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RISK AND PROTECTIVE FACTORS INFLUENCING OUTCOMES AND RECOVERY IN SPORTS-RELATED CONCUSSION

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Abstract

Sports-related concussion (SRC) is a subtype of mild traumatic brain injury which occurs during participation in athletic activity. Like other types of mild traumatic brain injury, the symptoms and outcomes from SRC are very heterogeneous. Experiencing an SRC can have acute and more chronic implications for athletes and can affect various aspects of functioning (e.g., emotional, cognitive, academic, and social). These sequelae highlight the importance of a more comprehensive understanding of SRC through both improving how we assess SRC and factors that may contribute to risk for or resiliency against certain negative outcomes following injury. The overarching goal of this three-paper dissertation was to explore each of these facets. First, this dissertation explored the potential for improving SRC assessment by testing whether premorbid IQ should be considered when examining an athlete's post-concussion testing. The results indicated that premorbid IQ significantly affected the cognitive assessment of SRC and should be incorporated in a clinical decision-making algorithm. Second, this dissertation explored whether cognitive reserve had a significant moderating effect on different post-concussion outcomes. The results indicated that cognitive reserve did not provide a protective effect post-concussion against poorer cognitive functioning, depression symptoms, or time to return to play. Third, this dissertation explored in a population of athletes with persistent post-concussion symptoms whether specific types of symptoms put individuals at risk of poorer cognitive functioning. The results indicated that headache, over and above other post-concussion symptoms, was the significant symptom that predicted cognitive dysfunction. The results of these three studies will provide information that can be used to improve both the assessment and treatment of sport-related concussion.

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Chapter 1. Overview

Overview of Sports Related Concussion

Approximately 1.6 to 3.8 million sports-related concussions (SRC) occur annually in the United States, and given that many individuals who experience SRC do not seek medical attention, these numbers are likely an underestimate (Langlois et al., 2006). In collegiate athletics, it is estimated that a rate of 4.47 concussions per 10,000 athletic exposures occur per year across a variety of National Collegiate Athletic Association (NCAA) sports including men's and women's soccer, men's and women's basketball, men's and women's ice hockey, football, men's and women's lacrosse, men's and women's volleyball, and men's wrestling (Zuckerman et al., 2015). The incidence of SRC in collegiate athletes appears to be increasing, and this may be reflective of changes in policy with new concussion management plans and improved concussion education for athletes (Zuckerman et al., 2015). Additionally, an estimated 491,930 student-athletes participate annually in NCAA sports, and thus are at risk of exposure to SRC (Irick, 2016).

Further, SRC is an injury that presents unique challenges for the student-athlete (Putukian, 2016; Wolanin et al., 2016; Yang et al., 2007). SRC may have implications acutely and more long-term for athletes at the emotional, cognitive, academic, and social functioning levels. For example, athletes may demonstrate emotional/affective difficulties following concussion, experience adjustment difficulties with return-to-learn and return-to-play, and experience cognitive deficits as a result of their injury (Broglio & Puetz, 2008; Kontos & Collins, 2018; Kontos, Covassin, Elbin, & Parker, 2012; Sandel, Reynolds, Cohen, Gillie, & Kontos, 2017; Stein et al., 2017; Valovich McLeod, Bay, Heil, & McVeigh, 2008; Vargas, Rabinowitz, Meyer, & Arnett, 2015). All of these difficulties can affect a student-athlete's quality of life and highlight the importance of a more comprehensive understanding SRC at both the assessment and treatment level.

The most recent consensus statement on concussion in sport provides the definition of SRC as “a traumatic brain injury induced by biomechanical forces” with several common clinical features and “may be caused by either a direct blow to the head, face, neck or elsewhere on the body with an impulsive force transmitted to the head” (McCrory et al., 2017). SRC is usually characterized by a rapid onset of short-term impairment of neurological functioning but the clinical signs can also arise in minutes to hours following the injury. While loss of consciousness and amnesia can be present following SRC, they are not required for the diagnosis (McCrory et al., 2017). Other common symptoms include “headache, dizziness, loss of balance, blurred vision, ‘seeing stars,’ feeling in a fog or slowed down, memory problems, poor concentration, nausea, or vomiting” (Gardner et al., 2019). While sports-related concussions are often categorized as mild traumatic brain injuries (mTBIs), the etiologies and demographics of sports-related concussion are usually distinct from non-sports-related mTBI and as such they are often examined separately in research literature (Grossner et al., 2019).

Diagnosis of Sport-Related Concussion

Recent work has continued to search for objective biomarkers that could provide diagnostic indication of concussion. Sports-related concussions are often considered mTBIs which, unlike moderate or severe traumatic brain injuries, typically do not present with abnormal findings on standard imaging methodologies such as computed tomography (CT) or Magnetic Resonance Imaging (MRI) due to the limitations of these techniques to detect the axonal damage or neurochemical changes that occur following mTBI (Grossner et al., 2019). Therefore, other neuroimaging methods have been explored as potential diagnostic tools for concussion. These alternative imaging techniques have often been more functional in nature such as functional MRI (fMRI) and proton Magnetic Resonance Spectroscopy (MRS) but alternative structural methods such as Diffusion Tensor Imaging (DTI) are also being explored (Grossner et al., 2019). One study utilizing arterial spin labeling (ASL) and MRI found that concussed football players demonstrated a decrease in cerebral blood flow between 24 hours after injury and 8 days after injury while matched controls did not demonstrate this decrease (Wang et al., 2016). A systematic review of the literature on DTI and sport-related concussion found that studies demonstrated inconsistent findings regarding the affected regions and directionality of differences between athletes and controls (Asken et al., 2018). The authors posit that this could be due to the utilization of differing control groups (contact sport athletes versus non-contact sport athletes) and that future research should include further consideration of appropriate control groups to account for alternative explanations for white matter abnormalities. The authors conclude that, while DTI is able to detect differences in white matter diffusion metrics between concussed and non-concussed groups, there is currently a lack of specificity that precludes the use of such measures clinically (Asken et al., 2018).

Despite continued research on potential biomarkers of mTBI or concussion, there is still currently no one definitive diagnostic tool for SRC and there are often no abnormalities observed on standard clinical neuroimaging methods (McCrory et al., 2017). Therefore, assessment of concussion should be multimodal, including the use of symptom report and cognitive, balance, and vestibular-oculomotor testing. One study reported that when utilizing symptom report and neuropsychological assessment together, 94% of concussed athletes were correctly identified, compared with 65% utilizing symptom report alone (Kampen, Lovell, Pardini, Collins, & Fu, 2006).

Assessment of Sports-Related Concussion

The 2017 Concussion in Sport Group (CISG) consensus statement recognized sideline assessment of concussion as a critical component for rapid screening of concussions (McCrory et al., 2017). The most common sideline assessment is the Sport Concussion Assessment Tool-5 (SCAT-5), and this brief assessment includes the Graded Symptom Checklist (GSC) to assess total symptoms and symptom severity. However, a challenge in SRC diagnosis is the heterogenous presentation of symptoms along with possible delayed-onset and evolving symptoms over time (McCrory et al., 2017). Therefore, while this quick screening for concussions is necessary given limited time and resources on the sidelines, the CISG consensus statement also recognized the utility of follow-up neuropsychological evaluation in aiding clinical assessment and providing valuable information for return to play protocols (McCrory et al., 2017).

Concussion-specific neuropsychological protocols were initially developed in the late 1980's and utilized the typical paper-and-pencil assessments characteristic of most neuropsychological evaluations (Kontos et al., 2016). Computerized neurocognitive tests (CNT) were developed in the 1990's and have been increasingly popular due to their ease, short length, and the option of group administration. Much research has cited the benefits and costs inherent to both paper-and-pencil and CNT's. The traditional paper-and- pencil tests demonstrate reasonable validity and sensitivity for assessment of SRC, can be selected for the specific domains of cognition and needs of the athlete, and have larger normative databases (Echemendia et al., 2013). However, the tests require face to face, individual administration which is more labor intensive and potentially introduces more variance into administration and scoring. CNT's also have inherent limitations; their brevity means they assess a restricted sample of cognitive functioning, the research on their reliability and form equivalence has been mixed, and technological limitations can also result in measurement error (e.g. slow internet connection affecting response time calculations, use of a touchpad versus a mouse) (Echemendia et al., 2013). The "hybrid" approach refers to the use of a neuropsychological battery which includes both paper-and-pencil tests and CNT's. While this approach still carries with it some of the inherent drawbacks of the individual approaches that comprise it, it also attempts to utilize the strengths of both models to maximize both quantity and quality of clinical data.

While some research has indicated that neuropsychological testing can detect subtle cognitive deficits following SRC even after reported symptoms have resolved, other meta-analyses have shown that at 7 to 14 days following concussion, there are no longer detectable differences between concussed and non-concussed individuals on neuropsychological test scores (Johnson et al., 2011; Maerlender, 2019). The more consistent finding indicates that neuropsychological testing demonstrates better specificity then sensitivity for SRC, or in other words, the testing is more effective at accurately identifying when individuals are recovered rather than diagnosing individuals who are currently concussed (Maerlender, 2019). However, the high specificity of neuropsychological tests is arguably more important for concussion assessment as the presumption is that the injury has already occurred and the focus is on secondary prevention, or prevention of recurrence or exacerbations of the current condition (Maerlender, 2019).

Baseline testing occurs prior to an athlete's participation in a sport, and then following a concussion their post-injury testing performance can be compared to the results of their baseline testing (Echemendia & Julian, 2001). The goal of baseline testing is to increase diagnostic accuracy for cognitive deficits post-concussion by taking into account potential pre-injury confounds. This model may be particularly important for athletes who have conditions such as ADHD or LD which are known to affect cognition (Littleton et al., 2015). Despite the intuitive validity of this approach, there is not sufficient empirical evidence to suggest that it provides greater diagnostic accuracy than post-concussion assessment utilizing normative data (Echemendia et al., 2013; Randolph & Kirkwood, 2009). Additionally, there are concerns that baseline testing can have invalid administration and interpretation by underqualified personnel and invalid results due to failure to understand the instructions, a distracting environment, or intentional poor effort (Kontos et al., 2016). Given that the most recent consensus statement determined that baseline testing is not a mandatory part of concussion care, the importance of accurate, thorough normative data for comparison of post-concussion assessments is potentially even more critical (Echemendia et al., 2013; McCrory et al., 2017).

SRC Symptoms and Recovery

Concussions are heterogeneous injuries, and any two individuals who have experienced a concussion can present quite differently clinically. Twenty-two common post-concussion symptoms have been shown to group into four main symptom clusters (Physical, Sleep, Cognitive and Affective), with evidence from factor analyses suggesting that headache is a salient symptom that stands on its own (Merritt & Arnett, 2014). Following SRC, individuals can present with any and all of these symptoms. Additionally, there is also some variability in recovery from SRC. Although approximately 80% of concussed athletes recover with 3 weeks following injury, approximately 20% of athletes take longer than 3 weeks to recover (Collins et al., 2014). Studies also vary on what exactly is “typical” recovery from a concussion, with some citing 7-10 days following injury and others less than 2 weeks, and research suggests that these timelines might differ depending on the age of the athlete (Iverson et al., 2017). These estimates are also often derived from group analyses and such statistical approaches may obscure effects of individual differences and subgroup effects (Iverson et al., 2017). Although many athletes recover within a relatively short period of time (generally between 7 days and 2 weeks), there is still a significant minority of individuals who take 3 weeks or more to recover, and understanding who might be at risk for protracted recovery has been a topic of much interest in the field (Collins et al., 2014). Risk factors for increased deficits and prolonged recovery have been characterized as either premorbid (present prior to injury) or prognostic (occurring post-injury). Some premorbid risk factors include history of concussion, history of migraine, diagnosis of LD or ADHD, being female, and younger age (Collins et al., 2014). Some prognostic factors include post-traumatic migraine, immediate dizziness following injury, and the occurrence of specific symptoms within 3–7 days following injury (fogginess, difficulty concentrating, vomiting, dizziness, nausea, headache, slowness, imbalance, photo-/phono-sensitivity, and numbness). Despite this variety in presentation and recovery, concussion management has generally been fairly homogeneous in its approach to treatment and care of athletes. Research has worked to encourage a more comprehensive and tailored approach to care by exploring multiple clinical trajectories that athletes could fall into based on their specific presentation of symptoms (Collins et al., 2014).

