PREDICTORS OF OUTCOME DURING SUB-ACUTE RECOVERY FROM MILD TRAUMATIC BRAIN INJURY

By

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To my grandfather who taught me the keys to success: compassion, humor, & garlic

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LIST OF ABBREVIATIONS

ACRM	American Congress of Rehabilitation Medicine
ADHD	Attention-deficit/hyperactivity disorder
BDI-II	Beck Depression Inventory, 2nd Edition
CT	Computed tomography
DMN	Default mode network
Dx	Diagnosis
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
EEG	Electroencephalogram
fMRI	Functional magnetic resonance imaging
Hx	History
LD	Learning disorder
LOC	Loss of consciousness
MRI	Magnetic resonance imaging
mTBI	Mild traumatic brain injury
NCATS	National Center for Advancing Translational Sciences
NIH	National Institute of Health
PCS	Post-concussion syndrome
PTA	Post-traumatic amnesia
REDCap	Research Electronic Data Capture
S3SE	SCAT-3 Symptom Evaluation
SCAT-3	Sport Concussion Assessment Tool, 3rd Edition
STAI	State-Trait Anxiety Inventory
TBI	Traumatic brain injury
UFSHCC	University of Florida Student Health Care Center
WHO	World Health Organization

Abstract of Thesis Presented to the Graduate School
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Researchers have successfully identified several predictors of patient outcome following mild traumatic brain injury (mTBI). However, the lack of evidence-based post-injury interventions and assessment of recovery for mTBI leaves many health care providers unsure of how to most effectively manage their patient's care. The current study evaluates relationships between demographic, injury characteristics, and prior medical history variables that have been identified as risk factors for protracted recovery following mTBI. Data of 25 participants diagnosed with concussion/mTBI within the prior 14-25 days were retrospectively withdrawn form a larger clinical trial. Symptoms were quantified using the Sport Concussion Assessment Tool, 3rd Edition Symptom Evaluation, Beck Depression Inventory, Second Edition, and the State-Trait Anxiety Inventory which were administered at two time points; approximately M=15.2 (SD=3.5) days post-injury and again M=29 (SD=5.3) days post-injury. Hierarchical regression modeling bootstrapped for 1,000 95% bias-corrected and accelerated bootstrapped parameter estimates were used to assess the relationship between the predictors and symptom outcome. Results indicate that sex and injury characteristics such as loss of consciousness weakly predict symptom outcome. However, pre-existing medical history may serve as a

promising prediction tool for symptoms of depression and anxiety during sub-acute recovery from mTBI in a non-elite athlete, university population. Such findings suggest the need to further investigate predictors of recovery, to establish extended models of support for post-mTBI patient care, to evaluate mood symptoms in the aftermath of concussion, and to implement risk-assessment to identify patients who might develop more protracted post-injury symptoms and thus benefit from intervention.

CHAPTER 1
INTRODUCTION

Once an expected consequence of any contact sport, “getting your bell rung” has assumed a new status in the modern American consciousness: “epidemic” (Langlois, Rutland-Brown, & Wald, 2006; Prevention & Control, 2003). Concussions have risen to the top of news headlines prompting nationwide legislation, securing self-titled dramatization in theatres, and increasingly becoming a point of discussion at both the layman’s dinner table and international scientific conferences.

The increasing exposure to, and awareness of, concussions in the public sphere has resulted in an increase in the demand for concussion-related medical care in both primary and specialty care settings (Bakhos, Lockhart, Myers, & Linakis, 2010; Daneshvar, Nowinski, McKee, & Cantu, 2011; Gibson, Herring, Kutcher, & Broglio, 2015). In response, medical communities have created and disseminated evidence-based diagnostic and treatment methods to improve care and fill the concussion “knowledge gap” (Bires, Leonard, & Thurber, 2017; Stoller et al., 2014). This gap is made more complicated by the complex, multifaceted nature of mild traumatic brain injury (mTBI) which contributes to the widespread inconsistency of concussion definitions, diagnostic criteria, and research outcomes (Carroll et al., 2004; Chan, Thurairajah, & Colantonio, 2015; Frémont, 2016).

In an effort to develop consensus within the clinical and scientific communities, and enhance patient care, task forces such as the International Conference on Concussion in Sport and The World Health Organization (WHO) Task Force have formed (Carroll et al., 2004; McCrory et al., 2012; McKay & Velikonja, 2016). The Zurich Conference created one of the most highly recognized and referenced definitions of concussion (McKay & Velikonja, 2016). Conceptualized as a traumatically-induced complex pathophysiological process affecting the brain, (McCrory et al., 2013) concussions produce heterogeneous symptoms and recovery trajectories in multiple domains such as cognition, somatic symptoms, sleep functioning, mood, behavior, vestibular function, and physical signs (McCrory et al., 2013). The WHO Task Force further defined the boundaries of mTBI favoring the definition developed by the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (Carroll et al., 2004).

Though the majority of patients who sustain a single concussive event are expected to recover pre-concussion neurocognitive and symptomatic function in approximately 7-14 days (Belanger & Vanderploeg, 2005; McCrory et al., 2013), some individuals display persisting problems, and predicting individual outcome is often difficult. An estimated 10-15% of individuals experience protracted recoveries (>10 days), the majority of which will eventually recover within three months after injury (Alexander, 1995; Binder, Rohling, & Larrabee, 1997; Ponsford et al., 2000). However, a smaller but sizeable percentage of individuals, who researchers have described as the "miserable minority," remain symptomatic for several weeks, months, and sometimes years following their injury (Bigler, 2008; McCrory et al., 2013).

Predictors of Outcome

The development of tools that can predict clinical recovery from mTBI is considered a high priority for future research as no validated practical tool yet exists (Kristman et al., 2014; Zemek et al., 2016). This has become particularly relevant as medical providers seek methods that will enable the identification of those most in need of intervention. Without prognosticators or clear guidance, many medical providers often prescribe highly conservative management methods to avoid symptom exacerbation. However, such methods are largely based on clinical folklore or customary practice preferences. For example, the overuse of such strategies as “cocooning” or “total rest” may actually hinder recovery and produce new problems of their own (Thomas, Apps, Hoffmann, McCrea, & Hammeke, 2015).

Because of this, researchers have sought to identify variables that predict recovery following mTBI. Several factors have been identified through prospective studies, as described below:

Sex

Though several animal studies have demonstrated that females show better recovery from TBI than their male counterparts (Bazarian, Blyth, Mookerjee, He, & McDermott, 2010), the data in human females has been less convincing. Within both adult and pediatric populations, female sex has demonstrated an increased risk for protracted recovery and increased symptom reporting.(Babcock et al., 2013; McNally et al., 2013; Meares et al., 2011; Sharp & Jenkins, 2015; Tator et al., 2016) with the minority of results suggesting otherwise in NCAA athletes (Zuckerman et al., 2016). There are several explanations for longer recovery times in females than in males. Regarding psychological factors, Harmon and colleagues suggest that females are simply more likely to report symptoms (Harmon et al., 2013), and thus continue to report problems long after the males have ceased to do so. Biologically, differences in endogenous levels of progesterone and estrogen have been posited to predict recovery, with better outcomes presenting in post-menopausal and pre-menarche females (Bazarian et al., 2010) as well as during the luteal phase of menstruation when progesterone levels are increased (Wunderle, Hoeger, Wasserman, & Bazarian, 2014). Others have hypothesized that the reduced size and musculature of the neck in females decreases the ability to stabilize the head, increasing the acceleration-deceleration component of injury “head-neck segment peak, angular acceleration, and displacement” and risk of rotational damage (Dvorak, McCrory, & Kirkendall, 2007; Tierney, 2005) .

