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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[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[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[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[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[28]. ADHD is predominantly characterized by age or developmentally inappropriate degrees of inattention, hyperactivity, impulsivity, and risk taking behaviors[29]. These behavioral characteristics may contribute to the increased prevalence of negative outcomes such as anxiety or depression[30-39], social impairments[40, 41], academic difficulty[42], poor vocational performance[43], vehicular accidents[44, 45], and bodily injuries[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 [25, 26, 47-51]. 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.[52] suggests that athletes with ADHD have greater symptom burden following concussion, which is consistent with other reports[53]. While greater symptomology does not necessarily result in prolonged recovery, greater initial symptoms is considered the strongest risk factor for slower recovery[24]. 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"[50, 54-56]. 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[50, 57-61]. 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[62-64]. 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[74]. However, surveillance methods likely underestimate actual prevalence as most are based on emergency department visits and do not account for concussions treated elsewhere[74]. Additional injury reports created by team medical personnel may not always account for concussions occurring outside of school-based sports[75]. Furthermore, athletes may fail to report concussions because they did not think the symptoms were severe enough[20, 76], or they did not want to be removed from play[77]. 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[5]." 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[78], including the Head Injury Scale[79], Graded Symptom Checklist (GSC)[80], Balance Error Scoring System (BESS)[81, 82], vestibular-ocular motor screening (VOMS), Standard Assessment of Concussion (SAC)[83], Concussion Symptom Inventory[84], and a collected version of these tests often called the Sport Concussion Assessment Tool [85, 86]. 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 training[89, 90]. Regardless of impact or impulse each force can be transferred to the brain and result in some degree of deformation[91, 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 gravity[93]. 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 force[94, 95]. While most research is dedicated to the role of linear acceleration[96], evidence suggests that both linear and rotational forces occur in every concussion[97] which may contribute to resultant neurometabolic impairments[98].

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"[16, 98, 99]. This subsequent hypoactive state may reflect neuronal refractory periods during which ATP-dependent Na^+-K^+ pumps are hyperactive, attempting to restore resting ionic concentrations. These Na^+-K^+ 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^+-K^+ 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[100] further impairing oxidative phosphorylation[101]. This resultant energy crisis is concurrent with normal or reduced cerebral blood flow, and therefore no increase in solute delivery[102], resulting in an uncoupling of energy supply and demand[16]. Overall, this period of glucose hyper metabolism appears to be relatively transient, lasting 30-minutes to several hours in animal models[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[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[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[107-111]. There are also reports of abnormal white matter integrity following concussion which has been associated with neurocognitive impairments[112]. While some evidence exists reporting

volumetric reductions in the frontal cortex, cerebellum, and hippocampus months after concussion[113-116], other studies have failed to find similar differences[115].

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[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[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[18, 22, 118, 121], whereas females have higher rates for concussion in soccer, basketball, and ice hockey at different levels of competition[122]. Interestingly, compared to males in ice hockey, females demonstrated significant greater injury rates, despite prohibition of body checking in female ice hockey[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[122-124]. Furthermore, female athletes

appear to report greater symptom burden following concussion[125] as well as prolonged symptoms three months post-injury[126], although when compared to males in the same sports recovery rates normalize[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[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[61], to date however there is no consensus of the mechanisms by which sex modifies risk.

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[11, 98, 113, 128-133] that are most severe within the first week post-injury[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)[134]. Signs and symptoms of concussion are generally categorized as physical, cognitive, emotional, and sleep related, with some overlap[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[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)[136]. Emotional presentation is commonly reported as anxiety, depression, and other mood disruptions (e.g., anger)[137]. Sleep is considered a potential marker for predicting recovery[138, 139], and athletes may report sleep disruptions such as difficulties falling asleep, staying asleep, sleeping more or less than usual[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[141]. Similarly, athletes may present varying degrees of retrograde or anterograde amnesia, both LOC and amnesia may be important indicators of more serious injury[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[142].

Acute Management

Generally, mean symptom recovery occurs in about 14 days[5, 143], and seems relatively consistent with the associated neurometabolic cascade and impairments following concussion[16, 128]. While this period is considered "normal recovery", it is important to distinguish clinical symptomology from neurological recovery. McCrea et al.[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.[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[6-14].

The clinical evaluation of concussion has evolved beyond clinical measures to incorporate multi-modal assessments of cognitive, neurophysiological, and psychological function[5] as the search for more objective biomarkers recovery continues[145, 146]. Research has grown exponentially in recent years regarding the nature of concussion, risk factors, outcomes, treatments, rule changes, and equipment related concerns[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[151-153]. Among these characteristics, existing literature demonstrates that pre-existing conditions such as anxiety and depression[154], migraine[152], neurodevelopmental disorders[26, 50, 61, 155], and concussion history[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[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[26, 50].

Definition and Diagnosis

ADHD is characterized by age or developmentally inappropriate levels of inattention, hyperactivity, impulsivity, and risk-taking behaviors[29] that persist into adulthood for approximately 70% of cases, with varying degrees of severity[157]. ADHD is

typically observed during childhood as chronic impairments to attention and self-regulation during situations which require self-monitoring[157-160]. The hallmark triad—inattention, hyperactivity, and impulsivity—are chronic and relatively stable across the lifespan[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[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[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[162]. Although, a recent systematic review demonstrates that an overall ADHD diagnosis (i.e., unspecified sub-type) in adults is reliable and consistent[161].

ADHD is considered an impairment of behavioral inhibition (i.e., disinhibition) and self-regulation [163] which suggests impaired executive functionality [164-166]. Generally, it is agreed there are three core executive functions: inhibition (e.g., behavioral, and cognitive inhibition), working memory, and cognitive flexibility[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.[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[42, 170-185]. These overall reductions in executive function contributes to lifelong difficulties such as mood disorders (i.e., anxiety depression)[30-39], social impairments[40, 41], academic difficulty[42], poor vocational performance[43], vehicular accidents[44, 45], and bodily injuries[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.[55, 186]

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[187]. Similarly, 25% of adults with ADHD reported having a parent also diagnosed with ADHD[188]. There are several genetic association studies with dissimilar findings and small sample sizes[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[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 activation[200-204] 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 ADHD[206-209]. 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 stimuli[211]. Depending on task demands, the PFC can also sustain attention to a single task[212] or rapidly shift attention for

multitasking [213]. 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[214] while orbital and ventromedial PFC regulate emotions[215]. 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[216-220]. As cognitive loading or demand increase the DMN is attenuated by the task-positive network (TPN) of the dorsolateral prefrontal cortex (DLPFC)[221]. 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[222], and result in slower reaction times and inaccurate attention control[223].

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[224]. Also, Schweitzer et al.[225], 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[226, 227].

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 [228-230]. Dopamine (DA) is a neurotransmitter (NT) believed to play important roles in regulating cognition, attention, movement, motivation, and reward[231-234]. Norepinephrine (NE) is another NT associated with arousal, set-shifting and sustained

attention[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[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[237]. PFC concentrations of these NTs are positively associated with arousal level. For example, during low arousal conditions, NT concentrations are low[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[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.

Management

Currently, the most common approach to treating ADHD are psychostimulant medications[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[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)[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[244]. Additionally AMPH inhibits vesicular packaging of dopamine, thus increasing cytoplasmic dopamine concentrations ready for "reverse transport"[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[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[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[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.)[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[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.[26] reported college athletes with ADHD may have greater history of single and multiple concussions. Similarly, an aggregate study by Nelson et al.[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,[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"[50, 56]. Of note, these symptoms share significant overlap with the inattentiveness among individuals with ADHD which commonly persists into adulthood[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'.[252] 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[62-64]. 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[65, 69-71]. Stimulant medications are known to influence performance on neurocognitive test commonly used in the management of concussion[59, 63, 65-68]. Indeed, a recent study by Cook et al.[54] 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[66]. 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.[253] 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[253]. 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[254]. 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.[78, 255, 256] 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

(OR = .959, 95% CI .676 – 1.358), limited contact (OR = .820, 95% CI .522 – 1.288), or non-NCAA categories (OR = 1.346, 95% CI .577 – 3.140).

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 (η^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.

24-48hours 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

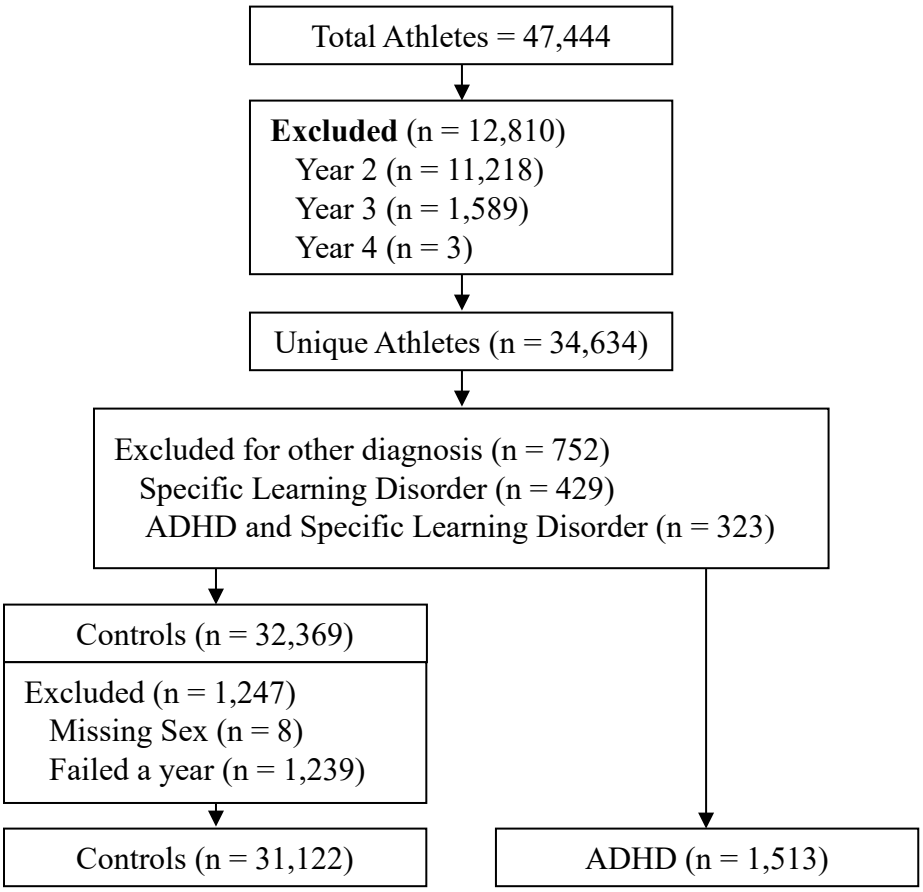

Figure 4.1. Selection Criteria for Specific Aims 1 & 2

Table 4.1 Sample Characteristics for Aim 1.

