Predicting Length of Care Following Concussion

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Abstract

Concussions have become a prominent injury treated across medical care settings. Due to a complicated underlying pathophysiological process, concussions are subtle and produce a wide array of signs, including cognitive, somatic, and sensorimotor symptoms. The diverse symptomatology makes clinical assessment and management of concussions challenging for clinicians. Additionally, this complexity makes determining recovery trajectory after injury difficult for practitioners. Identifying individuals at risk for long durations of treatment early in their care would allow for early restorative interventions, reduced cost of care, and improved patient quality of life.

This need lead to a series of studies attempting to add evidence to support the clinical assessment process of individuals following both suspected and diagnosed concussions. Our first study evaluated the rates and reasons for under-reporting of concussions and symptoms in female high school athletes, a neglected population of study in concussion research. We found female athletes often failed to report concussion symptoms to coaches and trainers. Additionally, only 2/3rds of athletes reported receiving concussion education that may explain the lack of reporting.

Different clinical assessment techniques were also explored. Balance and reaction time assessment are commonly completed to help identify individuals with suspected concussion, but these assessments are subjective and often require equipment not available outside of clinical settings. We evaluated the validity and reliability of a mobile device application to assess balance and reaction time as part of a concussion screening. We found *Sway*™ to be comparable to force platform balance assessments and computerized reaction time measurement in healthy subjects, indicating these assessments have clinical utility. Additionally, the assessment only

required a mobile device, allowing for assessment in clinics and sports settings without computers or force platform equipment.

The last assessment method we evaluated involved neuroimaging techniques. Diffusion tensor imaging (DTI) has been used in the assessment of individuals with moderate to severe brain injury to objectively track recovery of function after trauma. We explored the similar use of DTI to objectively track recovery of function after concussion. We assessed 10 female participants experiencing slowed recovery of function after a concussion. We found no significant associations between DTI metrics for white matter pathway integrity and changes in symptoms over time, indicating that symptom improvement may occur in a non-congruent fashion with underlying neurological functioning. We did find improvements in pathway integrity were associated with improved reaction time and visual processing, adding to the clinical importance of assessing these skills.

A lack of understanding as to which objective clinical features leads to increased risk of prolonged care adds to the complexity of determining a person's recovery trajectory following concussion. This gap in evidence lead to an exploratory study evaluating differences in clinical presentation patterns between groups of individuals with typical treatment durations (≤ 28 days) and extended lengths of care (> 28 days). The exploratory factor analysis yielded different factor structures for each group. Notable differences included age, sex, history of psychiatric disorders, and neurocognitive abilities at the evaluation. These findings suggest clinical differences between individuals with longer and shorter lengths of care are observable at evaluation.

After detecting differences between these groups, we sought to clarify the impact of each variable on length of care. A survival analysis was completed, evaluating the effects of clinical, demographic, and social factors on estimating length of care after concussion. We found males had shorter durations of care, while individuals with a history of concussion and better access to housing and transportation had longer durations of care. This study added evidence to support sex and concussion history as influential of longer durations of care. Additionally, while significant, housing and transportation access is likely not a protective feature for concussion recovery, but likely reflects the ability to attend follow-up treatments for concussion care.

A final study was conducted to assess the predictive ability for each variable identified in the previous studies, with the primary outcome focused on determining which features best predict whether someone will have a typical duration of care (≤ 28 days) or an extended duration of care (> 28 days). A multivariable, logistic regression model was used to evaluate the significance of each variable. History of previous concussion and slowed reaction times at the evaluation had significant effects. Additionally, individuals from lower socioeconomic areas had lower odds of an extended length of care, although these findings should reflect ability to pursue care, rather than a reduction of recovery time.

In summary, these studies add to the foundational knowledge of concussion assessment for diagnostic and recovery purposes. Additionally, these studies contribute to our understanding of factors that contribute to prolonged lengths of care for individuals after concussion. Clinicians should continue to complete thorough evaluation of individuals with suspected concussion, documenting concussion histories, sex, age, reaction times, and external social factors that may prevent or impede necessary follow-up care.

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Chapter 1: Introduction

Concussions, often referred to as mild traumatic brain injuries, have been a growing public concern and research focus for the last decade. Concussions are a relatively common occurrence, accounting for at least 80% of all traumatic brain injuries (TBI) and have an annual incidence rate in the United States of 500 injuries per 100,000 people (Bazarian et al., 2005; Cassidy et al., 2004; Ryu, Feinstein, Colantonio, Streiner, & Dawson, 2009). While the definition of what constitutes a concussion varies depending on the defining source, a vast majority of healthcare professionals define concussion as a complex, physiological process affecting the brain, induced by biomechanical forces, with common features incorporating clinical, pathologic, and biomechanical constructs (McCrory et al., 2013). Studies have consistently shown that up to 90% of individuals after a concussion have full symptom recovery within one month (Meehan, d'Hemecourt, Collins, & Comstock, 2011). The remaining subset of individuals experience prolonged symptoms that necessitate continued medical care and potential disability (King & Kirwilliam, 2011; Lundin, de Boussard, Edman, & Borg, 2006).

Post-concussion syndrome (PCS), a diagnosis given after a person has abnormally persistent symptoms following a concussion, has been a recent research focus. One of the biggest needs has been to clearly define PCS (Rose, Fischer, & Heyer, 2015). There have been multiple publications proposing different durations of post-concussion symptoms that should be considered "abnormal". For example, the widely referenced Zurich Concussion in Sport conference proposed that post-concussion symptoms lasting more than 10 days should be considered "persistent" (McCrory et al., 2013), yet the most commonly cited PCS definitions derives from the Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV) (American Psychological Association, 1994). In this definition of PCS, at least 3 symptoms must be present for 3 months, well past the 10 day presence suggested by the Zurich conference. This lack of agreement has made the study of PCS difficult, as study populations are not consistently defined, individuals are inconsistently diagnosed in accordance to specified criteria, and health outcomes are not tracked longitudinally over time.

Problem Description

Although commonly referred to as ‘mild’ traumatic brain injuries, concussions can produce long-term reductions in quality of life for individuals sustaining head trauma. One of the most glaring gaps in the current understanding of concussions is an inability to determine whether a person will recover quickly from a concussion (i.e. 7 to 10 days) or will have prolonged symptoms (lasting more than 28 days). My research aims to provide clarity to this gap by evaluating a retrospective sample of patients being clinically cared for after a concussion, exploring factors that influence a person’s length of care after a concussion.

Preliminary work

Prior to adding to the knowledge base around concussion injuries and treatment, a more thorough personal understanding of brain injury was needed. For my first project, I focused on a thorough literature review detailing both the functional changes in neurological functioning after brain injury and how clinicians generally assess and classify brain injured patients (Appendix A). Inherent differences exist both functionally and neurologically between primary and secondary brain injury. Specifically, primary injury is described as either focal or diffuse, often resulting from traumatic physical events (Yokobori & Bullock, 2013). The secondary sequalae of a brain injury deals with the body’s physiological response to the trauma, often resulting in edema, ischemia, increased intracranial pressure, cerebral perfusion, cell death, inflammation, and abnormal metabolism mechanisms (Chesnut et al., 1993).

How an individual is assessed following brain injury is dependent on the continuum of injury severity and the clinical setting where the evaluation occurs. Brain injured patients are commonly assessed in emergency departments or inpatient acute units of most hospitals. Assessments like the Glasgow Coma Scale, Disability Rating Scale, and Rancho Los Amigos Scale provide clinicians with a determination of injury severity, and thus guide interventional approaches (Choi et al., 1998). Additionally, the Glasgow Outcome Scale gives prognostic outcomes that allow clinicians and caretakers to provide long term planning considerations.

One outcome of the review project was the lack of objective measurements available for clinicians to assess individuals with less severe, but impactful, head injuries. Traditionally, individuals with less severe head trauma, including concussion, were evaluated using the Glasgow Coma Scale, but the assessment lacked the discriminative psychometric properties to accurately identify individuals with injury (Dziemianowicz et al., 2012). In recent years, more thorough assessments were created for concussion assessment and include the Sports Concussion Assessment Tool (SCAT) and the Immediate Post-Concussion Assessment and Cognitive Test (ImPACT™). These assessments have good clinical utility (Collins et al., 2003; Iverson et al., 2006; Iverson, Lovell, & Collins, 2005; Lovell et al., 2004), but require additional training, equipment, and computers for accurate and repeatable assessment.

The lack of objective assessments available for concussion identification lead to a study evaluating how smartphone technology could be used to evaluate individuals experiencing concussion symptoms. We recruited 22 healthy, female American football players to participate in the study to determine the feasibility of using smartphone technology for immediate screening of concussion symptoms during sports activity. The participants individually completed a SCAT2 assessment, a paper and pen neurocognitive test created to identify individuals who might have altered cognitive abilities following concussion. Additionally, participants also completed a cognitive test via a smartphone application called ‘Concussion Manager’, which was later re-branded as *Sway* (Burghart, Craig, Radel, & Huisinga, 2017). We compared results from each assessment in a pairwise fashion, producing moderate to good agreement via a Bland-Altman analysis. We concluded that in sporting environments, the Concussion Manager application produced similar results seen to the SCAT2 assessment in healthy individuals, and thus, further research should consider alternative populations.

Focus of Dissertation

After completing these projects, one apparent theme was the lack of information regarding concussion reporting rates in young, female populations. In most studies involving athletes, nearly all participants were male, high school or college aged, and clarified the concussion reporting incidence and education in these populations. In chapter 2, we sought to further evaluate the behavior of high school female athletes in regards to reporting suspected concussions. Additionally, the rates of individuals reporting they had received education about concussions and symptoms was evaluated.

Another evident theme was the sparse availability of concussion-specific evaluations and assessments, specifically needed for identify if the person had sustained a concussion and objectively tracking recovery. Chapters 3, 4, and 5 assess the reliability and validity of both a concussion assessment via mobile device use, as well as medical neuroimaging techniques to track recovery of time. Chapters 3 and 4 document the reliability and validity of *Sway*™, a smart-device application for Apple iOS devices. Chapter 3 specifically assesses the balance component of the assessment, comparing results produced by the application with gold-standard, laboratory-based force plate assessments. Chapter 4 assesses the utility of the reaction time component of the assessment, comparing results produced by the application to validated, computerized assessments.

Diffusion tensor imaging (DTI) is an emerging MRI technique that maps how water molecules diffuse across fiber tract. DTI has been shown to effectively quantify and isolate specific fiber pathways that appear injured after severe and moderate brain injury (Lipton et al., 2008), although less severe forms of brain injury (i.e. concussions) have yet to be fully assessed. Chapter 5 documents a study evaluating individuals with persisting concussion symptoms past 28 days. Participants completed a battery of neurocognitive and symptom assessment measures and DTI scans at different time points. Recovery was then quantified and assessed longitudinally.

The last gap identified from the projects related to identifying individuals at risk for longer recoveries early in the course of care. Many health conditions have benefitted from early identification of individuals who are likely to encounter longer recoveries, as the early identification would allow for earlier restorative interventions. An applicable example would be moderate-to-severe TBI patients (Perel, Edwards, Wentz, & Roberts, 2006). The researchers developed a predictive model placing emphasis on Glasgow Coma Scale (GCS) results at the time of evaluation, neuroimaging results, and pupil reactivity to light as the best predictors of outcome in the study population. Using these results, clinicians could better treat individuals after injury, interact with fellow clinicians, and educate caregivers throughout the course of recovery. These variables lose their predictive power when applied to individuals after a concussion, as most individuals following a concussion present with normal neuroimaging results, GCS results near the assessment's ceiling, and normal pupillary response (Carroll et al., 2004; Lingsma, Yue, Maas, Steyerberg, & Manley, 2015). A specific model developed for a concussion population is needed to better identify individuals at risk for a long recovery.

The remaining chapters are the primary focus of my dissertation and are devoted to this need, using retrospective electronic medical records information and open source social determinants of health (SDH) data. Chapter 6 details and clarifies patterns of variables that are influential of longer care durations for individuals presenting to sports medicine clinics following concussion. Two groups of patients were evaluated: Individuals with a typical duration of care after concussion lasting less than or equal to 28 days, and individuals with extended lengths of care lasting more than 28 days.

Chapter 7 describes a time-to-event analysis, identifying clinical, demographic, and social factors that are predictive of longer care after concussion. Building from the study in chapter 6, this analysis looked at the discriminative ability of each variable in determining differences in care durations. The relationship between length of care and each predictor was assessed via Kaplan Meier survival analysis, along with long-rank tests and Cox proportional hazards regressions to determine the statistical significance of each effect. Clinical, demographic, and social variables were assessed.

Last, chapter 8 describes and details early predictors of extended lengths of care for individuals seeking services from a sports medicine clinic after a concussion. A multivariable logistic regression analysis was completed, utilizing clinical assessment data, demographics information, and open-source SDH data, with the intention of identifying and quantifying the effects of each variable on prediction of care lasting more than 28 days. To aide the clinical interpretation of these findings, odds ratios were calculated for each variable. Additionally, the role of social determinants information was elaborated and explored upon.

Aims and Hypotheses.

The long-term goal of this research is to add to the knowledge related to predictors of slowed recovery after concussion, to ultimately develop an accurate predictive model for determining a person's risk for long care after concussion. The following research addresses the foundational components of this goal.

The first research aim addressed the question of whether individuals who are slow to recover from concussion present differently at their evaluation than individuals who recover in a typical timeframe. Should differences exist in the evaluation presentation between these two groups, rationale would exist for creating and evaluating a predictive model for length of care. I addressed this aim by using a retrospective cohort of individuals following a concussion. I hypothesize that individuals with typical recoveries would have different clinical presentation when compared to individuals with longer treatment duration. I tested this hypothesis with an exploratory factor analysis, evaluating factor structures between the two groups.

The second research aim of this project was to explore personal and clinical factors assessed at a concussion evaluation and determine which factors independently influence recovery following a concussion. I used a retrospective cohort of individuals cared for after a concussion through a concussion clinic. I hypothesized that specific factors, such as gender and concussion history, would be more informative of recovery and treatment duration. I tested this hypothesis using a survival analysis, with the primary modeling outcome being treatment time (measured in days).

The third and final aim of this project was to determine variables that can predict longer lengths of care following concussion, utilizing a logistic regression model. Additionally, SDH data were utilized and assessed, a novel component of my research. I hypothesized that concussion history, gender, socioeconomic status, access to housing and transportation, and age would be significant factors, increasing the odds of a person having a longer length of care.

Length of Care vs Length of Recovery.

Prior to addressing the proposed aims of these studies, clear outcomes of interest need to be defined. Originally, assessing a person's 'Length of Recovery' (LOR) following a concussion was proposed. Conceptually, a person would receive medical care from a provider when symptomatic after a concussion, and thus, 'recovery' would be assumed when a person discontinues medical care. Additionally, clinical documentation at the time of discharge should typically indicate a person has returned to a normal level of functioning.

These assumptions were tested and discovered to be false. After IRB approval, a manual chart review was conducted for every patient diagnosed with a concussion and text-based notations were electronically available for review. The purpose of this manual process was twofold:

1. Find documentation for each person's date of injury and assess whether there was an extended delay in receiving services by comparing the injury date to the clinical evaluation date.
2. Find documentation for each person's discharge from services.

Objective determination of recovery relied heavily on the outcome of these two tasks. Originally, recovery time for each person was going to be determined from the following formula:

$$\text{LOR (days)} = [\text{Date of Discharge}] - [\text{Date of Injury}]$$

LOR would represent the time (in days) from the date of injury to the date of discharge, thus representing the length of time a person was experiencing concussion symptoms and undergoing treatment for recovery.

One consideration I did not reflect on during the planning process was the discrete electronic capture of these events. While injury date is often clearly documented, along with how the injury occurred, the actual reason for discharge is not commonly known. Due to the outpatient nature of care for this type of injury, most clinical notes never included a formal 'Discharge' from services. There were seldom examples of notes containing any documented information regarding a person who 'returned to normal functioning' or 'does not need continued services'. Rather, individuals being cared for stopped coming for treatments. If a person is feeling better and back to normal, why would they return to the clinic for final approval?

One major assumption is the person being cared for has stopped returning to the clinic only because they have improved or are recovered. Alternative explanations for interruption of service could include financial constraints, lack of transportation, or seeking alternative providers or therapies. As there is no way to validate these data, as the dataset was purposely de-identified, 'LOR' as an outcome variable of interest was reconsidered, and 'Length of Care' was determined as the best outcome of interest. Length of care can be discretely captured from electronic medical record data, without the need for manual evaluation of clinical notes. Length of care from this point forward is defined as:

$$\text{Length of Care (days)} = [\text{Date of Discharge}] - [\text{Date of Evaluation}]$$

Chapter 2: Under-reporting of concussions and concussion-like symptoms in female high school athletes

This chapter has previously been published in whole without any adaptations since publication and is reprinted here with permission. McDonald, T., Burghart, M., & Nazir, N. (2016). Underreporting of Concussions and Concussion-like Symptoms in Female High School Athletes. *Journal of Trauma Nursing*, 23(5).

Abstract

Under-reporting of concussions and concussion-like symptoms in athletes continues to be a serious medical concern and research focus. Despite mounting worry, little evidence exists examining incidence of under-reporting and documenting characteristics of head injury in female athletes participating in high school sports. This study examined the self-reporting behaviors of female high school athletes. Seventy-seven athletes participated, representing 14 high school sports. Nearly half of the athletes (31 participants) reported a suspected concussion, with 10 of the 31 athletes refraining from reporting symptoms to training staffs after injury. Only 66% reported receiving concussion education. Concussion education appeared to have no relationship with diagnosed concussion rates in athletes, removing athletes from play, or follow up medical care after injury. In conclusion, female high school athletes under-report signs and symptoms of concussions. Concussion education should occur at higher rates among female athletes to influence reporting behaviors.

Introduction

Under-reporting of concussions by athletes occurs at an estimated rate of 50% to 75% of all injury incidence (McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004; Register-Mihalik et al., 2013) and continues to be a concern for clinicians and athletic training staffs (Kaut, Depompei, Kerr, & Congeni, 2003; McCrea et al., 2004; McCrory et al., 2013; Williamson & Goodman, 2006). Concussions may occur subtly during play, increasing difficulty for even trained observers to identify a potentially injured athlete and thus rely heavily on an athlete's self-report of symptoms. Subjective symptom reporting by injured athletes to coaches and trainers is a necessary component for injury identification and subsequent removal of the athlete from play (McCrory et al., 2013). Greater compliance in reporting of symptoms by players is necessary for limiting further neurological trauma. Furthermore, the need for improved injury reporting may be highest in young athletes, as these individuals may be more susceptible to injury (Buzzini & Guskiewicz, 2006; Patel & Greydanus, 2002; Patel, Shivdasani, & Baker, 2005) and may be at higher risk for a second concussion (Broshek et al., 2005; Dick, 2009; Marar, Mcilvain, Fields, & Comstock, 2012). An estimated 44 million children play at least one form of an organized recreational sport in the United States (Moreno, 2011), with up to 3.8 million sports-related pediatric concussions reported annually (Moreno, 2012). Despite growing numbers of recreationally-active youth, evaluating adolescent sports has received relatively little emphasis.

Adding to the need for research in younger populations is the possibility of sex differences in concussion rates and recovery between male and female athletes. Evidence suggests that females may sustain concussions at higher rates than their male counterparts in the same sport (Dick, 2009; Marar et al., 2012) and may possess a higher risk for recurrent concussions (Marar et al., 2012). Young female athletes are at a greater risk for a longer recovery period following injury and tend to require additional treatment outside the standard of care (Kostyun & Hafeez, 2015). Available research reports offer limited evidence addressing the reporting rates of female athletes sustaining concussive injuries and symptoms, with even fewer studies focused on younger populations. Register-Mihalik et al. (2013) investigated the influence of concussion knowledge and attitude towards reporting rates of both male and female high school athletes. The study found most concussions sustained by athletes were not reported and that concussion knowledge and attitudes both play a crucial role in the reporting behaviors of athletes. These results did not differentiate between male or female survey responses, negating an ability to determine female reporting propensity. Only 3 female sports (cheerleading, soccer, lacrosse) were included in the study, limiting generalizability to other high school sports often played by female student athletes.

Despite concerns related to under-reporting of concussions in young athletes, little evidence currently exists examining the intersection of reporting behaviors and the characteristics of female athletes who choose to participate in high school sports. Understanding behaviors that influence injury reporting is critical for increasing the rates of athletes reporting their injuries to training staffs and may provide the foundation for more effective educational approaches. The primary aim of this study was to explore the prevalence of under-reporting concussions and concussion-like symptoms among different sports played by female high school athletes and potential factors influencing their reporting behavior.

Methods

Participants

A convenience sample of 77 female athletes was recruited from 3 large suburban high schools located in large metropolitan areas during the 2011-2013 academic years (3 years total; Table 1). Inclusion criteria required female student-athletes in 9^{th}-12^{th} grade to participate in at least one school-organized sport at the varsity, junior varsity, or freshmen level. All parent/guardians provided informed consent and the participants (all were younger than 18 years old) provided their assent before completing the survey. The total number of surveys distributed was not collected, and thus, participation rate could not be determined.

Procedures

Approval from the university's institutional review board and from each school was obtained before initiation of the study. Study enrollment was completed by school athletic trainers during preseason training for all female sports. A cross-sectional, self-report survey was developed for this study with the aim of identifying the incidence of head injuries and concussion symptoms in sport. The survey was adapted from the symptom-based concussion survey used with collegiate athletes (LaBotz, 2005).

The survey inquired about each athlete's previous injury history and sports participation. Briefly, the survey recorded basic demographic information, history of diagnosed or suspected concussions, presence and duration of concussion-like symptoms following a hit to the head, the sports played by the athlete, whether the athlete received concussion education at school, coach response to a suspected injury, and previous reporting behavior. Face validity of the instrument was established informally from academic and clinical concussion experts, along with content testing among female high school athletes. Participants were instructed to complete the survey only once, regardless of whether they played multiple sports during the academic year. Surveys were completed anonymously, thus eliminating the ability for researchers to verify that each participant completed the survey only once.

Statistical Analysis

General descriptive statistics characterized survey responses. Associations among categorical variables were evaluated with chi-square tests or Fisher exact tests. Nonparametric Wilcoxon rank sums tests were used to assess differences in age across athletes reporting a diagnosed concussion and symptoms. The alpha level was set *a priori* at 0.05 for all tests. All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Table 1 summarizes sport participation characteristics among the student athletes. The average age of participating athletes was 15.7 years (SD = 1.20), with 14 sports represented. Soccer (36.4%), softball (33.8%), basketball (19.5%), and volleyball (19.5%) received the highest participation totals. Twenty-three athletes (29.9%) reported a previously diagnosed concussion, while 8 athletes (10.3%) reported a suspected concussion that was not medically diagnosed, leading to a total of 31 athletes reporting a potential concussion. Two participants reported multiple diagnosed concussions and brought the total number of potential concussions to 33. Two athletes (cheerleading, motocross) were the only participants to report multiple concussions while taking part in a single sport. The sports producing the highest number of potential concussions, which included both diagnosed and suspected concussions, were basketball (53.3% of basketball respondents) and soccer (42.9% of soccer respondents). Although motocross is not a school-sponsored activity, participants were allowed to include other physical activities where head injury might have taken place. Seven potential concussions reported by athletes occurred outside of sports, and one athlete did not specify which sport she was playing when the injury occurred. These injuries were excluded from analysis. Symptoms reported by subjects after injury and duration of symptoms are reported in Table 2.

Among athletes who reported experiencing symptoms after contact (n=58), 10 indicated that they never informed a parent, guardian, or coach of their symptoms. These athletes stated they chose not to report symptoms for multiple reasons, including the athlete's perception of the 'injury was not a big deal' (n = 5), athlete wanted to keep playing (n = 3), and symptoms 'wouldn't last long' (n = 2). Of the athletes who did report symptoms to the training staff (n = 48), 34 were removed from play and 20 were referred to a physician for medical evaluation. A majority (51 of 77; 66.2%) of respondents reported they had received concussion education at their school.

Separate chi-square tests of independence revealed no statistical significance in the relation of concussion education with the number of diagnosed concussions (χ^2(1, N = 77) = 0.58, p = 0.45), with removal from play after reporting symptoms (χ^2(2, N = 77) = 0.68, p = 0.71), or with follow-up medical care after a suspected concussion (χ^2(2, N = 77) = 0.62, p = 0.73).

The average age of athletes reporting a concussion was compared to that of athletes not reporting injury to determine if a difference in age might contribute to reporting behavior. Wilcoxon rank sums tests indicated a significant difference for the average age of athletes reporting a concussion diagnosis (Z = 2.35, p = 0.02), with older athletes reporting more diagnosed concussions. No significant differences were found between the ages of athletes reporting or not reporting a suspected concussion ($Z = 1.85$, $p = 0.06$), or the average age and if symptoms were reported following injury ($Z = 1.68$, $p = 0.09$).

Discussion

Nearly half of the participating female athletes reported either a diagnosed or suspected concussion during their school sports activities. The high reporting rate may be explained as arising from reported concussion diagnoses being combined with undiagnosed concussive injuries perceived by athletes. Combining these two variables was done to evaluate what might be the ‘potential’ concussion rate in the study population, although the perceived concussions may have been symptomatic events without neurological involvement. It is impossible to state retrospectively whether some of the suspected concussions reported actually were diagnosable as concussions, although all of the symptoms reported by athletes are the same as those used for concussion diagnosis (McCrory et al., 2013).

Some athletes (17%) reported experiencing symptoms of a concussion but did not report these symptoms to their coaches or training staff, a rate lower than previously reported in male athletes.[13] Athlete responses, such as “I wanted to keep playing,” coincide with reports by a previous study identifying barriers to concussion symptom reporting in male and female high school athletes (Chrisman, Quitiquit, & Rivara, 2013). However, athletes in the present study stated other reasons for not reporting that have not been noted previously. Several said they didn’t think their symptoms or the injury were serious, or that their symptoms wouldn’t last long. These responses indicate a limited understanding of the risks associated with concussion injuries. This level of knowledge may be related to our finding that only 66% of the student athletes reported receiving prior concussion education as part of their school curriculum or athletic program. Current state legislation does not require schools to provide concussion education to athletes. However, prior to sports participation, guardians and athletes are required to sign a Concussion and Head Injury Information Release Form, which explains the risks associated with possible concussions, symptoms experienced after injury, and return to play guidelines after injury.

Concussion frequency across female sports coincided with previously reported studies (Marar et al., 2012; Meehan et al., 2011). Soccer and basketball players appear to sustain sports concussions most frequently in our sample population, while basketball produced the highest rate of diagnosed concussions in our population. We note older athletes in our study reported concussion diagnoses in higher numbers, possibly due to a longer history of risk exposure playing contact sports. Similar comparisons have been made between collegiate and high school athletes (Field, Collins, Lovell, & Maroon, 2003). Another explanation may be older athletes have more opportunities to experience concussion education than did our study participants (Bramley, Patrick, Lehman, & Silvis, 2012).

No relation was apparent between students receiving concussion education and the number of diagnosed concussions, frequency of symptom reporting to coaches, trainers, or guardians, instances of athletes being removed from play after reporting symptoms, or to seeking subsequent medical evaluation following potential injurious contact. Independence among these factors suggests a need to enhance effectiveness of current concussion educational practices directed toward adolescents. The purpose of educating young athletes about concussions is multifaceted: to increase knowledge about the injury as a means to understand the potential seriousness of the condition and the challenges for recovery (Register-Mihalik et al., 2013), to encourage reporting of symptoms after injury to avoid the potential for subsequent neurological trauma (McCrory et al., 2013), and to reduce the burden of concussion history as young athletes age if they continue to play sports and risk successive injuries (Covassin, Elbin, Kontos, & Larson, 2010). If current concussion education efforts were effective, we'd expect to see a stronger relation of awareness from education and student reporting behaviors. Although not a focus in this study, the lack of clear relation of education and removal of symptomatic athletes from play also suggests a lack of knowledge on the part of coaches and training staffs about the risks of continued play after injury. Other social and societal factors certainly play a role in the decision process, and have been explored by other studies (Kirschen, 2014; Tomei, Doe, Prestigiacomo, & Gandhi, 2012).

The surveys were completed voluntarily and anonymously, and findings are limited by the reporting honesty and accuracy of the participants' retrospective responses. Similarly, a convenience sample recruited from local high schools and a small sample size limits external validity and generalizability of these results. A related element important for interpretation is a low number of participants in some sports, which may not reflect participation or reporting behaviors by the general population. The overall participation rate of all athletes could not be calculated because the total number of surveys distributed by the school athletic trainers could not be determined, thus selection bias may be possible, as athletes with a concussion history could be more invested in participating. Providing a clear definition of a "concussion" and the associated symptoms at the onset of recruiting may be especially important when interpreting the rate of individuals reporting a suspected concussion. In hindsight, we realized no description of what a concussion injury entails was provided as part of this study in the instructions to participants. The latter factor, however, reinforces our belief that there exists a critical need for more effective concussion awareness education for all people associated with youth sports, including coaches, training staffs, parents, administrators, teachers, and the athletes themselves.

Conclusions

Under-reporting of concussions and concussion-like symptoms is common in female high school sports, although this may be attributable to low reporting rates resulting from less effective concussion education programs. Creating uniform, evidence-based educational practices across youth sports programs, regardless of sex, may lead to improved concussion reporting and ultimately fewer secondary complications.

Table 1: Sport participation and potential concussions

Sport	No. of responders	Potential concussions	Potential concussions
Soccer	28 (36.4)	12	42.9
Softball	26 (33.8)	3	11.5
Basketball	15 (19.5)	8	53.3
Volleyball	15 (19.5)	1	6.7
Track	11 (14.3)	0	0.0
Cross Country	11 (14.3)	0	0.0
Dance	3 (3.9)	1	33.3
Cheerleading	3 (3.9)	4	*100
Equestrian	2 (2.6)	0	0.0
Swimming	1 (1.3)	0	0.0
Gymnastics	1 (1.3)	0	0.0
Tennis	1 (1.3)	0	0.0
Bowling	1 (1.3)	0	0.0
Motocross	1 (1.3)	2	*100

Note: Some participants competed in multiple sports during the academic calendar; thus, there are 119 responses for 77 participants. Potential concussions include both diagnosed and suspected concussions reported on the survey. 7 athletes reported concussions outside of school-sponsored sports and were excluded. One athlete reported a diagnosed concussion without identifying sport in which the injury occurred. *Indicates multiple concussions during participation.

Table 2: Athlete responses to selected concussion survey questions

Concussion Survey Question	Responses (% of total)
Symptoms reported after contact	
Headache	51 (66.2)
Dizziness	32 (41.6)
Sensitivity to light	20 (26.0)
Sensitivity to noise	15 (19.5)
Blurred vision	13 (16.9)
Nausea	10 (13.0)
Balance problems	10 (13.0)
Memory changes	10 (13.0)
Confusion	6 (7.8)
Loss of consciousness	2 (2.6)
Duration of symptoms	
Less than 30 minutes	18 (32.1)
Less than a day	19 (33.9)
Less than a week	14 (25.0)
Less than a month	4 (7.1)
Greater than a month	1 (1.8)
Reported symptoms to coach/guardian	*51/61 (83.6)
Received concussion education	51 (66.2)

* Not all athletes reported symptoms. Only frequencies from reporting athletes were calculated.

Chapter 3: Reliability and validity of a mobile device application for use in sports-related concussion balance assessment

This chapter has previously been published in whole without any adaptations since publication and is reprinted here with permission. Burghart, M., Craig, J., Radel, J., & Huisinga, J. (2017). Reliability and validity of a mobile device application for use in sports-related concussion balance assessment. *Current Research: Concussion,* 4(1), e1-e6.

Abstract

Balance assessment is necessary when evaluating athletes after a concussion. We investigated a mobile device application (app) for providing valid, reliable, and objective measures of static balance. We hypothesized the mobile device app would demonstrate similar test-retest reliability to force platform COP sway variables, and that SWAY scores and force platform COP sway variables would demonstrate good correlation coefficients. Twenty-six healthy adults performed balance stances on a force platform while holding a mobile device equipped with SWAY (Sway Medical, LLC) to measure postural sway based on acceleration changes detected by the mobile device's accelerometer. Participants completed 4 series of three 10-second stances (feet together, tandem, and single leg), twice with eyes open, twice with eyes closed. Test-retest reliability was assessed using intraclass correlation coefficients (ICC). Concurrent validity of SWAY scores and center of pressure sway variables were determined with Pearson correlation coefficients. Reliability of SWAY scores was comparable to force platform results for the same test condition (ICC = 0.21 to 0.57). Validity showed moderate associations between SWAY scores and center of pressure sway variables during tandem stance (r = -0.430 to -0.493). Lower SWAY scores, indicating instability, were associated with greater center of pressure sway. The SWAY app is a valid and reliable tool when measuring balance of healthy individuals in tandem stance. Further study of clinical populations is needed prior to assessment use.

Introduction

Concussions continue to be a primary concern for sports medicine clinicians. Sport-related concussions are a major contributor to the number of traumatic brain injuries, accounting for an estimated 1.6 to 3.8 million injuries each year in the United States alone (Langlois, Rutland-Brown, & Wald, 2006). Due to a complicated underlying pathophysiological process, concussions are subtle and produce a wide array of signs, including cognitive, somatic, and sensorimotor symptoms (Harmon et al., 2013a). The diverse symptomatology makes clinical assessment and management of concussions challenging for sports medicine clinicians.

Consensus statements regarding the evaluation and care of individuals after a suspected concussion repeatedly emphasize the importance of balance assessment during a multicomponent evaluation (Harmon et al., 2013a; McCrory et al., 2017). Balance assessments allow clinicians to determine a person's ability to integrate somatosensory, visual, and vestibular information in order to maintain an upright posture. Failure of a person to maintain balance following a concussion may be indicative of sensorimotor alterations (Guskiewicz, 2011). Balance assessment also provides information for estimating prognosis, allowing clinicians to predict the extent of expected recovery (Yang et al., 2009).

The most common method for assessing balance in potentially concussed athletes is the Balance Error Scoring System (BESS) (Harmon et al., 2013a). The BESS is a free assessment, requires little to no special equipment, and can be done on the sidelines of sporting events. The BESS relies on thoroughly trained observers to determine the number of balance errors a person made during static standing trials (Guskiewicz, 2011). Balance errors determined by the trained observers include stepping out of place, removing one's hands from hips, etc. Although this approach is cost-effective and portable, the assessment has mixed evidence supporting its use

(Bell, Guskiewicz, Clark, & Padua, 2011; Mulligan, Boland, & Mcilhenny, 2013). Specifically, studies have questioned the sensitivity of the BESS (Giza et al., 2013), as well as the intra- and inter-rater reliability of the assessment (Hunt, Ferrara, & Bornstein, 2009). The BESS has only been found useful within the initial 48 hours following injury (McCrea, Guskiewicz, Marshall, Barr, Randolph, Cantu, Onate, Yang, et al., 2003), making long-term tracking of balance recovery difficult when using only the BESS.

The gold standard method for assessing balance in healthy and injured people is to measure changes in body sway during static stances while standing on a force platform (Guskiewicz, Perrin, & Gansneder, 1996). Force platforms are sensitive, reliable, and objective tools to measure balance (Visser, Carpenter, Kooij, & Bloem, 2008). Center of pressure (COP) sway variables are calculated from measured ground reaction forces acquired during standing balance. The COP sway variables give information regarding an individual's ability to control their center of mass and maintain stable balance and are used widely to assess balance in healthy and pathological populations (Gray, Ivanova, & Garland, 2014; Lafond & Prince, 2004). Although force platform technology provides this precise method for assessing balance, the platforms are costly and require proper installation, maintenance, and skilled interpretation of the collected data. The platforms also have limited portability, making assessment difficult outside of clinics or laboratories. Due to these constraints, force platform balance assessment is often not possible in many clinical and athletic settings. Accelerometers have been evaluated as potential alternatives to force platform measurement, as body-worn accelerometers provide a relatively more affordable and portable method for assessing postural control (Moe-Nilssen & Helbostad, 2002; Whitney et al., 2011). Accelerometer technology is promising and is available in most mobile devices, making accelerometer-based balance assessment available to clinicians without the need for extra equipment.

Mobile devices may serve as alternatives for use in objective balance assessment when force platforms and accelerometer systems are not feasible because many mobile devices contain tri-axial accelerometers accessible to downloadable applications (apps) created for clinical use. SWAY (Sway Medical, Tulsa, OK) is one such app developed for concussion balance assessment. SWAY works with iOS products (Apple Inc.) and uses the acceleration time series collected during static stances to quantify balance. Previous research evaluated the mechanical accuracy of SWAY results of healthy adults recorded during single leg stance compared to force platform measurement (Patterson, Amick, Thummar, & Rogers, 2014). However, no other stances typically used in clinical settings for assessing individuals with a suspected concussion (i.e. Two-Foot stance, Tandem stance) have not been studied. In addition, the clinical validity and reliability of the SWAY app have not been evaluated, which is essential prior to wide-spread adoption of this technology in sports medicine environments.

The purpose of this study was to evaluate the ability of SWAY, a mobile device app used to access the device's tri-axial accelerometer, to quantify balance in healthy individuals. The first aim of this study was to determine if accelerometry-based measures of balance produced by SWAY are as reliable as force platform obtained COP sway variables under the same testing conditions. The second aim of the study was to assess the validity of the accelerometry-based measures by determining the relation of accelerometry data collected by SWAY and force platform COP sway variables when collected concurrently. We hypothesized SWAY would demonstrate similar test-retest reliability to force platform COP sway variables, and that SWAY scores and force platform COP sway variables would demonstrate good correlation coefficients (Portney & Watkins, 2009).