Prior Medical History

Pre-existing history of concussion

Concern about the potential long-term consequences of recurrent concussion exposure is one of the most potent driving forces in the rise of concussion awareness. Abnormal accumulation of p-tau in the depth of the cortical sulci suggests a harmful neuropathological consequence for individuals with a history of repeated brain trauma (McKee et al., 2016). However, very little is known about the pathological processes that give rise to neurodegeneration after repetitive concussions, and caution should be exercised in attributing mechanism solely to repetitive head injury (Asken et al., 2016).

There is a lack of unanimous agreement regarding whether prior history of concussion predicts protracted recovery. While some researchers have argued that pre-existing concussion is associated with protracted recovery (Zemek, Farion, Sampson, & McGahern, 2013; Harmon et al., 2013, Zuckerman et al., 2016; Morgan et al., 2015), others have not found this effect (McCrea et al., 2013). One reason for this disagreement is that some studies have attempted to predict recovery using the number of prior concussions, while others have used dichotomous measures (i.e., presence v. absence of prior history). One question that remains unanswered is whether recovery is different after two closely-spaced concussions (e.g. two concussions separated by days-weeks) than it is when the second concussion is separated from the first by a longer time duration (months-years). Due to the complex cerebral pathophysiological process that follows concussion (described below) and the window of vulnerability that follows, the time interval between successive concussion events may affect recovery trajectory (Prins, Alexander, Giza, & Hovda, 2013; Vagnozzi et al., 2008). Despite this, such data are rarely reported within these studies.

Following mTBI, a cascade of neurometabolic and physiological changes of the brain occurs (referred to as the "neurometabolic cascade of concussion"), lowering the threshold for subsequent injury (Giza & Hovda, 2001). If a second subconcussive or concussive blow is sustained during this vulnerable metabolic window, the brain may be unable to accommodate the additional demands leading to increased neuronal death, risk of seizure activity, and neurobehavioral deficits (Giza & Hovda, 2001; MacFarlane & Glenn, 2015). Revealed by specialized neurodiagnostic testing, this vulnerable window for insult generally extends beyond the point at which symptoms resolve and may persist for periods up to a year; creating a false sense of recovery as the individual returns to activity (MacFarlane & Glenn, 2015).

Pre-existing history of mood disorder

Pre-existing history of anxiety and/or depression has been found in the majority of studies to predict protracted recovery in both pediatric and adult populations (Ponsford et al., 2012; Morgan et al., 2015; Emery et al., 2016; Meares et al., 2011), though some studies have not found this effect (Eisenberg, Andrea, Meehan, & Mannix, 2013). In those individuals with pre-existing mood disorder, it might be argued that post-injury mood symptoms represent simple continuation of the disorder. However, Gould and colleagues found that development of novel mood disorder post-TBI occurs frequently (Gould, Ponsford, Johnston, & Schönberger, 2011).

Pre-existing history of Attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder (ADHD) is a relatively common neurodevelopmental disorder that is hypothesized to reduce the brain's tolerance to neurological insult (Mautner, Sussman, Axtman, Al-Farsi, & Al-Adawi, 2015). Children with ADHD have a higher probability of sustaining head injuries than their neurotypical counterparts, and they experience increased disability post-mTBI (Bonfield, Lam, Lin, & Greene, 2013; Owens, Goldfine, Evangelista, Hoza, & Kaiser, 2007). Because of this, many studies have explicitly excluded ADHD participants, and as a result, we know less than we could about their post-mTBI presentation and recovery trajectory (Yeates, 2010). However, many studies that have included injured participants with a prior history of ADHD have reported that a positive history increases the risk of protracted recovery after mTBI (Gessel, Collins, & Dick, 2007; Kimberly G Harmon et al., 2013; Mautner et al., 2015; Zemek, 2013) as have not (Asplund et al., 2004; Eisenberg et al., 2013; Lau, Collins, & Lovell, 2011).

Pre-existing history of migraine

Prior medical history of migraine is recognized by the 2012 Zurich Convention as a modifier of concussion (McCrory et al., 2012). Study results are mixed regarding whether history of migraine predicts prolonged recovery from concussion. Several studies of pediatric and adult samples have confirmed its significance (Kuczynski, Crawford, Bodell, Dewey, & Barlow, 2013; Sharp & Jenkins, 2015;Hoffman et al., 2011; K. G. Harmon et al., 2013), while some studies of pediatric samples have not (Eisenberg et al., 2013); (Morgan et al., 2015). However, a family history of migraine has been found to predict prolonged post-concussive symptoms in the absence of personal history which may suggest some degree of heritability (Morgan et al. 2015, Kuczynski, 2013).

Injury Characteristics

Loss of consciousness (Bakhos et al.,2010) after concussion represents acute brain dysfunction attributed to changes in ionic concentrations, metabolic activity, and cerebral blood flow termed “spreading depression” (Giza & Hovda, 2001; McKay & Velikonja, 2016). Importantly, LOC is not required for a diagnosis of concussion (Harmon et al., 2013). Within military and athletic populations, the presence of LOC has been associated with a protracted course of symptom expression (Asplund, McKeag, & Olsen, 2004; Wilk, Herrell, Wynn, Riviere, & Hoge, 2012) and when combined with blast injury, is associated with a greater likelihood of white matter abnormalities on MRI (Hayes, Miller, Lafleche, Salat, & Verfaellie, 2015). LOC lasting longer than 60 seconds is considered by neurologic evaluation standards as a more serious injury; its presence triggers the use of neuroimaging protocols (McKay & Velikonja, 2016). In contrast, some studies of athletic and non-athletic populations suggest that the presence of LOC does not necessarily signal a more significant injury and does not strongly predict outcome after concussion (Silverberg et al., 2015; Standaert, Herring, & Cantu, 2007; Zuckerman et al., 2016). It remains unclear whether the presence, versus the duration, of LOC is the most important predictive variable. In prevailing definitions of concussion, LOC (if present) is by definition less than 30 minutes and is frequently much shorter (Harmon et al., 2013).

The Current Study

The current study seeks to determine demographic, injury, and medical history characteristics of university students during sub-acute recovery from mTBI and their relationship with self-reported symptoms of concussion-related sequelae, anxiety, and depression at approximately 14 days and 30 days after injury. Individuals who report three or more symptoms at these time points are thought to reflect protracted and persistent postconcussional syndrome, respectively. We selected predictors based on the foregoing review and chose clinically-validated questionnaires to evaluate self-reported symptoms. The population of interest, college students who are not elite athletes, is underrepresented in a literature dominated by mostly pediatric and elite athletic populations. As the data suggests that non-sport-related mTBI populations recover more slowly than do their athletic counterparts, and that the collegiate lifestyle has unique health implications, investigation of this sub-population is warranted.

The current study seeks to identify predictors of outcome in this sub-population to better inform patient care and ultimately decrease recovery time via early identification and intervention of at-risk patients.

Specific Aims

Aim 1

To determine demographic, injury, and pre-existing medical history characteristics of participants post-mTBI and their relationship with concussion-related, anxiety, and depressive symptom report as measured by the Sport Concussion Assessment Tool, Third Edition Symptom Evaluation (S3SE), State-Trait Anxiety Inventory (STAI), and Beck Depression Inventory, Second Edition (BDI-II) at 14-25days post-injury.