	Controls				ADHD			
	No History		History		No History		History	
	n	%	n	%	n	%	n	%
Overall History (n = 7398)	24256	77.9	6866	22.1	981	64.8	532	35.2
Female (n = 2681)	9205	78.6	2506	21.4	351	66.7	175	33.3
Male (n = 4717)	15051	77.5	4360	22.5	630	63.8	357	36.2
Concussion History by Quantity								
One Prior (n = 5607)	-	-	5221	93.1	-	-	386	6.9
Female (n = 1970)	-	-	1841	93.5	-	-	129	6.5
Male (n = 3637)	-	-	3380	92.9	-	-	257	7.1
Two + Prior (n = 1791)	-	-	1645	91.8	-	-	146	8.2
Female (n = 711)	-	-	665	93.5	-	-	46	6.5
Male (n = 1080)	-	-	980	90.7	-	-	100	9.3
Concussion History by Contact Category								
Contact (n = 3508)	7026	68.7	3204	31.3	386	55.9	304	44.1
Female (n = 1043)	1923	66.5	969	33.5	97	56.7	74	43.3
Male (n = 2465)	5103	69.5	2235	30.5	289	55.7	230	44.3
Limited Contact (n = 1393)	5400	80.8	1284	19.2	259	70.4	109	29.6
Female (n = 708)	2834	81.1	662	18.9	122	72.6	46	27.4
Male (n = 685)	2566	80.5	622	19.5	137	68.5	63	31.5
Non-Contact (n = 794)	4101	84.9	730	15.1	209	76.6	64	23.4
Female (n = 576)	2664	83.4	531	16.6	114	71.7	45	28.3
Male (n = 218)	1437	87.8	199	12.2	95	83.3	19	16.7
Non-NCAA (n = 1704)	7728	82.4	1649	17.6	127	69.8	55	30.2
Female (n = 354)	1784	83.8	344	16.2	18	64.3	10	35.7
Male (n = 1350)	5944	82.0	1305	18.0	109	70.8	45	29.2

Table 4.2 Retrospective Odds Ratios

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

F/M designates females relative to males.

ADHD odds ratios are relative to control athletes.

Table 4.3 Retrospective Odds Ratios by Contact Category

	Contact				Limited Contact			
	OR	95% CI	χ^2	*p*	OR	95% CI	χ^2	*p*
Controls F/M	1.151	1.050 - 1.261	8.961	< .01	0.964	0.853 - 1.088	0.355	
ADHD	1.727	1.478 - 2.019	48.104	< .01	1.770	1.404 - 2.232	23.843	< .01
F/M	0.959	0.676 - 1.358	0.057		0.820	0.522 - 1.288	0.743	
	Non - Contact				**Non - NCAA**			
	OR	95% CI	χ^2	*p*	OR	95% CI	χ^2	*p*
Controls F/M	1.439	1.208 - 1.715	16.748	< .01	0.878	0.77 - 1.000	3.831	< .05
ADHD	1.720	1.286 - 2.301	13.657	< .01	2.030	1.47 - 2.797	19.455	< .01
F/M	1.974	1.082 - 3.601	5.008	< .05	1.346	0.58 - 3.140	0.474	

F/M designates females relative to males.

ADHD odds ratios are relative to control athletes.

Table 4.4 Sample Characteristics for Aim 2

	Controls				ADHD			
	No Cx		Cx		No Cx		Cx	
	n	%	n	%	n	%	n	%
Overall Concussions (n = 2699)	28576	91.8	2546	8.2	1360	89.9	153	10.1
Female (n = 1116)	10645	90.9	1066	9.1	476	90.5	50	9.5
Male (n = 1583)	17931	92.4	1480	7.6	884	89.6	103	10.4
Incurred Concussion by History								
No History (n = 1708)	22617	93.2	1639	6.8	912	93.0	69	7.0
Female (n = 708)	8518	92.5	687	7.5	330	94.0	21	6.0
Male (n = 1000)	14099	93.7	952	6.3	582	92.4	48	7.6
History (n = 991)	5959	86.8	907	13.2	448	84.2	84	15.8
Female (n = 408)	2127	84.9	379	15.1	146	83.4	29	16.6
Male (n = 583)	3832	87.9	528	12.1	302	84.6	55	15.4
Incurred Concussion by Category								
Contact (n = 1365)	-	-	1266	92.7	-	-	99	7.3
Female (n = 393)	-	-	368	93.6	-	-	25	6.4
Male (n = 972)	-	-	898	92.4	-	-	74	7.6
Limited Contact (n = 394)	-	-	370	93.9	-	-	24	6.1
Female (n = 279)	-	-	266	95.3	-	-	13	4.7
Male (n = 115)	-	-	104	90.4	-	-	11	9.6
Non-Contact (n = 220)	-	-	209	95.0	-	-	11	5.0
Female (n = 166)	-	-	157	94.6	-	-	9	5.4
Male (n = 54)	-	-	52	96.3	-	-	2	3.7
Non-NCAA (n = 720)	-	-	701	97.4	-	-	19	2.6
Female (n = 278)	-	-	275	98.9	-	-	3	1.1
Male (n = 442)	-	-	426	96.4	-	-	16	3.6

Table 4.5 Prospective Relative Risk Ratios

	Risk of Concussion				**Risk Without History**				**Risk With History**			
	RR	95% CI	χ^2	*p*	RR	95% CI	χ^2	*p*	RR	95% CI	χ^2	*p*
Controls F/M	1.194	1.107 - 1.287	21.242	< .01	1.180	1.073 - 1.297	11.73	< .01	1.249	1.105 - 1.412	12.632	< .01
ADHD	1.236	1.059 - 1.443	7.097	< .01	1.041	0.825 - 1.340	0.11		1.195	0.973 - 1.468	2.836	
Females	1.044	0.797 - 1.369	0.099		0.802	0.526 - 1.221	1.08		1.096	0.776 - 1.547	0.266	
Males	1.369	1.133 - 1.654	10.369	< .01	1.204	0.911 - 1.592	1.69		1.272	0.985 - 1.644	3.316	
F/M	0.911	0.661 - 1.255	0.326		1.076	0.713 - 1.624	0.92		0.785	0.478 - 1.289	0.823	

F/M designates females relative to males.

ADHD risk ratios relative to control athletes.

Table 4.6 Prospective Relative Risk Ratios by Contact Category

	NCAA Contact				NCAA Limited Contact			
	Risk	95% CI	χ^2	*p*	Risk	95% CI	χ^2	*p*
Controls								
F/M	1.040	0.928 - 1.165	0.454		2.332	1.94 - 3.080	60.241	< .01
ADHD	1.159	0.959 - 1.401	0.299		1.178	0.790 - 1.756	0.643	
F/M	1.025	0.67 - 1.559	0.014		1.407	0.647 - 3.058	0.750	
	NCAA Non-Contact				**Non-NCAA**			
	Risk	95% CI	χ^2	*p*	Risk	95% CI	χ^2	*p*
Controls								
F/M	1.546	1.140 - 2.103	7.873	< .01	2.199	1.905 - 2.539	118.085	< .01
ADHD	0.931	0.514 - 1.687	0.055		1.396	0.907 - 2.150	2.252	
F/M	3.226	0.710 - 14.652	*	0.09	1.031	0.322 - 3.308	*	0.588

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

* Indicates Fisher's exact *p*-value is reported.

<table>
<tr><td colspan="3">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)</td></tr>
<tr><td colspan="3">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</td></tr>
<tr><td colspan="3">Unique Eligible Athletes (n = 869)</td></tr>
<tr><td>Controls (pre-exclusion n = 771)</td><td>ADHD+Rx (n = 46)</td><td>ADHD_uRx (n = 52)</td></tr>
<tr><td>Excluded Controls (n = 155)
46 failed a year of high school.
75 taking medications with known cognitive effects.
34 significant outliers</td><td>Excluded ADHD+Rx (n = 10)
6 Missing Rx name
1 Non-stimulant Rx
3 Significant Outlier on more than one data point</td><td>Excluded ADHD_uRx (n = 14)
8 Reported no Rx but listed a stimulant Rx name.
6 Significant outliers on more than one data point</td></tr>
<tr><td colspan="3">Unique Athletes Eligible for Matching Criteria (n = 690)</td></tr>
<tr><td>Double Matched Controls
(n = 140)</td><td>Matched ADHD+Rx
(n = 35)</td><td>Matched ADHD_uRx
(n = 35)</td></tr>
</table>

Figure 4.2 Selection Criteria for Specific Aim 3

Table 4.7 Sample Characteristics for Aim 3 (Mean ± S.D.)

	Controls	**ADHD+Rx**	**ADHD_uRx**			
Total Sample	140	35	35			
Male	100	26	24			
Female	40	9	11			
Characteristics				***F***	***p***	η^2
BMI	24.6 ± 4.6	24.7 ± 4.2	26.2 ± 2.9 *	4.001	.02	.038
Age at Baseline	18.9 ± 1.5	19.2 ± 1.3	19.1 ± 1.4	1.018	.363	.010
Age at Injury	20.4 ± 1.6	20.9 ± 1.6	21.1 ± 1.	1.586	.211	.040
Years of Sport Participation	10.1 ± 3.5	10.9 ± 2.9	10.4 ± 4.0	.683	.506	.008
Concussion History	50 (35.7%)	10 (28.6%)	21 (60%) **	5.353	.005	.049
One	39 (27.9%)	8 (22.9%)	15 (42.9%)			
Two or more	11 (7.9%)	2 (5.7%)	6 (17.1%)			
Age at first concussion	15.6 ± 2.8	15.8 ± 1.2	15.0 ± 2.6	.827	.441	.021
Post-Concussion (Days from injury to time point)						
Injury reported	1.2 ± 2.2	1.7 ± 2.6	1.8 ± 4.1	1.099	.335	.011
Symptom resolution	5.4 ± 3.5	6.2 ± 4.9	9.2 ± 6.9 **	9.452	< .001	.084

* Significant from controls only; ** Significant from all other groups

Table 4.8 ImPACT Scores (Mean ± S.D.)

