EXAMINING THE RELATIONSHIP AND NEURAL UNDERPINNINGS OF MILD TRAUMATIC BRAIN INJURY, SUBSTANCE USE, AND MENTAL HEALTH IN EMERGING ADULTS

ALYSSIA WILSON

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Abstract

Substance use is increasingly more common among emerging adults and is often linked to poor mental health, though the direction of this relationship remains unclear. Mild traumatic brain injury (mTBI) is also a known risk factor for both substance use and mood disorders, potentially due to its impact on brain regions involved in decision-making and emotional regulation. University athletes are especially vulnerable due to higher exposure to mTBI, placing them at increased risk for both substance misuse and mental health challenges. The complex interplay between these factors, along with observed sex differences, underscores the need for more targeted research and intervention.

The overall objective of this research program was to examine the relationship between mTBI history and recent substance use, while exploring how mental health and mTBI interact and vary by sex and athlete status. Across four studies, important links emerged between substance use, mental health, and brain connectivity in both athletes and non-athletes. Study 1 found that in female athletes, cannabis use was associated with higher depression and altered resting-state functional connectivity (rsFC) in brain regions related to emotional regulation and self-monitoring, including reduced OFC-fusiform and increased hippocampus-cerebellum connectivity. Study 2 showed that among university athletes, mTBI and anxiety predicted alcohol and polysubstance use, with polysubstance users reporting the highest levels of depression, anxiety, and mTBI history. Study 3 extended these findings to a larger non-athlete sample, where hazardous substance use was linked to mTBI, anxiety, and depression. Sex-specific patterns emerged: in females, cannabis use was closely tied to mood symptoms, especially when combined with mTBI; in males, depression predicted both alcohol and cannabis use, with mTBI moderating alcohol use. Study 4 found that athletes with mTBI reported greater depression, anxiety, stress, and substance use, along with increased DMN-striatum connectivity related to anxiety, although no direct rsFC changes were associated with substance use.

These findings emphasize the need for early screening, tailored mental health support, and integrated care. Further research into the temporal and causal relationships between mTBI, mental health, and substance use, particularly across sexes, is essential for developing effective interventions.

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List of Abbreviations

AFNI	Analysis of Functional Neuroimages
AU	Alcohol Use Only
AUDIT-C	Alcohol Use Disorder Identification Test-Clinical
CSF	Cerebrospinal fluid
CSU	Combined substance use
CT	Computed tomography
CUDIT-R	Cannabis Use Disorder Identification Test-Revised (CUDIT-R)
DAI	Diffuse axonal injury
DASS	The Depression, Anxiety, and Stress Scale - 21 Item
DMN	Default mode network
DSM-IV	Diagnostic Statistical Manual Fourth Edition
EPI	Echo-planar imaging
FDR	False Discovery Rate
FPN	Frontoparietal Network
GAD-7	Generalized Anxiety Disorder-7 item
GLM	General Linear Model
GM	Grey matter
ICA	Independent Component Analysis
LOC	Loss of consciousness
MP-RAGE	Magnetization Prepared Rapid Acquisition Gradient Echo
MNI	Montreal Neurological Institute
mTBI	Mild traumatic brain injury
MTL	Medial Temporal Lobe
NU	Non-use [Non-substance use]
OFC	Orbital frontal cortex
PCC	Posterior cingulate cortex
PCSS	Post-Concussion Symptom Scale
PHQ-9	Patient Health Questionnaire-9
PTA	Post traumatic amnesia
ROI	Region of interest
rsFC	Resting state functional connectivity

SAC	Standardized Assessment of Concussion
SCAT5	Sport Concussion Assessment Tool-5
SN	Salience Network
SPSS	Statistical Package for the Social Sciences
ST	Striatum
TBI	Traumatic brain injury
WM	White matter

Chapter 1: Introduction

1.1 Overview of mild traumatic brain injury

A mild traumatic brain injury (mTBI), refers to a head injury resulting in clinical signs and may temporarily affect mental status (Silverberg et al., 2023). While the terms mTBI and concussion are sometimes used interchangeably, not all concussions meet the clinical criteria for a mTBI. Further, mTBIs may present with a variety of symptoms. These include physical, cognitive and emotional symptoms such as, loss of consciousness or memory, blurred vision, dizziness, nausea, loss of balance, headaches, difficulties with concentrating or thinking, and mood changes (Silverberg et al., 2023). Acute symptoms of mTBI typically resolve within weeks without intervention, however a subset of individuals report lasting symptoms (Alexander, 1995). MTBIs represent 75% of all TBIs, affecting over one million individuals annually in the United States (Faul et al., 2010) and affect 224 per 100,000 people annually worldwide (Nguyen et al., 2016).

Etiology and Diagnostic Criteria

MTBIs are a heterogeneous group of injuries resulting from head trauma or acceleration and deceleration forces that may occur with or without external visible injuries. Common causes of mTBI include injuries related to sport, falls, being struck in the head, assaults, and motor vehicle accidents (Kusher, 1998). These modes of injury are varied, resulting in varying types and degrees of damage to the brain, but in each, mechanical forces imposed on the brain can lead to deformation and strain. Over time, these forces may also cause delayed damage through processes such as cell dysfunction or death (Rabinowitz et al., 2014). Certain populations have greater exposure to these incidents, such as contact sport athletes who may sustain multiple mTBIs or concussions throughout their careers and military personnel exposed to blast-related injuries (Laskowski et al., 2015).

There is a lack of a standard definition of mTBI across various organizations, including the US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO), the American Congress of Rehabilitation Medicine (ACRM) has recently published updated diagnostic criteria for mTBI. According to ACRM 2023 diagnostic criteria, an mTBI is defined as a traumatically induced physiological disruption of brain function, as manifested by at least one of the following symptoms (Silverberg et al., 2023):

Box 1. Diagnostic Criteria for mild traumatic brain injury adapted from American Congress of Rehabilitation Medicine (Silverberg et al., 2023)

Mild traumatic brain injury (mTBI) is diagnosed when, following a biomechanically plausible mechanism of injury, one or more of the criteria (i-iii) listed below are met.

i) **Presence of at least one clinical sign attributable to brain injury.**

a. Clinical signs may include loss of consciousness, lasting no longer than 30 minutes.

b. Alteration of mental status such as reduced responsiveness, inappropriate responses to external stimuli, slowed responding, agitation, inability to follow two-part commands, disorientation to time, place, situation, but a Glasgow Coma Score (GCS) no lower than 13 after 30 minutes.

c. Complete or partial amnesia for events immediately following injury, lasting no longer than 24 hours.

ii) At least two acute symptoms and at least one clinical or laboratory finding attributable to brain injury.

Acute symptoms:

a. Alteration in mental status (feeling confused, disoriented, dazed).

b. Physical symptoms (headache, nausea, dizziness, balance or vision problems, light or noise sensitivity).

c. Cognitive symptoms (feeling slowed down, "mental fog", difficulty concentrating, memory problems).

d. Emotional symptoms (uncharacteristic emotional lability, irritation).

Clinical Examination:

a. Cognitive impairment on acute clinical examination.

b. Balance impairment on acute clinical examination.

c. Oculomotor impairment or symptom provocation in response to vestibular-oculomotor challenge on acute clinical examination.

d. Evaluated blood biomarkers indicative of intracranial injury.

Neuroimaging

iii) Neuroimaging evidence of TBI, such as unambiguous trauma-related intracranial abnormalities on CT or structural MRI.

Mild Qualifier: An injury cannot be labelled as "mild" if any of the following are met.

i) Loss of consciousness duration greater than 30 minutes.

ii) After 30 minutes, a Glasgow Coma Scale (GCS) of less than 13.

As the data used in the following studies were collected prior to the updated 2023 criteria, our questionnaires used the 1993 ACRM diagnostic criteria for mTBI:

Box 2. Diagnostic Criteria for mild traumatic brain injury adapted from American Congress of Rehabilitation Medicine (1993) (Silverberg et al., 2023)

A patient with mild traumatic brain injury is a person who has had a traumatically induced physiological disruption of brain function, as manifested by at least one of the following:

i) Any period of loss of consciousness.

ii) Any loss of memory for events immediately before or after the accident.

iii) Any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused).

iv) Focal neurological deficit(s) that may or may not be transient.

v) But where the severity of the injury does not exceed the following:

a) Loss of consciousness of approximately 30 minutes or less.

b) After 30 minutes, an initial Glasgow Coma Scale (GCS) of 13–15.

c) *Posttraumatic amnesia (PTA) lasting no longer than 24 hours.*

Symptoms

According to diagnostic criteria, individuals in the acute and subacute phases following mTBI typically experience three general clusters of symptoms: somatic (e.g., physical and/or sensory), cognitive, and affective (e.g., emotional) (Prince & Bruhns, 2017; Silverberg et al., 2023). Somatic symptoms often include headache, nausea, dizziness, balance or vision problems, light or noise sensitivity, and sleep disruptions. Commonly reported cognitive challenges include feeling slowed down, "mental fog", difficulty concentrating, and memory problems. Affective symptoms

commonly reported include irritability, emotional lability, anxiety, and depression (Bergersen et al., 2017; Prince & Bruhns, 2017; Silverberg et al., 2023). In particular, within the first 24 hours following mTBI, individuals may experience significant adverse effects on cognition and balance (Broglio & Puetz, 2008; Dougan et al., 2014). Typically, symptoms are expected to improve rapidly in most cases over the first two weeks (Iverson et al., 2017). However, these diverse symptoms may not only cause impairment on their own but may also exacerbate each other. This can result in a dysfunctional feedback loop, maintaining symptoms even after recovery of medical signs (Kay et al., 1992). For example, cognitive complaints may be caused by pain and emotional distress, rather than being the direct result of a brain injury. (Prince & Bruhns, 2017). The severity of acute and subacute symptoms is a known indicator of slower recovery. Headache and depression, in particular, are significant risk factors for persisting symptoms (Iverson et al., 2017). A minority of individuals (10%-20%) continue to experience symptoms for up to years following injury (Ruff, 2005). These cases have previously been referred to as post-concussive syndrome. However, this remains highly debated among professionals, as research aims to determine whether these sustained symptoms are neurogenic or psychogenic in nature (Prince & Bruhns, 2017).

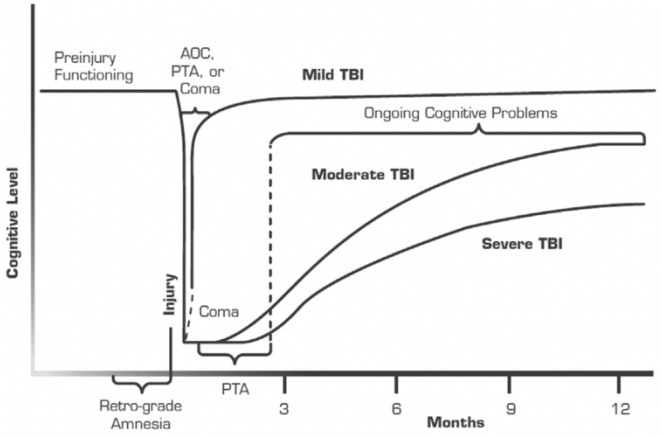


Figure 1. Hypothetical cognitive function recovery paths. (Adapted from Employee Education System. Traumatic Brain Injury: Independent Study Course. Department of Veterans Affairs; 2010: p. 17.) AOC, alteration of consciousness; PTA, posttraumatic amnesia; TBI, traumatic brain injury.

Pathophysiology and Neuroimaging features

Diffuse axonal injury (DAI) is a hallmark of all TBIs, resulting from the vulnerability of white matter to traumatic inertial forces (Adams et al., 1989). Brain contusions may occur when there is an area of focal injury, either due to direct external contact to the head, or from the brain coming into contact with the inside of the skull but are rare among mTBIs (Rabinowitz et al., 2014). Bleeding within the membranous layers surrounding the brain or within the brain itself is not typically associated with mTBI (Silverberg et al., 2023).

In the case of a mTBI, the head is subjected to biomechanical forces, which are believed to trigger a neurochemical and neurometabolic cascade, leading to acute signs and symptoms (Giza

& Hovda, 2001). As described by Giza and Hovda (2001), neuronal membranes are disrupted by mechanical tearing forces, and axons are stretched. This allows ions to pass through now open voltage-gated ion channels. This leads to excitatory neurotransmitters triggering receptors and further depolarizing the cells. To restore homeostasis, the sodium-potassium pump is required to work harder to regain equilibrium, requiring more energy, triggering increased glucose metabolism to support this process. At the same time, diminished cerebral blood flow limits glucose availability in the brain, leading to an "energy crisis" (Giza & Hovda, 2001; Rabinowitz et al., 2014).

This increased energy demand may create vulnerability to reinjury immediately following the initial injury (Rabinowitz & Levin, 2014). Evidence from animal models suggests a limited window of vulnerability during which chemical and metabolic imbalances resolve within 10 days, a pattern that aligns with neuropsychological recovery observed in sports studies (Belanger & Vanderploeg, 2005; Guskiewicz, McCrea, et al., 2003; Hovda et al., 1995). However, as described by Schneider (1973) and Saunders and Harbaugh (1984), second impact syndrome is a rare condition that occurs when an individual, still suffering from post-concussive symptoms, sustains a second, potentially mild, mTBI, leading to severe disability or fatality. This second injury is believed to be caused by diminished autoregulation of cerebral blood flow, leading to vascular engorgement, increased intracranial pressure, and ultimately herniation. In these rare instances, rapid brainstem failure may occur within minutes (Cantu, 1998).