Methods

Participants

Twenty-seven healthy volunteers participated in the study (12 men, 15 women; age 29.7 ± 10.9 years; height 170.1 ± 10.5 cm; weight 72.1 ± 16.6 kg). Individuals were excluded if they reported a known orthopedic, musculoskeletal, or neurologic injury in the prior 6 months. One subject was unable to complete all balance stances independently and was excluded, bringing the total to 26 participants. All participants reported they had not consumed substances or medications prior to testing that could have affected their ability to maintain stability. All participants provided written informed consent prior to participation in accordance with requirements of the Institutional Review Board for this study.

Materials

SWAY was downloaded and installed on a single mobile device that was used throughout all testing (Apple iPod Touch 5th Gen, iOS Version 7.1, Apple Inc., Cupertino, CA). SWAY is an FDA-approved app for detecting changes in postural control using the integrated accelerometers of Apple iOS mobile devices. The app instructs users through a series of balance stances, replicating the stances used in the BESS (Bell et al., 2011). The SWAY app collects data at 10 Hz during each 10-second test period. SWAY provides a score at the end of each trial, calculated from total jerk units produced during each 10 second testing period, compiled across three planes of movement, and normalized to a 0–100 scale (Fig. 1). An AMTI force platform embedded in the floor was used to simultaneously record ground reaction forces at 100 Hz (AMTI 1000, Advanced Mechanical Technology Inc., Watertown, MA). Force platform COP sway variables were calculated by a custom MATLAB program (MATLAB, The MathWorks, Inc., Natick, Massachusetts, USA; Prieto, Myklebust, Hoffmann, Lovett, & Myklebust, 1996).

Procedures

Demographic information was collected prior to balance testing. Participants then performed a series of static balance stances while standing on the force platform and holding the mobile device in an upright position against their chest (Fig. 1). Participants remained in each balance stance for 10 seconds and were instructed to maintain a steady balance to the best of their ability. Each test sequence included three stances: Feet Together, Tandem with the dominant foot forward, and a Single-Leg standing on the dominant foot (Fig 1). Participants repeated this stance sequence four times: twice with eyes open and then twice with eyes closed. All four tests of Single-Leg stance were, however, completed with eyes open due to frequent postural corrections causing participants to step off the force platform and thus invalidate data collection during the development of the test protocol. At the end of each stance sequence, participants rested in a chair for one minute before the next stance sequence was initiated. Testing sessions lasted approximately 15 minutes, including rest breaks.

Data Processing

A custom Matlab program was created to calculate force platform COP sway variables from the COP time series, including sway area (total area enclosed by the outermost edge of the COP path), root mean square (RMS) distance (RMS of the distance from the mean COP), and mean velocity (the average velocity of the COP; Prieto et al., 1996). All force platform data were resampled to 20 Hz and truncated to include only the middle 7 seconds of data to control for any imprecision in simultaneous initiation of data collection between the mobile device and the force platform.

The SWAY application uses a proprietary algorithm to calculate a SWAY score ranging from 0 to 100, with higher scores indicating better balance control. Mechanical validity of the tri-axial accelerometers housed in the mobile devices has been described previously (Amick, Patterson, & Jorgensen, 2013; Khoo et al., 2014). SWAY scores were calculated for each of the 12 balance trials and were used in the analysis. A quality check of these data included omitting force platform and corresponding SWAY data where the subject failed to complete the trial for a balance condition successfully. These included trials where participants stepped off the force platform, hopped to recover loss of balance, or instances of a toe-touch by the non-supporting foot during Singe-Leg stance.

Statistical Analysis

Statistical comparisons were performed using SPSS (Version 20, SPSS Inc., Chicago, IL, USA). Test-retest reliability was assessed using an intraclass correlation coefficient (ICC 3,1) calculation and the *p*-value and 95% confidence intervals for each ICC determined. A Pearson product-moment correlation was used to assess the concurrent validity between SWAY and COP variables. The *p*-value and *r*-value for each comparison were determined. An alpha level of 0.05 was set *a priori.*

Results

SWAY and force platform results are listed in Table 3. Participants produced the largest amount of postural sway during the Tandem stance/eyes closed condition as measured by both SWAY scores and COP sway variables. SWAY identified Feet Together stance/eyes closed as the condition producing the least amount of postural sway in the participants, while COP sway area was lowest during Feet Together/eyes open stance.

Reliability

Test-retest reliability of SWAY and force platform COP sway variables are presented in Table 4. Generally, SWAY produced similar ICC values to those of sway area, RMS distance, and mean velocity. The ICC value produced by the SWAY scores for Tandem stance/eyes open (ICC = 0.206) was relatively low in comparison to COP sway area, RMS, and mean velocity for the same test condition (ICC = 0.595 to 0.654). SWAY scores for Feet Together/eyes open, Tandem stance/eyes closed, and Single-Leg stance/eyes open produced higher ICC values than all COP variables in each stance condition.

Validity

Table 5 summarizes the Pearson product-moment correlations between SWAY and the force platform COP variables. The sway area, RMS, and mean velocity showed significant correlations with the SWAY scores during Tandem stance/eyes open (r = -0.430 to -0.493). SWAY scores were also significantly correlated with mean velocity during single leg stance/eyes open (r = -0.486). No significant correlations were found between SWAY scores and force platform COP variables during the feet together stance, regardless of visual condition.

Discussion

The present study sought to evaluate the reliability and validity of SWAY, a software app for iOS mobile devices that uses the device's built-in accelerometer to quantify balance control. We hypothesized SWAY would demonstrate similar test-retest reliability to force platform COP sway variables. This hypothesis was supported, although ICC values remained relatively low for both methods. We also hypothesized that SWAY and COP sway variables would demonstrate good correlation coefficients across all stance conditions. This hypothesis was partially supported. Correlation coefficients between SWAY scores during Tandem stance/eyes open and Single-Leg stance/eyes open showed a significant correlation with force platform COP variables. The SWAY scores from other combinations of stance and visual conditions did not display a significant association with coinciding COP variables.

Comparisons between SWAY scores and the COP variables produced similar ICC values, indicating that the two methods produced comparable test-retest reliability results. A surprising outcome was the relatively low ICC values produced by SWAY scores and the COP variables. This may indicate repeated measures taken in quick succession can lead to measurement inaccuracies. The low values for both methods also may be attributable to low variability between recruited participants. The study population consisted entirely of healthy individuals who were well within their capacity for balance during the tests. The standard deviations for each stance condition were relatively narrow, indicating low variability between participants and thus limited the magnitude of ICC calculations (Weir, 2005). This also may explain why the test-retest ICC values for the force platform COP variables were much lower than previously reported in similar populations (Mehkati, Namazizadeh, Salavati, & Mazaheri, 2011). Our finding, however, that SWAY is comparable in reliability to the gold standard force platform

COP variables illustrates that SWAY could be useful in objective monitoring of changes in a person's static balance over time following a concussion. This often is necessary for use in clinical settings when repeated assessments are conducted to monitor improvements or regressions in balance control over time.

The current study also documented significant correlations between SWAY scores and force platform COP variables used to characterize balance, although the correlations produced only moderate associations (Portney & Watkins, 2009). The lack of strong associations for the remaining stances and conditions may be due to the devices measuring different aspects of balance (Moe-Nilssen & Helbostad, 2002). The mobile device was held by each subject at the chest, capturing accelerations relatively close to each participant's approximate center of mass (COM). By contrast, COP sway variables are approximations of the COM sway based on ground reaction force measurements captured at the floor. Measuring balance control near the COM may be more representative of postural control ability and responses to fluctuations in body sway. Conversely, displacement of COP measured by force platforms represent neuromuscular responses necessary to control torque at the ankle (Winter, 1995), rather than only COP sway path (Heebner, Akins, Lephart, & Sell, 2015). Measurement of balance at the approximate COM allows clinicians and researchers to directly investigate the influence of sensory systems on postural sway without the compounding influence of the neuromuscular response necessary to activate ankle musculature.

The significance of association between SWAY and COP variables during Tandem stance is an important finding for clinicians assessing individuals after a suspected concussion. Evaluations incorporating narrow stances increase the sensitivity and specificity of clinical balance assessments (Lehmann, 1990), allowing for accurate measurement of postural sway changes over time. This may be helpful to clinicians that are interested in tracking the recovery of balance over time. While Tandem stance was the only valid stance in this study of healthy individuals, populations with balance deficits may produce more variability with other stances. Future research should evaluate individuals with balance instability as they complete the SWAY assessment protocol.

Recently, several methods have been proposed to improve the reliability and validity of the BESS protocol, including using Wii Balance Boards (Chang, Levy, Seay, & Goble, 2014), portable force platform systems (Alsalaheen, Haines, Yorke, Stockdale, & Broglio, 2015), and accelerometers (King et al., 2014). While most of these methods improve the reliability and validity of the BESS, these approaches add costly equipment to the free assessment, add data processing time for interpretation of results, and limit the portability of the assessment. The SWAY app may be a worthwhile alternative to consider without the need for additional equipment or a dedicated space for administration. Future research should evaluate alternative methods for SWAY administration that may eliminate variability between tests, such as strapping the mobile device to eliminate any accelerations detected from unintended hand movements.

To our knowledge, this is the first study evaluating the reliability and validity of a mobile device application intended for use as an assessment of balance in athletes with a suspected concussion. SWAY is an innovative application allowing sports medicine clinicians the ability to assess balance objectively, quickly, and efficiently. Perhaps equally important, the SWAY app eliminates a need for specialized and costly equipment, as well as the extensive post-processing of data necessary with force platforms and other accelerometers. As Mancini and Horak state, "clinical practice needs automatic algorithms for quantifying balance control during tasks, normative values, composite scores, and user-friendly interfaces so tests can be accomplished quickly…" (Mancini & Horak, 2010). SWAY has the potential to address these needs without the necessity of specialized equipment. Ultimately, balance assessment is just one tool available to clinicians assessing injured athletes. Pairing balance assessment with other multidimensional tools is necessary when evaluating athletes with a suspected concussion.

Although the results of the present study are promising, our study had limitations addressable by future research. First, the study population was comprised of healthy individuals without injuries that could impact balance. While appropriate for a study focused on determining reliability and validity of the technology, this limits generalizability of results intended for diagnostic purposes. Second, reliability of measures collected sequentially over several days may be more representative of how SWAY would be used in clinical settings, but was not feasible with the design of the current study. Finally, participants were required to hold the device to their sternum. In addition to increasing the challenge to maintain balance while assuming an uncommon stance, any extraneous hand movements may have produced unintended accelerations. Using a harness to hold the mobile device against the person's trunk was not done in this study, as our intent was to conduct testing with SWAY exactly according to the app's instructions for use. Future research should investigate the clinical utility of the app in athletic populations, as well as determine the diagnostic utility of the app when compared to clinical and sideline balance measures, such as the BESS.

Conclusions

SWAY, a software application for iOS mobile devices, demonstrated both reliability and validity while testing healthy individuals across static stances. Based on our findings, SWAY scores during Tandem stance/eyes open produced the strongest association when compared to force platform COP variables. Although some correlations were low between SWAY and force platform measures of balance, SWAY demonstrated a similar pattern in reliability testing observed with COP variables. Despite being a promising tool for clinical evaluation of balance ability after a concussion, further research must investigate the use of SWAY as a measure of balance in athletic populations prior to widespread implementation and use.

Acknowledgments

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Table 3: Averaged trial results of SWAY scores and COP measures across stances and conditions

	Mean (SD)			
Stance, Condition	SWAY	Area	RMS	Velocity
Feet together, EO	99.18 (1.31)	25.33 (14.84)	6.14 (1.98)	13.75 (3.00)
Feet together, EC	99.34 (0.91)	40.03 (24.28)	6.83 (2.26)	18.84 (5.89)
Tandem stance, EO	98.76 (1.60)	52.22 (32.44)	6.72 (2.64)	27.35 (7.45)
Tandem stance, EC	96.01 (3.32)	133.18 (69.83)	9.80 (2.87)	50.14 (15.13)
Single leg stance, EO	97.13 (2.70)	108.59 (54.49)	8.74 (2.28)	39.87 (9.01)

Note: Intraclass correlation coefficient (ICC), 95% confidence interval (CI), SWAY = SWAY score, RMS = root mean square, EO = eyes open, EC = eyes closed. Units for COP variables: mm^2 (Area); mm (RMS); mm/s (Velocity). SWAY score is an arbitrary unit.

Table 4: Test-retest reliability coefficients of SWAY and COP sway variables.

	ICC Values (95% CI)			
Stance, Condition	SWAY	Area	RMS	Velocity
Feet together, EO	*0.41 (0.03-0.69)	027 (-0.13-0.60)	0.187 (-0.21-0.54)	*0.35 (-0.05-0.65)
Feet together, EC	*0.45 (0.08-0.71)	**0.78 (0.56-0.90)	**0.63 (0.31-0.82)	**0.79 (0.57-0.90)
Tandem stance, EO	0.21 (-0.20-0.55)	**0.63 (0.32-0.82)	**0.65 (0.36-0.83)	**0.60 (0.27-0.80)
Tandem stance, EC	*0.57 (-0.18-0.80)	*0.41 (-0.06-0.73)	*0.51 (0.10-0.77)	*0.41 (-0.03-0.71)
Single leg stance, EO	*0.36 (-0.06-0.67)	0.243 (-0.19-0.60)	0.08 (-0.35-0.48)	0.31 (-0.12-0.64)

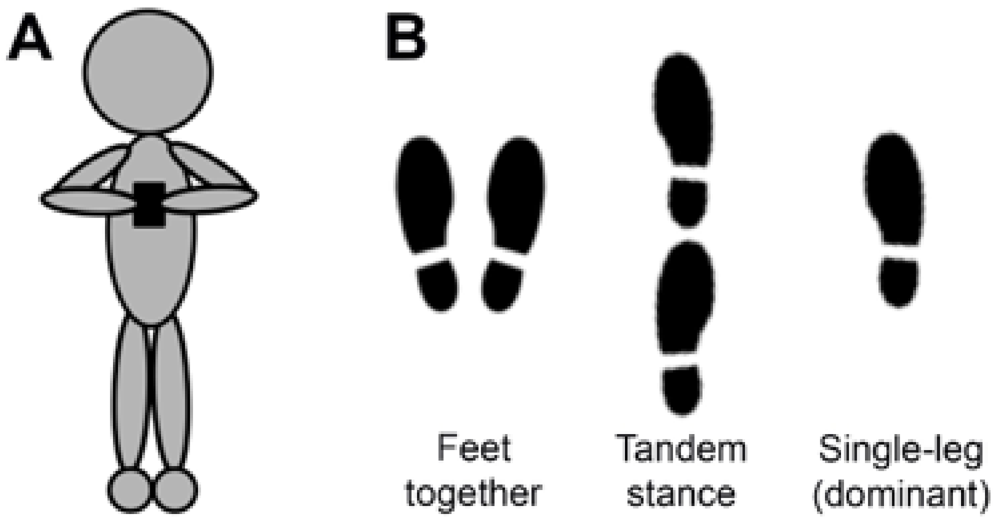
Note: * ICC values were significant at (p <0.05), ** ICC values were significant at (p <0.001), Intraclass correlation coefficient (ICC), 95% confidence interval (CI), SWAY = SWAY score, RMS = root mean square, EO = eyes open, EC = eyes closed.

Table 5: Correlation of SWAY scores with COP sway variables across test conditions

Stance, Condition	Area	RMS	Velocity
Feet together, EO	-0.342-	-0.361	-0.245
Feet together, EC	-0.218	-0.200	-0.181
Tandem, EO	-0.433*	-0.493*	-0.430*
Tandem, EC	*-0.319	-0.394	-0.353
Single leg stance, EO	-0.417	-0.420	-0.486*

Note: * *p*-Values were significant at (p <0.05), RMS = root mean square, EO = eyes open, EC = eyes closed.

Figure 1: Balance stances



A: Scheme depicting subject holding mobile device during test sequence; B: Stances used during test sequence.

Chapter 4: Reliability and validity of a motion-based reaction time assessment using a mobile device

This chapter has previously been published in whole without any adaptations since publication and is reprinted here with permission. Burghart, M., Craig, J., Radel, J., & Huisinga, J. (2018). Reliability and validity of a motion-based reaction time assessment using a mobile device. *Applied Neuropsychology: Adult*, 1-6. doi: 10.1080/23279095.2018.1469491.

Introduction

Concussions are difficult injuries for healthcare providers to identify and manage. The challenges in managing individuals following a concussion are in part due to the highly variable symptoms following injury and the lack of objective biomarkers that indicate progression of recovery (Echemendia, Giza, & Kutcher, 2015). Clinical teams are left to determine when an athlete is safe to return to sport even without baseline neurocognitive and functional assessments to measure recovery. The American Medical Society for Sports Medicine recommends all concussion symptoms should be resolved before returning athletes to sport using a step-wise increase in exercise and sports-specific activities (Harmon et al., 2013b). Without objective tests evaluating an athlete’s current functioning to pre-injury status, sports medicine clinicians must rely on subjective symptom assessment, which may lead to underestimating full recovery (Makdissi et al., 2010). However, prematurely returning athletes back to play before full recovery poses serious risk for further brain injury (Wetjen, Pichelmann, & Atkinson, 2010).

Slowed information processing abilities are common after a concussion (Warden et al., 2001). Changes in a person’s ability to react quickly to external stimuli has important prognostic utility, as slow simple reaction times after concussion have been correlated with a longer time needed to recover of function (Norris, Carr, Herzig, Labrie, & Sams, 2013). Slowed reaction time can persist even after athletes report physical symptoms have resolved (Warden et al., 2001). Assessing reaction time may help prevent premature return to play recommendations and thus limit the potential for further neurological injury.

Many different clinical tests of reaction time exist, although most require computerized programs and specialized equipment. An exception was developed by Eckner et al. required no specialized equipment, being a measuring stick coated in high friction tape and embedded in a weighted rubber disk (Eckner, Kutcher, & Richardson, 2010). The device is released by the tester and caught as quickly as possible by the subject. Although equipment for this test is easily obtainable and affordable, the test itself has low between season test-retest reliability (Eckner, Kutcher, & Richardson, 2011) and poor validity (MacDonald et al., 2014).

Mobile devices may provide clinical teams with a readily accessible alternative for objective evaluation of reaction time. Many mobile devices now contain tri-axial accelerometers used by downloadable applications (apps) created for a variety of clinical uses. The Sway app (Sway Medical, Tulsa, OK) quantifies a person's ability to react by collecting acceleration data from device movement during motion-based movement tests. However, establishing the reliability and validity of mobile device apps for use in reaction time assessment is essential prior to more wide-spread adoption of this technology in clinical settings.

The purpose of this study was to evaluate the ability of Sway to measure accurate reaction times in healthy individuals using the mobile device's tri-axial accelerometer. The first aim of this study was to determine the reliability Sway reaction time tests across a series of repeated trials conducted during the same testing session. The second aim of the study was to assess validity of reaction time data collected by Sway relative to a computerized standard reaction time test. We hypothesized that Sway would demonstrate good test-retest reliability, and that Sway reaction times and computer-based reaction times would show strong correlation coefficients.

Methods

Participants

Twenty-seven healthy volunteers between the ages of 18 and 60 were recruited from a public university's medical center and participated in the study. Individuals reporting known orthopedic, musculoskeletal, or neurologic injury in the prior 6 months were excluded. All subjects reported they had not consumed substances or medications prior to testing that may affect reaction times during the study. All subjects provided written informed consent prior to participation in accordance with requirements for this study set forth by the Institutional Review Board.

Outcome Measures

The Sway app (version 2.1.1) was downloaded from the Apple App Store® and installed on the mobile devices used for simple reaction time (SRT) testing (Apple iPod Touch 5th Gen, iOS Version 7.1, Apple Inc., Cupertino, CA). Sway is an FDA-approved app for assessing balance using the integrated tri-axial accelerometers of mobile devices. The original balance-only version of the testing protocol was modified to include a simple reaction time protocol by having subjects tilt the device in response to a change in screen color. Sway records this movement by sampling the acceleration data at a frequency of 1000 Hz during each trial. Sway determines a latency response time at the end of each trial, which is the difference in time between the color change and the onset of user-initiated tilt of the mobile device. Each test block consisted of 5 trials, with randomized between-trial pauses to prevent the user anticipating when to respond to the stimulus. A mean Latency Response Time was calculated across the 5 trials. Each subject performed four test blocks (4 x 5 trials).

The Computerized Test of Information Processing (CTIP, Version V.5 software kit, PsychCorp, Toronto, Ontario, Canada) was used for SRT method comparison. The CTIP software was installed on a desktop PC (Hewlett Packard Compaq 8200 Elite, Hewlett Packard Company, Palo Alto, CA). The CTIP software has been used to assess information processing abilities in individuals with brain injury (Tombaugh, Rees, Stormer, Harrison, & Smith, 2007) and multiple sclerosis (Reicker, Tombaugh, Walker, & Freedman, 2007; Tombaugh, Berrigan, Walker, & Freedman, 2010). The CTIP test has shown to be sensitive to the information processing changes taking place after brain injury and is used to clinically discriminate between uninjured and mild brain injury patients (Willison & Tombaugh, 2006). The software contains 3 different reaction time assessments: Simple reaction time, choice reaction time, and semantic reaction time (Tombaugh et al., 2007). The simple reaction time subtest of the CTIP was used for comparison to Sway SRT trials.

Procedures

Prior to SRT testing, demographic information was obtained. Participants were seated in a comfortable and upright position, while holding the mobile device with both hands. Participants read on-screen instructions to react to changes in the screen color by quickly shaking the device. Researchers verified each participant's understanding of on-screen instructions and visually demonstrated the appropriate shaking motion. Participants then performed SRT test blocks using Sway. Each participant completed 4 SRT test blocks while seated, with each test block including 5 separate trials. Twenty total trials for each participant were used to evaluate both test-retest reliability and learning/fatigue effects after repeated measures. Latent response times were recorded in milliseconds (ms). Participants rested for 2 minutes between each test.

After completing the 4 Sway tests, participants then completed the SRT subtest from the CTIP. Participants were seated comfortably in front of a computer screen and were instructed to react as quickly as possible to randomly-timed visual stimulus changes, represented by a large 'X' appearing on the computer monitor. Participants were instructed to react by clicking the spacebar on the computer's keyboard with their dominant hand's index finger. Participants were given 10 practice trials to familiarize themselves with the test procedure, per the CTIP SRT test protocol (Tombaugh et al., 2007). Following the practice trials, subjects completed total 30 trials. Latent response times were recorded in ms. Each complete session lasted between 10 and 15 minutes.

Statistical Analysis

Statistical analyses were performed using R, a statistical computing language (version 3.4.1). First, data was screened for any potential outliers resulting from technical errors. Sway reaction time results for each test block were averaged together for use in reliability testing, using an intraclass correlation coefficient (ICC) (3,k). Learning and fatigue effects from repeated Sway tests were evaluated using a one-way analysis of variance (ANOVA) to compare differences in mean reaction times across trials. SRT outcomes from each participant's Sway and CTIP tests were averaged separately for validity testing. Agreement of the two SRT measurement methods was assessed with Bland-Altman analysis and descriptions of the limits of agreement (Bland & Altman, 1986). Pearson product-moment correlations coefficients were calculated to assess criterion validity and the strength of association between Sway and CTIP reaction time test means. Lastly, a post hoc power analysis was conducted to report the achieved power of the Pearson product moment correlation test. Inferential statistics were tested at $p < 0.05$.

Results

Twenty-seven participants were included in the study. The 27 subjects (12 men, 15 women) ranged in age from 18 to 59 years, with a mean age of 30.96 years (SD = 12.07). The mean Sway reaction time from participants was 284.31 ms (range: 185.50 - 450.25 ms). The mean CTIP reaction time from participants was 328.01 ms (range: 242.40 - 452.50 ms).

Results from Sway SRT trials are presented in Table 6. The ICC comparisons demonstrated significant reliability during repeated measurements for Sway tests (ICC = 0.713, p <0.001, 95% CI = 0.56 – 0.84). A one-way ANOVA was conducted to determine whether there were statistically significant differences in Sway reaction times over the course of the 4 trials, assessing for learning and fatigue effects. Comparison of reaction times across trials did not yield statistically significant differences in reaction times (Figure 2; $F_{3,104}$ =1.35, p = 0.26).

Agreement between Sway and CTIP as a method for SRT measurement was assessed via Bland-Altman analysis. The mean difference between pairwise Sway and CTIP results was -43.7 ms, again indicating Sway results were faster in nature. The Bland-Altman limits of agreement, represented by the mean difference d ± 1.96 standard deviations (SD), were -140.8 ms to 53.4 ms. Bland-Altman results are presented in Figure 3.

Criterion validity was assessed by calculating Pearson correlation coefficients between mean Sway and CTIP reaction tests (Figure 4). Participants had an average response time of 284.31 ± 59.10 ms, while average response time on CTIP test were 328.01 ± 48.12 ms. The Sway app was positively correlated with the CTIP test [r (25) = 0.590, p = 0.001]. A post-hoc power analysis was conducted and returned an observed power of 0.96 (n = 27, α < 0.05, effect size = 0.59).

Discussion

Establishing reliability and validity of an assessment is vital to ensure clinical interpretation is appropriate and trusted. Our study evaluated Sway, a mobile device app, to measure reaction time in healthy individuals. Our first aim assessed the test re-test reliability of Sway reaction time tests repeated over time. While there is a noticeable decrease in mean response times after the first trial, we found no statistically significant differences between the trials. We attribute the difference in means to a possible learning effect, as the subsequent trials required less time overall. The current testing procedures described by Sway did not include a practice trial to allow the person to acclimate to the motion-based assessment, and thus, clinicians should consider multiple test trials to reach accurate SRT consensus.

The second aim of the study assessed criterion validity of motion-based SRT measurement by examining the relation of data collected by Sway and computerized reaction time tests. We found a moderate positive correlation between means produced from the Sway app and CTIP results. Eckner et al (2010) compared computerized reaction time assessment with a novel clinical reaction time test and found a significant correlation ($r = 0.445$, $p < 0.001$). Similarly, MacDonald et al (2014) assessed the same method in a younger population and found a weaker correlation ($r = 0.229$, $p < 0.001$). It should be noted that while the correlations were significant ($p < 0.05$), the statistic of interest for correlational analysis is the Pearson's product moment correlation coefficient (Mukaka, 2012). While the magnitude of the strength of association should always be considered with the context of data, the coefficients produced in the previous studies signify a fair relationship (Portney & Watkins, 2009). Our study produced a stronger association and can be classified as a moderate to good relationship.

Additionally, we sought to assess the agreement between the two SRT measurement methods via the popular Bland-Altman analysis. While these two methods appear to agree well, there are some notable differences. First, the mean difference between the two methods as -43.7 ms, which should be accounted for if these two methods need a direct comparison. For instance, adding 43.7 ms to an individual's Sway result could produce a reliable comparison to an expected CTIP in this sample. Second, all but one pairwise difference fell outside the limits of agreement, thus providing evidence for agreement between these two measurement methods. Lastly, the limits of agreement range spans nearly 200 milliseconds (-140.8, 53.4). In the context of concussion assessment, this range is acceptable for clinical interpretation of SRT. This range of agreement should be considered when considering Sway for clinical use in alternative settings.

Our results should be considered with several limitations. First, our procedures assessed healthy non-athletes in an isolated laboratory environment. This established a controlled setting to assess the Sway application, and we acknowledge testing athletes in busy sporting environments is drastically different. Additionally, randomization of measurement order did not occur. Future work should randomize testing order of participants to evaluate measurement order effects. We also evaluated the Sway application on a single type of mobile device. Clinicians in the field may have access to other products for testing purposes and our results may not generalize to these other mobile devices. Finally, we evaluated a total of 27 healthy individuals, a relatively small and homogenous sample. However, despite the small sample size, our study was adequately powered to detect a significant effect. Future studies now have justification for including a larger, diverse population to verify the generalizability of these present findings.

Conclusions

Our study found the Sway application to be a valid and reliable tool for assessing SRT in healthy adults in a controlled environment. While these results are promising, continued research in non-laboratory settings and across a diverse population is needed prior to regular use of Sway in clinical settings.

Figure 2: Mean Sway motion-based reaction times across trials

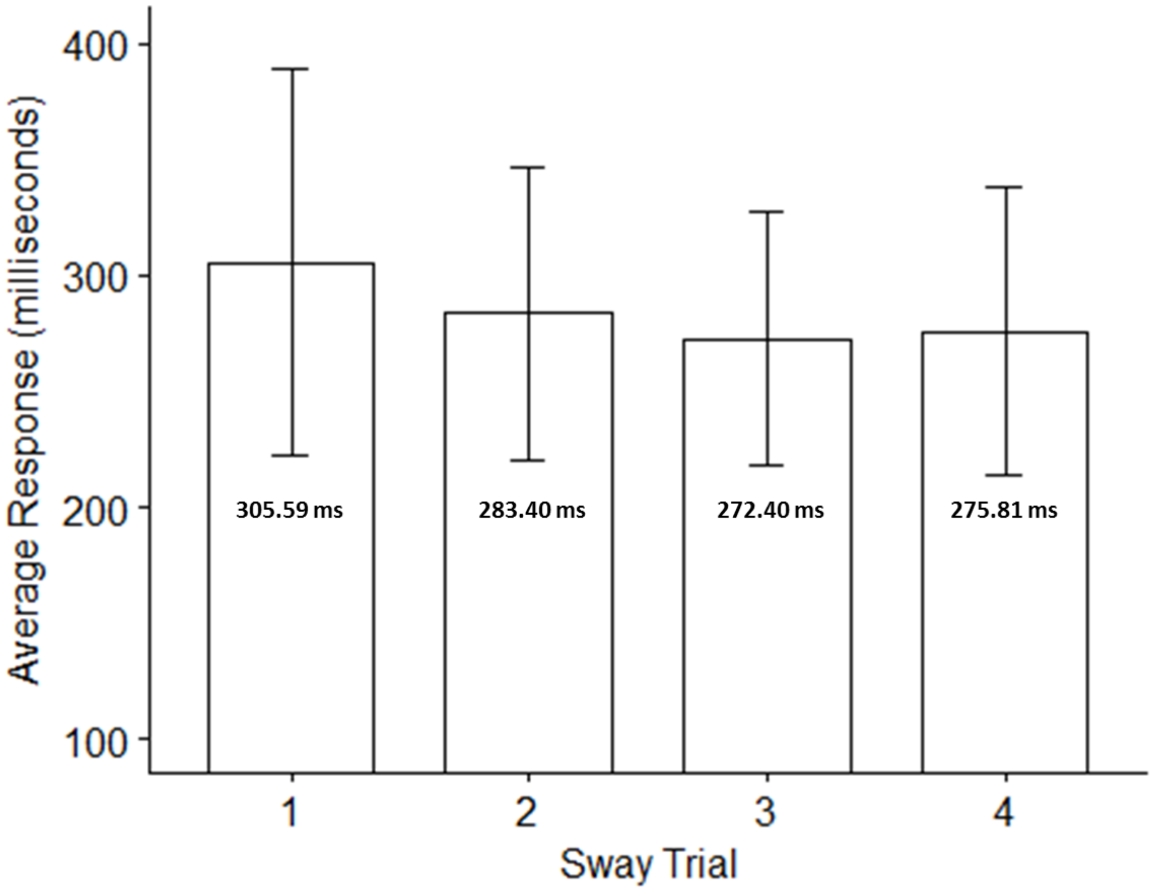


Figure 3: Bland-Altman plot with limits of agreement

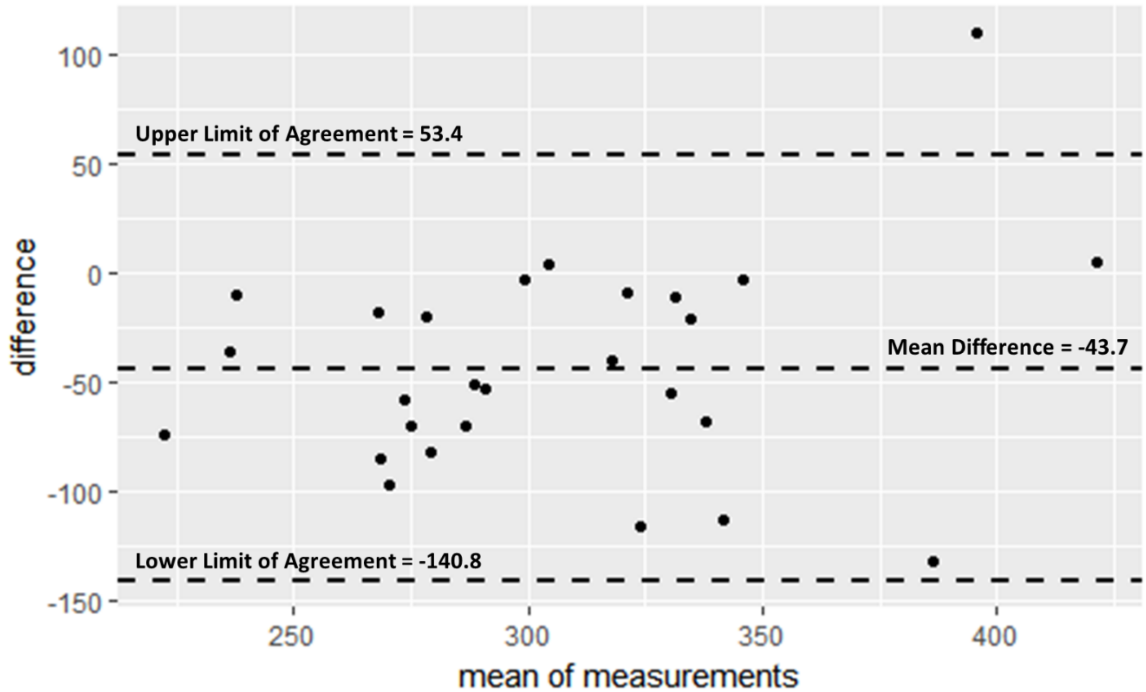


Figure 4: Pearson Correlation results between Sway and CTIP tests

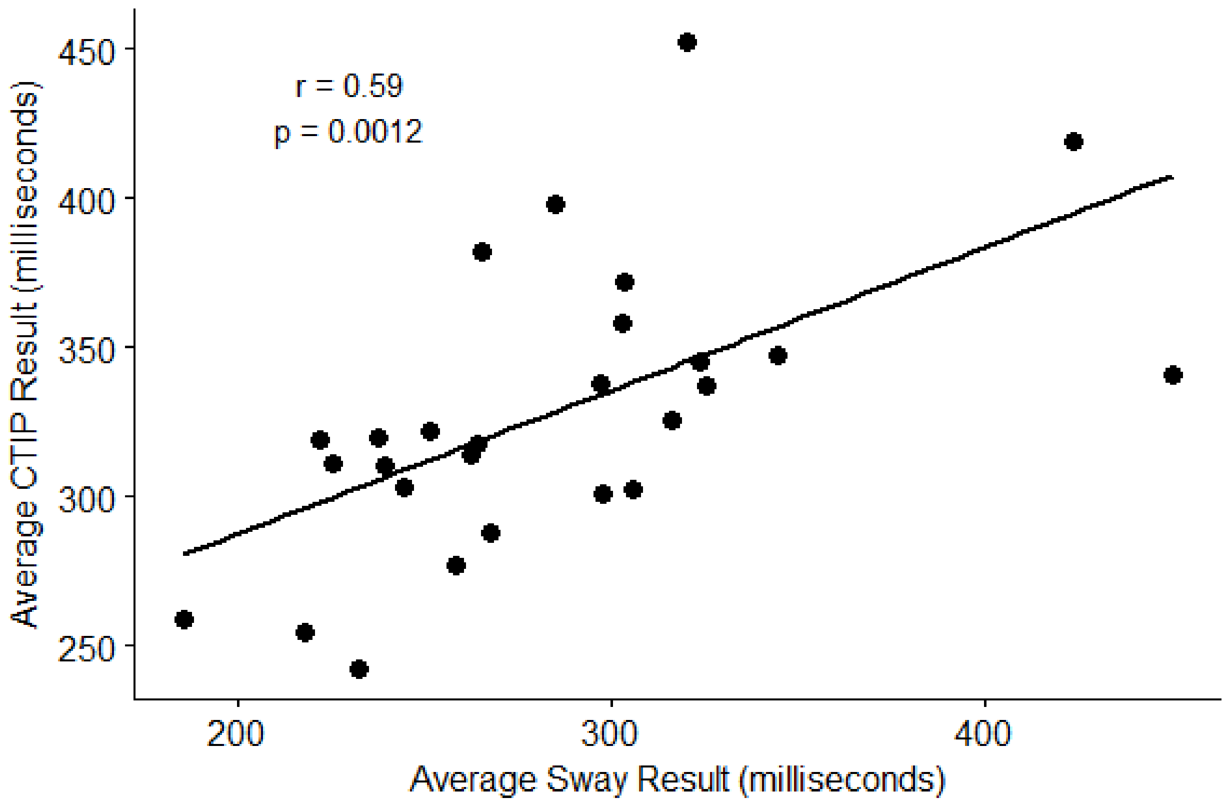


Table 6: Sway SRT results across trials

Sway Trial	Mean (SD)	Range
Trial 1	305.59 ms (83.50)	161-527
Trial 2	283.40 ms (63.32)	187-470
Trial 3	272.41 ms (54.72)	190-409
Trial 4	275.81 ms (62.08)	202-445

Note: ms = milllseconds; SD = standard deviation; SRT = simple reaction time;

Chapter 5: Exploring associations between cognitive performance and white matter fiber tract changes in individuals with persisting concussion symptoms

This work has been submitted for publication as:

Burghart, M., Harris, J.L., Rippee, M.A., & Radel, J. (2018). Exploring associations between cognitive performance and white matter fiber tract changes in individuals with persisting concussion symptoms. *Injury*.