		Control	ADHD+Rx	ADHD_uRx	F	p	η2
Impulse Control Composite	Baseline	4.686 ± 0.342	6.486 ± 0.684	7.343 ± 0.684*	7.463	0.001	0.067
	24 - 48hr	6.071 ± 0.473	9.400 ± 0.946*	8.000 ± 0.946	5.689	0.004	0.052
	uRTP	5.771 ± 0.429	9.057 ± 0.858**	5.829 ± 0.858	6.074	0.003	0.055
Reaction Time (seconds)	Baseline	0.584 ± 0.007	0.581 ± 0.014	0.631 ± 0.014*	4.670	0.010	0.043
	24 - 48hr	0.606 ± 0.009	0.636 ± 0.018	0.683 ± 0.018*	7.403	0.001	0.067
	uRTP	0.567 ± 0.007	0.565 ± 0.014	0.608 ± 0.014**	3.817	0.024	0.036
Total Symptom Score	Baseline	7.257 ± 0.786	8.200 ± 1.571	7.543 ± 1.571	0.146	0.865	0.001
	24 - 48hr	18.507 ± 1.588	23.486 ± 3.176	22.771 ± 3.176	1.424	0.243	0.014
	uRTP	0.629 ± 0.151**	1.429 ± 0.302	1.486 ± 0.322	3.230	0.042	0.030
Verbal Memory Composite	Baseline	86.393 ± 0.897	84.571 ± 1.793	83.886 ± 1.793	3.010	0.051	0.028
	24 - 48hr	87.179 ± 1.115**	80.343 ± 2.229	78.743 ± 2.229	7.951	0.000	0.071
	uRTP	92.029 ± 0.702	91.400 ± 1.403	87.857 ± 1.403*	3.545	0.031	0.033
Visual Memory Composite	Baseline	78.364 ± 1.231	75.114 ± 2.463	71.971 ± 2.463	2.962	0.054	0.028
	24 - 48hr	75.300 ± 1.233	71.514 ± 2.466	69.514 ± 2.466*	2.675	0.071	0.025
	uRTP	79.036 ± 1.174	76.200 ± 2.348	71.514 ± 2.348*	4.239	0.016	0.039
Visual Motor Speed Composite	Baseline	42.602 ± 0.591	41.871 ± 1.181	38.350 ± 1.181*	5.184	0.006	0.048
	24 - 48hr	42.156 ± 0.654	39.331 ± 1.307	35.248 ± 1.307**	11.673	0.000	0.101
	uRTP	44.974 ± 0.566	42.813 ± 1.131	41.877 ± 1.131*	3.769	0.025	0.035
Cognitive Efficiency Index	Baseline	0.337 ± 0.012	0.313 ± 0.025	0.286 ± 0.025	1.816	0.165	0.017
	24 - 48hr	0.367 ± 0.012	0.313 ± 0.025	0.281 ± 0.025*	5.666	0.004	0.052
	uRTP	0.421 ± 0.013	0.416 ± 0.026	0.351 ± 0.026	3.010	0.051	0.028

* 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.[26] 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.[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[20, 22, 79, 118, 120]. 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 [258-262]. 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 [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[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[265]. Mitochondria localized to synapses are necessary to manage the energetic requirements of ATP-depended processes and regulate

Ca^{2+} concentrations during periods of intense activation[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[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[274]. Following a concussion there is increased demand for ATP in order restore ionic concentrations[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[275], cellular membrane damage, cause genetic mutations, and/or result in apoptosis [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[277, 278], Parkinson's disease[279], amyotrophic lateral sclerosis[280, 281], acute neurodegeneration resulting from cerebral ischemia,[282] and traumatic brain injury[283-285]. Several studies have reported that individuals

with ADHD have abnormally elevated levels of oxidative stress [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 [293, 294]. While evidence regarding mitochondrial bioenergetics in ADHD pathogenesis is limited, there is some evidence that OxS is a characteristic in ADHD[295].

In summary, mitochondria help regulate Ca^{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[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[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[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[65]. 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.[49] 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.[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.[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.

REFERENCES

1. Peterson AB, Xu L, Daugherty J, Breiding MJ. Surveillance report of traumatic brain injury-related emergency department visits, hospitalizations, and deaths, United States, 2014. 2019;

2. Goodell R. NFL Commitment to Player Health and Safety: A Letter from Commissioner Roger Goodell. Digital Media. Play Smart. Play safe. Accessed September 22, 2019.

3. Roach R. U.S. Defense Department, NCAA Collaborating on Brain Injury Research. June 5, 2014. Accessed October 2, 2019.

4. Spataro K. NCAA and Department of Defense expand concussion study with $22.5 million in new funding. October 31, 2018. Accessed October 2, 2019.

5. McCrory P, Meeuwisse W, Dvorak J, et al. Consensus statement on concussion in sport-the 5(th) international conference on concussion in sport held in Berlin, October 2016. *Br J Sports Med*. Jun 2017;51(11):838-847. doi:10.1136/bjsports-2017-097699

6. Makdissi M, Schneider KJ, Feddermann-Demont N, et al. Approach to investigation and treatment of persistent symptoms following sport-related concussion: a systematic review. *Br J Sports Med*. Jun 2017;51(12):958-968. doi:10.1136/bjsports-2016-097470

7. Maruta J, Spielman LA, Yarusi BB, Wang Y, Silver JM, Ghajar J. Chronic Post-Concussion Neurocognitive Deficits. II. Relationship with Persistent Symptoms. *Front Hum Neurosci*. 2016;10:45. doi:10.3389/fnhum.2016.00045

8. Oldenburg C, Lundin A, Edman G, Nygren-de Boussard C, Bartfai A. Cognitive reserve and persistent post-concussion symptoms--A prospective mild traumatic brain injury (mTBI) cohort study. *Brain Inj*. 2016;30(2):146-55. doi:10.3109/02699052.2015.1089598

9. Moore RD, Sauve W, Ellemberg D. Neurophysiological correlates of persistent psycho-affective alterations in athletes with a history of concussion. *Brain Imaging Behav*. Dec 2016;10(4):1108-1116. doi:10.1007/s11682-015-9473-6

10. Broglio SP, Pontifex MB, O'Connor P, Hillman CH. The persistent effects of concussion on neuroelectric indices of attention. *J Neurotrauma*. Sep 2009;26(9):1463-70. doi:10.1089/neu.2008-0766
10.1089/neu.2008.0766

11. Moore RD, Pindus DM, Raine LB, et al. The persistent influence of concussion on attention, executive control and neuroelectric function in preadolescent children. *Int J Psychophysiol*. Jan 2016;99:85-95. doi:10.1016/j.ijpsycho.2015.11.010

12. Moore RD, Pindus DM, Drolette ES, Scudder MR, Raine LB, Hillman CH. The persistent influence of pediatric concussion on attention and cognitive control during flanker performance. *Biol Psychol*. Jul 2015;109:93-102. doi:10.1016/j.biopsycho.2015.04.008

13. Warden DL, Bleiberg J, Cameron KL, et al. Persistent prolongation of simple reaction time in sports concussion. *Neurology*. Aug 14 2001;57(3):524-6.

14. Marshall S, Bayley M, McCullagh S, et al. Updated clinical practice guidelines for concussion/mild traumatic brain injury and persistent symptoms. *Brain Inj*. 2015;29(6):688-700. doi:10.3109/02699052.2015.1004755

15. Giza CC, Hovda DA. Ionic and metabolic consequences of concussion. *Neurologic Athletic Head and Spine Injuries Philadelphia, PA: WB Saunders*. 2000;2000:80-100.

16. Giza CC, Hovda DA. The Neurometabolic Cascade of Concussion. *J Athl Train*. Sep 2001;36(3):228-235.

17. Kamins J, Bigler E, Covassin T, et al. What is the physiological time to recovery after concussion? A systematic review. *Br J Sports Med*. Jun 2017;51(12):935-940. doi:10.1136/bjsports-2016-097464

18. Schulz MR, Marshall SW, Mueller FO, et al. Incidence and risk factors for concussion in high school athletes, North Carolina, 1996–1999. *American journal of epidemiology*. 2004;160(10):937-944.

19. Delaney JS, Frankovich R. Head injuries and concussions in soccer. *Clin J Sport Med*. Jul 2005;15(4):216-9; discussion 212-3.

20. Delaney JS, Lacroix VJ, Leclerc S, Johnston KM. Concussions among university football and soccer players. *Clin J Sport Med*. Nov 2002;12(6):331-8.

21. Delaney JS, Lacroix VJ, Gagne C, Antoniou J. Concussions among university football and soccer players: a pilot study. *Clin J Sport Med*. Oct 2001;11(4):234-40.

22. Guskiewicz KM, McCrea M, Marshall SW, et al. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. *JAMA*. Nov 19 2003;290(19):2549-55. doi:10.1001/jama.290.19.2549

23. Zemper ED. Two-year prospective study of relative risk of a second cerebral concussion. *Am J Phys Med Rehabil*. Sep 2003;82(9):653-9. doi:10.1097/01.PHM.0000083666.74494.BA

24. McCrory P, Meeuwisse W, Dvorak J, et al. Consensus statement on concussion in sport-the 5th international conference on concussion in sport held in Berlin, October 2016. *Br J Sports Med*. Apr 26 2017;doi:10.1136/bjsports-2017-097699

25. Kutcher JS, Eckner JT. At-risk populations in sports-related concussion. *Curr Sports Med Rep*. Jan-Feb 2010;9(1):16-20. doi:10.1249/JSR.0b013e3181caa89d

26. Alosco ML, Fedor AF, Gunstad J. Attention deficit hyperactivity disorder as a risk factor for concussions in NCAA division-I athletes. *Brain Inj*. 2014;28(4):472-4. doi:10.3109/02699052.2014.887145

27. Han DH, McDuff D, Thompson D, Hitchcock ME, Reardon CL, Hainline B. Attention-deficit/hyperactivity disorder in elite athletes: a narrative review. *British Journal of Sports Medicine*. 2019;53(12):741-745. doi:10.1136/bjsports-2019-100713

28. Albrecht B, Uebel-von Sandersleben H, Gevensleben H, Rothenberger A. Pathophysiology of ADHD and associated problems—starting points for NF interventions? *Frontiers in human neuroscience*. 2015;9:359.

29. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. 2013.

30. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry*. Apr 2006;163(4):716-23. doi:10.1176/ajp.2006.163.4.716

31. Nelson JM, Liebel SW. Anxiety and depression among college students with attention-deficit/hyperactivity disorder (ADHD): Cross-informant, sex, and subtype differences. *J Am Coll Health*. Feb-Mar 2018;66(2):123-132. doi:10.1080/07448481.2017.1382499

32. Newstadt M. ADHD and anxiety. *J Ky Med Assoc*. Aug 2007;105(8):397-8.

33. Schatz DB, Rostain AL. ADHD with comorbid anxiety: a review of the current literature. *J Atten Disord*. Nov 2006;10(2):141-9. doi:10.1177/1087054706286698

34. Davidsson M, Hult N, Gillberg C, Sarneo C, Gillberg C, Billstedt E. Anxiety and depression in adolescents with ADHD and autism spectrum disorders; correlation between parent- and self-reports and with attention and adaptive functioning. *Nord J Psychiatry*. Nov 2017;71(8):614-620. doi:10.1080/08039488.2017.1367840

35. Mayes SD, Calhoun SL, Bixler EO, et al. ADHD subtypes and comorbid anxiety, depression, and oppositional-defiant disorder: differences in sleep problems. *J Pediatr Psychol*. Apr 2009;34(3):328-37. doi:10.1093/jpepsy/jsn083

36. Himanen L, Portin R, Tenovuo O, et al. Attention and depressive symptoms in chronic phase after traumatic brain injury. *Brain Inj*. Mar 2009;23(3):220-7. doi:10.1080/02699050902748323

37. Taylor E. Children with ADHD at increased risk of adolescent ADHD, ODD, anxiety or depression and functional impairment. *Evid Based Ment Health*. Nov 2010;13(4):110. doi:10.1136/ebmh.13.4.110

38. Biederman J. Impact of comorbidity in adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2004;65 Suppl 3:3-7.

39. Steinhausen HC, Winkler Metzke C. Prevalence of affective disorders in children and adolescents: findings from the Zurich Epidemiological Studies. *Acta Psychiatr Scand Suppl*. 2003;(418):20-3.

40. Greene RW, Biederman J, Faraone SV, et al. Social impairment in girls with ADHD: patterns, gender comparisons, and correlates. *J Am Acad Child Adolesc Psychiatry*. Jun 2001;40(6):704-10. doi:10.1097/00004583-200106000-00016

41. Greene RW, Ablon JS. What does the MTA study tell us about effective psychosocial treatment for ADHD? *J Clin Child Psychol*. Mar 2001;30(1):114-21. doi:10.1207/S15374424JCCP3001_13

42. Biederman J, Monuteaux MC, Doyle AE, et al. Impact of executive function deficits and attention-deficit/hyperactivity disorder (ADHD) on academic outcomes in children. *J Consult Clin Psychol*. Oct 2004;72(5):757-66. doi:10.1037/0022-006X.72.5.757

43. Murphy K, Barkley RA. Attention deficit hyperactivity disorder adults: comorbidities and adaptive impairments. *Comprehensive psychiatry*. 1996;37(6):393-401.