Treatment

The medical management of mTBI has evolved significantly in recent decades, but it remains variable and lacks standardization (Prince & Bruhns, 2017). The general approach to mTBI recovery involves a brief period of mental and physical rest, typically lasting 24 to 48 hours. Individuals are generally advised to limit activities requiring significant concentration, such as screen time, reading, work, or physical exertion, all of which may provoke symptoms. After this rest period, a gradual return-to-activity plan is implemented as tolerated, including shortened work or school days and light exercise. Recent reviews suggest that the current approach to mTBI management requires further investigation to determine its efficacy. However, exercise as an appropriate therapy for certain individuals is better supported in the literature (De Luigi et al., 2023; Silverberg & Otamendi, 2019). In particular, approaches involving strict rest, prolonged rest periods, or high-intensity physical activity have been shown to hinder mTBI recovery (De Luigi et al., 2023; Silverberg & Otamendi, 2019).

For athletes, return-to-play timelines typically follow a 10-day recommendation (McCrea et al., 2003), based on the assumption that recovery occurs within that time frame. The symptom-free waiting period model is based on research showing that most repeat concussions occur within the 7-10 day acute phase, indicating neurological vulnerability (Pfaller et al., 2016). However, this model does not account for individual recovery differences, and evidence suggests that a significant number of student athletes require more than 10 days to recover from their clinical symptoms (Baker et al., 2016; Henry et al., 2016). Gradual return-to-play guidelines, recommended by the Concussion in Sport Group, have become more common (Patricios et al., 2023).

Athletes and mTBI

Athletes, especially those involved in high-contact sports, face unique challenges when it comes to mTBI due to the physical demands and increased risk of head collisions (Abrahams et al., 2014; Schulz et al., 2004; Scopaz & Hatzenbuehler, 2013). Repeated injuries elevate the risk of cumulative effects over time (Guskiewicz, Mccrea, et al., 2003; Iverson et al., 2004; Rabadi & Jordan, 2001). While the risk of mTBI is well-established, diagnosing symptoms such as headaches, dizziness, and confusion can be challenging, as these non-specific symptoms may evolve over time instead of presenting immediately following the injury (Makdissi et al., 2015). Secondary factors, such as the pressure to return to play, may lead to underreporting of symptoms, increasing the risk of further injuries shortly after the initial mTBI (Davies & Bird, 2015; Meiera et al., 2015). Returning to play before symptoms have fully resolved not only exposes athletes to the risk of re-injury but also increases the likelihood of experiencing lingering symptoms, like balance issues or blurred vision, which can impair performance and increase the risk of further injury (McPherson et al., 2019; Reneker et al., 2019; Schulz et al., 2004). External pressures, such as cultural norms encouraging 'playing through pain,' stigma around being sidelined, and pressure to support teammates, coaches, and fans, contribute to athletes' reluctance to report symptoms (Davies & Bird, 2015; Meiera et al., 2015). Repeated concussions over the course of an athlete's career can result in a unique neurological profile, with long-term cognitive and emotional consequences that impact overall well-being (Guskiewicz, Mccrea, et al., 2003; Iverson et al., 2004; Rabadi & Jordan, 2001).

1.2 Mental health in mTBI

Although most individuals are expected to recover fully within weeks of sustaining an mTBI, research suggests that some continue to experience persistent affective symptoms, leading to

mental health conditions such as anxiety and depression (Alcock et al., 2018). These issues may arise both directly from the injury's impact on brain function or indirectly from the added stress of coping with cognitive and physical symptoms, such as memory difficulties, concentration issues, headaches, and dizziness (Howlett et al., 2022). These symptoms can significantly disrupt daily life (Howlett et al., 2022). Post-mTBI mental health problems may be key in predicting long-term functional outcomes, such as cognitive performance and quality of life (May, 2008). Individuals with a prior history of mental health issues may be especially vulnerable to prolonged psychological challenges following their injury (Kontos et al., 2016).

Research indicates that individuals with mTBI are at increased risk of developing psychiatric disorders. A study of 9,428 Californian adults with mTBI and 18,856 healthy controls found that 23% of individuals with mTBI developed affective disorders, including depression, anxiety, and adjustment disorder, with the majority developing these conditions within the first-year post-injury (Delmonico et al., 2022). In comparison, only 14% of the control group reported experiencing these conditions, highlighting a significant increased risk in the mTBI group. Over a four-year period, individuals with a prior history of affective disorders had 1.2 times higher odds of developing a new disorder. For those without a pre-existing condition, the odds were 1.5 times higher (Delmonico et al., 2022). A similar prospective cohort study involving 1,084 trauma patients diagnosed with mTBI at four major Australian hospitals examined psychiatric disorders, quality of life, and mental health service use, assessed at 3 and 12 months post-injury (Bryant et al., 2010). One year post-injury, 31% of patients reported a psychiatric disorder, with 22% developing a new condition, most commonly depression (9%), generalized anxiety disorder (9%), PTSD (6%), and agoraphobia (6%) (Bryant et al., 2010). Further supporting these findings, a recent systematic review of 705,024 individuals with mTBI found that 17.45% experienced post-injury anxiety symptoms and were 1.9 times more likely to develop anxiety than healthy controls, regardless of TBI severity (Dehbozorgi et al., 2024). Similarly, a scoping review of 18 studies on persistent post-concussion symptoms in adult mTBI populations found that 17 of the studies reported increased mood symptoms. The prevalence of increased depressive symptoms was as high as 44%, while anxiety symptoms were reported in up to 24% of individuals. Notably, studies that combined both anxiety and depression symptoms reported even higher prevalence rates, reaching up to 76% (Sheldrake et al., 2022).

Sport-related concussions are frequently studied in relation to mental health outcomes. University athletes, in particular, face a unique set of stressors that contribute to their mental

health risks, often at rates comparable to or exceeding those of the general population (Castaldelli-Maia et al., 2019; Knowles et al., 2021; Rice et al., 2016). However, some research suggests that sports participation may have protective effects, potentially mitigating mental health risks (Kuettel & Larsen, 2020; Solomon et al., 2016). Regardless of potential protective effects, athletes experience additional challenges that their non-athlete peers do not face. In addition to academic demands, athletes must also cope with sports injuries, intense performance expectations, overtraining, and conflicts with coaches, all of which can significantly impact their well-being (Castaldelli-Maia et al., 2019; Sutcliffe & Greenberger, 2020; Wolanin et al., 2015). The highly competitive nature of collegiate sports, combined with the physical and psychological demands of training and competition, may exacerbate stress, anxiety, and emotional exhaustion, further impacting mental health. Additionally, the pressure to maintain a resilient image may discourage athletes from seeking help for mental health concerns, further complicating recovery. Following an injury, athletes experience heightened emotional distress due to psychosocial and physical factors, including perceived declines in athletic ability, lack of social support, persistent pain, and fear of reinjury (Podlog et al., 2011).

Pre-existing mental health conditions are associated with an increased likelihood of developing persistent post-concussive symptoms. A study by Yang et al. (2015) examined baseline and post-mTBI depression and anxiety in 67 concussed collegiate athletes. They found that athletes with pre-existing depressive symptoms were 4.59 times more likely to experience post-concussion depression. Similarly, athletes who had baseline anxiety were 3.40 times more likely to develop state anxiety following a concussion. In another study, Morgan et al. (2015) conducted retrospective cases analyses on 40 athletes with prolonged symptoms using a sports concussion registry. Their findings identified a history of concussion, pre-injury mood disorders, delayed symptom onset, and a family history of mood disorders as strong predictors of extended symptomology. While mood and anxiety symptoms generally resolve within the typical recovery trajectory, some individuals continue to experience significant, persistent symptoms that require professional intervention (Covassin et al., 2014; Hutchison et al., 2009).

Depression is common following sports-related concussions, with up to 20% of collegiate athletes reporting increased symptoms post-mTBI (Vargas et al., 2015). A review of sports-related concussions in elite adult athletes found a significant association between concussions and increased symptoms of depression. Evidence of a dose-response relationship was observed, with greater concussion exposure correlating with higher depression symptoms (Rice et al., 2018).

However, evidence regarding other mental health concerns, such as anxiety or PTSD, was less consistent (Rice et al., 2018). Research on retired NFL players further supports a link between repetitive head injuries and long-term depression, with one study showing that depression rates increased from 3% among players with no reported concussions to 26.8% in those with 10 or more concussions (Guskiewicz et al., 2007; Kerr et al., 2012).

Short-term depressive symptoms are also observed in athletes following a concussion. One study found that concussed varsity athletes exhibited depression scores three times higher than baseline at four days post-injury, though these scores returned to baseline within a week (Mainwaring et al., 2010). Similarly, high school and collegiate athletes reported significantly higher depression levels at 2, 7, and 14 days post-concussion (Hutchison et al., 2009). Notably, collegiate athletes displayed greater symptom severity than high school athletes at the 14-day mark. However, not all cases of post-concussion depression reach clinical significance (Hutchison et al., 2009). Hutchison et al. (2009) found that while concussed athletes exhibited elevations in depression during the two weeks following mTBI, these symptoms were not severe enough to meet clinical thresholds.

Although anxiety following mTBI in sports is less frequently studied and appears to be less common than depression, many injured athletes do experience anxiety symptoms after injury (Podlog et al., 2011). Covassin et al. (2014) examined anxiety in 63 athletes with mTBI and 63 athletes with orthopedic injuries, finding that both groups reported increased anxiety and similar symptoms. However, concussed athletes expressed lower satisfaction with their support systems. The prevalence of anxiety and mood disruptions in athletes following mTBI may also be influenced by baseline affective symptoms. In a study of 2,248 college athletes, 40.6% reported baseline anxiety and/or mood disruption(Lumba-Brown et al., 2023). Among 150 athletes who sustained sports-related mTBI, 94.7% experienced symptoms of anxiety or mood disruption during recovery. Higher baseline affective symptoms were predictive of greater symptom severity post-mTBI (Lumba-Brown et al., 2023).

1.3 Substance use and mTBI

TBI and substance use frequently co-occur. Individuals with a history of substance use are at greater risk for brain injury, and those with brain injuries have been shown to have higher rates of substance use both before and after injury (Bogner et al., 2001; Bombardier et al., 2002; Corrigan, 1995). At higher levels of use, substance intoxication can contribute to sustaining an mTBI by

impairing judgment and motor coordination, increasing the risk of injury due to hazardous behaviours such as falls or accidents(Bombardier et al., 2002; Walker et al., 2023). Following injury, individuals recovering from TBI who had a pre-injury history of substance use are at increased risk for relapse (Bjork & Grant, 2009; Felde et al., 2006; Parry-Jones et al., 2006), and continued substance use following injury increases the likelihood of sustaining additional injuries, leading to a poorer prognosis (Bogner et al., 2001; Bombardier et al., 2002; Corrigan, 1995). While there is a well-established link between pre-injury substance use and intoxication at the time of injury in individuals treated for TBI, it is less clear whether the reverse is true. Bjork and Grant (2009) concluded that there is insufficient evidence to definitively determine whether TBI or mTBI contributes to increased substance use. They highlighted the challenges of distinguishing psychiatric outcomes stemming from the pathophysiological consequences of brain injury versus those arising from psychosocial stressors following functional changes. However, they suggested that individuals with no prior substance use history may develop deficits in executive functioning, such as decision-making, which could increase the risk of subsequent substance use (Bjork & Grant, 2009).

While most research on substance use and brain injury has focused on moderate to severe TBIs, recent studies indicate that mTBIs are also associated with increased substance use. A study of high school students found that a history of mTBI was significantly linked to a higher risk of current substance use. Notably, students with two or more reported mTBIs were twice as likely to engage in substance use, including cigarette smoking, binge drinking, and marijuana use, compared to those with only one reported mTBI (Veliz et al., 2021). Similarly, high school students with a history of sports-related mTBIs were almost twice as likely to engage in binge drinking and 1.42 times more likely to use marijuana compared to their peers without sports-related mTBIs (Baiden et al., 2022). In a university athlete population, Alcock et al. (2018) reported an association between a history of mTBI and increased alcohol use that could not be solely attributed to athlete status. Additionally, a history of multiple subclinical to mild TBIs was associated with increased odds of marijuana and prescription drug use among university students (Kort-Butler, 2017). Likewise, young adults who had experienced "a significant head injury, brain injury, or concussion" were more likely to engage in hazardous use of alcohol, marijuana, and illicit drugs (Rosenthal et al., 2023).

