The Influence of ADHD on Concussion in NCAA College Athletes

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THE INFLUENCE OF ADHD ON CONCUSSION IN NCAA COLLEGE ATHLETES

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CHAPTER 1: INTRODUCTION

Concussion, a type of brain injury, has risen to the forefront of sports medicine research. An estimated 1.6 to 3.8 million sport and recreation concussion-related injuries occur annually in the United States\(^1\). This complex and often controversial injury has generated significant discourse regarding player safety and the rules by which sports are regulated. The National Football League and National Collegiate Athletics Association (NCAA) have attempted to protect players by implementing rule changes (e.g., penalties for targeting, helmet to helmet contact, etc.) and a concussion protocol, in which athletes are removed from play and evaluated following a suspected concussion. Since 2012 the NFL Foundation has dedicated nearly $500 million toward safety initiatives and research\(^2\), and the NCAA - Department of Defense (NCAA-DOD) Grand Alliance Concussion Assessment, Research and Education (CARE) Consortium has allocated over $50 million to produce research on concussion risks, treatment and management by studying how concussions evolve over time\(^3,4\). Collectively, these events reflect the immediate need to increase our awareness and understanding of the factors that influence concussion.

Concussion is the result of a biomechanical force to the head or body resulting in neurometabolic impairments which manifest in varying degrees of symptom severity. The most common symptoms following concussion are balance disturbances, headache, dizziness, fatigue, sleep disturbances, light and/or sound sensitivity, cognitive impairment, and mood disturbances\(^5\). Concussion has been called a transient injury (i.e., short-lived) because most clinical symptoms typically resolve within a month of injury\(^5\). However, this
view of concussion has undergone scrutiny as evidence accumulates suggesting deficits persist beyond clinical recovery\textsuperscript{6-14}. These deficits are thought to reflect sub-clinical metabolic impairments which may increase the probability of subsequent re-injury following early RTP prior to complete metabolic recovery or permanent change in neurologic function which may lower the physiological threshold for concussive injuries\textsuperscript{15-23}. Accordingly, current consensus guidelines call for the identification of factors that may increase risk for concussion and negatively influence recovery to better inform management of concussion and maximize athlete health and safety\textsuperscript{24,25}.

**Attention Deficit Hyperactivity Disorder**

Attention deficit hyperactivity disorder (ADHD), a common neurodevelopmental disorder, is reported to be prevalent in up 10% of college athletes\textsuperscript{26,27}. Due to the heterogeneity of symptoms, an unitary pathology of ADHD remains unclear, however ADHD is believed to reflect structural, functional, and bioenergetics impairments, along with compensatory alterations\textsuperscript{28}. ADHD is predominantly characterized by age or developmentally inappropriate degrees of inattention, hyperactivity, impulsivity, and risk taking behaviors\textsuperscript{29}. These behavioral characteristics may contribute to the increased prevalence of negative outcomes such as anxiety or depression\textsuperscript{30-39}, social impairments\textsuperscript{40,41}, academic difficulty\textsuperscript{42}, poor vocational performance\textsuperscript{43}, vehicular accidents\textsuperscript{44,45}, and bodily injuries\textsuperscript{46} consistently observed in ADHD.

**ADHD and Concussion**

Research is beginning to reveal significant associations between concussion and ADHD. Recent evidence suggests athletes with ADHD are more likely to have greater history of single and multiple concussions, yet the literature regarding recovery remains
unclear. However, the degree to which the individual and combined influences of ADHD and concussion history contribute to the likelihood of future concussions remains unknown.

Accumulating evidence suggests ADHD may negatively influence concussion recovery. A meta-analysis by Biederman et al. suggests that athletes with ADHD have greater symptom burden following concussion, which is consistent with other reports. While greater symptomology does not necessarily result in prolonged recovery, greater initial symptoms is considered the strongest risk factor for slower recovery. Interestingly however, athletes with ADHD without a history of concussion reported concussion-like symptoms at baseline such as: “problems learning”, “emotional lability”, “difficulty concentrating”, and “difficulty remembering”. These self-report measures are subjective and therefore subject to interpretation bias, however objective computerized neurocognitive testing (CNT) consistently reveals pronounced impairments in verbal memory, visual memory, visual motor speed, reaction time, and response inhibition among athletes with ADHD. These findings provide evidence suggesting antecedent ADHD, absent a history of concussion, mimics impairments induced by concussion. Thus, given the overlap in impairments the management of concussion may be more complicated in this population.

**Stimulant Medications**

Stimulant medications are the front-line treatment for ADHD and may further compound the management of concussion in athletes with ADHD. These medications consistently demonstrate an ability to enhance executive functions (i.e., working memory,
inhibition, attentional focus) on neurocognitive test performance\(^{59, 63, 65-68}\), and functional outcomes of daily activities in both individuals with ADHD and healthy controls\(^{65, 69-73}\).

**Purpose**

Athletes with ADHD may be more vulnerable for incurring concussion due to behavioral or physiological impairments. Furthermore, these pre-existing features may negatively influence symptom severity and duration following concussion. Therefore, the purposes of this investigation are 1) to determine whether athletes with ADHD have greater likelihood of incurring a concussion than athletes without ADHD, and 2) to investigate whether pre-existing ADHD symptoms result in greater symptoms and delayed recovery following concussion.

**Rationale**

Expanding our understanding of the relationships between concussion and ADHD has important clinical and scientific implications. If ADHD is an antecedent risk factor for sustaining a first concussion, then it becomes vital to closely monitor these athletes and begin to develop prevention strategies. Additionally, if ADHD with concussion history further increases risk for future concussion, we can better identify athletes at greatest risk for injury. Furthermore, this knowledge may lead to early prevention strategies or the identification of ADHD specific characteristics that result in increased risk for concussion. Finally, if ADHD is found to complicate recovery, clarifying this relationship while considering medication status may lead to a more robust understanding of the difficulties in the management of concussion in athletes with ADHD.
CHAPTER 2: REVIEW OF THE LITERATURE

To better understand why concussion may be more prevalent and more severe in athletes with ADHD, it is necessary to review existing literature on concussion and ADHD to establish the theoretical framework on which this investigation is based. First, we will provide an overview of concussion including the prevalence, definition and diagnosis, injury biomechanics, pathophysiology, risk factors, signs and symptoms, and management. Next, an analysis of ADHD including prevalence, definition and diagnosis, pathophysiology and impairments, and management will be discussed to provide a framework for understanding this unique population. Lastly, existing research regarding the complex relationship between concussion and ADHD symptoms, incidence, and recovery will be examined justify the proposed investigations.

Concussion

Prevalence

The Centers for Disease Control and Prevention estimate up to 3.8 million concussions occur annually in sport and recreational activities. However, surveillance methods likely underestimate actual prevalence as most are based on emergency department visits and do not account for concussions treated elsewhere. Additional injury reports created by team medical personnel may not always account for concussions occurring outside of school-based sports. Furthermore, athletes may fail to report concussions because they did not think the symptoms were severe enough, or they did not want to be removed from play. Collectively, the prevalence of concussion likely
exceeds current estimates further emphasizing the need to increase our knowledge of factors that may predispose athletes for concussion.

*Definition and Diagnosis*

The most recent definition of concussion is “… a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces.” The consensus further identifies common clinical, pathological, and biomechanical concepts useful for defining the nature of concussion:

1. A direct blow to the head, face, neck or elsewhere on the body with an impulsive force transmitted to the head.

2. Rapid onset of short-lived impairment of neurological function that resolves spontaneously, or in some cases evolve over minutes to hours.

3. Acute clinical symptoms that represent primarily functional alterations, rather than structural injury.

4. Clinical signs and symptoms that may or may not involve loss of consciousness.

Resolution of the clinical and cognitive features typically follows a sequential course, but in some cases prolonged recovery has been observed.

While useful, this statement does not include standardized diagnostic criteria for clinical symptom-evaluation of concussion, although, most medical teams use common concussion inventories, including the Head Injury Scale, Graded Symptom Checklist (GSC), Balance Error Scoring System (BESS), vestibular-ocular motor screening (VOMS), Standard Assessment of Concussion (SAC), Concussion Symptom Inventory, and a collected version of these tests often called the Sport Concussion Assessment Tool. However, many assessments are subject to self-report symptoms or subjective interpretations. Unfortunately, concussion is a clinical diagnosis without an objective gold
standard and relies heavily on subjective interpretation potentially preventing accurate
diagnosis and therefore management of concussion.

Biomechanics of Concussion

A concussion may occur when applied forces cause rapid changes to the velocity
vector of the brain which can be categorized according to their characteristics. Impact
forces are those forces which directly contact the head, whereas impulse forces are
transmitted to the head without direct contact, such as a blow to the body or pressure wave
87, 88. Additionally, blast-induced neurotrauma (BINT), or concussions induced by an
explosions pressure wave are a major concern for U.S. military personnel whether actively
deployed in a war zone or in training89, 90. Regardless of impact or impulse each force can
be transferred to the brain and result in some degree of deformation91, 92.

Following force transmission to the head, the brain may experience two types of
movement: linear or rotational. Linear force is the application of force to the head’s center
of gravity, whereas rotational force is the non-central application of force that creates
rotational movement around the head’s center of gravity93. It has been suggested that linear
force results in a localized injury due to transient intracranial pressure alterations within
the brain and that rotational force induces diffuse injuries due to shearing force94, 95. While
most research is dedicated to the role of linear acceleration96, evidence suggests that both
linear and rotational forces occur in every concussion97 which may contribute to resultant
neurometabolic impairments98.

Acute Pathophysiology of Concussion

Biomechanical energy transference causes mechanoporation of neuronal plasma
membranes. This allows for excessive ionic fluctuation (i.e., potassium efflux, and sodium
and calcium influx) and glutamate release resulting in a feedforward loop of depolarization
and hyper excitability followed by a hypoactive “spreading depression-like state”\textsuperscript{16, 98, 99}. This subsequent hypoactive state may reflect neuronal refractory periods during which ATP-dependent Na\textsuperscript{+}-K\textsuperscript{+} pumps are hyperactive, attempting to restore resting ionic concentrations. These Na\textsuperscript{+}-K\textsuperscript{+} pumps require high levels of adenosine triphosphate (ATP) which is typically replenished in the mitochondria by the slow but highly efficient oxidative phosphorylation (i.e., 26 ATP per glucose). However, this period of Na\textsuperscript{+}-K\textsuperscript{+} pump hyperactivity rapidly depletes intracellular ATP reserves and to meet immediate energy demands neurons revert to the rapid but inefficient glycolysis, which only produces 2 ATP per glucose. This bioenergetic deficiency is also compounded by excessive calcium influx and sequestration into the mitochondria\textsuperscript{100} further impairing oxidative phosphorylation\textsuperscript{101}. This resultant energy crisis is concurrent with normal or reduced cerebral blood flow, and therefore no increase in solute delivery\textsuperscript{102}, resulting in an uncoupling of energy supply and demand\textsuperscript{16}. Overall, this period of glucose hyper metabolism appears to be relatively transient, lasting 30-minutes to several hours in animal models\textsuperscript{103}. However, following the hyper-metabolism of glucose there is a period of impaired glucose metabolism that can last 3 - 10 days and has been associated with behavioral and cognitive impairment\textsuperscript{104, 105}.