44. Cox DJ, Humphrey JW, Merkel RL, Penberthy JK, Kovatchev B. Controlled-release methylphenidate improves attention during on-road driving by adolescents with attention-deficit/hyperactivity disorder. *J Am Board Fam Pract*. Jul-Aug 2004;17(4):235-9.

45. Cox DJ, Merkel RL, Penberthy JK, Kovatchev B, Hankin CS. Impact of methylphenidate delivery profiles on driving performance of adolescents with attention-deficit/hyperactivity disorder: a pilot study. *J Am Acad Child Adolesc Psychiatry*. Mar 2004;43(3):269-75. doi:10.1097/00004583-200403000-00007

46. DiScala C, Lescohier I, Barthel M, Li G. Injuries to Children With Attention Deficit Hyperactivity Disorder. *Pediatrics*. 1998;102(6):1415-1421. doi:10.1542/peds.102.6.1415

47. Biederman J, Feinberg L, Chan J, et al. Mild Traumatic Brain Injury and Attention-Deficit Hyperactivity Disorder in Young Student Athletes. *J Nerv Ment Dis*. Nov 2015;203(11):813-9. doi:10.1097/NMD.0000000000000375

48. Iverson GL, Atkins JE, Zafonte R, Berkner PD. Concussion History in Adolescent Athletes with Attention-Deficit Hyperactivity Disorder. *J Neurotrauma*. Dec 01 2016;33(23):2077-2080. doi:10.1089/neu.2014.3424

49. Iverson GL, Wojtowicz M, Brooks BL, et al. High School Athletes With ADHD and Learning Difficulties Have a Greater Lifetime Concussion History. *J Atten Disord*. Jul 18 2016;doi:10.1177/1087054716657410

50. Nelson LD, Guskiewicz KM, Marshall SW, et al. Multiple Self-Reported Concussions Are More Prevalent in Athletes With ADHD and Learning Disability. *Clin J Sport Med*. Mar 2016;26(2):120-7. doi:10.1097/JSM.0000000000000207

51. Yang LY, Huang CC, Chiu WT, Huang LT, Lo WC, Wang JY. Association of traumatic brain injury in childhood and attention-deficit/hyperactivity disorder: a population-based study. *Pediatr Res*. Sep 2016;80(3):356-62. doi:10.1038/pr.2016.85

52. Biederman J, Feinberg L, Chan J, et al. Mild traumatic brain injury and attention-deficit hyperactivity disorder in young student athletes. *The Journal of nervous and mental disease*. 2015;203(11):813.

53. Bonfield CM, Lam S, Lin Y, Greene S. The impact of attention deficit hyperactivity disorder on recovery from mild traumatic brain injury. *J Neurosurg Pediatr*. Aug 2013;12(2):97-102. doi:10.3171/2013.5.PEDS12424

54. Cook NE, Huang DS, Silverberg ND, et al. Baseline cognitive test performance and concussion-like symptoms among adolescent athletes with ADHD: examining differences based on medication use. *Clin Neuropsychol*. Apr 21 2017:1-12. doi:10.1080/13854046.2017.1317031

55. Zuckerman SL, Lee YM, Odom MJ, Solomon GS, Sills AK. Baseline neurocognitive scores in athletes with attention deficit-spectrum disorders and/or learning disability. *J Neurosurg Pediatr*. Aug 2013;12(2):103-9. doi:10.3171/2013.5.PEDS12524

56. Iverson GL, Gardner AJ, Terry DP, et al. Predictors of clinical recovery from concussion: a systematic review. *Br J Sports Med*. Jun 2017;51(12):941-948. doi:10.1136/bjsports-2017-097729

57. Collins MW, Grindel SH, Lovell MR, et al. Relationship between concussion and neuropsychological performance in college football players. *Jama*. 1999;282(10):964-970.

58. Lau BC, Collins MW, Lovell MR. Sensitivity and specificity of subacute computerized neurocognitive testing and symptom evaluation in predicting outcomes after sports-related concussion. *The American journal of sports medicine*. 2011;39(6):1209-1216.

59. Cook NE, Huang DS, Silverberg ND, et al. Baseline cognitive test performance and concussion-like symptoms among adolescent athletes with ADHD: examining

differences based on medication use. *The Clinical Neuropsychologist*. 2017;31(8):1341-1352.

60. Slaats-Willemse D, Swaab-Barneveld H, De Sonneville L, Van Der Meulen E, Buitelaar J. Deficient response inhibition as a cognitive endophenotype of ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2003;42(10):1242-1248.

61. Broshek DK, Kaushik T, Freeman JR, Erlanger D, Webbe F, Barth JT. Sex differences in outcome following sports-related concussion. *Journal of neurosurgery*. 2005;102(5):856-863.

62. Putukian M, Kreher JB, Coppel DB, Glazer JL, McKeag DB, White RD. Attention deficit hyperactivity disorder and the athlete: an American Medical Society for Sports Medicine position statement. *Clinical journal of sport medicine*. 2011;21(5):392-400.

63. Reardon CL, Factor RM. Considerations in the use of stimulants in sport. *Sports Medicine*. 2016;46(5):611-617.

64. Spencer T, Biederman J, Wilens T, et al. A large, double-blind, randomized clinical trial of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. *Biological psychiatry*. 2005;57(5):456-463.

65. Smith ME, Farah MJ. Are prescription stimulants "smart pills"? The epidemiology and cognitive neuroscience of prescription stimulant use by normal healthy individuals. *Psychol Bull*. Sep 2011;137(5):717-41. doi:10.1037/a0023825

66. Gardner RM, Yengo-Kahn A, Bonfield CM, Solomon GS. Comparison of baseline and post-concussion ImPACT test scores in young athletes with stimulant-treated and untreated ADHD. *The Physician and sportsmedicine*. 2017;45(1):1-10.

67. Advokat C, Scheithauer M. Attention-deficit hyperactivity disorder (ADHD) stimulant medications as cognitive enhancers. *Front Neurosci*. 2013;7:82. doi:10.3389/fnins.2013.00082

68. Advokat C. What are the cognitive effects of stimulant medications? Emphasis on adults with attention-deficit/hyperactivity disorder (ADHD). *Neurosci Biobehav Rev*. Jul 2010;34(8):1256-66. doi:10.1016/j.neubiorev.2010.03.006

69. Kolar D, Keller A, Golfinopoulos M, Cumyn L, Syer C, Hechtman L. Treatment of adults with attention-deficit/hyperactivity disorder. *Neuropsychiatric disease and treatment*. 2008;4(2):389.

70. Nelson A, Galon P. Exploring the relationship among ADHD, stimulants, and substance abuse. *J Child Adolesc Psychiatr Nurs*. Aug 2012;25(3):113-8. doi:10.1111/j.1744-6171.2012.00322.x

71. Spencer TJ, Brown A, Seidman LJ, et al. Effect of psychostimulants on brain structure and function in ADHD: a qualitative literature review of magnetic resonance imaging-based neuroimaging studies. *J Clin Psychiatry*. Sep 2013;74(9):902-17. doi:10.4088/JCP.12r08287

72. Spencer RC, Devilbiss DM, Berridge CW. The cognition-enhancing effects of psychostimulants involve direct action in the prefrontal cortex. *Biological psychiatry*. 2015;77(11):940-950.

73. Berridge CW, Devilbiss DM. Psychostimulants as cognitive enhancers: the prefrontal cortex, catecholamines, and attention-deficit/hyperactivity disorder. *Biological psychiatry*. 2011;69(12):e101-e111.

74. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. *J Head Trauma Rehabil*. Sep-Oct 2006;21(5):375-8.

75. Bell JM, Breiding MJ, DePadilla L. CDC's efforts to improve traumatic brain injury surveillance. *J Safety Res*. Sep 2017;62:253-256. doi:10.1016/j.jsr.2017.04.002

76. Valovich McLeod TC, Bay RC, Heil J, McVeigh SD. Identification of sport and recreational activity concussion history through the preparticipation screening and a symptom survey in young athletes. *Clin J Sport Med*. May 2008;18(3):235-40. doi:10.1097/JSM.0b013e3181705756

77. McCrea M, Hammeke T, Olsen G, Leo P, Guskiewicz K. Unreported concussion in high school football players: implications for prevention. *Clinical journal of sport medicine*. 2004;14(1):13-17.

78. Broglio SP, Cantu RC, Gioia GA, et al. National Athletic Trainers' Association position statement: management of sport concussion. *J Athl Train*. Mar-Apr 2014;49(2):245-65. doi:10.4085/1062-6050-49.1.07

79. Piland SG, Motl RW, Ferrara MS, Peterson CL. Evidence for the Factorial and Construct Validity of a Self-Report Concussion Symptoms Scale. *J Athl Train*. Jun 2003;38(2):104-112.

80. Guskiewicz KM, Bruce SL, Cantu RC, et al. National Athletic Trainers' Association Position Statement: Management of Sport-Related Concussion. *J Athl Train*. Sep 2004;39(3):280-297.

81. Guskiewicz KM. Balance assessment in the management of sport-related concussion. *Clin Sports Med*. Jan 2011;30(1):89-102, ix. doi:10.1016/j.csm.2010.09.004

82. Bell DR, Guskiewicz KM, Clark MA, Padua DA. Systematic review of the balance error scoring system. *Sports Health*. May 2011;3(3):287-95. doi:10.1177/1941738111403122

83. McCrory P, Johnston K, Meeuwisse W, et al. Summary and agreement statement of the 2nd International Conference on Concussion in Sport, Prague 2004. *Br J Sports Med*. Apr 2005;39(4):196-204. doi:10.1136/bjsm.2005.018614

84. Randolph C, Millis S, Barr WB, et al. Concussion symptom inventory: an empirically derived scale for monitoring resolution of symptoms following sport-related concussion. *Arch Clin Neuropsychol*. May 2009;24(3):219-29. doi:10.1093/arclin/acp025

85. Davis GA, Purcell L, Schneider KJ, et al. The Child Sport Concussion Assessment Tool 5th Edition (Child SCAT5): Background and rationale. *Br J Sports Med*. Jun 2017;51(11):859-861. doi:10.1136/bjsports-2017-097492

86. Echemendia RJ, Meeuwisse W, McCrory P, et al. The Sport Concussion Assessment Tool 5th Edition (SCAT5): Background and rationale. *Br J Sports Med*. Jun 2017;51(11):848-850. doi:10.1136/bjsports-2017-097506

87. Shaw NA. The neurophysiology of concussion. *Progress in neurobiology*. 2002;67(4):281-344.

88. Broglio SP, Surma T, Ashton-Miller JA. High school and collegiate football athlete concussions: a biomechanical review. *Ann Biomed Eng*. Jan 2012;40(1):37-46. doi:10.1007/s10439-011-0396-0

89. Champion HR, Holcomb JB, Young LA. Injuries from explosions: physics, biophysics, pathology, and required research focus. *J Trauma*. May 2009;66(5):1468-77; discussion 1477. doi:10.1097/TA.0b013e3181a27e7f

90. Mendez MF, Owens EM, Reza Berenji G, Peppers DC, Liang LJ, Licht EA. Mild traumatic brain injury from primary blast vs. blunt forces: post-concussion consequences and functional neuroimaging. *NeuroRehabilitation*. 2013;32(2):397-407. doi:10.3233/NRE-130861

91. Barth JT, Freeman JR, Broshek DK, Varney RN. Acceleration-deceleration sport-related concussion: the gravity of it all. *Journal of athletic training*. 2001;36(3):253.