Substance use and hazardous drug use behaviours have significant negative health implications, including poor mental health (Degenhardt et al., 2016; Gobbi et al., 2019; Grant et al.,

2004b; Hines et al., 2020; Mchugh & Weiss, 2019; Moore et al., 2007). These issues share both environmental and genetic risk factors, increasing the likelihood of experiencing both conditions concurrently (Khantzian, 1997; Sadock et al., 2016). Consequently, substance use and mental health problems have long been associated (Brook et al., 1998; Rachbeiscl et al., 1999). In Canada, an estimated 282,000 individuals aged 15 to 64 experienced concurrent substance use and mental health disorders within the past year (Khan, 2017). These individuals were more likely to have longstanding mental health challenges and demonstrated higher engagement with health services compared to those with only one condition (Khan, 2017). However, the causality and directionality of this relationship remain highly debated (Esmaeelzadeh et al., 2018). Two primary theories attempt to explain this bidirectional relationship. The self-medication hypothesis suggests that individuals may use substances as a coping mechanism to manage psychological stressors, including mental health disorders (Khantzian, 1997) Conversely, the substance-induced model posits that substance use and its physiological and psychological sequelae may induce or exacerbate mental health problems (Sadock et al., 2016; Vorspan et al., 2015).

The relationship between substance use, mental health, and mTBI is multifaceted and complex (Adams et al., 2023; Chan et al., 2022; McHugo et al., 2017). While substance use and mental health problems often exacerbate one another, mTBI introduces additional complexity by independently affecting both. A history of mTBI has been identified as a predisposing risk factor for substance misuse and mood disorders, although the exact mechanisms underlying these associations remain unclear and warrant further investigation (Adams et al., 2023; Alcock et al., 2018; Olsen & Corrigan, 2022; Rosenthal et al., 2023). Disruptions to neural pathways following mTBI, particularly in frontal regions implicated in decision-making (Shaw, 2002) and emotional regulation (Van Der Horn et al., 2016), may increase vulnerability to substance use and heighten the risk of developing mental health disorders. This relationship is further complicated by evidence suggesting that mTBI can influence substance use habits both directly, through alterations in neural pathways mediating risk-taking behaviour, and indirectly, through the onset of mood disorders (Newman et al., 2020). For instance, alcohol use prior to sustaining a TBI has been associated with a higher risk of developing mood disorders following injury (Walker et al., 2003), while recent work by Newman and colleagues (2020) demonstrated that individuals with a history of mTBI were more likely to experience panic disorder and substance misuse, with mental health factors (i.e., panic disorder) and female sex influenced this relationship.

Moreover, mTBI and substance use can produce overlapping functional deficits, including cognitive, behavioural, and psychological challenges (Alcock et al., 2018; Gobbi et al., 2019; Hines et al., 2020; Iverson et al., 2005; Kontos et al., 2016). Mechanistically, the pathways implicated in depression and mood disorders share overlap with neural disruptions caused by mTBI, further explaining the interconnectedness of these conditions (Van Der Horn et al., 2016). Recent research has highlighted that exposure to mTBI can have both direct and indirect effects on substance use through depression, with symptoms of depression and suicidal ideation accounting for 12% of the association between substance use post-concussion and binge drinking, and 19% of the association between substance use post-concussion and marijuana use (Baiden et al., 2022). Collectively, these findings suggest that the intersection between mTBI, substance use, and mental health is driven by overlapping neural pathways and psychosocial factors that perpetuate a cycle of vulnerability and increased risk.

1.4 Sex differences in mTBI, substance use, and mental health

It is particularly important to investigate the correlations between mTBI, substance use, and mental health factors, especially for women, who may be at greater risk of sustaining mTBIs and experiencing worse outcomes following injury. At baseline, or pre-injury, sex differences exist in substance use and mental health problems. For example, adolescent males are more likely to engage in substance use (Skidmore et al., 2016) and transition to riskier substance use behaviour compared to females (Choi et al., 2018; Skidmore et al., 2016). In contrast, females are more likely to suffer from mental health problems such as depression and anxiety (Piccinelli & Wilkinson, 2000). The gender gap in the proportion of individuals with substance use disorders is narrowing (Keyes et al., 2008) and women may be particularly at risk of experiencing higher rates of co-occurring psychiatric and substance use disorders, which complicates treatment (Conway et al., 2006).

While there is some debate in the literature, evidence suggests that women are more likely to sustain mTBIs from similar head impacts due to physical differences, such as smaller neck size and hormonal variations (Covassin et al., 2003, 2007; Gessel et al., 2007; Preiss-Farzanegan et al., 2017; Zuckerman et al., 2014). Females not only report more severe and prolonged symptoms post-injury (Covassin et al., 2007; Preiss-Farzanegan et al., 2017; Zuckerman et al., 2014), but also experience depression more frequently following mTBI (Rapoport et al., 2003; Vargas et al., 2015).

Additionally, recent research indicates that the associations between concussion history, substance use, and mental health may be stronger in females than in males (Newman et al., 2020). Female athletes, in particular, may be more vulnerable to post-injury mental health challenges, as they are 1.8 times more likely than their male counterparts to report clinical-level mental health symptoms, which are often more severe (Wolanin et al., 2016). They also experience higher rates of anxiety and depression, further compounding their susceptibility to poor post-injury outcomes (Piccinelli & Wilkinson, 2000). Despite comprising 43% of the collegiate athlete population (Irick, 2015), female athletes remain significantly underrepresented in sport-related concussion research, highlighting a critical gap in understanding and addressing their unique needs. The intersection of gender, athletic identity, and mental health underscores the need for targeted interventions and support systems that address both the psychological and behavioural health risks specific to female university athletes.

1.5 Neuroimaging

The majority of patients meeting criteria for mTBI show no positive findings on imaging and, as such, are diagnosed functionally rather than structurally (Pulsipher et al., 2011). Advances in neuroimaging allow examination of complex neurometabolic processes. Historically, computed tomography (CT) has been used to detect fractures, bleeding, and herniation in moderate to severe TBI. In contrast, magnetic resonance imaging (MRI) and diffusion-weighted imaging (DWI) are more sensitive in detecting traumatic lesions and shear injuries (Pulsipher et al., 2011). Diffusion tensor imaging (DTI) is an MRI technique that characterizes white matter tracts within the brain (Le Bihan et al., 2001). Neuronal cell bodies consist of gray matter, while axons sheathed in myelin form the white matter, which connects and transmits information across the brain. Axonal tracks are vulnerable to mechanical stretch injury, which can be visualized using DTI by measuring the diffusion of water through the tissues and estimating pathways integrity (Le Bihan et al., 2001; Rabinowitz & Levin, 2014). Several studies have used DTI to examine concussed athletes, though results have been mixed and sometimes inconsistent across samples (Asken et al., 2018; Pulsipher et al., 2011).

Functional magnetic resonance imaging (fMRI)

Functional magnetic resonance imaging (fMRI) has become a popular technique of investigating patterns of brain activity during cognitive tasks or during rest in mTBI populations. FMRI measures neural activity indirectly by quantifying the blood-oxygen-level-dependent (BOLD)

response. This measures changes in cerebral blood flow associated with energy demands produced by active neurons firing (Logothetis, 2002). FMRI is also used to measure functional connectivity, which refers to the temporal correlation between distinct brain regions that are activated together during tasks or at rest (Buckner et al., 2013). This coupled activity between regions is thought to reflect functional cooperation supporting higher-order cognitive processes. Through this, we can identify brain networks, such as the frontoparietal and sensorimotor networks, which show coordinated activity (Buckner et al., 2013). Resting-state fMRI captures intrinsic brain networks active while participants are at rest, such as the default mode network (DMN) (Raichle et al., 2001). This line of imaging is useful for understanding both normal brain function, and especially for appreciating disruptions which can occur due to diseases, mental health conditions, and injury (Fox & Greicius, 2010). In these cases, fMRI can reveal these changes and help assess the effects of rehabilitation (Matthews et al., 2006). A recent systematic review concluded that despite varied findings across highly studied areas of the DMN, salience network, and whole brain analyses, there may be a slight trend towards decreased whole-brain connectivity acutely following mTBI and that time since injury may associate with changes in connectivity (Dogra et al., 2024).

Neural networks

The frontoparietal network (FPN), supports goal-directed cognitive processes, both externally and internally focused. (Marek & Dosenbach, 2018; Scolari et al., 2015; Spreng et al., 2010; Zanto & Gazzaley, 2013). The FPN primarily comprises the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC) which support functions such as planning, decision-making, working memory, and spatial attention. (Corbetta & Shulman, 2002; Seeley et al., 2007). Cooperation between these regions is essential for aligning behaviour with goal-oriented outcomes (Marek & Dosenbach, 2018; Scolari et al., 2015; Zanto & Gazzaley, 2013).

Importantly, the FPN does not function in isolation but interacts with other networks, most notably, the salience (SN) and the DMN (Chen et al., 2013; Spreng et al., 2010). The anterior portion of the DMN includes the medial prefrontal cortex (mPFC), while the posterior DMN includes the precuneus and posterior cingulate cortex (PCC), which plays a central role in mediating DMN and supporting self-reflective processing (Davey et al., 2016; Fransson & Marrelec, 2008; Raichle, 2015).

The SN, which includes the anterior insula and anterior cingulate cortex (ACC), functions as a key regulatory hub, commonly referred to as the "control switch", between the FPN and DMN in the triple network model (Menon, 2019). The SN engages different networks as it identifies and prioritizes relevant stimuli, directing attention and integrating information (V. Menon & Uddin, 2010). This interplay supports cognitive flexibility and adaptation to changing internal and external demands (Hellyer et al., 2014).

In addition to these cortical networks, subcortical regions play a crucial role in cognitive and emotional processing (Kober et al., 2008; Müller et al., 2003). These include the ventral striatum and the medial temporal lobe system, which is composed of the amygdala, hippocampus, and parahippocampus. These regions are essential for learning, memory, and reward processing (Daniel & Pollmann, 2014; Haber, 2011; Palombo et al., 2015; Squire et al., 2004).

Neural networks and clinical implications

Several key brain regions and large-scale functional networks are central to emotional regulation, including the DMN, FPN, and SN. Emotional regulation depends on the coordinated activity and interaction of these systems, which support both internal self-reflection and external control of thoughts and actions (Chen et al., 2013; Pan et al., 2018). The FPN contributes to flexible cognitive control and decision-making (MacDonald et al., 2000), while the DMN supports self-referential thought, meditative processing, and emotional reflection (Andrews-Hanna et al., 2014; Raichle et al., 2001). The SN, particularly the anterior cingulate cortex (ACC), helps modulate the dynamic switching between the DMN and FPN in response to emotionally salient stimuli (Sutherland et al., 2012).

Together, the DMN and FPN underlie self-awareness and the regulation of emotional responses, making them particularly relevant in the context of mental health and brain injury (Pan et al., 2018). Disruptions to these networks have been implicated in emotional dysregulation and impaired cognitive control, especially in individuals with anxiety and depression (D'Avanzato et al., 2013; Sheline et al., 2009). Altered connectivity within the DMN has been commonly observed across several psychiatric disorders, including depression, panic disorder, social anxiety disorder, and generalized anxiety disorder (Andrews-Hanna et al., 2014; Brakowski et al., 2017; Northoff, 2020). These findings support the growing view that psychiatric conditions are not limited to localized brain dysfunction but instead arise from disrupted connectivity across broader neural networks (Li et al., 2018).

Substance use disorders also involve widespread network dysregulation. Individuals with substance use issues frequently show hypoconnectivity across the limbic system, SN, and FPN, as well as complex patterns of hypo- and hyperconnectivity within the DMN (Taebi et al., 2022). These disruptions are believed to reflect impairments in inhibitory control, self-awareness, and reward processing, which contribute to the persistence of substance use behaviors (Kamarajan et al., 2020; Shokri-Kojori et al., 2017; Taebi et al., 2022; Wetherill et al., 2015). Dysfunction within cortico-striatal circuits, in particular, has been linked to problems with motivation, emotional learning, and reward-based decision-making (Koob & Volkow, 2010; Kravitz et al., 2015). Other subcortical structures, such as the hippocampus, contribute to the maintenance of substance use by reinforcing maladaptive learning patterns (Kutlu & Gould, 2016).

These same subcortical circuits, the striatum (ST) and medial temporal lobe (MTL), including the hippocampus and amygdala, are also implicated in mood disorders, reflecting overlapping neural mechanisms between addiction and psychiatric illness (Campbell & MacQueen, 2004; Gabbay et al., 2013; Taebi et al., 2022). Thus, both addiction and mental health conditions share a common profile of neural network dysregulation involving cognitive control, emotional processing, and reward systems.

Similar patterns of neural disruption have been observed in individuals with a history of mTBI. mTBI is known to affect frontal lobe function and connectivity within large-scale networks such as the DMN and FPN, potentially reducing one's ability to anticipate negative consequences and regulate emotional responses in unpredictable or risky situations (Shaw, 2002; Van Der Horn et al., 2016). Given the role of these networks in emotional control, their dysregulation following mTBI may contribute to the onset or worsening of anxiety and depression, particularly in populations already at risk, such as athletes.

To further understand these relationships, three brain regions are of particular interest: the PCC, orbitofrontal cortex (OFC), and hippocampus. The PCC, a central node of the DMN, is involved in self-reflective and introspective processing (Davey et al., 2016; Fransson & Marrelec, 2008). The OFC supports reward valuation and guides decision-making, while the hippocampus plays a critical role in episodic memory, emotional learning, and the integration of contextual information (Rolls, 2015). Evaluating the rsFC of these brain regions may provide insight into how substance use, mental health symptoms, and mTBI are linked to emotional regulation difficulties, particularly in at-risk groups such as varsity athletes.