Concussion is primarily considered to be a functional injury, however there is evidence of structural alterations. Rapid acceleration changes to the brain apply shearing forces to a neuron\textsuperscript{106, 107}. Shearing force often results in microstructural axonal damage called diffuse axonal injury (DAI), a well-established structural disruption post-injury and has been associated with cognitive impairments, headache, dizziness, and fatigue\textsuperscript{107-111}. There are also reports of abnormal white matter integrity following concussion which has been associated with neurocognitive impairments\textsuperscript{112}. While some evidence exists reporting
volumetric reductions in the frontal cortex, cerebellum, and hippocampus months after concussion\textsuperscript{113-116}, other studies have failed to find similar differences\textsuperscript{115}.

\textit{Risk Factors for Concussion}

There are several factors that may increase the probability of incurring a concussion such as history of concussion, sport-type, sex, and preexisting disorders\textsuperscript{5}. These may be direct behavioral mechanisms such as a lapse in attention during dynamic sport performance and being struck with an object, or a vulnerability factor such as the case in neurodevelopmental disorders with pre-existing alterations to brain function and bioenergetics which may decrease the threshold at which concussion occurs.

Researchers have established that having a history of concussion appears to predispose athletes for future concussion. Multiple prospective studies have identified history of concussion as a risk factor for subsequent concussion\textsuperscript{117-120}. Athletes with prior concussion demonstrated twice the likelihood of incurring a concussion, even when adjusting for demographic factors (i.e., body-mass index, age) and sport criteria (i.e., contact level).

Sport-type is also considered a risk factor for concussion. Collision sports (i.e., football, ice hockey, rugby) have the highest rates of concussion for males at various levels of competition\textsuperscript{18, 22, 118, 121}, whereas females have higher rates for concussion in soccer, basketball, and ice hockey at different levels of competition\textsuperscript{122}. Interestingly, compared to males in ice hockey, females demonstrated significant greater injury rates, despite prohibition of body checking in female ice hockey\textsuperscript{122}.

The potential influence of sex characteristics on concussion incidence has expanded rapidly. When specifically examining similar sports (i.e., soccer, basketball, etc.) female athletes have greater risk for concussion than males\textsuperscript{122-124}. Furthermore, female athletes
appear to report greater symptom burden following concussion\textsuperscript{125} as well as prolonged symptoms three months post-injury\textsuperscript{126}, although when compared to males in the same sports recovery rates normalize\textsuperscript{127}. The mechanisms of injury also appear different, males showed greater percentage of player contact concussions, whereas females showed greater percentage of concussion resulting from contact with the playing surface or ball\textsuperscript{122}. These trends remain underexplored regarding biomechanical (e.g., joint angles), physiological (e.g., hormonal differences), and sociocultural (e.g., females may be more honest in reporting symptoms) factors which may elucidate potential sex differences\textsuperscript{61}, to date however there is no consensus of the mechanisms by which sex modifies risk.

\textit{Acute Signs and Symptoms}

Studies using advanced neuroimaging techniques have consistently demonstrated that structural and functional alterations are associated with a wide range of signs and symptoms following injury\textsuperscript{11, 98, 113, 128-133} that are most severe within the first week post-injury\textsuperscript{5}. Signs are objective and visible by some other individual (e.g. balance problems or loss of consciousness), whereas a symptom is some phenomenon experienced by the patient (e.g., headache or fatigue)\textsuperscript{134}. Signs and symptoms of concussion are generally categorized as physical, cognitive, emotional, and sleep related, with some overlap\textsuperscript{135}, we will refer to signs and symptoms collectively as ‘presentation’.

Physical presentation of concussion may include headache, nausea, vomiting, balance problems, dizziness, light/sound sensitivity, and fatigue. Among physical presentations, headache is the most commonly reported symptom, followed by balance problems, dizziness, and fatigue following concussion\textsuperscript{136}. Cognitive presentation is often determined by a combination of athlete self-report, and computerized neurocognitive testing (CNT). Athletes often report feeling foggy or feeling slowed down (i.e., cognitive
processing speed), difficulty concentrating (i.e., attention), or problems remembering (i.e., memory)\textsuperscript{136}. Emotional presentation is commonly reported as anxiety, depression, and other mood disruptions (e.g., anger)\textsuperscript{137}. Sleep is considered a potential marker for predicting recovery\textsuperscript{138, 139}, and athletes may report sleep disruptions such as difficulties falling asleep, staying asleep, sleeping more or less than usual\textsuperscript{140}. Among all signs and symptoms of concussion, the most obvious indicator is a loss of consciousness (LOC), however, this event occurs in less than 10\% of concussions\textsuperscript{141}. Similarly, athletes may present varying degrees of retrograde or anterograde amnesia, both LOC and amnesia may be important indicators of more serious injury\textsuperscript{141}. Whether injury localization plays a significant role in modulating the severity of signs and symptoms following concussion is a matter of some debate. However, the neurometabolic alterations in the acute phase are strongly correlated with symptom severity\textsuperscript{142}.

\textit{Acute Management}

Generally, mean symptom recovery occurs in about 14 days\textsuperscript{5, 143}, and seems relatively consistent with the associated neurometabolic cascade and impairments following concussion\textsuperscript{16, 128}. While this period is considered “normal recovery”, it is important to distinguish clinical symptomology from neurological recovery. McCrea et al.\textsuperscript{143} found that concussed athletes reported greater symptoms at 7-days post injury, relative to their own baseline symptoms, however, even at 90-days post-injury concussed players performed more poorly than controls on neurocognitive measures. However, Henry et al.\textsuperscript{144} examined 66 concussed athletes using similar measures and reported that total symptoms resolution occurred between 21 to 28 days after injury. Intriguingly, both studies report the greatest symptom improvement during the first two weeks, with domain-specific neurocognitive impairments lingering beyond clinical symptom resolution. Accordingly,
the transient view of concussion has undergone scrutiny as evidence of persisting sub-clinical deficits accumulates\textsuperscript{6-14}.

The clinical evaluation of concussion has evolved beyond clinical measures to incorporate multi-modal assessments of cognitive, neurophysiological, and psychological function\textsuperscript{5} as the search for more objective biomarkers recovery continues\textsuperscript{145, 146}. Research has grown exponentially in recent years regarding the nature of concussion, risk factors, outcomes, treatments, rule changes, and equipment related concerns\textsuperscript{147-150}. Subsequently, experts agree the heterogeneous nature of concussion causality coupled with unique demographic characteristics of an athlete can synergistically alter the manifestation, severity, and duration of symptoms\textsuperscript{151-153}. Among these characteristics, existing literature demonstrates that pre-existing conditions such as anxiety and depression\textsuperscript{154}, migraine\textsuperscript{152}, neurodevelopmental disorders\textsuperscript{26, 50, 61, 155}, and concussion history\textsuperscript{5} can negatively influence outcomes following concussion.

**Attention Deficit Hyperactivity Disorder**

*Prevalence*

Attention Deficit Hyperactivity Disorder (ADHD) is prevalent in 6% of children and adolescents\textsuperscript{156} and 5% of adults. While the prevalence of ADHD in college athletes has not been epidemiologically studied, some evidence exists to suggest ADHD occurs in 7% - 10% of college athletes\textsuperscript{26, 50}.

*Definition and Diagnosis*

ADHD is characterized by age or developmentally inappropriate levels of inattention, hyperactivity, impulsivity, and risk-taking behaviors\textsuperscript{29} that persist into adulthood for approximately 70% of cases, with varying degrees of severity\textsuperscript{157}. ADHD is
typically observed during childhood as chronic impairments to attention and self-regulation during situations which require self-monitoring\textsuperscript{157-160}. The hallmark triad—inattention, hyperactivity, and impulsivity—are chronic and relatively stable across the lifespan\textsuperscript{161}. There is no dichotomous test for ADHD, rather clinicians must “rule in” the probability of ADHD based on self-, parent-, and observational report of symptoms\textsuperscript{29}. To aid in the proper diagnosis of ADHD, as opposed to another disorder (e.g., oppositional defiant disorder), updated versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) contain commonly used criteria for defining and diagnosing ADHD in the United States\textsuperscript{29}.

ADHD is divided into subtypes categorized by the presence of six out of nine symptoms within one of two distinct lists, inattention, and hyperactivity-impulsivity. These symptoms must have been present for at least six months and at an inappropriate age or developmental level. In this way, individuals are categorized as either inattentive (ADHD-I), hyperactive-impulsive (ADHD-HI), or a combined (ADHD-C) subtype. However, the design of DSM diagnostic criteria emerged from field trials with children and no adults were included\textsuperscript{162}. Although, a recent systematic review demonstrates that an overall ADHD diagnosis (i.e., unspecified sub-type) in adults is reliable and consistent\textsuperscript{161}.

ADHD is considered an impairment of behavioral inhibition (i.e., disinhibition) and self-regulation\textsuperscript{163} which suggests impaired executive functionality\textsuperscript{164-166}. Generally, it is agreed there are three core executive functions: inhibition (e.g., behavioral, and cognitive inhibition), working memory, and cognitive flexibility\textsuperscript{164, 167-169}. Disinhibition may result in acting or responding before processing the appropriate contextual features of a situation. Behavioral disinhibition may manifest as hyperactivity (e.g., inability to wait for their turn) or impulsive actions (e.g., crossing the street without looking) consequently resulting in
risky behaviors. Cognitive disinhibition may manifest as inattentive behaviors (e.g., failing to attend to instructions), or impulsive responses (i.e., responding before thinking). Silverstein et al.\textsuperscript{170} reported that symptoms of ADHD were significantly correlated with executive dysfunction. Indeed, a plethora of studies have demonstrated that executive functions are impaired in individuals with ADHD resulting in poor cognitive performance\textsuperscript{42,170-185}. These overall reductions in executive function contributes to lifelong difficulties such as mood disorders (i.e., anxiety depression)\textsuperscript{30-39}, social impairments\textsuperscript{40,41}, academic difficulty\textsuperscript{42}, poor vocational performance\textsuperscript{43}, vehicular accidents\textsuperscript{44,45}, and bodily injuries\textsuperscript{46} observed in ADHD. There is some data to suggest that males with ADHD may experience greater severity of and variance in symptoms than females with ADHD\textsuperscript{55,186}.