92. Cernak I. Blast Injuries and Blast-Induced Neurotrauma: Overview of Pathophysiology and Experimental Knowledge Models and Findings. In: Kobeissy FH, ed. *Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects*. 2015. *Frontiers in Neuroengineering*.

93. Ommaya A, Goldsmith W, Thibault L. Biomechanics and neuropathology of adult and paediatric head injury. *British journal of neurosurgery*. 2002;16(3):220-242.

94. Meaney DF, Smith DH. Biomechanics of concussion. *Clinics in sports medicine*. 2011;30(1):19-31.

95. Ommaya A. Biomechanics of trauma. *Appleton-Century-Crofts, Eat Norwalk, CT, Biomechanics of Head Injuries: Experimental Aspects*. 1985;

96. Rowson S, Duma SM. Brain injury prediction: assessing the combined probability of concussion using linear and rotational head acceleration. *Annals of biomedical engineering*. 2013;41(5):873-882.

97. Guskiewicz KM, Mihalik JP, Shankar V, et al. Measurement of head impacts in collegiate football players: relationship between head impact biomechanics and acute clinical outcome after concussion. *Neurosurgery*. 2007;61(6):1244-1253.

98. Giza CC, Hovda DA. The new neurometabolic cascade of concussion. *Neurosurgery*. Oct 2014;75 Suppl 4:S24-33. doi:10.1227/NEU.0000000000000505

99. Leo AA. Further observations on the spreading depression of activity in the cerebral cortex. *Journal of neurophysiology*. 1947;10(6):409-414.

100. Barkhoudarian G, Hovda DA, Giza CC. The molecular pathophysiology of concussive brain injury. *Clinics in sports medicine*. 2011;30(1):33-48.

101. Cheng G, Kong Rh, Zhang Lm, Zhang Jn. Mitochondria in traumatic brain injury and mitochondrial-targeted multipotential therapeutic strategies. *British journal of pharmacology*. 2012;167(4):699-719.

102. Obenaus A, Ng M, Orantes AM, et al. Traumatic brain injury results in acute rarefication of the vascular network. *Scientific reports*. 2017;7(1):239.

103. Yoshino A, Hovda DA, Kawamata T, Katayama Y, Becker DP. Dynamic changes in local cerebral glucose utilization following cerebral concussion in rats: evidence of a hyper-and subsequent hypometabolic state. *Brain research*. 1991;561(1):106-119.

104. Bergsneider M, Hovda DA, Shalmon E, et al. Cerebral hyperglycolysis following severe traumatic brain injury in humans: a positron emission tomography study. *Journal of neurosurgery*. 1997;86(2):241-251.

105. Yoshino A, Hovda DA, Kawamata T, Katayama Y, Becker DP. Dynamic changes in local cerebral glucose utilization following cerebral conclusion in rats: evidence of a hyper- and subsequent hypometabolic state. *Brain Res*. Oct 4 1991;561(1):106-19. doi:10.1016/0006-8993(91)90755-k

106. Rowson S, Bland ML, Campolettano ET, et al. Biomechanical perspectives on concussion in sport. *Sports medicine and arthroscopy review*. 2016;24(3):100.

107. Johnson VE, Stewart W, Smith DH. Axonal pathology in traumatic brain injury. *Experimental neurology*. 2013;246:35-43.

108. Smith DH, Meaney DF, Shull WH. Diffuse axonal injury in head trauma. *The Journal of head trauma rehabilitation*. 2003;18(4):307-316.

109. Adams JH, Doyle D, Ford I, Gennarelli T, Graham D, McLellan D. Diffuse axonal injury in head injury: definition, diagnosis and grading. *Histopathology*. 1989;15(1):49-59.

110. Parizel P, Özsarlak Ö, Van Goethem J, et al. Imaging findings in diffuse axonal injury after closed head trauma. *European radiology*. 1998;8(6):960-965.

111. Maruta J, Lee SW, Jacobs EF, Ghajar J. A unified science of concussion. *Ann N Y Acad Sci*. Oct 2010;1208:58-66. doi:10.1111/j.1749-6632.2010.05695.x

112. Davenport EM, Whitlow CT, Urban JE, et al. Abnormal white matter integrity related to head impact exposure in a season of high school varsity football. *Journal of neurotrauma*. 2014;31(19):1617-1624.

113. Bigler ED. Structural neuroimaging in sport-related concussion. *Int J Psychophysiol*. Oct 2018;132(Pt A):105-123. doi:10.1016/j.ijpsycho.2017.09.006

114. Meyer JE, Arnett PA. Changes in symptoms in concussed and non-concussed athletes following neuropsychological assessment. *Developmental neuropsychology*. 2015;40(1):24-28.

115. Singh K, Trivedi R, Devi MM, Tripathi RP, Khushu S. Longitudinal changes in the DTI measures, anti-GFAP expression and levels of serum inflammatory cytokines following mild traumatic brain injury. *Experimental neurology*. 2016;275:427-435.

116. Coughlin JM, Wang Y, Munro CA, et al. Neuroinflammation and brain atrophy in former NFL players: an in vivo multimodal imaging pilot study. *Neurobiology of disease*. 2015;74:58-65.

117. Guskiewicz KM, McCrea M, Marshall SW, et al. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. *Jama*. 2003;290(19):2549-2555.

118. Hollis SJ, Stevenson MR, McIntosh AS, Shores EA, Collins MW, Taylor CB. Incidence, risk, and protective factors of mild traumatic brain injury in a cohort of Australian nonprofessional male rugby players. *Am J Sports Med*. Dec 2009;37(12):2328-33. doi:10.1177/0363546509341032

119. Schulz MR, Marshall SW, Mueller FO, et al. Incidence and risk factors for concussion in high school athletes, North Carolina, 1996-1999. *Am J Epidemiol*. Nov 15 2004;160(10):937-44. doi:10.1093/aje/kwh304

120. Guskiewicz KM, Weaver NL, Padua DA, Garrett WE, Jr. Epidemiology of concussion in collegiate and high school football players. *Am J Sports Med*. Sep-Oct 2000;28(5):643-50. doi:10.1177/03635465000280050401

121. Covassin T, Swanik CB, Sachs ML. Epidemiological considerations of concussions among intercollegiate athletes. *Appl Neuropsychol*. 2003;10(1):12-22. doi:10.1207/S15324826AN1001_3

122. Dick R. Is there a gender difference in concussion incidence and outcomes? *British journal of sports medicine*. 2009;43(Suppl 1):i46-i50.

123. Gessel LM, Fields SK, Collins CL, Dick RW, Comstock RD. Concussions among United States high school and collegiate athletes. *J Athl Train*. Oct-Dec 2007;42(4):495-503.

124. Lincoln AE, Caswell SV, Almquist JL, Dunn RE, Norris JB, Hinton RY. Trends in concussion incidence in high school sports: a prospective 11-year study. *Am J Sports Med*. May 2011;39(5):958-63. doi:10.1177/0363546510392326

125. Chiang Colvin A, Mullen J, Lovell MR, Vereeke West R, Collins MW, Groh M. The role of concussion history and gender in recovery from soccer-related concussion. *The American journal of sports medicine*. 2009;37(9):1699-1704.

126. Preiss-Farzanegan SJ, Chapman B, Wong TM, Wu J, Bazarian JJ. The relationship between gender and postconcussion symptoms after sport-related mild traumatic brain injury. *PM&R*. 2009;1(3):245-253.

127. Master CL, Katz BP, Arbogast KB, et al. Differences in sport-related concussion for female and male athletes in comparable collegiate sports: a study from the NCAA-DoD Concussion Assessment, Research and Education (CARE) Consortium. *Br J Sports Med*. Dec 21 2020;doi:10.1136/bjsports-2020-103316

128. Chancellor SE, Franz ES, Minaeva OV, Goldstein LE. Pathophysiology of Concussion. *Semin Pediatr Neurol*. Jul 2019;30:14-25. doi:10.1016/j.spen.2019.03.004

129. Churchill NW, Hutchison MG, Richards D, Leung G, Graham SJ, Schweizer TA. Neuroimaging of sport concussion: persistent alterations in brain structure and function at medical clearance. *Sci Rep*. Aug 24 2017;7(1):8297. doi:10.1038/s41598-017-07742-3

130. Davis GA, Iverson GL, Guskiewicz KM, Ptito A, Johnston KM. Contributions of neuroimaging, balance testing, electrophysiology and blood markers to the assessment of sport-related concussion. *Br J Sports Med*. May 2009;43 Suppl 1:i36-45. doi:10.1136/bjsm.2009.058123

131. Ellis MJ, Leiter J, Hall T, et al. Neuroimaging findings in pediatric sports-related concussion. *J Neurosurg Pediatr*. Sep 2015;16(3):241-7. doi:10.3171/2015.1.PEDS14510

132. Moore RD, Broglio SP, Hillman CH. Sport-related concussion and sensory function in young adults. *J Athl Train*. Jan-Feb 2014;49(1):36-41. doi:10.4085/1062-6050-49.1.02

133. Wang Y, Nencka AS, Meier TB, et al. Cerebral blood flow in acute concussion: preliminary ASL findings from the NCAA-DoD CARE consortium. *Brain Imaging Behav*. Oct 2019;13(5):1375-1385. doi:10.1007/s11682-018-9946-5

134. Nature.

135. CDC. Heads Up: Facts for Physicians About Mild Traumatic Brain Injury (mTBI).

136. Blinman TA, Houseknecht E, Snyder C, Wiebe DJ, Nance ML. Postconcussive symptoms in hospitalized pediatric patients after mild traumatic brain injury. *Journal of pediatric surgery*. 2009;44(6):1223-1228.

137. Mainwaring LM, Hutchison M, Bisschop SM, Comper P, Richards DW. Emotional response to sport concussion compared to ACL injury. *Brain injury*. 2010;24(4):589-597.

138. Jaffee MS, Winter WC, Jones CC, Ling G. Sleep disturbances in athletic concussion. *Brain injury*. 2015;29(2):221-227.

139. Lau B, Lovell MR, Collins MW, Pardini J. Neurocognitive and symptom predictors of recovery in high school athletes. *Clinical Journal of Sport Medicine*. 2009;19(3):216-221.

140. Kostyun R. Sleep disturbances in concussed athletes: A review of the literature. *Connecticut medicine*. 2015;79(3):161-165.

141. Collins MW, Iverson GL, Lovell MR, McKeag DB, Norwig J, Maroon J. On-field predictors of neuropsychological and symptom deficit following sports-related concussion. *Clinical Journal of Sport Medicine*. 2003;13(4):222-229.