Chapter 2: Aims and Hypotheses

Our first aim was to examine the associations between substance use, mental health symptoms, and rsFC of key neural hubs involved in self-monitoring and emotional regulation in a sample of female varsity athletes. University athletes are more likely to engage in substance use and risky behaviors compared to their non-athlete peers (Ford, 2007; Nelson & Wechsler, 2001) and may be particularly vulnerable to mental health challenges (Cox et al., 2017). Given that female athletes are more prone to experiencing anxiety and depression than their male counterparts (Piccinelli & Wilkinson, 2000), it is important to focus on these psychological factors within this population.

There is considerable evidence highlighting the overlap between brain-behavior relationships related to emotional regulation, substance use, and mental health. Effective emotional regulation is crucial for decision-making, and disruptions in the neural processes supporting this function can influence social decision-making (Grecucci et al., 2013). We hypothesize that brain regions responsible for these processes may exhibit dysregulation in their rsFC, in line with prior research linking altered activity in areas involved in self-monitoring and emotion regulation to both risky substance use (Cranea et al., 2018; Filbey et al., 2014) and mental health disorders (Cheng et al., 2016; Coutinho et al., 2016). In particular, the PCC, which plays a critical role in mediating the DMN and driving self-reflective processing (Davey et al., 2016; Fransson & Marrelec, 2008), the OFC, which is involved in monitoring reward valuation and subsequent decision-making; and the hippocampus, which is primarily involved in episodic memory, and receiving and associating information (Rolls, 2015).

Aim 1: To quantify differences in rsFC within the PCC, OFC, and hippocampus in female athletes.

Hypothesis: We hypothesize that substance use will correlate with increased symptoms of anxiety and depression in female athletes, and that these behavioral differences will be reflected in underlying differences in rsFC.

While the first goal focused on evaluating the associations between substance use, mental health, and the regulation of brain regions, it is important to consider the heightened exposure to mTBI within an athlete population (Langlois et al., 2006). MTBIs can have long-term effects on psychological health, increasing the risk for both substance use and mood disorders (Alcock et al., 2018). One proposed mechanism that links mTBI with increased substance use involves alterations in frontal brain regions caused by head injury, which may disrupt the ability to anticipate

negative outcomes in risky or unpredictable situations (Shaw, 2002). These disruptions in frontal brain regions may similarly influence mental health outcomes (Van Der Horn et al., 2016).

The role of sex in these outcomes is also important to consider. Female athletes are debated to be at a higher risk for sustaining a mTBI (Covassin et al., 2003; Gessel et al., 2007) and may be more susceptible to experiencing symptoms and longer recovery trajectories (Covassin et al., 2007; Preiss-Farzanegan et al., 2017; Zuckerman et al., 2014)

Aim 2: To characterize the relationships between mTBI history, mental health, and single and polysubstance use in males and females.

Hypothesis: mTBI history will be associated with increased substance use and mood-related symptoms, with greater effects observed in female athletes.

Building upon the findings from the previous two objectives, we aimed to expand the scope of this research by collecting data from a larger and more diverse sample of athlete and non-athlete young adults. While the initial study allowed for an exploration of risk factors related to single and polysubstance use, it did not fully explore the role of sex in these relationships. A larger dataset allowed for a more nuanced understanding of substance use, mental health, and mTBI history, and provide greater variability within the mTBI histories of non-athletes, enhancing the exploration of these associations.

Aim 3a: To identify the relationship between mTBI history and current substance use habits, and how mental health and mTBI interact to influence substance use patterns.

Hypothesis: mTBI history, along with mental health symptoms, will be associated with substance use patterns

Aim 3b: To characterize the potential influence of sex on these relationships.

Hypothesis: The effects of mTBI and mental health on substance use will be moderated by sex, with female athletes potentially exhibiting stronger associations than males.

Finally, we aimed to determine how substance use, mental health, and mTBI history may interact to influence rsFC within these networks in a sample of varsity athletes in preliminary exploratory analyses.

Aim 4: To characterize potential underlying differences in key neural networks related to substance use and mental health in athletes with and without a history of mTBI.

Hypothesis: A history of mTBI and higher levels of substance use will be associated with disrupted rsFC within the DMN, FPN, SN, ST, and MTL. Additionally, greater symptoms of anxiety and depression will be related to altered rsFC connectivity within the DMN, and MTL. The combined presence of mTBI history with these risk factors is expected to show compounded effects on neural network dysregulation.

Chapter 3: Substance use is associated with worse mental health and altered resting state functional connectivity in female university athletes at baseline: A pilot study

3.1 Publication status and author contributions

The following chapter is based on the manuscript: Alyssia Wilson, Kristina Gicas, W. Dale Stevens, Lauren Sergio, & Magdalena Wojtowicz. (2021). Substance use is associated with worse mental health and altered resting state functional connectivity in female university athletes at baseline: A pilot study. PloS One, 16(6):e025326, doi: 10.1371/journal.pone.0253261

This manuscript does not exactly replicate the final version published in PloS On.

It is not a copy of the original published article and is not suitable for citation.

Alyssia Wilson, the first author, developed the conceptual rationale for the study, analyzed and interpreted the data. She was also the primary contributing author to the manuscript, producing the initial draft and completing all major revisions.

3.2 Abstract

Objective. University athletes are at high risk for both substance use and mental health problems. This study examined associations between substance use, mental health symptoms, and the resting state functional connectivity (rsFC) of key neural regions involved in self-monitoring and emotional regulation in a sample of female varsity athletes.

Methods. 31 female university athletes completed measures of substance use, mental health symptoms, and underwent functional MRI scans during the pre-season.

Results. Athletes who were substance users had higher symptoms of depression than non-users ($p=0.04$; Hedge's $g=0.81$). RsFC differences were observed between users and non-users in orbital frontal cortex (OFC) and bilateral hippocampal seeds, and negative associations between depression symptoms and rsFC in the left hippocampus and posterior cingulate cortex were observed in cannabis users.

Conclusion. In female athletes, substance use is associated with greater self-reported depression symptoms and altered rsFC in self-monitoring and emotional regulation regions of the brain.

3.3 Introduction

Despite being targeted for substance-intervention and education, university athletes are more likely to use substances than their non-athlete peers (Nelson & Wechsler, 2001). In particular, athletes are more likely to engage in risky substance use behaviours, such as regular heavy alcohol use (Ford, 2007) and are at an increased risk for using other substances such as cannabis (Hilderbrand, 2011). Team bonding, normative views of substance use, and increased pressures have been suggested to contribute to high use of substances among athletes (Ford, 2007).

In addition to being more susceptible to risky substance use behaviours, university athletes experience mental health problems at a similar rate or higher than the general population (Cox et al., 2017). Athletes experience not only the same academic pressures experienced by all students but are also exposed to unique mental health risk factors including sports injury, performance pressure, overtraining, and conflict with coaches, when compared to their non-athlete peers (Wolanin et al., 2015) . Evaluating the associations between mental health and substance use is particularly important for young women, who are more likely to experience symptoms of anxiety and depression compared to males in general (Piccinelli & Wilkinson, 2000). Specifically within the athlete population, females are 1.8 times more likely than males to endorse clinical-level symptoms in addition to reporting more severe symptoms (Wolanin et al., 2016) .

There is evidence of overlapping brain-behaviour relationships between emotional regulation, substance use, and mental health. Differential activity in brain areas involved in self-monitoring and emotion regulation (e.g., the amygdala, prefrontal cortex, orbital frontal cortex; OFC, anterior and posterior cingulate cortices, and inferior parietal lobule) have been associated with both risky substance use (Cranea et al., 2018; Filbey et al., 2014) and mental health disorders (Cheng et al., 2016; Coutinho et al., 2016). Altered rsFC in depression is associated with inadequate reappraisal of emotions, increased rumination, and increased use of expressive suppression as a coping strategy (Joormann & Gotlib, 2010). Individuals with anxiety have been found to also have difficulty with adequate use of emotional regulation strategies (Amstadter, 2008).

Appropriate use of emotional regulation strategies is essential for decision making, and dysregulation of the neural processes underlying this function can affect social decision making (Grecucci et al., 2013). Several key brain regions and neural networks have been implicated in supporting emotional regulation processes. These regions include the posterior cingulate cortex

(PCC), which plays a critical role in mediating the default mode network (DMN) and driving self-reflective processing (Davey et al., 2016; Fransson & Marrelec, 2008); the OFC, which is involved in monitoring reward valuation and subsequent decision-making; and the hippocampus, which is primarily involved in episodic memory, and for receiving and associating information (Rolls, 2015). Evaluating the rsFC of these brain regions may provide insight into how mental health and substance use are associated with an athlete's ability to regulate emotion. The present study explored associations between substance use, mental health symptoms, and the rsFC of significant neural hubs involved in self-monitoring and emotional regulation in a sample of female varsity athletes. We hypothesized that substance use would correlate with increased symptoms of anxiety and depression in female athletes, and these behavioural differences would be reflected in underlying rsFC differences.

3.4 Method

Participants

Thirty-one female varsity athletes from York University, Toronto, between the ages of 18 and 25 years (*M*= 19 years 9 months, *SD*= 1 year 6 months) were recruited at preseason through the York University Sports Medicine Clinic and baseline data was collected. Participants were eligible if: i) they were over 18-years-old, ii) were rostered to play on a university team for the current season, and iii) met the requirements for safe MRI scanning. Participants were predominately Caucasian (79%). A sample size of 31 was more than sufficient to detect an effect for planned comparisons, based on a calculation using 80% power, a medium effect size (0.5), and a p-value of 0.05 (N=12) (Erdfelder et al., 1996). Participants were first active in sports by approximately six years of age (*M*= 6 years 2 months, *SD*= 2 years 11 months). At the time of the study, the athletes were engaged in one of the following sports: hockey (*n*=13, 42%), volleyball (*n*=6, 19%), soccer (*n*=7, 23%), or basketball (*n*=5, 16%). Ninety-four percent of participants (n=29) were right-handed.

Procedure

This study was approved by the Human Participants Review Sub-Committee of York University's Ethics Review Board. Participants gave written informed consent to complete the imaging and behavioural components of the study, which were conducted on the same day. Participants were compensated $50 for their time.

Measures

Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 (Kroenke & Spitzer, 2002) is a 9-item questionnaire of self-reported symptoms of depression. Participant total depression severity score is calculated by summing the items; total scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, respectively.

Generalized Anxiety Disorder-7 item (GAD-7)

The GAD-7 (Spitzer et al., 2006) is a well validated, 7-item questionnaire to assess self-reported anxiety. Total score cut-offs of 5, 10, and 15, represent mild, moderate, and severe anxiety, respectively

Substance use

The Alcohol Use Disorder Identification Test-Clinical (AUDIT-C) screening index (Babor et al., 2001) was used to assess alcohol use. Total scores of 4 or more in men and 3 or more in women indicate hazardous or harmful drinking. Cannabis use was evaluated using a health questionnaire, which includes the question “how often do you smoke marijuana?” Possible responses to this question were never, monthly or less, 2-4 times a month, 2-3 times per week, 4+ times per week. Alcohol use was determined by a score of 3 or higher on the AUDIT-C and participants were considered cannabis users if they indicated any answer other than “never” to “how often do you smoke marijuana?” on the health questionnaire. Using these criteria, participants were divided into non-users and users. Users were further divided into alcohol users (alcohol but not cannabis use), and cannabis users (cannabis use regardless of alcohol use).

Sport Concussion Assessment Tool-5 (SCAT5)

The SCAT5 is a widely used standardized tool for assessing concussion which combines the Standardized Assessment of Concussion (SAC), the Post-Concussion Symptom Scale (PCSS), and on-field signs of concussion (McCrory et al., 2005).

MRI acquisition

Using a Siemens TIM Trio 3T MRI scanner (Siemens, Erlangen, Germany), T1-weighted, high-resolution anatomical scans were acquired using ascending multi-slice 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) (FOV = 256 mm, 1.0 x 1.0 x 1.0 mm voxels, TR = 2300, TE =2.62 ms). A whole brain multi-echo echo-planar imaging (EPI) sequence, which is T2*-weighted, was used to acquire functional data in 240 volumes (43 slices, FOV = 216 mm, 64 x 64

matrix, 3.4 x 3.4 x 3.0 mm^3 voxels, TR = 3000 ms, echo times [TEs] = 14 ms, 30 ms, 46 ms, flip angle = 83°). During fMRI scanning, participants laid still with their eyes closed.

Functional imaging preprocessing

Functional imaging data (i.e., the second echo from the multi-echo scan) were preprocessed and analyzed using the CONN toolbox Version 18.b (Whitfield-Gabrieli & Nieto-castanon, 2012) using a standard preprocessing pipeline in which functional data were functionally realigned and unwarped by estimating and correcting the change in the distortion map with respect to the motion parameters, translated by centering to (0,0,0) coordinates, slice-time corrected, scrubbed with ART-based identification for outlier scans, segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF), normalized to the Montreal Neurological Institute (MNI) template MNI152, and smoothed using an 8 mm Gaussian kernel, full width at half maximum (Kornelsen et al., 2020). The toolbox's aCompCor protocol was used to reduce physiological and movement effects (i.e., white matter, cerebrospinal fluid, and outliers detected by the ART toolbox, and realignment parameters from preprocessing were entered into the linear regression as confounding effects). A band-pass filter (0.008-0.09 Hz) was applied to the data.