Dissertation Goals

With the above considerations in mind, the broad overarching goal of my dissertation is to examine specific risk and protective factors that may influence outcomes and recovery following SRC. One of the primary roadblocks in such a process is that currently there is no definitive diagnostic tool for diagnosing the presence or absence (clinical recovery) of SRC. Therefore, any research that attempts to explore risk factors of prolonged recovery trusts that the measurement of recovery is as accurate as possible. Given that neuropsychological testing is often utilized as part of the multi-model assessment of SRC, it is critical that testing provide the most accurate picture of an individual's cognitive functioning to ensure appropriate clinical recommendations (McCrory et al., 2017). Additionally, the current recommendation is that baseline testing is not considered mandatory for concussion care and instead, normative samples can be used for making determinations regarding and individual's cognitive functioning. Previous work has attempted to clarify more quantitative and objective cut-offs to guide clinicians in this endeavor by developing an RTP algorithm based on normative neuropsychological data (Arnett, Meyer, Merritt, & Guty, 2016). However, this algorithm does not take into account an individual's premorbid IQ, which may be related to the rate of impairment for individuals, and research indicates that premorbid IQ predicts performance across neuropsychological domains (Diaz-Asper et al., 2004). The first goal of my dissertation, then, is to determine whether premorbid IQ is a relevant factor in assessing cognitive impairment following a concussion, and whether it should be incorporated into determining base rate of impairments in an RTP algorithm.

While much research has explored the risk factors for prolonged recovery or negative outcomes following concussion, less research has explored potential protective factors that may contribute to faster recovery or less negative outcomes following SRC. One such potential protective factor is cognitive reserve. Cognitive reserve is a construct that was developed from Alzheimer's disease research to help explain the repeated observation that there is no direct one-to-one relationship between the amount of brain pathology and its cognitive and functional manifestations (Stern, 2009). This effect has been demonstrated in various neurological populations including Alzheimer's disease, Parkinson's disease, Multiple Sclerosis (MS), chronic traumatic encephalopathy (CTE), and TBI (Alosco et al., 2017; Hindle et al., 2016; Mathias & Wheaton, 2015a; Stern, 2002; Sumowski & Leavitt, 2013). Much of the research on cognitive reserve has focused on moderate and severe TBI rather than mild TBI (Mathias & Wheaton, 2015). Research on cognitive reserve in SRC has been even more limited and often utilizes samples with prolonged concussion recovery or Post-Concussion Syndrome (Oldenburg et al., 2016; Stewart-Willis et al., 2018). Given this, the second goal of my dissertation aims to see whether cognitive reserve has a moderating effect on recovery and outcomes in a broad sample of athletes with SRC who have not been selected specifically due to prolonged recovery.

Given that a minority of individuals experience prolonged recovery from concussion, it is often a more difficult sample to study but also provides an important frontier for more targeted clinical treatment. While there has been some work to explore different treatments for athletes depending on their symptoms in order to improve quality of care, this is still a developing approach (Collins et al., 2014). Symptom reports and neuropsychological testing are both important methods in the multi-modal assessment of SRC, and greater understanding of the link between symptomology and cognitive performance following SRC may provide insights into patterns of clinical recovery and best treatment practices. Thus, the third goal of my dissertation is to explore how patterns of symptom reporting may be differentially related to cognitive outcomes for individuals with prolonged recovery (chronic SRC).

Specific Paper Topics and Aims

Paper 1: Evaluate whether an RTP algorithm should include premorbid IQ as a factor for whether athletes have returned to their cognitive baseline following sports-related concussion. Aim 1a is to test whether student athletes with differing levels of premorbid IQ vary at baseline assessment on number of cognitive impairments. Based on the results of Aim1a, Aim 1b would be to update the clinical decision-making algorithm to either incorporate or not incorporate premorbid IQ.

Paper 2: Evaluate whether cognitive reserve (operationalized as premorbid IQ) moderates any observed relationship between concussion severity and three different post-concussion clinical outcomes.

Aim 2a is to determine whether cognitive reserve moderates the effect of concussion severity on cognitive impairment following concussion. Aim 2b will explore that same relationship but examine return to play (RTP) time post-concussion as the outcome measure. Aim 2c will explore that relationship but examine post-concussion depression as the main outcome measure.

Paper 3: Evaluate whether symptom type is differently related to cognitive outcomes in individuals with chronic post-concussion symptoms.

Aim 3a is to examine the relationship between each of the different post-concussion symptom factors and memory performance. Aim 3b is to examine the relationship between each of the different post-concussion symptom factors and attention/executive functioning performance.

Note that there may be some redundancy among the three papers, as each is designed as a stand-alone manuscript that can be submitted for publication.

Chapter 2. Paper 1: Improving clinical interpretation of performance on a neuropsychological concussion battery by utilizing premorbid IQ

Introduction

An Overview of Sports-Related Concussion

The Center for Disease Control (CDC) estimates that between 1.6 to 3.8 million concussions occur during sport and recreational activities annually in the United States (Daneshvar et al., 2011). Sports-related concussion (SRC) is generally defined as a traumatic brain injury "caused by either a direct blow to the head, face, neck or elsewhere on the body with an impulsive force transmitted to the head" and results in a variety of common clinical symptoms (McCrory et al., 2017). Such clinical symptoms can include physical markers such as loss of consciousness and post-traumatic amnesia, but these are not required for the diagnosis of SRC. Other markers include cognitive symptoms such as memory problems, poor concentration, and feeling "foggy," and physical symptoms such as headache, dizziness, balance problems, photo- and phono-sensitivity, blurred vision, nausea, and vomiting (Gardner et al., 2019). Individuals also report problems with sleep and fatigue and emotional difficulties such as irritability, sadness, nervousness, and feeling more emotional than usual (Johnson et al., 2011). Concussions are heterogeneous injuries, and concussed athletes can present with multiple different symptom profiles (Collins et al., 2014).

Neuropsychological Testing in SRC

Although there is ongoing research to elucidate more quantitative biomarkers of mild traumatic brain injury (mTBI) or concussion, there is still currently no one definitive clinical tool to diagnose the presence or absence of SRC and typically no abnormalities that can be detected from standard neuroimaging methods (McCrory et al., 2017). Therefore, the most recent consensus statement on concussion in sport recommends that the assessment of concussion be multimodal and include self-reported symptoms as well as neurocognitive, balance, and vestibular-oculomotor testing (McCrory et al., 2017). One study reported that when utilizing symptom report alone, only 65% of concussed athletes were correctly identified. However, when neuropsychological testing results were utilized in conjunction with symptom report, correct identification of concussed athletes increased to 94% (Kampen, Lovell, Pardini, Collins, & Fu, 2006). This highlights the important role that neuropsychological testing can play in the diagnosis of SRC.

The main role of neuropsychological testing in concussion assessment is to determine whether the athlete has recovered cognitively. There is some evidence to suggest that cognitive impairment can persist past the resolution of self-reported symptoms (Johnson et al., 2011). For individuals for whom this is the case, neuropsychological testing would be crucial in preventing premature return to play. Baseline testing prior to an athlete's participation in sport was introduced as a method to further improve diagnostic accuracy by utilizing reliable change index methodology and accounting for individual differences (Kontos et al., 2016). However, there has actually been very little empirical evidence to support the use of baseline testing, although there may be some benefit for younger athletes and subpopulations with potential cognitive deficits (e.g., attention-deficit hyperactivity disorder [ADHD]/learning disability [LD]). Baseline testing can also introduce more potential issues due to invalid administration and interpretation by underqualified personnel, distracting environments, and athlete motivation to underperform on testing (Kontos et al., 2016). However, if baseline data are not used, then robust normative comparison samples are needed for post-concussion evaluations, and it is critical that such samples are utilized in the most effective manner for clinical decisions (Echemendia et al., 2013). Additionally, some research suggests that as many as 92% of neuropsychologists conduct post-concussion assessments in the absence of baseline data (LeMonda et al., 2017), which also underscores the importance of having evidence-based procedures for utilizing normative databases in clinical evaluations.

Base Rates of Impairment

Given that neuropsychological assessment of SRC often involves the administration of multiple tests to gather information about various cognitive domains, a clinician must consider the multivariate base rates of impairment. This concept is formulated from the observation that even healthy individuals will demonstrate an impaired score or two on a battery of multiple tests (Brooks & Iverson, 2013). There are five psychometric principles to consider when interpreting multiple test scores from a battery, including: 1) Low scores occur in all batteries of tests; 2) the cutoff score used relates to the number of low scores; 3) as the number of tests administered and interpreted increases, the number of low scores obtained increases; 4) demographic characteristics of a sample affect the number of low scores; and 5) different levels of intellectual functioning have different rates of low scores (Brooks & Iverson, 2013).

Previous research has incorporated the overarching principle of multivariate base rates (MBR's) into the assessment of SRC. Studies that have examined MBR's and predictors of neurocognitive performance in SRC have often specifically looked at the ImPACT computerized test, given its widespread use in university/athletic medicine settings (Asken et al., 2020; Houck et al., 2019). However, while the ImPACT may be given frequently to athletes, there are a significant subset of athletes who require more thorough neuropsychological testing and receive a full battery of cognitive tests that are commonly administered following SRC (Echemendia et al., 2019; Merritt et al., 2017). A previous study employed a full neuropsychological battery using paper-and-pencil and computerized tests to develop a return-to-play algorithm including the principle of base rates of impairments into the decision-making rules (Arnett et al., 2016). This study used a large normative sample of college athletes at baseline to determine the base rates of impaired scores on the standard neuropsychological assessment battery that is administered to athletes post-concussion (Arnett et al., 2016). The results from this study indicated that male and female athletes had a different number of impaired scores at baseline. Less than 10% of males in the sample had three or more impaired scores and less than 10% of females in the sample had two or more impaired scores (impairment was defined as 2 SD below the mean and borderline impairment was 1.5 SD below the mean). These cutoffs were then included in the algorithm to determine whether the athletes were neurocognitively “normal” again following concussion.

Present Study

Determining quantitative cutoffs that clinicians can use to inform clinical decisions regarding cognitive functioning and return-to-play recommendations is clearly important. However, given the recent recommendations which shift away from baseline testing (Echemendia et al., 2013; McCrory et al., 2017), it is also important to continue to evaluate and potentially adjust how neuropsychologists use normative comparison samples to make clinical decisions post-concussion. The aforementioned algorithm does not take into account principle five of MBR’s (individuals of differing intellectual functioning will have differing base rates of impairment). Therefore, including intellectual functioning in the determination of base rates could improve the diagnostic accuracy of cognitive functioning after SRC.

Specific Aim 1a: To test whether athletes with differing levels of premorbid IQ vary at baseline assessment on the number of cognitive impairments.

Hypothesis 1a: For many neuropsychological tests, performance correlates with premorbid IQ (Diaz-Asper et al., 2004). Additionally, principle five of multivariate base rates states that individuals of differing intellectual functioning will have differing base rates of impairment (Brooks & Iverson, 2013). Given these considerations, we predict that individuals in the High group will have fewer impairments at baseline than the individuals in the Mid group, and both of the latter groups will have fewer impairments than those in the Low group.

Specific Aim 1b: To use the results of the aforementioned analyses to determine whether there should be an update to a previously developed Return-to-Play (RTP) algorithm which includes premorbid IQ.

Hypothesis 1b: Given the relationship between IQ and many neurocognitive domains, we predict that differing levels of IQ will be related to different degrees of impairment on a baseline assessment battery and will require adjustments to account for these differences in the RTP algorithm.