142. Henry LC, Tremblay S, Boulanger Y, Ellemberg D, Lassonde M. Neurometabolic changes in the acute phase after sports concussions correlate with symptom severity. *J Neurotrauma*. Jan 2010;27(1):65-76. doi:10.1089/neu.2009.0962

143. McCrea M, Guskiewicz KM, Marshall SW, et al. Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *JAMA*. Nov 19 2003;290(19):2556-63. doi:10.1001/jama.290.19.2556

144. Henry LC, Elbin RJ, Collins MW, Marchetti G, Kontos AP. Examining Recovery Trajectories After Sport-Related Concussion With a Multimodal Clinical Assessment Approach. *Neurosurgery*. Feb 2016;78(2):232-41. doi:10.1227/NEU.0000000000001041

145. Asken BM. Concussion Biomarkers: Deviating From the Garden Path. *JAMA neurology*. 2019;76(5):515-516.

146. Tripathi A, Dhanju S, Rowson S, et al. Greater Accuracy in Concussion Diagnosis in Collegiate Athletes through the use of Blood Brain Biomarkers. *Neurology*. 2019;93(14 Supplement 1):S5-S5.

147. McGuine T, Post E, Pfaller AY, et al. Does soccer headgear reduce the incidence of sport-related concussion? A cluster, randomised controlled trial of adolescent athletes. *British journal of sports medicine*. 2019:bjsports-2018-100238.

148. O'Brien T. Review impact of NCAA, NFL collaboration to address concussion concerns. *College Athletics and the Law*. 2019;16(5):1-3.

149. Ventresca M, McDonald MG. Sociocultural Examinations of Sports Concussions'. 2019;

150. Smith AM, Alford PA, Aubry M, et al. Proceedings from the Ice Hockey Summit III: action on concussion. *Current sports medicine reports*. 2019;18(1):23-34.

151. Borgaro SR, Prigatano GP, Kwasnica C, Rexer JL. Cognitive and affective sequelae in complicated and uncomplicated mild traumatic brain injury. *Brain Injury*. 2003;17(3):189-198.

152. Terry D, Gardner A, Iverson G. Systematic Review of Pre-Injury Migraine Disorder as a Risk Factor for Worse Outcome Following Sport-Related Concussion. *Archives of Clinical Neuropsychology*. 2019;34(5):754-754.

153. Coppel DB, Herring SA. Traumatic Brain Injury: Sports Concussion. *Physician's Field Guide to Neuropsychology*. Springer; 2019:327-361.

154. McCauley SR, Boake C, Levin HS, Contant CF, Song JX. Postconcussional disorder following mild to moderate traumatic brain injury: anxiety, depression, and social support as risk factors and comorbidities. *Journal of Clinical and Experimental Neuropsychology*. 2001;23(6):792-808.

155. Adeyemo BO, Biederman J, Zafonte R, et al. Mild traumatic brain injury and ADHD: a systematic review of the literature and meta-analysis. *J Atten Disord*. Oct 2014;18(7):576-84. doi:10.1177/1087054714543371

156. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *International journal of epidemiology*. 2014;43(2):434-442.

157. Barkley RA, Fischer M, Edelbrock CS, Smallish L. The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1990;29(4):546-557.

158. Barkley RA, Murphy K, Kwasnik D. Psychological adjustment and adaptive impairments in young adults with ADHD. *Journal of Attention Disorders*. 1996;1(1):41-54.

159. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. *Nat Rev Dis Primers*. Aug 6 2015;1:15020. doi:10.1038/nrdp.2015.20

160. Faraone SV, Biederman J. ADHD: disorder or discipline problem? *Science*. Feb 23 2001;291(5508):1488-9. doi:10.1126/science.291.5508.1488

161. Spencer T, Biederman J, Wilens T, Faraone SV. Is attention-deficit hyperactivity disorder in adults a valid disorder? *Harvard Review of Psychiatry*. 1994;1(6):326-335.

162. Lahey BB, Applegate B, McBurnett K, et al. DMS-IV field trials for attention deficit hyperactivity disorder in children and adolescents. *The American Journal of Psychiatry*. 1994;

163. Nigg JT. Is ADHD a disinhibitory disorder? *Psychological bulletin*. 2001;127(5):571.

164. Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. *Journal of child psychology and psychiatry*. 1996;37(1):51-87.

165. Makris N, Buka SL, Biederman J, et al. Attention and executive systems abnormalities in adults with childhood ADHD: A DT-MRI study of connections. *Cereb Cortex*. May 2008;18(5):1210-20. doi:10.1093/cercor/bhm156

166. Antshel KM, Faraone SV, Maglione K, et al. Executive functioning in high-IQ adults with ADHD. *Psychol Med*. Nov 2010;40(11):1909-18. doi:10.1017/S0033291709992273

167. Diamond A. Executive functions. *Annual review of psychology*. 2013;64:135-168.

168. Hofmann W, Schmeichel BJ, Baddeley AD. Executive functions and self-regulation. *Trends in cognitive sciences*. 2012;16(3):174-180.

169. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cogn Psychol*. Aug 2000;41(1):49-100. doi:10.1006/cogp.1999.0734

170. Silverstein MJ, Faraone SV, Leon TL, Biederman J, Spencer TJ, Adler LA. The Relationship Between Executive Function Deficits and DSM-5-Defined ADHD

Symptoms. *J Atten Disord*. Oct 8 2018:1087054718804347. doi:10.1177/1087054718804347

171. Miklos M, Futo J, Komaromy D, Balazs J. Executive Function and Attention Performance in Children with ADHD: Effects of Medication and Comparison with Typically Developing Children. *Int J Environ Res Public Health*. Oct 10 2019;16(20)doi:10.3390/ijerph16203822

172. Krieger V, Amador-Campos JA, Gallardo-Pujol D. Temperament, executive function, and attention-deficit/hyperactivity disorder (ADHD) in adolescents: The mediating role of effortful control. *J Clin Exp Neuropsychol*. Aug 2019;41(6):615-633. doi:10.1080/13803395.2019.1599824

173. Pineda-Alhucema W, Aristizabal E, Escudero-Cabarcas J, Acosta-Lopez JE, Velez JI. Executive Function and Theory of Mind in Children with ADHD: a Systematic Review. *Neuropsychol Rev*. Sep 2018;28(3):341-358. doi:10.1007/s11065-018-9381-9

174. Berenguer Forner C, Rosello Miranda B, Baixauli Fortea I, Garcia Castellar R, Colomer Diago C, Miranda Casas A. ADHD Symptoms and peer problems: Mediation of executive function and theory of mind. *Psicothema*. Nov 2017;29(4):514-519. doi:10.7334/psicothema2016.376

175. Krieger V, Amador-Campos JA. Assessment of executive function in ADHD adolescents: contribution of performance tests and rating scales. *Child Neuropsychol*. Nov 2018;24(8):1063-1087. doi:10.1080/09297049.2017.1386781

176. Karalunas SL, Bierman KL, Huang-Pollock CL. Test-Retest Reliability and Measurement Invariance of Executive Function Tasks in Young Children With and Without ADHD. *J Atten Disord*. Feb 9 2016;doi:10.1177/1087054715627488

177. Tamm L, Nakonezny PA. Metacognitive executive function training for young children with ADHD: a proof-of-concept study. *Atten Defic Hyperact Disord*. Sep 2015;7(3):183-90. doi:10.1007/s12402-014-0162-x

178. Paloscia C, Baglioni V, Alessandrelli R, et al. [Executive function deficits in ADHD and Asperger syndrome]. *Riv Psichiatr*. Nov-Dec 2013;48(6):441-7. Deficit delle funzioni esecutive nell'ADHD e nella sindrome di Asperger. doi:10.1708/1379.15338

179. Miller M, Nevado-Montenegro AJ, Hinshaw SP. Childhood executive function continues to predict outcomes in young adult females with and without childhood-diagnosed ADHD. *J Abnorm Child Psychol*. Jul 2012;40(5):657-68. doi:10.1007/s10802-011-9599-y

180. Shoham R, Sonuga-Barke E, Yaniv I, Pollak Y. ADHD Is Associated With a Widespread Pattern of Risky Behavior Across Activity Domains. *J Atten Disord*. Oct 4 2019:1087054719875786. doi:10.1177/1087054719875786

181. Marx I, Hacker T, Yu X, Cortese S, Sonuga-Barke E. ADHD and the Choice of Small Immediate Over Larger Delayed Rewards: A Comparative Meta-Analysis of Performance on Simple Choice-Delay and Temporal Discounting Paradigms. *J Atten Disord*. May 1 2018:1087054718772138. doi:10.1177/1087054718772138

182. Van Dessel J, Morsink S, Van der Oord S, et al. Waiting impulsivity: a distinctive feature of ADHD neuropsychology? *Child Neuropsychol*. Jan 2019;25(1):122-129. doi:10.1080/09297049.2018.1441819

183. Sonuga-Barke E, Brandeis D, Holtmann M, Cortese S. Computer-based cognitive training for ADHD: a review of current evidence. *Child Adolesc Psychiatr Clin N Am*. Oct 2014;23(4):807-24. doi:10.1016/j.chc.2014.05.009

184. Petrovic P, Castellanos FX. Top-Down Dysregulation-From ADHD to Emotional Instability. *Front Behav Neurosci*. 2016;10:70. doi:10.3389/fnbeh.2016.00070

185. Szekely E, Sudre GP, Sharp W, Leibenluft E, Shaw P. Defining the Neural Substrate of the Adult Outcome of Childhood ADHD: A Multimodal Neuroimaging Study of Response Inhibition. *Am J Psychiatry*. Sep 1 2017;174(9):867-876. doi:10.1176/appi.ajp.2017.16111313

186. Arnett AB, Pennington BF, Willcutt EG, DeFries JC, Olson RK. Sex differences in ADHD symptom severity. *Journal of Child Psychology and Psychiatry*. 2015;56(6):632-639.

187. Faraone SV, Perlis RH, Doyle AE, et al. Molecular genetics of attention-deficit/hyperactivity disorder. *Biological psychiatry*. 2005;57(11):1313-1323.

188. Biederman J, Faraone SV, Keenan K, Knee D, Tsuang MT. Family-genetic and psychosocial risk factors in DSM-III attention deficit disorder. *J Am Acad Child Adolesc Psychiatry*. Jul 1990;29(4):526-33. doi:10.1097/00004583-199007000-00004

189. Franke B, Neale BM, Faraone SV. Genome-wide association studies in ADHD. *Human genetics*. 2009;126(1):13-50.

190. Kahn RS, Khoury J, Nichols WC, Lanphear BP. Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors. *The Journal of pediatrics*. 2003;143(1):104-110.

191. Brookes K-J, Mill J, Guindalini C, et al. A common haplotype of the dopamine transporter gene associated with attention-deficit/hyperactivity disorder and interacting with maternal use of alcohol during pregnancy. *Archives of general psychiatry*. 2006;63(1):74-81.

192. Neuman RJ, Lobos E, Reich W, Henderson CA, Sun L-W, Todd RD. Prenatal smoking exposure and dopaminergic genotypes interact to cause a severe ADHD subtype. *Biological psychiatry*. 2007;61(12):1320-1328.