Hypothesis 2

In line with the literature, demographic factors such as sex, and existence of pre-existing medical history in the form of ADHD, migraine, mood disorder, and/or history of concussion will predict increased symptom reporting upon the S3SE, BDI-II, and STAI at Pre-Intervention. However, LOC will fail to predict symptom reporting across any of the self-report measures.

Aim 2

Investigate the relationship between demographic factors such as sex, and positive existence of pre-existing medical history (i.e., ADHD, migraine, mood disorder, history of concussion) in predicting symptom change in self-report measures of concussion-related symptoms (S3SE), depression (BDI-II), and anxiety (STAI) from approximately 14days post-injury to 30days post-injury.

Hypothesis 2

In line with Hypothesis 2, demographic factors such as sex and pre-existing medical history in the form of ADHD, migraine, mood disorder, and/or history of concussion will predict change scores in S3SE, BDI-II, and STAI between the two time points. However, LOC will not predict symptom change across the two time points.

Table 1-1. American Congress of Rehabilitation Medicine definition of mild traumatic brain injury

"A patient with mild traumatic brain injury is a person who has had a traumatically induced physiological disruption of brain function as manifested by"	
At least one of the following:	Where severity does not exceed:
• Any period of loss of consciousness • Any peri-injury amnesia • Any injury-acute change in mental state • Focal neurological deficits that may or may not be transient	• Loss of consciousness <30 minutes • 30 minutes post-injury, Glasgow Coma Scale =13-15 • Post-traumatic amnesia < 24 hours

**Note.* CT, MRI, EEG, or routine neurological evaluation may be normal.

CHAPTER 2
METHODS

Procedure

Participant data were extracted from the University of Florida prospective controlled clinical trial “The Effect of Exercise on Neurorecovery Following Mild Traumatic Brain Injury”.

Participant Recruitment

Prospective participants diagnosed with mTBI per the American Congress of Rehabilitation Medicine Guidelines (Mild Traumatic Brain Injury Committee, 1993; see Table 1-1.) were recruited from the University of Florida Student Health Care Center (UFSHCC), UFSHCC Sports Concussion Center, and UFHealth Emergency Department in Gainesville, Florida between 2015 and 2016. Ninety-two patients interested in the study were referred by their diagnosing physician to an on site research study staff member. The study staff obtained the prospective participant’s consent to be contacted using an IRB-approved form, which collected their name, telephone number, and/or email address.

Participant Eligibility

Study staff contacted prospective participants via phone and/or email using the patient-provided consent to be contacted information. Of the 92 candidates for whom consent to be contacted was obtained, 31 were lost to follow-up as they were unable to be reached. Those contacted (N=61) were administered a brief eligibility screening via telephone (see Table 2-1. for eligibility criteria). Of the sample, four individuals failed to meet inclusion criteria; three stating that they had not sustained a concussion, one having sustained a severe TBI. Three individuals did not meet the study’s exclusion criteria; two due to pre-existing medical conditions and one due to lacerations sustained during their injury that prevented their participation in aerobic activity. Fifty-three individuals underwent eligibility screening and met inclusion and exclusion criteria. However, due to the fact that the study required weekend on-campus participation, 23 individuals declined to participate due to reported scheduling conflicts (e.g., football game conflict, social events, etc.). One additional individual declined to participate as they did not have regular transportation available to them. Thirty participants met study inclusion and exclusion criteria, agreed verbally to participate, and were scheduled for an initial appointment in which final eligibility and consent to participate would be administered by one of the study's research coordinators. Of these 20, one prospective participant failed to show to their first appointment citing scheduling conflicts, two participants were removed after failing to attend their second and third appointments, and one participant was discontinued by the study Safety Monitor due to exacerbation of symptoms because of injury-related soft tissue damage. The complete eligibility flow diagram is presented at the end of the chapter within Figure 2-1.

Study Design

The first (Pre-Intervention) appointment was scheduled 14-25 days post-injury (*M*=15.2, *SD*=3.5) in line with the literature which estimates that the majority of patients will recover within 7-14 days post-concussion (Belanger & Vanderploeg, 2005; McCrory et al., 2013). Following completion of the informed consent protocol, participants were administered measures assessing demographic information, concussion-related symptoms, symptoms of depression, and symptoms of anxiety via REDCap-administered questionnaire. Participants were then scheduled to attend daily exercise sessions for a period of one week at the Clinical Research Center with trained study staff. Following this seven-day exercise intervention, participants were scheduled for their Post-Intervention appointment approximately 30 days after injury (*M*=29.0 days post-injury, *SD*=5.3), in which they were again assessed using the same measures of concussion-related symptoms, symptoms of depression, and symptoms of anxiety which were administered at the Pre-Intervention appointment. An overview of the study's measurement timeline and design may be viewed in Figure 2-2.

Measures

Demographic Questionnaire

A demographic questionnaire was administered via REDCap, assessing the participant's age, sex, date of injury, education, and Race/Ethnicity. Presence of LOC in addition to pre-existing medical history of ADHD, concussion, mood disorder (i.e., depression or anxiety), and migraine were also obtained.

Sport Concussion Assessment Tool, 3rd Edition Symptom Evaluation (S3SE)

The Sport Concussion Assessment Tool, 3rd Edition Symptom Evaluation (S3SE) is a 22-item (Guskiewicz et al., 2013) self-report questionnaire measuring the presence (i.e., Symptom Score) and severity of symptoms (i.e., Symptom Severity) following a concussion. The S3SE assesses multiple domains of common post-concussion symptoms including somatic, sleep, mood, and physical signs which it measures using a six-point Likert scale. Psychometrics suggest high specificity (0.91-1.0), moderate to high sensitivity (0.64-0.89), and moderately high to high reliability (0.88-0.94) (Guskiewicz et al., 2013). The S3SE is approved for use in individuals above the age of 12 and is available for free use by medical providers via the British Journal of Sports Medicine (McCrory et al., 2013).

Beck Depression Inventory, Second Edition (BDI-II)

The Beck Depression Inventory, second edition (BDI-II) is a psychometrically-validated self-report measure of depressive symptomology that is frequently used in clinical populations. Developed to map onto the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) diagnostic criteria for depressive disorders, the BDI-II surveys several symptoms of depression (i.e., sadness, pessimism, past failure, loss of pleasure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts or wishes, crying, agitation, loss of interest, indecisiveness, worthlessness, loss of energy, changes in sleeping pattern, irritability, changes in appetite, concentration difficulty, tiredness or fatigue, and loss of interest in sex) over the span of a two week period and is appropriate for use in individuals over the age of 13. Higher scores indicate greater depression severity (Beck, Steer, & Brown, 1996). Nonclinical sample coefficient alpha estimates of reliability is 0.93 and it demonstrates moderately high concurrent validity with other validated depression rating scales (Beck et al., 1996). The BDI-II utilizes four cut scores of minimal (0-13), mild (14-19), moderate (20-28), and severe (29-63) to demonstrate depression severity. However, their use in nonclinical populations in which the rate of major depressive disorder is lower, is not advised (Meehl & Rosen, 1955).