Methods

Participants

This study includes 771 (Males = 572, Females = 199) student athletes at a Division I University who were involved in a concussion management program. The athletes' mean age was 18.50 (SD = 1.03), with a range of 17 to 24 years old. The athletes completed baseline testing prior to their participation in collegiate athletics, and they were tested with a hybrid model which included both traditional paper-and-pencil neuropsychological tests and computerized tests. The athletes participated in a variety of varsity sports including football, wrestling, men's and women's basketball, men's and women's lacrosse, men's and women's soccer, men's and women's ice hockey, rugby, baseball, softball, and volleyball. The athletes also self-reported their race/ethnicity and the majority of the sample identified as Caucasian American (74.2%). The athletes also self-identified as African American (19.5%), Biracial or Multiracial (3.0%), Hispanic American (1.2%), Asian American (.9%), and Other (1.2%).

Participants in this sample were selected from a larger sample of 972 college athletes who had been baseline tested between 2002-2019. Participants were excluded from the current study sample if they did not complete the measure of premorbid IQ (Wechsler Test of Adult Reading - WTAR) at baseline (N = 107), had previous diagnoses of ADHD or LD (N = 49) or had an ImPACT Impulse Control Composite Score greater than 30, as an indicator of poor effort (N= 32). For some analyses, there may be fewer participants included due to missing data.

Procedures

At this NCAA Division I University, the sports-concussion program is modeled after the “Sports as a Laboratory Assessment Model (SLAM)” (Bailey et al., 2009). The athletes were referred to the program by either their team physician or athletic trainer, and each athlete completed an approximately two-and-a-half-hour comprehensive battery of neuropsychological testing. This battery was administered to each athlete individually and was conducted in a quiet room. The testing included both paper-and-pencil and computerized cognitive assessments as well as neurobehavioral and symptom questionnaires. The battery was administered by trained undergraduate research assistants or graduate students who were supervised by a Ph.D.-level clinical neuropsychologist. All athletes provided informed consent, and the study was approved by the university’s Institutional Review Board and was conducted in accordance with American Psychological Association ethical guidelines.

Measures

Participants completed questionnaires which inquired about demographic characteristics and medical history (e.g., history of previous head injuries, history of ADHD/LD). Participants also completed a self-report measure, the Post-Concussion Symptom Scale (PCSS), which includes a list of 22 commonly reported post-concussion symptoms. Participants rated the extent to which they were currently experiencing each symptom on a scale from 0 to 6, with 0 indicating the absence of the symptom, and 6 indicating the symptom is severe.

Participants were also administered a neuropsychological battery of tests that assess domains of cognitive functioning which are typically affected following concussion. The cognitive domains tested include learning, memory, attention, processing speed, and executive functioning. The paper-and-pencil tests that were used include: the Brief Visuospatial Memory Test-Revised (BVMT-R) (Benedict, 1997), total correct immediate and delayed recall; the Hopkins Verbal Learning Test-Revised (HVLT-R) (Brandt & Benedict, 2001), total correct immediate and delayed recall; the Symbol Digit Modalities Test, total correct within 90 seconds (Smith, 1991); a modified Digit Span Test (Wechsler, 1997), total correct forward and backward sequences; the PSU Cancellation Task (Echemendia & Julian, 2001), total correct within 90 seconds; Comprehensive Trail Making Test (CTMT) (Reynolds, 2002), Trails 2 and 4 or 3 and 5, completion times for both parts; and the Stroop Color-Word Test (Trenerry et al., 1989), time to completion for both Color-Naming and Color-Word conditions. The computerized tests included the ImPACT (Lovell et al., 2000) and the Vigil/W Continuous Performance Test (Cegalis & Cegalis, 1994). The Verbal Memory Composite, Visual Memory Composite, Visuomotor Speed Composite, and Reaction Time Composite were the ImPACT indices used. A reaction time index, Average Delay, was used for the Vigil. In total, 17 test indices were used, with alternate forms of tests used where available.

Participants' premorbid IQ was also assessed by utilizing the Wechsler Adult Reading Test (WTAR) (Wechsler, 2001). The WTAR is a brief test which allows for an estimation of an individual's Full-Scale Intelligence Quotient (FSIQ) and was co-normed with the Wechsler Adult Intelligence Scale-III (WAIS-III). This measure assesses crystallized knowledge, which has been shown to be resistant to the effect of neurological damage, and it has been demonstrated to be valid as a measure of premorbid IQ in TBI populations (Green et al., 2008).

Data Analyses

The 17 neurocognitive variables were converted from raw scores to standard scores (M = 100, SD = 15) using sex-specific means and standard deviations from a large normative sample of college athletes at baseline (Merritt et al., 2017). As this study attempts to potentially refine the previously developed algorithm, we adjusted the cutoff scores for impairment on each neurocognitive variable from how they were defined in Arnett et al. (2016). Previously impairment was defined as 2 SD below the mean (less than or equal to 70 in Standard Scores) and borderline impairment is 1.5 SD below the mean (less than or equal to 78 in Standard Scores). For this paper, we utilized the same cutoff for impairment (less than or equal to 70 in Standard Scores), but labeled this as less than or equal to the 2nd percentile, as this metric and cutoff is commonly used by clinicians (Lezak et al., 2012). Instead of using a cutoff of 1.5 SD below the mean, we instead examined borderline impairment defined as less than 80 in Standard Scores or less than the 10th percentile. This cutoff is a commonly used guideline for defining borderline impairment in clinical practice (Lezak et al., 2012). The WTAR FSIQ score was utilized to divide the athletes into High, Mid, and Low groups, based on the full sample's quartile ranges, which has been suggested from prior work (Rabinowitz & Arnett, 2012). A one-way analysis of variance (ANOVA) was used to compare the means of each IQ group on number of impaired and borderline impaired scores. Descriptive statistics were used to identify the number of impairments that occur in less than 10% of individuals for each group, which determines the clinical cut off score for the algorithm. Performance on neuropsychological testing generally falls along a bell curve distribution, and in clinical practice, the lowest 10% of performance is considered the broadly impaired range (Lezak et al., 2012). In previous work, men and women showed different base rates of impairment (3 impaired scores for men, 2 impaired scores for women), and this was factored into the algorithm (Arnett et al., 2016). In the present study, independent samples t-tests were used to determine if there were significant differences between men and women's number of impairment scores within each IQ group.

Results

Specific Aim 1.

Examinees were placed into their respective premorbid IQ groups (High, Mid, or Low) based on the quartiles of the sample. Individuals with WTAR FSIQ scores below 100 were placed in the Low group, those with scores ranging from 101 to 107 were placed in the Mid group, and those with scores of 108 or above were placed in the High group. The number of individuals in each group and demographics of individuals in each group are presented in Table 1.

The results of the one-way ANOVA revealed that, overall, the IQ groups differed significantly on number of borderline scores at the $<10^{th}$ percentile cutoff ($F(2,713) = 23.78$, $p < .001$, $\eta_p^2 = .06$)[1]. Individuals in the Low group ($M = 2.06$, $SD = 2.03$) had more borderline scores than the Mid group ($M = 1.22$, $SD = 1.61$, $p < .001$, 95% CI [.46, 1.21]) and the High group (M=

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[1] η_p^2 = partial eta squared; small = .01, medium = .06, large = .14 (Field, 2013)

.82, SD= 1.32, p< .001, 95% CI [.80 1.68]). The Mid group also had significantly more borderline and impaired scores than the High group (p< .001, 95% CI [.04, .77]).

The IQ groups also differed significantly on number of impaired scores at the <=2nd percentile cutoff ($F(2,712) = 8.00$, $p<.001$, $\eta_p^2 = .02$). Individuals in the Low group (M= .66, SD= 1.14) had significantly more impaired scores than the Mid group (M= .45 SD= .85, p=.045, 95% CI [.003, .416]) and the High group (M= .26 SD= .80, p< .001, 95% CI [.16, .65]). However, the Mid group and High groups did not significantly differ on their number of impaired scores, but the effect was marginally significant (p=.062).

Specific Aim 2.

The frequencies of impaired scores at the different cutoffs were calculated to define the rules of the algorithm and are displayed in Table 2. Falling below the 10th percentile of individuals for number of impairments is broadly considered within the abnormal range, and the number of borderline/impaired scores which less than 10% of individuals obtained were highlighted in the table. Additional analyses were also conducted exploring any potential differences by sex given that the original algorithm included sex in the branching logic. Independent samples t-tests revealed that there were no significant or even marginally significant differences on average between males and females regarding their total number of borderline/impaired scores at either cutoff.

Discussion

It has been well-documented that one of the factors that can influence base rates of impairment is intelligence (Brooks & Iverson, 2013; Diaz-Asper et al., 2004; Karr et al., 2017). Despite this, neuropsychological evaluations of athletes following SRC may not always factor intelligence or premorbid IQ into the clinical interpretation of neuropsychological test results.

For example, clinicians using the ImPACT, a widely used computerized test for SRC, generally rely on the automated clinical interpretations that flag scores that are impaired based on the normative data. Some more recent studies have specifically examined how IQ may be related to an athlete's cognitive performance on the ImPACT (Asken et al., 2020; Houck et al., 2019) and found that it is a significant predictor of an athlete's performance on that test. While the ImPACT is used frequently due to ease of administration, it is only a brief evaluation of cognitive functioning. A significant minority of athletes who experience SRC require more thorough neuropsychological evaluation which can include a hybrid test battery composed of computerized and paper-and-pencil neuropsychological tests. The purpose of this study was to identify whether this effect of IQ on base rates of impairments could be replicated in a hybrid post-concussion battery and if so, then update a clinical decision-making algorithm to reflect that influence.

Specific Aim 1. Borderline and Impaired Scores

The results generally supported our hypothesis for the first specific aim of this study. We found that individuals in the Low group consistently had a greater number of total impaired and borderline impaired scores compared to the Mid and High groups, regardless of the cutoff employed. However, whether there were significant differences between the Mid and High groups depended on the cutoff used. The cutoff of $<10^{th}$ percentile (borderline impairment) appeared to be the best at differentiating all three of the IQ groups because at this cutoff the Mid Group also had significantly more borderline impaired scores than the High Group. However, for the cutoff of $<= 2^{nd}$ percentile, the Mid and High groups were not significantly different from each other on the total number of impaired scores.

Specific Aim 2. Updating the Algorithm

Given the absence of sex differences in the current study, we are recommending an updated algorithm that no longer includes sex, but instead incorporates different cutoffs based on an individual's premorbid IQ. Additionally, the purpose of this algorithm is to have easy guidelines for clinicians to follow. The classifiers of less than the 10^{th} percentile (below 80 SS) and less than or equal to the 2^{nd} percentile (<=70 SS) are commonly utilized by clinicians to designate borderline impairment and moderate to severe impairment, (Lezak et al., 2012); therefore, the algorithm will utilize both of these two cutoffs. When utilizing cutoff scores that fall below the 10^{th} percentile, the number of scores that would be considered abnormal (occurred in less than 10 percent of the sample) would be 6 or more for the Low group, 4 or more for the Mid group, and 3 or more for the High group. When utilizing a more stringent cutoff equal to or below the 2^{nd} percentile, 3 or more impaired scores would be abnormal for the Low group and having 2 or more impaired scores for the Mid and High group would be abnormal. Additionally, we have reconceptualized the former model by Arnett et al. (2016) as a clinical algorithm for cognitive functioning rather than a Return-to-Play algorithm. This reconceptualized model is now simply designed for neuropsychologists who want to determine whether an athlete is performing outside the cognitively normal range. It leaves the ultimate determination of Return-to-Play up to medical professionals who can consider an athletes' cognitive recovery in the context of other factors relating to recovery. Given the increasing amount of literature on the benefits of graded exercise in athlete recovery following concussion, there is likely benefit to allowing athletes to engage in appropriate levels of physical activity even if they are not fully back to their cognitive baseline (Lal et al., 2018; Lawrence et al., 2018; Powell et al., 2020). This algorithm could instead be more useful for helping medical professionals further assess athletes who are having prolonged difficulty or as a final determination before allowing an athlete to return to full participation in competitive sport. An updated algorithm is shown in Figure 1.