Statistical analysis

Variables were examined for normality and univariate outliers; there were no violations to assumptions of normality and therefore, parametric tests were used. T-tests and Hedge's g (effect size) were conducted between users and non-users and alcohol and cannabis users to evaluate differences in age, age at first sport, concussion history, SCAT symptoms, SAC scores, depression and anxiety symptoms. Follow-up analyses were performed between non-users and alcohol users, and non-users and cannabis users.

ROI-to-ROI Analysis

CONN toolbox ROI-to-ROI analyses were used with weighted General Linear Model (GLM) correlation analysis settings (described in detail elsewhere) (Whitfield-Gabrieli & Nieto-castanon, 2012). Using the default atlas in CONN toolbox, source seeds selected included the PCC (x = 1, y = -37, z = 30), the left and right hippocampus (Left, x = -25, y = -23, z = -14; Right, x = 26, y = -21, z = -14), and the left and right OFC (Left x = -30, y = 24, z = -17; Right x = 29, y = 23, z = -16). All atlas seeds (132) were selected as targets to the analysis. ROI-to-ROI matrices represent the level of functional connectivity between each pair of ROIs. Each element is defined as the Fisher-

transformed bivariate correlation coefficient between a pair of ROI BOLD timeseries (Alfonso Nieto-Castanon, 2020). Between-subjects contrasts were run comparing [Users (1) non-Users (-1)] and [Cannabis Users (1) Alcohol Only Users (-1)]. A within-group follow-up analysis was run investigating the effect of depression in cannabis users using demeaned PHQ-9 scores. ROI-to-ROI rsFC was examined using intensity-based thresholding set to a False Discovery Rate (FDR) of $p \leq 0.05$ seed-level correction, two-sided.

3.5 Results

From the sample, 21 participants were classified as substance users and 10 were classified as non-users. Among the substance users, 13 used alcohol only, and 8 reported concurrent cannabis use. There were no significant differences between users and non-users in age, age of first sport, concussion history, SAC scores, or GAD-7 scores. However, users had significantly higher PHQ-9 scores [$t(29) = -2.165$, $p = 0.039$, Hedge's $g = 0.81$; large effect] and higher SCAT symptom total scores [$t(29) = -2.106$, $p = 0.04$, Hedge's $g = 0.79$; large effect] (See Table 1). PHQ-9 and SCAT symptom totals were significantly higher in the cannabis group when comparing the non-users and cannabis users ($p<.05$) but not alcohol only users (see Table 1). There were no statistically significant differences in clinical characteristics between alcohol only users and cannabis users except in PHQ-9 scores where cannabis users had significantly higher scores [$t(19) = 2.759$, $p = 0.012$, Hedge's $g = 1.20$; large effect].

Table 1. Participant characteristics of non-users, users, alcohol users and cannabis users in study 1

	Non-Users (n = 10)	Users (n = 21)	p(g)	Alcohol (n = 13)	p(g)[a]	Cannabis (n = 8)	p(g)[b]
Age *M(SD)*	19.7 (1.42)	19.8 (1.54)	0.8 (0.07)	19.54 (0.97)	--	20.2 (2.19)	--
Age at First Sport *M(SD)*	5.6 (2.67)	6.38 (3.04)	0.49 (0.26)	7.00 (3.37)	--	5.38 (2.26)	--
Concussion History *Md(Range)*	1.0 (0-4.0)	1.0(0-6.0)	0.94 (0.03)[c]	0 (0-3.0)	--	1.5 (0-6)	--
SCAT Symptoms Total *M(SD)*	1.40 (2.84)	4.57 (4.32)	**0.04 (0.79)**	3.38 (3.20)	0.14 (0.63)	6.50 (5.37)	**0.004 (1.50)**
SAC Total Score *M(SD)*	26.6 (1.35)	27.24 (1.30)	0.22 (0.47)	26.92 (1.19)	--	27.75 (1.39)	--
PHQ-9 Total *M(SD)*	1.60 (2.8)	4.14 (3.17)	**0.04 (0.81**)	2.85 (2.48)	0.27 (0.46)	6.25 (3.15)	**0.019 (1.17)**
GAD-7 Total *M(SD)*	1.70 (3.02)	3.29 (2.85)	0.17 (0.53)	2.77 (3.22)	--	4.13 (2.03)	--

Note: g= Hedge's g; [a]Comparison between non-users and alcohol users; [b]Comparison between non-users and cannabis users; [c]Mann-Whitney U Test to examine differences between distributions.

ROI-to-ROI results

Results from the ROI-to-ROI analyses are summarized in Table 2 and shown in Figure 2. Users showed decreased rsFC between the left OFC and the occipital fusiform gyrus ($p = 0.032$) and increased rsFC between both hippocampal seeds and the right cerebellum ($ps \leq 0.05$) compared to non-substance users. When breaking down the user group into alcohol and cannabis users, no significant differences in rsFC were found between cannabis use and alcohol use only participants ($ps > 0.05$). To further examine potential associations between rsFC and PHQ-9 scores in cannabis users, an exploratory within-group correlation was conducted. PHQ-9 scores were negatively correlated with rsFC between the left hippocampus and the right posterior temporal fusiform cortex ($p = 0.020$), and between the PCC and the cerebellum ($p = 0.027$; See Figure 3).

Table 2. ROI results comparing users and non-users and effects of PHQ-9 scores among cannabis users.

			MNI coordinates					Connectivity	
			x	y	z			Users	Non-Users
Contrast	Seed	Target				T	pFDR	*Mean(SD)*	*Mean(SD)*
Users > Non-Users									
	OFC left	Occipital fusiform gyrus right	-27	-77	-14	-4.18	0.032	-0.04(0.12)	0.14(0.09)
	Hippocampus right	Cerebellum right	33	-63	-48	4.44	0.016	-0.03(0.10)	-0.21 (0.12)
	Hippocampus left	Cerebellum right	33	-63	-48	4.11	0.038	0.01(0.12)	-0.18(0.13)
Effect of PHQ-9 for Cannabis Users									
	Hippocampus left	Posterior temporal fusiform cortex right	36	-24	-28	-8.42	0.020	0.16(0.11)	--
	PCC	Vermis45	1	-52	-7	-7.97	0.027	0.37(0.19)	--

Note: OFC=orbitofrontal cortex; PCC=posterior cingulate cortex; PHQ-9= Patient Health Questionnaire-9.

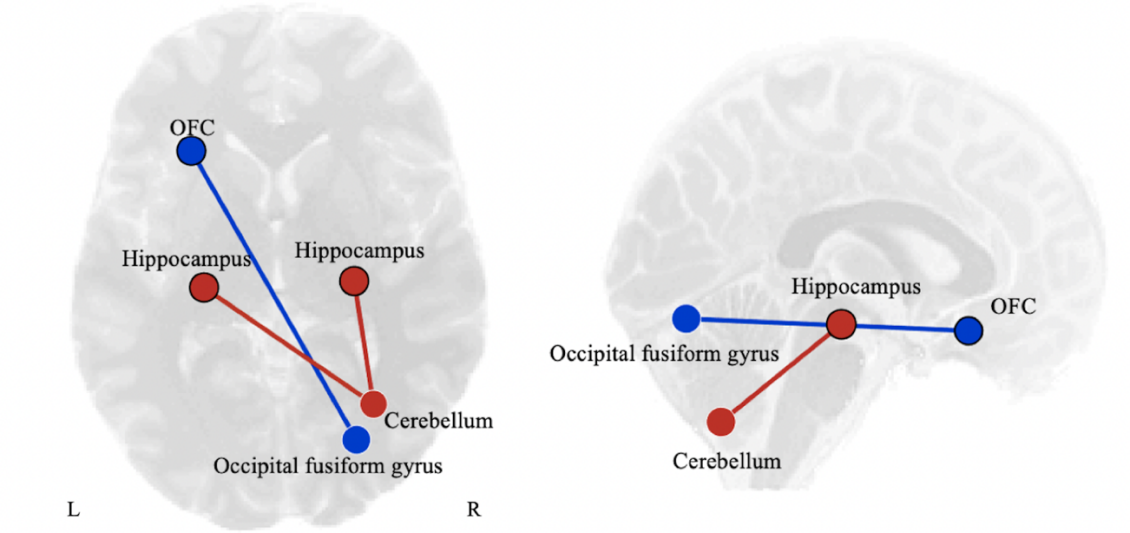


Figure 2. Differences between substance users and non-users showing increases (red) and decreases (blue) in resting state functional connectivity in substance users displayed from an axial view on the left and from a sagittal view on the right.

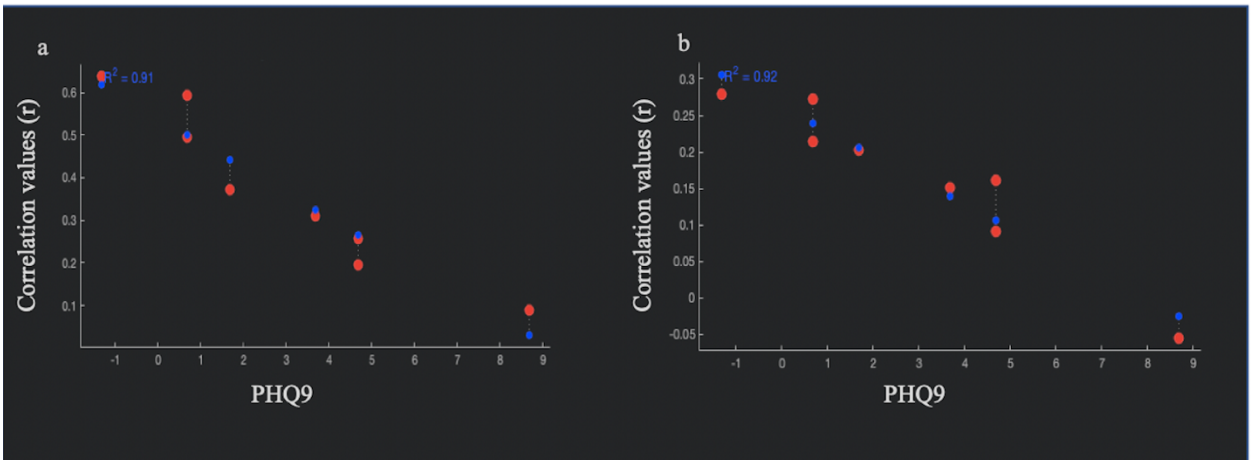


Figure 3. Correlation between demeaned PHQ9 scores and functional connectivity between (a) the fusiform cortex and hippocampus and, (b) the cerebellum and the posterior cingulate.
Note: red dots= observed values; blue dots= fitted values.

3.6 Discussion

The present study showed that within a relatively small female university athlete sample, approximately two thirds (21/31; 67.7%) endorsed moderate alcohol use and/or combined alcohol and cannabis use. Combined substance users also endorsed significantly greater symptoms of depression and total symptoms on the SCAT5. Prior systematic reviews have reported that

cannabis use, and heavy cannabis use, in particular, is associated with elevated risk of depression (Lev-Ran et al., 2014) and negative affective outcomes (e.g., depression, suicidal thoughts, and anxiety) (Moore et al., 2007). Furthermore, co-use of alcohol and cannabis has been associated with greater risk of comorbid mental health disorders (Yurasek et al., 2017). Our findings demonstrate increased symptom endorsement (i.e., of depressive and other psychological and somatic symptoms) in female athletes with self-reported cannabis use compared to alcohol only users and non-users. Concussion history has also been associated with higher alcohol and cannabis use in college students (Newman et al., 2020). Athletes are at greater risk for concussion (Harmon et al., 2013), and prior research has suggested that higher exposure to repetitive head injuries is associated with increased substance use (Alcock et al., 2018) and symptoms of depression (Rapoport et al., 2003; Vargas et al., 2015). Higher exposure to repetitive head impacts has been suggested to affect vulnerable brain areas involved in impulsive and risk-taking behaviours, which may account for increased substance use (Alcock et al., 2018). Within our limited sample size, we did not observe differences in concussion history between substance users and non-user; however, the relationship between cannabis use and symptom endorsement in athletes requires further investigation to explore whether associations between substance use and mental health status are mediated by concussion history.

This study also examined associations between substance use and rsFC in regions of the brain involved in emotion processing and regulation. Relative to non-users, athletes who used alcohol or cannabis exhibited hypoconnectivity between the left OFC and the occipital fusiform gyrus while showing hyperconnectivity between the bilateral hippocampus and the right cerebellum. Within the cannabis users, depression symptoms correlated negatively with connectivity of the left hippocampus and the PCC. These associations suggest that alterations in rsFC exist in substance-using athletes relative to their non-using athlete peers. Emotion and hippocampal networks of the limbic system are involved in reward-related decision making (Rolls, 2015) and altered connectivity patterns within these networks may dysregulate decision-making abilities with implications for risky substance use behaviour.