State-Trait Anxiety Inventory (STAI)

The State-Trait Anxiety Inventory (STAI) is a psychometrically validated self-report questionnaire of current and enduring anxious symptomology frequently used in clinical settings with higher scores representing greater anxiety. Comprised of two scales, the State Anxiety Scale assesses feelings of anxiety which increase with temporal danger and stress. The Trait Anxiety scale evaluates long-standing anxiety and is effective in non-clinical populations to screen for anxiety problems. The STAI is written at a sixth-grade reading level and is appropriate for use in individuals between the ages of 14-69. The STAI demonstrates moderately-high to high internal consistency, moderate to moderately-high test-retest reliability coefficients, as well as adequate construct and concurrent validity (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983).

Analysis Plan

Descriptive Statistics

Descriptive statistics for participant sample characteristics are presented in Table 2-2. Twenty-five participants were ultimately included in the current analyses. Participants were 48% female and ranged in age from 18-32 (M=21, SD=3.3) with educational attainment ranging from 12-20 years (M=14.5, SD=2.1). Regarding Race/Ethnicity, 68% of the participants identified as White or Caucasian, 20% as Hispanic or Latino, 8% as African American or Black, and 4% as Pacific Islander or Native Hawaiian. Regarding prior medial history, 8% reported migraines, 4% reported ADHD, 76% concussion, and 12% mood disorder. Injury characteristic of LOC following their most recent concussion was present in 36% of the sample.

Analyses

Data were analyzed using the IBM SPSS Statistics 24.0 statistical software. Effect-size indices of 0.1, 0.3, and 0.5 are defined as small, medium, and large effects, respectively (**Cohen, 1992**). Individuals were considered "symptomatic" if they reported three or more symptoms upon the S3SE Symptom Evaluation at Pre-Intervention in line with ICD-10 diagnostic criteria for postconcussional syndrome (World Health Organization, 1992). Those who were symptomatic were assigned a dummy-coded value of "1," while those who were not symptomatic were coded as "0." Injury characteristics, and pre-existing injury characteristics were dichotomized in a similar fashion in which individuals who reported the presence of a characteristic were assigned a value of "1," and those that denied the presence of a specific characteristic were assigned a value of "0" for that specific variable. Symptom report as measured by the BDI-II and STAI remained continuous, reflecting their raw and standard scores, respectively.

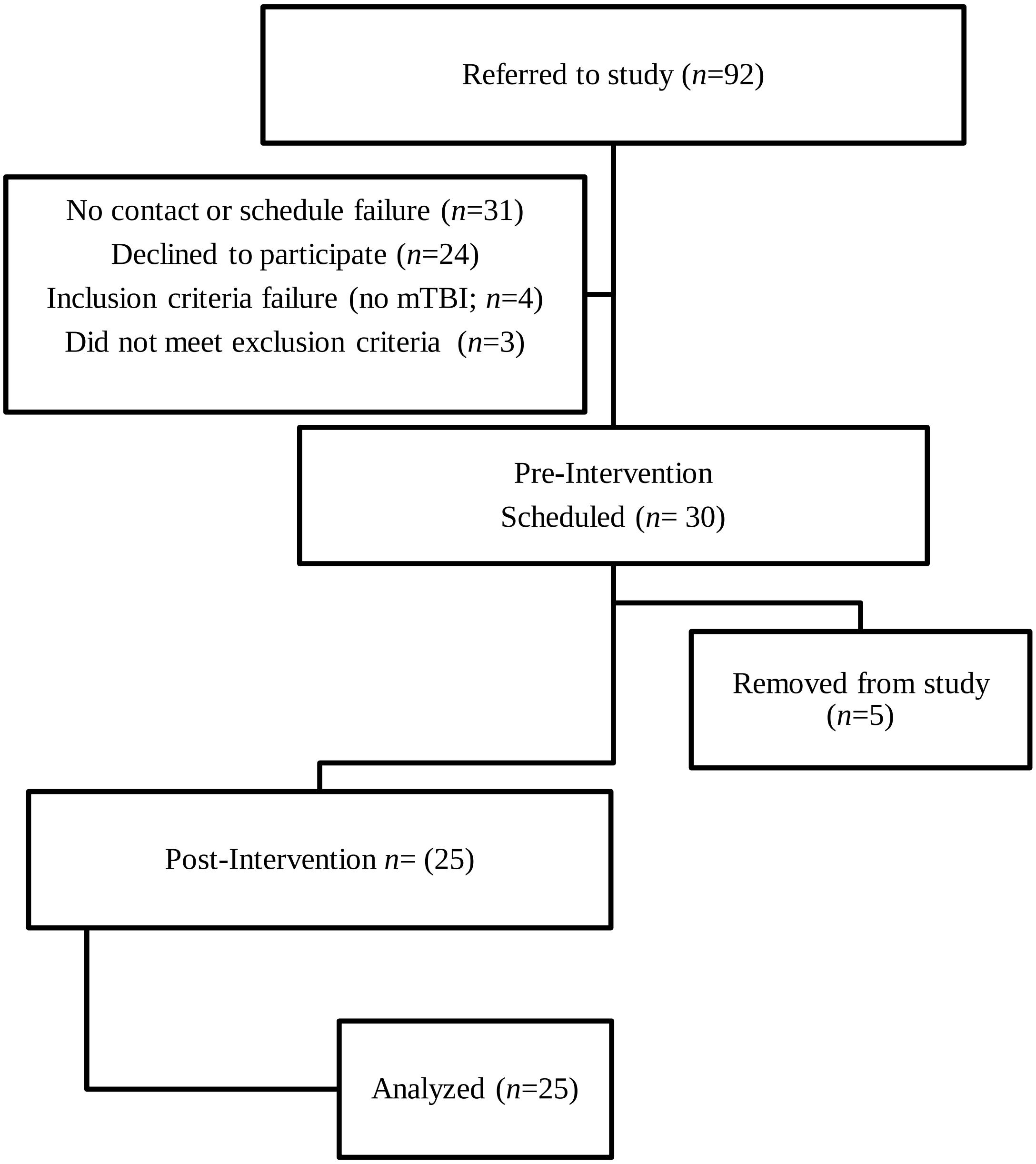


Figure 2-1. Eligibility flow diagram

mTBI incurred	Eligibility assessed	Informed consent obtained	**Pre-intervention assessment**	One week exercise intervention	**Post-intervention assessment**
			M=15.2 (*SD*=3.5) days post-injury		*M*=29.0 (*SD*=5.3) days post-injury
			Demographics		X
			BDI-II		BDI-II
			S3SE		S3SE
			STAI		STAI

Figure 2-2. Overview of study design and measures administered

Table 2-1. Participant eligibility criteria

Inclusion criteria	Exclusion criteria
• Diagnosed mTBI per American Congress of Rehabilitative Medicine • mTBI sustained in past 14-25 days • Aged 18-40 • Speak English	• Comorbid orthopedic injury that inhibits movement • History of psychiatric hospitalization • Diabetes • History of moderate-severe TBI • Neurological disorder unrelated to TBI • Physician recommends against exercise • Non-neurological explanation for symptoms

Table 2-2. Sample characteristics

Age in years *M*(*SD*)	21 (3.3)
Education	14.5 (2.1)
Gender *n* (%)	
Male	13 (52)
Female	12 (48)
Race/Ethnicity *n* (%)	
White/Caucasian	16 (68)
Hispanic/Latin American	5(20)
Black/African American	3 (8)
Pacific Islander/ Native Hawaiian	1(4)
Predictor *n*(%)	
Female	12(48)
History of migraine	2 (8)
History of ADHD	1(4)
History of concussion	19 (76)
History of mood disorder	3(12)
Loss of consciousness	9 (36)