Limitations and Future Directions

This study has some limitations, and these limitations will likely inform future directions and expansions upon this work. First, this sample included significantly more male athletes than female athletes. While our sample of female athletes was still large (N= 199), the conclusions regarding equivalencies would be stronger with even more women in the sample to ensure robust numbers within each IQ group (e.g., the high IQ group only included 25 female athletes). Second, while our sample did include some racial and ethnic diversity, our sample is not entirely representative of the ethnic composition of the United States, particularly with regard to individuals who identify as Hispanic or Asian. More ethnic diversity among the sample could better ensure that our results are more generalizable to athletes of various racial and ethnic backgrounds. Third, these numbers are based on a specific battery with 17 test indices, and while this battery is likely quite comparable to other post-concussion hybrid neuropsychological batteries that are being used by many clinicians, future work should focus on how cutoffs may vary by the number of test indices that are included in a clinician's battery.

Conclusions

Current recommendations state that post-concussion clinical care should include a variety of assessment modalities, including neuropsychological assessment of cognitive functioning (McCrory et al., 2017). This research has multiple important implications for the clinicians who perform such assessments. First, it should be standard practice for clinicians performing neuropsychological assessment to collect a measure of premorbid IQ, given how previous research has repeatedly demonstrated that it is significantly related to an individual's performance on cognitive test batteries (Asken et al., 2020; Brooks & Iverson, 2013; Houck et al., 2019; Karr et al., 2017). The results of the impairment score analyses were consistent with our hypothesis regarding the role of premorbid IQ and the previous literature on base rates of impairment. This study shows the importance of collecting IQ data during an evaluation generally, but also specifically for athletes who are referred post-concussion to undergo full neuropsychological batteries. While it may not be feasible for clinicians to include full intelligence tests, there are many brief assessments that provide reliable estimates of premorbid IQ. Addition of such measures would unlikely drastically increase the length of evaluation or burden on the athlete. Second, this type of research is critical to ensuring that the normative data used to make clinical decisions are as accurate as possible and informed by recent empirical data. This manuscript includes an explicit practical guideline so that real-world clinical decision-making can be easily updated to reflect the most recent scientific information. Overall, such adaptations could improve post-concussion clinical care so that athletes are neither returned to full activity in sport too early, nor held back too long.

Table 1. Demographic Variables by IQ Group

Table 1.

	Low Group			Mid Group			High Group		
Variables	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Age	18.47	.92	17-23	18.27	.81	17-22	19.04	1.35	17-24
Previous Head Injuries	0.54	.81	0-4	0.61	1.01	0-15	0.63	0.92	0-5
Variables	N	%	--	N	%	--	N	%	--
Sex	169	100 %	--	419	100%	--	183	100%	--
Male	121	70%	--	293	69.9%	--	158	86.3%	--
Female	48	28%	--	126	30.1%	--	25	13.7%	--

Table 2. Frequency of Borderline and Impaired Scores by IQ Group

a)

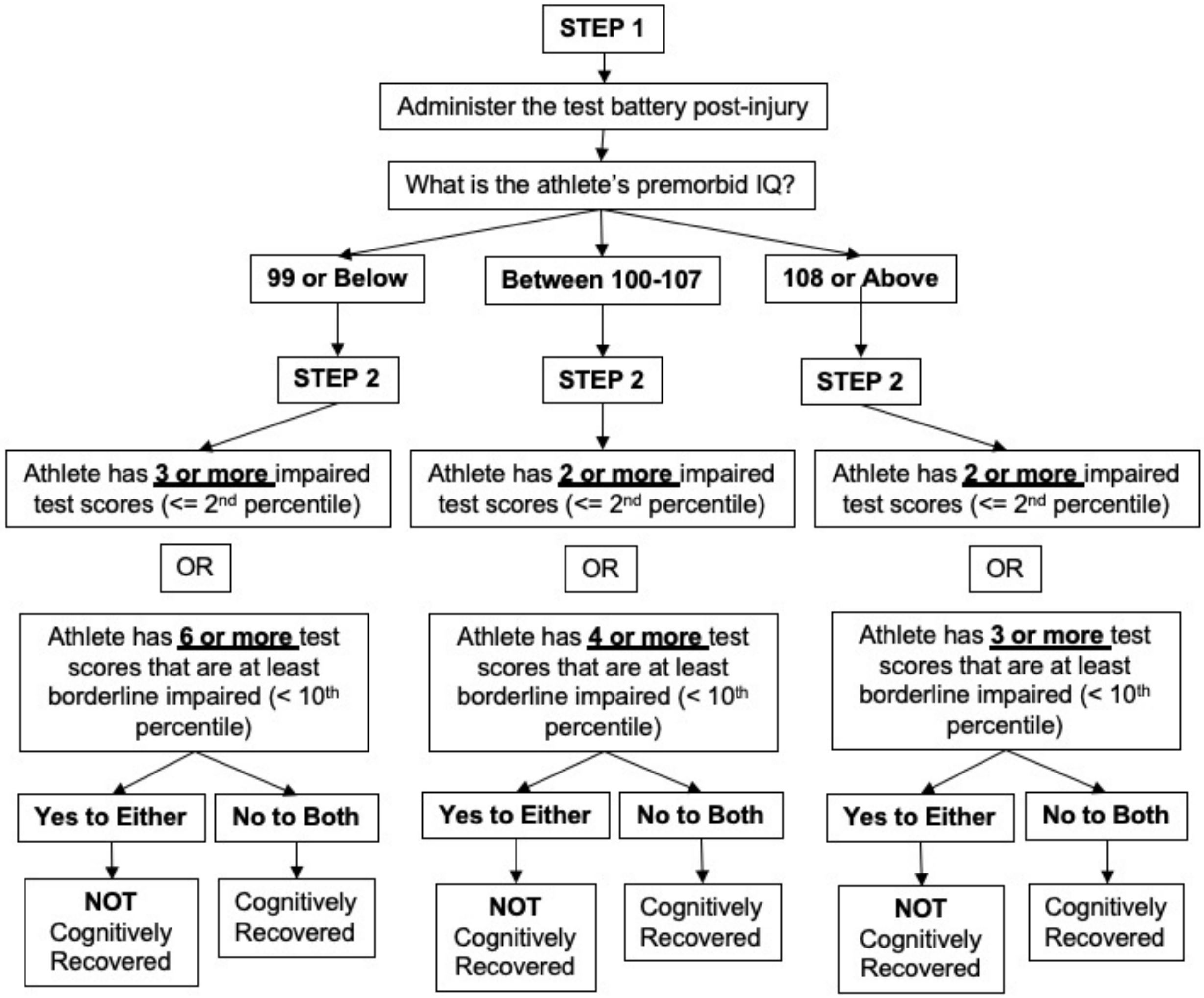
Number of Borderline Scores	0	1	2	3 or more	4 or more	5 or more	6 or more
Low Group	26.8%	21.0%	17.8%	34.4%	19.1%	11.5%	7.0%
Mid Group	44.8%	23.3%	15.1%	15.9%	8.2%	4.4%	2.1%
High Group	55.5%	25.0%	11.6%	7.3%	3.0%	2.4%	1.8%

b)

Number of Impaired Scores	0	1	2 or more	3 or more
Low Group	63.1%	19.7%	17.2%	7.6%
Mid Group	70.1%	20.2%	9.7%	3.3%
High Group	81.4%	12.2%	3.6%	2.4%

Table 2. Percentage of individuals in each of the IQ groups who demonstrated a certain number of borderline (2a) or impaired scores (2b). Bolded numbers highlight where the percentage is below 10%, indicating a significantly small group of individuals.

Figure 1. Updated Clinical Algorithm



Chapter 3. Paper 2: Does cognitive reserve moderate any observed relationship between concussion severity and three different post-concussion clinical outcomes?

Introduction

Overview of Cognitive Reserve

The concept of cognitive reserve (CR) was developed to explain the non-direct relationship between the amount of brain pathology observed in individuals with neurological damage and the functioning of those individuals (Stern, 2009). For example, aging studies have shown that 25% of elderly individuals who demonstrated no cognitive impairment on neuropsychological testing prior to death still met full pathologic criteria for Alzheimer's disease (Stern, 2009). This indicates that some individuals can sustain a significant amount of neurological damage with no observable deficits in cognitive functioning. Cognitive reserve postulates that this discrepancy is due to individual differences in neural networks or cognitive processes which allow for better coping and adaptation following brain damage. CR has also been dissociated from another potential factor in this phenomenon, brain reserve (BR). The BR model proposes that individuals with greater brain volume or neural count can sustain greater damage before functioning is impaired. While BR and CR have been demonstrated to be related, they have also been shown to be discrete factors with each playing a role in preserving functioning (Stern, 2009; Sumowski et al., 2014).

Although there is currently no definitive, direct method of measuring CR (e.g. via biomarkers or neuroimaging), several important proxies have been identified including intelligence, education, and occupational attainment (Stern, 2009). While it could be conceptualized that education and occupational attainment are simply markers of intelligence, research has demonstrated that education and occupational attainment have impacts over and above IQ as well (Stern, 2009). Additionally, engagement in cognitively stimulating leisure activities has also been shown to be related to CR. This adds further support to the idea that CR is somewhat malleable and could reflect the brain's increased capacity for adaptation due to enriching life experiences. Importantly, however, there is evidence that CR is only effective until a certain threshold of damage to the brain has occurred, implying that the brain can no longer compensate after significant pathological burden (Stern, 2009).

Cognitive Reserve in TBI & SRC

Research has shown evidence for CR in multiple neurological populations including Alzheimer's disease, Parkinson's disease, Multiple Sclerosis (MS), chronic traumatic encephalopathy (CTE), and TBI (Alosco et al., 2017; Hindle et al., 2016; Mathias & Wheaton, 2015a; Stern, 2002; Sumowski & Leavitt, 2013). Research on the role of CR in cases of TBI has focused mainly on moderate and severe TBI, with less done on mild TBI (Mathias & Wheaton, 2015). The work in mild TBI has also primarily focused on prolonged concussion recovery or Post-Concussion Syndrome (Oldenburg et al., 2016; Stewart-Willis et al., 2018). These studies have also found CR has a predictive or moderating role in outcomes following mild TBI. One article that specifically looked at sport-related concussion, examined retired American football players and found that a composite measure of CR (highest educational degree attained, highest occupational obtainment and estimated premorbid intellectual ability) had a significant protective effect against concussion severity factors on global cognitive ability (Wright et al., 2016). One study found that patients with mTBI who also had lower cognitive reserve were 4.14 times more likely to suffer from post-concussion syndrome (Oldenburg et al., 2016), while another study found that CR was a better predictor of cognitive outcomes following mTBI than having post-concussion syndrome (Stenberg et al., 2020). To our knowledge, there has been no research to date examining whether CR moderates outcomes in college athletes who have sustained a sports-related concussion.

The conceptual model states that CR moderates the effect of brain pathology on cognitive functioning. However, in studies where there are no data on physical brain pathology, proxies of damage (e.g. measures of disability or disease severity) have been utilized (Hindle et al., 2016; Sumowski, Chiaravalloti, & Deluca, 2009). Given that in most cases of mTBI and SRC, there is no observable brain damage on typical neuroimaging methods, utilizing a measure of symptom severity would likely be necessary in order to approximate brain pathology or damage.

Most often CR has been explored as a protective factor against the effect of damage on cognitive functioning. However, there has been recent exploration of the buffering effect of CR on psychiatric functioning. Previous research has demonstrated that a measure of disease burden (EDSS) predicted depression (BDI-FS total score) but only in those with low CR in a sample of individuals with MS (Cadden et al., 2019), suggesting that individuals with high CR were protected from the effects of disease burden on psychological functioning.