Abstract

Introduction: Concussions, also referred to as mild traumatic brain injuries, have received increased attention from the medical community, general public, and popular media. Despite the increased interest, a subset of individuals have slow and lengthy recoveries after trauma. The primary aim of this study was to longitudinally investigate white matter integrity using diffusion tensor imaging (DTI) and its relation to neurocognitive function and clinical symptoms in individuals slow to recover after concussion. We hypothesized that changes in fractional anisotropy (FA) and mean diffusivity (MD) values of white matter pathways would correlate with changes in symptoms over time. A secondary hypothesis was that changes in white matter integrity over time would be correlated with changes in functional cognitive assessments.

Research design: A longitudinal cohort study.

Methods and procedures: Ten adult women with persisting symptoms after concussion were enrolled in the study. Patients were scanned and evaluated at 4 - 6 weeks after injury, and again 12 - 14 weeks after injury.

Results: 8 of 10 participants reported improved symptoms. There were no statistically significant associations between DTI values and changes in symptoms over time. FA results showed strong associations with improved reaction time composite scores, whereas MD results showed strong negative associations with improved visual performance.

Conclusions: The current study indicates changes in cognitive performance measures are associated with changes in DTI metrics related to distinct white matter pathways after concussion.

Introduction

Concussions have received increased attention from the medical community, general public, and popular media. While knowledge and care for individuals after concussion has deepened in recent years, there remains a subset of individuals who take an extended period of time to recover after injury. While most individuals recover from concussive injury in 7 to 10 days,(McCrea, Guskiewicz, Marshall, Barr, Randolph, Cantu, Onate, Kelly, et al., 2003) the remaining 10-15% of individuals with sports-involved concussions require longer periods for symptoms to resolve, lasting weeks to months,(Binder, Rohling, & Larrabee, 1997) leading to prolonged time away from employment or school, and reduced quality of life.(Bigler, 2008) Approximately 33% of all individuals with non sports-related concussion exhibit symptoms lasting greater than 3 months.(Boake et al., 2005) If a person experiences symptoms for 3 months or longer, a formal diagnosis of Post-Concussion Syndrome (PCS) is given.(Horsfield, Larsson, Jones, & Gass, 1998; Murugavel et al., 2014) Symptoms can be diverse, but include: headaches, difficulty concentrating, light and noise sensitivity, irritability, changes in balance, memory alterations, and general mental 'fogginess'.(Horsfield et al., 1998) Given the diversity of symptoms across individuals, research on the underlying mechanisms of PCS would provide insight into specialized treatment approaches. One way to characterize the underlying mechanisms of PCS is utilizing neuroimaging.

The inability to fully characterize the underlying mechanisms of PCS has led to further exploration using neuroimaging techniques. Traditional radiological methods such as magnetic resonance imaging (MRI) and computed tomography (CT) lack sensitivity to identify alterations in neural tissue after a concussion, despite the injury producing functional changes.(Basser & Jones, 2002) Diffusion tensor imaging (DTI), a quantitative MRI technique used to study the movement of water molecules within white matter fiber tracts in the brain, is a suitable alternative. DTI offers a more sensitive assessment of focal and diffuse injury,(Toga & Mazziotta, 2002) specifically measuring fiber tract microstructure and integrity.(Mori, 2007)

DTI analysis allows for the calculation of certain measures that quantify fiber tract integrity that may provide insight into the underlying pathology of PCS. Fractional anisotropy (FA) is a metric that quantifies the directional water diffusion for a given fiber tract. FA reflects white matter fiber tract density, axonal diameter, and myelination, and is sensitive to the effects of aging, cognitive ability, traumatic injury, and neurodegenerative disease.(Lipton et al., 2008) Mean diffusivity (MD) for each fiber tract also is commonly reported and represents the overall diffusion in the tissue.(Miles et al., 2008) Decreased FA values and increased MD values have been reported in individuals following a concussion after 6 months.(Miles et al., 2008) However, no studies to date have specifically evaluated DTI metrics in individuals with persisting symptoms following a concussion, nor documented whether changes seen with DTI are related to changes in clinical measures of functioning in these individuals, which include symptomatology, neurocognitive, and postural tests. Gaining a better understanding longitudinal white matter and neurocognitive changes in individuals slow to recover from concussion may make it possible to refine the management and treatment of PCS, allowing for earlier and more effective intervention in individuals who are at risk for a longer recovery.

In this study, we investigated the association between DTI measures of white matter integrity in predefined regions of interest (ROIs) and neurocognitive functioning in individuals not improving in a typical timeframe following concussion. We tested the hypothesis that changes over time in DTI measures of white matter pathway integrity would correlate with recovery of symptoms and cognitive measures.

Methods

We performed a prospective, longitudinal pilot study of ten adults following an isolated concussion. The study was approved by the University of Kansas Medical Center's Institutional Review Board.

Participants

Participants were recruited from the University of Kansas Medical Center, a level I trauma center equipped with a specialized concussion clinic, allowing for accurate concussion diagnoses based on the AAN guidelines.(Giza et al., 2013) Individuals were recruited to the study if (a) they were between the ages of 18 – 65 years, (b) they were experiencing active concussion symptoms (concussion symptom severity score ≥ 10/132), and (c) 4 – 6 weeks of time had passed after the injury that resulted in a concussion diagnosis. Exclusion criteria were: residual biomechanical or orthopedic limitations (e.g. spinal fractures) that would interfere with MRI scanning, pre-existing mental health diagnoses, neurologic conditions other than a concussion, a history of alcohol or substance abuse, or individuals involved in a lawsuit related to the injury. Subjects were also excluded if they had a significant head injury within 6 months prior to the concussion injury or if another head injury occurred while enrolled in the study. Subjects with any metal in the body, those who experience claustrophobia in confined spaces, or women who were pregnant also were excluded.

Procedures

Participants meeting the inclusion criteria were recruited and consented 4 to 6 weeks following the initial date of head injury. Participants completed study procedures at two separate time points: 4 to 6 weeks after the injury date, and 8 weeks following the first visit (12 to 14 weeks after the injury). The two time points were chosen to capture individuals with a recovery slower than is typical after concussion, and to document changes taking place after an acute injury but prior to a potential PCS diagnosis.

At each visit, participants completed a series of clinical measures, including symptom reporting and neurocognitive testing, followed by DTI scans. Approximately 30 minutes of rest was given to participants between the functional tests and DTI scans to offset any increased symptoms caused by testing, although no subjects reported additional symptoms or increased severity of symptoms following the clinical measures. The study was approved by the Institutional Review Board, all subjects provided written informed consent, and subjects were financially compensated for their participation. A careful screening of MR compatibility took place prior to scanning.

Clinical measures

Several common clinical outcome measures were used in the study. Cognitive function was assessed using the Immediate Post-Concussion Assessment and Cognitive Test (ImPACT™), a 30-minute computerized neuropsychological test battery created and validated for concussion assessment.(Collins et al., 2003; G L Iverson et al., 2006; Grant L Iverson et al., 2005; Lovell et al., 2004) The test consists of five individual test modules measuring aspects of cognitive functioning commonly affected following head injury.(Grant L Iverson, Lovell, & Collins, 2003) The modules used were: 1). word discrimination (assesses attention and verbal memory), 2). design (attention and visual memory), 3). X’s and O’s (working memory and information processing speed), 4). symbol matching (information processing speed, impulse control, response inhibition), and 5). three letters (working memory and visual motor response time). Additionally, the battery assesses symptom and severity by asking test takers to rate their current symptoms and the severity of each symptom on a 0 – 10 likert scale. The symptoms assessed include: headaches, nausea, balance problems, dizziness, fatigue, trouble falling asleep, sleeping more or less than usual, drowsiness, sensitivity to light or noise, irritability, sadness, nervousness, feeling emotional, numbness or tingling, difficulty concentrating, memory problems, visual changes, and mental fog. From these modules, composite scores for symptom severity, attention, memory, reaction time, and information processing were calculated and used in analysis.(Grant L Iverson et al., 2005)

Postural control also was assessed at each visit using SWAY™, a mobile device application utilizing accelerometer measurement to detect postural movement during static balance stances.(Burghart, Craig, Radel, & Huisinga, 2017; Patterson, 2014) SWAY uses the stances from the Balance Error Scoring System (BESS), a common balance assessment used following a concussion.(Guskiewicz, 2011). Participants completed three sequences of stances: Standing with feet together, tandem stances (alternating which foot is placed in front) and single legs stances (balancing on left leg and right leg). Each stance lasted 10 seconds, with participants instructed to remain as still as possible. During each stance, participants held the mobile device (Apple iPod) on the sternum with both hands and were instructed to refrain from making any unintended hand or arm movements. Participants kept their eyes open during the balance stances, as many of the participants reported an inability to balance when eyes were closed. The entire balance testing procedure lasted approximately 5 minutes. Balance scores are calculated on a 0 – 100 scale, with 100 representing superior postural control.

Imaging acquisition

DTI data was collected using a whole body 3T Siemens Skyra scanner (Siemens, Erlangen, Germany). Subjects were placed in the scanner and underwent an anatomical localizing scan to position the ROIs. The localization scan produced a high-resolution T1 anatomic image (MPRAGE; 1x1x1mm voxels; repetition time (TR)=2500, echo time (TE)=4.38, T1=1100, FOV 256x256 with 18% oversample, 1 mm slice thickness). In addition, a diffusion-weighted sequence was designed and implemented to minimize the scanner duration while collecting optimal results. The diffusion-weighted acquisition had a TR=1000 ms and TE of 90 ms. Diffusion gradients were applied in 65 directions (b_0= 0 s/mm^2 and b_{1-64}=1000 s/mm^2). Seventy-five 2-mm sections were acquired in an in-plane resolution of 128 x 128 with a 300 mm field of view (FOV). Total scan time was 14 minutes.

Data analysis

We processed the diffusion-weighted images using FSL version 5.0.4 of the FMRIB Software library.(Smith et al., 2004) The two averages of the weighted images for each participant were concatenated in the order of image acquisition and were visually inspected for signal drop-offs and other artifacts. Images were eddy-current corrected for small distortions and simple head motion by alignment of the diffusion weighted images to the b_0 image. A brain extraction tool was then applied to strip the brain from the skull. Diffusivity measures were calculated using DTIFIT and FSLMATHS, part of the FSL toolbox. Ten ROIs from Johns

Hopkins University's Mori white matter probabilistic atlas (Hua et al., 2008) were transformed into each subject's diffusion space using transformation matrices created from nonlinear registration between the subject's diffusion space and standard space (FMRIB58). Using fslstats,(Smith et al., 2004) average FA and MD values were calculated for each ROI and were correlated against the clinical measures using Spearman Rank-Order correlations. Bonferroni corrections were considered for p-value adjustments but not used for significance, due to the exploratory nature of the study, the robustness of Spearman Rank-Order correlations coefficients, and increased likelihood of type II errors found with Bonferroni corrections.(L. G. Portney & Watkins, 2009) The less conservative Benjamini-Hochberg p-value adjustments were used as an alternative correction for the multiple comparisons, as this method is recommended for exploratory analyses.(Goeman & Solari, 2011)

Results

A total of 10 women (average age 39.8 ± 16.7 years) with diagnosed concussion and persisting symptoms were enrolled in and completed the study. The study population comprised entirely of women occurred purely by coincidence. All participant injuries occurred outside of sports-related activities. Participants joined the study 4-6 weeks following injury (average time post-injury 35.4 ± 10.6 days from injury to 1st scan; see Table 7). Mean performance scores from the clinical measures are reported in Tables 8 and 9. Individual performance varied across neurocognitive and balance measures, as evidenced by the large range in scores between participants. No significant correlations were noted between age and changes in neurocognitive or SWAY scores.

Clinical and cognitive measures

Clinical and cognitive measures were analyzed to assess changes in participant symptoms. Table 9 shows a comparison of ImPACT scores assessed at 4-6 weeks and 12-14 weeks after concussion. A reduction in symptom severity was the only comparison to yield a significant change during the two-month period between test dates, although every performance test yielded improved scores. All symptoms improved over the 8-week period, except visual problems and self-reported sadness (Table 8). SWAY balance scores averaged across trials for each participant also improved over time but did not yield significant differences. Table 10 shows comparisons between FA and MD values for each ROI at the two measurement dates. Generally-speaking, FA values tended to decrease over time after injury, while MD values tended to increase. However, there was no statistically significant difference between FA and MD values for any white matter tract over time.

Associations between changes in clinical and DTI measures

We also evaluated associations between changes in clinical measures and changes in FA and MD over time (Table 11). After adjusting p-values for multiple comparisons, we found no statistically significant associations between change in neurocognitive composite scores and DTI metrics across several neurocognitive domains.

Several subtests of the ImPACT test were significantly correlated with changes in DTI measures. Decreased reaction time was directly correlated with change in FA collected from the left superior longitudinal fasciculus (p=0.03) and the left inferior longitudinal fasciculus (p=0.05). Improved visual memory was negatively correlated with changes in MD collected from the inferior longitudinal fasciculus (p=0.02). Additionally, visual motor speed was negatively correlated with the changes in MD collected from the inferior longitudinal fasciculus (p=0.03).

Despite a lack of statistical significance, several correlations still showed strong associations, producing r values greater than 0.5.(Portney & Watkins, 2009) Changes in reaction time correlated strongly with changes in FA values from every white matter tract in the left hemisphere (r-values ranged from 0.51-0.68), as well as the superior longitudinal fasciculus in the right hemisphere (r-values ranged from 0.29-0.51). Changes in reaction time also was strongly correlated with changes in MD values collected from the right inferior longitudinal fasciculus (r = 0.613, p = 0.60). Changes in visual motor speed was strongly correlated with changes in FA values collected in the left superior longitudinal fasciculus (r = -0.539, p = 0. 85). Visual memory changes were also strongly correlated with changes in FA values collected in the right inferior longitudinal fasciculus (r = 0.523, p = 0. 71), as well as changes in MD values collected from the left corticospinal tract (r = -0.553, p = 0. 49). Verbal memory changes were strongly correlated with changes in MD values collected from the genu of the corpus callosum (r = -0.511, p = 0. 64). Changes in symptom severity scores and impulse control did not show a strong correlation with FA or MD change in any white matter tract.

Discussion

Using DTI as a proxy to study the neuroanatomic basis for cognitive changes taking place after a concussion, we found white matter metrics (FA and MD values) related to changes in performance in distinct cognitive domains commonly assessed following injury. Our findings suggest that longitudinal changes in clinical measures used in clinical management after concussion are associated with structural white matter integrity. Reductions in reaction time were associated with improvements in several left hemisphere white matter tract FA values. While not statistically significant, mean reaction times of our participants did improve over time, as did FA values for the associated reaction time tracts (genu and splenium of corpus callosum, superior longitudinal fasciculus, splenium, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and corticospinal tract). Previous research has found similar associations between these tracts and changes in reaction time and information processing in healthy and injured adults.(Ashtari, 2012; Wolfers et al., 2015) These associations support validity of serial testing of reaction time in the evaluation process following concussive injury. Improved visual motor speed and visual memory were also associated with improved FA and MD values, specifically in the superior longitudinal fasciculus, inferior longitudinal fasciculus, and corticospinal tract. Both the superior longitudinal fasciculus and inferior longitudinal fasciculus are connected to the occipital lobe and deceased FA values have been associated with visual neglect and decreased visual spatial skills in both tracts.(Shinoura et al., 2009)

The observed relationships between DTI metrics and reaction time and visual motor skills may provide evidence for use of these clinical outcomes in patients with persisting concussion symptoms as they recover from injury. Reaction time, in particular, is often used as an assessment procedure following a suspected concussion.(Guskiewicz et al., 2004; Harmon et al., 2013a; McCrory et al., 2013) Contrary to reaction time, visual assessment after injury is seldom done. Some position statements recommend inquiring about double or blurred vision,(Guskiewicz et al., 2004) while other position statements recommend no visual assessment of any kind.(Harmon et al., 2013a; McCrory et al., 2013) The results of our study suggest that visual disturbances may be common in adult women with persisting concussion symptoms, and changes in white matter pathways involved in visual processing were correlated with improved overall functioning. Including measures of vision and visual spatial skills early in the evaluation process may provide useful information allowing clinicians to identify individuals at increased risk for a lengthy recovery. Early identification of these individuals may allow earlier targeted interventions leading to improved recovery time.

Participants tended to improve their postural control over the course of the study, although the improvements were not statistically significant. Additionally, no fiber tract changes were associated with balance improvements. These results may indicate that our study subjects had returned to their baseline, pre-injury postural control abilities and were already close to their testing ceiling. This notion is supported by previous research indicating that vestibular impairments following concussion, resulting in impaired postural control, are often present soon after injury (Valovich McLeod & Hale, 2015) and often resolve spontaneously with minimal medical intervention.(Curthoys & Halmagyim, 1995)

Although we predicted that changes in DTI metrics over time would be associated with improved symptom resolution, no significant associations were observed between any white matter tract metrics and improvements in symptoms. This result was surprising, as 8 of the 10 participants reported they experienced notable reductions in their symptoms over the course of the 8-week study period. Based on patient self-report, we thus anticipated associations with improved FA and MD values. Our small sample size may be an explanation for the lack of significant correlations. Alternatively, concussed individuals who appear to be recovering more slowly and trending towards a PCS diagnosis may recover from somatic symptoms with a more rapid time course than they exhibit for recovery of white matter integrity. This notion of incongruent recovery following head trauma has been described in a prior sports-related concussion study, with somatic symptom resolution and clearance for return to normal activity occurring between days 3 and 15 following a sports-related concussion, despite the same individuals exhibiting delayed neurometabolic recovery until approximately day 30 (Vagnozzi et al., 2010). This course of recovery poses challenges clinically, as individuals may experience recovery from somatic symptoms before neurological and cognitive measures have normalized.

Our DTI analyses revealed no statistically significant changes in FA or MD values over time in any of the ROIs, despite patient report of reduced symptoms and objective measures documenting improved neurocognitive functioning. These results conflict with previously reported DTI results involving athletes during concussion recovery, which showed decreased FA values at 2 months post-injury compared to timepoints near the injury date (Murugavel et al., 2014). It should be noted that our data did trend in a similar pattern, as FA values decreased longitudinally despite failing to reach statistical significance, but our population didn't involve athletes or sports-related head trauma. Our sample was comprised of females with professional careers who might not have been able to truly follow rest recommendations during their recovery. Future research using a larger sample size, control group without TBI, and both male and female subjects will help elucidate these inconsistencies.

One limitation of the current study is the small sample size, which may be attributed to our rigorous inclusion criteria and a lengthy follow-up period. Additionally, it should be noted that our population was comprised of solely female participants, by coincidence, who were not professional or semi-professional athletes. Thus, caution should be used in generalizing results to other populations.

Conclusions

The present study is a longitudinal DTI analysis of white matter changes that may contribute to altered cognitive functioning in individuals experiencing prolonged symptoms following concussion. As such, this study provides evidence that changes in DTI metrics within distinct white matter pathways are associated with changes in reaction time, visual memory, and visual motor speed. This information will allow for improved evaluation and assessment of individuals following injury, emphasizing more thorough visual assessment.

Acknowledgments

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Table 7: Demographic and neuropsychological data

	Mean	**SD**
Age (years)	39.8	16.725
Education (years)	16.5	3.0
Injury to 1st Scan (days)	35.4	10.6
Injury to 2nd Scan (days)	96.3	10.9
Height (cm)	169.2	7.8
Weight (kg)	77.6	17.2
Handedness	8 (R)	2 (L)
Subjects with prior concussion	4	(Range= 1-6)

Table 8: Longitudinal symptom severity changes

	4-6 weeks post (SD)	12-14 weeks post (SD)	*p*-value
Headaches	2.5 (1.6)	1.8 (2.0)	0.41
Nausea	0.9 (1.3)	0.3 (0.7)	0.21
Balance problems	2.4 (1.9)	1.6 (1.7)	0.33
Dizziness	2.1 (1.7)	1.0 (1.4)	0.14
Fatigue	2.6 (2.4)	1.8 (2.0)	0.43
Trouble sleeping	1.9 (1.8)	1.4 (2.3)	0.55
Drowsiness	2.7 (2.2)	1.5 (1.6)	0.19
Light sensitivity	3.6 (1.6)	2.1 (2.4)	0.11
Noise sensitivity	2.8 (2.4)	1.8 (2.5)	0.38
Irritability	1.6 (1.3)	1.1 (1.9)	0.50
Sadness	1.3 (1.9)	1.3 (1.9)	1.00
Nervousness	1.9 (1.9)	2.2 (2.0)	0.73
Emotional	1.6 (1.8)	1.2 (1.5)	0.61
Feeling slowed down	2.9 (1.9)	1.5 (1.9)	0.11
Mental fog	2.6 (2.1	1.4 (1.8)	0.19
Difficulty concentrating	3.0 (2.1)	2.0 (1.9)	0.28
Memory problems	2.3 (1.6)	1.7 (1.8)	0.44
Visual problems	0.6 (1.0)	1.3 (1.8)	0.29

Mean and standard deviations (SD) presented for symptoms. Severity was recorded on a 0-10 likert scale. Paired t-tests compared results from 1st scan and 2nd scan.

Table 9: Longitudinal ImPACT and SWAY results

	4-6 weeks post (SD)	12-14 weeks post (SD)	*p*-value
Verbal Memory	78.4 (14.9)	84.9 (10.7)	0.22
Visual Memory	59.8 (19.6)	68.3 (15.9)	0.16
Visual Motor Speed	31.5 (9.4)	35.1 (8.4)	0.15
Reaction Time	0.82 (0.19)	0.77 (0.27)	0.52
Impulse Control	6.1 (6.7)	3.6 (3.9)	0.10
Symptom Severity	42.8 (25.6)	29.9 (28.9)	**0.03***
Cognitive Efficiency	0.17 (0.19)	0.22 (0.22)	0.40
SWAY Balance Test	66.6 (17.3)	71.5 (13.9)	0.49

Mean and standard deviations (SD) presented for clinical measures. Paired t-tests compared results from 1st scan and 2nd scan; SRT = Simple Reaction Time.

Table 10: DTI metrics by region of interest

	FA T1 (SD)	FA T2 (SD)	p	MD T1 (SD)	MD T2 (SD)	p
Genu (CC)	.581 (.02)	.578 (.02)	0.33	$9.6x10^{-4}$ ($5.7x10^{-5}$)	$9.5x10^{-4}$ ($5.4x10^{-5}$)	0.22
Splenium (CC)	.720 (.02)	.718 (.03)	0.59	$7.9x10^{-4}$ ($4.5 x10^{-5}$)	$8.0x10^{-4}$ ($4.7 x10^{-5}$)	0.73
Superior Longitudinal Fasc. (L)	.447 (.02)	.446 (.02)	0.75	$7.1x10^{-4}$ ($1.6x10^{-5}$)	$7.1x10^{-4}$ ($2.1 x10^{-5}$)	0.50
Inferior Longitudinal Fasc. (L)	.476 (.02)	.474 (.02)	0.49	$7.5x10^{-4}$ ($2.2 x10^{-5}$)	$7.6x10^{-4}$ ($2.5 x10^{-5}$)	0.34
Inferior Fronto-Occipital Fasc. (L)	.465 (.02)	.462 (.02)	0.54	$7.6x10^{-4}$ ($1.9 x10^{-5}$)	$7.7x10^{-4}$ ($2.1 x10^{-5}$)	0.33
CorticoSpinal Tract (L)	.583 (.01)	.580 (.02)	0.36	$6.9x10^{-4}$ ($2.0 x10^{-5}$)	$7.0x10^{-4}$ ($1.9 x10^{-5}$)	0.53
Superior Longitudinal Fasc. (R)	.443 (.02)	.441 (.03)	0.50	$7.1x10^{-4}$ ($1.7 x10^{-5}$)	$7.2x10^{-4}$ ($2.1 x10^{-5}$)	0.11
Inferior Longitudinal Fasc. (R)	.476 (.02)	.474 (.02)	0.34	$7.7x10^{-4}$ ($1.9 x10^{-5}$)	$7.8x10^{-4}$ ($2.7 x10^{-5}$)	0.20
Inferior Fronto-Occipital Fasc. (R)	.459 (.02)	.458 (.03)	0.33	$7.8x10^{-4}$ ($2.5 x10^{-5}$)	$7.8x10^{-4}$ ($2.8 x10^{-5}$)	0.24
CorticoSpinal Tract (R)	.576 (.02)	.576 (.02)	0.53	$7.2x10^{-4}$ ($2.0 x10^{-5}$)	$7.3x10^{-4}$ ($2.4 x10^{-5}$)	0.25

Paired t-tests between DTI metrics at scan 1 (T1) and scan 2 (T2); CC = Corpus Callosum; FA = Fractional Anisotropy; Fasc = Fasciculus; L = Left Hemisphere MD = Mean Diffusivity; R = Right hemisphere; SD = Standard Deviation;

Table 11: Associations between changes in clinical measures and DTI metrics over time

Fractional Anisotropy Values	Symptoms Severity Score	Verbal Memory	Visual Memory	Visual Motor Speed	Reaction Time	Impulse Control
Genu Corpus Callosum	.231 (.920)	-.195 (.764)	.219 (.709)	-.358 (.845)	.614 (.182)	.213 (.894)
Splenium Corpus Callosum	0.061 (.920)	-.176 (.764)	.237 (.709)	-.200 (.845)	.511 (.189)	.079 (.894)
Superior Longitudinal Fasciculus (L)	.292 (.920)	-.055 (.881)	.091 (.802)	-.539 (.845)	.681 (.182)	.280 (.894)
Inferior Longitudinal Fasciculus (L)	.055 (.920)	-.237 (.764)	.334 (.709)	-.212 (.845)	.632 (.182)	-.195 (.894)
Inferior Fronto-Occipital Fasiculus (L)	.091 (.920)	-.298 (.764)	.267 (.709)	-.309 (.845)	.590 (.182)	-.073 (.894)
Corticospinal Tract (L)	.116 (.920)	-.201 (.764)	.486 (.709)	-.333 (.845)	.523 (.189)	-.195 (.894)
Superior Longitudinal Fasciculus (R)	.103 (.920)	-.389 (.764)	.207 (.709)	-.152 (.845)	.511 (.189)	.049 (.894)
Inferior Longitudinal Fasciculus (R)	.036 (.920)	.146 (.764)	.523 (.709)	-.042 (.987)	.444 (.249)	-.073 (.894)
Inferior Fronto-Occipital Fasiculus (R)	.152 (.920)	-.316 (.764)	.170 (.709)	-.152 (.845)	.407 (.270)	.238 (.894)
Corticospinal Tract (R)	-.036 (.920)	-.316 (.764)	.347 (.709)	-.006 (.987)	.292 (.413)	-.061 (.894)
Mean Diffusivity Values						
Genu Corpus Callosum	.267 (.999)	-.511 (.642)	-.116 (.939	-.321 (.947)	.109 (.894)	-.012 (.973)
Splenium Corpus Callosum	-.091 (.999)	.213 (.642)	-.201 (.826)	.067 (.947)	-.188 (.894)	-. 183(.973)
Superior Longitudinal Fasciculus (L)	-.134 (.999)	.316 (.642)	.006 (.987)	.079 (.947)	-.231 (.894)	-.195 (.973)
Inferior Longitudinal Fasciculus (L)	-.176 (.999)	-.201 (.642)	-.723 (.180)	-.139 (.947)	.049 (.894)	.098 (.973)
Inferior Fronto-Occipital Fasciculus (L)	-.037 (.999)	.399 (642)	-.320 (.712)	.024 (.947)	-.171 (.894)	.028 (.973)
Corticospinal Tract (L)	.012 (.999)	.231 (642)	-.553 (.485)	-.139 (.947)	-.073 (.894)	.152 (.973)
Superior Longitudinal Fasciculus (R)	.260 (.999)	.309 (.642)	-.070 (.941)	-.152 (.947)	.092 (.894)	-.040 (.973)
Inferior Longitudinal Fasciculus (R)	.381 (.999)	-.262 (.642)	-.284 (.712)	-.675 (.320)	.613 (.600)	.086 (.973)
Inferior Fronto-Occipital Fasciculus (R)	.134 (.999)	.058 (.874)	-.348 (.712)	-.304 (.947)	.213 (.894)	.028 (.973)
Corticospinal Tract (R)	.000 (.999)	.329 (.642)	-.345 (.712)	.079 (.947)	-.329 (.894)	.141 (.973)

Associations were determined using Spearman rank-order correlations; R values (*p* values) reported; No significant associations at $p < 0.05$ were noted after Benjamini-Hochberg adjustments; (L) = Left hemisphere pathway; (R) = Right hemisphere pathway.

Chapter 6: Patterns of factors influencing duration of treatment after concussion

Abstract

Care for an individual following concussion is challenging, as many symptoms and clinical presentations vary. This complexity makes determining recovery trajectory after injury difficult for clinicians. This exploratory study presents differences in clinical presentation patterns between groups of individuals with extended treatment durations (> 28 days) and typical treatment durations (≤ 28 days). Exploratory factor analyses were conducted using electronic medical records from concussion evaluations and open-source social determinants data. Between-group factor differences were assessed using Tucker's congruence coefficient index. A total of 340 participants were included (Extended group = 81; Typical group = 259). Both groups yielded a 4-factor structure, although factor compositions varied. Notable differences in factor loadings include age, sex, history of other psychological diagnoses, and neurocognitive abilities at evaluation. Shared attributes between groups included socioeconomic constructs and previous concussions. Between group factor differences were statistically meaningful for factor 2 (Tucker's index = 0.46), factor 3 (Tucker's index = 0.05) and factor 4 (Tucker's index = 0.02). This study demonstrates factor patterns that differ between groups of individuals with typical and extended treatment durations after concussion. These differences may allow for identification of patients at risk for long treatments at their evaluation, thus allowing for early restorative intervention.

Introduction

Concussions are a relatively common occurrence, accounting for at least 80% of all traumatic brain injuries (TBI) and an annual incidence rate in the United States of 500 injuries per 100,000 people (Bazarian et al., 2005; Cassidy et al., 2004; Ryu et al., 2009). Each year, an estimated 1.6-3.8 million sports-related brain injuries occur, although this figure is likely an underestimate, as many concussions go unreported or unrecognized (Langlois et al., 2006). Evaluation and management of an individual following a suspected concussion is challenging, as many symptoms and clinical features vary across patients (McCrory et al., 2013).

This complexity makes determining a person's recovery trajectory difficult. Many studies have been conducted that evaluate the influence individual variables have on recovery from a concussion, including age (Field et al., 2003), sex (Leddy, Baker, & Willer, 2016), history of concussions (Iverson et al., 2017; Meehan, Mannix, Oêbrien, & Collins, 2013), neurocognitive functioning (Iverson, 2007), histories of psychiatric disorders (Zemek et al., 2016), slowed reaction times (Norris et al., 2013), and increased acute symptomology (Brown et al., 2014; Resch et al., 2015). Many of these studies evaluated the influence these factors had on long recoveries, often defined as treatments and care lasting greater than 28 days (Rose et al., 2015). Despite these advances, prospectively determining if a person will be at risk for a recovery lasting longer than 28 days remains elusive for clinicians, thus delaying interventions and treatments that may help.

Exploratory factor analysis between groups of individuals with long and typical recoveries may describe differences in clinical presentation between the two groups. Exploratory factor analysis attempts to uncover complex patterns in individual clinical presentation by finding latent constructs (i.e. factors) that can explain the common variance shared by observed variables (Bartholomew, Knotts, & Moustaki, 2011). Any noted differences in the factor structure between these groups could provide further discriminatory information between typical and extended treatment durations. Additionally, by using information present to a clinician at the injury evaluation, discriminatory properties of the factor analysis could potentially be applied to groups of individuals at risk for a long recovery, thus allowing a clinician to prescribe restorative interventions sooner.

The goals of this exploratory study were 1). To determine the factor structures of patients with extended treatment durations (> 28 days) and typical treatment durations (≤ 28 days) using retrospective electronic medical records (EMRs) and open-source social data and 2). Assess the discriminative ability of these factor structures by evaluating differences and similarities between the groups.

Methods

Study Participants

A retrospective review of EMR data identified patients with a diagnosed concussion, based on the consensus definition (McCrory et al., 2013) and documentation of an appropriate ICD9 or ICD10 billing code for a concussion diagnosis. Patients were seen at one of five sports medicine clinics operated by the University of Kansas Health System in the Kansas City metropolitan area between July 2013 and December 2016. Patients were included if they were between the ages of 13 and 65 years of age on the initial visit, were being treated clinically for a primary diagnosis of concussion and were not also being seen for another injury. This study was approved by the institutional review board of the University of Kansas Medical Center, and a full waiver of informed consent was granted in recognition that the retrospective nature of the study, the de-identification of patient medical data, and the study involved no more than minimal risk to subject privacy.

Information from each participant's course of clinical care were manually queried and extracted from the electronic medical record system (Waitman, Warren, Manos, & Connolly, 2011). Individuals were categorized into two discrete groups for assessment of factor structure composition and differences. Individuals with treatment durations greater than 28 days were classified as 'extended duration', coinciding with previous research identifying these individuals as having a delayed recovery (Rose et al., 2015). The remaining individuals were classified as 'typical duration', representing a normal course of care following concussion. Length of treatment duration was determined for each participant by taking the difference in days between the evaluation date and last date seen, representing discharge from care.

Outcome Measures

Collected clinical evaluation data included the person's age at the time of the first clinic visit, sex, race, history of previous concussion, county of residence, and any history of mood, anxiety, migraine, or attention-deficit disorders. History of previous or ongoing conditions was determined from presence of ICD9 or ICD10 codes discretely recorded in the person's EMR.

The Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) test battery is a formal concussion assessment and is commonly completed at clinical evaluations. ImPACT results from participant evaluations were queried and included in the analysis. The ImPACT is a computerized concussion battery consisting of composite scores on the Post-Concussions Symptoms Scale and 4 neurocognitive modules: verbal memory, visual memory, visual motor processing speed, and reaction time (ImPACT Applications, 2007). The assessment has been well studied in concussion populations, is widely used, and is valid for people 10-60 years of age (ImPACT Applications, 2007; Iverson, Brooks, Collins, & Lovell, 2006; Iverson, Lovell, & Collins, 2005).

Open-source Social Determinants of Health (SDH) data were included in the analysis. The Social Vulnerability Index (SVI) from the Geospatial Research, Analysis, and Services Program primarily is used by public health officials and emergency responders to identify and map communities that will most likely need support during a hazardous event (Flanagan, Gregory, Hallisey, Heitgerd, & Lewis, 2011). The SVI indicates relative vulnerability of every U.S. Census tract and ranks each tract on 15 social factors, including unemployment, minority status, and disability, collapsing these factors into 4 themes: socioeconomic status; household composition and disability; minority status and language; and housing and transportation (Agency for Toxic Substances and Disease Registry (ATSDR), 2014; Tate, 2012). These four themes were used in this analysis to assess the role of social determinants in concussion treatment duration. County-level SVI data were used in the analysis due to lack of geospatial coding information available for each participant. The themes are reported as percentile rankings, with county-level data compared across the entire US population. The percentile ranking values range from 0 to 1, with the higher values indicating greater vulnerability for each county (Agency for Toxic Substances and Disease Registry (ATSDR), 2014). An example ranking of 0.149 for a county indicates the present county is more socially vulnerable than 14.9% of all other counties in the United States.

Statistical Analysis

Statistical analyses were performed using the open-source statistical programming language *R* (R Core Development Team, 2016). Descriptive statistics were calculated by group for each demographic, social, and clinical factor. These statistics included measure of central tendency and dispersion of continuous variables and both frequencies and proportions for categorical variables. Differences of distributions between group factors was assessed with the independent samples *t*-test for continuous variables and with chi-squared tests for categorical variables. Exploratory factor analysis (EFA) was conducted for each group using a promax oblique rotation, as factor correlations were expected. The number of factors for each group EFA was determined from review of scree plots (i.e. number of factors before elbow in plot) and explained variance > 5% (Costello & Osborne, 2005). Item responses with loading > 0.3 were considered significantly associated with that factor (Costello & Osborne, 2005). Differences between group factor structure as assessed using Tucker's coefficient of congruence (Lorenzo-Seva & ten Berge, 2006). Factor structure producing a congruence coefficient between 0.85 – 0.94 were determined as similar, while values greater than 0.95 were determined to be equal (Lorenzo-Seva & ten Berge, 2006). The significance level was set at $\alpha = 0.05$ for statistical inference.

Results

A total of 665 participants were identified for the study. Of those, 325 participants did not meet the inclusion criteria; 20 did not meet the age criteria, 210 had missing ImPACT data, 32 were being treated for multiple injuries, and 63 had missing demographic information (see Figure 5). Thus, a total population of 340 participants was included in the study.

The total sample ($N = 340$) comprised the two groups: 81 participants had treatment durations lasting > 28 days and were categorized into the 'extended duration' group, while the remaining 259 participants had typical treatment durations and were classified into the 'typical duration' group (see Table 12). The average age of participants was 16.9 years, and consisted of

54% males, 78% Caucasian, and had an average treatment duration of 20.3 days. All non-Caucasian races were aggregated due to small sample representation. There were some significant differences ($p > 0.05$) between typical and extended duration groups. Compared to the typical duration group, the extended duration population had higher housing and transportation percentile rankings, indicating greater vulnerability ($p = 0.03$), more previous concussions ($p = 0.02$), greater history of mood, anxiety, migraines, or attention-deficit disorders ($p = 0.002$), and slower reaction times ($p < 0.001$) (see Table 12).