***Note*.** (*N*=25)

CHAPTER 3
RESULTS

Aim 1: To Determine Demographic, Injury, and Pre-existing Medical History Characteristics of Participants Post-mTBI and Their Relationship with S3SE, STAI, and BDI-II Symptom Report at Pre-Intervention

Pre-Intervention Characteristics

One quarter of the population was symptomatic at Pre-Intervention (*N*=5). The average age of the symptomatic sample was within one standard deviation of the entire group (*M*=20, *SD*=1.41), and was composed of mostly White/Caucasian individuals (*N*=4). Regarding injury characteristics, two of the participants reported LOC at the time of injury. In regards to pre-injury characteristics, 100% of the sample reported a prior history of concussion, 20% a prior history of mood disorder, 20% a prior history of migraines, and none of the symptomatic population reported a history of ADHD. Sixty percent of the sample was male (*N*=3). The number of symptoms reported upon the S3SE ranged from four to twenty (*M*=11.40, *SD*=6.47) with symptom severity ranging from four to forty-eight (*M*=21.40, *SD*=16.99). Regarding symptoms of depression, symptomatic participants reported symptom scores of 7-16 (*M*=10, *SD*=3.54) upon the BDI-II, which in a clinical population would range from “minimal” to “mild” depressive symptomology. Regarding State and Trait anxiety, participants reported anxiety within normal limits ranging from a T-score of 41-60 (*M*=52.4, *SD*=7.83) and 45-68 (*M*=57.6, *SD*=8.47), respectively.

In contrast, 75% of the sample were not symptomatic (i.e., individuals who reported less than three symptoms). The non-symptomatic sample at Pre-Intervention ranged in age from 18-32 (*M*=21.65, *SD*=3.61), and were 65% White/Caucasian, 20% Hispanic/Latin American, 10% African American/Black, and 5% Native Hawaiian/ Pacific Islander. Regarding injury characteristics, seven of the participants reported LOC at the time of injury. In regards to pre-injury characteristics, 70% of the sample reported a prior history of concussion, 20% a prior history of mood disorder, 10% a prior history of migraines, and 5% a history of ADHD. Fifty percent of the sample was male. Number of symptoms reported upon the S3SE ranged from zero to two (*M*=0.65 *SD*=0.88) with 60% percent of the non-symptomatic participants reporting zero symptoms. Symptom severity for the non-symptomatic sample also ranged from zero to two with identical mean and standard deviation (*M*=0.65 *SD*=0.88). Regarding symptoms of depression, non-symptomatic participants reported symptom scores of 0-47 (*M*=9, *SD*=11.64) upon the BDI-II, which in a clinical population would range from "minimal" to "severe" depressive symptomology. Regarding State and Trait anxiety, participants reported anxiety ranging from a T-score of 34-76 (*M*=45.85, *SD*=11.32) and 34-82 (*M*=47.45, *SD*=10.04), respectively suggesting what should be interpreted cautiously as reaching into the "clinically-elevated" range.

Predicting Pre-Intervention symptom report

A three stage hierarchical multiple regression with 1,000 95% bias-corrected and accelerated bootstrapped parameter estimates were used to assess the predictive power of sex, pre-existing medical history, and the injury characteristic LOC to predict the dependent variables: symptomatic classification, concussion-related symptoms, depressive symptoms, and anxiety symptoms as measured by the S3SE Symptom Severity and Symptom Score, BDI-II, and STAI State and Trait at Pre-Intervention for all participants. The robust method of bootstrapping was utilized due to the non-normal distribution of the current dataset. The variables were assembled within each block by order of support within the literature; sex within the first block, pre-existing medical history in the second block, and the injury characteristic LOC in the third block. Assumption of non-collinear independent variables was met; *VIF* values were well below

10 and tolerance statistics were greater than 0.2 (**Field, 2013**). Tables 3-1, 3-2, 3-3, 3-4, 3-5, and 3-6 depict the predictors, their associated steps, and the resulting regression statistics.

Symptomatic classification hierarchical logistic regression model. Results suggested that having a prior history of concussion or migraine predicted whether a participant would be symptomatic at pre-intervention with medium effect sizes. Prior history of mood predicted symptomatic classification whereas absence of ADHD predicted symptomatic classification with medium effect size. Sex and presence of LOC appeared to explain minimal variance in whether an individual was classified as symptomatic (Table 3-1).

STAI-State hierarchical regression model. Results suggested that having a prior medical history of ADHD was associated with heightened self-report of current anxiety with a large positive magnitude of effect (β= .58). Having a prior history of concussion also predicted heightened current self-report of anxiety, with a medium positive magnitude of effect (β= .29). Being male, history of migraine, and history mood disorder also all showed relationships suggestive of increased symptom report, however with small-medium magnitudes of effect. LOC appeared to contribute very little to the model and did not predict increased State anxiety self-report. Of note, sex as a predictor fails to explain much variance in the model until the addition of the medical history variables in Block 2. Together, all 6 predictors explained 63% of the variance in STAI-State symptom report. Results are presented at the end of the chapter in Table 3-2.

STAI-Trait hierarchical regression model. Regarding self-reported Trait or enduring anxiety, results suggested that having a prior medical history of migraine was associated with lower self-report of enduring anxiety with a large negative magnitude of effect (β= -.83). Having a prior history of a mood disorder had the opposite impact resulting in over a one standard deviation (15.88 point) higher STAI-Trait score, with a large effect size of (β=.51). History of concussion, history of ADHD, and being male predicted heightened self-report of trait anxiety, with medium-large, small-medium, and small-medium positive magnitudes of effect, respectively. Again, LOC appeared to contribute little to the model with an effect size of 0. Of note, similar to Trait anxiety report, sex as a predictor failed to explain much variance in the model until the addition of the medical history variables in Block 2. Likewise, having a prior history of migraine appears to explain little of the model until LOC was added in Block 3. Together, all 6 predictors explained 65 % of the variance in STAI- Trait symptom report (Table 3-3).

BDI-II hierarchical regression model. Results revealed (Table 3-4.) that having a prior medical ADHD exerted a large positive magnitude of effect, predicting heightened self-report of depressive symptoms. Both having a prior history of concussion and experiencing LOC following mTBI suggested a small-medium magnitude of effect, predicting higher self-report of depressive symptoms as well. History of migraine, history of mood disorder, and sex appeared to explain minimal variance in self-report depression symptoms. Together, all 6 predictors explained 65.4% of the variance in BDI-II symptom report.

S3SE-Symptom Score hierarchical regression model. Results revealed (Tables 3-5) weaker effect sizes, with a prior history of ADHD predicting lower S3SE symptom scores (medium effect size, β= -.31) magnitude decreased symptoms reported. History of concussion and history of mood disorder demonstrated small-medium positive magnitudes of effect, and LOC represented a small positive magnitude of effect. Neither sex nor history of migraine appeared to contribute much variance to the model. Overall, the model explained 17.5% of the variance in Symptom Score.

S3SE-Symptom Severity hierarchical regression model. Results revealed (Table 3-6) small-medium effect sizes for being female, having a prior history of concussion, history of mood disorder, history of ADHD, and LOC. With the exception of history of ADHD, all predicted higher symptom severity scores. A prior history of ADHD was associated with lower reported Symptom Severity scores. Prior history of migraine appeared to contribute little to the model. Overall, the model explained 16% of the variance in Symptom Severity.