Present Study

The present study examines whether CR plays a role in differential outcomes for individuals in the acute phase of concussion. This study explores the relationship between CR, concussion severity, and three separate outcome measures related to concussion (cognitive functioning, depression symptoms, RTP time).

Specific Aim 2a: To test whether cognitive reserve moderates the effect of concussion severity on cognitive functioning following concussion.

Hypothesis 2a: CR will moderate the relationship between concussion symptom severity and cognitive outcomes such that individuals with higher cognitive reserve will demonstrate better cognitive functioning at high levels of symptom severity. In other words, symptom severity will predict poorer cognitive outcomes only among those with low levels of CR.

Specific Aim 2b: To test whether cognitive reserve moderates the effect of concussion severity on depression symptoms following concussion.

Hypothesis 2b: CR will moderate the relationship between concussion symptom severity and depression such that individuals with higher cognitive reserve will demonstrate lower depression symptoms at high levels of symptom severity. Symptom severity will predict depression symptoms only among those with low levels of cognitive reserve.

Specific Aim 2c: To test whether cognitive reserve moderates the effect of concussion severity on RTP time following concussion.

Hypothesis 2c: CR will moderate the relationship between concussion symptom severity and return to play time such that individuals with higher cognitive reserve will demonstrate faster return to play time at high levels of symptom severity. In other words, symptom severity will predict slower return to play times only in individuals with low levels of CR.

Methods

Participants

This study's total sample includes 175 (Males = 131, Females = 44) student-athletes at a Division I University who were involved in a concussion management program. The athletes' mean age was 19.07 (SD = 1.28) with a range of 17 to 22 years old. The athletes were tested post-concussion using a hybrid model which included both traditional paper-and-pencil neuropsychological tests and computerized tests. All athletes in the sample demonstrated sufficient effort as measured by an ImPACT Impulse Control Composite (ICC) less than 30. The athletes participated in a variety of sports: football, wrestling, men's and women's basketball, men's and women's lacrosse, men's and women's soccer, men's and women's ice hockey, rugby, baseball, softball, swimming/diving, golf, cheerleading, tennis, and volleyball. They also self-reported their race/ethnicity and the majority of the sample identified as Caucasian American (72.0%). The athletes also self-identified as African American (20.0%), Biracial or Multiracial (4.0%), Asian American (2.3%), and Other (1.1%). One athlete did not provide this information (.6%).

For Aim 2c, only subset of participants had RTP data available (N = 72; Males = 57, Females = 15). Within this subset, the athletes' mean age was 18.88 (SD = 1.29) with a range of 17 to 22 years old. The athletes also self-identified as Caucasian American (63.9%), African American (26.4%), Biracial or Multiracial (5.6%), Asian American (1.4%), and Other (2.8%).

Procedures

The data for this study was collected through the sports-concussion program and is modeled after the "Sports as a Laboratory Assessment Model (SLAM)" (Bailey et al., 2009). Team physicians or athletic trainers referred the athletes to the program following a concussive injury and each athlete completed a two-and-a-half-hour comprehensive battery of neuropsychological testing. This battery included traditional paper-and-pencil and computerized neuropsychological tests as well as neurobehavioral and symptom questionnaires. The testing was administered to each athlete individually, by trained undergraduate research assistants or graduate students who were supervised by a Ph.D.-level clinical neuropsychologist, and all procedures were conducted in a quiet room free from distractions. All athletes provided informed consent and the study was approved by the university's Institutional Review Board.

Measures

Participants completed questionnaires which inquired about demographic characteristics, medical history (e.g., history of previous head injuries, and history of attention-deficit hyperactivity disorder [ADHD]/learning disability [LD]). Participants also completed the Post-Concussion Symptom Scale (PCSS), a self-report measure that includes a list of 22 commonly reported post-concussion symptoms. Participants rate the extent to which they are currently experiencing each symptom on a scale from 0 to 6, with 0 indicating the absence of the symptom, and 6 indicating the symptom is severe. The total score of PCSS was used as the index of concussion severity. Participants also completed a self-report measure of depression, the Beck Depression Inventory – Fast Screen (BDI-FS), which does not include the neurovegetative symptoms of depression that can overlap with physical, cognitive, and sleep symptoms of concussion (Beck et al., 2000). Participants' time to RTP was collected from their sports medicine records and is their number of days from their concussion until they were cleared to return to full activity in their sport.

The neuropsychological battery assessed multiple domains of cognitive functioning including learning, memory, attention, processing speed, and executive functioning. The paper-and-pencil tests that were used include: the Brief Visuospatial Memory Test-Revised (BVMT-R) (Benedict, 1997), total correct immediate and delayed recall; the Hopkins Verbal Learning Test-Revised (HVLT-R) (Brandt & Benedict, 2001), total correct immediate and delayed recall; a modified Digit Span Test (Wechsler, 1997), total correct forward and backward sequences; the PSU Cancellation Task (Echemendia & Julian, 2001), total correct within 90 seconds; Comprehensive Trail Making Test (CTMT) (Reynolds, 2002), Trails 2 and 4 or 3 and 5, completion times for both parts; and the Stroop Color-Word Test (Trenerry et al., 1989), time to completion for both Color-Naming and Color-Word conditions. The computerized tests included the ImPACT (Lovell et al., 2000) and the Vigil/W Continuous Performance Test (Cegalis & Cegalis, 1994). The Verbal Memory Composite, Visual Memory Composite, Visuomotor Speed Composite, and Reaction Time Composite from the ImPACT were also used. A reaction time index, Average Delay, was used for the Vigil. In total, 17 test indices were used, with alternate forms of tests used where available.

Participants' IQ was also assessed by utilizing the Wechsler Adult Reading Test (WTAR) (Wechsler, 2001), which is a brief reading test that can be used to estimate an individual's Full-Scale Intelligence Quotient (FSIQ). The WTAR assesses crystallized verbal knowledge, which is often resistant to the effect of neurological damage, and this test has been demonstrated as a valid measure of premorbid IQ in TBI populations (Green et al., 2008). While there is no direct way of measuring cognitive reserve, intelligence is commonly used as a proxy (Stern, 2009) and the FSIQ estimate from the WTAR served as the measure of cognitive reserve for the current study.

Data Analyses

The main analyses examine whether cognitive reserve (WTAR FSIQ) has a moderating effect of concussion severity (PCSS total score) on multiple different outcome measures (cognitive functioning, RTP time, or depression symptoms). Initially, the 17 neurocognitive variables were converted from raw scores to standard scores (M = 100, SD = 15) using sex-specific means and standard deviations from a large normative sample of college athletes at baseline (Merritt et al., 2017). These indices were averaged together to create an overall neurocognitive composite to assess broad cognitive functioning.

Demographic variables (age and sex), as well as an injury-related variable (days tested post-concussion), and number of previous head injuries, were examined as potential covariates.

Such variables were included as covariates if they significantly correlated with any of the three outcome measures (cognitive functioning, RTP time or depression symptoms) and were not highly correlated and conceptually related with any of the main variables of interest (PCSS total score and CR). The following variables had a skewed distribution and were log transformed to adjust for this: PCSS total score, RTP time, BDI-FS total score. All of the analyses utilizing these variables included the log-transformed version of that variable.

Aim 2a Analysis: CR, PCSS total score, and their interaction were entered into a regression analysis with cognitive functioning (the neurocognitive composite score) as the dependent variable.

Aim 2b Analysis: CR, PCSS total score, and their interaction were entered into a regression analysis with depression (BDI-FS total score) as the dependent variable.

Aim 2c Analysis: CR, PCSS total score, and their interaction were entered into a regression analysis with return to play time (Days to RTP) as the dependent variable.

Simple effects: Simple effect tests were run to elucidate the direction of any significant interactions; the effect of concussion severity on the three dependent variables will be tested at high and low (+/- 1 SD) levels of cognitive reserve.

Results

Covariate Analyses

Of the covariates that were examined (sex, age, days tested since concussion, and number of previous head injuries), only sex was found to be significantly correlated with any of the outcome variables. Sex was found to be moderately positively correlated with the overall neurocognitive composite such that females had better performance on the cognitive testing than males, $r(175) = .32$, $p=<.001$. Sex was also found to be strongly positively correlated with days to RTP, such that females had much longer return to play times than males, r(72) = .45, p=<.001. However, it should be noted that the sample size of female athletes in the RTP analysis was small, with N=15. Sex was not significantly correlated with our depression outcome measure, the BDI-FS.

Aim 2a.

The results of the regression analyses are listed in Table 3. A multiple linear regression was calculated to predict neurocognitive performance based on CR, PCSS total score, and their interaction. Sex was also included in the model as a covariate. A significant regression equation was found ((F(4, 149) = 10.53, p<.000, R^2 =.22). Sex (t = 4.63, p<.000, r_p[2]=.35) was a significant predictor in the model while PCSS total score was marginally significant (t = -1.92, p=.057, r_p=-.16). CR and the interaction of PCSS and CR did not significantly predict neurocognitive performance.

Aim 2b.

A multiple linear regression was calculated to predict level of depression symptoms based on CR, PCSS total score, and their interaction. A significant regression equation was found, ((F(3, 149) = 6.87, p<.000, R^2 =.12). PCSS (t = 4.52, p<.000, r_p=.35) was a significant predictor in the model. Neither CR nor the interaction of PCSS and CR significantly predicted depression symptoms. Given that the PCSS includes four affective symptoms (e.g. feeling sad, anxious, irritable, more emotional than usual) and the overlap between these symptoms and some of the symptoms on the BDI-FS, we also created a PCSS total score variable that did not include those affective symptoms. The regression was run again using this modified PCSS variable. A significant regression equation was still found ((F(3, 128) = 5.00, p=.003, R^2 =.11), and the

[2] r_p = partial correlation

modified PCSS without affective symptoms ($t = 3.83$, $p<.001$, $r_p=.32$) was still the only significant predictor in the model.

Aim 2c.

A multiple linear regression was calculated to predict RTP time based on CR, PCSS total score, and their interaction. Sex was also included in the model as a covariate. A significant regression equation was found (($F(4, 61) = 4.26$, $p=.004$, $R^2 =.218$). Sex ($t = 3.89$, $p<.000$, $r_p=.44$) was the only significant predictor in the model. PCSS, CR, and their interaction did not significantly RTP time.

Simple Effects.

There were no significant interactions between PCSS and CR for any of the regression models so the simple effects for the interactions were not tested. We further examined the significant predictors for each of the three models. Regarding Aim 2a, an independent samples t-test revealed that male and female athletes were significantly different in their neurocognitive performance, $t(173)=-4.48$, $p<.001$, $d=-.78$. These results suggest that males ($M = 99.38$; $SD = 10.04$) performed significantly worse than females ($M = 107.34$; $SD = 10.62$), and this was a medium to large effect. Regarding Aim 2b, given a violation of Levene's test for homogeneity of variances, $F(1,70)=22.59$, $p=.000$, a t-test not assuming equal variances was calculated. The independent samples t-test revealed that male and female athletes were significantly different in the RTP time, $t(15.97)=-3.02$, $p=.008$, $d=-1.26$. These results suggest that males ($M = 37.33$; $SD = 48.96$) had significantly shorter RTP times than females ($M = 114.60$; $SD = 95.94$), and this was a large effect. Regarding Aim 2c, a bivariate correlation revealed the significant, moderate relationship between PCSS total score (including the affective items) and the BDI-FS total score, $r(169) = .33$, $p<.001$. The relationship was also significant between the modified PCSS total score (minus the affective items) and the BDI-FS total score, $r(169) = .31$, $p<.001$.