\textit{Pathophysiology and impairments of ADHD}

Currently, a single underlying cause of ADHD has not been identified, and ADHD is most likely a confluence of genetic and environmental factors which synergistically contribute to clinical features of ADHD. This multifactorial etiology is reflected in the heterogeneity of symptoms, outcomes, and extensive comorbidities in individuals with ADHD. Though there is no single underlying etiology, there are several factors that are strongly associated with ADHD. ADHD is a heritable disorder with twenty twin studies demonstrate a 76\% heritability rate\textsuperscript{187}. Similarly, 25\% of adults with ADHD reported having a parent also diagnosed with ADHD\textsuperscript{188}. There are several genetic association studies with dissimilar findings and small sample sizes\textsuperscript{189} and attributing specific genes with causation is a somewhat controversial topic in ADHD research. However, genetic variants of dopamine receptors (i.e., D1, D2, D3, D4, D5 receptors) and dopamine transporters remain of great interest to researchers\textsuperscript{187}. While independent genetic variants alone are
considered insufficient to be causative, however when combined with environmental factors the cumulative effect may reflect ADHD symptomology. For example, a genetic variant of the dopamine transport protein DAT1 combine with prenatal exposure to alcohol, and nicotine have been shown to increase risk for ADHD and common symptoms, such as hyperactivity and impulsivity 190-192.

There are numerous studies demonstrating significant structural brain alterations in ADHD. The most common finding is a reduction in overall brain volume particularly in frontal regions and regional connectivity pathways 193-196. There are volumetric reductions throughout the frontal lobe particularly the prefrontal cortex (PFC) in ADHD 197-199. Furthermore, the dorsolateral prefrontal cortex (DLPFC) is reported to have reduced grey and white matter density, asymmetric activation200-204 and white matter tracts linking the prefrontal cortex to other brain areas is less organized and functional connectivity is reduced 205.

ADHD related structural impairments may result in less effective prefrontal regulation of cortical and subcortical structures, resulting in diminished top-down self-regulation and the hallmark characteristics of ADHD206-209. The PFC plays an integral role in cognitive processing related to reward, emotional processing, response inhibition, and attention. The PFC uses a network of interconnected pyramidal neurons that are self-excitatory, that is they can excite each absent environmental stimulus, thus they may be considered a “mental sketch pad”210. Additionally, a vast network of projections to sensory association areas enable PFC to suppress processing of irrelevant stimuli (i.e., distractors) while enhancing attention to important yet boring stimuli211. Depending on task demands, the PFC can also sustain attention to a single task212 or rapidly shift attention for
multitasking. In addition to attention regulation, the PFC is also vital for regulating emotions and behaviors. The right inferior PFC is of particularly important for minimizing impulsive behaviors and inhibiting inappropriate actions while orbital and ventromedial PFC regulate emotions. Furthermore, the medial PFC is a key node of the default mode network (DMN), an intrinsic network primarily signaling a state of rest reflecting a physiological baseline activity of the brain. As cognitive loading or demand increase the DMN is attenuated by the task-positive network (TPN) of the dorsolateral prefrontal cortex (DLPFC). Therefore, structural alterations, reduced volume or activation of the DLPFC may result in failure of the TPN to sufficiently suppress the DMN, which interferes with task performance, and result in slower reaction times and inaccurate attention control.

Beyond structural alterations, there is an 8.1% reduction in global glucose metabolism during an auditory-attention task in ADHD, with particular decrements in prefrontal (e.g., attention) and premotor (i.e., motor control) areas. Also, Schweitzer et al. found reduced cerebral blood flow (CBF) in frontal areas during a working memory task among individuals with ADHD. This reduction in CBF suggests that there is reduced activation in frontal areas.

Structural and metabolic impairments also modify aspects of neurotransmitter (NT) bioavailability, including regional activation and biosynthesis. Indeed, dysregulation of catecholaminergic (i.e., dopamine and norepinephrine) signaling is regularly reported in ADHD. Dopamine (DA) is a neurotransmitter (NT) believed to play important roles in regulating cognition, attention, movement, motivation, and reward. Norepinephrine (NE) is another NT associated with arousal, set-shifting and sustained
attention\textsuperscript{235}. Furthermore, DA is a precursor for NE, via mechanism of dopamine β-hydroxylase, an enzyme which catalyzes the conversion of DA into NE and thus helps to balance DA and NE concentrations in the brain. Therefore, abnormalities in DA signaling or altering DA concentrations will subsequently increase NE concentrations\textsuperscript{236}.

Thus, the PFC environment is extremely sensitive to alterations in the neurochemical environment and require that catecholamine concentration levels are maintained at optimal levels for proper functioning further demonstrated by positive influence of increased dopamine in healthy controls\textsuperscript{237}. PFC concentrations of these NTs are positively associated with arousal level. For example, during low arousal conditions, NT concentrations are low\textsuperscript{238,239}. Indeed, low levels of catecholamines are known to impair executive functions in the prefrontal cortex, to such a degree that they mimic most symptoms of ADHD\textsuperscript{240}. Additionally, alterations to TPN/DMN synchronization modifies the basal arousal state, subsequently changing the availability of catecholamines, thus modifying PFC activity and therefore executive functions. Collectively, the evidence suggests that many behaviors and outcomes associated with executive dysfunction in ADHD result from a variety of structural, metabolic, and biochemical alterations.

\textit{Management}

Currently, the most common approach to treating ADHD are psychostimulant medications\textsuperscript{241}. These psychostimulant medications directly cause an increase in synaptic NT concentrations, resulting in increased neuronal activity and therefore activation of a circuit, or network. In sum, the magnitude of neuronal receptor activation depends on 1) the quantity of the NT (e.g., amount of NT released), 2) the duration the NT remains in the synaptic cleft (e.g., time until reuptake/degradation), and 3) receptor concentration for a
NT. Normally, specialized transport proteins actively transport NTs back into the cell to decrease synaptic concentrations so that 1) postsynaptic activation is limited and 2) NTs are recycled for homeostatic efficiency\textsuperscript{242}. These are important considerations to consider because psychostimulant medications manipulate these processes to improve cognitive processing and attention in individuals with ADHD.

Currently, the Food and Drug Administration (FDA) have only approved two psychostimulant molecules, amphetamine (AMPH), and methylphenidate (MPH)\textsuperscript{243}. There are numerous brand names and preparations (e.g., Ritalin, Adderall, etc.) however, we will henceforth use the generic names AMPH and MPH. While both stimulants primarily act to enhance the effects of dopamine and/or norepinephrine, each operate via slightly different mechanisms.

AMPH acts as a “reverse-transport” mechanism that is AMPH binds to dopamine active transport proteins (DAT) and they now actively carrying dopamine out of the cytoplasm and into the synaptic cleft\textsuperscript{244}. Additionally AMPH inhibits vesicular packaging of dopamine, thus increasing cytoplasmic dopamine concentrations ready for “reverse transport\textsuperscript{244}. Thus, AMPH decreases dopamine reuptake and increases release, thereby increasing synaptic cleft concentrations, enhancing dopaminergic activation and functionality, particularly in the PFC.

MPH actively blocks the reuptake of dopamine and norepinephrine from the synaptic cleft increasing the duration in which these NTs can act on their receptors, however unlike AMPH it does not interfere with vesicular packaging\textsuperscript{245}. In addition to these direct catecholaminergic effects, MPH has been shown to improve the TPN/DMN
synchronization, that is oscillatory variations in activation patterns are normalized allowing more optimal cognitive functioning\textsuperscript{246, 247}.

Regardless of their mechanism of action, the catecholaminergic activity caused by these stimulant medications demonstrate a dose-effect response, that is too much or too little can be just as detrimental\textsuperscript{248}. With appropriate dosing, medications which increase the availability of catecholamines optimize the neurochemical environment which enhances executive functions and therefore outcomes (e.g., academic performance, behaviors, etc.)\textsuperscript{73, 249, 250}.

**Concussion and ADHD**

Given the significant overlap of physiological impairments and symptoms between concussion and ADHD, the current consensus is to consider ADHD a modifier for increased risk for, and atypical recovery from concussion\textsuperscript{5}. However, there is relatively sparse conformational evidence in adult athletes with ADHD as most research in this area has focused on children and adolescent athletes. In a retrospective study with a limited sample size, Alosco et al.\textsuperscript{26} reported college athletes with ADHD may have greater history of single and multiple concussions. Similarly, an aggregate study by Nelson et al.\textsuperscript{50} reported that college athletes with ADHD have 2.93 (95% CI 2.05 – 4.19) times the prevalence of a history of three or more concussions, relative to controls. It important to note that this study was primarily male (97%) potentially neglecting concussion-related sex differences. In the general population, female athletes appear to have greater risk for incurring a concussion,\textsuperscript{122-124} however it remains unknown whether ADHD compounds or supersedes sex differences regarding risk for concussion. It is possible that the reported increased ADHD severity in males would result in a similar risk for concussion among
females with ADHD. Thus far, all findings have been cross-sectional. While these studies provide important information, without establishing temporality, no inferences regarding causation can be made. To date, no longitudinal studies regarding concussion likelihood in college athletes with ADHD exist.

There is also evidence to suggest athletes with ADHD demonstrate concussion-like symptoms at baseline which reflect inherent characteristics of ADHD. Several studies have reported that college athletes absent a history of concussion, but with ADHD demonstrated concussion-like symptoms at baseline, such as “problems learning”, “emotional lability”, “difficulty concentrating”, and “difficulty remembering”\textsuperscript{50, 56}. Of note, these symptoms share significant overlap with the inattentiveness among individuals with ADHD which commonly persists into adulthood\textsuperscript{251}. The importance of this consideration cannot be overstated since most computerized cognitive tests (CNTs), and common clinical scales utilize normative data to determine levels of acceptable performance useful for determining clinical recovery. However, the Immediate Post-Concussion Assessment and Cognitive Testing battery (ImPACT) does provide a “special education” group for the total symptom score that may reflect average symptoms in populations with preexisting disorders, but the samples are heterogeneous and remain in the early phase of development. Furthermore, the ImPACT uses an algorithm to provide a marker for ‘invalid results’ that are determined by more impulsive responses, misunderstanding instructions, deliberate under-performance, or other factors. Among these factors, of major concern for athletes with ADHD are those of impulsive responses (i.e., poor response inhibition or inattention), and misunderstanding instructions (i.e., cognitive control or inattention). Therefore, it is possible that among athletes with ADHD, ‘invalid’ results may represent greater ADHD symptomology rather
than truly being ‘invalid’. Understanding the pre-injury profile of athletes with ADHD is of utmost importance when interpreting post-injury results due to potentially confounding pre-existing symptoms.

Further compounding concussion management in athletes with ADHD is stimulant medications (i.e., Amphetamines and Methylphenidate), the front-line treatments for ADHD. Research has consistently demonstrated that stimulant medications enhance executive functions (i.e., working memory, inhibition, attentional focus), and functional outcomes of daily activities in both individuals with ADHD and healthy controls. Stimulant medications are known to influence performance on neurocognitive test commonly used in the management of concussion. Indeed, a recent study by Cook et al. reported that athletes with un-medicated ADHD had greater rates of invalid ImPACT results, compared to those with medicated ADHD on a pre-season baseline assessment. Furthermore, this study also demonstrated that athletes with medicated ADHD showed no differences either in rate of invalid results or in cognitive performance than controls. To date only one study has investigated the influence of stimulant medication pre- and post-concussion. Unmedicated athletes with ADHD demonstrated poorer performance for verbal, and visual memory, visual motor speed, and slower reaction times than controls pre- and post-concussion, however, medicated athletes with ADHD demonstrated similar visual motor speed and reaction time to controls, pre- and post-concussion.