Extended Duration group

Visual inspection of the scree plot indicated a possible 2 to 4-factor structure (see Figure 6). 4 factors seemed to fit the data well, as variance explained by a 4-factor structure was 20%, 10%, 9%, and 8% for factors 1, 2, 3, & 4, respectively. Table 13 shows the factor loading of each item for these 4 potential factors. Factor 1 consists of 4 items that we describe as '*social indicators'*, including "socioeconomic", "household composition", "minority status", and "housing and transportation" themes from the SVI. Factor 2 consists of 2 items and we describe as *'memory indicators'* and included both "visual memory" and "verbal memory" components of the ImPACT test. Factor 3 included 3 items and we refer to as '*personal indicators',* including "age", "minority status" of the SVI, and a "history of mood, anxiety, migraine, or attention-deficit disorders". Factor 4 included 3 items and can be described as *'neurocognitive indicators',* being represented by "reaction time speed", "total concussion symptoms and severity", and "visual motor" ImPACT performance. "Minority status" theme from the SVI was the only cross-loading observed, and was finalized into Factor 3, as the highest loading was observed with this factor. "Sex", "race" and “concussion history” did not have loadings greater than 0.30 on any of the factors and thus were not including in the final structure.

Typical duration group

The scree plot had 3 factors before the bend and one after, indicating a 4-factor structure (see Figure 7). Additionally, the variance explained by the 4-factor structure was 19%, 10%, 6%, and 6% for factors 1, 2, 3, & 4. Factor loadings for each item on these 4 factors are presented in Table 13. Factor 1 consists of 3 items and could be similarly labeled ‘*social indicators’* as the extended recovery group, although only 3 of the 4 SVI themes loaded on this factor (“socioeconomic”, “household composition”, and “housing and transportation”, respectively). Factor 2 consists of 5 factors and could be similarly to the ‘*memory indicators’ and ‘neurocognitive indicators’* factors in the extended duration group. Factor 2 consists of items “visual memory”, “reaction time”, “total symptoms and severity”, and “visual motor” items from the ImPACT test, as well as the “race” item. Factor 3 could be labeled as ‘*sex’,* as the “sex” item comprised this category. Lastly, Factor 4 was comprised of the items “minority status” and the “verbal memory” component of the ImPACT test. No cross loadings were observed in the typical recovery group. “Age”, “concussion history”, and “history of mood, anxiety, migraine, or attention-deficit disorders” failed to yield any loadings greater than 0.30 and thus were not included in the final group structure.

Factor structure differences

While each group consisted of 4 factors, the composition of the factor pattern differed across the two groups. To test whether these differences were statistically meaningful, Tucker’s coefficient of congruence was determined by multiplying each loading in the extended duration group with the corresponding loading in the typical duration group. Table 14 contains congruence values in the form of a 4x4 matrix. Factor 1 produced a congruency value of 0.98, indicating these factors are equal. The remaining factors had high congruence coefficients, indicating similarities between groups.

Discussion

The primary purpose of this study was to determine and compare the factor structures of individuals with extended and typical treatment durations after a concussion. The main finding was that both factor analyses supported a 4-factor structure for the extended and typical duration groups, although several of the group-based factors differed in their composition. To date, four studies have attempted to demonstrate and explain the factor structures of reported symptoms and clinical presentation in a concussion population. Three studies (Benge, Pastorek, & Thornton, 2009; Caplan et al., 2010; Franke, Czarnota, Ketchum, & Walker, 2015) evaluated the factor structures of concussion symptoms in a military population after a concussion without group comparison. Another study (Lannsj, Af Geijerstam, Johansson, Bring, & Borg, 2009) evaluated the factor structure of symptoms 3 months after a concussion injury. These previous studies were limited to describing factors influencing symptom presentation in military and civilian populations, neglecting the demographic, social, and neurocognitive aspects of concussive injury that generalize across populations. The present study addressed these limitations by incorporating a more complete examination of clinical and personal information in our analysis.

No study to date has evaluated the influence of social factors on concussion treatment duration. It is important to note, however, these social factors (represented by SVI themes) accounted for the largest amount of variability in both subject groups (20% for extended duration, 19% for typical duration). While these features do not discriminate between treatment duration groups, they do help capture variability in the data and should be considered in future concussion recovery research. Alternative models should evaluate access to appropriate concussion resources and education, quality of concussion-specific medical care, and likelihood of individuals seeking out concussion services after suspected injury, as intuition suggests that these factors can influence concussion evaluation and treatment duration.

The noted differences in the congruence between group factor patterns raise important questions regarding dimensions of clinical presentation after a concussion. Although there was clear overlap between the two groups for the first factor '*social indicators'*, as this factor matched on items and had similar loadings, the remaining factors were comprised of different items between the groups. Neurocognitive functioning was a key component for factor 2 in both groups, although only the memory components of the ImPACT test comprised the extended duration group. These differences coincide with previous research indicating slowed memory improvements after sports-related concussion (McClincy, Lovell, Pardini, Collins, & Spore, 2006). Factor 3 was comprised of general demographic information for both groups, but "sex" was the only item comprising factor 3 for the typical duration group and was not comprised in the extended duration group. Factor 3 was the least congruent factor when compared across the groups, yielding a maximum congruence coefficient of 0.29. The extended duration Factor 2 and the typical duration factor 4 may have been most similar, yielding a low congruence coefficient indicating differences, while still capturing similarity (0.63 and 0.76, respectively).

The differences in factor structures between the treatment duration groups sheds light on clinical and personal characteristics influencing treatment duration and recovery following a concussion. Consistent with previous research, we found age (Field et al., 2003), sex (Baker et al., 2016), history of mood, anxiety, migraine, or attention-deficit disorders (Zemek et al., 2016), and neurocognitive functioning at the time of evaluation (Iverson, 2007) potential indicators of treatment duration, representing the length of time a person seeks treatment after a concussion. While numerous studies have shown history of concussions (Iverson et al., 2017; Meehan, Mannix, Oêbrien, et al., 2013), symptom severity (Brown et al., 2014; Resch et al., 2015), and slowed reaction time (Norris et al., 2013) as potential indicators of longer recovery after a concussion, the present research findings do not support these items as features correlating with an individual's treatment duration through factor structure alone.

We collected data retrospectively from patients seeking care from sports medicine clinics, and thus the findings may not generalize more widely to head trauma populations. This approach may have created a degree of selection bias, targeting patients at increased risk for longer treatment durations. Open-source SVI data were evaluated only at the county-level, leading to a potential loss of data granularity. Census-tract data ideally should be included and evaluated, as this represents the most specific level of aggregated data, and this would allow for more accurate representations of the studied population. Last, due to the retrospective nature of this study, controlling for extraneous variables influencing the treatment durations was unresolvable and may have led to confounding bias.

Tables

Table 12: Demographic characteristics of subjects (n = 340)

Characteristic	Total Sample (*n* = 340)	Extended Duration (*n* = 81)	Typical Duration (*n* = 259)	Group difference (*p* value)
Age, M (SD)	16.9 (3.7)	16.9 (4.6)	16.9 (3.3)	0.95
Sex				0.06
Male	182 (54%)	36 (44%)	146 (56%)	
Female	158 (46%)	45 (56%)	113 (44%)	
Race				0.38
Caucasian	265 (77.9%)	66 (81%)	199 (77%)	
Minority	75 (22.1%)	15 (19%)	60 (33%)	
SVI				
Socioeconomic, M (SD)	0.08 (0.21)	0.12 (0.25)	0.07 (0.19)	0.1
Household Composite, M (SD)	0.20 (0.14)	0.23 (0.17)	0.20 (0.13)	0.12
Minority Status, M (SD)	0.78 (0.10)	0.78 (0.14)	0.78 (0.92)	0.77
Housing & Transportation, M (SD)	0.21 (0.17)	0.25 (0.22)	0.19 (0.16)	0.03*
Previous Concussion	75 (22%)	25 (31%)	50 (19%)	0.02*
History of anxiety, migraines, ADHD	33 (10%)	14 (17%)	19 (7%)	0.002**
ImPACT				
Verbal Memory Composite, M (SD)	87 (13.4)	86 (12.0)	88 (13.7)	0.45
Visual Memory Composite, M (SD)	77 (13.3)	75.0 (13.7)	77 (13.1)	0.18
Reaction Time Composite, M (SD)	0.72 (0.15)	0.77 (0.18)	0.70 (0.13)	<0.001***
Visual Motor Composite, M (SD)	38 (7.7)	36 (6.6)	38 (8.0)	0.07
Symptom Severity Composite, M (SD)	21.6 (21.6)	26 (24.1)	20 (20.7)	0.07
Treatment Duration, M (SD)	20.3 (28.1)	60.7 (31.4)	7.7 (7.4)	<0.001***

Note: M (SD) = Mean (Standard Deviation). SVI = Social Vulnerability Index. SVI themes are reported as percentile ranks of county-level data. Group differences were analyzed with independent samples t-test for continuous variables and χ^2 for categorical variables.

Table 13: Factor structure and loadings by group

	Extended Duration (*n* = 81)				Typical Duration (*n* = 259)			
Item Responses	Factor 1	Factor 2	Factor 3	Factor 4	Factor 1	Factor 2	Factor 3	Factor 4
Age	0.17	0.05	**0.78**	0.02	-0.01	-0.14	-0.04	0.09
Sex	0.05	-0.26	0.08	-0.29	0	0	**0.82**	0
Race (Caucasian)	-0.02	0.04	0.19	0.06	0.01	**0.32**	-0.23	-0.2
History of concussion	-0.15	0.26	0.29	0.22	0.05	0.06	0	-0.04
History of psychologic conditions	-0.1	-0.14	**0.43**	0.01	-0.08	-0.25	0.01	-0.13
SVI								
Socioeconomic rank	**0.99**	0	-0.04	0	1	-0.01	0	0.04
Household composition rank	**0.87**	-0.04	0.13	-0.02	**0.91**	0.06	0.02	-0.06
Minority status rank	**0.41**	0.09	**-0.49**	0.12	0.23	-0.24	-0.11	**0.37**
Housing/transportation rank	**0.84**	0	0.02	-0.02	**0.85**	-0.05	-0.02	0.01
ImPACT								
Verbal memory	-0.03	**0.88**	0.04	-0.05	-0.03	0.13	0.02	**0.72**
Visual memory	0.03	**0.65**	-0.08	0.05	0.05	**0.61**	0.06	0.14
Reaction time	0	0	0.03	**0.79**	-0.04	**-0.49**	0.03	0.13
Visual motor	0.07	0.25	0.04	**-0.5**	-0.07	**0.58**	-0.07	0.17
Total symptom severity	-0.05	0.11	-0.02	**0.37**	-0.04	**-0.39**	-0.19	0.02

Note: SVI = Social Vulnerability Index. SVI themes are reported as percentile ranks of county-level data. Item responses were deemed significant for the factor if loadings >= 0.30.

Table 14: Group factor structure differences

	Typical duration group			
Extended duration group	Factor 1	Factor 2	Factor 3	Factor 4
Factor 1	**0.98***	0.02	0.00	0.12
Factor 2	**0.00**	0.46	0.20	0.76
Factor 3	**0.03**	0.03	0.05	0.21
Factor 4	**0.00**	0.63	0.29	0.02

Note: Group factor structure differences were analyzed using Tucker's congruence coefficient. * = values > 0.85 were determined to be similar.

Figures

Figure 5: Flowchart of included and excluded participants

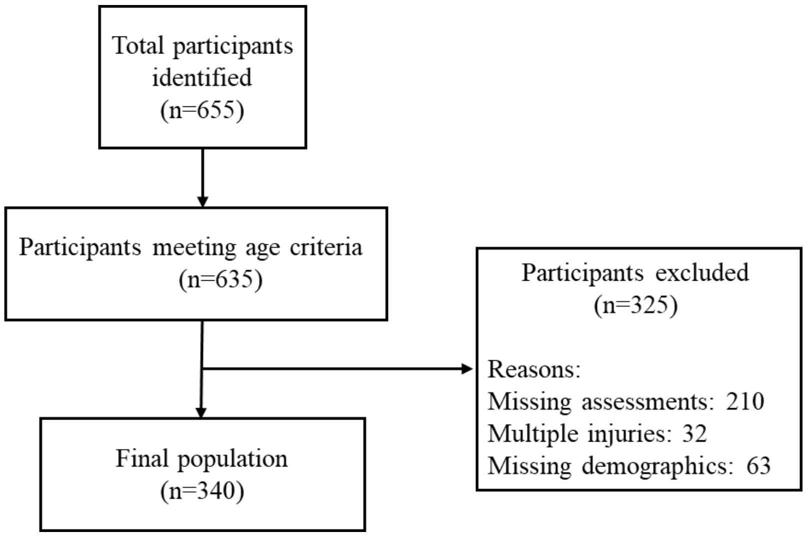


Figure 6: Scree plot of extended duration group

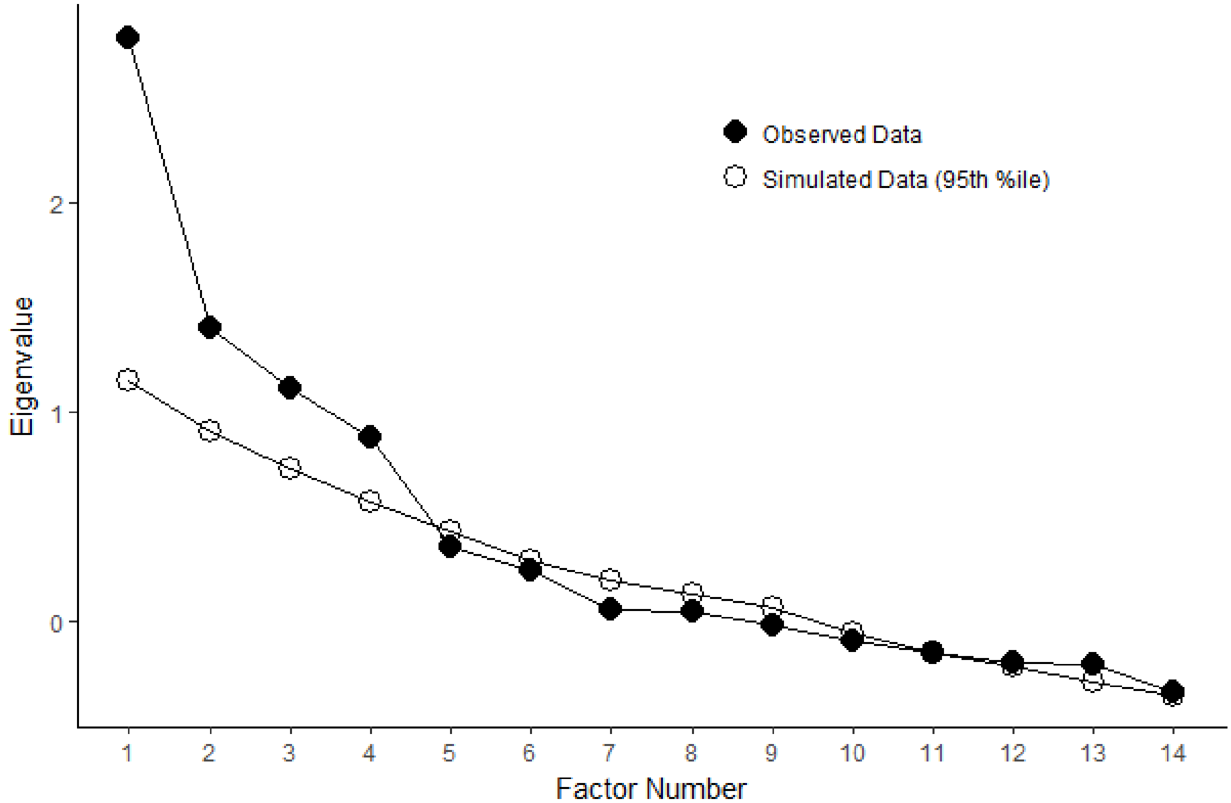
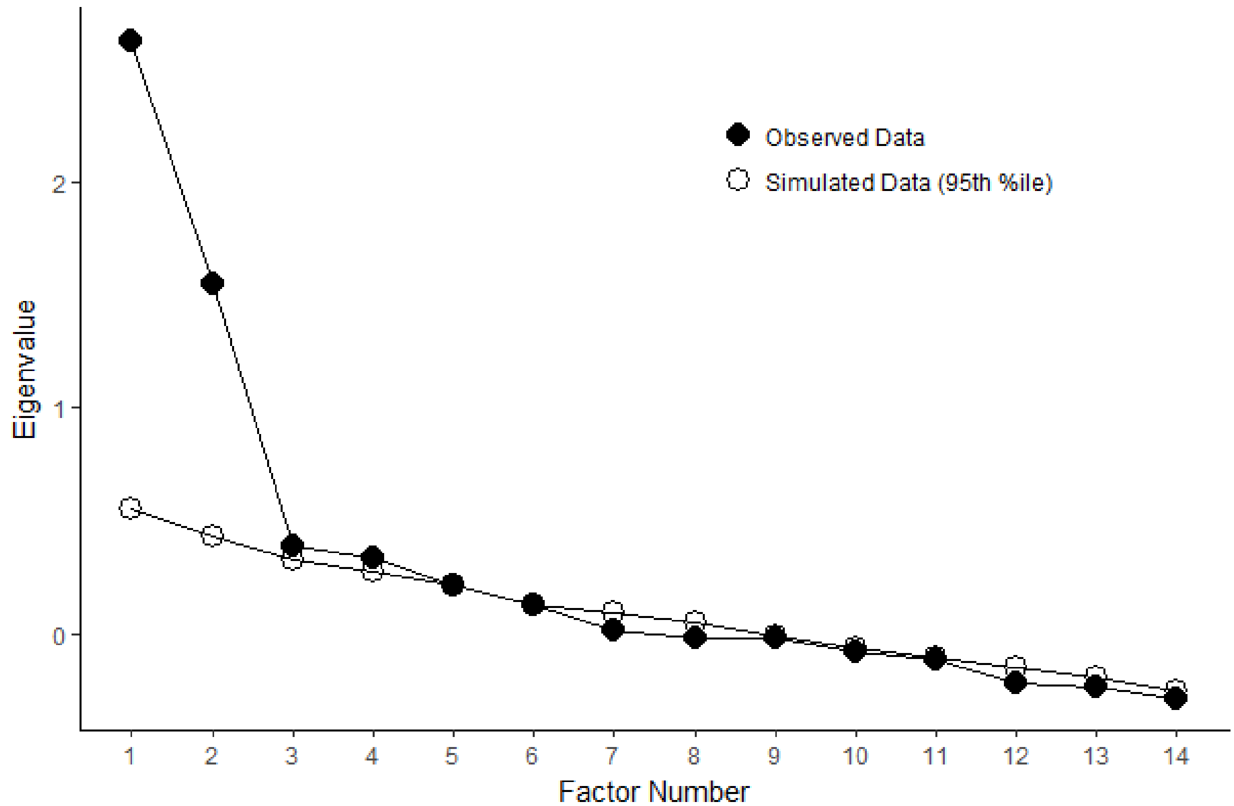


Figure 7: Scree plot of typical duration group



Chapter 7: Evaluation of clinical, demographic, and social factors on length of care after concussion

Abstract

Background: Identifying patients at risk for long care durations following concussion is challenging. This survival analysis assessed variables influencing length of care after a concussion.

Objectives: Identify clinical, demographic, and social factors that are predictive of longer care following concussion. We hypothesized that females, individuals with prior concussions, and individuals with lower socioeconomic indicators will have longer care durations.

Methods: Inclusion criteria for participation in the retrospective observational study included age 13-65, treated for concussion, and not concurrently treated for another injury. Demographics and medical histories were collected from patient medical records. Open-source Social Vulnerability Index (SVI) data were used and represented 4 social factors: socioeconomic status, household composition, minority status, and housing/transportation access. Lengths of care were inspected via Kaplan-Meier survival analysis along with log-rank tests of predictor variables and Cox proportional hazards regression.

Results: 665 patients were included and had a median length of care of 8 days. Log-rank tests indicated males had shorter care durations ($p < 0.001$). Individuals with a history of concussion ($p = 0.02$) and individuals with better access to housing and transportation had longer care durations ($p = 0.003$). The final Cox regression model demonstrated these variables as significant.

Discussion: This study provided additional evidence that prior concussions influence the length of cares after injury and adds further evidence to support differences in length of care for males and females. Further research is needed to examine the role social factors, including housing and transportation access, play in length of care following concussion.

Introduction

Concussions have become an increasingly prevalent form of brain injury, accounting for at least 80% of all traumatic brain injuries (Cassidy et al., 2004). Each year, an estimated 1.6-3.8 million sports-related brain injuries occur, although this figure is likely an underestimate as many concussions go unreported or unrecognized (Langlois et al., 2006). While the incidence rate of concussions is alarming, the evaluation and treatment of individuals following suspected concussive injury poise unique challenges for sports medicine practitioners, as symptom severity and presentation varies across individuals (McCrory et al., 2013).

The complexity of the injury's clinical presentation makes determining a person's recovery trajectory and anticipated length of care needs difficult. Studies have evaluated some risk factors that may prolong care. For example, age (Field et al., 2003), sex (Baker et al., 2016), history of concussions (Iverson et al., 2017; Meehan, Mannix, Stracciolini, Elbin, & Collins, 2013), reduced neurocognitive functioning (Iverson, 2007), slowed reaction times (Norris et al., 2013), and increased acute symptomology (Brown et al., 2014; Resch et al., 2015) have shown an increased risk of care lasting greater than 28 days after concussion. Despite these advances, prospectively identifying individuals at risk for long care durations following concussion remains elusive for clinicians.

The impact of social factors on length of care following concussion has not been well studied. Race has been evaluated in younger populations in respect to length of recovery after concussion (Eisenberg, Andrea, Meehan, & Mannix, 2013; Morgan et al., 2015). While these studies report little effect of race on recovery outcomes, the study samples were comprised of mostly white participants (78% and 90%, respectively). General socioeconomic factors are beginning to be considered in relation to recovery trajectory following concussion. For example, Kroshus and colleagues (2018) evaluated the relationships between lower socioeconomic status (SES) and the availability of both flag and tackle football. They found youth in lower SES communities were less likely to have non-contact football available, leaving tackle football as the only option for football participation. These results suggest inequitable odds of brain trauma from participation in youth football (Kroshus et al., 2018). While this example is specific to youth football participation, the unknown impact of SES is being brought to light on specific examples pertaining to injuries in sport. Specific evaluation of social factors in relation to length of care needed after a concussion is warranted.

While identification of risk factors for extended recovery after concussion has improved in recent years, gaps in knowledge remain. The goal of this study was to identify clinical (e.g. previous concussions, comorbid diagnoses), demographic (e.g. age, sex, race), and social factors (e.g. housing and transportation access, socioeconomic status) that are predictive of longer lengths of care following concussion. We hypothesized that females, individuals with prior concussions, and individuals with lower socioeconomic indicators will have longer care durations.

Methods

Design

This study used a retrospective observational cohort design with clinical data obtained from July 2013 and December 2016. The dates were selected based on when the health system clinics were opened for clinical management until the conclusion of the study. Approval was obtained from the University of Kansas Medical Center's Institutional Review Board prior to data collection and analysis.

Study population

A retrospective review of EMR data identified patients with a diagnosed concussion, based on the consensus definition (McCrory et al., 2013) and documentation of an appropriate ICD9 or ICD10 diagnostic billing code for a concussion diagnosis. Patients were seen at one of five sports medicine clinics operated by the University of Kansas Health System in the Kansas City metropolitan area between July 2013 and December 2016 (Waitman et al., 2011). Patients were included if they were between the ages of 13 and 65 years of age on the initial visit, were being treated clinically for a primary diagnosis of concussion and were not also being seen for another injury. This study was approved by the institutional review board of the University of Kansas Medical Center, and a full waiver of informed consent was granted in recognition that the retrospective nature of the study, the de-identification of patient medical data, and the study involved no more than minimal risk to subject privacy.

Data collection procedure

Data were collected on the following demographic and clinical variables: age, sex, race, English-speaking (yes, no), religious (yes, no), history of psychiatric diagnosis, number of previous concussions, migraine history, learning disability (yes, no), history of ADHD, and history of depression. Racial categories were as follows: White, Black, Asian, Pacific Islander, Bi-racial, and Other. The outcome measure of interest was the duration of treatment for concussion symptoms, represented by the difference between the initial concussion evaluation date and the date of the last visit for concussion treatment.

Additionally, open-source Social Determinants of Health (SDOH) data were included in the analysis. The Social Vulnerability Index (SVI) from the Geospatial Research, Analysis, and Services Program primarily is used by public health officials and emergency responders to identify and map communities that will most likely need support during a hazardous event (Flanagan et al., 2011). The SVI indicates relative vulnerability of every U.S. Census tract and ranks each tract on 15 social factors, including unemployment, minority status, and disability, collapsing these factors into 4 themes: socioeconomic status; household composition and disability; minority status and language; and housing and transportation (Agency for Toxic Substances and Disease Registry (ATSDR), 2014; Tate, 2012). These four themes were used in this analysis to assess the role of social determinants in concussion treatment duration. County-level SVI data were used in the analysis due to lack of geospatial coding information available for each participant. The themes are reported as percentile rankings, with county-level data compared across the entire US population. The percentile ranking values range from 0 to 1, with the higher values indicating greater vulnerability for each county (Agency for Toxic Substances and Disease Registry (ATSDR), 2014). An example ranking of 0.149 for a county indicates the present county is more socially vulnerable than 14.9% of all other counties. Additionally, each percentile-rank theme was dichotomized into high and low categories by sampling at the median 0.50 ranking.

Statistical Analysis

Descriptive statistics were determined for each demographic and clinical factor. Differences in distributions of variables between sex were tested with independent *t*-tests for continuous variables or chi-squared tests for categorical variables. Length of care durations were inspected with the Kaplan-Meier survival analysis method with a log-rank test and multivariate Cox proportional hazards regression model. Statistical assumptions of normality for *t*-tests and proportional hazards for Cox regressions were inspected. Statistical analysis was completed with *R*, an open-source statistical programming language (R Core Development Team, 2016). The significance level was set at $\alpha = 0.05$ *a priori* for statistical inference.

Results

A total of 665 patients were seen in the clinics from July 2013 to December 2016 and were included for analysis. The sample was comprised of 58% males, 77% Caucasians, 33% Minorities, 18% had history of previous concussion, and 52% were religious (see Table 15). When compared to males, females were more likely to be Caucasian ($p = 0.02$), more likely to be diagnosed with anxiety ($p = 0.01$) or depression ($p = 0.01$), and less likely to be diagnosed with ADHD ($p = 0.03$).

The mean and median length of care for the full population were 20 days and 8 days, respectively. Males had a shorter length of care than females (median 7 vs. 10 days) and produced a significant log-rank test ($p < 0.001$; Table 16 and Figure 8). Log-rank tests were significant for a history of prior concussions, with participants with a prior concussion having a longer length of care (median 9 days vs. 8 days, $p = 0.02$; Table 16 and Figure 9). The dichotomized Housing and Transportation theme of the SVI was also significant, with participants with higher percentile ranks for the theme having longer lengths of care (median 14 days vs 7 days, p = 0.003). There were no statistical differences between groups with respect to race, religious affiliations, or prior medical diagnoses (ADHD, anxiety, migraines, depression).

In the Cox proportional hazards regression model, the event of interest, length of care after concussion, is indicated by an increase in the hazard ratio for each variable. In the present analysis, a lower hazard represents a longer length of care and is indicative of a negative outcome. The Cox proportional hazards regression demonstrated that 3 out of 12 variables had significant prognostic value for length of care following concussion ($p \leq 0.05$). Males had an increase in the hazard by 135%, indicating a favorable outcome towards shorter length of care following concussion. There was a 21% reduction of the hazard (less favorable) in individuals with a prior concussion, indicating a longer length of care. Higher housing and transportation percentile ranking of the SVI showed a 33% reduction of the hazard (less favorable), again indicating longer length of care (see Table 17).

Discussion

The main objective of the present study was to evaluate the impacts of different factors on the length of care following a concussion. Prior concussions, the housing and transportation SVI theme, and sex were predictor variables associated with length of care. A history of prior concussions and high percentile ranking for housing and transportation predicted longer lengths of care, and females predicting longer lengths of care, respectively.

Our findings from this study align with previous research. Wojcik (2014) determined that concussion history was indicative of longer recovery after concussion (n = 85, $p < 0.001$). Additionally, Aggarwal and colleagues (2017) reported prior concussions as a significant predictor of longer recovery times in adolescents after concussion (n = 118, $p = 0.03$). Our study confirmed prior concussions as a predictor of long duration of care after a concussion in a larger (n = 665) and more balanced sample, in respect to sex (58% male, 42% female). History of prior concussion has been associated with several changes in a person’s overall functioning, including postural control (Sosnoff, Broglio, Shin, & Ferrara, 2011), gait (Martini et al., 2011), memory (Alsalaheen et al., 2017), information processing speed (Bernick et al., 2015), and attention (Moore et al., 2015). These neurofunctional changes and increased risk for longer lengths of care make identifying patients with prior concussion imperative at the point of clinical management, as these individuals may experience longer physical symptoms, cognitive changes, and impaired functioning in respect to peers who are injured and have not had prior concussions.

Additionally, in this study, sex was an important predictor of length of care after injury. Our results coincide with several studies indicating females have longer symptom resolution and treatment than male counterparts (Bock et al., 2015; McCrory et al., 2017; Miller et al., 2015). Conversely, several studies have not replicated these results (Aggarwal et al., 2017; Ono et al., 2016; Wojcik, 2014). One explanation for the lack of consensus may be sample size and balance of sex in sample size, as these previous studies had relatively small samples (n < 200) and imbalanced sex distributions. Our sample size and gender distributions are larger and more balanced, thus yielding improved ability to assess the variable.

The Berlin Consensus statement recommends careful planning of intervention for individuals with ADHD, but substantially greater risk of persisting symptoms beyond one month does not appear evident (McCrory et al., 2017). Our results coincide with this recommendation, as we only observed an 8% reduction of the hazard, indicating a slight risk of longer care duration. Our research did not find that a prior diagnosis of ADHD is predictive of longer recovery times, which differs from previous studies (Aggarwal et al., 2017; Miller et al., 2015), although ADHD as a predictor has mixed evidence.

A unique attribute of this study was the assessment of open-source social determinants of health data in relation to length of care after concussion. Social determinants of health are conditions in the environments in which people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks (U.S. Department of Health and Human Services, 2010). To date, only one study has evaluated the role of socioeconomic indicators on length of care after concussion. Aggarwal et al. (2017) used insurance type (e.g. Medicaid, student-athlete insurance) as a proxy for socioeconomic status and found significant predictor performance for shorter symptom resolution. Our study certainly trended to similar conclusions. Access to appropriate housing and transportation produced significant outcomes indicating a relationship with length of care following concussion. The association may indicate social and economic factors exist that may influence recovery from injury, indicating this type of injury has both medical and social implications. Studies have addressed some social and societal issues related to concussions, including under-reporting of injuries in sports populations (Chrisman et al., 2013; McDonald, Burghart, & Nazir, 2016), and collegiate athletes being pressured by coaches, teammates, fans, or parents to underreport injuries (Kroshus, Garnett, Hawrilenko, Baugh, & Calzo, 2015). Societally, athletes purposefully may mask symptoms and artificially shorten recovery in response to economic pressures to keep playing their sport, in the hopes of earning an athletic scholarship for college or lucrative pay professionally.

Significance of this specific theme may shed light on ability to attend future visits and appointments, as individuals with lower access to transportation via the SVI had shorter care durations. It would be unwise to categorically state that individuals with lower socioeconomic status have shorter recoveries. Rather, access to transportation for clinic appointments may be more influential in determining care durations but not explicitly related to recovery of symptoms. Clinicians should be aware of this information and provide recovery education at the evaluation and alternative care approaches (e.g. Telehealth) for additional visits. Future research must further expand and clarify the impact of social factors on length of care.

We collected participant data retrospectively from outpatient sports medicine facilities, and thus the findings may not generalize more widely to head trauma populations. This approach may have created a degree of selection bias, targeting patients at increased risk for longer treatment durations. Open-source SVI data were evaluated only at the county-level, leading to a potential loss of data granularity. Census-tract data ideally should be included and evaluated, as this represents the most specific level of aggregated data, and this would allow for more accurate representations of the studied population. Last, controlling for extraneous variables influencing the treatment durations is unresolvable because this study was retrospective in nature. This may contribute to confounding bias.

Conclusions

This study provided insights into the relationship between clinical and demographic variables and length of care following concussion. This study provided additional evidence that prior concussions influence the length of treatment a person requires after injury and adds further evidence to support differences in length of care for males and females. Further research is needed to examine the role played by social determinants of health in influencing length of care following concussion, including access to housing and transportation.

Conflicts of interest

The authors have no conflicts to disclose. The researchers did not receive external funding to support this work.

Tables

Table 15: Demographic characteristics of participants

Characteristic	Total Sample (*n* = 665)	Males (*n* = 389)	Females (*n* = 276)	Sex differences (*p* value)
Age, years; M (SD)	17.6 (5.5)	17.5 (5.3)	17.7 (5.7)	0.64
Race				0.02*
Caucasian	511 (77%)	287 (43%)	224 (34%)	
Minority	154 (23%)	102 (15%)	52 (8%)	
Religious	343 (52%)	203 (31%)	140 (21%)	0.71
SVI				
Socioeconomic, M (SD)	0.11 (0.24)	0.11 (0.25)	0.11 (0.24)	1.00
Household Composite, M (SD)	0.23 (0.17)	0.24 (0.17)	0.23 (0.16)	0.44
Minority Status, M (SD)	0.79 (0.11)	0.78 (0.12)	0.79 (0.09)	0.24
Housing & Transportation, M (SD)	0.24 (0.21)	0.24 (0.20)	0.24 (0.21)	1.00
Previous Diagnosis				
Concussion	117 (18%)	66 (10%)	51 (8%)	0.61
Anxiety	13 (2%)	3 (<1%)	10 (2%)	0.01*
Depression	10 (2%)	2 (<1%)	8 (1%)	0.01*
Migraine	8 (1%)	3 (<1%)	5 (1%)	0.23
ADHD	28 (4%)	22 (3%)	6 (1%)	0.03*
Length of care, days; M (SD)	19.9 (34.5)	15.8 (25.7)	25.7 (43.4)	<0.001***

Note: Sex differences were assessed with independent samples t-test for continuous variables and χ^2 for categorical variables. M (SD) = Mean (Standard Deviation). ADHD = Attention Deficit Hyperactivity Disorder. SVI = Social Vulnerability Index.

Table 16: Kaplan-Meier survival analysis (Log-Rank test) for select predictors of length of care following concussion (N = 665)

		Length of Care (days)		
Variables	# of cases	Mean	Median	*p*-value
Sex				<0.001***
Male	389	15.84	7	
Female	276	25.72	10	
Race				0.9
Caucasian	511	20.04	8	
Minority	154	19.62	8	
Prior Concussion				0.02*
1 or more	117	26.83	9	
None	548	18.47	8	
Religious				0.9
Yes	343	19.75	8	
No	322	20.15	8	
Housing/Transport				0.003**
High	122	31.23	14	
Low	543	17.48	7	
History of ADHD				1.0
Yes	28	20.46	8	
No	637	19.92	8	

Note: ADHD = Attention Deficit Hyperactivity Disorder. Minorities included all non-Caucasian races. Housing/Transport represents the dichotomized SVI theme for housing and transportation split at 50^{th} percentile.

Table 17: Cox proportional hazard regression results for length of care following concussion (N = 665)

Predictor	*p*	Hazard Ratio	95% CI
Sex	<0.001***	1.35	1.15 – 1.59
Race	0.98	1.00	0.82 – 1.21
Religious	0.83	0.98	0.84 – 1.15
Previous Diagnosis			
Concussion	0.03*	0.79	0.64 – 0.98
Anxiety	0.60	0.83	0.41 – 1.66
Depression	0.49	1.30	0.61 – 2.77
Migraine	0.50	1.28	0.63 – 2.58
ADHD	0.66	0.92	0.62 – 1.35
SVI			
Socioeconomic	0.90	0.95	0.34 – 2.61
Household Composite	0.75	1.18	0.43 – 3.24
Minority Status	0.76	1.11	0.57 – 2.16
Housing & Transportation	0.001**	0.67	0.52 – 0.86

Note: Overall significance of model $p < 0.001$. Proportional hazards assumption was met for all variables. SVI variables were dichotomized into high/low classifications set at 50th percentile. ADHD = Attention Deficit Hyperactivity Disorder. CI = Confidence Interval.

