion and prevention of repeat injury, which may impact duration of recovery (McCrory et al., 2009; McCrory et al., 2013; U.S.

Centers for Disease Control and Prevention, February 2015); however, future studies should endeavor to define a timeframe in which post-injury evaluation should occur to reduce the risk of delayed recovery. Moreover, the current study did not control for premorbid medication and/or behavioral management of mental health conditions or headache conditions. Therefore, prospective future studies should be conducted to control for the management of these premorbid conditions. Furthermore, prior research has indicated that estrogen may play a role in females' susceptibility to concussion, so future studies should examine how hormonal fluctuations during the menstrual cycle relate to the development and/or symptomatology of concussion in females. Extensive research has examined the factors that predict recovery from concussion in athletes, and these factors should also be examined more closely in the general population. Research has demonstrated a potential link between multiple concussions and chronic traumatic encephalopathy (CTE) specifically in athletes, and future studies should also aim to longitudinally evaluate athletes and their development of CTE relative to duration of initial recovery (i.e., prolonged versus expected duration of recovery).

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