Collectively, the symptoms of concussion and ADHD have many similarities and some of these symptoms may share some physiological disruptions. However, prior to dedicating significant resources (i.e., financial, time, workforce) to investigating
underlying etiology, we must first unravel whether 1) there is a relationship between incidence of concussion and ADHD, and 2) whether the symptoms of concussion are compounded by the presence of ADHD. In so doing, we stand to further enhance our knowledge base regarding 1) whether athletes with ADHD are more likely to incur a concussion, and 2) the synergistic nature of concussion symptoms regarding the degree to which pre-injury concussion-like symptoms are exacerbated.
CHAPTER 3: AIMS & METHODS

Specific aim 1: To determine the likelihood of having experienced a concussion among male and female athletes with ADHD. We hypothesize that:

1. *Hypothesis 1a:* Athletes with ADHD will have greater odds of single and multiple concussions, *relative to athletes without ADHD.*

2. *Hypothesis 1b:* Both male and female athletes with ADHD will have greater odds of single and multiple concussions, *relative to biological sex specific athletes without ADHD.*

3. *Hypothesis 1c:* Female athletes with ADHD would not have greater odds of single or multiple concussions, *relative to male athletes with ADHD.*

Specific aim 2: To determine the likelihood of incurring a concussion among male and female athletes with ADHD. We hypothesize that:

1. *Hypothesis 2a:* Athletes with ADHD will have greater risk for incurring a concussion, irrespective of concussion history, *relative to athletes without ADHD.*

2. *Hypothesis 2b:* Both male and female athletes with ADHD will have greater risk for incurring a concussion, irrespective of concussion history, *relative to biological sex specific athletes without ADHD.*

3. *Hypothesis 2c:* Female athletes with ADHD will not have greater risk for incurring a concussion, irrespective of concussion history, *relative to male athletes with ADHD.*
Specific aim 3: To evaluate whether medication status influences concussion symptom profiles throughout recovery in athletes with ADHD. We hypothesize that:

1. *Hypothesis 3a*: Athletes with un-medicated ADHD will perform worse on ImPACT measures and symptom reports at baseline than athletes with medicated ADHD, and athletes without ADHD.

2. *Hypothesis 3b*: Athletes with un-medicated ADHD will perform worse on ImPACT measures and symptom reports at 24-48 hours post injury than athletes with medicated ADHD, and athletes without ADHD.

3. *Hypothesis 3c*: Athletes with un-medicated ADHD will take longer to be cleared for unrestricted return-to-play than athletes with medicated ADHD, and athletes without ADHD.

Methodology

For all specific aims, a de-identified database was provided by the National Collegiate Athletic Association Department of Defense Grand Alliance (NCAA-DOD): Concussion Assessment, Research and Education (CARE) Consortium. The CARE Consortium enrolled over 34,000 unique athletes and military service academy members and consisted of multiyear multimodal assessment of the natural concussion history, described in detail elsewhere. All athletes and cadets signed a site-specific institutional review board approved consent form, also approved by the US Army Medical Research and Materiel Command Human Research Protection Office. In brief, prior to the onset of specific sport-seasons or academic year all participants received a comprehensive demographics and health history questionnaire including questions regarding prior ADHD diagnoses and medications and completed a clinical concussion battery as baseline.
Concussions occurring after CARE enrollment were verified by team medical personnel using evidence-based DoD criteria. These concussed athletes were reassessed at multiple time points across recovery: within 6-hours of injury, 24-48 hours post-injury, time when asymptomatic, time of unrestricted return-to-play, and six months post-injury.

Participants

We categorized according to their answers into control and ADHD groups. ADHD was a self-report of physician diagnosis. All athletes who reported another disorder (e.g., learning disability, autism spectrum disorder), brain surgery, history of migraines, severe brain injury, or psychological disorders (e.g., schizophrenia, bipolar disorders, etc.), or take psychological medications other than psychostimulants (e.g., anti-psychotics) will be excluded from analysis. Intramural athletes and military service academy cadets will be grouped as ‘non-NCAA’ athletes for NCAA contact category analyses, varsity athletes at the academies will be categorized into standard NCAA contact categories. Control athletes who reported no diagnoses of ADHD but repeated a year of school or reported prior individualized education program (IEP) or a 504 plan were excluded from analyses to control for possible undiagnosed or unreported ADHD. Additionally, for all aims, control athletes who reported taking psychostimulant medications were excluded from analysis.

Specific aim 3

Only for specific aim 3, athletes with ADHD were further stratified by whether they are taking psychostimulant medication (ADHD+Rx, or not taking medication (ADHD_uRx). We defined psychostimulant medications as any brand using Amphetamine or Methylphenidate, and athletes taking other prescription medications will be excluded from
analyses. Only concussed athletes with complete ImPACT performances at baseline, 24-
48 hours post-injury, and unrestricted return-to-play (uRTP) were included.

Eligible participants were grouped into 1) controls, 2) ADHD+Rx, 3) ADHD_uRx). We
used double-matched controls based on biological sex, age, body-mass index, and
history of diagnosed concussion.

Assessment Measures

The ImPACT is a 25-minute computerized neurocognitive tests which evaluates
impulse control, reaction time, total symptoms, verbal memory, visual memory, visual
motor speed, and cognitive efficiency. We will examine performance in each measure at
baseline, 24-48 hours post-injury, and at uRTP. uRTP was determined by medical staff
clearance after completing all stages of a return-to-play progression. Herein, we
define recovery as duration of symptoms as reported in the clinical battery and symptom
inventory prior to uRTP.

All significant outliers (± 2 times the standard deviation) were removed following
within group analyses prior to final matching. A one-way analysis of variance (ANOVA)
with Tukey post hoc correction revealed no statistically significant differences exist
between groups for age, body-mass index, and concussion history.

Statistical Analysis

All analyses were performed using SPSS (Version 26; SPSS Inc., Chicago, IL).

Specific aim 1: To determine the likelihood of having experienced a concussion among
male and female athletes with ADHD.

Retrospective odds ratios (ORs) with 95% confidence intervals (CIs) were
calculated across three contexts: 1) Odds of having any concussion history prior to
enrollment, 2) odds of having had a single concussion prior to enrollment, and 3) odds of having a history of multiple concussions prior to enrollment. Each context was separately analyzed 1) by group relative to controls (i.e., ADHD vs controls), 2) within sexes (e.g., males with ADHD vs. males without ADHD), and 3) between sexes (e.g., females with ADHD vs. males with ADHD).

To control for potential sport-contact type bias, we further stratified groups by similar sports by NCAA contact, NCAA limited-contact, NCAA non-contact sports, and non-NCAA and repeated analyses 1) by group, and 2) between sexes.

**Specific aim 2:** To determine the likelihood of incurring a concussion among male and female athletes with ADHD.

Prospective estimates of relative risk (RRs) with 95% CIs were calculated across three contexts: 1) Risk for incurring a concussion, 2) risk incurring a concussion with concussion history, and 3) risk for incurring a concussion absent concussion history. Each context will be separately analyzed 1) by group relative to controls (i.e., ADHD vs controls), 2) within sexes (e.g., males with ADHD vs. males without ADHD), and 3) between sexes (e.g., females with ADHD vs. males with ADHD).

To control for potential sport-contact type bias, we further stratified groups by similar sports by NCAA contact, NCAA limited-contact, NCAA non-contact sports, and non-NCAA and repeated analyses 1) by group, and 2) between sexes.

**Specific aim 3:** To evaluate whether medication status influences concussion symptom profiles throughout recovery in athletes with ADHD.

Using our participant inclusion and grouping criteria for specific aim 3, a one-way ANOVA was used to identify baseline differences for all ImPACT measures (i.e., impulse
control, reaction time, total symptoms, verbal memory, visual memory, visual motor speed, and cognitive efficiency) between groups. A repeated measures ANOVA for all ImPACT measures was used as the within-subjects factor and group as the between-subjects factor will be performed to examine whether cognitive performance is different for each ImPACT measure throughout recovery. Significant interactions will be decomposed using a univariate ANOVA using baseline ImPACT values as a between groups covariate to account for pre-existing differences in ImPACT score/performance.

A one-way ANOVA with Tukey post hoc correction was used to determine whether there were differences between groups for days between injury and: reporting the injury, being determined clinically asymptomatic, eligible for return-to-play, and symptom resolution.
CHAPTER 4: RESULTS

Inclusion and exclusion criteria for aims 1 and 2 are provided in Figure 4.1.

Specific Aim 1

Final analyses included 32,635 athletes comprised of 31,122 controls and 1,513 athletes with ADHD. Sample characteristics are provided in Table 4.1. Retrospective odds can be found in Tables 4.2 & 4.3.

Overall odds: Analyses revealed that athletes with ADHD had greater odds of having a concussion history (Odds Ratio; OR = 1.915, 95%CI 1.72 – 2.14), and further investigation substantiated this finding for both single (OR = 1.699, 95%CI 1.51 – 1.92) and multiple prior concussions (OR = 1.914, 95%CI 1.60 – 2.29) relative to control athletes.

Odds within sex: Analyses revealed that among female athletes, those with ADHD had greater odds of having a concussion history (OR = 1.931, 95%CI 1.52 – 2.21), and further investigation substantiated this finding for both single (OR = 1.742, 95%CI 1.42 - 2.14) and multiple prior concussions (OR = 1.592, 95%CI 1.17 – 2.18) relative to female control athletes.

Analyses revealed that among male athletes, those with ADHD had greater odds of having a concussion history (OR = 1.956, 95%CI 1.71 – 2.24), and further investigation substantiated this finding for both single (OR = 1.670, 95%CI 1.44 – 1.93) and multiple prior concussions (OR = 2.120, 95%CI 1.71 – 2.63) relative to male control athletes.
**Odds between sexes:** An exploratory analysis between sexes among control athletes revealed that females had slightly reduced overall odds of concussion (OR = .940, 95%CI .889 – .995) relative to males. Further investigation revealed that while females had reduced odds of a single concussion (OR = .885, 95%CI .931 - .941), however females had greater odds of multiple prior concussions (OR = 1.132, 95%CI 1.023 - 1.253) relative to male athletes.

No significant differences were found among athletes with ADHD when comparing female to male athletes’ odds of overall (OR = .880, 95% CI .704 – 1.100), single (OR = .923, 95% CI .723 – 1.178), or multiple prior concussions (OR = .850, 95% CI .589 – 1.226).