Figures

Figure 8: Kaplan-Meier curve of the days of care by sex

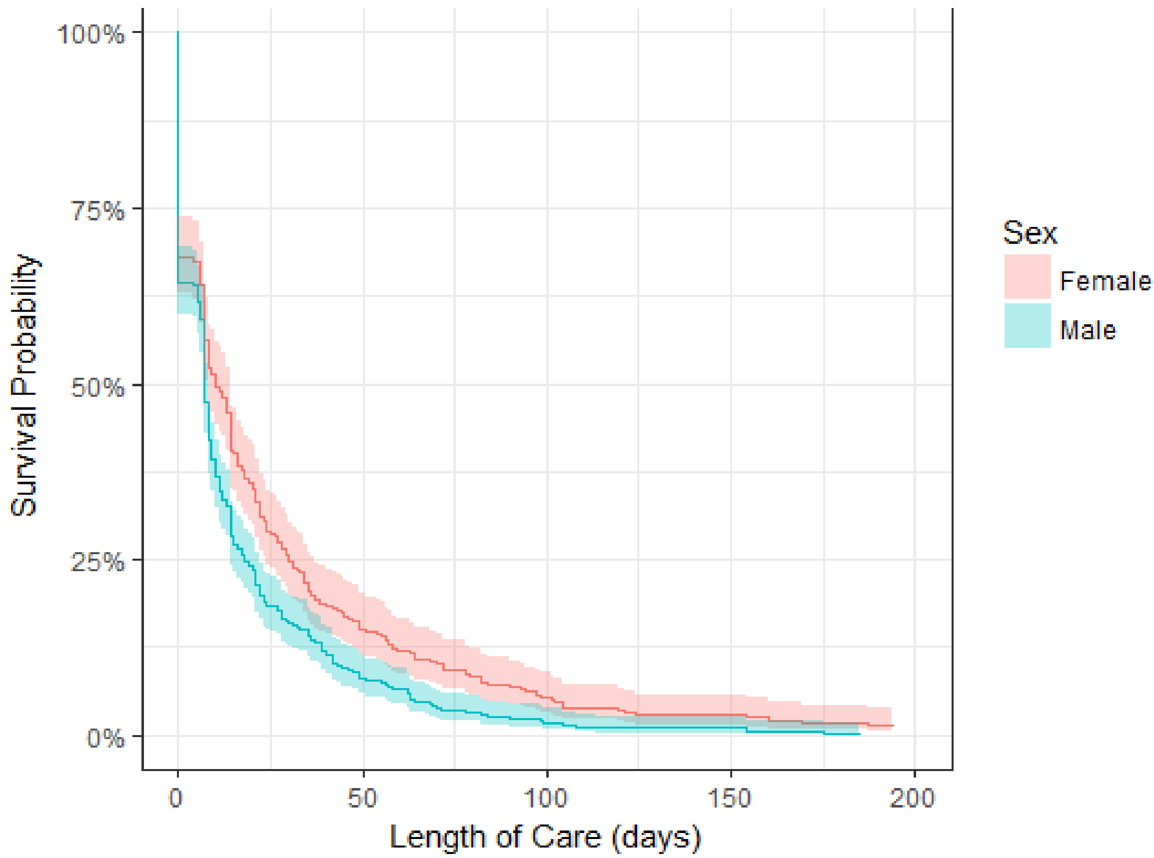
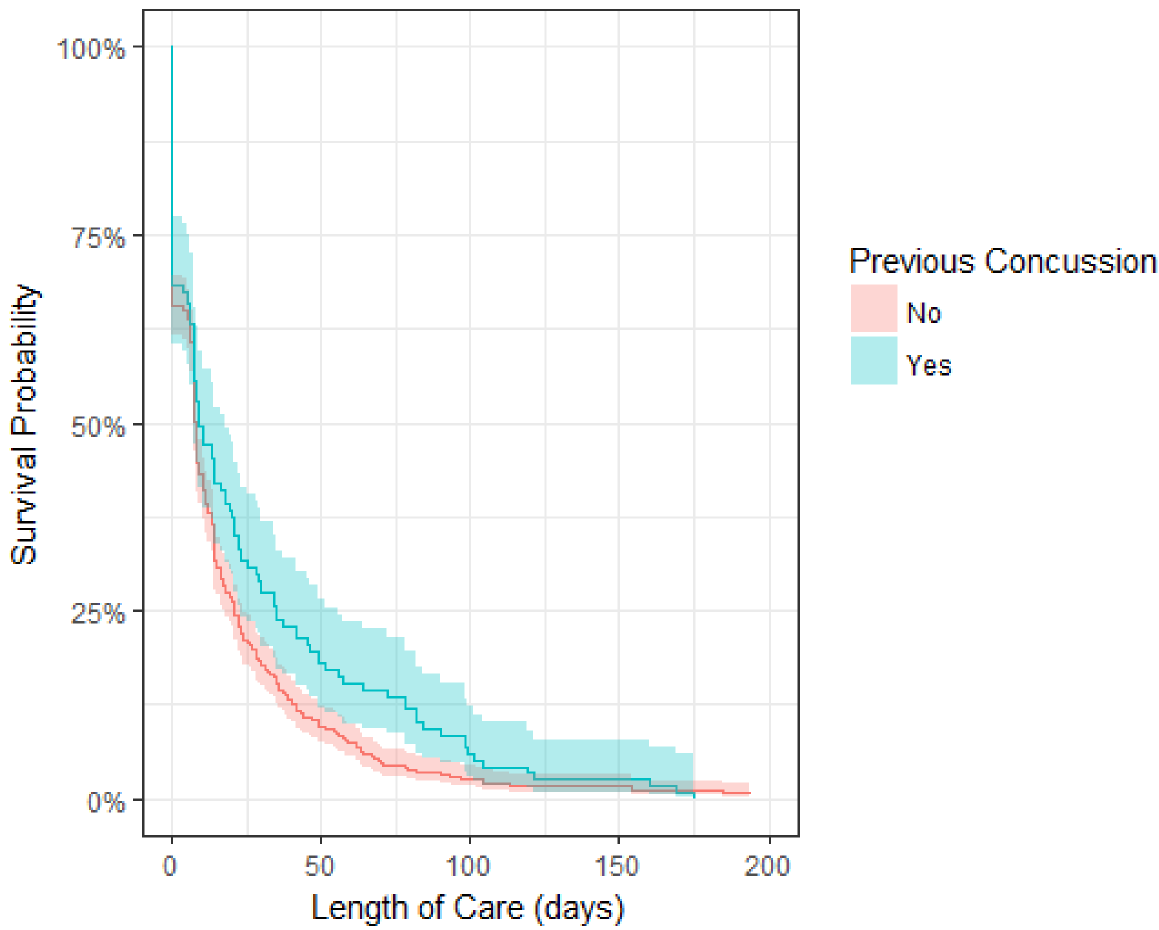


Figure 9: Kaplan-Meier curve of the days of care for participants with a history of concussion



Chapter 8: Early predictors of length of care following concussion

Abstract

Objectives: To identify early predictors of extended lengths of care for individuals seeking services from sports medicine clinics following concussion.

Methods: A retrospective study was conducted at five sports medicine clinics specialized in concussion assessment and management. Length of care was determined by the difference in time between discharge and evaluation dates. Demographic data, clinical assessments done at evaluation, and open source social determinants of health (SDH) data were considered. Adjusted binomial logistic regression analysis was used to model the effects of patient and injury characteristics on extended care lasting greater than 28 days.

Results: Data from 340 patients were analyzed. Median length of care was 10 days. 28.5% (97/340) of patients experienced a length of care lasting longer than 28 days. History of previous concussions and slowed reaction times at evaluation were significantly associated with longer care (p-value < 0.05). Additionally, individuals from lower socioeconomic areas had lower odds of an extended length of care (Odds Ratio = 0.48, 95% CI = 0.02-12.31).

Discussion: Slowed reaction times and a history of previous concussion(s) were associated with longer durations of care. Individuals from lower socioeconomic areas were less likely to have longer care, which may be attributable to lack of financial and transportation resources available to continue care. Further research is needed to elucidate the complex role SDH play in clinical outcomes after concussion.

Conclusions: History of concussion and reaction times should be considered and assessed at the initial evaluation to help identify patients at risk for longer durations of care. Continued evaluation of SDH data is needed to further clarify the impacts of social features on concussion outcomes.

Introduction

Concussions have emerged as one of the most prominent injuries treated in sports medicine settings. Roughly 75% of the estimated 1.7 million people sustaining traumatic brain injuries each year in the United States are diagnosed as having a concussion ((CDC), 2003; Faul, Xu, Wald, & Coronado, 2010). Concussions were once viewed as a ‘silent’ epidemic (Wojcik, 2014), as many people experience problems after injury that are difficult to observe, creating difficulties for clinicians to assess and treat (Bay & McLean, 2007).

Clinical assessment and care following concussion inherently is challenging due to diverse and sometimes delayed presentation of symptoms. Additionally, prognosis after injury is challenging in particular, since subsets of individuals experience differing lengths of care, including pediatric populations (Kostyun & Hafeez, 2015; Morgan et al., 2015), female populations (Eisenberg et al., 2013; Kostyun & Hafeez, 2015; Marar et al., 2012), and individuals with previous concussions (Colvin et al., 2009; Eisenberg et al., 2013; Morgan et al., 2015). Individuals with extended lengths of care have reported impaired return-to-work, return-to-school, and psychosocial functioning (De Krujik et al., 2002; Savola & Hillbom, 2003), stressing the importance of quickly identifying and treating individuals at risk for longer care.

Limited information exists on the role of Social Determinants of Health (SDH) on outcomes following concussion. Socioeconomic status, a common construct included in SDH data, has been mostly studied in patients after moderate to severe traumatic brain injury, where lower socioeconomic status has been associated with worse outcomes (Hart et al., 2016; Yeates et al., 2004). Specific to concussions, lower socioeconomic status was a significant predictor of poor cognitive outcomes at 3 months post-injury (Rabinowitz et al., 2015), although these results are mixed (Zuckerman et al., 2017). Other aspects of SDH, like housing and transportation access, minority status, and community structure have yet to be explored in relation to concussion outcomes.

The aim of this study was to explore the complex relationships between demographic information, injury characteristics, open source SDH data, and length of care among patients presenting to sports medicine clinics. Data available during or obtained from the clinical evaluation was used for analysis, as to better assess early prediction of extended lengths of care. We hypothesized that younger individuals, females, individuals with previous concussions, and higher initial symptom severity would be significantly associated with longer care. Additionally, we hypothesized that individuals from areas with more social vulnerability would be associated with longer lengths of care.

Methods

Study Population and Design

This study analyzed retrospective concussion data from electronic medical records and identified patients with a diagnosed concussion, based on the consensus definition (McCrory et al., 2013) and documentation of an appropriate ICD9 or ICD10 diagnostic code for a concussion. Patients were seen at one of five sports medicine clinics operated by the University of Kansas Health System in the Kansas City metropolitan area between July 2013 and December 2016. Patients were included if they were between the ages of 13 and 65 years of age on the initial visit, were being treated clinically for a primary diagnosis of concussion and were not also being seen for another injury. This study was approved by the institutional review board of the University of Kansas Medical Center, and a full waiver of informed consent was granted in recognition that the retrospective nature of the study, the de-identification of patient medical data, and the study involved no more than minimal risk to subject privacy.

A total of 665 individuals were identified for the study. Of those, 325 did not meet the inclusion criteria: 20 did not meet the age criteria, 210 had missing clinical assessment data, 32 were being treated for multiple injuries, and 63 had missing demographic information (see Figure 10). Thus, a total population of 340 participants was included in the study.

Variables

Length of care, our outcome variable of interest, was defined as the number of days between the date of concussion evaluation in the sports medicine clinic until the patient was formally discharged from clinical services. Length of care was further categorized into two discrete groups: ‘Extended Duration’, representing individuals with care durations > 28 days, and ‘Typical Duration’, representing individuals with an expected length of care lasting ≤ 28 days.

Demographic and clinical data were collected during the first clinical evaluation and was extracted from the electronic medical record using the Healthcare Enterprise Repository for Ontological Narration (HERON), an i2b2-based data analytics tool (Waitman et al., 2011). Age at the time of visit, sex, race, history of previous concussion, and county of residence were documented and considered as predictors of length of care.

Open-source SDH data were also included in the analysis. The source of SDH data used was the Social Vulnerability Index (SVI) from the Agency for Toxic Substances and Disease Registry (Agency for Toxic Substances and Disease Registry (ATSDR), 2016). The SVI is primarily used by public health officials and emergency responders to identify communities that will need support during a hazardous event (Flanagan et al., 2011). The SVI indicates relative vulnerability of every US Census tract and ranks each tract on 15 social factors, including unemployment, minority status, and disability. The factors are consolidated into 4 composite scores: socioeconomic status; household composition and disability; minority status and language; and housing and transportation (Agency for Toxic Substances and Disease Registry (ATSDR), 2014; Tate, 2012). The SVI composite scores assess the following:

Socioeconomic status: Rates of individuals below the poverty line, unemployed, low household income, and high school graduates.

Household composition and disability: Rates of individuals aged 65 or older, 17 or younger, diagnosed disability, and single-parent households.

Minority status and language: Rates of individuals identifying themselves as a minority, speak English “less than well”.

Housing and transportation: Rates of individuals living in multi-unit structures (ex. apartments), mobile homes, over-crowding of homes, no personal vehicle, and group quarters.

The four composite scores were used in this analysis to assess the role of social constructs in concussion treatment duration. County-level SVI data were used in the analysis, due to lack of geospatial coding information available for each participant. The themes are reported as percentile rankings, with county-level data compared across the entire US population. The percentile ranking values range from 0 to 1, with the higher values indicating greater vulnerability for each county (Agency for Toxic Substances and Disease Registry (ATSDR), 2014). An example ranking of 0.149 for a county indicates the present county is more vulnerable than 14.9% of all other counties in the US.

The Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) test battery is a formal concussion assessment and is commonly completed at evaluation. The ImPACT is a computerized concussion battery consisting of composite scores on the Post-Concussions Symptoms Scale and 4 neurocognitive modules: verbal memory, visual memory, visual motor processing speed, and reaction time (ImPACT Applications, 2007). The assessment has been well studied in concussion populations, is widely used, and is valid for people 10-60 years of age (ImPACT Applications, 2007; Iverson, Brooks, Collins, & Lovell, 2006; Iverson, Lovell, & Collins, 2005). ImPACT results from participant evaluations were queried and included in the analysis.

Statistical Analysis

Statistical analyses were performed using the open-source statistical programming language *R* (R Core Development Team, 2016). Descriptive statistics were calculated for each demographic, social, and clinical factor. Differences in length of care across patients and variables were compared using χ^2 tests for categorical variables, and *t*-tests for continuous variables. A multivariable, binomial logistic regression analysis was used to model the effect of patient and injury characteristics on length of care after concussion. The resulting odds ratios were adjusted to include potential confounding variables, accounting for effects due to all additional variables included in the analysis. Statistical significance was set at 0.05 *a priori*.

Results

Population Characteristics

Evaluation and demographic data from 340 patients were analyzed. Most patients were male (53%), white (78%), young (mean age 17.6 years), religious (55%), and had not had a previous concussion (88%). The median length of care for the entire population was 10 days. Of the 340 participants, 97 individuals (29%) had extended lengths of care lasting more than 28 days. Increased length of care was associated with a documented history of concussion (p = 0.005). Sex (p = 0.06), specifically females, trended towards a significant association with longer care duration following injury. Age was not associated with length of care (see Table 18).

SVI composites

SVI averages for the total population, along with extended and typical durations subgroups, are reported in Table 18. Participants generally came from affluent communities (average socioeconomic composite = 0.02), had adequate housing and transportation (0.14), stable households (0.16), and had higher minority status (0.77). No group differences were noted between individuals with typical and extended care durations.

ImPACT composites

Clinical results from the ImPACT assessment were consistent across participants, with one exception. Average results from the reaction time component of the ImPACT assessment produced significant differences in people with typical and extended care durations, with averages results of 0.70 and 0.76 seconds, respectively (p-value < 0.001). Averages for verbal memory composite (87.3), visual memory composite (76.8), efficiency (0.39), impulse control composite (8.0), and visual motor composite (37.8) did not yield significant differences between individuals with typical and extended lengths of care (Table 19). While differences were not statistically significant, individuals in the extended population had higher total symptom severity component scores (24.0) than the typical population (20.7) at evaluation.

Adjusted odds ratios of length of care

Individuals with a previously diagnosed concussion were more likely to experience an extended length of care when compared to participants being treated for their first concussion, with 103% greater risk for having care last more than 28 days (odds ratio [OR] = 2.03, 95% confidence interval [CI] = 1.14-3.58) (Table 20). Compared with male counterparts, female participants were more likely to have extended recoveries lasting more than 28 days (OR = 0.85, 95% CI = 0.50-1.45). Caucasian participants were more likely to have extended care when compared with minority participants (OR = 1.36, 95% CI = 0.72-2.66).

Participants at evaluation with slower reaction times experienced longer care durations when compared to individuals with faster reaction times. For each one unit increase in reaction time (seconds), the odds of care lasting more than 28 days increased by 26.7 units (95% CI = 4.27-181.39). This difference between populations was statistically significant (p-value <0.001).

Individuals with lower socioeconomic status, indicated by the SVI socioeconomic composite score, were less likely to have longer treatment durations (OR = 0.48, 95% CI = 0.02-12.31). Additionally, higher housing and transportation composite scores, indicating less access to housing and transportation, had higher odds of longer treatment durations (OR = 12.00, 95% CI = 0.91-158.55).

Discussion

This study analyzed associations between patient information, injury characteristics, open source SDH data, and length of care among patients presenting to sports medicine concussion clinics, using data available at the time of evaluation. The median length of care for the full population was 10 days. Reaction time measurement at the concussion evaluation, along with a history of previous concussion(s) were associated with increased odds of extended lengths of care. While not statistically significant, females had increased odds of extended care (*p*-value = 0.06). Our results did not support relationships between age and length of care, although the sample was comprised of a younger population (average age 17.6 years) and may limit the generalizability to more wide-ranging age groups.

Although most studies focusing on younger populations indicate younger individuals experience longer post-concussion recovery (Zemek et al., 2016), our results indicated that the median length of care was 10 days, which coincides with the 7 to 10 day adult recovery estimates (McCrea et al., 2013; McCrea, Guskiewicz, Marshall, Barr, Randolph, Cantu, Onate, Yang, et al., 2003; McCrory et al., 2013). While the median length of care resides on the high side of this range, the longer treatment times could be explained by patients falling on the more severe spectrum for concussion injuries tend to seek out care at sports medicine clinics trained in concussion care (Kirkwood, Yeats, & Wilson, 2006).

A novelty of this study was inclusion of open-source SDH predictors as a way of evaluating the influence of social constructs on length of care following concussion. There has been increased use of SDH concepts for the evaluation of health-specific outcomes studies in research years, mainly driven by the thought that factors apart from medical care can influence and shape health in powerful ways (Braveman & Gottlieb, 2014). To our knowledge, this study was the first to assess the community makeup of a person as it relates to length of care durations following concussion. Individuals from lower socioeconomic areas were less likely to have longer treatment durations in our study. This differed from our original hypothesis that people from more vulnerable areas (e.g. lower socioeconomic communities) would have longer care durations. We hypothesized that people living in more vulnerable communities will possess fewer resources and have more life stressors impeding the recovery process.

Further discussion and research related to this observation is warranted. While our study assessed care durations after injury, an important distinction to make is that length of care does not truly equate to resolution of concussion symptoms. Rather, length of care encompasses both having symptoms severe enough to necessitate continued medical intervention and having sufficient resources to pursue extended treatment. Individuals from areas with greater vulnerability may not have childcare arrangements, transportation, time off of work, or financial resources to pursue continued concussion care, thus impacting our outcome of interest. This could explain the somewhat conflicting odds results between the Socioeconomic and Housing and Transportation SVI composites, as individuals with greater socioeconomic vulnerability typically saw shorter lengths of care, but also had less access to transportation. If individuals are less able to afford care or have an inability to attend treatment sessions, shorter lengths of care would be expected. Zuckerman et al (2017) drew similar conclusions after the study of the influence on socioeconomic status on concussion outcomes, finding that individuals with private health insurance were more likely to receive medical care by a concussion specialist, and therefore had longer care durations.

The predictive ability of slowed reaction times is a finding emerging from this study that is highly relevant to clinical practice and the management of individuals after concussion. Slowed information processing abilities assessed by reaction times have been studied previously, including as an aide in diagnosis of a concussion (McCrory et al., 2017; Warden et al., 2001) and for prognostic utility during care (Norris et al., 2013). Warden et al. (2001) also indicated slowed reaction times can persist even after self-reported symptoms have resolved, representing an important distinction for practitioners weighing return-to-sport decisions. Multiple validated reaction time measures exist for clinicians to use during evaluation, including computerized tests

(Tombaugh et al., 2007), mobile devices (Burghart, Craig, Radel, & Huisinga, 2018), and homemade devices (Eckner et al., 2010).

Coinciding with existing studies on concussion recovery, our research revealed having a history of concussion was associated with longer lengths of care (Colvin et al., 2009; Eisenberg et al., 2013; Morgan et al., 2015). While this finding is not novel, the continued findings add to the importance of evaluating both diagnosed and potential concussions after head trauma. As concussions commonly remain un-diagnosed (Khurana & Kaye, 2012), clinicians should prioritize patient interviews around previous injuries, even undocumented or unevaluated concussions, as individuals were twice as likely to have an extended care duration with a history of diagnosed concussion.

Gender was associated with longer care following injury. Females were more likely to experience extended lengths of care, coinciding with sports-related concussion research (Kostyun & Hafeez, 2015; Majerske et al., 2008; Marar et al., 2012). Explanations for this difference include physical differences between genders (Kostyun & Hafeez, 2015), as well as reports of female athletes having high likelihood to report concussions and seek medical care than their male counterparts (Colvin et al., 2009; Kostyun & Hafeez, 2015).

Symptom severity scores at the time of evaluation were not significantly associated with length of care, which is inconsistent with previous studies (Meehan, Mannix, Monuteaux, Stein, & Bachur, 2014; Meehan, Mannix, Stracciolini, et al., 2013). While individuals with extended lengths of care had more symptoms with greater severity when compared to individuals with typical care durations, this factor failed to yield any increased odds of longer care when compared to typical individuals. One explanation for this could be specific symptoms and severity indicate longer care, while assessing the composite symptom severity score lost granularity into these relationships.

No difference was observed between extended and typical recovery groups using age as a predictor. This finding conflicts with previous research indicating younger ages tend to have longer recoveries (Kostyun & Hafeez, 2015; Morgan et al., 2015). One explanation for this difference could be controlling for injury severity. Younger individuals may take longer to recover than older individuals from a similarly severe injury (Thomas et al., 2017).

Limitations

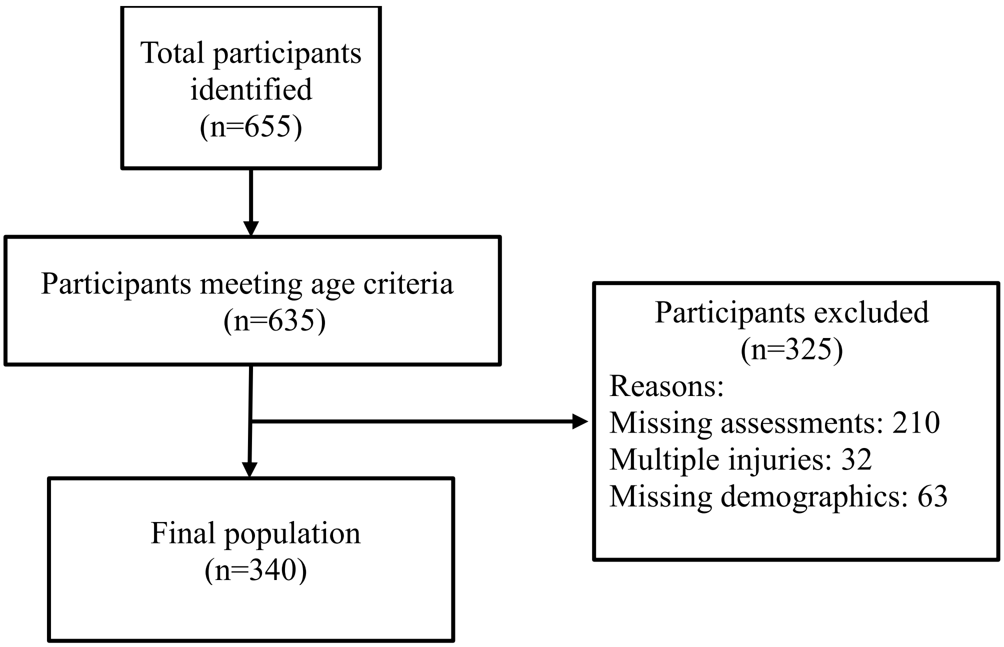
Our study had several limitations. First, our sample only included people seeking care from a sports medicine clinic. Our sample may not be representative of the overall population of individuals presenting to emergency departments, primary care physicians, or athletic trainers after experiencing a concussion. Second, we used existing data from prior clinical evaluations, which did not include information about previous concussion treatments and management prior to the initial evaluation at the concussion clinics. Therefore, any prior injury events or treatments administered to concussion patients may have influenced the length of care. Lastly, only composite scores were available for both the ImPACT and SVI data. Greater data granularity into specific symptoms or geographical areas would allow continued assessment of factors influencing length of care.

Conclusions

Being female, having a history of prior concussion(s), and having slower reaction times at initial evaluation were risk factors for extended lengths of care following concussion. Age, race, SVI composites, or other ImPACT composites did not significantly influence odds of longer care durations. Clinically, gender and concussion history are important factors to consider when planning interventions and treatments at evaluation. The addition of reaction time testing will aide in the prognostic ability at the time of evaluation. Future research should continue to assess the impact of social constructs and environments on both the ability to pursue care and length of care after concussion.

Figures

Figure 10: Participant selection and exclusion



Tables

Table 18: Demographic characteristics of participants

Characteristic	Total Sample (*n* = 340)	Extended Recovery (*n* = 97)	Typical Recovery (*n* = 243)	Group differences (*p* value)
Age, years; M (SD)	17.6 (5.5)	17.5 (5.3)	17.7 (5.7)	0.64
Race				0.38
Caucasian	265 (78%)	66 (19%)	199 (58%)	
Minority	75 (22%)	15 (4%)	60 (18%)	
Religious				0.57
Yes	188 (55%)	47 (14%)	141 (41%)	
No	152 (45%)	34 (10%)	118 (35%)	
Sex				0.06
Male	182 (53%)	36 (11%)	146 (43%)	
Female	158 (47%)	45 (13%)	113 (33%)	
SVI Composites				
Socioeconomic, M (SD)	0.02 (0.21)	0.02 (0.25)	0.02 (0.19)	1.00
Household, M (SD)	0.16 (0.14)	0.16 (0.17)	0.16 (0.13)	1.00
Minority Status, M (SD)	0.77 (0.10)	0.77 (0.14)	0.77 (0.09)	1.00
Housing & Transportation, M (SD)	0.14 (0.17)	0.14 (0.22)	0.14 (0.16)	1.00
Previous Concussion				0.005**
Yes	75 (22%)	31 (9%)	44 (13%)	
No	265 (88%)	66 (19%)	199 (59%)	
Length of care, days; M (SD)	9 (28.1)	51 (31.4)	7 (7.4)	<0.001***

Note: Group differences were assessed with independent samples t-test for continuous variables and χ^2 for categorical variables. M (SD) = Mean (Standard Deviation). SVI = Social Vulnerability Index.

Table 19: ImPACT results between individuals with extended and typical treatments

ImPACT Composite	Total Sample (*n* = 340)	Extended Recovery (*n* = 97)	Typical Recovery (*n* = 243)	Group differences (*p* value)
Verbal Memory	87.3 ± 13.4	87.5 ± 11.6	87.2 ± 14.0	0.85
Visual Memory	76.8 ± 13.3	76.2 ± 13.2	77.0 ± 13.4	0.61
Efficiency	0.39 ± 0.12	0.38 ± 0.11	0.39 ± 0.13	0.50
Impulse Control	8.0 ± 7.7	8.5 ± 9.9	7.7 ± 6.6	0.39
Reaction Time	0.72 ± 0.15	0.76 ± 0.18	0.70 ± 0.13	<0.001***
Visual Motor	37.8 ± 7.7	37.4 ± 6.7	38.0 ± 8.0	0.51
Total Symptom Severity	21.6 ± 21.6	24.0 ± 23.0	20.7 ± 21.0	0.20

Note: Group differences were assessed with independent samples t-tests. Results reported as sample mean ± standard deviation.

Table 20: Odds ratios of length of care by patient and assessment characteristics

Characteristic	Extended Recovery (*n* = 97) OR (95% CI)
Age	1.00 (0.93-1.07)
Race	
Minority	Ref
Caucasian	1.36 (0.72-2.66)
Religious	
No	Ref
Yes	1.18 (0.67-1.89)
Sex	
Female	Ref
Male	0.85 (0.50-1.45)
SVI Composites	
Socioeconomic	0.48 (0.02-12.31)
Household	1.23 (0.02-53.98)
Minority Status	1.18 (0.10-16.40)
Housing & Transportation	12.00 (0.91-158.55)
Previous Concussion	
No	Ref
Yes	2.03 (1.14-3.58)
ImPACT Composites	
Verbal Memory	1.01 (0.99-1.03)
Visual Memory	0.99 (0.97-1.02)
Efficiency	0.83 (0.06-11.94)
Impulse Control	1.01 (0.98-1.05)
Reaction Time	26.69 (4.27-181.39)
Visual Motor	1.02 (0.99-1.07)
Total Symptom Severity	1.00 (0.98-1.01)

Note: Adjusted odds ratios (OR) were calculated from the adjusted logistic regression model, using the typical duration group as the reference group. 95% CI = 95% Confidence Intervals. Ref = Dichotomous outcome serving as a reference for odds.

Chapter 9: Concluding remarks

The research for this dissertation collectively aimed to advance knowledge about assessment of individuals following concussion, specifically the ability to predict longer durations of care following concussion. These studies add new information to these domains, emphasizing the importance of thorough and necessary concussion evaluation. Clinically, the studies help accentuate guidelines clinicians should consider for deciding when restorative treatments and interventions should be administered to prevent longer durations of care.

Gender differences in concussion recovery have been well documented (Chrisman, Quitiquit, & Rivara, 2012; Dick, 2009; Patel et al., 2005; Thomas et al., 2017), but there is a lack of clear evidence for evaluating the precedence of suspected concussions in younger, athletic, female populations. Chapter 2 provided evidence that female high school athletes under-report concussions and concussion-like symptoms (McDonald et al., 2016), much like their male counterparts (McCrea et al., 2004). Additionally, only 2/3rds of responders reporting ever receiving concussion education. This lack of education may have influenced the under-reporting rates, as individuals would be less aware of potential concussion symptoms. Additionally, individuals may not have been aware the serious medical complications that could have arose after continued play after a potential concussion. The most evident finding from this study was resolving the myth that under-reporting only occurs with male athletes. Our data demonstrates this notion is false, at least among our cohort of subjects at that time, and may be in part due to lack of systematic and effective education for all athletes, regardless of gender, sports played, or age.

In conjunction with education about symptoms of a suspected concussion, adequate and accurate assessment of individuals after suspected injury is vital, as symptom reporting may be inaccurate, subjective or not always possible. Additionally, clinicians need access to valid and reliable concussion-specific assessments, without the need for specialized laboratory-based equipment, specialized training, or complex analytic protocols. Chapters 3 and 4 evaluated such an assessment. *Sway*™ demonstrated to be a valid and reliable assessment for both balance and simple reaction time in controlled, laboratory settings. In both studies, the application paired well with previously established gold-standard measures for both balance assessment (force plate dispersion measurement) and reaction time (computer-based simple reaction time responses). The most intriguing aspect of this application is portability. Valid and reliable assessments are paramount, but oftentimes people are assessed for a concussion outside medical clinics without access to computers (i.e. sports fields, gyms, playgrounds), under less-than-ideal distraction-laden testing conditions, by evaluators with variable degrees of training in the testing protocols, using subjective performance measures. The *Sway*™ assessment could be easily conducted in all such environments, with the only need for equipment being a cell phone or tablet device. More research is needed prior to widespread adoption of the application, but our research sets the foundation and establishes a sound rationale for future efforts.

Neuroimaging techniques are an important and useful tool for clinicians and researchers assessing individuals after head trauma. DTI and the associated metrics for evaluating white matter pathway integrity (fractional anisotropy and mean diffusivity) provide clinicians with an objective measure of neuronal injury. In our study detailed in chapter 5, we found DTI metrics were correlated strongly with improvements in both reaction time and visual processing, indicating improvements in these cognitive skills are indicative of recovery. Interestingly, participants reported a reduction of concussion symptoms and severity over the course of the study, but comparing symptom reduction and improved DTI metrics yielded no associations. This finding is clinically relevant, suggesting the individuals may experience a reduction in symptoms prior to true neurological recovery. Clinicians who are deciding if athletes are safe to return to contact sports participation should be aware of this finding and adopt a more cautious approach, rather than relying on symptom reporting or neuropsychological testing for return-to-play decisions.

The primary focus of the remaining work was to further refine our knowledge of early prediction of individuals at risk for prolonged recovery. Chapter 6 explored clinical presentations of individuals at the time of their concussion evaluation in sports medicine settings. Our rationale for using only evaluation data and demographic data specific to each person was that if group differences exist between individuals with typical and longer lengths of care using information from this first visit, a predictive model conceivably could be created to approximate discriminative features for each group. Clinically, this would lead to early interventions and treatments for patients at higher risk for longer care. We found group differences did exist, specifically for the factors age, sex, history of psychiatric disorders, and lower neurocognitive assessment results at the time of evaluation. Many of these findings align with previously published research (Bock et al., 2015; Iverson et al., 2017; Morgan et al., 2015; Nelson et al., 2016), confirming differences in care durations exist, even at the patient's evaluation. These findings are meaningful for clinical management and represent the first steps towards early identification of individuals at risk for longer care.

These findings also clarified that individuals who will experience short and longer lengths of care present differently at their initial evaluations, thus providing evidence in support of a predictive method for early identification of individuals at risk for long care. We then sought to identify the effects of specific factors on length of care. Chapter 7 utilized a survival analysis to clarify these points. A history of previous diagnosed concussion and being female both were significant factors in predicting longer lengths of care when compared to alternatives, which coincides with previous findings (Bock et al., 2015; Grant L. Iverson et al., 2017). Additionally, individuals with higher rankings on the SVI Housing and Transportation composite, indicating higher vulnerability and less access, had shorter lengths of care. Conceptually, individuals with less access to public and personal transportation would have added burden to attend follow-up appointments and care, thus yielding shorter lengths of care. As discussed in the introduction section, length of care and the time needed to recover following injury are not synonymous. These two features are related, each serving as proxies for differing clinical and social features. We believe it highly possible our subjects in this category may have been forced to end their treatments prior to fully recovering due to inability to travel to appointments, or to fiscal limitations on seeking additional care.

Conclusions

To conclude, we applied findings about the clinical presentation of individuals at their evaluation and significant variables influencing length of care durations. The true discriminative ability for predicting if individuals will have a typical or extended length of care after concussion was evaluated. The resulting logistic regression model found concussion history and reduced reaction time as significant features, both of which are clinically relevant. Additionally, lower socioeconomic status produced lower odds of having longer durations of care after injury, aligning with findings evident in chapter 7. This finding was counter to our hypothesis and is likely more reflective of access and ability to afford continued treatment, rather than a protective element for concussion recovery.

This dissertation summarizes the early identification of risk factors present in individuals who experienced longer lengths of care following concussion. The most evident findings from these studies support the continued importance of thorough evaluations and emphasize objective assessment of an individual's previous head traumas and concussions, as this factor was influential of longer care. Additionally, sex, age, and history of other psychiatric disorders were additional important factors to consider when evaluating length of care decisions, and ultimately, alternative interventions. Specific clinical assessments were also important. The reaction time component of the ImPACT test had good predictive ability to differentiate individuals with typical and extended durations of care. This finding stresses the importance of reaction time assessment at evaluation. Our work also provides a valid and reliable alternative to computerized reaction time assessment, should clinics and individuals operate in environments not suitable to computerized testing.

The addition of social determinants data was a novel feature of our studies. We sought to describe and clarify how different social factors influence care durations after injury. Ultimately, we have more additional questions to address, such as what features of the contextual social data influence length of care. The findings that social factors tend to reduce the length of care should likely be interpreted as reflective of a person's ability to receive or access care, rather than an inherent mechanism influencing brain function after injury.

Future Directions

Our research provides a foundation for predicting which individuals are at risk for longer lengths of care following concussion. Future work should begin to assess predictions by building statistical models with the intention of accurately predicting which individuals have longer recoveries early in their care. An accurate predictive model would allow for early identification of these individuals within the first days after concussion, leading to earlier implementations of restorative treatments to reduce length of care. This framework lends itself well to enhanced software algorithms that could be embedded in electronic medical records to automate risk assessment, flag at-risk individuals, and suggest earlier treatments.

Additional research should be conducted to continue the understanding of how social factors impact length of care and recovery after concussion. Specific study of how social factors influence the ability to attend evaluation and treatment after injury is a direct line of evaluation from our work. Continued exploration would allow for the potential of government and/or insurance accommodations to better support individuals attempting to recovery from injury.

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Appendix

Appendix A: Comprehensive Review I

Neurological features that underlie changes in function common to traumatic brain injury (TBI) populations

This work was approved June, 2015.

In the public's perception, brain injuries have become a progressively complicated and harrowing condition. In the United States alone, an estimated 1.7 million traumatic brain injuries (TBI) occur each year, contributing to 30% of all injury-related deaths (Faul, Xu, Wald, & Coronado, 2010). TBI accounts for roughly 10 billion dollars spent annually in the United States as a result of the direct and indirect long term care costs associated with moderate to severe injury and the loss of work productivity (Faul, Wald, Rutland-Brown, Sullivent, & Sattin, 2007). Advances in emergency medicine have led to more people surviving initial brain trauma, including severe injuries, but surviving a more substantial injury often results in profound impairment that often requires costly lifelong care. Brain injuries can produce drastic changes in personality, behavior, and function. In recent years though, research and clinical interest has focused on mild to moderately severe brain injuries, as transient, but substantial changes impact the daily lives of individuals after injury. Furthermore, the changes in daily functioning are not often accompanied by obvious clinical signs of brain trauma depicted by conventional imaging techniques (Johnston, Ptito, Chankowsky, & Chen, 2001; Kirkwood, Yeates, & Wilson, 2006), making progression and recovery from injury difficult to quantify. This review has dual purposes: to describe how brain injuries are most often categorized on a continuum of severity by healthcare professionals, and to identify and describe neurological and vascular changes a person experiences after brain injury that lead to alterations in daily life.

Early in the course of healing from severe injuries, symptom reporting is often unnecessary or impossible. Many patients are unconscious or unable to respond to diagnostic questions in a meaningful and accurate way. Physicians assess injuries of this magnitude by examining the person's ability to respond to simple stimuli, such as pupillary response to light, ability to follow a simple verbal command, or appearance of primitive reflexes elicited by pain

(Teasdale & Jennett, 1974). The type of response (reflexive, motoric, or verbal) resulting from each stimulus indicates the extent of neurological injury at the time of assessment, with the absence of response indicating severe damage. Physicians initiate these brief assessments early in the management process to quantify injury severity. Ongoing assessments are conducted hourly and/or daily to measure progression and improvement in people with brain injury.