Discussion

The majority of TBI and CR research has focused on moderate and severe TBI, with less done on mild TBI (Mathias & Wheaton, 2015). Research on cognitive reserve in mild TBI (mTBI) has been even more limited and often utilizes samples with prolonged concussion recovery or Post-Concussion Syndrome (Oldenburg et al., 2016; Stenberg et al., 2020; Stewart-Willis et al., 2018; Wright et al., 2016). There has been little, if any, research focused on whether the protective effects of CR can be detected even in collegiate athletes who have experienced a recent SRC. This study examined whether CR is protective against deleterious effects of SRC on three relevant outcomes for athletes who experienced an acute concussion. The results of this study indicate that CR reserve was not a significant moderator of the relationship between concussion severity on any of the three outcomes. This could be due to some of the inherent limitations of this study and such possibilities will be discussed below in the limitations section. However, it is possible that the effect of CR is not detectable or even necessarily present in a sample that is overall very young and healthy. The main construct necessitates that CR moderates the contribution of neural damage to an individual's functioning. It is possible that the level of neural damage sustained in most SRCs, which are often mild traumatic brain injuries, does not have a significant enough impairment on functioning for these acutely injured athletes to detect any buffering effect from CR.

From the regression analyses, relevant predictors of the various outcomes did emerge as significant. The results indicated that sex was significantly related to neurocognitive performance, with females having higher overall scores compared to males. Much of the research on neurocognitive performance in SRC both at baseline and post-concussion has utilized briefer assessments such as the ImPACT or SAC rather than a full neuropsychological battery and the evidence for differences in performance based on sex has been mixed (Broshek et al., 2005; Cottle et al., 2017; Covassin et al., 2006). One study utilizing a full neuropsychological battery found that at the mean level there were no significant differences between male and female athletes' cognitive performance post-concussion (Merritt et al., 2019). More research is needed to explore any potential sex differences post-concussion on a full neuropsychological battery of tests. Sex was also significantly predictive of RTP time, with females having longer times to return to play. The findings that women often have more complex SRC recoveries (e.g. greater symptom report, longer recovery time) than their male counterparts has been demonstrated in multiple research studies (Covassin et al., 2018; Iverson et al., 2017), and our finding is consistent with that literature. It is also notable that the observed sex difference in the return to play time for female athletes is counterintuitive given their superior cognitive performance on the post-concussion testing compared to the male athletes. While it may simply be due to the fact that women often demonstrate greater symptom reporting, future work could elucidate other potential reasons why females may perform well on post-concussion testing but continue to be held back longer than males.

The PCSS total score was found to be a significant predictor of the BDI-FS total score. This indicates that concussion symptom load is related to depression symptoms. This effect also held true even with the affective and mood symptoms removed from the total PCSS score. While these cross-sectional data cannot determine the directionality of this effect, higher symptom report could be reflective of a general malaise that comes with depression or that having a greater severity of concussion symptoms may contribute to a more depressed mood. The first interpretation would be consistent with the literature that individuals with mental health disorders at baseline are more likely to have persistent symptoms as well as experiencing depression post-concussion predicting longer lasting symptoms (Iverson et al., 2017; Vargas et al., 2015).

Limitations

This study has three main limitations. First, CR is a complex construct and has been shown to be captured by multiple different measures beyond IQ including education, job attainment, and cognitively stimulating activities (Scarmeas & Stern, 2003; Stern, 2002; Sumowski et al., 2014). Ideally, multiple measures or proxies of CR would have been included to create a more comprehensive CR "composite." However, some of these typical proxies of CR would not be relevant for this sample (e.g. these college students are all around the same level of education, and they don't yet have employment) or the data were not collected (e.g. cognitively stimulating leisure activities). Second, many studies of CR have assessed severity of impact on the brain from measures of physical brain damage or degeneration (e.g. lesion load, atrophy, Alzheimer's disease pathology, etc.) (Sumowski & Leavitt, 2013; Tucker & Stern, 2010). In a concussed sample, there are often no markers of physical injury on typical clinical neuroimaging. There has been some work measuring damage following mild traumatic brain injury (mTBI) through functional MRI (fMRI), Electroencephalography (EEG), Diffusion Tensor Imagine (DTI), and Magnetic resonance spectroscopy (MRS), but there is currently no clear, established clinical pattern for what indicates a more severe mTBI or concussion with any particular one of these current methods (Asken et al., 2018; Slobounov et al., 2012). However, having additional physical, quantitative measures of concussion severity (e.g., measures of ocular function, vestibular function, gait and balance) would improve upon this study's reliance on a self-report of symptoms severity. However, non-direct methods of brain involvement have been utilized in other CR research in MS through the Expanded Disability Status Scale (EDSS) when imaging data of lesions and or atrophy was unavailable (Cadden et al., 2019). Finally, while the overall size of our sample was robust, there were some sample size limitations based on the specific analyses and for the representation of women and certain unrepresented groups. Although our sample size for the RTP analyses was still reasonably large (N=72), there were only 15 female athletes. While the finding from this analysis was consistent with previous research, we cannot rule out the possibility that this study's sex-related findings are simply a result of the small sample of females. Additionally, athletes who identify as Asian or Hispanic are unrepresented in our sample, which limits the broader generalizability of these findings.

Conclusion

Much of the previous research on cognitive reserve in traumatic brain injury has focused on moderate and severe TBI. Less work has been done on mild TBI and virtually no work has explored the potential role of CR as a moderator in SRC. Our study did not find evidence to support a buffering effect of CR for any of the three main concussion outcomes that we explored (cognitive functioning, depression symptoms, or return to play time). There has been evidence in other mild traumatic brain injury samples of CR, but more specifically for individuals with post-concussion syndrome. Therefore, our results may simply be demonstrating the general model of CR, which is that it is a moderator of the effect of damage on impairment/dysfunction, and if the damage sustained is not significant enough for major impairment or dysfunction, then we would not detect a CR effect. Future work should explore whether this effect could be detectable in SRC if the sample included athletes who were experiencing PCS or protracted recovery. This would allow for greater variance in impairment and dysfunction among the athletes to ensure that if CR did have a buffering effect against such outcomes, then it would be detectable. This study may provide evidence for a neurological population (collegiate athletes who experience acute SRC) where the model of CR may not apply, but future research could elucidate this further. By understanding whether CR is a predictive factor in better or worse outcomes following SRC, clinicians could have another piece of useful information when assessing athletes following concussion. Given the variable and often less than predictable nature of concussion outcomes, having such additional information would likely be helpful in improving post-concussion clinical care for collegiate athletes.

Table 3

a) Regression Examining Predictors of Neurocognitive Performance

Source	B	SE B	β	t	p	r[3]
Constant	103.49	1.18		87.86	.000	
PCSS Total Score	-2.58	1.40	-.14	-1.92	.057'	-.15
Cognitive Reserve	.21	.16	.15	1.31	.19	.11
Sex	8.07	1.74	.34	4.63	<.001**	.35
PCSS x CR interaction	.29	.19	.18	1.59	.11	.13

b) Regression Examining Predictors of Depressive Symptoms

Source	B	SE B	β	t	p	r
Constant	1.65	.04		4.25	.000	
PCSS Total Score	.21	.05	.35	4.52	<.001**	.35
Cognitive Reserve	-.001	.005	-.02	-.18	.85	-.02
PCSS x CR interaction	-.002	.006	-.03	-.25	.80	-.02

c) Regression Examining Predictors of Return to Play Time

Source	B	SE B	β	t	p	r
Constant	1.48	.08		17.601	.000	
PCSS Total Score	.04	.11	.05	.39	.70	.05
Cognitive Reserve	-.004	.01	-.06	-.32	.75	-.04
Sex	.475	.13	.43	3.77	<.001**	.43
PCSS x CR interaction	-.006	.01	-.08	-.41	.68	-.05

**Significant at p < .01; `Marginally significant at p < .10

[3] ***r*** = partial correlation: .1 = small, .3 = medium, .5 = large

Chapter 4. Paper 3: Symptom Factors and Neuropsychological Performance in Collegiate Athletes with Chronic Concussion Symptoms

Introduction

Overview of sports-related concussion

An estimated rate of 4.47 concussions per 10,000 athletic exposures occur annually in collegiate athletics in the United States (Zuckerman et al., 2015). In the United States, an estimated 491,930 student-athletes participate annually in NCAA sports, and thus are at risk of exposure to sports-related concussion (SRC) (Irick, 2016). Further, SRC is an injury that presents unique challenges for the student-athlete (Putukian, 2016; Wolanin et al., 2016; Yang et al., 2007). SRC may have implications acutely and more long-term for athletes in their emotional, cognitive, academic, and social functioning. For example, athletes may demonstrate emotional/affective difficulties following concussion (Kontos & Collins, 2018; Meyer & Arnett, 2015; Sandel et al., 2017; Stein et al., 2017; Vargas et al., 2015), experience adjustment difficulties with return-to-learn and return-to-play (Asplund et al., 2004; Halstead et al., 2013), and experience cognitive deficits as a result of their injury (Broglio & Puetz, 2008; Kontos et al., 2012). The above difficulties following SRC may be increased for individuals with prolonged recovery, complicating return-to-play. Therefore, understanding the impact of concussion in the chronic phase warrants attention. Further, understanding factors, such as symptom profiles or patterns of cognitive functioning that may identify athletes at risk for poorer functional outcomes is of clinical importance.

SRC Symptoms and Recovery

Concussions are heterogeneous injuries, and any two individuals who have experienced a concussion can present quite differently clinically. Twenty-two common post-concussion symptoms are generally assessed following SRC, and individuals can present with any number of these symptoms (Pardini et al., 2004). Additionally, there is some variability in recovery from SRC. Although many athletes recover within a relatively short period of time (generally between 7-14 days), there is still a significant minority of individuals (about 17%) who take 3 weeks or more to recover, and understanding pre- and post-injury risk factors for protracted recovery has been a topic of much interest in the field (Collins et al., 2014; Iverson et al., 2017; McCrea et al., 2003, 2013; McCrory et al., 2017).

While research has explored the role of specific symptoms in the acute phase for predicting prolonged recovery, less work has explored the relationship between specific symptoms reported in the chronic phase and their relationship to functional outcomes, such as cognitive functioning. Despite this variety in presentation and recovery, concussion management has generally been fairly homogeneous in its approach to treatment and care of athletes. Some research has worked to encourage a more comprehensive and tailored approach to care by exploring multiple clinical trajectories that athletes could fall into based on their specific presentation of symptoms (Collins et al., 2014). Understanding how specific symptoms in the chronic phase of injury are related to cognitive functioning could further inform research on improving clinical care.

Chronic Concussion

Post-Concussion Syndrome (PCS) was coined to describe the condition in which concussion symptoms persist for a more extended period of time (ranging from months to years), but the etiology of this "syndrome" has caused controversy in the field. Given that concussion symptoms are non-specific to concussion, it is more difficult to determine whether these are a result of physiological changes due to injury or due to pre- or post-injury physical or psychological factors (Ryan & Warden, 2003). Importantly, the terminology for individuals with extended recovery times varies widely in the literature. This has been referred to as protracted or prolonged recovery, persistent post-concussion symptoms, Post-Concussion Syndrome or the chronic phase of concussion (Collins et al., 2014; Conder et al., 2020; Ryan & Warden, 2003; Walter et al., 2017). Our paper will mainly use the term chronic concussion, but it should be acknowledged that there is currently no clearly defined diagnostic difference among these terms.

Chronically concussed individuals have been less well studied than those with acute concussions, and literature on the cognitive functioning of these individuals has been additionally sparse. Specifically, less is known about the link between the current experience of persistent concussion symptoms and cognitive functioning in the sports concussion population. Additionally, the potential interplay between mood factors (depression, anxiety, somatization), other common concussion symptoms, and cognitive functioning in the chronic phase of concussion warrants further attention.