**Overall odds by contact category:** Analyses revealed that athletes with ADHD had greater odds of concussion in contact (OR = 1.727, 95%CI 1.478 – 2.019), limited contact (OR = 1.770, 95%CI 1.404 - 2.232), non-contact (OR = 1.720, 95%CI 1.286 – 2.301) and non-NCAA categories (OR = 2.030, 95%CI 1.473 – 2.797) relative to category specific controls.

**Odds by contact category between sexes:** An exploratory analysis between sexes among control athletes revealed that females had greater overall odds of concussion history in contact (OR = 1.151, 95%CI 1.050 – 1.261) and non-contact categories (OR = 1.439, 95%CI 1.208 – 1.715), but reduced odds of concussion history in the non-NCAA category (OR = .878, 95% CI .771 – 1.00), relative to category specific male controls.

Among athletes with ADHD in the non-contact category, females had greater odds of concussion (OR = 1.974, 95%CI 1.082 – 3.601) than male athletes. There were no significant differences were found between females and males with ADHD among contact
Specific Aim 2

Sample characteristics are provided in Table 4.4. Prospective relative risk estimates can be found in Tables 4.5 & 4.6.

*Overall risk*: Analyses revealed that athletes with ADHD had greater risk for concussion (Relative Risk Ratio; RR = 1.236, 95%CI 1.059 – 1.443). However, no significant differences were found among athletes with ADHD without history (RR = 1.041, 95% CI .825 – 1.340) or with history of concussion (RR = 1.195, 95% CI .973 – 1.47).

*Risk within sex*: Analyses revealed that among female athletes, those with ADHD had greater risk of incurring a concussion history (RR = 1.044, 95% CI .797 – 1.369). Analyses failed to reveal significant differences between female athletes with ADHD without history (RR = .802, 95% CI .526 – 1.221), or with history of concussion (RR = 1.096, 95% CI .776 – 1.547), relative to female controls.

Analyses revealed that among male athletes, those with ADHD had greater risk for concussion (RR = 1.369, 95% CI 1.133 – 1.654) than male controls. However, no significant differences were found among male athletes with ADHD without history (RR = 1.204, 95% CI .911 – 1.592) or with history of concussion (RR = 1.272, 95% CI .985 – 1.644).

*Risk between sexes*: An exploratory analysis between sexes among control athletes revealed that female athletes had greater overall risk for concussion (RR = 1.194, 95% CI
1.107 – 1.287), without history (RR = 1.180, 95% CI 1.073 – 1.297), and with history of concussion (RR = 1.249, 95% CI 1.105 – 1.412) relative to male control athletes.

Analyses failed to reveal significant differences among athletes with ADHD when comparing female to male athletes for overall risk for concussion (RR = .911, 95% CI .661 – 1.255), without history (RR = 1.076, 95% CI .71 – 1.624), or without history of concussion (RR = .785, 95% CI .478 – 1.289).

Risk by contact category: Analyses failed to reveal significant differences between athletes with ADHD and control for risk of concussion in any contact category (RR ranges = .931 – 1.396).

Risk by contact category between sexes: An exploratory analysis between sexes among control athletes revealed that females had greater risk for concussion than male control athletes in limited contact (RR = 2.332, 95% CI 1.936 – 3.080), non-contact (RR = 1.546, 95% CI 1.136 – 2.103), and non-NCAA (RR = 2.199, 95% CI 1.905 – 2.539) categories.

Analyses failed to reveal significant differences between female and male athletes with ADHD for risk of concussion in any contact category (RR ranges = 1.025 – 3.226).

Specific Aim 3

Inclusion and exclusion criteria for aim 3 are provided in Figure 4.2 Final analyses included 210 athletes comprised of 140 controls double-matched to 35 athletes with ADHD taking psychostimulant medications (ADHD+Rx), and 35 athletes with ADHD but not taking psychostimulant medications (ADHD_uRx). Sample characteristics and accompanying statistics are provided in Table 4.7. The ADHD_uRx group demonstrated a statistically significant larger BMI than controls. There were no significant differences
between groups for age at baseline, age at injury during the study, or for the age at which the athletes incurred their first ever concussion among athletes with a positive concussion history. The ADHD_uRx group reported significantly greater history of concussion (60%) than both controls (35.7%) and ADHD+Rx (28.6%). There were no differences between groups in the amount of time between the injury and reporting the injury, being programmatically determined to be asymptomatic, or being programmatically determined eligible for RTP (14-15 days). However, the ADHD_uRx reported a greater number of days with self-reported concussion related symptoms (9 days) than both controls (5 days) and ADHD+Rx (6 days).

ANOVA post-hoc results for baseline and results for 24-48 hours post injury and uRTP post-hoc comparisons can be found in Table 4.9. Pairwise effect sizes suggest most effect sizes were small-to-medium (\(\eta^2\) from .01 to .101) suggesting caution may be needed for clinical or practical interpretation.\(^{257}\)

**Baseline:** Analyses revealed that the ADHD_uRx group performed significantly worse than controls for impulse control (7.343 vs. 4.686), reaction time (0.631 vs. 0.584), and visual motor speed (38.350 vs. 42.602). There were no statistically significant differences between ADHD+Rx and ADHD_uRx groups for any other baseline ImPACT measure.

**24-48 hours post-injury:** Analyses using baseline scores as a covariate revealed that the ADHD+Rx group performed worse than controls for impulse control (9.40 vs. 6.07). Additionally, the ADHD_uRx group performed significantly worse than controls for reaction time (.683 vs. .606), visual memory (69.5 vs. 75.3), and cognitive efficiency (.281 vs. .367). Furthermore, the ADHD_uRx group performed worse than both controls and ADHD+Rx for visual motor speed (35.248 vs. 39.331 and 42.156), this was the only
difference between ADHD+Rx and ADHD_uRx for any 24-48hour post-injury ImPACT measure.

*Unrestricted return-to-play (uRTP):* Analyses using baseline scores as a covariate revealed the ADHD+Rx group performed significantly worse than both controls and ADHD_uRx for impulse control (9.057 vs. 5.771 and 5.829). Also, the ADHD_uRX and ADHD+Rx groups reported greater total symptoms than controls (1.429 and 1.486 vs. .629). Additionally, the ADHD_uRx group performed significantly worse than controls for verbal memory (87.857 vs. 92.029), visual memory, and visual motor speed (41.877 vs. 44.974). Furthermore, the ADHD_uRx group performed worse than both controls and ADHD+Rx for reaction time (.608 vs. .567 and .565). There were no differences between groups for cognitive efficiency at uRTP.
**Tables & Figures**

**Figure 4.1.** Selection Criteria for Specific Aims 1 & 2

- Total Athletes = 47,444
  - Excluded (n = 12,810)
    - Year 2 (n = 11,218)
    - Year 3 (n = 1,589)
    - Year 4 (n = 3)
  - Unique Athletes (n = 34,634)
    - Excluded for other diagnosis (n = 752)
      - Specific Learning Disorder (n = 429)
      - ADHD and Specific Learning Disorder (n = 323)
    - Controls (n = 32,369)
      - Excluded (n = 1,247)
        - Missing Sex (n = 8)
        - Failed a year (n = 1,239)
    - Controls (n = 31,122)
    - ADHD (n = 1,513)
Table 4.1 Sample Characteristics for Aim 1.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>ADHD</th>
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<tr>
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<td>History</td>
</tr>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Overall History (n = 7398)</td>
<td>24256    77.9</td>
<td>6866 22.1</td>
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<tr>
<td>Female (n = 2681)</td>
<td>9205 78.6</td>
<td>2506 21.4</td>
</tr>
<tr>
<td>Male (n = 4717)</td>
<td>15051 77.5</td>
<td>4360 22.5</td>
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Concussion History by Quantity

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<td>History</td>
</tr>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>One Prior (n = 5607)</td>
<td>- -</td>
<td>5221 93.1</td>
</tr>
<tr>
<td>Female (n = 1970)</td>
<td>- -</td>
<td>1841 93.5</td>
</tr>
<tr>
<td>Male (n = 3637)</td>
<td>- -</td>
<td>3380 92.9</td>
</tr>
<tr>
<td>Two + Prior (n = 1791)</td>
<td>- -</td>
<td>1645 91.8</td>
</tr>
<tr>
<td>Female (n = 711)</td>
<td>- -</td>
<td>665 93.5</td>
</tr>
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<td>Male (n = 1080)</td>
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<td>980 90.7</td>
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Concussion History by Contact Category

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<tr>
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<td>History</td>
</tr>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Contact (n = 3508)</td>
<td>7026 68.7</td>
<td>3204 31.3</td>
</tr>
<tr>
<td>Female (n = 1043)</td>
<td>1923 66.5</td>
<td>969 33.5</td>
</tr>
<tr>
<td>Male (n = 2465)</td>
<td>5103 69.5</td>
<td>2235 30.5</td>
</tr>
<tr>
<td>Limited Contact (n = 1393)</td>
<td>5400 80.8</td>
<td>1284 19.2</td>
</tr>
<tr>
<td>Female (n = 708)</td>
<td>2834 81.1</td>
<td>662 18.9</td>
</tr>
<tr>
<td>Male (n = 685)</td>
<td>2566 80.5</td>
<td>622 19.5</td>
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<tr>
<td>Non-Contact (n = 794)</td>
<td>4101 84.9</td>
<td>730 15.1</td>
</tr>
<tr>
<td>Female (n = 576)</td>
<td>2664 83.4</td>
<td>531 16.6</td>
</tr>
<tr>
<td>Male (n = 218)</td>
<td>1437 87.8</td>
<td>199 12.2</td>
</tr>
<tr>
<td>Non-NCAA (n = 1704)</td>
<td>7728 82.4</td>
<td>1649 17.6</td>
</tr>
<tr>
<td>Female (n = 354)</td>
<td>1784 83.8</td>
<td>344 16.2</td>
</tr>
<tr>
<td>Male (n = 1350)</td>
<td>5944 82.0</td>
<td>1305 18.0</td>
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Table 4.2 Retrospective Odds Ratios

<table>
<thead>
<tr>
<th></th>
<th>History of Concussion</th>
<th>One Prior Concussion</th>
<th>Two or More Concussions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR  95% CI  ( \chi^2 )  ( p )</td>
<td>OR  95% CI  ( \chi^2 )  ( p )</td>
<td>OR  95% CI  ( \chi^2 )  ( p )</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F/M</td>
<td>0.940  0.889 - 0.995 4.845  &lt;.05</td>
<td>0.885  0.931 - 0.941 14.987  &lt;.01</td>
<td>1.132  1.023 - 1.253 5.786  &lt;.05</td>
</tr>
<tr>
<td><strong>ADHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>1.915  1.718 - 2.136 141.173  &lt;.01</td>
<td>1.699  1.508 - 1.915 77.393  &lt;.01</td>
<td>1.914  1.602 - 2.286 52.979  &lt;.01</td>
</tr>
<tr>
<td>Males</td>
<td>1.931  1.520 - 2.207 41.465  &lt;.01</td>
<td>1.742  1.419 - 2.138 28.890  &lt;.01</td>
<td>1.592  1.165 - 2.176 8.651  &lt;.01</td>
</tr>
<tr>
<td>F/M</td>
<td>1.956  1.710 - 2.236 99.201  &lt;.01</td>
<td>1.670  1.442 - 1.934 47.698  &lt;.01</td>
<td>2.120  1.708 - 2.633 48.396  &lt;.01</td>
</tr>
<tr>
<td></td>
<td>0.880  0.704 - 1.100 1.266</td>
<td>0.923  0.723 - 1.178 0.414</td>
<td>0.850  0.589 - 1.226 0.757</td>
</tr>
</tbody>
</table>

F/M designates females relative to males.