Occupational therapists contribute to the care of individuals across the brain injury spectrum and provide care in many different settings, including hospitals, outpatient day clinics, homes, the community, and long term care facilities. After a severe brain injury, an individual may work in conjunction with an occupational therapist on fostering alertness and behavioral responsiveness (Giacino et al., 1997), preventing complications associated with prolonged bed immobilization (Mysiw, Fugate, & Clinchot, 1996), limiting involuntary alterations in muscle tone (Giacino & Kalmar, 1997), initiating sensory stimulation (Davis & Gimenez, 2003), and reducing possible agitation (Earnes, Haffey, & Cope, 1990). As the person's recovery progresses, occupational therapists begin using activities the person values (i.e. occupations) to regain functional skills and return to meaningful life roles.

Diagnostic and prognostic decisions for people with mild to moderately severe brain injuries depend heavily on subjective symptom reporting by the individual who is injured. However, relying on accurate and truthful symptom reporting may be problematic, as "all patients lie" (Moran & Spicer, 2004). For example, if an athlete sustains a head injury at a sporting event and experiences symptoms of 'concussion', indicative of a mild TBI (mTBI), he/she may under-report symptoms in the hopes of returning back to play (McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004). The head trauma in this situation is a medical concern, as returning an athlete to play following even a minor brain injury can have fatal consequences

(McKee et al., 2013; Saunders & Harbaugh, 1984). To reduce the need for subjective symptom reporting for mild to moderate injuries, the need for objective assessments has become more of a focus in clinics and hospitals. However, ,many of these assessments require expensive specialized equipment often inaccessible in clinical settings.

A wide range of healthcare professionals are involved in the care and rehabilitation efforts for someone following brain injury, regardless of injury severity. Physicians, nurses, neuropsychologists, psychiatrists, physical therapists, occupational therapists, speech language pathologists, and recreational therapists form interdisciplinary plans for care throughout a person's recovery. Stage of injury, injury severity, personal factors of the individual with injury, and patient/caregiver goals inform clinicians of the most appropriate interventions to consider for each individual.

Cognitive changes occurring after brain injury are complex and depend on a myriad of physiological and neurochemical factors. Like many other conditions, severity of the injury plays a critical role in the prognostic outcome and the ability to return to previous functioning. In order to describe both subtle and obvious changes in neural functioning following brain injury, it is first necessary to describe how researchers and physicians classify the severity of injury.

Classification of Traumatic Brain Injury

Traumatic brain injuries in current practice are classified on a continuum, ranging from mild (subtle and often transient changes in cognitive functioning or daily life) to severe (profound neurocognitive alterations producing long-term neurological damage and disability). Historically, clinicians and scientists used inconsistent terms, such as 'comatose', 'decerebrate', and 'stupor', to describe injury severity, making comparisons between severity and extent of injury impossible (Barlow, 2012). This imprecise categorization changed in 1974, with the advent of the Glasgow Coma Scale.

Glasgow Coma Scale

The Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974) has become one of the most often used neurological assessments worldwide and is one of the standard clinical tools evaluating neurological status of patients with brain injury upon hospital admission. The GCS was the first assessment to allow clinicians and researchers to categorize people objectively based on the severity of the neurological trauma. The intent of the GCS was to assess the extent of altered consciousness and predict the duration of coma in people with neurological impairment (Teasdale & Jennett, 1974). The GCS is most appropriate when assessing patients after severe injury, as the main purpose of the assessment is to identify moderate to severe neurological injury and categorize risk of mortality in patients. The GCS is not sensitive to detecting minor impairment in neurologic function and patients may benefit from further, more in-depth assessment. The GCS is widely used during emergency room examinations for patients admitted for head injury, regardless of severity (Dziemianowicz et al., 2012).

The GCS score is dependent on the injured person's ability to produce responses to specific forms of stimuli, which indicates to the depth of altered consciousness. The scale is based on responses observable at bedside, grading is simple, and high consistency has been observed between providers (Holdgate, Ching, & Angonese, 2006). The type of stimulus the injured person responds to will factor into the scale (light, sound, pain), as well as the type of response (motor movement, speech, eye opening) the person elicits (Teasdale & Jennett, 1974). Finally, the quality of response is considered, with responses generated spontaneously and following verbal commands tallying the highest possible score (Table 1). The total score produced can range from 3 to 15, with a score of 3 indicating most severe non-fatal injury possible, and 15 indicating normal function (Matis & Birbilis, 2008). Three ranges of GCS score intervals are accepted to standardize injury severity: a GCS score of 13-15 is classified as mild, 9-12 as moderate injury, and any score ≤ 8 is indicative of severe injury (Sternbach, 2000). It should be noted that although a mild classification is possible in many individuals, the term 'mild' is deceiving and has fallen out of favor, 'mild' insinuates the injury may not be of significant concern.

Table 1: Glasgow Coma Scale

Assessed Ability	Response	Score
Eye opening (E)	Spontaneous	4
	To speech	3
	To pain	2
	Nil	1
Best motor response (M)	Obeys	6
	Localizes	5
	Withdraws	4
	Abnormal flexion	3
	Extensor response	2
	Nil	1
Verbal Response (V)	Oriented	5
	Confused conversation	4
	Inappropriate words	3
	Incomprehensible sounds	2
	Nil	1

Patients after mild injury typically score 13, 14, or 15 on the GCS at their initial evaluation (Guskiewicz et al., 2013), indicating minimal alterations in neurological functioning. The GCS is useful in gross categorization of brain injury severity, but it is not sensitive to more minor changes in neurological functioning and does not provide assessment of high level cognitive abilities (i.e. executive functioning), particularly in patients with mild TBI. Despite the recent recommendation for the GCS to be used for mild TBI assessment (Guskiewicz et al., 2013), others question utility of the assessment in mild brain injury populations, due to the inability to differentiate between injured and non-injured individuals (Dziemianowicz et al., 2012). The GCS will remain prevalently used with individuals with a suspected TBI because of the need to determine the extent of neurological injury.

Through the use and implementation of the GCS, physicians and researchers are more able to accurately quantify and communicate about the extent and severity of each injury, while formulating quick hypotheses regarding prognosis and outcome. The GCS has moderate to good intra-rater reliability (Fischer et al., 2010; Gill, Reiley, & Green, 2004), which needs to be considered in hospital settings where different administrators determine improvements in functioning over time. The GCS can be useful for less severe injuries, but more specific neuropsychological testing is typical necessary to assess subtle cognitive changes (McCrory, Meeuwisse, et al., 2013a). While the GCS is indicative of a person's consciousness at the time of the assessment, it does not offer any form of long-term prognosis. Because of this limitation, researchers created the Glasgow Outcome Scale to evaluate long-term outcomes.

Glasgow Outcome Scale

The Glasgow Outcome Scale (GOS) is one of the first scales created to objectively assess prognosis and predict the burden of care a person with TBI may encounter at the 'final' recovery level and this instrument now is widely used measure to classify outcome after brain injury (Jennett & Bond, 1975). The GOS was developed in conjunction with the GCS and offers a simple outcome scale, classifying patients into five hierarchal categories: dead, vegetative, severely disabled, moderately disabled, and good recovery (Jennett, Snoek, Bond, & Brooks, 1981). Unlike the GCS being administered upon admission to emergency departments, the GOS assessment is intended for use after a person with head injury is discharged from the hospital, as recovery would be difficult to assess while still undergoing continuous care (Wilson, Pettigrew, & Teasdale, 1998).

The initial GOS had some shortcomings, including lack of sensitivity to small improvements in patient functioning and low inter-rater reliability (Anderson, Housley, Jones, Slattery, & Miller, 1993; Maas, Braakman, Schouten, Minderhoud, & van Zomeren, 1983). As a result, a structured interview format for the GOS was adopted to improve reliability between testers (Wilson et al., 1998), and the scale was expanded to include eight categories: dead, vegetative state, low severe disability, high severe disability, low moderate disability, high moderate disability, low good recovery, and high good recovery (Jennett et al., 1981). The subdivided categories for severe disability, moderate disability, and good recovery improved the specificity of the assessment to document small changes in a person's functioning (Teasdale, Pettigrew, Wilson, Murray, & Jennett, 1998).

The extended GOS (GOSE) uses a structured interview to facilitate consistency in ratings between administers and can be done in person, via telephone, or through written communication. The scale requires no training to administer and can be answered by the person with TBI, their caretakers, or together. The interview includes questions about the person's ability to follow simple commands, if the person requires assistance for activities of daily living (ADLs), the person's prior level of functioning before the injury, how independent the person is outside the home, if the person is currently working or if they have restrictions/reduced workload, how the person's relationships have been with family and friends since the injury, and if there are any current (at the time of the interview) problems impacting the person's daily life (Wilson et al., 1998). Categorization of outcomes result from specific responses to questions, with severe disability represented by questions regarding the amount of assistance a person needs daily, moderate disability represented by returning to work and social activities with restrictions or accommodations, and good recovery represented by returning to their previous life roles with only mild symptoms (e.g. headaches, some concentration problems, dizziness) (Wilson et al., 1998).

The expanded version of the GOS demonstrates greater criterion validity and sensitivity when compared to the prior version (Levin et al., 2001), as well as improved inter-rater reliability (Teasdale et al., 1998). Many healthcare practitioners and researchers use this gold standard assessment today for TBI outcomes (Narayan et al., 2002).

Disability Rating Scale

The Disability Rating Scale (DRS) is another assessment often used to evaluate neurological functioning following brain injury. While the DRS was originally developed to assess individuals with TBI during the rehabilitation phase of recovery (Nichol et al., 2011), it can also be used throughout the injury continuum, from transient alterations of consciousness to more severe injuries (Rappaport, Hall, Hopkins, Belleza, & Cope, 1982). The DRS is unique in being suited to assess progress made by a person with brain injury spanning a range of function from coma to community reintegration.

The DRS incorporates similar response criteria to the GCS (i.e. eye-opening, communication ability, motor response) and also includes functional tasks in the assessment. The assessment evaluates a person's ability complete feeding, toileting, and grooming from a cognition standpoint. Administrators are instructed to ignore motor disabilities that may impact the score and focus on the person's cognitive abilities to complete tasks. Lastly, the assessment asks about the person's overall level of functioning, including physical, mental, emotional, and social functioning. Scoring of these categories ranges from completely independent (no restrictions or problems) to totally dependent (requiring 24 hour care; Rappaport et al., 1982). The assessment is administered within 72 hours of rehabilitation admission, and within 72 hours before rehabilitation discharge (Rappaport, Herrero-Backe, Rappaport, & Winterfield, 1989).

The DRS demonstrates good inter-rater reliability (Gouvier, Blanton, LaPorte, & Nepomuceno, 1987; Rappaport et al., 1982) and validity (Hall, Hamilton, Gordon, & Zasler, 1993). The DRS also predicts acute hospital length of stay and functional status at discharge (Eliason & Topp, 1984; Gouvier et al., 1987). However, use of the DRS with individuals following mild brain injury is not recommended and has shown difficulty assessing clinically-significant improvements in a person's functional status after mild injury, leading practitioners and researchers to prefer the extended GOS in assessing outcome (Choi et al., 1998).

Rancho Los Amigos Levels of Cognitive Functioning Scale

The Rancho Los Amigos Levels of Cognitive Functioning Scale (LCFS) is a descriptive measurement used in rehabilitation settings assessing the levels of awareness and cognitive functioning in individuals following brain injury (Hagen, Malkmus, & Durham, 1979). The measure was created to allow clinicians to better communicate with other providers and caretakers about a person's level of cognitive functioning (Hagen, 1998). Clinicians also use the measure to design and implement appropriate rehabilitation interventions at each specific stage of recovery, tailoring approaches to the individual. Rehabilitation professionals prefer the LCFS because it is based on identified patterns of recovery for people with brain injury, as opposed to a current state of impairment. The scale utilizes behavioral characteristics and cognitive changes associated with the brain injury to assess a person's level of cognition.

The scale uses a single item rating system to evaluate individuals following brain injury, originally developed with eight categorical levels, ranging from level I (no response) to level VIII (purposeful and appropriate) (Hagen et al., 1979). Later, two additional levels were including in the scale, adding specificity and validity to the assessment (Hagen, 1998). Each of these levels is described in Table 2. Clinicians observe different cognitive skills and behaviors and check to see if the skills are present or absent during observation of the people they are serving. No specific training is needed to administer the assessment.

Table 2: Rancho Los Amigos Levels of Cognitive Functioning

Level	Description
I	No Response: unresponsive to stimuli
II	Generalized Response: nonspecific, inconsistent and non-purposeful response to stimuli
III	Localized Response: response directly related to type of stimulus but still inconsistent or delayed
IV	Confused Agitated: response heightened, severely confused, may be aggressive
V	Confused Inappropriate: some response to simple commands, but confusion with more complex commands; high level of distractibility
VI	Confused Appropriate: response more goal directed but cues necessary
VII	Automatic Appropriate: response robot-like, judgment and problem solving lacking
VIII	Purposeful Appropriate (with stand by assistance): response adequate to familiar tasks, subtle impairments require standby assistance with acknowledging other people's needs and perspectives, modifying plans
IX	Purposeful Appropriate (with stand by assistance upon request): responds effectively to familiar situations but generally needs cues to anticipate problems and adjust performance; low frustration tolerance possible
X	Purposeful and Appropriate (modified independence): responds adequately to multiple tasks but may need more time or periodic breaks; independently employs cognitive compensatory strategies and adjusts tasks as needed

The Rancho Los Amigos Scale demonstrates excellent test-retest reliability (Gouvier et al., 1987), excellent inter-rater reliability (Beauchamp et al., 2001; Gouvier et al., 1987), and excellent construct validity (Gouvier et al., 1987; Labi, Brentjens, Shaffer, Weiss, & Zielezny, 1998). The scale is most appropriately used to assess cognitive functioning in the first year following brain injury (Hagen et al., 1979). Much like the previously described assessments, the LCFS is most helpful in describing and progressing individuals following moderate to severe brain injury, and is unable to quantify small, yet significant changes in higher level cognitive functions.

Clinically, the LCFS is helpful to identify when an individual is capable to fully participate in inpatient rehabilitation. When a person is evaluated at Rancho levels V and VI, the person can demonstrate stimulus-specific responses and post-traumatic confusion and agitation has resolved or does not present a barrier to participation in intensive activities (Radomski, 2008). Specifically, at Rancho level V, individuals may be still disoriented and confused, but are goal-oriented (Heinemann et al., 1990) and are able to participate in teaching-learning interactions (Abreu & Toglia, 1987). As individuals progress through recovery to Rancho level VI, they will remain inconsistently oriented, but begin to be aware of appropriate response to staff and family and demonstrate carryover for relearned and familiar tasks (Hagen, 1998).

Implications

While these assessments are the most often used and cited evaluations in moderate to severe TBI literature, each possess unique shortcomings that limit clinical utility and interpretability. Due to the complex nature of brain injury evaluation and outcome prediction, a model incorporating multiple assessments is typically employed by clinicians and researchers to accurately assess functional and neurological status. Using multiple comparisons and continued longitudinal assessment may provide a better indication of the person's overall functioning, leading to a more accurate prognosis. Factors that need to be considered during the interpretation of each assessment are the inter-rater reliability and validity of each assessment. Precisely evaluating current functioning is a critical component to the care of individuals after TBI, as each stage of injury presents unique challenges that influence the care and rehabilitation interventions the person receives.

Evaluation of specific cognitive abilities across the continuum of brain injury has become increasingly important, but recently, more emphasis has been placed on evaluating milder forms of injury. Mild TBI (mTBI) is defined as a traumatically induced physiological disruption of brain function, manifesting in at least one of the following symptoms: loss of consciousness 30 minutes or less, loss of memory before or after trauma (not greater than 24 hours), alteration of mental state (i.e. confusion, dazed), and/or focal neurological deficit(s) that may or may not be transient (Kay et al., 1993). An initial GCS of 13-15 taken 30 minutes after injury is also indicative of mild TBI (Teasdale & Jennett, 1974). Both of these definitions include 'concussions', but mTBI and concussions are not synonymous. MTBI include concussions, but concussions are not inclusive of every mTBI that occurs (Brain Injury Association of America, 2014).

Mild brain injuries can be difficult to identify initially, but also even when the brain has fully healed and regained previous functioning. Clinicians employ a vast array of assessments, including evaluation of gross motor skills (e.g., balance, coordination, and gait) and specific cognitive abilities (e.g., long and short-term memory, ocular reflex response, attention-to-task, information processing speed) (McCrory et al., 2013). The specificity of each assessment allows clinicians to identify alterations in neurological functioning, providing insight for appropriate treatment recommendations for improved care.

Skilled assessment enables clinicians and researchers to more objectively quantify injury severity, allowing for improved communication and interpretability of research. The objective measures provide better insight about what the person is experiencing, but each assessment still lacks sensitivity and specificity. Continued development of accurate and specific neurological assessments, paired with innovative neurological imaging techniques, will likely enhance the future treatment and care of patients following a brain injury. Along with improved assessment and imaging, a thorough understanding of the neurological mechanisms that take place after trauma will guide clinicians through the process of recovery.

Primary Traumatic Brain Injury

Primary traumatic brain injury is described as encompassing the destructive events occurring at the moment of trauma, which may be preventable but not reversible. Primary brain injury results from the direct forces of impact, leading quickly to decreased axonal conductivity, irregular vascular perfusion, focal cortical contusions, and intracranial hemorrhaging (Yokobori & Bullock, 2013). Injuries can be focal, resulting from contact forces to the head, or diffuse, caused by non-contact, rotational forces to the brain (Meaney et al., 1995).

Focal Brain Injury

Physicians and scientists categorize focal brain injuries by the localized destruction of neural and anatomical structures immediately occurring as a result of trauma. These injuries can result from falls, motor vehicle collisions, inter-personal violence, and accidental injury. The mechanism of the injury is an object coming into contact with the cranium, leading to the direct destruction of underlying tissue, vasculature, and connections. Penetrating injuries result from moving projectiles or sharp objects fracturing the cranium, perforating the meninges, disrupting the vasculature of the brain producing ischemia, and/or destroying brain matter along the object's trajectory. Blunt injuries result from a mechanical force imparted on the head through direct contact with a blunt object or surface and typically do not produce any perforation in the dura mater when the skull is not fractured (Santiago, Oh, Dash, Holcomb, & Wade, 2012). It is possible for a person to sustain both penetrating and blunt force injuries after a traumatic event.

Forceful deceleration of the brain, as typically seen in motor vehicle accidents, is capable of producing blunt trauma to the brain without the head sustaining any direct contact. The anterior and inferior surfaces of the frontal and temporal lobes tend to be a site for this trauma, as these areas are adjacent to the sharp ridges of the anterior and middle cranial fossa. This type of injury can occur in conjunction with diffuse brain injury, as deceleration forces cause the brain to be displaced within the skull (Yokobori & Bullock, 2013). Cerebral contusions and hemorrhaging are two major complications resulting from focal brain injury.

Focal Cerebral Contusion

Cerebral contusions significantly contribute to the severity and complexity of traumatic brain injuries. Contusions progress rapidly after injury, and although contusions can be described as a secondary effect of injury, this acute response is also associated as a direct result of focal injury. Contusions that occur secondarily will be described in greater detail in subsequent sections.

Shearing forces from the traumatic event lead to injured blood vessels and other structures within the neural tissue that remain tethered in place. Due to the force, blood vessels hemorrhage in the vasculature of the brain, resulting in a brain contusion as blood collects. Cerebral contusions typically are seen along the superior surface of the cerebral cortex, but larger lesions occurring in the deeper portions of the cerebrum are not uncommon (Yokobori & Bullock, 2013), as the inferior portion of the cranial vault contains bony prominences that can injure inferior portion of the brain. Contusions present similarly to brain lacerations, as both produce vascular damage and hemorrhaging. The main distinction between the two conditions is the pia-arachnoid membrane remains intact following a contusion. A laceration from a penetrating injury severs these membranes and underlying vascular and neural structures along the trajectory of the object (Yokobori & Bullock, 2013).

Contusions resulting from direct acceleration or deceleration of the brain without direct contact are referred to as coup-contrecoup contusions (Morrison, King, Korell, Smialek, & Troncoso, 1998). While the direct mechanisms of this injury are still debated, especially in regard to the etiology of the contre-coup injuries (Shaw, 2002), these contusions have been a focus for researchers for many years (Ommaya, Grubb, & Naumann, 1971). Coup injuries refer to specific damage of neural matter beneath the point of impact on the skull (Shaw, 2002). The coup injury is the initial location of trauma or force (Poirier, 2003) and may be due to blunt trauma.

By contrast, contre-coup injuries occur elsewhere on the surface of the brain, most often opposite to the site of the initial cranial impact (Shaw, 2002). Historically, researchers hypothesized that contre-coup injuries result from the brain moving inside the skull, following the direction of the force applied to the head. This formally became known as the positive pressure theory, with the belief that when the head accelerates prior to impact, the brain is displaced in the opposing direction within the skull and is pressed against the interior of the skull prior to impact (Dawson, Hirsch, Lucas, & Sebek, 1980; Drew & Drew, 2004). The force from the accident then carries the brain again as quick deceleration takes place, causing lobes to forcefully contact the cranium. Cerebrospinal fluid (CSF) distribution likely plays a significant role in this theory of injury (Cantu, 1992), as a brain surface deprived of the normal concentration of shock-absorbing CSF is more vulnerable to accelerative/decelerative injury (Shaw, 2002).

The negative pressure theory, also known as the cavitation theory, is another popular explanation for the contre-coup phase of injury. This theory states the injury may be due to negative pressure generated in the contre-coup area at the time of impact (Drew & Drew, 2004). The theory hypothesizes that upon impacting the skull with an object when the head is suddenly stopped, the brain continues to move forward and creates tensile stress at the contre-coup site (Dawson et al., 1980). The negative pressure pulls the brain apart, causing extensive injury (Drew & Drew, 2004) and/or ischemia. Cavitation has been proposed as part of the injury mechanisms for blast-induced mTBI (Goeller, Wardlaw, Treichler, O'Bruba, & Weiss, 2012). Other theories of contre-coup injury etiology involve strain on the fixed cerebrum after the abrupt movement of the head following transfer of inertial force. In place of the brain coming in contact with the skull during deceleration, scientists hypothesize that the strain caused by the inertial forces from the traumatic event, either linear or rotational, cause the brain parenchyma to be maximally stressed while fixed to the dura mater, leading to the contusion (Dawson et al., 1980).

Regardless of the specific mechanism of injury, coup/contre-coup injuries are complications that need to be addressed quickly. Contusions degenerate rapidly following injury, resulting in a collective inflammatory response in the damaged neural tissue and accumulated substrate. During the first 24 hours after injury, the inflammation occurs within the vascular tissue (Holmin, Soderlund, Biberfeld, & Mathiesen, 1998; Yokobori & Bullock, 2013). Within the next 3 to 5 days, the inflammation spreads throughout the cerebrum, increasing the vasogenic edema (Holmin et al., 1998). Over time (days to weeks), injured neurons can degenerate, delaying functional recovery and resumption of life roles (Cervos-Navarro & Lafuente, 1991). In addition to the typical cellular degeneration and necrosis that takes place following neuronal damage, apoptosis of neurons can also occur (Raghupathi, 2004; Raghupathi, Graham, & McIntosh, 2000). This programmed cell death can be observed as soon as 24 hours after injury (Conti, Raghupathi, Trojanowski, & McIntosh, 1998), with lasting effects seen 12 months after injury in white matter tracts (Williams et al., 2001). These secondary effects are detailed in later sections of this review.

The presence of a contusion is closely related to long term disability following injury, as opposed to the risk of mortality (Maas et al., 2007). Functionally, patients presenting with focal contusions often experience impairments with verbal fluency, concept formation, and overall cognitive skills (Wallesch, Curio, Galazky, Jost, & Synowitz, 2001). Individuals with cerebral contusions present with lower initial GCS scores upon hospital admission compared to TBI patients without evidence of contusions (Wallesch, Curio, Kutz, et al., 2001), suggesting greater alterations in cognition and functioning.

Hemorrhage

Cerebral hemorrhaging is a second complication arising immediately after focal brain injury. Hemorrhages are classified by the localization of blood within or between specific meninges of the brain. These bleed locations are categorized into four different types of hemorrhages after TBI: epidural, subdural, subarachnoid, and intracerebral hemorrhaging.

Epidural hemorrhages are defined as bleeds that occur between the dura mater and cranium and most often result from a skull fracture of the bone overlaying the hemorrhage location, as the disruption of the vasculature would likely not occur otherwise. Blood collects in the epidural space between the brain and cranium, which could lead to a development of a hematoma. The middle meningeal artery is a common site for hemorrhaging in older adults, as vessels become embedded in bone with age. Thus, the arteries are at greater risk for tears after falls or accidents that cause bone fractures or displacement (Yokobori & Bullock, 2013).

The presence of an epidural hemorrhage and resulting hematoma after injury does not necessarily lead to a poor outcome. Epidural hemorrhaging and a developed hematoma are associated with better outcomes and good long-term prognosis (Maas et al., 2007), since emergency medical treatment involves evacuation of the hematoma, which reduces intracranial pressure. Rather, factors such as age, initial severity score (i.e., GCS score), and neurological status immediately following injury predict functional outcomes after TBI (Leitgeb, Mauritz, Brazinova, Majdan, & Wilbacher, 2013).

Subdural hemorrhaging encompasses more of the cortical space, and is more widespread than epidural hemorrhages. Blood accumulates from the subarachnoid space due to tears in the arachnoid membrane. The subdural space allows these hematomas to cross the midline of the brain and expand into both cortical hemispheres, whereas epidural hematomas only encompass one hemisphere. Subdural hematomas are associated with a high mortality rate reported between

50%-90% (Wilberger, Harris, & Diamond, 1991), as the expansive nature of the hematoma leads to ischemic complications. One of the most important causes of ischemia is increased intracranial pressure (ICP), which reduces blood circulation in the brain (Johnston, Rowan, Park, & Rennie, 1975) and compresses the brain. Evacuation of the hematoma may result in immediate recovery; however, a resumption of blood flow leakage may lead to secondary injury after an initial reduction of the mass lesion (Kuroda & Siesjo, 1997).

Subarachnoid hemorrhaging results from vascular tears in the subarachnoid space, located between the arachnoid and pia mater. Unlike epidural and subdural hemorrhaging, subarachnoid bleeding can result in hydrocephalus, giving rise to increased intracranial pressure and abnormal ventricular expansion (Srinivasan, O'Neill, Jho, Whiting, & Oh, 2014). Appearance of subarachnoid hemorrhaging on CT scans is indicative of moderate to severe trauma, since the forces necessary to cause this type of vascular disruption are profound. Subarachnoid bleeds are generally associated with poor outcomes (Feigin et al., 2005). The location of the bleed has not been found to predict mortality or outcome. Rather, the depth of the hemorrhage on CT scans is associated with poor prognosis (Wong et al., 2011).

Intracerebral hemorrhages are the fourth and final form of vascular damage resulting from focal injury, and are associated with an overall poor prognosis and high mortality rate (Wong et al., 2009). This hemorrhage is caused by rupturing of intracerebral blood vessels located in the brain parenchyma (Yokobori & Bullock, 2013). Multiple small vessel injuries may pool into one larger deep hemorrhage, which can expand with time. The impact from the injury itself plays a role in the location of the hemorrhage and subsequent hematoma resulting from the bleed. Boto et al. (2001) reviewed 37 cases with basal ganglia hematomas after severe brain injury and found that 76% (28 cases) developed the hemorrhages on the contralateral side of impact, with only 16% of these cases (6 participants) making a "favorable" recovery. This data indicates that deep intracerebral hemorrhages, including basal ganglia hematomas, may indicate poor outcomes following injury and represents severe underlying brain damage (Boto et al., 2001). It also adds to the complexity of coup-contrecoup injury mechanics.

Intracerebral hemorrhaging may also occur hours to days after the traumatic event. Delayed traumatic intracerebral hemorrhage occurs with patients with severe TBI, as well as patients who appear to be trending towards recovery, only to regress to a state of unconsciousness (Baratham & Dennyson, 1972). The delayed hemorrhage occurs because of damaged endothelial linings of the blood vessels that lead to structural failure, altered regulatory tone of vascular smooth muscle, and increased vascular permeability in the cerebral parenchyma in the days to weeks after the injury (Baratham & Dennyson, 1972; Yokota et al., 2002).

Diffuse Brain Injury

The second form of primary brain injury is diffuse injury. Diffuse brain injuries occur after sudden deceleration and/or acceleration of a person's body and head. Motor vehicle collisions, falls from high surfaces, and blast injuries may result in diffuse injury, as well as focal injury. Forces causing the brain to rotate in a non-linear plane within the skull (torsion or rotation forces), also contribute to diffuse injuries (Rowson & Duma, 2013). Unlike focal injuries, diffuse brain injuries transcend multiple areas of the brain and are not localized to the specific area of trauma. Diffuse injuries can span across the continuum of brain injury severity, ranging from mild injury depicted on the GCS, to patients following severe TBI (Johnson, Stewart, & Smith, 2013). Diffuse injuries produce changes in axonal and vascular integrity are described below.

Axonal Injury

Axonal degeneration is a complex process that arises following injury to the brain. Conventionally, this degeneration is recognized as a progression from a disruption in axonal transport leading to axonal swelling, followed by secondary disconnection, and finally, Wallerian degeneration and death of the injured axon and neuron cell body (Johnson et al., 2013). Axonal degeneration can be widespread and not confined to a single specific axonal pathway. This has been termed as diffuse axonal injury (DAI) (Adams, Graham, Gennarelli, & Maxwell, 1991; Adams, Graham, Murray, & Scott, 1982) and has been identified across all severities of closed head injury (Adams et al., 1989; Povlishock & Christman, 1995; Povlishock & Katz, 2005; Smith, Meaney, & Shull, 2003). Although defined as "diffuse," implying alterations throughout the entire nervous system, the pattern of axonal damage is more accurately described as multifocal, appearing throughout the deep and subcortical white matter and corpus callosum (Smith et al., 2003).

Strich (1956) was first to describe diffuse brain injury resulting from traumatic events in a human population. The histological study reviewed 5 brain injured cases post-mortem, with each person unconscious after injury and without skull fracture. Diffuse degeneration of white matter was noted in all cases, without the obvious causes of edema, vascular disturbances, embolism, or physical injury (Strich, 1956).

Historically, the force exerted on the brain from a traumatic event was thought to physically shear and tear axons, causing them to expel a portion of axoplasm and forming a swollen "retraction ball," later referred to as an axonal bulb (Adams et al., 1982; Povlishock, Becker, Cheng, & Vaughan, 1983; Povlishock & Katz, 2005; Smith et al., 2003; Strich, 1956). These axonal bulbs became the pathological marker for traumatically-induced axonal damage (Povlishock & Katz, 2005). Contemporary evidence suggests that shearing and separation of axons is caused by the most severe traumatic brain injuries resulting from direct mechanical forces, with axon disruption leading to focal alterations in axolemma or complete axotomies (Maxwell, Povlishock, & Graham, 1997; Maxwell, Watt, Graham, & Gennarelli, 1993; Pettus, Christman, Giebel, & Povlishock, 1994). This mechanism of altering the axolemma is referred to as a primary axotomy, or the direct separation of axons elicited by outside forces.

Non-disruptive injured axons may still undergo a sequence of changes that culminate in a delayed secondary axotomy (Maxwell et al., 1993; Povlishock et al., 1983). This secondary disconnection begins at the traumatic event, with the inertial force of trauma altering the membranous axolemma in axons not directly damaged. The disruption of the axolemma allows for an influx of extracellular calcium ions into the axon, leading to disruption of the intra-axonal cytoskeleton (Buki, Okonkwo, Wang, & Povlishock, 2000; Pettus et al., 1994; Pettus & Povlishock, 1996). This disruption in cytoskeletal structures interferes with localized cellular substrate transport, leading to focal swelling within the axon due to continued delivery of substrate via normal cellular functioning. The backup of substrate and swelling causes the collapse and detachment of the axon at the point of focal swelling (Buki et al., 2000; Christman, Grady, Walker, Holloway, & Povlishock, 1994; Pettus & Povlishock, 1996). This is a delayed process, taking place hours to days after the initial trauma (Blumbergs et al., 1995; Christman et al., 1994).

Distal to the white matter axotomy, degeneration of the axon begins. This neurodegenerative process, referred to as “Wallerian” degeneration, represents the parent neuron permanently losing the ability to communicate with the downstream target. While some patients diagnosed with DAI achieve functional recovery through behavioral compensation and physical modifications, actual repair of the disconnected axon is limited to localized plasticity in the gray matter (Povlishock & Katz, 2005; Smith et al., 2003). This pathological process may lead to cerebral atrophy in chronic, TBI patients (Ding et al., 2008).

Vascular Injury

Shearing, compression, and tension forces elicited on the brain after trauma leads to vascular damage and differs from other hemorrhages. This vascular damage occurs to blood vessel walls and hemorrhaging into the peri-vascular tissue. The term diffuse vascular injury (DVI) is used to describe these small hemorrhages that occur throughout the cortex and white matter after a traumatic brain injury (Iwamura et al., 2012; Onaya, 2002). These vascular alterations also can occur without direct impact or contusion. Hemorrhaging in neural structures occurs in conjunction with DAI when it is typically seen in areas of brain matter with the greatest vascularity, or as isolated microvascular bleeds identified without DAI pathology (Gentry, Godersky, & Thompson, 1988). The severity and spread of hemorrhaging depends on a myriad of systemic factors at the time of injury, including blood pressure, body temperature, hypoxia, age, alcohol intoxication, effects of medications, and substance abuse (Yokobori & Bullock, 2013).

The spectrum of brain injury ranging from purely focal to diffuse should be viewed as a clinical disorder resulting from neural and vascular events brought on by the mechanical alteration of the head (Gennarelli & Graham, 1998). When the brain undergoes moderate to severe trauma from inertial forces, it is often the case that combined diffuse and focal injury occurs (Gaetz, 2004). Emphasis has been placed on public prevention of primary traumatic brain injuries over the past several decades (seat belts laws, DUI enforcement, fall safety in older adults) and has led to a reduction in the overall number and severity of brain injuries due to trauma. Despite these public health initiatives, primary brain injuries occur at high rates.

Secondary Brain Injury

Secondary injury after brain trauma sequentially follows the primary injury. While the primary injury is due to direct trauma or vascular damage from inertial forces, the secondary injury is caused by a complex cascade of biochemical, cellular, and molecular changes, resulting in continued neurological deterioration. The physiological sequelae following the primary injury can result in varying degrees of edema, ischemia, elevated intracranial pressure, and inadequate cerebral perfusion. These processes potentiate one another, leading to an ongoing and escalating cycle of degenerative effects. On the cellular level, energy failure occurs in conjunction with a cascade of events that leads to cellular death. All of these potential injury mechanisms will be discussed in detail.

Edema

Cerebral edema, or swelling within the cranium, is a hallmark feature in moderate to severe brain injury. Edema is a source of secondary injury due to the inability for the skull to expand under pressure, thus injuring the brain. As swelling increases, expansion of the brain is not possible, and the brain becomes damaged from compression of neural structures and reduced blood flow. The presence of edema is strongly correlated with injury severity and provides useful clinical information regarding long-term prognosis and functional outcomes (Li, Wang, Li, Li, & Wang, 2012).

While not a hallmark feature, edema complications can be profound following more mild forms of TBI, including concussions. Second Impact Syndrome (SIS) has been defined as a condition that occurs in primarily young athletes “who sustain an initial head injury, most often a concussion, and who then sustains a second head injury before symptoms associated with the first have fully cleared” (Cantu, 1998; McCrory & Berkovic, 1998; Saunders & Harbaugh, 1984). The injury produces rapid catastrophic brain swelling and results in severe neurological injury or death (McCrory, Davis, & Makdissi, 2012). SIS is very uncommon, with an estimated injury rate for athletes taking place once for every 205,000 athletic seasons (Randolph & Kirkwood, 2009).

Edema is classified into two types after injury: Vasogenic edema and cellular edema. Vasogenic edema results from the disruption of the blood-brain barrier, allowing extracellular fluid and proteins to accumulate in the interstitial space (Baron & Jallo, 2007; Kochanek, Clark, & Jenkins, 2013). Cellular edema results from the inability to maintain cellular ion homeostasis and functions after trauma (Kochanek et al., 2013). Both vasogenic and cellular edema occur in unison, each contributing to the degradation of the nervous system. Historically, vasogenic edema was thought to contribute a significant amount to the overall swelling within the brain following injury, with cellular edema contributing a negligible amount. Recent evidence suggests the contrary. Cellular edema appears to play a much greater role in the swelling, regardless of whether the injury is diffuse or focal in nature (Marmarou, Signoretti, Aygok, Fatouros, & Portella, 2006). Cellular swelling is an important feature in individuals with TBI, where secondary edema influences the ability for blood to perfuse into the damaged tissue (Barzo, Marmarou, Fatouros, Ito, & Corwin, 1997).

Due to the increased intracranial pressure caused by elevated edema, cerebrospinal fluid may be involuntarily released, but this drop in volume typically is not enough to relieve the compression. Once this compensatory reserve is exhausted, intracranial pressure rises steeply (Baron & Jallo, 2007). Following intracranial hypertension, deformation of neural tissue is likely through herniation, producing damage to the existing cerebral vasculature and tissue (Kochanek et al., 2013). Intracranial hypertension may also compromise cerebral perfusion, leading to another form of secondary injury: Ischemia.