Post-intervention characteristics

Sixteen percent of the population (*N*=4) were symptomatic at Post-Intervention. However, of the five participants that were symptomatic at Pre-intervention, only three remained symptomatic at Post-Intervention. The average age of the Post-intervention symptomatic sample was also within one standard deviation of the entire group (*M*=19.75, *SD*=1.50), and was 50% White/Caucasian, 25% African American/Black, and 25% Hispanic. Regarding pre-existing medical history, 100% of the sample reported a prior history of concussion but denied a prior history of mood disorder. One individual reported a prior history of migraine, and again none of the symptomatic population reported a history of ADHD. Seventy-five percent of the sample was male. Number of symptoms reported upon the S3SE ranged from three to five (*M*=3.50 *SD*=1.00) with symptom severity ranging from three to seven (*M*=4.50 *SD*=1.91). Regarding symptoms of depression, symptomatic participants reported symptom scores of 2-27 (*M*=12, *SD*=10.68) upon the BDI-II, which in a clinical population would range from “minimal” to “moderate” depressive symptomology. Regarding State and Trait anxiety, participants reported anxiety within normal limits ranging from a T-score of 37-60(*M*=51.00, *SD*=10.80) and 38-56 (*M*=48.25, *SD*=8.73), respectively.

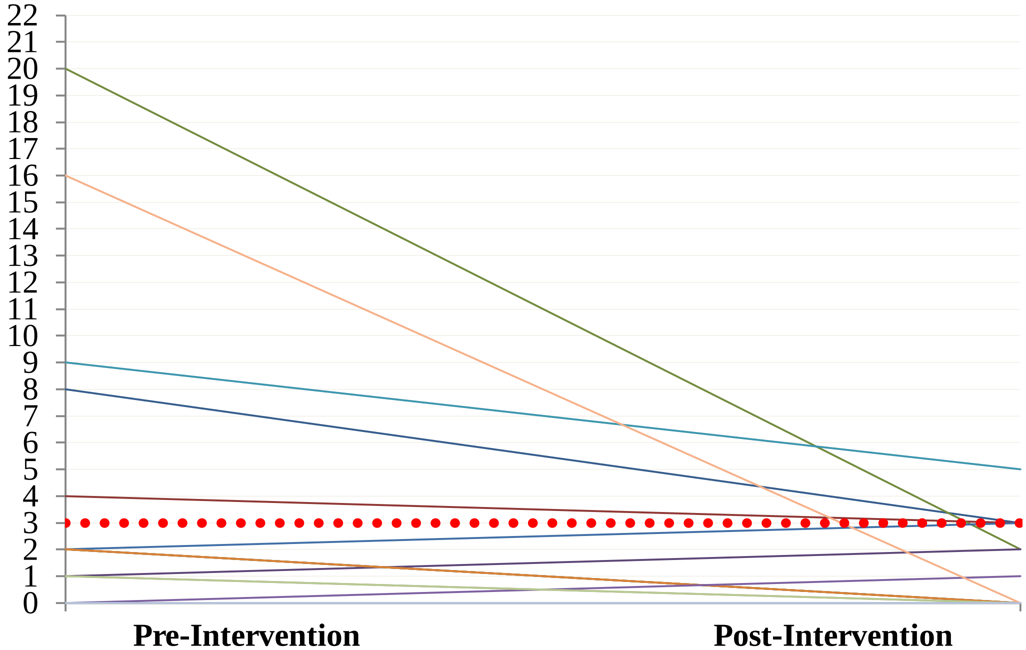
In contrast, 84% of the sample was asymptomatic (i.e., reported less than three symptoms) at Post-Intervention. The non-symptomatic sample ranged in age from 18-32

(*M*=21.62, *SD*=3.53), and was 71.4% White/Caucasian, 19% Hispanic, 4.8% African American, and 4.8% Native Hawaiian/ Pacific Islander. Regarding injury characteristics, eight of the participants reported LOC at the time of injury. In regards to pre-injury characteristics, 15 of the participants reported a prior history of concussion, three a prior history of mood disorder, one a prior history of migraines, and one a history of ADHD. Fifty-two percent of the sample was female. Number of symptoms reported upon the S3SE ranged from zero to two (*M*=0.24 *SD*=0.62) with 85.7% percent of the non-symptomatic participants reporting no symptoms. Symptom severity for the non-symptomatic sample also ranged from zero to two (*M*=0.29 *SD*=0.72). Figure 3-1 depicts S3SE Symptom Score report from each participant from Pre-Intervention to Post-Intervention. Regarding symptoms of depression, non-symptomatic participants reported symptom scores of 0-28 (*M*=6.42, *SD*=8.38) on the BDI-II, which in a clinical population would range from "minimal" to "moderate" depressive symptomology. Regarding State and Trait anxiety, participants reported anxiety ranging from a T-score of 34-69 (*M*=43.67, *SD*=9.80) and 34-71 (*M*=45.86, *SD*=11.47), respectively.

Aim 2: Investigate the Relationship Between Injury Characteristics, Pre-existing Medical History, and Sex and Symptom Change in Measures of Depression, Anxiety, and Concussion-related Symptoms

To address Aim Two, Analysis of Covariance (ANCOVA) was utilized to create residual gain scores (change from Pre-Intervention to Post-Intervention, corrected for Pre-Intervention values) with 1,000 95% Bias-corrected and accelerated bootstrapped estimates to provide robust methods to counter violations to normality. Covariate by outcome interactions were not significant, suggesting that the assumption of homogeneity of regression slopes had been met. Levels of the covariate did not appear to be significantly different across time points. Levene's test was non-significant, suggesting homogeneity of variance. To predict the role of injury characteristics (i.e., LOC), pre-existing medical history of concussion, mood disorder, ADHD, and /or migraine, sex, and symptomatic classification at Pre-Intervention upon the change in depression, anxiety, and concussion-related symptom report, Post-Intervention symptom reports were treated as the dependent variable with Pre-Intervention symptom report treated as a covariate.

Regarding change in outcome between Pre-Intervention and Post-Intervention, being classified as symptomatic at 14-25days post-injury did not differentially predict change in reported depression or anxiety. Prior history of migraine differentially predicted pre-post change in STAI-Trait anxiety symptoms with a small-medium magnitude of effect. Prior history of migraine predicted less pre-post change in anxiety than seen in those without prior history. Small-medium effect sizes were noted for the predictive role of prior concussion on pre-post change in state anxiety and S3SE Symptom Score. Similarly, history of ADHD predicted less pre-post change in Symptom Severity score with a small-medium effect size. Neither LOC nor sex appeared to explain a notable amount of variance across symptom change in of the described domains.