193. Castellanos FX, Lee PP, Sharp W, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA*. Oct 9 2002;288(14):1740-8. doi:10.1001/jama.288.14.1740

194. Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nat Rev Neurosci*. Aug 2002;3(8):617-28. doi:10.1038/nrn896

195. Murias M, Swanson JM, Srinivasan R. Functional connectivity of frontal cortex in healthy and ADHD children reflected in EEG coherence. *Cereb Cortex*. Aug 2007;17(8):1788-99. doi:10.1093/cercor/bhl089

196. Tripp G, Wickens JR. Neurobiology of ADHD. *Neuropharmacology*. Dec 2009;57(7-8):579-89. doi:10.1016/j.neuropharm.2009.07.026

197. Shaw P, Stringaris A, Nigg J, Leibenluft E. Emotion dysregulation in attention deficit hyperactivity disorder. *Am J Psychiatry*. Mar 2014;171(3):276-93. doi:10.1176/appi.ajp.2013.13070966

198. Luman M, Oosterlaan J, Sergeant JA. The impact of reinforcement contingencies on AD/HD: a review and theoretical appraisal. *Clin Psychol Rev*. Feb 2005;25(2):183-213. doi:10.1016/j.cpr.2004.11.001

199. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic

review. *Biol Psychiatry*. Jun 01 2005;57(11):1336-46. doi:10.1016/j.biopsych.2005.02.006

200. Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN, Biederman J. Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. *Neurology*. Mar 1997;48(3):589-601. doi:10.1212/wnl.48.3.589

201. Overmeyer S, Bullmore ET, Suckling J, et al. Distributed grey and white matter deficits in hyperkinetic disorder: MRI evidence for anatomical abnormality in an attentional network. *Psychol Med*. Nov 2001;31(8):1425-35. doi:10.1017/s0033291701004706

202. Kates WR, Frederikse M, Mostofsky SH, et al. MRI parcellation of the frontal lobe in boys with attention deficit hyperactivity disorder or Tourette syndrome. *Psychiatry Res*. Nov 30 2002;116(1-2):63-81. doi:10.1016/s0925-4927(02)00066-5

203. Mostofsky SH, Cooper KL, Kates WR, Denckla MB, Kaufmann WE. Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. Oct 15 2002;52(8):785-94. doi:10.1016/s0006-3223(02)01412-9

204. Castellanos FX, Giedd JN, Marsh WL, et al. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Arch Gen Psychiatry*. Jul 1996;53(7):607-16. doi:10.1001/archpsyc.1996.01830070053009

205. Castellanos FX, Margulies DS, Kelly C, et al. Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. *Biological psychiatry*. 2008;63(3):332-337.

206. Carpenter PA, Just MA, Reichle ED. Working memory and executive function: Evidence from neuroimaging. *Current opinion in neurobiology*. 2000;10(2):195-199.

207. Miller E, Wallis J. Executive function and higher-order cognition: definition and neural substrates. *Encyclopedia of neuroscience*. 2009;4(99-104)

208. Gazzaley A, D'Esposito M. Unifying prefrontal cortex function: Executive control, neural networks, and top-down modulation. 2007;

209. Johnson MH. Executive function and developmental disorders: the flip side of the coin. *Trends in cognitive sciences*. 2012;16(9):454-457.

210. Goldman-Rakic PS. Cellular basis of working memory. *Neuron*. 1995;14(3):477-485.

211. Barbas H, Medalla M, Alade O, Suski J, Zikopoulos B, Lera P. Relationship of prefrontal connections to inhibitory systems in superior temporal areas in the rhesus monkey. *Cerebral Cortex*. 2005;15(9):1356-1370.

212. Wilkins AJ, Shallice T, McCarthy R. Frontal lesions and sustained attention. *Neuropsychologia*. 1987;25(2):359-365.

213. Robbins T. Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. *Philosophical Transactions of the Royal Society B: Biological Sciences*. 2007;362(1481):917-932.

214. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex: one decade on. *Trends in cognitive sciences*. 2014;18(4):177-185.

215. Best M, Williams JM, Coccaro EF. Evidence for a dysfunctional prefrontal circuit in patients with an impulsive aggressive disorder. *Proceedings of the National Academy of Sciences*. 2002;99(12):8448-8453.

216. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature reviews neuroscience*. 2007;8(9):700.

217. Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews Neuroscience*. 2001;2(10):685.

218. Gusnard DA, Akbudak E, Shulman GL, Raichle ME. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proceedings of the National Academy of Sciences*. 2001;98(7):4259-4264.

219. Fransson P. How default is the default mode of brain function?: Further evidence from intrinsic BOLD signal fluctuations. *Neuropsychologia*. 2006;44(14):2836-2845.

220. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proceedings of the National Academy of Sciences*. 2001;98(2):676-682.

221. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences*. 2005;102(27):9673-9678.

222. Li CSR, Yan P, Bergquist KL, Sinha R. Greater activation of the "default" brain regions predicts stop signal errors. *Neuroimage*. 2007;38(3):640-648.

223. Weissman DH, Roberts K, Visscher K, Woldorff M. The neural bases of momentary lapses in attention. *Nature neuroscience*. 2006;9(7):971.

224. Zametkin AJ, Nordahl TE, Gross M, et al. Cerebral glucose metabolism in adults with hyperactivity of childhood onset. *N Engl J Med*. Nov 15 1990;323(20):1361-6. doi:10.1056/NEJM199011153232001

225. Schweitzer JB, Faber TL, Grafton ST, Tune LE, Hoffman JM, Kilts CD. Alterations in the functional anatomy of working memory in adult attention deficit hyperactivity disorder. *American Journal of Psychiatry*. 2000;157(2):278-280.

226. Krieger SN, Streicher MN, Trampel R, Turner R. Cerebral blood volume changes during brain activation. *Journal of Cerebral Blood Flow & Metabolism*. 2012;32(8):1618-1631.

227. Donahue MJ, Blicher JU, Østergaard L, et al. Cerebral blood flow, blood volume, and oxygen metabolism dynamics in human visual and motor cortex as measured by whole-brain multi-modal magnetic resonance imaging. *Journal of Cerebral Blood Flow & Metabolism*. 2009;29(11):1856-1866.

228. Biederman J. Attention-deficit/hyperactivity disorder: a selective overview. *Biological psychiatry*. 2005;57(11):1215-1220.

229. Arnsten A. Fundamentals of attention-deficit/hyperactivity disorder: circuits and pathways. *The Journal of clinical psychiatry*. 2006;67:7-12.

230. Aboitiz F, Ossandón T, Zamorano F, Palma B, Carrasco X. Irrelevant stimulus processing in ADHD: catecholamine dynamics and attentional networks. *Frontiers in psychology*. 2014;5:183.

231. Berke JD, Hyman SE. Addiction, dopamine, and the molecular mechanisms of memory. *Neuron*. 2000;25(3):515-532.

232. Wise RA. Neuroleptics and operant behavior: the anhedonia hypothesis. *Behavioral and brain sciences*. 1982;5(1):39-53.

233. CADOR M. Limbic-striatal interactions in reward related processes: modulation by the dopaminergic system. *Clinical neuropharmacology*. 1992;15:548A-549A.

234. Robbins T, Cador M, Taylor J, Everitt B. Limbic-striatal interactions in reward-related processes. *Neuroscience & Biobehavioral Reviews*. 1989;13(2-3):155-162.

235. Greene CM, Bellgrove MA, Gill M, Robertson IH. Noradrenergic genotype predicts lapses in sustained attention. *Neuropsychologia*. 2009;47(2):591-594.

236. Xing B, Li Y-C, Gao W-J. Norepinephrine versus dopamine and their interaction in modulating synaptic function in the prefrontal cortex. *brain research*. 2016;1641:217-233.

237. Arnsten AF. Catecholamine and second messenger influences on prefrontal cortical networks of "representational knowledge": a rational bridge between genetics and the symptoms of mental illness. *Cerebral cortex*. 2007;17(suppl_1):i6-i15.

238. Aston-Jones G, Rajkowski J, Cohen J. Locus coeruleus and regulation of behavioral flexibility and attention. *Progress in brain research*. Elsevier; 2000:165-182.

239. Foote S, Aston-Jones G, Bloom F. Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal. *Proceedings of the National Academy of Sciences*. 1980;77(5):3033-3037.

240. Arnsten AF, Li B-M. Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. *Biological psychiatry*. 2005;57(11):1377-1384.

241. Steer C. Managing attention deficit/hyperactivity disorder: unmet needs and future directions. *Archives of disease in childhood*. 2005;90(suppl 1):i19-i25.

242. Lesch KP, Bengel D. Neurotransmitter reuptake mechanisms. *CNS drugs*. 1995;4(4):302-322.

243. Administration FaD. FDA Drug Safety Communication: Safety Review Update of Medications used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in adults. 2011;

244. Robertson S, Matthies H, Galli A. A closer look at amphetamine-induced reverse transport and trafficking of the dopamine and norepinephrine transporters. *Molecular neurobiology*. 2009;39(2):73-80.

245. Seeman P, Madras B. Anti-hyperactivity medication: methylphenidate and amphetamine. *Molecular psychiatry*. 1998;3(5):386.

246. Querne L, Fall S, Le Moing A-G, et al. Effects of methylphenidate on default-mode network/task-positive network synchronization in children with ADHD. *Journal of attention disorders*. 2017;21(14):1208-1220.

247. Liddle EB, Hollis C, Batty MJ, et al. Task-related default mode network modulation and inhibitory control in ADHD: Effects of motivation and methylphenidate. *Journal of Child Psychology and Psychiatry*. 2011;52(7):761-771.

248. Wood S, Sage JR, Shuman T, Anagnostaras SG. Psychostimulants and cognition: a continuum of behavioral and cognitive activation. *Pharmacological reviews*. 2014;66(1):193-221.

249. Berridge CW, Devilbiss DM, Andrzejewski ME, et al. Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. *Biological psychiatry*. 2006;60(10):1111-1120.

250. Seiden LS, Sabol KE, Ricaurte GA. Amphetamine: effects on catecholamine systems and behavior. *Annual review of pharmacology and toxicology*. 1993;33(1):639-676.

251. Wilens TE, Dodson W. A clinical perspective of attention-deficit/hyperactivity disorder into adulthood. *J Clin Psychiatry*. Oct 2004;65(10):1301-13. doi:10.4088/jcp.v65n1003

252. Manderino L, Carroll I, Azcarate-Peril MA, et al. Preliminary Evidence for an Association Between the Composition of the Gut Microbiome and Cognitive Function in Neurologically Healthy Older Adults. *J Int Neuropsychol Soc*. Sep 2017;23(8):700-705. doi:10.1017/S1355617717000492

253. Broglio SP, McCrea M, McAllister T, et al. A National Study on the Effects of Concussion in Collegiate Athletes and US Military Service Academy Members: The NCAA-DoD Concussion Assessment, Research and Education (CARE) Consortium Structure and Methods. *Sports Med*. Jul 2017;47(7):1437-1451. doi:10.1007/s40279-017-0707-1

254. Carney N, Ghajar J, Jagoda A, et al. Concussion guidelines step 1: systematic review of prevalent indicators. *Neurosurgery*. 2014;75(suppl_1):S3-S15.