Ischemia

Ischemia after TBI is a complex condition resulting from insufficient blood flow within the brain to meet metabolic demands. Reduction of blood flow may be due to occlusion of cerebral vessels, systemic hypotension following injury, or ruptures of vessels after trauma (Bramlett & Dietrich, 2004). Prolonged reductions in blood flow lead to deprivation of oxygen and glucose, as well as build-up of toxic substances within the brain tissue (Bramlett & Dietrich, 2004).

Ischemia after TBI plays a major role in determining clinical status and mortality (Bouma et al., 1992). Ischemia is present after severe TBI, while mild to moderate injuries typically do not see such drastic changes in cerebral blood flow (Marion, Darby, & Yonas, 1991; Zauner, Bullock, Kuta, Woodward, & Young, 1996). Clinical studies in adults indicate that there is significant decrease in cerebral blood flow (CBF) and perfusion early after severe TBI (1-4 hours), leading to an overall poor outcome (Bouma et al., 1992; Marion et al., 1991). The length of time a person remains hypotensive following injury to time of resuscitation is a factor influencing ischemia and overall prognosis (Chesnut et al., 1993).

Elevated Intracranial Pressure

Elevated intracranial pressure (ICP) is another physiological response involved in the secondary injury cycle. ICP rises in conjunction with increased in cerebral edema. As brain swelling occurs within the fixed skull, the mechanisms normally providing outlets for mounting fluid pressure are rapidly overcome. As ICP continues to increase, cerebral blood flow and perfusion decrease, resulting in ischemia and herniation of brain tissue.

Increases in ICP typically follow all forms of TBI and are tolerated poorly by the brain. A non-injured and healthy adult brain maintains an ICP under 15 mmHg, allowing adequate cerebral perfusion to maintain homeostasis. A small, yet sustained increase in ICP to 20 mmHg has been associated with increased mortality in TBI patients (Juul, Morris, Marshall, & Marshall, 2000; Miller, 1982; Narayan et al., 1982). A threshold of 20-25 mmHg typically is used to define an elevated ICP at anytime following injury. ICP monitoring has become a cornerstone in the management of severe head injury in intensive care units in the United States, along with monitoring cerebral perfusion pressure (Baron & Jallo, 2007; Juul et al., 2000).

Cerebral Perfusion and Autoregulation

Maintaining adequate cerebral blood flow is one of the most important factors influencing outcome and recovery following injury (Chan, Dearden, Miller, Andrews, & Midgley, 1993). Restoring and maintaining blood flow becomes increasingly difficult as the injury progressively becomes more severe. Cerebral blood flow is also very difficult to measure accurately in a healthy person, let alone someone who has sustained a brain injury. Cerebral perfusion pressure (CPP) is a metric created to allow clinicians and researchers to evaluate the effects of blood flow without direct measurement. CPP can be calculated by taking the difference between mean arterial pressure (MAP) and intracranial pressure (ICP): CPP= MAP – ICP (Baron & Jallo, 2007). A healthy brain maintains a CPP of 50-140 mmHg (Rosner & Daughton, 1990), allowing for adequate autoregulation of blood flow and cerebral perfusion. When perfusion pressure falls below 50mmHg due to decreased blood pressure and increased ICP resulting from edema, the vasculature in the brain becomes maximally dilated and perfusion rate cannot meet the energy demands of the tissue.

Neurophysiology dictates the cerebral autoregulatory response to changes in blood pressure. While this is an important aspect to blood flow throughout the brain and body, the autoregulatory paradigm was constructed around the presumption that physiological responses are the same in both a healthy and injured brain. This hypothesis now appears to be false, especially with respect to severe brain injuries. While the norm for autoregulatory CPP in the healthy brain range from 50-140 mmHg, outcomes are significantly worse for severely injured patients with a CPP at 60mmHg or below (Changaris et al., 1987), a value still well within normal parameters. Interventions implemented to maintain a CPP of at least 70mmHg produce more favorable outcomes in severely injured brains (Rosner, Rosner, & Johnson, 1995), indicating that patients with brain injuries require a greater CPP to maintain adequate autoregulation and cerebral blood flow and prevent ischemic conditions (Fortune, Feustel, Weigle, & Popp, 1994). ICPs higher than 70mmHg in individuals after brain injury may increase the risk of respiratory distress syndrome, however, offsetting the potentially beneficial intervention (Robertson et al., 1999). Respiratory distress syndrome occurs because of the need to create a hypertensive condition in the brain to increase CPP to 70mmHg. The increased blood pressure increases pulmonary hydrostatic pressure, leading to increased amounts of fluid accumulating within the lungs (Smith & Matthay, 1997).

Cell Death Response to Injury

Cell death after brain injury is common, and occurs on a continuum (Portera-Cailliau, Price, & Martin, 1997; Rink et al., 1995). After injury, neurons will either undergo cell membrane alterations leading to cellular necrosis, or will undergo an intrinsic cascade of events culminating in a programmed cell death (termed apoptosis). Necrosis can be considered as based on the pathological response to injury, whereas apoptosis is based in the physiological response to neuronal disruption (Portera-Cailliau et al., 1997). Apoptosis is characterized by cell shrinkage, DNA fragmentation, and nuclear condensation (Kochanek et al., 2013). The intrinsic metabolic cascade triggering apoptotic cell death begins in the mitochondria, where homeostasis is altered following trauma (Zamzami et al., 1996), and ultimately leads to an energy crisis in the cell.

Autophagy is the third cell death pathway following secondary brain injury. Autophagy is a normal cellular function, being a carefully regulated and dynamic process for intracellular recycling of proteins, lipids, and cellular byproducts (Todde, Veenhuis, & van der Klei, 2009). Autophagy occurs in all tissues and cell types, including the nervous system, and is a necessary cellular response to external stress (Au, Bayir, Kochanek, & Clark, 2010). Elevated byproducts of autophagy were first identified in mice following a closed head injury (Diskin et al., 2005), and has also been described in ischemic and hypoxic injuries (Zhu et al., 2005).

The role autophagy plays in cell death following TBI is controversial. Autophagy is a naturally occurring process in the human body and provides many benefits. Eliminating autophagy may lead to the accumulation of toxic levels of proteins associated with various pathological conditions, including mutated Tau, amyloid- β, and Huntington proteins (Goedert & Jakes, 2005). This information suggests that elevated levels of autophagy after TBI represent a necessary part of the healing process, as the removal of accumulating proteins and malfunctioning organelles may improve the nervous system's ability to heal and prevent long-term degradation of the neural tissue. The counterpoint to this argument deals with the process of autophagy itself. Autophagy, under non-traumatic circumstances, removes aging and dysfunctional organelles, but some scholars believe that this process may also remove damaged organelles that have the ability to repair themselves following injury. For instance, damaged mitochondria may undergo fusion to inhibit mitochondrial fragmentation, while mitochondrial fragmentation leads to apoptotic death of the cell (Rintoul, Filiano, Brocard, Kress, & Reynolds, 2003). Enhanced autophagy following trauma may increase the elimination of potentially viable organelles, such as fusing mitochondria, and leading to energy failure throughout the brain (Au et al., 2010).

Metabolism

Injuries resulting in any form of disrupted neuronal membranes, stretched axons, or severed connections will produce some form of altered neuro-metabolic physiology, regardless of severity. Acutely, potassium ion (K+) channels are opened, leading to increased accumulation of extracellular K+ (Katayama, Becker, Tamura, & Hovda, 1990; Takahashi, Manaka, & Sano, 1981). As the K+ channels open, global depolarization occurs, leading to increases in the excitatory amino acid glutamate (Giza & Hovda, 2001; Katayama et al., 1990). Glutamate influx exacerbates the extracellular K+ influx cycle, leading to disturbances in normal neuronal activity (Takahashi et al., 1981). In healthy individuals, excessive K+ is taken up by surrounding glial cells, resulting in the maintenance of homeostasis (Ballanyi, Grafe, & ten Bruggencate, 1987; Kuffler, 1967). In more severe cases resulting from ischemia or contusions, the glial cells are unable to maintain the uptake of elevated amounts of extracellular K+ (D'Ambrosio, Maris, Grady, Winn, & Janigro, 1999). As extracellular K+ increases, further neuronal depolarization occurs, leading to increased levels of excitatory glutamate, and still greater K+ levels (Giza & Hovda, 2001).

In an effort to restore normal ion levels, membrane pumps normally become activated, requiring higher amounts of glucose to reach homeostasis (Shah & West, 1983; Sunami et al., 1989; Yoshino, Hovda, Kawamata, Katayama, & Becker, 1991). In an uninjured state, the energy demands of the brain are supplied by oxidative metabolism, which typically runs at a near maximum level to maintain brain functioning. An increase in energy demands following trauma cannot be satisfied solely by oxidative means, thus glycolysis is increased to meet the energy needs (Ackermann & Lear, 1989; Lear & Ackermann, 1989). The hyperglycolitic response occurs immediately following injury (Kuroda et al., 1992; Yoshino et al., 1991) and persists up to 30 minutes for less severe injuries (Yoshino et al., 1991) to 4 hours for severe trauma (Kuroda et al., 1992). The accelerated glycolytic metabolism produces elevated levels of lactate, regardless of injury severity (Meyer, Kondo, Nomura, Sakamoto, & Teraura, 1970; Nilsson & Nordstrom, 1977; Yang, DeWitt, Becker, & Hayes, 1985), resulting in lactate accumulation that disrupts neuronal functioning and can leave neurons vulnerable to a second ischemic injury (Krishnappa, Contant, & Robertson, 1999). Along with glycolytic metabolism, oxidative metabolism is also impaired following brain trauma (Xiong, Gu, Peterson, Muizelaar, & Lee, 1997; Xiong, Peterson, Muizelaar, & Lee, 1997; Xiong et al., 1998), likely due to mitochondrial damage. Mitochondrial dysfunction only increases the need for glycolysis, as the remaining functional mitochondria are unable to produce adequate amounts of adenosine triphosphate (ATP) following the injury (Giza & Hovda, 2001).

Mitochondrial dysfunction partly may be due to calcium ion (Ca2+) accumulation. Energy and respiratory dysfunction within the mitochondria after traumatic brain injury are linked to excess intracellular Ca2+ accumulation (Xiong, Gu, et al., 1997), resulting in impaired oxidative metabolism and energy failure (Giza & Hovda, 2001). Ca2+ accumulation begins within hours of the trauma, and may persist up to 4 days after injury (Osteen, Moore, Prins, & Hovda, 2001).

After the initial period of elevated glycolysis, cerebral glucose use is decreased 24 hours after injury, and this decrease may last 2-4 weeks in individuals with brain injury (Bergsneider et al., 2000; Bergsneider et al., 2001). This hypo-metabolism does not correlate closely with consciousness after injury (Bergsneider et al., 2000), but does correlate well with long term behavioral changes (Colle, Holmes, & Pappius, 1986). The metabolic fluctuations following TBI follow a 'tri-phasic pattern,' as there is an observed initial increase and then decrease in metabolic functioning after injury before returning to homeostasis. The tri-phasic metabolic recovery spans the injury continuum, with mild and severe injuries responding similarly through triphasis (Bergsneider et al., 2001).

Inflammation

Adding to the already complex pathogenesis of secondary brain injury is neuroinflammation. Inflammation is the final delayed response after injury, with recruitment of inflammatory cells continuing the secondary damage cascade (Finnie, 2013). The inflammatory process after TBI has dual and opposing roles, producing both deleterious and favorable outcomes. Post-traumatic inflammation can promote neuronal repair mechanisms if the inflammation is controlled in a regulated manner for a short, defined period of time (Kumar & Loane, 2012; Ziebell & Morganti-Kossmann, 2010). When the inflammatory response is excessive, however, numerous neuropathologies are likely due to the release of neurotoxins (Correale & Villa, 2004), promoting a further exacerbation of the secondary brain injury response and adverse clinical outcomes.

Acute neuroinflammation is characterized by production of inflammatory mediators, endothelial cell injury, polymorphonuclear leukocyte infiltration, increased vascular permeability, and vasogenic edema (Finnie, 2013). Infiltration of polymorphonuclear leukocytes is the hallmark of CNS inflammation, particularly after TBI. Accumulation of leukocytes starts within 24 hours after a traumatic event (Soares, Hicks, Smith, & McIntosh, 1995). Infiltration of polymorphonuclear leukocytes is likely due to a disruption of the blood brain barrier, the regulating interface between the circulatory system and the CNS. Under normal circumstances, the blood brain barrier ensures an adequate supply of nutrients and oxygen to the brain and guides inflammatory cells to respond to changes homeostasis (Abdul-Muneer, Chandra, & Haorah, 2014). Disruption of the blood brain barrier is typical in moderate to severe TBI patients (Morganti-Kossmann et al., 1999) and plays a significant role in the response to injury.

Neuronal tissue dysfunction after acute neuroinflammation is largely attributed to the accumulated polymorphonuclear leukocytes, which attracts substances that are highly toxic to neural tissue. Reactive oxygen species (ROS), reactive nitrogen species (RNS), and pro-inflammatory cytokines became prevalent in areas with elevated polymorphonuclear leukocyte levels in the CNS (Finnie, 2013; Morganti-Kossmann et al., 2001; Morganti-Kossmann et al., 2002), further exacerbating the traumatic condition with oxidative stress, delaying functional recovery (Lucas, Rothwell, & Gibson, 2006; Werner & Engelhard, 2007) and exacerbating neuronal death (Kreutzberg, 1996). These post-injury inflammatory cascades of cytokines and free radicals also contribute to the further dysfunction of the blood brain barrier, leading to a greater influx of inflammatory cells from the blood to the brain (Soares et al., 1995).

The inflammatory response can, however, serve as a beneficial process after TBI. While the influx of reactive oxygen and nitrogen species and pro-inflammatory cytokines is detrimental to axonal repair and regrowth, the presence of these substances around the lesion leads to the accumulation of astrocytes. The activated astrocytes allow for the upregulation of neurotrophic factors at the lesion site, specifically brain-derived neurotrophic factor (BDNF), which promotes tissue repair and neurogenesis (Bush et al., 1999; Correale & Villa, 2004; Zhao et al., 2004). Astrocytes also play a critical role in regulating excitatory glutamate levels, which can reduce toxicity to the injured neurons and other cells (Schousboe & Waagepetersen, 2005). Reduced or impaired astrocyte performance increases neuronal dysfunction, leading to negative long term outcomes following TBI (Myer, Gurkoff, Lee, Hovda, & Sofroniew, 2006).

The inflammatory process has provided researchers and physicians an opportunity to use the biomarkers of inflammation as a way of quantitatively confirming a traumatic brain injury has occured. This process may be helpful in identifying ‘mild’ injuries, as the transient neurological changes associated with more mild forms of injury are difficult to assess functionally. Two markers of tissue damage have been evaluated for use today: S100 calcium-binding protein β (S100β) and neuron-specific enolase (NSE).

High concentrations of S100β are found in the blood following traumatic injury. When cells are damaged, S100β is released into the circulation (Mussack, Biberthaler, Kanz, Heckl, et al., 2002), allowing for easy measurement via a standard serum blood sample (Ingebrigtsen & Romner, 1996). While the literature suggests S100β may be a useful marker for brain injury (de Kruijk, Leffers, Menheere, Meerhoff, & Twijnstra, 2001; Herrmann et al., 2001; Ingebrigtsen & Romner, 2002, 2003; Mussack, Biberthaler, Kanz, Wiedemann, et al., 2002), this biomarker does have limitations. First, S100β serum must be collected quickly following injury, as the serum concentration peaks within 20 minutes following injury (Mussack, Biberthaler, Kanz, Heckl, et al., 2002). This may be impossible for individuals in extreme distress (e.g., battlefield conditions, multi-trauma events) or those with minor injuries who do not seek emergency service. These limitations may not be concerns in the future with the development of quick finger-stick tests for S100β levels (Kiechle et al., 2014), similar to blood-glucose testing for diabetic individuals.

A second limitation of S100β as a diagnostic marker for brain injury relates to the extracranial release of S100β. Higher S100β are observed in non-head injured trauma patients sustaining orthopedic or musculoskeletal injuries when compared to healthy, non-injured controls (Anderson, Hansson, Nilsson, Dijlai-Merzoug, & Settergren, 2001). Similarly, the release of S100β increases after physical exertion (Otto et al., 2000; Stalnacke, Tegner, & Sojka, 2003, 2004), thus limiting the clinical interpretability of the biomarker for individuals following sports-related mTBI. Despite these shortcomings, S100β is considered the most widely reviewed biomarker and may have potential to be used in the future for injury identification.

NSE is another biomarker proposed for use in assessing neuronal damage (de Kruijk et al., 2001). NSE is passively released into the peripheral circulatory system as a result of structural damage to nerve cells (Guzel et al., 2008; Pelinka et al., 2005; Yamazaki, Yada, Morii, Kitahara, & Ohwada, 1995). Much like S100β, NSE can also be collected by a simple blood draw (Dash, Zhao, Hergenroeder, & Moore, 2010). NSE levels peak within 6-12 hours following injury (Dash et al., 2010), making it less necessary to collect a blood sample immediately following injury.

Several studies have examined the influence of injury severity on NSE levels across the injury continuum. The studies report mixed results. Researchers report no correlation between GCS scores and NSE levels (Ross, Cunningham, Johnston, & Rowlands, 1996; Yamazaki et al., 1995), while other studies have found a significant negative correlation between GCS and NSE levels (Ergun et al., 1998; Herrmann et al., 2000). Other researchers have reported an association between elevated NSE levels and worse functional outcomes following mTBI (Herrmann et al., 1999), poor neurological outcome (Meric, Gunduz, Turedi, Cakir, & Yandi, 2010), and lower GCS scores after moderate-to-severe TBI (Vos et al., 2004). Similar to S100β, NSE levels are elevated following bodily trauma with or without the presence of head injury (Pelinka et al., 2005). These inconsistencies indicate that further research is needed before NSE is considered an adequate biomarker for TBI diagnosis, clinical interpretation, and outcome prediction.

Summary

This review has described underlying neural alterations leading to changes in overall functioning of individuals after TBI. Brain injury severity was described as ranging from mild injuries producing transient alterations of cognitive functioning, to severe injuries causing long-term neurological damage and disability. Clinicians and researchers use many assessments to evaluate and categorize each patient. The Glasgow Coma Scale, the Glasgow Outcome Scale, the Disability Rating Scale, and the Rancho Los Amigos Scale are the most prevalently used assessments today for moderate to severe injury. While the assessments are critical for assessing the neurological status of a person after injury, there is a lack of consistency in the literature when describing brain injury severity, as several different assessments are used to quantify injury in individuals. These assessments are also not sufficiently specific to detect subtle neurological alterations, including improvements, following more mild forms of TBI. Evaluation of specific neurocognitive skills provide greater insight into what pathological alterations have occurred, allowing clinicians to identify the most appropriate treatment recommendations for recovery. Evaluation and assessment of brain injury across the injury spectrum will continue to progress as new tools and methods are developed.

The neurological mechanisms of primary brain injuries also were described. Primary TBI encompasses events occurring at the moment of neurological trauma, which are preventable but not reversible. This initial sequence can produce diffuse and focal damage in brain tissue. Diffuse injury can be categorized as axonal or vascular, each producing alterations throughout the cerebrum. Both axonal degeneration and vascular hemorrhaging occur throughout the cortex and white matter, leading to altered neurological functioning and initiation of secondary effects of TBI. Focal injuries result from the direct and immediate destruction of neural tissue, often caused by an object penetrating the skull, although focal injuries can be caused by non-penetrating forces. Penetrating injuries produce contusions, hemorrhaging of cerebral vasculature, and localized lesions in the brain, resulting in altered neurological functioning.

Secondary injury begins in response to physiological challenges imposed on the nervous system after the preceding primary injury. These complex processes potentiate one another, leading to an ongoing cycle of neurological deterioration if not intervened. Increased cerebral edema and elevated intracranial pressure limit cerebral blood perfusion and autoregulation. This inability to maintain homeostasis, along with direct cellular damage, creates a metabolic crisis in the brain, leading to cycles of cell death. Inflammatory processes also take place, having potential for both beneficial and harmful roles.

Future Implications

While this review described underlying mechanisms influencing functional changes a person can experience after a brain injury across all severities, finding relevant literature on the effects of mild brain injury on daily activities proved difficult. Once viewed as a minor injury, health professionals and the public now see mTBI as a growing concern. Many questions remain about how mTBI and concussions can affect a person's life. Current research has focused on describing neurological changes of athletes acquiring the injury while playing sports in predominantly male subjects, with comparatively little evidence existing for other demographic groups. Little research also exists for the efficacy of treatment interventions, including parameters to optimize the effects of prescribed rest.

The expertise of multiple healthcare disciplines must be considered when addressing the needs of individuals after mTBI. Rehabilitation professionals, including physical therapists, occupational therapists, speech language pathologists, and neuropsychologists each possess unique skillsets that may shorten the recovery time needed after a brain injury. Occupational therapists, for example, have the expertise in tailoring activities and environments to different abilities of people, allowing for improved and more rapid participation in valued roles and routines (AOTA, 2014).

Occupational therapists support individuals after brain injury by adapting environments to facilitate improvements in participation (Fleming, Nalder, Alves-Stein, & Cornwell, 2014), adjusting different tasks to increase the independence of the person (Preissner, 2010), addressing the underlying activity skills that may have been altered following injury (Giuffrida, Demery, Reyes, Lebowitz, & Hanlon, 2009), and using activities the person values to progress recovery (AOTA, 2002). Incorporating occupational therapists into the care of individuals following mTBI would allow for sooner return to work and/or school for people after injury, possibly even before symptoms fully resolve. Returning individuals to their previous roles and routines after injury can be accomplished by evaluating the person's symptoms and supports, adapting the environments to better support the individual during their daily life, working on specific performance skills that have been affected after the mTBI, and educating the person on compensatory changes they could make to offset their temporarily-altered abilities (AOTA, 2014).

Prior to the systematic implementation of the GCS in hospitals, health professionals viewed individuals with moderate-to-severe TBI as a homogenous cohort, receiving similar evaluation and treatment. Individuals with mTBIs, including individuals following a concussion, were considered 'dazed' and often returned back to their typical routines (work, sports, military activity) without being evaluated and treated for neurologic injury (Saucier, 1955). The overall culture was to 'toughen up' and resume their lives, despite sometimes persistent symptoms.

Healthcare professionals and the general public rarely considered the possibility that there could be further neurological changes and long-term effects.

Recently, professionals and the public have made a drastic shift in thinking about the impact of mTBI. People see concussions as potentially serious injuries requiring immediate assessment and further evaluation by trained clinicians. The growing public awareness of the injury and further research dedicated to studying more mild forms of TBI are significant contributors to this changing perspective. An emerging body of evidence suggests repeated brain trauma, including concussions, may lead to conditions like chronic traumatic encephalopathy (Stern et al., 2011), Alzheimer's disease (Fleminger, Oliver, Lovestone, Rabe-Hesketh, & Giora, 2003; Jellinger, Paulus, Wrocklage, & Litvan, 2001; Mehta et al., 1999; Rasmusson, Brandt, Martin, & Folstein, 1995), and Parkinson's disease (Bower et al., 2003; Goldman et al., 2006), although these findings remain controversial and are not accepted universally (Daneshvar et al., 2011; McCrory, Meeuwisse, et al., 2013).

Quick and accurate identification of injured athletes in sports settings and injured soldiers in training and combat have dominated the concussion research landscape. Studies have focused on neuropsychological evaluation (Echemendia et al., 2013; Johnson, Kegel, & Collins, 2011; King, Brughelli, Hume, & Gissane, 2014), subjective symptom reporting by injured individuals (Grubenhoff et al., 2014; Kroshus, Baugh, Daneshvar, & Viswanath, 2014; Silverberg et al., 2013; Tsushima, Shirakawa, & Geling, 2013), performance-based motor assessment (Eckner, Kutcher, Broglio, & Richardson, 2014; Galetta et al., 2011), postural stability (Murray, Salvatore, Powell, & Reed-Jones, 2014), and neuroimaging (Dettwiler et al., 2014; Dimou & Lagopoulos, 2014). While extensive reviews and consensus statements exist for evaluation and assessment of individuals who have had a concussion (Harmon et al., 2013; McCrory et al., 2009; McCrory, Meeuwisse, et al., 2013; Meehan, d'Hemecourt, Collins, & Comstock, 2011; Patel, Shivdasani, & Baker, 2005), most of the studies include predominantly male athletes competing at the collegiate and professional level. Few studies address concussions in female athletics, or incidence and pathology of non-sporting concussions, including falls in the elderly and motor vehicle accidents. Future mTBI research needs to include representatives of other athletic groups and the general public.

One possible way to evaluate different groups after injury is to involve health systems that serve a wide spectrum of ages and cases. Much like typical TBI outcome studies, the mTBI populations would be comprised of both men and women across the lifespan, as opposed to the current focus of a male cohort of athletes typically between the ages of 15-23 years. By studying a diverse population, researchers can analyze variables that may translate to the care of entire populations, not just male athletes having a confounding history of previous head injuries. Evaluating clinical data from health systems may also provide insights into improving the overall care of individuals with head injuries. Researchers may be able to identify features that prolong the length of recovery in individuals, making targeted treatments and interventions a future possibility.

Another area of need is to evaluate the efficacy of inactivity as a strategy to decrease neurological symptoms following injury. Currently, standard care includes complete cognitive and physical rest to decrease symptoms after mild head injury (Moser, Glatts, & Schatz, 2012). Professionals instruct patients to refrain from any types of physical or cognitive activity after symptoms begin, which restricts many of the daily activities people value. People must take days away from work, be absent from school, refrain from doing homework or work-related tasks at home, and abstain from any cognitively-demanding activity. Rest is recommended until the individual's symptoms have subsided to 'tolerable' levels, typically lasting 2 to 5 days (Kutcher & Giza, 2014). Refraining from cognitively and physically demanding tasks can be difficult to maintain after a few days, with individuals anxious to return back to their daily routines and roles. The lack of objective criteria to define duration and degree of the cognitive rest period limits uniform application of these recommendations and the ability to compare outcomes across cases.

Despite complete rest being recommended frequently and the importance of this strategy being stressed, limited evidence exists evaluating effectiveness of rest in assisting to resolve and/or alleviate active symptoms. Emerging evidence suggests an extended period of rest may lead to protracted recoveries and increased symptoms reported following acute concussive injury, with rest periods lasting longer than 48 hours suggested as being contraindicated (Thomas, Apps, Hoffmann, McCrea, & Hammeke, 2015). The length of recovery when 'cognitive and physical rest' serves as the only intervention used by clinicians is concerning, especially for children and adults refraining from attending school and work. Interventions and approaches must be developed, tailored for individual needs, and evaluated in future studies to minimize the amount of time needed to recover from injury.

To date, no research has addressed how mTBI specifically impacts the daily activities of individuals across the lifespan. Researchers have described many of the physical and cognitive abilities affected after concussive injuries, including alterations in information processing speed (Taylor, 2012), attention (Grubenhoff et al., 2014), memory and recall (Ozen, Itier, Preston, & Fernandes, 2013), reaction time (Eckner et al., 2014), physical and mental fatigue (Norrie et al., 2010), balance abilities (Powers, Kalmar, & Cinelli, 2014), and emotional regulation (Valovich McLeod & Register-Mihalik, 2011). These changes in abilities, many of them transient, may not reflect how head injury truly influences a person’s life. Researchers and clinicians need to look past simply determining affected abilities and skills after a person sustains a brain injury. There is systematic need to investigate how altered cognitive abilities affect a person’s daily life, a role best suited for occupational therapists. When researchers understand the relationship between changes in a person’s abilities and roles after injury, targeted rehabilitation interventions can be developed and implemented to help people return to a life free of symptoms.

Appendix B: Comprehensive Review II

Reliability and validity of a mobile device application for use in postural control assessment

This work was approved September, 2015

Introduction

Postural control supports functional independence. Postural control involves integrating sensory information from the visual, vestibular, and somatosensory systems in response to both anticipated and unanticipated stimuli [1]. Declines in postural control are common with age and are associated with increased risk of falls during daily life activities [2]. Neurologic [3-5] and musculoskeletal conditions [6] also can affect postural control, making balance assessments necessary in a variety of clinical settings. Balance assessment can occur outside of clinical settings, as is often done during sideline assessment of athletes with suspected concussions at sporting events [7].

The most common way to assess postural control in clinical environments is to use clinical rating scales and task-based balance tests to evaluate a person's stability including, for example, the timed single leg stance, the Berg Balance Scale, and the Timed Up and Go test [8]. While these assessments have moderately good reliability [9-11], the measures lack sensitivity and are not responsive enough to measure subtle changes in a person's postural control [9]. Another significant limitation of these clinical assessments is a lack of specificity regarding the type of postural stability problem in relation to directing clinical care [12].

Alternatively, clinicians may use force plates to measure ground reaction forces and calculate center of pressure (COP) sway during balance stances as an objective measure of postural control [13]. COP variables calculated from ground reaction forces are valid and reliable across different health conditions [14]. Although force platform technology provides a precise method for assessing postural control, the platforms themselves are costly, and require proper installation, maintenance, and skilled interpretation of COP data. These constraints often are not feasible in clinical settings. The platforms also have limited portability, making assessment difficult for home health and sports medicine providers. Accelerometers have been evaluated as potential alternatives to force platform measurement, as body-worn accelerometers provide a relatively more affordable and portable method for assessing postural control [15-17]. This technology is promising and is available in most mobile devices, making accelerometer-based postural assessment available to clinicians without the need for extra equipment.

Mobile devices may provide clinicians with an ideal alternative for use in objective postural control when force platforms and accelerometers are not feasible. Many mobile devices now contain tri-axial accelerometers accessible downloadable applications (apps) created for clinical use. One app, SWAY (Sway Medical, Tulsa, OK) was developed for Apple Inc. products and uses accelerometion values collected during static stances to quantify a person's postural control. Previous research evaluated single leg stances measured by SWAY [18]. Other stances typically used in clinical settings (i.e. Two-Foot stance, Tandem stance) have not been assessed, yet a wider selection of stance options is necessary for use with patients having sufficiently impaired balance to preclude the more challenging single leg stance posture. Establishing the validity and reliability of mobile device apps, including SWAY, for use in postural assessment is needed prior to wide-spread adoption of this technology in clinical settings.

The purpose of this study was to evaluate the ability of SWAY, a mobile device app accessing the device's tri-axial accelerometer, to quantify postural control in healthy individuals. The first aim of this study was to determine if accelerometry-based measures of postural control produced by SWAY are reliable. The second aim of the study was to assess validity, by measuring the relation of accelerometry data collected by SWAY and force platform COP variables when collected concurrently. We hypothesized SWAY would demonstrate good to excellent test-retest reliability, and that SWAY scores and force plate COP variables would demonstrate good correlation coefficients [19].

Methods

Subjects

Twenty-eight healthy volunteers participated in the study (13 men, 15 women; age 30.7 ± 12.1 years; height 170.7 ± 10.8 cm; weight 72.9 ± 16.9 kg). Individuals reporting a known orthopedic, musculoskeletal, or neurologic injury in the prior 6 months were excluded. All subjects reported they had not consumed substances or medications prior to testing that may affect postural stability. All subjects provided written informed consent prior to participation in accordance with requirements of the Institutional Review Board for this study.

Materials

SWAY was downloaded and installed on the single mobile device that was used throughout all testing (Apple iPod Touch 5th Gen, iOS Version 7.1, Apple Inc., Cupertino, CA). SWAY is an FDA-approved app for detecting changes in postural stability using the integrated tri-axial accelerometers of Apple iOS mobile devices. The application instructs users through a series of balance stances, replicating the stances used in the Balance Error Scoring System (BESS) [20]. The SWAY app collects data at 10 Hz during each 10-second test period. SWAY provides a score at the end of each trial, calculated from total jerk units produced during each 10 second testing period and normalized to a 0–100 scale (Fig. 1). An AMTI force plate embedded in the floor was used to record ground reaction forces at 100 Hz (AMTI 1000, Advanced Mechanical Technology Inc., Watertown, MA). COP values were calculated by a custom

MATLAB program (MATLAB version R2013b, The MathWorks, Inc., Natick, Massachusetts, USA) [14].

Procedure

Prior to balance testing, demographic information was collected. Subjects then performed a series of static balance stances while standing on the force platform and holding the mobile device in an upright position against their sternum (Fig. 1). Subjects remained in each balance stance for 10 seconds, with instructions to maintain a steady balance to the best of their abilities. Each test sequence included three stances: Feet Together stance, Tandem stance with the dominant foot forward, and a Single-Leg stance standing on the dominant foot (Fig 1.). Subjects repeated the stance sequence four times: twice with eyes open and then twice with eyes closed. All four tests of Single-Leg stance were, however, completed with eyes open due to frequent postural corrections causing subjects to step off the force platform and thus invalidate data collection. At the end of each 3-stance test sequence, subjects rested in a chair for one minute before the next test sequence was initiated. Testing sessions lasted approximately 15 minutes, including rest breaks.

Data Acquisition and Processing

A custom Matlab program to calculate COP measures from the COP time series. These measures include sway area, root mean square (RMS) distance, and mean velocity [14]. Sway area is a time-domain area measure that contains the total area enclosed by the outermost edge of the COP path. RMS distance is a time-domain measure of the RMS of the distance from the mean COP throughout the entire time series. Mean velocity is a measure of the average velocity of the COP throughout the entire time series. All force plate data were resampled to 20 Hz and truncated to include only the middle 7 seconds of data to control for any imprecision in simultaneous initiation of data collection between the mobile device and the force platform.

The SWAY application uses a proprietary algorithm to calculate a SWAY score ranging from 0 to 100, with higher scores indicating better postural control. Mechanical validity of the tri-axial accelerometers housed in the mobile devices has been described previously [21, 22]. A SWAY score was calculated for each of the 12 balance trials and an overall average was calculated for each of the four test sequences and was used in the analysis. A quality check of these data included omitting any trials from the force platform and corresponding SWAY measure where the subject failed to complete the trial for the balance condition successfully. These included trials where subjects stepped off the force platform, hopped to recover loss of balance, or instances of a toe-touch by the non-supporting foot during Singe-Leg stance.

Statistical Analysis

Statistical comparisons were performed using SPSS (Version 20, SPSS Inc., Chicago, IL, USA). Test-retest reliability was assessed using an intraclass correlation coefficient (ICC) calculation (2,1) and the *p*-value and 95% confidence intervals for each ICC determined. A Pearson product-moment correlation was used to assess the concurrent validity between SWAY and COP variables. The *p*-value and *r*-value for each comparison were determined. An alpha level of 0.05 was set *a priori.*

Results

SWAY and force platform results are listed in Table 1. Subjects produced the largest amount of postural sway across SWAY scores and COP variables during the Tandem stance/eyes closed condition. SWAY identified Feet Together stance/eyes closed as the condition producing the least amount of postural sway in subjects, while COP sway area was lowest during Feet Together/eyes open stance.

Reliability

Test-retest reliability of SWAY and force platform measures are presented in Table 2. Generally, SWAY produced similar ICC values to that of the COP variables for sway area, RMS distance, and mean velocity. The ICC value produced by the SWAY scores for Tandem stance/eyes open (ICC = 0.211) was relatively low in comparison to COP sway area, RMS, and mean velocity for the same test condition (ICC = 0.553 to 0.640). SWAY scores for Tandem stance/eyes closed and Single-Leg stance/eyes open produced higher ICC values than all COP variables in each stance condition.

Laboratory Validity

Table 3 summarizes the Pearson product-moment correlations between SWAY and COP variables. The sway area, RMS, and mean velocity showed significant correlations with the SWAY scores during Tandem and Single-Leg stances with eyes open (r = -0.552 to -0.661). Correlations between SWAY scores and sway area, RMS, and mean velocity during Tandem stance/eyes closed demonstrated a fairly strong association [19]. No significant correlations were found between SWAY scores and COP variables during the feet together stances, regardless of visual condition.

Discussion

This study was designed to evaluate the reliability and validity of SWAY, a software app for iOS mobile devices that uses the device's built-in tri-axial accelerometer, to quantify postural control. We hypothesized SWAY would demonstrate good to excellent test-retest reliability. This hypothesis was partially supported, as the ICC values for SWAY were comparable to ICC values calculated from the COP variables. We also hypothesized that SWAY and COP postural control measures would demonstrate good correlation coefficients across all stance conditions. This hypothesis also was partially supported. Correlation coefficients between SWAY scores during Tandem stance/eyes open and Single-Leg stance/eyes open showed a strong relation with force plate COP variables. The SWAY scores from other combinations of stance and visual condition did not display any relation to coinciding COP variables.

Comparisons between SWAY scores and the COP variables produced similar ICC values, indicating that the two methods produced comparable test-retest reliability results. A surprising outcome were the relatively low ICC values produced by SWAY scores and the COP variables, which may indicate quick repeated measures taken in succession may lead to measurement inaccuracies. The low values for both methods also may be attributable to low variability between recruited subjects. The study population consisted entirely of healthy individuals who were well within their capacity for postural control. The standard deviations for each stance condition were relatively narrow, indicating low variability between subjects and thus limited the magnitude of ICC calculations [23]. This may explain why the test-retest ICC values for the COP variables were much lower than previously reported in similar populations [24]. Our finding that SWAY is comparable in reliability to the gold standard COP variables illustrates that SWAY could be useful in monitoring changes in a person's static postural stability over time, which is often necessary for use in clinical settings when repeated assessments are conducted to monitor improvements or regressions of postural control over time.