**Note:* Red dotted line represents symptomatic cut point of three or more reported symptoms upon the S3SE.

Figure 3-1. S3SE symptom report at Pre-Intervention and Post-Intervention

Table 3-1. Linear logistic model of predictors of symptomatic classification at Pre-Intervention, with standard errors based on 1000 bootstrap samples

Variable	*b*	SE *B*	**β**	*p*	**Δ*R*²**
Step 1					
Sex	-0.06	0.16	-.08	.690	
					.01
Step 2					
Sex	-0.04	0.18	-.05	.837	
History of concussion	0.30	0.17	.32	.103	
History of mood disorder	0.25	0.41	.21	.679	.20
History of migraine	0.42	0.34	.29	.240	
History of ADHD	-0.05	0.39	-.25	.456	
Step 6					
Sex	-0.04	0.20	-.05	.844	
History of concussion	0.30	0.18	.32	.120	
History of mood disorder	0.26	0.43	.21	.670	.00
History of migraine	0.42	0.35	.28	.278	
History of ADHD	-0.5	0.39	-.25	.471	
Loss of Consciousness	-0.02	0.22	-.02	.959	

Table 3-2. Linear model of predictors of STAI-State symptom report at Pre-Intervention, with standard errors based on 1000 bootstrap samples

Variable	b	SE B	**β**	p	**Δ***R*^{2}
Step 1					.01
Sex	1.30	4.39	.06	.768	
Step 2					.63
Sex	5.40	2.95	.25	.094	
History of concussion	7.33	2.68	.29	.015	
History of mood disorder	6.94	7.87	.21	.543	
History of migraine	8.40	3.43	.21	.010	
History of ADHD	31.5	7.54	.58	.002	
Step 6					.00
Sex	5.43	3.28	.25	.107	
History of concussion	7.28	3.01	.29	.023	
History of mood disorder	6.67	8.12	.20	.561	
History of migraine	8.52	3.88	.22	.034	
History of ADHD	31.50	7.54	.58	.002	
Loss of Consciousness	0.43	4.07	.02	.924	

Table 3-3. Linear model of predictors of STAI-Trait symptom report at Pre-Intervention, with standard errors based on 1000 bootstrap samples

Variable	b	SE B	**β**	p	**Δ**R^2
Step 1					0.00
Sex	-1.08	4.1	-.05	.790	
Step 2					0.65
Sex	3.72	2.92	.18	.212	
History of concussion	8.84	3.01	.37	.006	
History of mood disorder	15.84	4.07	.50	.004	
History of migraine	-3.01	2.59	-.08	.208	
History of ADHD	12.5	3.50	.24	.002	
Step 6					
Sex	3.72	3.12	.18	.239	
History of concussion	8.85	3.18	.37	.008	0.00
History of mood disorder	15.88	5.17	.51	.010	
History of migraine	-3.12	2.88	-.83	.265	
History of ADHD	12.5	7.54	.24	.002	
Loss of Consciousness	-0.07	4.00	.00	.986	

Table 3-4. Linear model of predictors of BDI-II symptom report at Pre-Intervention, with standard errors based on 1000 bootstrap samples

Variable	b	SE B	**β**	p	**Δ**R^2
Step 1					0.01
Sex	-2.15	3.49	-.11	.636	
Step 2					0.62
Sex	1.13	3.21	.06	.683	
History of concussion	5.82	2.76	.24	.052	
History of mood disorder	1.27	2.97	.04	.708	
History of migraine	2.11	3.97	-.06	.545	
History of ADHD	37.5	1.19	.72	.002	
Step 6					
Sex	1.38	3.10	.07	.639	
History of concussion	5.32	2.56	.22	.061	0.03
History of mood disorder	-1.36	4.92	-.04	.805	
History of migraine	3.24	3.76	.09	.357	
History of ADHD	37.50	1.19	.72	.002	
Loss of Consciousness	4.13	4.97	.19	.450	

Table 3-5. Linear model of predictors of S3SE Symptom Score report at Pre-Intervention, with standard errors based on 1000 bootstrap samples

Variable	b	SE B	**β**	p	**Δ***R*^{2}
Step 1					0.00
Sex	-0.1	2.12	-.01	.962	
Step 2					0.16
Sex	0.52	2.01	.05	.813	
History of concussion	2.97	1.32	.25	.113	
History of mood disorder	5.09	6.30	.33	.586	
History of migraine	0.82	1.20	.04	.504	
History of ADHD	-8.00	6.22	-.31	.444	
Step 6					0.01
Sex	1.38	2.22	.07	.840	
History of concussion	5.32	1.35	.22	.121	
History of mood disorder	-1.36	7.26	-.04	.695	
History of migraine	3.24	1.33	.09	.358	
History of ADHD	37.50	6.22	.72	.469	
Loss of Consciousness	4.13	3.75	.19	.759	

Table 3-6. Linear model of predictors of S3SE Symptom Severity report at Pre-Intervention, with standard errors based on 1000 bootstrap samples

Variable	b	SE B	**β**	p	**Δ***R*^{2}
Step 1					0.01
Sex	2.47	4.52	.12	.632	
Step 2					0.11
Sex	3.62	4.25	.17	.474	
History of concussion	5.20	3.07	.21	.223	
History of mood disorder	8.69	9.69	.26	.518	
History of migraine	-0.52	2.52	-.01	.789	
History of ADHD	-12.5	9.54	-.23	.357	
Step 6					0.04
Sex	3.93	4.63	.18	.491	
History of concussion	4.67	2.86	.18	.200	
History of mood disorder	5.37	12.53	.16	.768	
History of migraine	0.90	2.81	.02	.689	
History of ADHD	-12.5	9.54	-.23	.384	
Loss of Consciousness	5.21	8.76	.23	.626	

Table 3-7. Residualized change scores between Pre-Intervention and Post-Intervention symptom report, with standard errors based on 1000 bootstrap samples

	BDI-II		STAI-State		STAI-Trait		S3SE-SxSc		S3SE SxS	
Variable	*p*	*b*	*p*	*b*	*p*	*b*	*p*	*b*	*p*	*b*
Symptomatic at Pre-Int.	.360	3.58	.265	-4.83	.410	-1.49	.037	-3.67	.001	-4.15
Sex	.211	3.36	.306	3.63	.882	0.175	.219	0.65	.418	0.57
History of Concussion	.158	-2.85	.056	-7.09	.929	0.206	.102	-0.68	.129	-0.93
History of Mood	.428	-8.58	.181	-14.38	.388	-2.31	.430	0.85	.684	0.61
History of Migraine	.851	0.65	.003	12.08	.081	2.54	.553	-0.84	.634	-0.76
History of ADHD	.462	7.56	.625	-3.16	.301	2.72	.141	-0.60	.073	-1.43
Loss of consciousness	.198	-5.42	.242	-5.77	.778	-0.40	.526	0.43	.469	0.69

***Note*.** Pre-Int. = Pre-Intervention

CHAPTER 4
DISCUSSION

Predictors of Symptom Report in Sub-acute Recovery From mTBI

The current study investigated the role of predictors of protracted recovery that had been identified in the literature on subacute recovery after mTBI. Overall, results suggest that having a prior medical history of ADHD increases risk of heightened reporting of anxiety and depression 15 days after injury, and is more likely to be seen in individuals who remain symptomatic at that point in time. The relationship between prior history of ADHD and report of anxiety and depression after concussion is likely multifactorial. Even in the absence of mTBI, ADHD shows strong comorbidity with mood disorders, and there is strong data to suggest some degree of developmental frontal/executive dysfunction in this population (American Psychiatric Association, 2013). When a patient with pre-existing ADHD is further exposed to neurological insult (Carroll et al., 2004), it is not surprising that positive signs of anxiety and depressive symptoms would be found. However, this "vulnerability" hypothesis would also predict that prior history of ADHD would also predict the kinds of post-concussion symptoms measured by the S3SE. It is unclear why the magnitude of effect in S3SE was not larger; one factor may be the relatively mild injuries suffered by study participants. It may be that the anxiety and depression symptoms are being primarily driven by psychosocial factors related to injury-related lifestyle disruption, while the S3SE symptoms are driven primarily by injury severity. Since most prior studies have excluded participants with prior ADHD, more research is needed to better understand these findings.