ADHD odds ratios are relative to control athletes.
### Table 4.3 Retrospective Odds Ratios by Contact Category

<table>
<thead>
<tr>
<th></th>
<th>Contact</th>
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<th>Limited Contact</th>
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<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>$\chi^2$</td>
<td>$p$</td>
<td>OR</td>
<td>95% CI</td>
<td>$\chi^2$</td>
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<tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F/M</td>
<td>1.151</td>
<td>1.050 - 1.261</td>
<td>8.961</td>
<td>&lt; .01</td>
<td>0.964</td>
<td>0.853 - 1.088</td>
<td>0.355</td>
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<tr>
<td>ADHD</td>
<td>1.727</td>
<td>1.478 - 2.019</td>
<td>48.104</td>
<td>&lt; .01</td>
<td>1.770</td>
<td>1.404 - 2.232</td>
<td>23.843</td>
</tr>
<tr>
<td>F/M</td>
<td>0.959</td>
<td>0.676 - 1.358</td>
<td>0.057</td>
<td></td>
<td>0.820</td>
<td>0.522 - 1.288</td>
<td>0.743</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F/M</td>
<td>1.439</td>
<td>1.208 - 1.715</td>
<td>16.748</td>
<td>&lt; .01</td>
<td>0.878</td>
<td>0.77 - 1.000</td>
<td>3.831</td>
</tr>
<tr>
<td>ADHD</td>
<td>1.720</td>
<td>1.286 - 2.301</td>
<td>13.657</td>
<td>&lt; .01</td>
<td>2.030</td>
<td>1.47 - 2.797</td>
<td>19.455</td>
</tr>
<tr>
<td>F/M</td>
<td>1.974</td>
<td>1.082 - 3.601</td>
<td>5.008</td>
<td>&lt; .05</td>
<td>1.346</td>
<td>0.58 - 3.140</td>
<td>0.474</td>
</tr>
</tbody>
</table>

F/M designates females relative to males.

ADHD odds ratios are relative to control athletes.
Table 4.4 Sample Characteristics for Aim 2

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Cx</td>
<td>Cx</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Overall Concussions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 2699)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n = 1116)</td>
<td>10645</td>
<td>90.9</td>
</tr>
<tr>
<td>Male (n = 1583)</td>
<td>17931</td>
<td>92.4</td>
</tr>
<tr>
<td></td>
<td>28576</td>
<td>91.8</td>
</tr>
<tr>
<td></td>
<td>2546</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>1360</td>
<td>89.9</td>
</tr>
<tr>
<td></td>
<td>153</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Incurred Concussion by History

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No History (n = 1708)</td>
<td></td>
</tr>
<tr>
<td>Female (n = 708)</td>
<td>8518</td>
<td>92.5</td>
</tr>
<tr>
<td>Male (n = 1000)</td>
<td>14099</td>
<td>93.7</td>
</tr>
<tr>
<td></td>
<td>22617</td>
<td>93.2</td>
</tr>
<tr>
<td></td>
<td>1639</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>912</td>
<td>93.0</td>
</tr>
<tr>
<td></td>
<td>69</td>
<td>7.0</td>
</tr>
<tr>
<td>History (n = 991)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n = 408)</td>
<td>2127</td>
<td>84.9</td>
</tr>
<tr>
<td>Male (n = 583)</td>
<td>3832</td>
<td>87.9</td>
</tr>
<tr>
<td></td>
<td>5959</td>
<td>86.8</td>
</tr>
<tr>
<td></td>
<td>907</td>
<td>13.2</td>
</tr>
<tr>
<td></td>
<td>448</td>
<td>84.2</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>15.8</td>
</tr>
</tbody>
</table>

Incurred Concussion by Category

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No History (n = 220)</td>
<td></td>
</tr>
<tr>
<td>Female (n = 166)</td>
<td>157</td>
<td>94.6</td>
</tr>
<tr>
<td>Male (n = 54)</td>
<td>52</td>
<td>96.3</td>
</tr>
<tr>
<td></td>
<td>209</td>
<td>95.0</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>701</td>
<td>97.4</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>2.6</td>
</tr>
</tbody>
</table>

39
Table 4.5 Prospective Relative Risk Ratios

<table>
<thead>
<tr>
<th></th>
<th>Risk of Concussion</th>
<th></th>
<th>Risk Without History</th>
<th></th>
<th>Risk With History</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>( \chi^2 )</td>
<td>( p )</td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F/M</td>
<td>1.194</td>
<td>1.107 - 1.287</td>
<td>21.242</td>
<td>&lt; .01</td>
<td>1.180</td>
<td>1.073 - 1.297</td>
</tr>
<tr>
<td>ADHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>1.236</td>
<td>1.059 - 1.443</td>
<td>7.097</td>
<td>&lt; .01</td>
<td>1.041</td>
<td>0.825 - 1.340</td>
</tr>
<tr>
<td>Males</td>
<td>1.369</td>
<td>1.133 - 1.654</td>
<td>10.369</td>
<td>&lt; .01</td>
<td>1.204</td>
<td>0.911 - 1.592</td>
</tr>
<tr>
<td>F/M</td>
<td>0.911</td>
<td>0.661 - 1.255</td>
<td>0.326</td>
<td></td>
<td>1.076</td>
<td>0.713 - 1.624</td>
</tr>
</tbody>
</table>

F/M designates females relative to males.

ADHD risk ratios relative to control athletes.
Table 4.6 Prospective Relative Risk Ratios by Contact Category

<table>
<thead>
<tr>
<th></th>
<th>NCAA Contact</th>
<th></th>
<th>NCAA Limited Contact</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk</td>
<td>95% CI</td>
<td>( \chi^2 )</td>
<td>( p )</td>
</tr>
<tr>
<td>Controls</td>
<td>1.040</td>
<td>0.928 - 1.165</td>
<td>0.454</td>
<td></td>
</tr>
<tr>
<td>F/M</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>1.159</td>
<td>0.959 - 1.401</td>
<td>0.299</td>
<td></td>
</tr>
<tr>
<td>F/M</td>
<td>1.025</td>
<td>0.67 - 1.559</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCAA Non-Contact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risk</td>
<td>95% CI</td>
<td>( \chi^2 )</td>
<td>( p )</td>
</tr>
<tr>
<td>Controls</td>
<td>1.546</td>
<td>1.140 - 2.103</td>
<td>7.873</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>F/M</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>0.931</td>
<td>0.514 - 1.687</td>
<td>0.055</td>
<td></td>
</tr>
<tr>
<td>F/M</td>
<td>3.226</td>
<td>0.710 - 14.652</td>
<td>*</td>
<td>0.09</td>
</tr>
</tbody>
</table>

F/M designates females relative to males. All ADHD risk ratios relative to control athletes.

* Indicates Fisher’s exact \( p \)-value is reported.
Unique athletes who experienced a single concussion during the study with complete ImPACT data at Baseline, 24-48hr post injury and at RTP (pre-exclusion n = 1,227)

Excluded (n = 358)
- 6 reported moderate-to-severe TBI
- 38 reported specific learning disorder, memory disorders, or psychiatric disorder (Bipolar, schizophrenia)
- 314 missing data for either injury or demographic data

Unique Eligible Athletes (n = 869)

<table>
<thead>
<tr>
<th>Controls (pre-exclusion n = 771)</th>
<th>ADHD+Rx (n = 46)</th>
<th>ADHD_uRx (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluded Controls (n = 155)</td>
<td>Excluded ADHD+Rx (n = 10)</td>
<td>Excluded ADHD_uRx (n = 14)</td>
</tr>
<tr>
<td>• 46 failed a year of high school.</td>
<td>• 6 Missing Rx name</td>
<td>• 8 Reported no Rx but listed a stimulant Rx name.</td>
</tr>
<tr>
<td>• 75 taking medications with known cognitive effects.</td>
<td>• 1 Non-stimulant Rx</td>
<td>• 6 Significant outliers on more than one data point</td>
</tr>
<tr>
<td>• 34 significant outliers</td>
<td>• 3 Significant Outlier on more than one data point</td>
<td></td>
</tr>
</tbody>
</table>

Unique Athletes Eligible for Matching Criteria (n = 690)

<table>
<thead>
<tr>
<th>Double Matched Controls (n = 140)</th>
<th>Matched ADHD+Rx (n = 35)</th>
<th>Matched ADHD_uRx (n = 35)</th>
</tr>
</thead>
</table>

**Figure 4.2** Selection Criteria for Specific Aim 3
### Table 4.7 Sample Characteristics for Aim 3 (Mean ± S.D.)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls</th>
<th>ADHD+Rx</th>
<th>ADHD_uRx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Sample</strong></td>
<td>140</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Male</td>
<td>100</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Female</td>
<td>40</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls</th>
<th>ADHD+Rx</th>
<th>ADHD_uRx</th>
<th>F</th>
<th>p</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>24.6 ± 4.6</td>
<td>24.7 ± 4.2</td>
<td>26.2 ± 2.9 *</td>
<td>4.001</td>
<td>.02</td>
<td>.038</td>
</tr>
<tr>
<td>Age at Baseline</td>
<td>18.9 ± 1.5</td>
<td>19.2 ± 1.3</td>
<td>19.1 ± 1.4</td>
<td>1.018</td>
<td>.363</td>
<td>.010</td>
</tr>
<tr>
<td>Age at Injury</td>
<td>20.4 ± 1.6</td>
<td>20.9 ± 1.6</td>
<td>21.1 ± 1.1</td>
<td>1.586</td>
<td>.211</td>
<td>.040</td>
</tr>
<tr>
<td>Years of Sport Participation</td>
<td>10.1 ± 3.5</td>
<td>10.9 ± 2.9</td>
<td>10.4 ± 4.0</td>
<td>.683</td>
<td>.506</td>
<td>.008</td>
</tr>
<tr>
<td>Concussion History</td>
<td>50 (35.7%)</td>
<td>10 (28.6%)</td>
<td>21 (60%) **</td>
<td>5.353</td>
<td>.005</td>
<td>.049</td>
</tr>
<tr>
<td>One</td>
<td>39 (27.9%)</td>
<td>8 (22.9%)</td>
<td>15 (42.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two or more</td>
<td>11 (7.9%)</td>
<td>2 (5.7%)</td>
<td>6 (17.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first concussion</td>
<td>15.6 ± 2.8</td>
<td>15.8 ± 1.2</td>
<td>15.0 ± 2.6</td>
<td>.827</td>
<td>.441</td>
<td>.021</td>
</tr>
</tbody>
</table>