The current study also documented strong correlations between SWAY scores and COP variables used to characterize postural control. Our results indicate SWAY can be used interchangeably with COP measures during Tandem and Single-Leg stances in healthy individuals. Two of the three stances used throughout testing yielded inversely significant results between SWAY scores and COP variables. The lack of correlation for Feet Together stance and all eyes closed conditions could be due to the devices measuring different aspects of postural control [16]. The mobile device held by each subject at the sternum captured accelerations relatively close to each individual's approximate center of mass (COM). Measuring postural control near a person’s COM may be more representative of balance ability and responds to fluctuations in postural sway. Conversely, displacement of COP measured by force platforms are more reflective of neuromuscular responses at the ankle [1, 25], as opposed to postural sway [26]. Measurement of postural control at the approximate center of mass allows clinicians and researchers to directly investigate the influence of sensory systems on postural sway, not only neuromuscular response to sensory input elicited by COM movement.

The significance of both Tandem and Single-Leg stances is an important clinical finding for clinicians assessing individuals with subtle postural changes. Evaluations incorporating narrow stances increase the sensitivity and specificity of the clinical assessment process [27], allowing for accurate measurement of postural sway changes over time. Tandem and Single-Leg stances are completed with a narrow base of support and provide greater challenges to maintaining postural control. While narrow stances were valid in this study of healthy individuals, populations with more severe postural control deficits are likely to find the narrow stances too difficult to complete safely. In these cases, and the Feet Together stance may provide sufficient assessment information regarding postural stability. Future research should evaluate individuals with postural instability as they complete the SWAY postural assessment.

To our knowledge, this is the first study evaluating the reliability and validity of a mobile device application for use in the assessment of postural control. SWAY is an innovative application allowing clinicians the ability to assess postural control objectively, quickly, and efficiently. Perhaps equally important, the SWAY app eliminates a need for specialized and costly equipment, as well as the extensive post-processing of data required by analytic processes using traditional force platforms and accelerometers to collect postural data. The increased portability provided by the SWAY app allows for assessment of postural sway in many environments, including hospitals, clinics, and athletic settings. As Mancini and Horak state, "clinical practice needs automatic algorithms for quantifying balance control during tasks, normative values, composite scores, and user-friendly interfaces so tests can be accomplished quickly…" [12]. SWAY has the potential to address all of these needs without the necessity of specialized equipment.

Although the results of the present study are promising, our study had limitations addressable by future research. First, the study population was comprised of healthy individuals without pathologies affecting postural stability. While appropriate for a study focused on determining reliability and validity of the technology, this necessarily limits the generalizability of results to other populations having severe challenges to postural control. Second, reliability of measures collected sequentially over several days may be more representative of how SWAY would be used in clinical settings, but was not feasible with the design of the current study.

Third, subjects were required to hold the device to their sternum. In addition to increasing the challenge to balance and being in an unnatural stance, any extraneous hand movements may have produced unintended accelerations. Using a harness to hold the mobile device against the person's trunk was not done in this study, as our intent was to conduct testing with SWAY exactly according to the app's instructions to hold the device in position. Finally, COP and SWAY data was not transformed to anteroposterior, mediolateral, and longitudinal axes as in previous studies have done when examining force plate COP data [16, 24]. Our method evaluated the SWAY score reported by the application, as clinicians are not likely to require analysis of postural displacements according to the anatomical coordinate plane. Future research should investigate the utility of coordinate system transformations from SWAY app data collected during stability tasks.

Conclusion

SWAY, a software application for iOS mobile devices, proved to be both reliable and valid while testing healthy individuals across static stances with eyes open. Based on our findings, Tandem stance/eyes open and Single-Leg stance/eyes open produced the most consistent results in our healthy cohort. Although some correlations were low between SWAY and force platform measures of postural control, SWAY demonstrated a similar pattern in reliability testing observed with COP variables. Despite being a promising tool for clinical evaluation of postural control integrity, further research must investigate the use of SWAY as a measure of postural control prior to widespread clinical implementation in assessing individuals with neurological or musculoskeletal conditions.

Table 1: Averaged trial results of SWAY scores and force platform measures across stances and conditions.

	Mean (SD)			
Stance, Condition	SWAY	Area	RMS	Velocity
Feet together, EO	99.19 (1.28)	26.93 (14.84)	6.22 (1.99)	14.27 (3.95)
Feet together, EC	99.35 (0.91)	40.03 (24.28)	6.83 (2.26)	18.84 (5.89)
Tandem stance, EO	98.63 (1.69)	56.10 (37.44)	6.87 (2.70)	28.43 (9.15)
Tandem stance, EC	95.75 (3.44)	175.39 (132.17)	10.15 (3.24)	52.34 (17.84)
Single leg stance, EO	97.13 (2.70)	108.59 (54.49)	8.74 (2.28)	39.87 (9.01)

Intraclass correlation coefficient (ICC), 95% confidence interval (CI), SWAY = SWAY score, RMS = root mean square, EO = eyes open, EC = eyes closed. Units for COP variables: mm^2 (Area); mm (RMS); mm/s (Velocity). SWAY score is an arbitrary unit.

Table 2: Test-retest reliability coefficients of SWAY and force platform measures.

	ICC Values (95%CI bounds)			
Stance, Condition	SWAY	Area	RMS	Velocity
Feet together, EO	0.406*	0.380*	0.177	0.546*
	(0.03-0.68)	(-0.01-0.67)	(-0.22-0.52)	(0.21-0.77)
Feet together, EC	0.451*	0.776**	0.625**	0.785**
	(0.08-0.71)	(0.56-0.90)	(0.31-0.82)	(0.57-0.90)
Tandem stance, EO	0.211	0.553**	0.611**	0.640**
	(-0.19-0.55)	(0.22-0.77)	(0.30-0.81)	(0.34-0.82)
Tandem stance, EC	0.569*	0.507*	0.563*	0.546*
	(-.019-0.80)	(0.11-0.77)	(0.18-0.80)	(0.16-0.79)
Single leg stance, EO	0.359*	0.243	0.083	0.312
	(-0.06-0.67)	(-0.19-0.60)	(-0.34-0.48)	(-0.12-0.64)

* ICC values were significant at (p <0.05), ** ICC values were significant at (p <0.001), Intraclass correlation coefficient (ICC), 95% confidence interval (CI), SWAY = SWAY score, RMS = root mean square, EO = eyes open, EC = eyes closed.

Table 3

Correlation of SWAY score with force platform measurements across test conditions

Stance, Condition	Area	RMS	Velocity
Feet together, EO	-0.129	-0.242	-0.111
Feet together, EC	-0.121	-0.016	-0.185
Tandem, EO	-0.615**	-0.552*	-0.551*
Tandem, EC	-0.405	-0.397	-0.426*
Single leg stance, EO	-0.639**	-0.598*	-0.661**

* *p*-Values were significant at (*p* <0.05), ** *p*-Values were significant at (*p* <0.001), RMS = root mean square, EO = eyes open, EC = eyes closed.

Figure 1

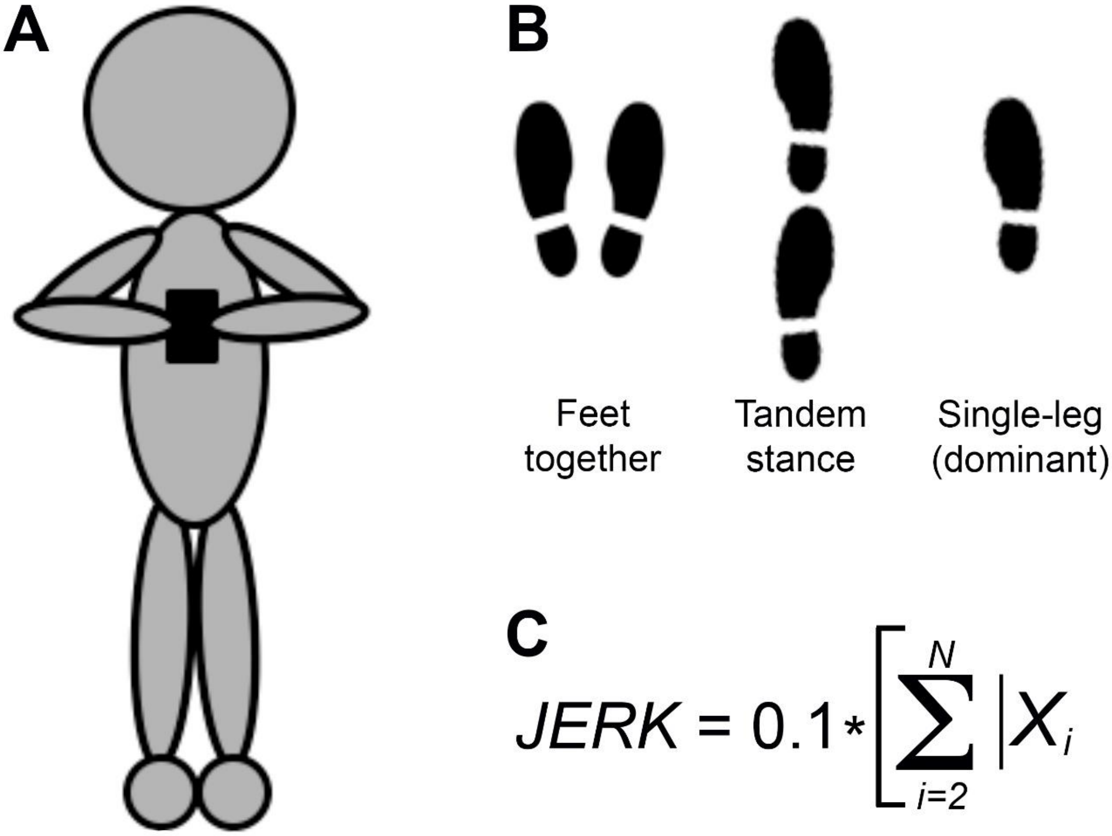


Fig. 1. A: Scheme depicting subject holding mobile device during test sequence; B: Stances used during test sequence; C: Jerk calculation for each SWAY data point.

Appendix C: Comprehensive Review III

Longitudinal analysis of white matter fiber tracts after mild traumatic brain injury: a pilot study

This work was approved August 2016

Introduction

Concussions have received increased attention from the medical community, general public, and popular media. While knowledge and care for concussions has deepened in recent years, there still remains a subset of individuals who take an extended period of time to recover after a concussion. While most individuals recover from concussive injury in 7 to 10 days (McCrea, Guskiewicz, Marshall, Barr, Randolph, Cantu, Onate, Yang, et al., 2003), the remaining 10-15% require extended periods of recovery time to reduce symptoms (Binder et al., 1997), leading to prolonged time away from employment, altered roles, and reduced quality of life (Willer & Leddy, 2006). If a person experiences symptoms for 3 months or longer, a formal diagnosis of Post-Concussion Syndrome (PCS) is given (Bigler, 2008; Boake et al., 2005). Symptoms can be diverse, but include: headaches, difficulty concentrating, light and noise sensitivity, irritability, changes in balance, memory alterations, and general mental 'fogginess' (Boake et al., 2005). Given the diversity of symptoms across individuals, research on the underlying mechanisms of PCS would provide insight into specialized treatment approaches. One way to characterize the underlying mechanisms of PCS is utilizing neuroimaging.

The inability to fully characterize the underlying mechanisms of PCS has led to further exploration using neuroimaging techniques. Traditional radiological methods using magnetic resonance imaging (MRI) and computed tomography (CT) lack sensitivity to identify alterations in neural tissue after a concussion, despite the injury producing functional changes (Murugavel et al., 2014). Diffusion tensor imaging (DTI), a quantitative MRI technique used to study the movement of water molecules within white matter fiber tracts in the brain, is a suitable alternative. DTI offers a more sensitive assessment of focal and diffuse injury (Horsfield et al., 1998), specifically measuring fiber tract microstructure and integrity (Basser & Jones, 2002).

DTI analysis allows for the calculation of several different measures that quantify fiber tract integrity that may provide a better understanding of the underlying pathology of PCS. Fractional anisotropy (FA) is a metric that quantifies the directional water diffusion for a given fiber tract. FA reflects white matter fiber tract density, axonal diameter, and myelination, and is sensitive to the effects of aging, cognition, trauma, or neurodegenerative disease (Toga & Mazziotta, 2002). Mean diffusivity (MD) for each fiber tract also is commonly reported and represents the overall diffusion in the tissue (Mori, 2007). Decreased FA values and increased MD values have been reported in athletes following a concussion (Lipton et al., 2008; Miles et al., 2008); however, no studies to date have evaluated diffusivity in individuals with persisting symptoms following a concussion , nor documented significant changes in DTI metrics to clinical measures of functioning specific to concussion assessment. Gaining a better understanding of white matter and neurocognitive changes taking place longitudinally in individuals slow to recover from concussion may make it possible to refine the management and treatments of this condition. This understanding may allow for earlier identification and intervention of individuals who are at risk for a longer recovery.

In this study, we investigated the association between measures of white matter integrity in predefined regions of interest (ROIs) via DTI and neurocognitive functioning in individuals not improving in a typical timeframe following a concussion. We tested three hypotheses: (1) FA values of white matter pathways will positively correlate to changes in symptoms over time. (2) MD values of white matter pathways will negatively correlate to changes in symptoms over time. (3) Changes in different clinical concussion measures (ImPACT, reaction time, and balance) are negatively associated with changes in white matter integrity over time.

Methods

We performed a prospective, longitudinal pilot study of ten female adult patients following an isolated concussion. The study was approved by the University of Kansas Medical Center's Institutional Review Board.

Participants

Participants were recruited from a level I trauma center equipped with a specialized concussion clinic, allowing for accurate concussion diagnoses based on the AAN guidelines (Giza et al., 2013). Individuals were recruited to the study if (a) they were between the ages of 18 – 65 years, (b) were experiencing active concussion symptoms (concussion symptom severity score $\geq$ 10/132), and (c) 4 – 6 weeks of time had passed after the injury that resulted in a concussion diagnosis. Exclusion criteria included residual biomechanical or orthopedic limitations (e.g. spinal fractures) that would interfere with MRI scanning, pre-existing mental health diagnoses, neurologic conditions other than a concussion, a history of alcohol or substance abuse, or individuals involved in a lawsuit related to the injury. Subjects were also excluded if they had a lifetime history of 5 or more diagnosed concussions, a significant head injury within 6 months prior to the concussion injury, or if another head injury occurred while enrolled in the study. Subjects with any metal in the body, those who experience claustrophobia in confined spaces, or women who were pregnant also were excluded.

Procedures

Participants meeting the inclusion criteria were recruited and consented 4 to 6 weeks following the initial date of head injury. Participants completed study procedures at two separate time points: 4 to 6 weeks after the injury date, and 8 weeks following the first visit (12 to 14 weeks after the injury). The two time points were chosen to capture individuals with a recovery slower than was typical after a concussion to document changes taking place after an acute injury but prior to a potential PCS diagnosis.

At each visit, participants completed a series of clinical measures and DTI scans. Approximately 30 minutes of rest was given to participants between the functional tests and DTI scans to offset any increased symptoms caused by testing, although no subjects reported additional symptoms or increased severity of symptoms following the clinical measures. The study was approved by the Institutional Review Board at the University of Kansas Medical Center, all subjects provided written informed consent, and subjects were financially compensated for their participation. A careful screening of MR compatibility took place prior to scanning.

Clinical Measures

A series of several common clinical outcome measures were used in the study. Cognitive function was assessed using the Immediate Post-Concussion Assessment and Cognitive Test (ImPACT™), a 30 to 40 minute long, computerized neuropsychological test battery. The test consists of five individual test modules measuring aspects of cognitive functioning commonly affected following head injury (Iverson, Brooks, Collins, & Lovell, 2006). The modules used were word discrimination (assesses attention and verbal memory), design (attention and visual memory), X's and O's (working memory and information processing speed), symbol matching (information processing speed, impulse control, response inhibition), and three letters (working memory and visual motor response time) (Bazarian, 2010). Composite scores for symptom severity, attention, memory, reaction time, and information processing were calculated (Collins et al., 2003) and used in analyses. Sensitivity of the ImPACT test battery to the acute effects of concussions has been examined in previous studies (Collins et al., 2003; Grant L Iverson et al., 2003, 2005; Lovell et al., 2004).

Postural control also was assessed at each visit using SWAY™, a mobile device application utilizing accelerometer measurement to detect postural movement during static balance stances (J. A. Patterson, 2014). SWAY uses the stances from the Balance Error Scoring System (BESS), a common balance assessment used following a concussion (Guskiewicz, 2011). Participants completed three sequences of stances: Standing with feet together, tandem stances (alternating which foot is placed in front) and single legs stances (balancing on left leg and right leg). Each stance lasted 10 seconds, with participants instructed to remain as still as possible. During each stance, participants held the mobile device (Apple iPod) on the sternum with both hands (Figure 1) and were instructed to refrain from making any unintended hand or arm movements. The entire balance testing procedure lasted approximately 5 minutes.

Imaging Acquisition

DTI data was collected using a whole body 3T Siemens Skyra scanner (Siemens, Erlangen, Germany). Subjects were placed in the scanner and underwent an anatomical localizing scan parallel to the hippocampus to position the ROIs. The localization scan produced a high-resolution T1 anatomic image (MPRAGE; 1x1x1mm voxels; repetition time (TR)=2500, TE=4.38, T1=1100, FOV 256x256 with 18% oversample, 1 mm slice thickness). In addition, a diffusion-weighted sequence was designed and implemented to minimize the scanner duration while collecting optimal results. The diffusion-weighted acquisition had a repetition time

TR=1000 ms and echo time (TE) of 90 ms. Diffusion gradients were applied in 65 directions (b_0= 0 s/mm^2 and $b_{1\text{-}64}$=1000 s/mm^2). Seventy-five 2-mm sections were acquired in an in-plane resolution of 128 x 128 with a 300 mm field of view (FOV). Total scan time required 14 minutes.

Data Analysis

We processed the diffusion-weighted images using FSL version 5.0.4 of the FMRIB Software library (Smith et al., 2004). The two averages of the weighted images for each participant were concatenated in the order of image acquisition and were visually inspected for signal drop-offs and other artifacts. Images were eddy-current corrected for small distortions and simple head motion by alignment of the diffusion weighted images to the b_0 image. A brain extraction tool was then applied to strip the brain from the skull. Diffusivity measures were calculated using DTIFIT and FSLMATHS, part of the FSL toolbox. Twenty-five ROIs from Johns Hopkins University's Mori white matter probabilistic atlas (Hua et al., 2008) were transformed into each subject's diffusion space using transformation matrices created from nonlinear registration between the subject's diffusion space and standard space (FMRIB58). Using fslstats (Smith et al., 2004), average FA and MD values were calculated for each ROI and were correlated against the clinical measures using Spearman correlations due to small sample size.

Results

A total of 10 females (average age 39.8 ± 16.7 years) with a diagnosed concussion and persisting symptoms were enrolled in and completed the study. All participant injuries occurred outside of sports-related activities. Participants joined the study approximately 5 weeks following injury (average time post-injury 35.4 ± 10.6 days before 1st scan; see Table 1). Mean performance scores from the clinical measures are reported in Table 2. Individual performance varied across neurocognitive and balance measures, as evidenced by the large range in scores between participants.

To evaluate changes in clinical measures and DTI metrics over time (i.e., 8 weeks) we used paired t-tests with Bonferroni adjustments. Changes in symptom severity scores were the only comparison to yield a significant change during the two-month period between test dates (Table 3). There was no statistically significant difference between FA and MD values for any white matter tract over time (Table 4). Additionally, there were no significant correlations between age and changes in neurocognitive scores, SWAY scores, or reaction times. No changes in FA and MD values were observed over time.

Results showed significant associations were identified among changes in neurocognitive composite scores and DTI metrics across several neurocognitive domains (Table 5). In general, FA results showed positive correlations with improved neurocognitive composite scores ($p<0.05$), whereas MD results showed negative correlations with improved neurocognitive performance ($p<0.05$).

Statistically significant results are summarized briefly. Decreased reaction time was directly correlated with FA values collected from the Superior Longitudinal Fasciculus ($p=0.03$) and the Inferior Longitudinal Fasciculus ($p=0.05$). Visual memory was negatively correlated with MD values collected from the Inferior Longitudinal Fasciculus ($p=0.02$). Additionally, visual motor speed was negatively correlated with the MD values collected from the Inferior Longitudinal Fasciculus ($p=0.03$). No other associations were significant.

Despite an overall lack of statistical significance given our small study sample, several correlations showed strong associations, producing *r* values greater than 0.5 (L. Portney & Watkins, 2009). Reaction time correlated strongly with FA values from every white matter tract in the left hemisphere (*r*-values ranged from 0.51-0.68), as well as the superior longitudinal fasciculus in the right hemisphere (*r*-values ranged from 0.29-0.51). Reaction time also was strongly correlated with MD values collected from the right inferior longitudinal fasciculus. Visual motor speed was strongly correlated with FA values collected in the left superior longitudinal fasciculus. Visual memory was also strongly correlated with FA values collected in the right inferior longitudinal fasciculus, as well as MD values collected from the left corticospinal tract. Verbal memory was strongly correlated with MD values collected from the genu of the corpus callosum. Changes in symptom severity scores and impulse control did not show a strong correlation with any white matter tract.

Discussion

Using DTI as a proxy to study the neuroanatomic basis for cognitive changes taking place after a concussion, we found unique patterns of white matter metrics (FA and MD values derived from DTI) related to changes in performance in distinct cognitive domains commonly assessed following injury. Novel findings from this study suggest that longitudinal changes in clinical measures used in clinical management after a concussion are associated with changes in DTI metrics. Reductions in reaction time over time were associated with improvements in several left hemisphere white matter tract FA values. While not statistically significant, mean reaction times of our participants did improve over time, as did FA values for the associated reaction time tracts (Genu, Superior Longitudinal Fasiculus (SLF), Splenium, Inferior Longitudinal Fasiculus (ILF), Inferior Fronto-Occipital Fasciculus (IFOF), and Corticospinal Tract (CST)). Previous research has found similar associations between these tracts and changes in reaction time and information processing in healthy and injured adults (Ashtari, 2012; Wolfers et al., 2015). These associations support validity of serial testing of reaction time in the evaluation process following concussive injury. Improved visual motor speed and visual memory were also associated with improved FA and MD values, specifically in the SLF, ILF, and CST. Both the SLF and ILF are connected to the occipital lobe and deceased FA values have been associated with visual neglect and decreased visual spatial skills in both tracts (Shinoura et al., 2009).

Changes in reaction time and visual motor skills may provide evidence for use of these clinical outcomes as a patient with persisting concussion symptoms recovers from injury. Reaction time, in particular, is often used as an assessment procedure following a suspected concussion (Guskiewicz et al., 2004; Harmon et al., 2013a; McCrory et al., 2013). Contrary to reaction time, visual assessment after injury is seldom done. Some position statements recommend inquiring about double or blurred vision (Guskiewicz et al., 2004), while other position statements recommend no visual assessment of any kind (Harmon et al., 2013a; McCrory et al., 2013). The results of our study indicate visual disturbances were common in this sample of patients with persisting concussion symptoms, and changes in white matter pathways involved in visual processing were correlated with improved overall functioning. Clinically evaluating vision and visual spatial skills early in the evaluation process may provide useful information allowing clinicians to identify individuals at increased risk for a lengthy recovery. Early identification of these individuals may provide earlier targeted interventions leading to recovery time.

We were unable to support our first hypothesis that changes in DTI metrics over time would be associated with improved symptom resolution. No significant associations were observed between any white matter tract metrics and improvements in symptoms reported. This result remains odd, as 8 of the 10 participants reported they experienced notable reductions in their symptoms over the course of the 8-week study period. Based on patient self-report, we thus anticipated associations with improved FA and MD values. Our small sample size may be an explanation for lack of correlations. A novel alternative explanation may be individuals trending towards a PCS diagnosis recover from somatic symptoms with a more rapid time course than they exhibit for recovery of WM tract integrity. This notion of incongruent recovery following head trauma has been described in prior sports-related concussion literature, with somatic symptom resolution and clearance for return to normal activity occurring between days 3 and 15 following a sports-related concussions, despite the same individuals exhibiting delayed neurometabolic recovery until approximately day 30 (Vagnozzi et al., 2010).

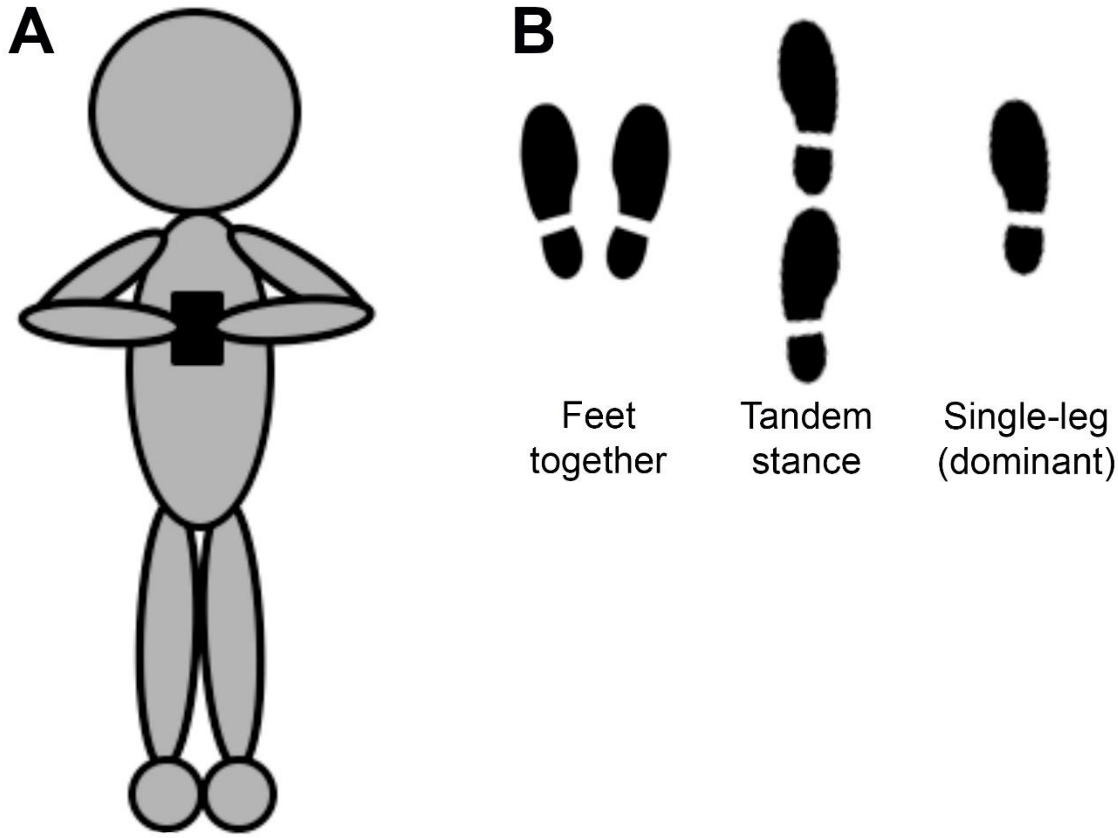
Our analysis of DTI images revealed no statistically different changes in FA or MD values over time in each of the ROIs, despite patient report of reduced symptoms and objective measures documenting improved neurocognitive functioning. These results conflict with previously reported DTI results involving athletes during concussion recovery, as FA values appear to decrease at 2 months post-injury (Murugavel et al., 2014). It should be noted that our data did trend in a similar pattern, as FA values decreased longitudinally despite failing to reach statistical significance, but our population didn’t involve athletes or sports-related head trauma. Our sample was completely comprised of females with professional careers and might not have been able to truly follow rest recommendations during their recovery. Future research using a larger sample size, similar time frames, and both male and female subjects may elucidate these conflicting results.

Limitations of the current study include small sample size, which may be attributed to our rigorous inclusion criteria and a lengthy follow-up period. These factors were necessary to address our hypotheses and were unavoidable. An additional limitation included the entirely female cohort by chance and subjects injured in non-sporting activities, limiting the validity of generalizing our results to male and psort-related injury populations. . Lastly, due to a lack of control group, the possibility of differences in FA and MD values between healthy and injured participants cannot be evaluated.

The present study is a longitudinal analysis and, although limited with respect to sample size, it does provide insight and direction into possible WM changes that may contribute to altered cognitive functioning in individuals experiencing prolonged symptoms following a concussion. As such, this study provides evidence that changes over time in clinical concussion measures are associated with changes in DTI metrics related to distinct white matter pathways among individuals following a concussion. This information will allow for improved evaluation and assessment of symptoms in individuals following concussion injury, emphasizing more thorough visual assessment. Further study is required to confirm and extend the current findings. The current study appears to demonstrate significant associations between white matter changes and distinct clinical measures of visual processing and reaction time, supporting and encouraging assessment of these measures following concussion injuries.

Figures

Figure 1: Balance testing procedures



A: Scheme depicting subject holding mobile device during test sequence; B: Stances used during test sequence;

Tables

Table 1: Demographic and neuropsychological data

	Mean	**SD**
Age (years)	39.8	16.725
Symptoms Severity Scale	42.8	25.6
Education (years)	16.5	3.0
Injury to 1st Scan (days)	35.4	10.6
Injury to 2nd Scan (days)	96.3	10.9
Height (cm)	169.2	7.8
Weight (cm)	77.6	17.2
Handedness	8 (R)	2 (L)
Subjects with prior concussion	4	(Range= 1-3)

Table 2: Longitudinal results of clinical measures

	T1 Mean (SD)	T2 Mean (SD)	P-value
Verbal Memory	78.4 (14.9)	84.9 (10.7)	0.22
Visual Memory	59.8 (19.6)	68.3 (15.9)	0.16
Visual Motor Speed	31.5 (9.4)	35.1 (8.4)	0.15
Reaction Time	0.82 (0.19)	0.77 (0.27)	0.52
Impulse Control	6.1 (6.7)	3.6 (3.9)	0.10
Symptom Severity	42.8 (25.6)	29.9 (28.9)	**0.03***
Cognitive Efficiency	0.17 (0.19)	0.22 (0.22)	0.40
Sway Test 1	67.0 (19.0)	69.33 (16.7)	0.76
Sway Test 2	69.5 (18.8)	73.7 (18.9)	0.65
Sway Test 3	63.3 (14.1)	71.6 (6.0)	0.10
Sway SRT	393.5 (86.6)	356.5 (68.9)	0.43

Paired t-tests compared results from 1st scan (T1) and 2nd scan (T2);
SD = Standard Deviation; SRT = Simple Reaction Time

Table 3: Longitudinal ImPACT results

	5 weeks after Injury		13 weeks after Injury		
	Mean (SD)	Range	Mean (SD)	Range	p-value
Verbal Memory	78.4 (14.9)	51-100	84.9 (10.7	60-97	0.22
Visual Memory	59.8 (19.6)	32-93	68.3 (15.9)	45-88	0.16
Visual Motor Speed	31.5 (9.4)	18.3-43.4	35.1 (8.4)	14.1-45.4	0.15
Reaction Time	0.81 (.19)	0.5-1.1	0.77 (.27)	0.5-1.46	0.52
Impulse Control	6.10 (6.7)	0-22	3.6 (3.9)	0-11	0.10
Symptom Severity	42.8 (25.6)	13-82	29.9 (28.9)	0-79	0.03*
Cognitive Efficiency	0.17 (.19)	-0.08-0.53	.22 (.22)	-0.25 - 0.55	0.39

Paired t-tests compared week 5 test results with week 13 results; * represents significant p-value <0.05

Table 4: DTI Region of Interest Values

	FA T1 (SD)	FA T2 (SD)	p	MD T1 (SD)	MD T2 (SD)	p
Genu (CC)	.581 (.02)	.578 (.02)	0.33	$9.6x10^{-4}$ ($5.7x10^{-5}$)	$9.5x10^{-4}$ ($5.4x10^{-5}$)	0.22
Splenium (CC)	.720 (.02)	.718 (.03)	0.59	$7.9x10^{-4}$ ($4.5\ x10^{-5}$)	$8.0x10^{-4}$ ($4.7\ x10^{-5}$)	0.73
Superior Longitudinal Fasc. (L)	.447 (.02)	.446 (.02)	0.75	$7.1x10^{-4}$ ($1.6x10^{-5}$)	$7.1x10^{-4}$ ($2.1\ x10^{-5}$)	0.50
Inferior Longitudinal Fasc. (L)	.476 (.02)	.474 (.02)	0.49	$7.5x10^{-4}$ ($2.2\ x10^{-5}$)	$7.6x10^{-4}$ ($2.5\ x10^{-5}$)	0.34
Inferior Fronto-Occipital Fasc. (L)	.465 (.02)	.462 (.02)	0.54	$7.6x10^{-4}$ ($1.9\ x10^{-5}$)	$7.7x10^{-4}$ ($2.1\ x10^{-5}$)	0.33
CorticoSpinal Tract (L)	.583 (.01)	.580 (.02)	0.36	$6.9x10^{-4}$ ($2.0\ x10^{-5}$)	$7.0x10^{-4}$ ($1.9\ x10^{-5}$)	0.53
Superior Longitudinal Fasc. (R)	.443 (.02)	.441 (.03)	0.50	$7.1x10^{-4}$ ($1.7\ x10^{-5}$)	$7.2x10^{-4}$ ($2.1\ x10^{-5}$)	0.11
Inferior Longitudinal Fasc. (R)	.476 (.02)	.474 (.02)	0.34	$7.7x10^{-4}$ ($1.9\ x10^{-5}$)	$7.8x10^{-4}$ ($2.7\ x10^{-5}$)	0.20
Inferior Fronto-Occipital Fasc. (R)	.459 (.02)	.458 (.03)	0.33	$7.8x10^{-4}$ ($2.5\ x10^{-5}$)	$7.8x10^{-4}$ ($2.8\ x10^{-5}$)	0.24
CorticoSpinal Tract (R)	.576 (.02)	.576 (.02)	0.53	$7.2x10^{-4}$ ($2.0\ x10^{-5}$)	$7.3x10^{-4}$ ($2.4\ x10^{-5}$)	0.25

Paired t-tests between DTI metrics at scan 1 (T1) and scan 2 (T2); CC = Corpus Callosum; FA = Fractional Anisotropy; Fasc = Fasciculus; L = Left Hemisphere MD = Mean Diffusivity; R = Right hemisphere; SD = Standard Deviation;

Table 5: Associations between changes in clinical measures and DTI metrics over time

Fractional Anisotropy Values	Symptoms Severity Score	Verbal Memory	Visual Memory	Visual Motor Speed	Reaction Time	Impulse Control
Genu Corpus Callosum	.231 (.531)	-.195 (.590)	.219 (.544)	-.358 (.310)	.614 (.059)	.213 (.554)
Splenium Corpus Callosum	0.061 (.868)	-.176 (.626)	.237 (.510)	-.200 (.580)	.511 (.132)	.079 (.828)
Superior Longitudinal Fasciculus (L)	.292 (.413)	-.055 (.881)	.091 (.802)	-.539 (.108)	**.681 (.030)***	.280 (.432)
Inferior Longitudinal Fasciculus (L)	.055 (.881)	-.237 (.510)	.334 (.345)	-.212 (.556)	**.632 (.050)***	-.195 (.589)
Inferior Fronto-Occipital Fasiculus (L)	.091 (.802)	-.298 (.403)	.267 (.455)	-.309 (.385)	.590 (.073)	-.073 (.841)
Corticospinal Tract (L)	.116 (.751)	-.201 (.578)	.486 (.154)	-.333 (.347)	.523 (.121)	-.195 (.589)
Superior Longitudinal Fasciculus (R)	.103 (.776)	-.389 (.266)	.207 (.567)	-.152 (.676)	.511 (.132)	.049 (.894)
Inferior Longitudinal Fasciculus (R)	.036 (.920)	.146 (.688)	.523 (.121)	-.042 (.907)	.444 (.199)	-.073 (.841)
Inferior Fronto-Occipital Fasiculus (R)	.152 (.675)	-.316 (.374)	.170 (.638)	-.152 (.676)	.407 (.243)	.238 (.508)
Corticospinal Tract (R)	-.036 (.920)	-.316 (.374)	.347 (.327)	-.006 (.987)	.292 (.413)	-.061 (.867)
Mean Diffusivity Values						
Genu Corpus Callosum	.267 (.455)	-.511 (.132)	-.116 (.751)	-.321 (.365)	.109 (.763)	-.012 (.973)
Splenium Corpus Callosum	-.091 (.802)	.213 (.555)	-.201 (.578)	.067 (.855)	-.188 (.602)	-. 183(.613)
Superior Longitudinal Fasciculus (L)	-.134 (.713)	.316 (.374)	.006 (.987)	.079 (.829)	-.231 (.521)	-.195 (.589)
Inferior Longitudinal Fasciculus (L)	-.176 (.626)	-.201 (.578)	**-.723 (.018)***	-.139 (.701)	.049 (.894)	.098 (.789)
Inferior Fronto-Occipital Fasiculus (L)	-.037 (.920)	.399 (.253)	-.320 (.367)	.024 (.947)	-.171 (.637)	.028 (.940)
Corticospinal Tract (L)	.012 (.973)	.231 (.521)	-.553 (.097)	-.139 (.701)	-.073 (.841)	.152 (.674)
Superior Longitudinal Fasciculus (R)	.260 (.468)	.309 (.385)	-.070 (.847)	-.152 (.674)	.092 (.801)	-.040 (.913)
Inferior Longitudinal Fasciculus (R)	.381 (.277)	-.262 (.464)	-.284 (.427)	**-.675 (.032)***	.613 (.060)	.086 (.814)
Inferior Fronto-Occipital Fasiculus (R)	.134 (.712)	.058 (.874)	-.348 (.325)	-.304 (.393)	.213 (.554)	.028 (.940)
Corticospinal Tract (R)	.000 (1.0)	.329 (.353)	-.345 (.330)	.079 (.828)	-.329 (.353)	.141 (.698)

Spearman rank-order correlations; R values (p values) reported; *Significant association at p < 0.05; (L) = left hemisphere pathway; (R) = right hemisphere pathway.