255. McCrory P, Meeuwisse WH, Aubry M, et al. Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport, Zurich, November 2012. *J Athl Train*. Jul-Aug 2013;48(4):554-75. doi:10.4085/1062-6050-48.4.05

256. Harmon KG, Drezner JA, Gammons M, et al. American Medical Society for Sports Medicine position statement: concussion in sport. *Br J Sports Med*. Jan 2013;47(1):15-26. doi:10.1136/bjsports-2012-091941

257. Miles J, Shevlin M. *Applying regression and correlation: A guide for students and researchers*. Sage; 2001.

258. Parker TM, Osternig LR, P VAND, Chou LS. Gait stability following concussion. *Med Sci Sports Exerc*. Jun 2006;38(6):1032-40. doi:10.1249/01.mss.0000222828.56982.a4

259. Sosnoff JJ, Broglio SP, Shin S, Ferrara MS. Previous mild traumatic brain injury and postural-control dynamics. *J Athl Train*. Jan-Feb 2011;46(1):85-91. doi:10.4085/1062-6050-46.1.85

260. Lee H, Sullivan SJ, Schneiders AG. The use of the dual-task paradigm in detecting gait performance deficits following a sports-related concussion: a systematic review and meta-analysis. *J Sci Med Sport*. Jan 2013;16(1):2-7. doi:10.1016/j.jsams.2012.03.013

261. Lapointe AP, Nolasco LA, Sosnowski A, et al. Kinematic differences during a jump cut maneuver between individuals with and without a concussion history. *Int J Psychophysiol*. Oct 2018;132(Pt A):93-98. doi:10.1016/j.ijpsycho.2017.08.003

262. Martini DN, Sabin MJ, DePesa SA, et al. The chronic effects of concussion on gait. *Arch Phys Med Rehabil*. Apr 2011;92(4):585-9. doi:10.1016/j.apmr.2010.11.029

263. Barkley RA. Attention-deficit hyperactivity disorder. *Sci Am*. Sep 1998;279(3):66-71. doi:10.1038/scientificamerican0998-66

264. Vyse SA, Rapport MD. The effects of methylphenidate on learning in children with ADDH: the stimulus equivalence paradigm. *J Consult Clin Psychol*. Jun 1989;57(3):425-435. doi:10.1037/0022-006X.57.3.425

265. Detmer SA, Chan DC. Functions and dysfunctions of mitochondrial dynamics. *Nat Rev Mol Cell Biol*. Nov 2007;8(11):870-9. doi:10.1038/nrm2275

266. Verstreken P, Ly CV, Venken KJ, Koh TW, Zhou Y, Bellen HJ. Synaptic mitochondria are critical for mobilization of reserve pool vesicles at Drosophila neuromuscular junctions. *Neuron*. Aug 4 2005;47(3):365-78. doi:10.1016/j.neuron.2005.06.018

267. Hollenbeck PJ, Saxton WM. The axonal transport of mitochondria. *J Cell Sci*. Dec 1 2005;118(Pt 23):5411-9. doi:10.1242/jcs.02745

268. Saxton WM, Hollenbeck PJ. The axonal transport of mitochondria. *J Cell Sci*. May 1 2012;125(Pt 9):2095-104. doi:10.1242/jcs.053850

269. Di Pietro V, Amorini AM, Tavazzi B, et al. Potentially neuroprotective gene modulation in an in vitro model of mild traumatic brain injury. *Mol Cell Biochem*. Mar 2013;375(1-2):185-98. doi:10.1007/s11010-012-1541-2

270. Di Pietro V, Amorini AM, Tavazzi B, et al. The molecular mechanisms affecting N-acetylaspartate homeostasis following experimental graded traumatic brain injury. *Mol Med*. Mar 24 2014;20:147-57. doi:10.2119/molmed.2013.00153

271. Amorini AM, Lazzarino G, Di Pietro V, et al. Metabolic, enzymatic and gene involvement in cerebral glucose dysmetabolism after traumatic brain injury. *Biochim Biophys Acta*. Apr 2016;1862(4):679-687. doi:10.1016/j.bbadis.2016.01.023

272. Di Pietro V, Lazzarino G, Amorini AM, et al. Neuroglobin expression and oxidant/antioxidant balance after graded traumatic brain injury in the rat. *Free Radic Biol Med*. Apr 2014;69:258-64. doi:10.1016/j.freeradbiomed.2014.01.032

273. Amorini AM, Lazzarino G, Di Pietro V, et al. Severity of experimental traumatic brain injury modulates changes in concentrations of cerebral free amino acids. *J Cell Mol Med*. Mar 2017;21(3):530-542. doi:10.1111/jcmm.12998

274. Vagnozzi R, Signoretti S, Cristofori L, et al. Assessment of metabolic brain damage and recovery following mild traumatic brain injury: a multicentre, proton magnetic resonance spectroscopic study in concussed patients. *Brain*. Nov 2010;133(11):3232-42. doi:10.1093/brain/awq200

275. Liemburg-Apers DC, Willems PH, Koopman WJ, Grefte S. Interactions between mitochondrial reactive oxygen species and cellular glucose metabolism. *Arch Toxicol*. Aug 2015;89(8):1209-26. doi:10.1007/s00204-015-1520-y

276. Uttara B, Singh AV, Zamboni P, Mahajan RT. Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. *Curr Neuropharmacol*. Mar 2009;7(1):65-74. doi:10.2174/157015909787602823

277. Santos RX, Correia SC, Wang X, et al. Alzheimer's disease: diverse aspects of mitochondrial malfunctioning. *Int J Clin Exp Pathol*. Jun 25 2010;3(6):570-81.

278. Tobore TO. On the central role of mitochondria dysfunction and oxidative stress in Alzheimer's disease. *Neurol Sci*. Aug 2019;40(8):1527-1540. doi:10.1007/s10072-019-03863-x

279. Exner N, Lutz AK, Haass C, Winklhofer KF. Mitochondrial dysfunction in Parkinson's disease: molecular mechanisms and pathophysiological consequences. *EMBO J*. Jun 26 2012;31(14):3038-62. doi:10.1038/emboj.2012.170

280. Shi P, Wei Y, Zhang J, Gal J, Zhu H. Mitochondrial dysfunction is a converging point of multiple pathological pathways in amyotrophic lateral sclerosis. *J Alzheimers Dis*. 2010;20 Suppl 2:S311-24. doi:10.3233/JAD-2010-100366

281. Shi P, Gal J, Kwinter DM, Liu X, Zhu H. Mitochondrial dysfunction in amyotrophic lateral sclerosis. *Biochim Biophys Acta*. Jan 2010;1802(1):45-51. doi:10.1016/j.bbadis.2009.08.012

282. Bracko O, Di Pietro V, Lazzarino G, et al. 3-Nitropropionic acid-induced ischemia tolerance in the rat brain is mediated by reduced metabolic activity and cerebral blood flow. *J Cereb Blood Flow Metab*. Sep 2014;34(9):1522-30. doi:10.1038/jcbfm.2014.112

283. Cheng G, Kong RH, Zhang LM, Zhang JN. Mitochondria in traumatic brain injury and mitochondrial-targeted multipotential therapeutic strategies. *Br J Pharmacol*. Oct 2012;167(4):699-719. doi:10.1111/j.1476-5381.2012.02025.x

284. Vagnozzi R, Tavazzi B, Signoretti S, et al. Temporal window of metabolic brain vulnerability to concussions: mitochondrial-related impairment--part I. *Neurosurgery*. Aug 2007;61(2):379-88; discussion 388-9. doi:10.1227/01.NEU.0000280002.41696.D8

285. Bulstrode H, Nicoll JA, Hudson G, Chinnery PF, Di Pietro V, Belli A. Mitochondrial DNA and traumatic brain injury. *Ann Neurol*. Feb 2014;75(2):186-95. doi:10.1002/ana.24116

286. Bulut M, Selek S, Bez Y, et al. Lipid peroxidation markers in adult attention deficit hyperactivity disorder: new findings for oxidative stress. *Psychiatry Res*. Oct 30 2013;209(3):638-42. doi:10.1016/j.psychres.2013.02.025

287. Selek S, Bulut M, Ocak AR, Kalenderoglu A, Savas HA. Evaluation of total oxidative status in adult attention deficit hyperactivity disorder and its diagnostic implications. *J Psychiatr Res*. Apr 2012;46(4):451-5. doi:10.1016/j.jpsychires.2011.12.007

288. Selek S, Savas HA, Gergerlioglu HS, Bulut M, Yilmaz HR. Oxidative imbalance in adult attention deficit/hyperactivity disorder. *Biol Psychol*. Oct 2008;79(2):256-9. doi:10.1016/j.biopsycho.2008.06.005

289. Archana E, Pai P, Prabhu BK, Shenoy RP, Prabhu K, Rao A. Altered biochemical parameters in saliva of pediatric attention deficit hyperactivity disorder. *Neurochem Res*. Feb 2012;37(2):330-4. doi:10.1007/s11064-011-0616-x

290. Ceylan MF, Uneri OS, Guney E, et al. Increased levels of serum neopterin in attention deficit/hyperactivity disorder (ADHD). *J Neuroimmunol*. Aug 15 2014;273(1-2):111-4. doi:10.1016/j.jneuroim.2014.06.002

291. Ceylan MF, Sener S, Bayraktar AC, Kavutcu M. Changes in oxidative stress and cellular immunity serum markers in attention-deficit/hyperactivity disorder. *Psychiatry Clin Neurosci*. Apr 2012;66(3):220-6. doi:10.1111/j.1440-1819.2012.02330.x

292. Ceylan M, Sener S, Bayraktar AC, Kavutcu M. Oxidative imbalance in child and adolescent patients with attention-deficit/hyperactivity disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. Dec 1 2010;34(8):1491-4. doi:10.1016/j.pnpbp.2010.08.010

293. Verma P, Singh A, Nthenge-Ngumbau DN, et al. Attention deficit-hyperactivity disorder suffers from mitochondrial dysfunction. *BBA Clin*. Dec 2016;6:153-158. doi:10.1016/j.bbacli.2016.10.003

294. Kul M, Unal F, Kandemir H, Sarkarati B, Kilinc K, Kandemir SB. Evaluation of Oxidative Metabolism in Child and Adolescent Patients with Attention Deficit Hyperactivity Disorder. *Psychiatry Investig*. Jul 2015;12(3):361-6. doi:10.4306/pi.2015.12.3.361

295. Joseph N, Zhang-James Y, Perl A, Faraone SV. Oxidative Stress and ADHD: A Meta-Analysis. *J Atten Disord*. Nov 2015;19(11):915-24. doi:10.1177/1087054713510354

296. Matochik JA, Nordahl TE, Gross M, et al. Effects of acute stimulant medication on cerebral metabolism in adults with hyperactivity. *Neuropsychopharmacology*. 1993;8(4):377-386.

297. Scaini G, Fagundes AO, Rezin GT, et al. Methylphenidate increases creatine kinase activity in the brain of young and adult rats. *Life Sci*. Dec 5 2008;83(23-24):795-800. doi:10.1016/j.lfs.2008.09.019

298. Kinnaman KA, Mannix RC, Comstock RD, Meehan WP, 3rd. Management of pediatric patients with concussion by emergency medicine physicians. *Pediatr Emerg Care*. Jul 2014;30(7):458-61. doi:10.1097/PEC.0000000000000161

299. Meehan WP, 3rd. Medical therapies for concussion. *Clin Sports Med*. Jan 2011;30(1):115-24, ix. doi:10.1016/j.csm.2010.08.003