Pre-existing history of mood disorders also emerged as significant predictors of both State and Trait anxiety, explaining an impressive 34.4% of the variance in Trait anxiety. One unanticipated finding was that a self-reported pre-existing history of mood disorders did not predict post-injury report of depressive symptoms. Limitations in study design prevent us from further deconstructing this predictive relationship in terms of the severity or chronicity of pre-existing mood disturbance or with regard to whether the participant's mood symptoms would meet diagnostic criteria for a current depressive episode. Furthermore, use of anxiolytic or antidepressant medication was not assessed, so it is not known whether, in some participants, current features of mood disturbance were attenuated pharmacologically. Clinically, the same medications typically used for the treatment of anxiety and depression in a non-TBI population are identical to those used for treatment of post-concussive syndrome so this a potential confound of treatment. Future studies should address these issues more directly.

Finally, a prior history of concussion was a positive predictor of post-injury Trait anxiety, which reflects likely mood dysregulation that stands as one of the strongest predictors of postconcussional syndrome at 14-25 days. Having a prior history of concussion positively predicted the frequency and severity of symptoms reported , though this effect was not statistically significant with the small sample size of this study. However, as mentioned in the introduction, there are multiple methodological differences that might account for this inconsistency.

Notably, our sample was dummy coded "0" and "1" to represent a lack of prior concussion or a history of prior concussion, respectively. There is evidence to suggest that using a continuous measure may better predict outcome and impairment (Guskiewicz, 2003). Furthermore, our study does not account for the interval between prior and current concussions in those with a positive concussion history. As the literature suggests that temporally contiguous concussions may increase neuropathological and neurobehavioral consequences, recent presence of a prior concussion could complicate their presentation (Vagnozzi et al., 2008). A final possibility is that our small sample size lacked power to detect a significant effect.

Regarding change, only prior history of migraines differentially predicted change in STAI-Trait anxiety symptoms between pre- and post-intervention measurement points. Contrary to expectations, results showed that individuals with a prior history of migraine reported significantly <u>less</u> anxiety than their counterparts who did not report a history of migraines. Small-medium effect sizes were noted for tests that evaluated the ability of prior history of concussion to predict changes in state anxiety change and S3SE Symptom Score. Similarly small effect sizes were seen for the ability of ADHD history to predict pre-post change in Symptom Severity Score.. One limiting factor is that this study addressed only the first month of recovery. Though ICD-10 criteria suggests that a specific constellation of symptoms past 30 days is considered abnormal, many studies suggest that symptom resolution, especially in a non-athletic population, may have longer recovery times. As such, future research with this population would likely benefit from evaluating symptomatic recovery over a longer time range.

Previous literature has provided a significant amount of support for female sex as being a predictive factor of protracted outcome in women of child-bearing age. Our results were not in line with this. Also of note, many studies fail to use standardized measures of symptom report (Zemek et al., 2016). Based on our results, it appears that the standardized measures used for assessment of depressive and anxious symptomology (BDI-II and STAI) were more sensitive at detecting subclinical mood-related symptomology. Though the S3SE does screen for mood-related symptoms, it does not do so with as much specificity as the BDI-II and STAI as represented in the current study. The S3SE is used widely in practice and has demonstrated its validity and reliability in detecting concussive symptoms (Guskiewicz, 2013). However, medical providers may be encouraged on the basis of this data to supplement their mTBI evaluation with a standardized measure of mood, particularly for those at risk for experiencing protracted outcome or mood symptomology beyond those individuals whom are considered asymptomatic following mTBI.

Clinical Application

This study attempted to provide initial data on ability of validated, practical, empirically-based tools to predict post-injury mood, cognitive, and symptom status in an mTBI population. Because broad awareness of concussion has emerged only recently, there is a general need not only to develop validated risk assessment tools, but also to develop individualized intervention pathways based on assessment results. In practice, many un-validated, pseudoscientific, and potentially harmful approaches (e.g., long term cocooning) obscure the picture with respect to expected recovery trajectories(Zemek et al., 2016; Zemek, 2013) . Because of this, there is a need for “objective, sensitive, and specific metrics and markers of concussion diagnosis, prognosis, and recovery” (Collins et al., 2016). The data from the current study adds to the body of literature in the underrepresented non-athletic collegiate population. Research indicates that athletic, non-athletic, and military populations recover differentially from mTBI, prompting the need for more specific data collection (Youth, 2013). Though collegiate populations make up a large proportion of research samples due to their proximity and availability to University-based researchers, data assessing non-athletic mTBI in a collegiate population is rather scant. The collegiate population itself is regarded as an at-risk group not only for mTBI, but also for the development of depression with estimates rising yearly (Collins et al., 2016). Of those university students diagnosed with depression, less than 25% of them were receiving treatment for their condition (American College Health Association, 2009; Buchanan, 2012). As such, students presenting with mTBI with untreated mood disorder may particularly benefit from early identification and extended follow-up so as to increase their awareness of, and enrollment in, appropriate interventions for mTBI and mood-related symptoms.

By recognizing the importance of pre-existing health factors, medical providers viewing the patient at both acute and sub-acute point of recovery may be more inclined to recommend early intervention, repeat follow-up, and make referrals for specialized care (e.g., psychotherapeutic therapy, neurology, etc.) for individuals at risk for persistent symptoms. If this became standard practice, it could shorten recovery and could prevent some patients from beginning on a complicated, protracted recovery trajectory (American College Health Association, 2009).

Study Limitations and Future Directions

There are several limitations to this study. The current analysis of recovery predictors would benefit from a larger and more diverse sample. Since the data were taken from an small clinical trial investigating the safety and tolerability of aerobic exercise during sub-acute recovery from mTBI, selection bias may further limit generalizability as individuals within the study had to receive physician clearance to participate, were capable of attending and scheduling several appointments (e.g., access to transportation, planning, motivation) resulting in an arguably less severely injured and possibly higher SES population. The study also collected data from only the Gainesville, Florida area and was comprised of largely university students. However, this also serves as strength of the study, since the majority of research performed in this segment of the population involves student athletes who, due to their elite status and support systems, are likely to have different recovery patterns when compared to non-athletes.

Regarding future directions, further analyses are ongoing as the study has collected follow-up data or each participant three months after their initial date of injury. This third Time period will allow for further assessment of participant outcome at a point which has been recognized as distinguishing chronic sequelae (Bigler, 2008). Additionally, all participants underwent repeated high-resolution MRI, and future investigation of the predictive value of these variables on brain-based functionality and structural integrity via analyses of associated regions is underway.

Conclusion

The current study serves to add to the standing literature of predictors of mTBI recovery. As the existing body of literature has variable results, future research utilizing consistent methodological technique in diverse populations is needed. Though standardization in a clinical setting is necessary before overall clinical utility can be determined, preliminary data may aid medical providers in utilizing a more tailored bio-psycho-social model in their assessment and treatment of mTBI (Collins et al., 2016). Such recommendations might include more in-depth assessment of depression and anxiety in mTBI populations, particularly of those with a prior history of ADHD, mood disorder, or concussion. Though current concussion check-lists do assess mood briefly, they may lack the ability to detect clinically relevant anxiety and depression in this population.

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BIOGRAPHICAL SKETCH

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