To our knowledge, this is one of the first studies examining substance use (in particular cannabis use) and its associations with mental health and neural functioning in athletes at baseline. Despite the limited sample size, this study found associations between substance use, mental health, and underlying brain functional connectivity in self-monitoring and emotional regulation regions in female varsity athletes (with moderate to large effect sizes). These preliminary

findings highlight the need to better understand relationships between substance use and mental health in athletes. However, the measurement of substance use was limited in this study and future research should further examine associations between cannabis use, affective disorders, and concussion history in athlete populations using more comprehensive measures of substance use. In addition, further research is necessary to examine whether differences in rsFC connectivity within default mode and limbic networks affects self-monitoring and emotional regulation that may, in turn, influence substance use behaviour. This work suggests a need to consider factors such as mental health and substance use when examining neural functioning of athletes at baseline and, potentially, post-injury. It also highlights the importance of assessing substance use and monitoring of mental health in athletes. Further research in the area may lead to the development targeted interventions to improve outcomes for athletes.

Chapter 4: Influence of mild traumatic brain injury history and mental health status on alcohol and cannabis use in university athletes

4.1 Publication status and author contributions

The following chapter is based on the manuscript: Alyssia Wilson, Kristina Gicas, & Magdalena Wojtowicz. (2023). Influence of mild traumatic brain injury history and mental health status on alcohol and cannabis use in university athletes. Clin J Sport Med, 2023 Mar 1;33(2):145-150. doi: 10.1097/JSM.0000000000001110.

This manuscript does not exactly replicate the final version published in the Clinical Journal of Sports medicine. It is not a copy of the original published article and is not suitable for citation. Alyssia Wilson, the first author, developed the conceptual rationale for the study, analyzed and interpreted the data. She was also the primary contributing author to the manuscript, producing the initial draft and completing all major revisions.

4.2 Abstract

Objective. This study examined the relationship between mild traumatic brain injury (mTBI) history, mental health, and sex with single and polysubstance use in university athletes.

Methods. Participants were identified from a dataset of 416 university athletes ages 18-21 who received baseline assessment which assessed substance use habits mTBI history, and past and present mental health. Participants were classified based on their substance use habits and 153 met criteria for the non-substance group, 195 for the alcohol only group, and 64 for the polysubstance use group (i.e., a combined substance use (CSU) group).

Results. MTBI history was a significant predictor of alcohol use ($p < .001$) and polysubstance use ($p < .001$). Anxiety endorsement was also a significant predictor of polysubstance use ($p < .001$) and there was a small but non-significant trend of males being more likely to engage in polusubstance use ($p = .057$).

Conclusions. University athletes who experience mTBI are more likely to engage in single or polysubstance use than those with no mTBI and athletes who experience anxiety are more likely to engage in polysubstance use than those without. Consideration of mTBI history and mental health may inform clinical concussion management for identifying potential high-risk behaviour such as polysubstance use in university athletes and tailoring intervention strategies (e.g., incorporating education about substance use).

4.3 Introduction

University athletes represent a unique population with high incidence of mTBIs (Langlois et al., 2006), experiencing mental health disorders(Schinke et al., 2018), and engaging in risky substance use behaviour (Nelson & Wechsler, 2001). The relationship between these factors is complex and not well understood. The recent rise in cannabis use has impacted the substance use patterns of youth, with 50% of substance using youth reporting that they engage in polysubstance use (Zuckermann et al., 2019). This trend in the use of multiple substances calls for a better understanding of how mTBI and mental health factors contribute independently and in concert to influence substance use, especially in high-risk populations. MTBIs can have long-term effects on psychological health, increasing the risk for both substance use and mood problems (Alcock et al., 2018). Substance use and mTBI have also both been associated with alterations in frontal brain regions that may disrupt anticipation of negative outcomes in unpredictable or risky situations (Shaw, 2002). Individuals with mTBI often experience changes in emotional functioning that may also be associated with disruptions to frontal brain regions, which may affect mental health outcomes (Van Der Horn et al., 2016). Further, examining the role of sex on outcomes is highly relevant as female athletes are at higher risk for sustaining an mTBI (Covassin et al., 2003; Gessel et al., 2007), report greater symptoms following injury (Covassin et al., 2007; Preiss-Farzanegan et al., 2017; Zuckerman et al., 2014), and may have longer recovery trajectories (Covassin & Elbin, 2011; Zuckerman et al., 2014). In general, females are more likely to experience anxiety and depression than males and may experience greater harm related to substance use disorders (Piccinelli & Wilkinson, 2000)·(McHugh et al., 2018). A recent pilot study by our group also identified altered brain activity in self-monitoring and emotion regulation regions associated with substance use and depression symptoms in female athletes with mTBI history (Wilson et al., 2021).

Recent work by Newman and colleagues (2020) suggested that those with a history of mTBI endorsed higher panic disorder and substance use. Additionally, both mental health (i.e., panic disorder) and female sex influenced the relationship between mTBI history and substance. The objective of the present study was to investigate the relationships between mTBI history and mental health on single and polysubstance use and to explore the possible influence of sex on these relationships. By increasing our understanding of the interconnections between these factors, clinicians will be better informed in assessing and providing treatment, psychoeducation, and intervention services to these populations.

4.4 Method

Participants

Data from 416 university athletes involved in various sports (basketball, football, hockey, soccer, rugby, tennis, track and field, volleyball, and wrestling) was collected through the York University Sports Medicine Clinic as part of their annual baseline testing. Participants were eligible if: i) they were over 18-years-old, and ii) were rostered to play on a university team for the current season. This sample was made up of 246 males (58.9%) and 170 females (41.1%) and were between the ages of 18 and 21 (M = 19 years 7 months, SD = 1 year 2 months).

Procedure

Alcohol as well as cannabis and other recreational drug use were evaluated using a health questionnaire with the questions “Do you consume alcohol?” and “Do you use cannabis or other "recreational/street" drugs for social purposes?” during their baseline assessment. Responses were never, past, and present. Given that there were no group differences in clinical variables between past or present users for either group, participants were included in alcohol use only (AU) group if they indicated past or present alcohol use and the combined substance use (CSU) group if they indicated past or present substance use in addition to past or present alcohol use. Alcohol use and CSU were both coded as binary variables. The CSU group captures poly-substance use as it identifies athletes who use more than one substance (alcohol in addition to one or more recreational substances). This sample consisted of n = 153 athletes who did not use alcohol or recreational substances, n = 195 athletes who used only alcohol, n=64 athletes were combined substance users who endorsed use of alcohol as well as cannabis or other recreational substances (i.e., polysubstance users). Four participants who used only substances (i.e., cannabis and recreational substances) and not alcohol were excluded from further analyses.

Measures

Mental Health Status

Mental health information was collected using the Personal Health Questionnaire-9 item (PHQ-9), and self-reported anxiety/panic (“Do you suffer from anxiety or panic attacks/ disorder?”) which was coded as a binary variable. The PHQ-9 (Kroenke & Spitzer, 2002) is a 9-item questionnaire derived from the Patient Health Questionnaire and is a useful screening tool and incorporates the 9 criteria for depression disorders included in the DSM-IV. Participants are asked

to indicate the extent to which they are bothered by the questionnaire items over the last two weeks. Questions are scored on a 4-point ordinal scale and total score is interpreted as follows; none (1 to 4), mild (5 to 9), moderate (10 to 14), moderately severe (15 to 19), and severe (20-27).

mTBI History

mTBI history was evaluated using a health questionnaire that inquired if participants had experienced a “concussion or head injury of any kind (includes any concussion, skull fracture, bleeding inside the skull, memory loss or confusion resulting from a blow to the head, "bell ringers", "dingers" or any other head injury)”. Self-reported mTBI history was coded as a binary variable and injury descriptions were screened to eliminate more severe brain injuries.

Statistical analysis

Demographic information of the non-use (NU) group, the alcohol use group, and the CSU group was compared using independent t-tests and chi square tests. T-tests were run where homogeneity of variance was met, nonparametric statistics were used for PHQ9 scores in the combined substance group. Binary logistic regressions were performed using SPSS version 26. Regression models predicting alcohol use and CSU were calculated using sex, mTBI history, and mental health (endorsement of mild PHQ9 score of 5 higher, or anxiety/panic) as predictors. Sex (female=1) was also examined as a moderator of both mTBI history and mood measures. A secondary regression analysis was performed to examine mood and anxiety separately in AU and CSU groups using depression as a continuous variable and anxiety endorsement as a categorical variable. A follow up ordinal regression was run using the same predictors to investigate whether there is an additive burden contributing to no use, alcohol use, or CSU. There were no major violations of assumptions. Cases with missing data on any variable were removed from the model.

Ethical Considerations

The present study involved a retrospective analysis of data collected by the York University Sports Medicine Clinic. This study was approved by the Human Participants Review Sub-Committee of York University’s Ethics Review Board. Participants provided written informed consent.

4.5 Results

Group differences

Demographic information is presented in Table 3. Frequency distribution of substance use across sports played is presented in Table 4. The AU group and NU group did not differ in sex distribution (p = .742), or PHQ9 score (p = .931). However, the mean age of the AU group was significantly higher than NU (p <.001; AU group mean age =20.77, NU group mean age= 19.83), and a significantly higher number of alcohol users endorsed experiencing anxiety (X^2 = 5.136, p = .023) as well as positive mTBI history (X^2 = 14.134, p < .001) compared to the NU group. The CSU group and NU group did not differ in sex distribution (p = .145), however, the mean age of the CSU group was significantly higher than the NU group (p = .031; CSU group mean age =20.53, NU mean age =19.83). The CSU group also endorsed significantly higher PHQ9 scores (p = .022), and a significantly higher number endorsed experiencing anxiety (X^2 = 13.657, p < .001) and mTBI history (X^2 = 14.325, p < .001) compared to NU.

When comparing the two substance use groups, there were no differences in sex distribution, age or mTBI history between the AU group and CSU group. However, compared to the AU group, the CSU group endorsed significantly higher PHQ9 score (p = .015). Anxiety endorsement also trended towards significance (X^2 = 3.630, p = .057).

Table 3. Descriptive variables by non-use, alcohol use and combined substance use groups and results of comparisons between alcohol use and non-use, and combined substance use and non-use in study 2.

	No Use (N = 153)	Alcohol Use (N = 195)	p values	Combined Substance Use (N = 64)	p values
Sex M/F	89/64	109/85	.742	44/20	.145
Age *M(SD)*	19.83(1.93)	20.77(1.86)	<.001	20.53(2.25)	.031
PHQ9 score *M(SD)*	2.25(3.74)	2.22(3.23)	.931	3.87(4.80)	.022
Anxiety *n(%)*	12(7.84%)	31(15.90%)	.023	17(26.56%)	<.001
mTBI History *n(%)*	29(18.95%)	73(37.43%)	<.001	28(43.75%)	< .001

Table 4. Frequency distribution of sex and substance use by sport played.

	M/F	No Use (N = 153)	Alcohol Use (N = 195)	Combined Substance Use (N = 64)
Basketball	21/13	19(12.42%)	13(6.67%)	2(3.13%)
Cross Country/ Track & Field	40/30	41(26.80%)	20(10.25%)	9(14.06%)
Field Hockey	0/23	8(5.22%)	12(6.15%)	3(4.69%)
Football	85/0	25(16.33%)	39(20.00%)	21(32.81%)
Hockey	32/25	3(2.00%)	46(23.59%)	8(12.50%)
Rugby	0/27	7(4.58%)	12(6.15%)	8(12.50%)
Soccer	38/27	31(20.26%)	28(14.36%)	6(9.38%)
Tennis	3/3	3(2.00%)	3(1.54%)	0(0.00%)
Volleyball	16/16	9(5.88%)	18(9.23%)	5(7.81%)
Wrestling	9/4	7(4.58%)	4(2.05%)	2(3.13%)

Associations between clinical variables and substance use

See Table 5 for results. Participants with missing data were excluded from all further regression models (i.e., eight participants in the no use group (n = 145), nine participants in the AU group (n = 186), and four participants in the CSU group (n = 60)). In adjusted models using alcohol use versus no use as the outcome, mTBI history (OR= 2.40, 95% CI [1.43, 4.01], p <.001), but not sex or mental health endorsement was a significant predictor of alcohol use in university athletes. However, in the CSU group, both mTBI history (OR= 3.11, 95% CI [1.58, 6.15], p <.001) and mental health endorsement (OR= 2.66, 95% CI [1.30, 5.44], p = .007) were significant predictors of use versus no use. Sex also approached significance as a predictor (OR= .495, 95% CI [.243, 1.01], p = .053), indicating a trend towards males being more likely to endorse CSU. In both models, sex was examined as a potential moderator of mTBI and mental health, but as it was not found to be significant at $p < 0.05$ for either alcohol or CSU, the interaction terms were not retained in the final models.

Table 5. Association between clinical and mental health variables and substance use outcomes in binary and ordinal logistic regression models.