Relationship between Symptomology and Cognitive Impairment

Research has been sparse on the specific link between symptomology following SRC and deficits in cognitive functioning. One study examined differences between symptomatic and asymptomatic Australian Rules Football players following concussion on a battery of computerized and paper-and-pencil neuropsychological assessments (Collie et al., 2006). The symptomatic athletes performed worse than the asymptomatic athletes on computerized assessments of motor and attention (Collie et al., 2006). Additionally, another study examined performance between three groups: a concussed symptomatic group, a concussed asymptomatic group, and a non-concussed control group (Fazio et al., 2007). The concussed symptomatic group performed worse than both other groups on the Processing Speed and Reaction Time

Composites on the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) (Fazio et al., 2007). These studies provide evidence that concussed athletes who are still symptomatic following a concussion demonstrate more cognitive deficits than either concussed athletes who are asymptomatic or non-concussed athletes.

There has also been a significant amount of research examining the effect of sleep dysfunction and fatigue on cognitive functioning more broadly, and this has also been explored to a lesser degree in post-concussion samples. Most research has focused on the effects of sleep on assessment of cognitive functioning at baseline in non-concussed athlete samples, and has demonstrated the negative effect of lack of sleep or sleep symptoms on cognitive performance (Riegler et al., 2020; Stocker et al., 2017). Some research has demonstrated a relationship between self-reported sleep symptoms and cognitive impairment (Kostyun et al., 2015). Previous work demonstrated that in a population of concussed college athletes who were tested within the first two weeks following concussion, self-reported sleep symptoms were associated with worse memory performance (Guty & Arnett, 2018).

A handful of studies have also examined the link between headache, one of the most commonly reported symptoms following SRC (Guskiewicz et al., 2000), and cognitive performance. Collins and colleagues (2003) compared a group of concussed athletes reporting headaches at 7-days post-injury and those not reporting headache. The concussed athletes experiencing headache had worse performance on Reaction Time and Memory Composites of the ImPACT and also reported more overall symptoms than concussed athletes not reporting posttraumatic headache (Collins et al., 2003). A recent paper by Guty & Arnett (2018) examined the association between specific post-concussion symptoms and cognitive outcomes. Concussed athletes were assessed within the first two weeks following concussion and post-concussion symptoms were grouped into five factors: cognitive, physical, affective, sleep, and headache based on previous factor analysis (Guty & Arnett, 2018; Merritt & Arnett, 2014). Athletes reporting headache symptoms performed significantly worse on an overall composite of neurocognitive performance and on composites of memory and attention/processing speed compared to athletes not reporting headache symptoms (Guty & Arnett, 2018). Given that research has demonstrated the importance of headache as a symptom following concussion, further exploration of the relationship between headache specifically and cognitive functioning, is warranted. Additionally, understanding the link between various symptomology and neuropsychological test performance may provide insights into patterns of clinical recovery and inform treatment following SRC.

Present Study

Previous work has demonstrated that headache symptoms were associated with worse overall cognitive performance among a population of concussed athletes tested within the first two weeks following concussion (Guty & Arnett, 2018). Additionally, previous research has supported taking a more focused approach examining the relationship between specific symptoms and cognitive outcomes following concussion (Guty & Arnett, 2018; Lau et al., 2011; Lau et al., 2009). The current study aims to replicate and extend these findings by exploring the relationship between five concussion symptom factors and cognitive performance in a sample experiencing more chronic concussion symptoms (six months to three years following concussion). These athletes are a vulnerable population, experiencing prolonged difficulties as a result of SRC, therefore, uncovering factors that could help explain this relationship is important.

Specific Aim 1: Examine the distinct relationship between each of the different post-concussion symptom factors (Cognitive, Physical, Affect, Sleep, and Headache) and memory performance.

Hypothesis 1: Given previous research demonstrating the association of headache and sleep symptoms with memory performance (Guty & Arnett, 2018), we predict that headache and sleep symptoms in this sample of chronically concussed athletes will be associated with worse memory performance.

Specific Aim 2: Examine the distinct relationship between each of the different post-concussion symptom factors (Cognitive, Physical, Affect, Sleep, and Headache) and attention/executive functioning performance.

Hypothesis 2: We also predict that headache will be related to worse performance in attention/executive functioning, based on previous research (Guty & Arnett, 2018).

Method

Participants

The sample includes 42 student-athletes from the same Division I university. The data for this study were previously collected between February and April of 2015 for research on the effect of Enzogenol Supplementation for treatment of chronic concussion (Walter et al., 2017). Data were collected both pre- and post-treatment and half of this sample was randomized to receive treatment and the other half was not. However, the present study examines only the pre-treatment data from all 42 participants who had experienced a sport-related concussion and were in the chronic phase of injury (ranging from six months to three years post-injury - additional information can be found in Table 4). These individuals had been previously diagnosed with an acute concussion by the University's sports medicine staff and were referred to the study due to ongoing complaints of symptoms following their injury. Individuals were included for their persistent symptoms following their concussion. Following analyses of outliers (flagged by SPSS as falling outside 1.5xInterquartile Range [IQR] for their performance on the cognitive outcome measure), 2 individuals were removed from specific analyses. The remaining 40 participants included 20 men and 20 women. The mean age of the participants was 19.88 years (SD = 1.18) with a range from 18 to 22 years old. See Table 4 for participant demographic information. Participants in this sample were screened to ensure no previous diagnoses of (a) spinal cord injury, (b) developmental disorder (ADHD/Learning Disability), (c) psychiatric disorder, or (d) neurological disorder.

Measures

The participants completed a battery of neuropsychological tests that assessed various domains of cognitive functioning including memory, executive functioning, attention, and processing speed. The participants also completed questionnaires assessing their symptomatology following their concussion. The neuropsychological battery for this study consisted of the Affective Word List: Total Immediate and Delay Recall (Meyer & Arnett, 2015), Brief Visuospatial Memory Test-Revised: Total Immediate and Delay Recall (BVMT-R; Benedict, 1997), the Symbol-Digit Modalities Test: Total Score and Incidental Memory (SDMT; Smith, 1991), a modified Digit Span Test: Forward and Backward (Wechsler, 1997), the PSU Cancellation Test (Echemendia & Julian, 2001), and the Stroop Color-Word Test: Time 1 and Time 2 (Trenerry et al., 1989). A self-report questionnaire, the Beck Depression Inventory-Fast Screen, was used to assess depression symptoms (Beck et al., 2000).

Participants also completed the Post-Concussion Symptom Scale (PCSS), rating their current, in-the-moment experience of 22 common post-concussion symptoms. The PCSS consists of a list of symptoms and prompts examinees to rate each on a scale of 0 (None) to 6 (Severe) how much they are experiencing that symptom “right now” (Lovell et al., 2006). This questionnaire was given both pre- and post- testing, but the analyses in this paper only examined the report of pre-testing symptoms. We aimed to restrict the focus to individuals who reported more symptoms as they might occur typically, rather than those that could occur following intense mental exertion. Some participants were missing certain cognitive measures and thus, in some analyses, there were fewer participants included due to missing data.

Procedures

Participants were diagnosed by the medical staff at a large Division I university, and then referred to the study due to their unresolved concussion symptoms. Participants were administered the neuropsychological measures, as well as the background information and neurobehavioral questionnaires. The neuropsychological tests were administered by clinical psychology graduate students and undergraduate research assistants, all under the supervision of a doctoral level clinical neuropsychologist. This study was approved by the University’s Institutional Review Board and informed consent was collected from all participants.

Approach to Data Analysis

All analyses were conducted with the Statistical Package for the Social Sciences (SPSS), Version 24.0 (IBM Corp, 2017).

Preliminary Analyses

The aim of this study was to examine the relationship between specific post-concussion symptoms in the chronic phase of concussion and neuropsychological outcomes. Previous research using factor analysis has shown that the items on the PCSS load onto four main factors: Cognitive, Physical, Affective, and Sleep (Merritt & Arnett, 2014; Guty & Arnett, 2018). New variables were created using the sum of the participants' scores from the questions that comprise the various symptom factors. Each symptom is rated on a scale of 0 (not experiencing that symptom) to 6 (experiencing that symptom severely). Therefore, higher values on these factor variables can indicate either a greater number of individual symptoms or greater severity for each type of symptom factor (See Table 5). Given the evidence that headache is an important symptom following concussion, and because it did not load on any of the other factors, it was also examined in the same manner as other symptom factors in line with the model of five factors from Guty and Arnett (2018).

In order to determine the best approach for analyzing the data, the PCSS factor variables were checked for skewness. All of the distributions were positively skewed. Because of this, each factor variable, the headache variable, and the total PCSS score were log transformed. The log transformations reduced the skewness of the variables so that they could be explored with parametric statistical analyses.

The neurocognitive variables were converted from raw scores to standard scores (M = 100, SD = 15) using sex-specific means and standard deviations from a large normative sample of college athletes at baseline (Merritt et al., 2017). The main neurocognitive outcome variables were composite scores created by averaging these standard scores. The memory composite was created by averaging the standard scores of the memory test indices (BVMT-R Total and Delayed Recall, AWL Total and Delayed Recall, SDMT Incidental Memory). The SDMT incidental memory is administered immediately after the SDMT is completed, and the participant is asked to fill in the missing numbers to their paired symbols from memory (Patel et al., 2018).

The attention/executive functioning composite was created by averaging the standard scores of the attention/executive functioning test indices (SDMT Total, Digits Forward and Backward, Stroop Time 1 and Time 2, and PSU Cancellation Total). See Table 6 for the means and standard deviations of neurocognitive composites.

Multiple covariates were also considered for these analyses including the number of previous head injuries, sex, depression scores, and months since injury. Bivariate correlations were conducted between each of these potential predictor variables and the two cognitive outcome measures. In order to preserve the degrees freedom in our relatively small sample for the regression analyses, only variables that were significantly correlated with the cognitive outcomes were included.

Bivariate correlations were conducted to examine the relationship between all of the symptom factors and overall symptom reporting (See Table 7 for the correlation matrix). Generally, each of the individual symptom factors were significantly correlated ($p < .05$) with one another and with the total symptom score. However, sleep and the affective cluster were not significantly correlated with the headache factor, and the headache factor had the weakest relationship with the total symptom score. While it is intuitive that there would be correlations between many of the symptom factors, given that the relationships are not one-to-one and that headache appears to be more distinct, there is empirical justification for exploring the factors and headache individually in the primary analyses.

Specific Aim 1 & 2. A stepwise multiple linear regression was conducted to examine the relationship between each of the five symptom factors (headache, physical, sleep, affective, and cognitive) and the memory composite. A second stepwise multiple linear regression was conducted to examine the relationship between the five symptoms factors and the attention/executive functioning composite.

Results

Covariate Analyses. Number of previous head injuries, sex, and depression scores were not significantly correlated ($p < .05$) with any of the cognitive outcome measures. Time since injury (in months) was significantly correlated with the memory composite ($r = -.38$, $p = .023$), such that individuals who had been experiencing their symptoms for a longer time demonstrated poorer cognitive performance. Time since injury was not significantly correlated with the attention/executive functioning composite. Given these results, time since injury was included at step 1 of the regression analyses only for the memory composite.

Specific Aim 1. In the model including time since injury at step 1, and the five symptom factors at step 2, we found that time since injury was significantly related to memory performance such that longer time since injury was related to worse memory performance ($F\ (1, 31) = 5.67$, $\beta = -.38$, $p = .023$), accounting for 14.7% of the variance. However, after accounting for time since injury, none of the symptom factors at step 2 significantly predicted performance on the memory composite (See Table 8a).

Specific Aim 2. In the model including all symptom factors at step 1 predicting the attention/executive functioning composite, only headache emerged as a significant predictor of worse performance ($F\ (1, 31) = 7.95$, $\beta = -.42$, $p = .008$), accounting for 18% of the variance (See Table 8b). Of note, inclusion of the two aforementioned outliers in the analyses did not significantly change either of these main findings.

Discussion

Results and Contributions from the Current Study

Both symptoms and cognitive dysfunction are common outcomes following SRC that can affect an individual's daily functioning, length of recovery, and return to play decisions. Recently, research has begun to explore how more specific types of symptoms may be related to different outcomes following SRC. However, much of this research has focused on individuals in the acute phase of concussion and little research has examined the minority of individuals who experience more chronic symptoms. The current study focused on how specific kinds of SRC symptoms could be differentially related to neuropsychological performance in a sample of individuals in the chronic phase of SRC.