**Post-Concussion (Days from injury to time point)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls</th>
<th>ADHD+Rx</th>
<th>ADHD_uRx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury reported</td>
<td>1.2 ± 2.2</td>
<td>1.7 ± 2.6</td>
<td>1.8 ± 4.1</td>
</tr>
<tr>
<td>Symptom resolution</td>
<td>5.4 ± 3.5</td>
<td>6.2 ± 4.9</td>
<td>9.2 ± 6.9 **</td>
</tr>
</tbody>
</table>

* Significant from controls only; ** Significant from all other groups
Table 4.8 ImPACT Scores (Mean ± S.D.)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>ADHD+Rx</th>
<th>ADHD_uRx</th>
<th>F</th>
<th>p</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impulse Control Composite</td>
<td>Baseline</td>
<td>4.686 ± 0.342</td>
<td>6.486 ± 0.684</td>
<td>7.343 ± 0.684*</td>
<td>7.463</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>24 - 48hr</td>
<td>6.071 ± 0.473</td>
<td>9.400 ± 0.946*</td>
<td>8.000 ± 0.946</td>
<td>5.689</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>uRTP</td>
<td>5.771 ± 0.429</td>
<td>9.057 ± 0.858**</td>
<td>5.829 ± 0.858</td>
<td>6.074</td>
<td>0.003</td>
</tr>
<tr>
<td>Reaction Time (seconds)</td>
<td>Baseline</td>
<td>0.584 ± 0.007</td>
<td>0.581 ± 0.014</td>
<td>0.631 ± 0.014*</td>
<td>4.670</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>24 - 48hr</td>
<td>0.606 ± 0.009</td>
<td>0.636 ± 0.018</td>
<td>0.683 ± 0.018*</td>
<td>7.403</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>uRTP</td>
<td>0.567 ± 0.007</td>
<td>0.565 ± 0.014</td>
<td>0.608 ± 0.014**</td>
<td>3.817</td>
<td>0.024</td>
</tr>
<tr>
<td>Total Symptom Score</td>
<td>Baseline</td>
<td>7.257 ± 0.786</td>
<td>8.200 ± 1.571</td>
<td>7.543 ± 1.571</td>
<td>0.146</td>
<td>0.865</td>
</tr>
<tr>
<td></td>
<td>24 - 48hr</td>
<td>18.507 ± 1.588</td>
<td>23.486 ± 3.176</td>
<td>22.771 ± 3.176</td>
<td>1.424</td>
<td>0.243</td>
</tr>
<tr>
<td></td>
<td>uRTP</td>
<td>0.629 ± 0.151**</td>
<td>1.429 ± 0.302</td>
<td>1.486 ± 0.322</td>
<td>3.230</td>
<td>0.042</td>
</tr>
<tr>
<td>Verbal Memory Composite</td>
<td>Baseline</td>
<td>86.393 ± 0.897</td>
<td>84.571 ± 1.793</td>
<td>83.886 ± 1.793</td>
<td>3.010</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>24 - 48hr</td>
<td>87.179 ± 1.115**</td>
<td>80.343 ± 2.229</td>
<td>78.743 ± 2.229</td>
<td>7.951</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>uRTP</td>
<td>92.029 ± 0.702</td>
<td>91.400 ± 1.403</td>
<td>87.857 ± 1.403*</td>
<td>3.545</td>
<td>0.031</td>
</tr>
<tr>
<td>Visual Memory Composite</td>
<td>Baseline</td>
<td>78.364 ± 1.231</td>
<td>75.114 ± 2.463</td>
<td>71.971 ± 2.463</td>
<td>2.962</td>
<td>0.054</td>
</tr>
<tr>
<td></td>
<td>24 - 48hr</td>
<td>75.300 ± 1.233</td>
<td>71.514 ± 2.466</td>
<td>69.514 ± 2.466*</td>
<td>2.675</td>
<td>0.071</td>
</tr>
<tr>
<td></td>
<td>uRTP</td>
<td>79.036 ± 1.174</td>
<td>76.200 ± 2.348</td>
<td>71.514 ± 2.348*</td>
<td>4.239</td>
<td>0.016</td>
</tr>
<tr>
<td>Visual Motor Speed</td>
<td>Baseline</td>
<td>42.602 ± 0.591</td>
<td>41.871 ± 1.181</td>
<td>38.350 ± 1.181*</td>
<td>5.184</td>
<td>0.006</td>
</tr>
<tr>
<td>Composite</td>
<td>24 - 48hr</td>
<td>42.156 ± 0.654</td>
<td>39.331 ± 1.307</td>
<td>35.248 ± 1.307**</td>
<td>11.673</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>uRTP</td>
<td>44.974 ± 0.566</td>
<td>42.813 ± 1.131</td>
<td>41.877 ± 1.131*</td>
<td>3.769</td>
<td>0.025</td>
</tr>
<tr>
<td>Cognitive Efficiency</td>
<td>Baseline</td>
<td>0.337 ± 0.012</td>
<td>0.313 ± 0.025</td>
<td>0.286 ± 0.025</td>
<td>1.816</td>
<td>0.165</td>
</tr>
<tr>
<td>Index</td>
<td>24 - 48hr</td>
<td>0.367 ± 0.012</td>
<td>0.313 ± 0.025</td>
<td>0.281 ± 0.025*</td>
<td>5.666</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>uRTP</td>
<td>0.421 ± 0.013</td>
<td>0.416 ± 0.026</td>
<td>0.351 ± 0.026</td>
<td>3.010</td>
<td>0.051</td>
</tr>
</tbody>
</table>

* Significant from controls only, ** Significant from all other groups.
CHAPTER 5: DISCUSSION

The primary aims of this study were to cross-sectionally and prospectively investigate the influence of ADHD on the 1) odds of concussion history, the 2) relative risk of incurring a concussion, and to 3) determine whether medication status influences recovery among college athletes with ADHD.

Specific Aims 1 & 2

Consistent with our hypotheses, we observed that both male and female athletes with self-reported diagnosis of ADHD had significantly greater odds of single and multiple concussions than controls, replicating prior results. Additionally, we observed the same pattern when stratifying by sport-contact category type, athletes with ADHD had significantly greater odds of single and multiple concussions than controls for contact, limited contact, non-contact, and non-NCAA categories. Interestingly, we observed that females with ADHD in the non-contact category had significantly greater odds of concussion than males with ADHD in the non-contact category. However, the reason behind this divergence is unclear. Thus, further investigation is needed regarding the confluence of sport-contact type and sex on concussion history.

Consistent with our hypotheses, we prospectively observed that all athletes with ADHD had greater risk for incurring a concussion during the study period. However, females with ADHD did not have increased risk for concussion despite having increased odds, relative to female controls. Based on these findings, a dissociation appears to exist between females and males with ADHD regarding the confluence of ADHD and prior
concussion history on concussion risk, relative to sex specific controls. There are several possible explanations for these findings, such as objective sex differences or varying degrees of aggressive styles of play between males and females. Additionally, it is possible that various sports males and females participate in have various levels of “contact” and differing rule sets, for example female ice hockey is a “no checking” sport, whereas male ice hockey allows full contact. Owing to the lack of comprehensive physiological data, any causally mechanistic discussion is speculative, however we will highlight features that are believed to contribute to our findings.

**Specific Aim 3**

*Baseline*

We hypothesized a priori differences between medicated and unmedicated athletes in terms of clinical symptoms and cognition. We observed that unmedicated athletes with ADHD performed worse on measures of impulse control, reaction time, and visual motor speed. These findings are consistent with previous findings from ADHD and concussion studies\(^{50, 57-61}\). However, while some results are statistically significant, we feel it is important to mention that this may not be a clinically meaningful difference (i.e., reaction time differences between 567 and 608ms).

*24 – 48 hours post injury*

In accordance with our hypotheses, we observed group differences at 24-48 hours post-injury while using baseline values as covariate. The unmedicated ADHD group performed worse than controls, but not the medicated ADHD group, for reaction time, visual memory, and cognitive efficiency. However, the unmedicated ADHD group performed worse than both medicated ADHD and controls for visual motor speed.
Interestingly, the medicated ADHD group performed worse than controls, but not unmedicated ADHD, for impulse control, suggesting a reemergence of self-regulatory difficulties for medicated ADHD.

*Unrestricted Return-to-play*

As hypothesized, there were some differences at uRTP between groups. The unmedicated ADHD group performed worse for reaction time than both controls and medicated ADHD. Controls also reported fewer total symptoms than either medicated or unmedicated. Additionally, the unmedicated ADHD group performed worse than controls, but not medicated ADHD for verbal memory, visual memory, and visual motor speed.

The unmedicated ADHD group reported greater duration of symptoms than either controls or medicated ADHD.

Interestingly, the three most closely related composites are impulse control, reaction time, and visual motor speed. For example, delayed reaction time and response speed suggest inefficient inhibition of a response or movement based on rule sets or decision making. Accordingly, there were differences between the medicated and unmedicated ADHD group, but no differences between the medicated ADHD group and controls for impulse control, reaction speed, and visual motor speed. This suggests that medications are working as expected given their abilities to regulate impulse control in those with ADHD. These findings appear to replicate previously reported effects of these stimulant medications on neurocognitive test performance.\textsuperscript{59, 63, 65-68} Acknowledging these preexisting differences reinforces the potential importance for ADHD medicated and unmedicated specific normative data for use when pre-season baseline testing is not
available or not a viable option. However, the only available normative data is non-ADHD specific as it includes any learning problems, special education needs, and is from 2003 using a limited sample size (total n = 256). Thus, the individual baseline analysis and inclusion as a covariate is an important feature of our study.

**Potential Mechanisms**

While this investigation did not employ any physiological measures, it is still important to mention mechanisms by which the presence of ADHD contribute to concussion (aims 1 & 2) as well as how ADHD medication may influence concussion symptoms (aim 3).

That all athletes with ADHD had greater odds for multiple prior concussions poses interesting questions regarding mechanisms (aims 1 & 2). Currently, it is not feasible to ascertain the underlying causative mechanisms for increased susceptibility for recurrent concussions, however we can speculate based on existing knowledge. First, it is widely acknowledged that a history of concussion is a probable risk factor for recurrent concussion. It is possible that structural and physiological alterations often observed in athletes with ADHD, such as reductions in axonal integrity, glucose metabolism, cerebral blood flow, and catecholamine levels, render these athletes more susceptible. Thus the “threshold at which concussion occurs” (i.e., velocity, impact ratings etc.) may be lessened in these athletes resulting in a greater incidence and risk for concussive injuries; however, to our knowledge no physiological or kinematic data exists in athletes with ADHD. There is some data suggesting there are motor control alterations which linger for weeks to years after concussion. Taken in consideration with reported motor control deficits commonly reported in ADHD, it is also possible that
increased rate of concussions in athletes with ADHD is partially a result of pre-injury motor deficits being exacerbated by concussion.