	B(SE)	Wald	Sig.	OR	95%CI OR	Model Adjusted R^2
Model 1: Any Mental health endorsement						
Alcohol use						.039
Sex	.017(.236)	.005	.944	1.017	.640/1.616	
mTBI History	.873(.262)	11.066	<.001	2.395	1.431/4.006	
Mental Health Endorsement	.183(278)	.437	.508	1.200	.699/2.063	
Constant	-0.43(.163)	.070	.791	.958	-	
Combined Substance use						.105
Sex	-.704(.363)	3.755	.053	.495	.243/1.008	
mTBI History	1.135(.347)	10.682	.001	3.111	1.575/6.145	
Mental Health Endorsement	.978(.365)	7.200	.007	2.660	1.302/5.435	
Constant	-1.287(.238)	29.271	<.001	.276	-	
Model 2: Unique contribution of depression and anxiety						
Alcohol Use						.047
Sex	.011(.236)	.002	.963	1.011	.636/1.607	
mTBI History	.882(.265)	11.083	<.001	2.417	1.437/4.063	
Depression	-0.041(.036)	1.307	.253	.959	.894/1.030	
Anxiety	.649(.405)	2.562	.109	1.913	.864/4.234	
Constant	.020(.167)	.014	.907	1.020	-	
Combined Substance Use						.118
Sex	-.698(.367)	3.624	.057	.497	.242/1.021	
mTBI History	1.045(.357)	8.564	.003	2.843	1.412/5.723	
Depression	.032(.046)	.484	.487	1.032	.944/1.129	
Anxiety	1.272(.489)	6.780	.009	3.570	1.370/9.302	
Constant	-1.258(.238)	27.952	<.001	.284	-	
Model 3: Ordinal regression						.066
Sex	-	1.818	.178	-.271	-.665/.123	
mTBI History	-	11.739	<.001	.732	.313/1.151	
Depression	-	.560	.454	.021	-0.35/.077	

Anxiety	-	6.947	.008	.798	.205/2.392

We then examined the contribution of depression and anxiety independently on substance use. Though mTBI history (OR= 4.42, 95% CI [1.437, 4.063], p <.001) continued to be a significant predictor of alcohol use versus no use, neither depression nor anxiety were significant predictors. However, in the combined use group, mTBI history (OR= 2.87, 95% CI [1.45, 5.69], p <.001) and anxiety endorsement (OR= 3.58, 95% CI [1.39, 9.20], p <.001) were both unique predictors of substance use, compared to no use. Depression and sex were not significant predictors of combined use although sex again trended towards significance (p = .057). Interactions between sex and mood and anxiety as well as between mood and anxiety were run but again, did not reach significance and were not retained in the final model.

Given the differences in the AU group and the CSU group, an ordinal logistic regression model was used to examine the association between cumulative use of substances with sex, mTBI and mental health burden. MTBI endorsement was associated with a 0.732 (95% CI [.313, 1.151]) increase in the ordered log odds of university athletes increasing the number of substances used. Anxiety endorsement was also a significant predictor of increase in number of substances used with an odds ratio of .798 (95% CI [.205, 1.392]).

4.6 Discussion

The aim of this study was to investigate the associations between mTBI history and mental health variables with various degrees of substance use and to determine if there was an effect of sex in this relationship. We investigated single (i.e., alcohol only use group) and polysubstance use (i.e., combined use group) groups separately to gain a better understanding the unique risk factors associated with various levels of engagement in substance use. Literature in this field has indicated that there are a number of associations between these variables and, in particular, that mTBI history may be a predisposing factor for higher risk substance use as well as mental health problems (Alcock et al., 2018; Chrisman & Richardson, 2014). Females may be at even greater risk for sustaining mTBIs (Covassin et al., 2003; Gessel et al., 2007) and experiencing worse physical symptoms and neurocognitive outcomes (Covassin et al., 2007; Covassin & Elbin, 2011; Preiss-Farzanegan et al., 2017; Zuckerman et al., 2014). However, in our study, sex was not predictive of increased substance use at any level of our models. It is notable, however, greater endorsement of polysubstance use in males in our sample trended towards significance. Other research has

shown that the relationship between panic disorder and mTBI history is stronger for females than males on alcohol and cannabis use habits, but not the relationship between depression and mTBI in a university student population (Newman et al., 2020). In our study, self-reported history of anxiety and panic was collected as a single binary variable and as a result, we may have not been able to capture this relationship in our sample. However, similar to Newman and colleagues (Newman et al., 2020), we did not detect an interaction between sex and continuous depression scores with substance use.

The results of our study indicate that mTBI seems to be consistently associated with both single (i.e., alcohol) and polysubstance use (i.e., our CSU group). Endorsement of a prior mTBI was predictive of alcohol use versus no use and appeared to have an additive effect on combined use of alcohol and other substances. Athletes experience increased susceptibility for sustaining one or more mTBIs as a consequence of engagement in sports, especially for those involved in contact and collision sports (Koh et al., 2003; Zuckerman et al., 2015). Risk-taking behaviours such as increased substance use following mTBIs has been well demonstrated in the literature (Gallant et al., 2020; McKinlay et al., 2014; Shin et al., 2013). Specifically, cannabis, alcohol, and cigarette use have been shown to be prevalent in the acute period following concussion (Lawrence et al., 2020). TBI has been shown to affect many of the neural substrates that mediate substance use behavior and has also been shown to alter neurocircuits, neurotransmitters, and trigger neuroinflammation in executive and reward related brain regions implicated in the development and maintenance of substance use disorders (Merkel et al., 2017). Despite much literature indicating increases in substance use following mTBI, we are unable to specifically establish temporality of these factors within the current study. Furthermore, studies also suggest that greater social-emotional pressure and a more normative view of substance use may be contributing factors to increased and high risk substance use among university athletes (Ford, 2007).

There is a significant amount of literature examining the relationship between mental health and substance use. One study by Cranford and colleagues, investigated substance use habits and mental health in college students which associated generalized anxiety disorder with higher risk alcohol use habits, which had stronger associations for males than females (Cranford et al., 2009). Our results suggest that endorsement of mental health problems was predictive of polysubstance use but not necessarily alcohol use on its own. However, it is possible that examining higher risk alcohol behaviours rather than occasional or recreational use in our sample would have resulted in a stronger relationship with endorsement of mental health problems. When investigating the

unique contributions of depression symptoms and anxiety endorsement in our sample, anxiety or panic attacks were predictive of polysubstance use. Changing attitudes towards cannabis and the legalization of cannabis has led to increased normative use of cannabis for recreational purposes (Azofeifa et al., 2016; Rotermann & Macdonald, 2018) and as an alternative treatment for anxiety (Van Ameringen et al., 2020). In particular, a recent systematic review noted that one in four university athletes report using cannabis within the past year (Docter et al., 2020) and that polysubstance use in Canadian youth has been rising at a steep rate in recent years (Zuckermann et al., 2019). Individuals with substance use disorders have been found to be twice as likely to endorse an anxiety or mood disorder (Kessler et al., 2005). A literature review indicated that early cannabis use was predictive of later depression but that early depression was not a significant predictive of later cannabis (Degenhardt et al., 2003), highlighting the importance of investigating the temporality of these factors. Furthermore, individuals with anxiety disorders have also been shown to have relatively high rates of cannabis use (Crippa et al., 2009). Within this sample, mTBI and mental health were unique contributors to substance use patterns and their combined presence did not interact to exert synergistic effects on odds of use. However, it is possible that there exists a relationship that we were unable to capture with our sample, as some prior research has identified interactions between mental health problems and mTBI history on substance use (Newman et al., 2020)

One limitation of our study is that much of the clinical data obtained was collected as self-reported endorsement (yes/no) rather than continuous symptom scores from validated measures for these variables. Additionally, though mTBI history and mental health have been shown to be predisposing factors for increased substance use, it is difficult in this cross-sectional sample to tease apart whether mTBI history increased the likeliness of endorsing mental health problems which increased the predisposition for higher substance use, or whether mTBI history and substance use were precursors to mental health endorsement, or another combination of these factors. As our variables were not very granular, they were unable to capture detailed information, and there are several other factors that make it difficult to discern these relationships (e.g., proximity of TBI event, frequency of substance use, and the specific number of substances used). In conclusion, this study sought to elucidate the associations between mTBI, mental health, and sex variables in relation to single and polysubstance use in university athletes, which have several clinical implications for concussion management programs. We found that mTBI was a consistent predictor of increased alcohol use and polysubstance use in university athletes. This finding

highlights the need for concussion management programs to routinely include a comprehensive assessment of substance use habits and screen for high-risk substance use behaviour, especially in emerging adult athlete populations. Additionally, in this study mental health was found to be a predictor of polysubstance use. More specifically, anxiety, but not depression was predictive of polysubstance use. However, no synergistic effect of mTBI and anxiety was identified which supports the role of anxiety as a unique predictor of polysubstance use in university athletes. As anxiety is a highly prevalent mental health condition in athletes (Schinke et al., 2018), special care should be given to clinical evaluation of anxiety within this population and the inclusion of early intervention strategies (e.g., psychoeducation regarding coping skills for anxiety) are warranted. This study did not identify sex as a moderator of these relationships, despite some prior evidence of females being at increased risk for sustaining concussions and experiencing mental health problems (Abrahams et al., 2014; Cyranowski et al., 2000). This finding highlights the need to evaluate both sexes with respect to substance use and mental health, though some trends of greater associations between these variables are evident in males (Cranford et al., 2009), suggesting the need for further evaluation.

Chapter 5: Differential of associations among mental health, mild traumatic brain injury and substance use between males and female university students

5.1 Publication status and author contributions

The following chapter is based on the manuscript: Alyssia Wilson, Jared Cherry, Kristina Gicas, & Magdalena Wojtowicz. (2025). Differential of associations of mental health, mild traumatic brain injury and substance use between males and female university students. *Under Review.* PLOS One.

This manuscript does not exactly replicate the final version published in the PLOS One. It is not a copy of the original published article and is not suitable for citation.
Alyssia Wilson, the first author, developed the conceptual rationale for the study, collected, analyzed and interpreted the data. She was also the primary contributing author to the manuscript, producing the initial draft and completing all major revisions.

5.2 Abstract

Objective. More severe substance use is increasing within young adult populations. Substance use has been associated with mild traumatic brain injury (mTBI) and mood disorders. We aimed to understand the relationship between these factors and sex differences in a university sample.

Methods. 894 university students self-reported their mTBI history, substance use, and psychological measures. Regression models were used to examine the associations between mTBI and mental health factors with alcohol and cannabis use.

Results. Individuals with multiple mTBIs reported more problematic substance use and a higher number of substances used. Hazardous substance use was associated with both a previous history of mTBI and greater scores on depression and anxiety measures. Individuals with higher scores on an anxiety measure were more likely to use cannabis, especially if they had a history of mTBI. A history of mTBIs and higher current depression scores among cannabis users was associated more problematic cannabis use. Among alcohol-using individuals, those with higher depression scores in addition to a history of mTBI were more likely to endorse more problematic alcohol use. Finally, males and females were affected differently by mental health and mTBI risk factors.

Conclusion. mTBI history and mental health problems may be associated with hazardous substance use but these relationships differ for males and females.

5.3 Introduction

Substance use is rising and becoming more common among emerging adults, with half of substance- using Canadian youth engaging in polysubstance use. Engagement in substance use and polysubstance use is complex in nature and has significant treatment and health implications (Compton et al., 2021; Crummy et al., 2020; Konefal et al., 2022; Zuckermann et al., 2019). Substance use and hazardous drug use behaviours among emerging adults are associated with negative health outcomes, including poor mental health (Degenhardt et al., 2016; Gobbi et al., 2019; Grant et al., 2004a; Hines et al., 2020; Mchugh & Weiss, 2019; Moore et al., 2007); however, the directionality of this relationship is highly debated (Esmaeelzadeh et al., 2018). Substance use and mental health disorders share environmental and genetic risk factors, increasing the likelihood of experiencing both (Khantzian, 1997; Sadock et al., 2016). For example, the self-medication hypothesis suggests that substance use is a coping mechanism for psychological stressors (Khantzian, 1997), whereas substance use and its sequelae may also induce additional mental health problems (Sadock et al., 2016).

A history of mild traumatic brain injury (mTBI) has also been suggested as a predisposing risk factor for substance use and mood problems; however, more research is needed to better understand the mechanisms driving the relationships and their directionality. Disruptions to neural pathways resulting from an mTBI may affect frontal brain regions involved in decision-making (Shaw, 2002) and emotional regulation (Van Der Horn et al., 2016), which, in turn, may increase vulnerability to substance misuse as well as the increased likelihood of mental health problems. The relationship between mTBI, substance use, and mental health is complex, with prior research demonstrating that both mTBI and mental health uniquely contribute to substance use habits (Wilson et al., 2023). Further, while disruption of brain regions mediating risk-taking behaviour are proposed to contribute to increased substance use, it is also suggested that mTBI may influence substance use habits indirectly via mood disorders (Newman et al., 2020).

Untangling the associations between health factors and substance use in young adulthood is critical for early intervention and reducing the likelihood of continued substance use into later adulthood. In developing effective intervention programs, it is also important to consider how these factors may differentially affect males and females. Sex differences have been noted across substance use, mental health problems such as depression and anxiety, and mTBI. For example, adolescent males are more likely to engage in substance use (Skidmore et al., 2016) and transition to more risky substance use behaviour than females (Choi et al., 2018; Skidmore et al., 2016),

whereas females are more likely to suffer from mental health problems such as depression and anxiety (Piccinelli & Wilkinson, 2000). Females may also have increased vulnerability to mTBIs (i.e., may be more likely to suffer an mTBI from a similar head impact due to physical differences, such as smaller neck size supporting head during impact, and hormonal differences) and research shows that females typically experience greater symptomology and may have longer recovery trajectory following mTBI (Bazarian et al., 2010; Covassin et al., 2003, 2007; Gessel et al., 2007; Gupte et al., 2019; Preiss-Farzanegan et al., 2017; Zuckerman et al., 2014). Despite sex differences in these risk factors, there is a lack of individualized treatment for males and females.