When each of the five factors were examined in relation to specific domains of cognitive performance, two discrete patterns emerged. Time since injury was significantly related to memory performance, over and above the influence of the five symptom factors, with worse cognitive performance being associated with longer time since injury. For attention/executive functioning, headache emerged as the only significant symptom factor, with greater headache symptoms significantly related to worse performance. The finding regarding headache is similar to what was found in a prior study of more acutely concussed individuals who were tested within two weeks of their injury (Guty & Arnett, 2018).

This observed relationship between headache following injury and cognitive functioning in athletes in the chronic phase of SRC has also been demonstrated in other literature. In a study of pediatric patients with traumatic brain injury who were assessed on average 7 months following injury, individuals who reported post-traumatic headache showed significantly lower performance on various measures of attention and executive functioning (McConnell et al., 2020). A review of adult patients with post-traumatic headache showed decreased performance on various neuropsychological tests including measures of verbal fluency, processing speed, attention, and cognitive flexibility (Martelli et al., 1999). There is additional evidence from neuroimaging studies regarding the relationship between post-traumatic headache and functional and structural brain changes such as functional connectivity, cerebral blood flood, and white matter integrity that suggest possible underlying mechanisms for the observed cognitive impairments (Branca, 2006; Schwedt, 2019).

Our results also showed that longer time since injury predicted worse memory performance. Interestingly, this effect is the inverse of what is typically observed in acute concussions samples, where cognitive performance improves with greater time since injury due to the recovery process. The results of this study suggest that the cumulative effect of experiencing long-standing symptoms may impact cognitive functioning, specifically memory, in chronically concussed individuals. One possible underlying mechanism could be that individuals who have had these symptoms for a longer period of time are also characterized by other psychological factors that might explain this relationship. While we were able to determine that depression symptoms were unrelated to the cognitive outcomes in the sample, we did not assess anxiety or history of mental health issues, which may also play a role. Given that a recent systematic review found that preinjury mental health issues were a risk factor for persistent symptoms, it is possible that psychological factors are contributing to this relationship (Iverson et al., 2017). Alternatively, some individuals experience somatization, and mood dysfunction presents as various physical symptoms, and this could provide some explanation for these chronically concussed individuals' long-standing symptoms and memory dysfunction. However, attention/executive functioning was more sensitive to the effects of post-concussion headache rather than time since injury. This may reflect that the current, ongoing experience of post-concussion headache has a greater impact on an individual's ability to focus and process information rapidly in the moment.

Limitations

One limitation of the current study is the relatively smaller sample size. However, this research is an examination of a unique population (the small subset of individuals whose symptoms persist long after the typical window of recovery for SRC) that is infrequently studied compared to individuals with acute concussion. Given that findings from individuals with acute concussion symptoms cannot be assumed to be the same in individuals with chronic symptoms, this is an important population to study. These results will need to be replicated in larger, more diverse samples, but our findings provide important information which is critical for the appropriate care of chronically concussed athletes. These results should be generalizable to athletes at a Division I university who are experiencing chronic concussion symptoms, although the sample in this study consisted of mostly white individuals. As such, further research should focus on replicating these findings with individuals of under-represented minority groups to ensure greater generalizability.

Another limitation was that the study's current sample size precluded a meaningful factor analysis to justify the neurocognitive composites. However, factor analyses have been conducted in a large sample of collegiate athletes who were tested in the acute phase of concussion and these tests loaded adequately onto each of their respective composites (Guty & Arnett, 2018). While there is literature to support the importance of headache with regard to cognitive functioning following acute SRC, there is also evidence that post-traumatic migraine may be an even stronger predictor of cognitive functioning deficits (Kontos et al., 2013; Mihalik et al., 2005). Unfortunately, data on post-traumatic migraine was not collected as part of our study, but future work should also consider the inclusion of a more detailed headache measure and migraine measure. Additionally, while sideline symptoms have been shown to predict prolonged recovery, these data were not collected for this sample and thus could not be explored in this study.

Conclusions

While many studies have examined predictors of prolonged recovery, our study specifically examined factors that may predict cognitive deficits in individuals who are currently experiencing prolonged recovery. Like work examining symptom predictors of cognitive outcomes in acutely concussed samples (Guty & Arnett, 2018), greater headache symptomology was related to worse attention/executive functioning. Unique to the chronically concussed sample is that longer length of time that one is symptomatic since injury predicted worse memory functioning. Tests that comprise the cognitive composites in this study are commonly used neuropsychological tests which are utilized clinically to make determinations of an individual's cognitive functioning. Individuals who are referred for neuropsychological testing and demonstrate lower performance (greater than a standard deviation below the mean) on these tests often report difficulties focusing in conversations, feeling forgetful, and difficulties organizing their thoughts. These issues would be particularly relevant to student-athletes who might be vulnerable to impairment in both their classes and social functioning. There has been some research indicating that individuals with acute concussion experience academic difficulties (Wasserman et al., 2016), and it is possible that these effects are exacerbated or prolonged in individuals with chronic concussion symptoms.

Future research should attempt to replicate these findings in a larger, more diverse sample, and this could be achieved through a multi-site study through various colleges' sport medicine departments collaborating together. Expanding the current study should also include the examination of other potential factors that could be contributing to these observed relationships between time since injury and cognitive functioning, such as anxiety, somatization, or cumulative effects on the brain. Additionally, given the role of post-traumatic headache in cognitive functioning, treatments focused on headache could prove to be beneficial, and longitudinal studies on how treatment of headache affects cognitive performance would be clinically relevant. Understanding more about the factors that contribute to lower cognitive functioning in individuals with chronic concussion could provide useful information for points of intervention for this unique population of student-athletes.

Table 4. Injury and Demographic Variables

Variables	Mean	SD	Range
Age	19.88	1.18	18-22
Months since injury	21.14	8.51	6-36
PCSS Total Score	9.05	10.57	0-51
Variables	N	%	
Sex	40	100	
Male	20	50	
Female	20	50	
Ethnicity	40	100	
Caucasian	33	82.5	
African American	1	2.5	
Asian American	2	5	
Biracial/Multiracial	2	5	
Other	1	2.5	
No answer	1	2.5	
Sport	40	100	
Soccer	9	22.5	
Football	4	1	
Lacrosse	2	5	
Basketball	3	7.5	
Wrestling	1	2.5	
Rugby	3	7.5	
Other	18	45	

Table 5. Symptom Factors

Factors	Factor 1: Cognitive	Factor 2: Physical	Factor 3: Affective	Factor 4: Sleep	Headache
Items in each factor	Feeling slowed down Feeling Mentally foggy Difficulty concentrating Difficulty remembering	Nausea Vomiting Balance Problems Dizziness Sensitivity to light Sensitivity to noise	Irritability Sadness Nervousness Feeling more emotional	Fatigue Trouble falling asleep Sleeping more/less than usual Drowsiness	Headache
Range:	0-13	0 – 11	0 – 21	0 – 12	0 – 4
Mean:	1.78	1.08	2.1	2.91	.38
SD:	2.60	2.22	4.47	2.91	.774

Table 2. The symptoms from the PCSS for each factor and headache are listed and the range of scores that participants reported are noted in the bottom row. Table adapted from Merritt, V. C., & Arnett, P. A. (2014). Premorbid predictors of postconcussion symptoms in collegiate athletes. Journal of Clinical & Experimental Neuropsychology, 36(10), 1098–1111; Table 5, p. 1105.

Table 6. Neurocognitive Composites

	M	SD	Range
Memory Composite	98.66	10.55	77.37 – 118.83
Attention/Executive Functioning Composite	99.09	6.52	82.90 – 111.20

Table 7. Symptom Factor Correlation Matrix

	Physical	Sleep	Affective	Cognitive	Headache	Total
Physical	1					
Sleep	.272	1				
Affective	.318*	.486**	1			
Cognitive	.410**	.474**	.545**	1		
Headache	.379**	.026	.156	.269	1	
Total	.586**	.793**	.670**	.800**	.333*	1

Table 4. Correlation matrix for symptom factors and total symptom score (given the distribution of the data Spearman's ρ was used rather than Pearson's r).
*Spearman's ρ correlation significant $p < .05$.
** Spearman's ρ correlation significant $p < .01$.

Table 8a. Regression Examining Predictors of Memory Performance

Model Summary	Adj R^2	Δr^2	ΔF	p-level
Step 1: Time Since Injury	.12	.15	5.61	.024*
Step 2: Symptom Factors - Physical - Sleep - Affective - Cognitive - Headache				
Coefficients		β	t	p-level
Time Since Injury		-.38	-2.37	.024*
Excluded Variables		β	t	p-level
Physical		-.11	-.66	.513
Sleep		.13	.81	.422
Affective		.07	.44	.664
Cognitive		-.10	-.65	.523
Headache		-.29	-1.83	.077`

*Significant at $p < .05$; `Marginally significant at $p < .10$

Table 8b. Regression Examining Predictors of Attention/Executive Functioning Performance

Model Summary	Adj R^2	Δr^2	ΔF	p-level
Step 1: Symptom Factors - Physical - Sleep - Affective - Cognitive - Headache	.15	.18	7.95	.008**
Coefficients		β	t	p-level
Headache		-.43	-2.82	.008**
Excluded Variables		β	t	p-level
Physical		-.19	-1.11	.274
Sleep		-.23	-1.55	.130
Affective		-.21	-1.37	.181
Cognitive		-.29	-1.84	.075`

**Significant at $p < .01$; `Marginally significant at $p < .10$

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Curriculum Vitae

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<u>Education</u>

The Pennsylvania State University, State College, PA — 2017-Present
Ph.D. Candidate, Clinical Psychology
Advisor: Peter Arnett, Ph.D.
Dissertation Title: Risk and Protective Factors Influencing Outcomes and Recovery in Sports-Related Concussion

The Pennsylvania State University, State College, PA — 2015-2017
Master of Science, Clinical Psychology
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Thesis Title: Relationship Between Post-Concussion Symptom Factors and Neuropsychological Outcomes in Collegiate Athletes

Princeton University, Princeton, New Jersey — June 2013
Bachelor of Arts, Psychology, Neuroscience Minor
Advisor: Daniel N. Osherson, Ph.D.
Senior Thesis: Examining Possible Practice Effects in the ImPACT Neuropsychological Test

<u>Selected Honors and Awards</u>

Wisniewski Family Enhancement Fund ($500), The Pennsylvania State University — 2021
Research and Graduate Studies Office Dissertation Award ($10,000), The Pennsylvania State University — 2020
Ellen V. Piers Award ($3300), The Pennsylvania State University — 2019
The Graduate Exhibition, First Place in Social and Behavioral Sciences ($500), The Pennsylvania State University — 2018

<u>Selected Publications</u>

1. Guty, E., Riegler, K., Meyer, J., & Arnett, P.A. (2020). Symptom Factors and Neuropsychological Performance in Collegiate Athletes with Chronic Concussion. Archives of Clinical Neuropsychology.
2. Riegler, K., Guty, E., Thomas, G., & Arnett, P.A. (2020). Sleep Deprived or Concussed? The Impact of Insufficient Sleep in College Athletes. Journal of the International Neuropsychological Society.
3. Riegler, K.E., Guty, E., & Arnett, P.A. (2019). Neuropsychological Test Performance in Depressed and Non-Depressed Collegiate Athletes. Neuropsychology, 34(1), 63–76.
4. Cadden, M.H., Guty, E.T., & Arnett, P.A. (2018). Cognitive Reserve Attenuates the Effect of Disability on Depression in Multiple Sclerosis. Archives of Clinical Neuropsychology, 34, 495-502.
5. Guty, E. & Arnett, P.A. (2018). Post-Concussion Symptom Factors and Neuropsychological Outcomes in Collegiate Athletes. Journal of the International Neuropsychological Society, 24, 684–692.