Although the physiology is likely complex, neuro-behavioral mechanism may be involved in the observed increased occurrence of concussion. ADHD is widely acknowledged to be a disorder of executive functions, particularly those of inhibition (i.e., impulse control) and attentional focus. Any deficits in inhibition and/or attentional focus represent a concern for athletes in sport environments.

Inhibition deficits in athletes may manifest as unnecessary risk taking, ignoring the potential outcomes of negative or dangerous actions, or heightened distractibility. Athletes with ADHD, due to lack of inhibitory control in the moment, may be placing themselves in potentially dangerous situations, such as head-to-head contact when unintended. Also, inhibition may result in the inability to filter out irrelevant information, resulting in distraction and a potentially hazardous situation. These situations may contribute to the observed increased prevalence of concussions among athletes with ADHD.

Similarly, any failure to attend to surrounding features, including the position, and/or intention of an opponent during active play could result in an impact related blow. If an athlete has ADHD, they may not be attending to the spatial position of these cues and place themselves at risk for concussive impacts or fall. Further, attending to a non-relevant cue in the environment may act as a distractor from potential hazards. Thus, behavioral lapses in attention to environment cues may also contribute to increased concussion occurrence in athletes with ADHD. However, this level of inattention during sport is most likely to be observed in children or adolescents and not observed as often in elite-level athletes as those most often seen in college.
Current evidence suggests that symptom severity is correlated with the degree to which metabolism is impaired\textsuperscript{17, 98, 133, 142, 144}. Accordingly, the deficits in neurocognitive performance observed in those with ADHD may be partly explained by a detrimental interaction between impairments inherent to ADHD and impairments induced by concussion. A possible consideration is the direct influence of stimulant medications, both AMPH (amphetamine) and MPH (methylphenidate) result in enhanced availability and/or activity of dopamine and, by extension, norepinephrine. Each of these neurotransmitters acts on key areas of the brain, particularly the areas involved in vigilance, impulse control, fine motor control, coordination, and reaction time\textsuperscript{263, 264}. Enhancing neurotransmitter signaling by using these medications may lead to improved metabolic activity, such as relatively normalizing glucose metabolism, leading to increased ATP production by the mitochondria, mitigating some of the acute effects of the neurometabolic cascade following concussion.

Healthy mitochondrial function includes a dynamic lifecycle called mitochondrial dynamics and is regulated by diverse complex mechanisms. However, this cycle can be simplified into 1) fusing with other mitochondria (fusion) and 2) dividing into separate mitochondria (fission). Fusion is a beneficial mechanism for consolidating multiple damaged organelles into a single organelle, and the subsequent fission into a healthy organelle and an organelle marked for autophagy. Mitochondrial dynamics are vital for axonal transport (i.e., anterograde and retrograde) to neuronal regions with the greatest energy requirements and is thought to be regulated by both the local metabolic state as well as the distribution of other mitochondria\textsuperscript{265}. Mitochondria localized to synapses are necessary to manage the energetic requirements of ATP-depended processes and regulate
Ca\textsuperscript{2+} concentrations during periods of intense activation\textsuperscript{266-268}. Additionally, this cycle is a particularly important facilitator of apoptosis during periods of increased cellular stress, such as the period following concussion.

In the concussion literature, several studies have reported that following an initial injury there exists a period following injury during which mitochondrial fission and autophagy exceeds mitochondrial fusion\textsuperscript{269-273}. This lag time appears to reflect the acute bioenergetic impairments that accompany concussion. Given the importance of mitochondrial function to homeostasis and meeting bioenergetic needs, this suggests that there is a period during which the neuron may be biochemically, metabolically, and perhaps even structurally attenuated due to mitochondrial dysfunction\textsuperscript{274}. Following a concussion there is increased demand for ATP in order restore ionic concentrations\textsuperscript{15, 16, 98}. This increased demand requires excessive ATP production which is accompanied by increased production of reactive oxygen species (ROS), a natural byproduct. However, if the quantity of oxidants exceeds the buffering abilities of cellular antioxidants, then ROS toxicity may occur. ROS toxicity impairs glucose uptake and metabolism\textsuperscript{275}, cellular membrane damage, cause genetic mutations, and/or result in apoptosis\textsuperscript{276}, all of which may be collectively referred to as oxidative stress (OxS).

The healthy brain may be particularly vulnerable to OxS due to increased energy demands and therefore dependency on mitochondria, thus with various injuries or disorders increased OxS may be increasingly detrimental. Indeed, OxS has been implicated in neurodegenerative diseases such as Alzheimer’s disease\textsuperscript{277, 278}, Parkinson’s disease\textsuperscript{279}, amyotrophic lateral sclerosis\textsuperscript{280, 281}, acute neurodegeneration resulting from cerebral ischemia,\textsuperscript{282} and traumatic brain injury\textsuperscript{283-285}. Several studies have reported that individuals
with ADHD have abnormally elevated levels of oxidative stress\textsuperscript{286-292}. Furthermore, it has been demonstrated that in ADHD, absent history of brain injury, there is an insufficient antioxidant response to increases in ROS, which activates intracellular signaling thereby modulating glucose uptake and metabolism and resulting in bioenergetic impairment. Collectively, it is plausible that increased ROS production may be a hallmark of mitochondrial dysfunction in ADHD and following concussion\textsuperscript{293, 294}. While evidence regarding mitochondrial bioenergetics in ADHD pathogenesis is limited, there is some evidence that OxS is a characteristic in ADHD\textsuperscript{295}.

In summary, mitochondria help regulate Ca\textsuperscript{2+} concentrations and produce ATP via cellular respiration using glucose and oxygen. In individuals with ADHD there are existing glucose deficits, reduced cerebral blood flow resulting in reduced oxygen availability, and increased OxS, particularly when not taking medication\textsuperscript{296}. Incurring a concussion exacerbates these deficits via the neurometabolic cascade and subsequent energy deficits as previously discussed. As seen in nearly all measures, individuals with medicated ADHD appeared to perform better than unmedicated ADHD. Physiologically, it is therefore plausible that psychostimulant medications mitigate some of these underlying ADHD specific deficits. For example, MPH not only regulates catecholamine uptake but also stimulates glycolysis and increases creatine kinase activity\textsuperscript{297} which may further help to mitigate energy deficiencies and therefore reduce suspected physiological underpinnings of ADHD. Indeed, early in the concussion treatment literature physicians were prescribing psychostimulants to treat concussion symptoms\textsuperscript{298}, however that practice has been called into question as more data on concussion is gathered.
The effects of psychostimulant medications are largely noticeable in the prefrontal cortex, striatum, and nucleus accumbens, areas closely associated with cognitive functions. Thus, these medications serve to enhance metabolic activity, neurotransmitter availability and activity, resulting in a net increase in cognitive functions. Further evidence suggesting these medications (i.e., MPH and AMPH) may enhance cognitive processes is reflected in the few studies demonstrating that athletes without a neurodevelopmental disorder taking these medications perform better on cognitive tasks than when not taking these medications (i.e., within subjects) absent concussion. Collectively, this may be a possible explanation why the medicated groups’ cognitive scores were more comparable to controls than to the unmedicated groups following concussion.

Limitations

These investigations have several methodological limitations. For Aims 1 & 2 we were unable to include exposure rates in our analysis. Of note, this sample contains sports in which there were disproportionate representations of a single sex and is therefore possible some findings are subject to sample bias. For Aim 1, the cross-sectional nature of retrospective self-reported ADHD diagnoses and prior concussions history prevents any determinations of temporality for concussion odds. However, since most ADHD diagnoses are made during early childhood it is likely they received a diagnosis before sustaining a concussion, although secondary ADHD following a moderate or severe brain injury has been reported previously. Additionally, diagnosis of ADHD was self-reported, therefore it is possible that some athletes did not report their diagnosis due to concern of stigma associated with ADHD. Furthermore, we did not exclude athletes with an IEP or 504-plan as there are many ways in which these may be provided to students without ADHD.
However, we excluded all participants who did not report ADHD but repeated a grade to control for this possibility. Furthermore, the rates of ADHD are relatively consistent with previous studies of collegiate athletes.\textsuperscript{30, 50, 55}

For Aims 1 & 2 we included athletes who did and did not take psycho-stimulant medications for their diagnoses to accurately represent the overall body of athletes with NDs. It is possible that differences exist between medicated and un-medicated athletes, or potential changes to medications during the study could influence injury odds and risk. However, there were no statistically significant differences in an exploratory analysis examining odds and risk by psycho-stimulant medication status within the ADHD group.

For aim 3 we feel it is important to note that impulsivity is often considered a marker of validity, rather than a cognitive-behavioral indices, additional the cognitive efficiency index has been removed from the ImPACT output as of version 4.0. We included self-report diagnosis of ADHD, as well as self-reported psychostimulant medications. While it is plausible that athletes or others involved were unaware of what constitutes a psychostimulant, we excluded all medications other than verifiable formulations of amphetamine and methylphenidate (i.e., Vyvanse, Ritalin, etc.). Additionally, we excluded athletes taking a combination of stimulant and non-stimulant medications. Thus, our sample may be biased towards higher performers in that we excluded mediations for anxiety and depression, which are very common among athletes, individuals with ADHD, and following concussion.\textsuperscript{299} Furthermore, we have no way of knowing if the athletes were consistent in their medication usage, dosage, or whether they continued taking their medications post-injury. Lastly, many psychostimulant medications are used to treat multiple conditions and not just ADHD, for example most psychostimulants may be used
to treat narcolepsy. However, we only included medicated individuals reporting ADHD which minimizes the likelihood of a prescription based on unknown or unreported diagnoses. Admittedly, we were unable to account for athletes who surreptitiously used these medications without a diagnosis or without a prescription.

**Conclusion**

In summary, this is the largest study to date to examine the influences of ADHD on concussion and concussion outcomes. Our findings for aims 1 and 2 further the existing literature by detailing the confluence of sex, neurodevelopment, and sport-contact type with concussion history and risk for incurring a future concussion. Our findings for aim 3 suggest there are some differences between athletes with ADHD control athletes, particularly regarding medication status. Athletes with medicated ADHD appear to have normalized baseline performance relative to unmedicated athletes with ADHD.

To our knowledge, these are the first findings of its kind and reinforces both the need to further examine the differential factors that predispose male and female athletes to concussion and the need for longitudinal investigation of concussion recovery, particularly regarding medications in athletes with ADHD. It is our hope that these results aid sport medical teams in determining “at-risk” athletes who may be more susceptible for concussive injury and potentially poorer injury outcomes.
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