This aim of this study was to determine how mental health and mTBI history are associated with recent patterns of substance use using regression models. Given the established sex differences in both substance use patterns and mental health outcomes, as well as possible differences in vulnerability to a recovery from mTBI, it is crucial to examine whether these relationships differ between males and females. To address this, we specifically conduced sex-based models to explore potential gender-specific variations in these interactions.

5.4 Method

Participants

Ethics was approved by the Human Participants Review Sub-Committee of York University's Ethics Review Board. Data were collected from 894 York University students through the undergraduate research participant pool in psychology or kinesiology who received partial course credit for their participation. Participants were eligible if: 1) they were between the ages of 17 and 25 and 2) were registered students in the Introduction to Psychology course.

Measures

Alcohol Use Disorder Identification Test-Clinical (AUDIT)

The AUDIT (Babor et al., 2001) is a 10-item screening index that was used to assess alcohol use in the past year. This questionnaire was designed for self-administration and is scored by adding each of the 10 items: questions 1-8 are scored on a 0-4 scale, questions 9 and 10 are scored 0, 2 or 4. Total scores of 0-7 indicate low risk, 8-15 indicate medium risk, 16-19 indicate high risk, and 20-40 points indicates likely alcohol addiction. Given that a large proportion of our sample indicated abstinence from alcohol in the past year, participants were considered alcohol users if they indicated any alcohol use in the past year. To better understand factors contributing to the

degree of alcohol use, some analyses looked at total AUDIT scores solely within the alcohol use group.

Cannabis Use Disorder Identification Test-Revised (CUDIT-R)

The CUDIT-R (Adamson et al., 2010) is an 8-item screening index used to assess cannabis use in the past six months that can be administered to individuals who indicate cannabis use within the last six months. This questionnaire was designed for self-administration and is scored by adding each of the 8 items: questions 1-7 are scored on a 0-4 scale, question 8 is scored 0, 2, or 4. Scores of 8 or more indicate hazardous cannabis use, while scores of 12 or more indicate a possible cannabis use disorder for which further intervention may be required. Participants were considered cannabis users if they indicated any use of cannabis in the past six months. To better understand factors contributing to the degree of cannabis use, some analyses looked at total CUDIT-R scores solely within the cannabis use group.

Substance Use History

Participants answered questions about their substance use history, which inquired about current use of various substances in the past year ("Have you ever used ____" and "How often have you used ____ in the past year") including tobacco/nicotine (including vaporizers), prescribed opioids/opioids in general, stimulants (e.g., cocaine, Adderall), steroids, and "other". To provide data for an exploratory analysis of "polysubstance use", the number of categories of substances used was included as a variable by summing the number of different types of substances used in the past year, including the above categories as well as cannabis and alcohol.

Patient Health Questionnaire-9 item (PHQ-9)

The PHQ-9 (Kroenke & Spitzer, 2002) is a screening tool derived from the Patient Health Questionnaire. The PHQ-9 is a brief self-report measure that evaluates 9 criteria for depressive disorders based on DSM-IV criteria. This self-administered tool assesses how often individuals were bothered by items over the last two weeks. Questions are scored on a 4-point ordinal scale (0; not at all, 1; several days, 2; more than half the days, 3; nearly every day). Total scores of 0-4 indicate none, 5-9 indicate mild depression, 10-14 indicate moderately severe depression, and 20-47 indicate severe depression. Possible major depressive disorder (MDD) was characterized by 5 or more items endorsed at least 'more than half the days' or if items 1 or 2 are endorsed as at least 'more than half the days'.

Generalized Anxiety Disorder-7 item (GAD-7)

The GAD-7 (Spitzer et al., 2006) is a well-validated, 7-item questionnaire to assess self-reported anxiety. This self-administered tool assesses how often individuals were bothered by items over the last two weeks. Questions are scored on a 4-point ordinal scale (0; not at all, 1; several days, 2; more than half the days, 3; nearly every day). Total scores of 0-4 indicate minimal anxiety, 5-9 indicate mild anxiety, 10-14 indicate moderate anxiety, and 15-21 indicate severe anxiety.

mTBI History

Participants were asked questions about their mTBI history. An operational definition of a concussion was provided, as follows, "For this section, we define a concussion as a blow to the head or whiplash that caused any one or more of the following: witnessed loss of consciousness (LOC) (being "knocked out", and someone saw it), loss of memory for events immediately before and/or after the injury (PTA), or feeling dazed and confused for at least 30 seconds. Participants indicated whether they had sustained zero, one, two, three, four, or five or more mTBIs. Participants provided dates (month and year) for each injury and indicated if their injury was obtained due to sports, a fall, being struck in the head by an object, a fight, a motor vehicle accident, or other. Each identified injury was followed up by a series of questions asking: i) Did someone see you lose consciousness? ii) Were you dazed and confused? iii) Did you have no memory for events immediately after the injury? iv) Did you go to the hospital? v) Were you medically diagnosed with a concussion or brain injury? vi) Did you miss any school or work because of this injury? vii) Did you have symptoms for more than 24 hours? viii) Did you have symptoms for more than one week? ix) Did you have symptoms for more than one month?

Clinical History

Information was also collected about years of education, endorsement of any previous diagnoses of attention deficit hyperactivity disorder (ADHD), learning disorders, anxiety, or depression, all through self-report.

Procedure

Substance use measures, mental health measures, as well as information about mTBI and sport history, and demographic information were collected via an online survey (Redcap). Data were collected from September 2022 to November 2022 as part of the fall course requirement. Individuals who agreed to participate were required to complete the survey in a quiet, distraction-free environment.

Data analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 28 (IBM Corp. Released, 2015). Although our questionnaire targeted mTBI history, some participants may have reported more severe injuries. We identified such cases (i.e., endorsement of both LOC and PTA, LOC and admission to the hospital, or LOC and an injury occurring due to a motor vehicle accident, for the same injury (n = 82)) and compared substance use outcomes with those reporting less severe mTBIs. As no group differences emerged, all participants were included in analyses. Independent t-tests were run where homogeneity of variance was met. Chi-square tests were used to compare mTBI history in users and non-users and hazardous and non-hazardous users. Moderate and above mental health scores were also compared between hazardous and non-hazardous users. Linear regression was used to determine if sustaining one, two, or three or more mTBIs compared to no mTBIs, was significantly associated with increased scores on the CUDIT-R or AUDIT among cannabis and alcohol users specifically, or with the number of different types of substances used in the past year.

A binary logistic regression model was used to determine whether endorsement of past mTBIs (none versus any), sex at birth, current psychological symptoms of depression or anxiety (PHQ-9, GAD-7 total scores) and the their interactions (i.e., mTBI history with sex, depression scores, or anxiety scores) were associated with the likelihood of use versus non-use of cannabis or alcohol among all participants. The same predictors were used in a linear regression to examine their relationship with total CUDIT-R and AUDIT scores within users.

The binary logistic regression models described above were run separately for males and females to identify substance use factors that may be obscured in combined models.. Chi-square tests were used to compare proportions of males and females who used substances and endorsed a history of mTBI, and t-tests were used to analyze sex differences in AUDIT, CUDIT-R, GAD-7, and PHQ-9 scores. T-tests were also used to compare differences between GAD-7 and PHQ-9 scores in females and males with and without a history of mTBI.

For each analysis, we investigated the extent to which the data met the assumptions of linearity, normality, and homoscedasticity of errors, as well as whether there was multicollinearity where relevant. Histograms and plots of studentized residuals were examined, and some minor violations were noted but did not warrant corrections or prevent the analyses. No participants were excluded for missing data.

5.5 Results

Sample characteristics

Demographic information is shown in Table 6 and clinical characteristics are shown in Table 7. This sample was made up of 894 individuals. Sex at birth (72.9% n=652) female, which was used in all analyses as our sample did not allow for a more in-depth investigation of potential effects of gender identity on substance use outcomes. Three hundred and twenty mTBIs were reported among 200 participants (i.e., 22% of the total sample). Of the 320 reported mTBIs, 146 (45.63%) occurred due to sports, 93 (29.06%) due to a fall, 58 (18.13%) due to being struck in the head by an object, 7 (2.19%) due to a fight, 21 (6.56%) due to a motor vehicle accident, and 34 (10.63%) were reported as other (some individuals reported multiple causes). It is noteworthy that 692 (77.40%) participants were engaged in sports and 213 (23.82%) were competitive athletes.

Table 6. Demographic variables of the university student sample.

Variable	
Age in years M(SD)	19.0 (1.5)
Range	17-25
Gender n (%)	
Female	647 (72%)
Male	241(27%)
Non-binary	3 (0.3%)
Prefer to self-describe or not disclose	2 (0.2%)
Female sex at birth n (%)	652 (72.9%)
Race	
Asian	364 (40.72%)
White	217 (24.27%)
Middle Eastern	104 (11.63%)
Black or African American	85 (9.51%)
South Asian	49 (5.48%)
Mixed Ethnicity	30 (3.36%)
Hispanic, Latino, or Latina	29 (3.24%)
American Indian or Alaska Native	3 (0.34%)
Native Hawaiian or Pacific Islander	2 (0.22%)
Prefer to not disclose	11 (1.23%)
Years of university education M (SD)	1.63 (.86)
Range	1-6

Table 7. Clinical characteristics of the university student sample.

Variable	
Cannabis use past six months n (%)	233 (26.05%)
CUDIT-R total M(SD)	2.07 (4.55)
Range	0-32

Hazardous cannabis use (over 8) n (%)		101 (11.30%)
Alcohol use past year n (%)		481 (53.80%)
AUDIT total M(SD)		1.99 (3.38)
Range		0-23
Hazardous alcohol use (over 8) n (%)		72 (8.05%)
PHQ9 total M(SD)		9.65 (6.33)
Range		0-27
PHQ9 mild or above n (%)		687 (76.85%)
PHQ9 moderate or above n (%)		407 (45.53%)
Possible MDD based on PHQ9 n (%)		369 (41.28%)
GAD7 total M(SD)		8.45 (5.87)
Range		0-21
GAD7 mild or above n (%)		619 (69.34%)
GAD7 moderate or above n (%)		351 (39.26%)
Hazardous cannabis use and PHQ9 moderate or above		59 (6.6%)
Hazardous cannabis use and GAD7 moderate or above		51 (5.7%)
Hazardous alcohol use and PHQ9 moderate or above		43 (4.8%)
Hazardous alcohol use and GAD7 moderate or above		41 (4.6%)
Previous diagnosis of anxiety n (%)		166 (18.57%)
Previous diagnosis of depression n (%)		116 (12.98%)
Tobacco use this year n (%)		231 (25.84%)
Opioid use this year n (%)		12 (1.34%)
Simulant use this year n (%)		27 (3.02%)
Steroid use this year n (%)		7 (0.78%)
Other drug use this year n (%)		39 (4.36%)
Number of substances used this year n (%)	0	338 (37.81%)
	1	257 (28.75%)
	2	160 (17.90%)
	3	112 (13.31%)
	4	19 (2.13%)
	5	7 (0.78%
	6	1 (0.11%)
Number of mTBIs endorsed across the lifetime n (%)	0	694 (77.62%)
	1	125 (13.98%)
	2	47 (5.26%)
	3	16 (1.79%)
	4	7 (0.78%)
	5 or more	5 (0.56%)
Time since last injury in years M(SD)		3.74(3.84)
Range		0-18
ADHD n (%)		48 (5.37%)
Learning disorder n (%)		39 (4.36%)

Abbreviations: ADHD = Attention deficit hyperactivity disorder, AUDIT = Alcohol Use Disorder Identification Test, CUDIT-R = Cannabis Use Disorder Identification Test-Revised, GAD7 =

Generalized anxiety disorder-7 item, MDD = major depressive disorder, mTBI = mild traumatic brain injury, PHQ9 = Patient Health Questionnaire-9 item.

Associations between mTBI and substance use outcomes

Of the individuals who endorsed cannabis use in the past 6 months, 25.3% had a history of mTBI, compared to 21.3% of those who did not use cannabis (X^2([1], N = 894) = 1.580, p = [.209]). Of the individuals who endorsed alcohol use in the past year, 24.9% had a history of mTBI, compared to 19.4% of those who did not use alcohol (X^2([1], N = 894) = 3.980, p = [.046]).

Individuals engaged in hazardous cannabis use (CUDIT-R score of 8 or above) or hazardous alcohol use AUDIT score of 8 or above) were significantly more likely to have had a history of mTBI ((X^2([1], N = 894) = 4.540 p = [.033]); (X^2([1], N = 894) = 4.132 p = [.042]) respectively). Individuals who endorsed clinically hazardous cannabis use were more likely to endorse moderate or greater scores on the GAD-7 (50.5%) compared to non-hazardous users (37.8%) ((X^2([1], N = 894) = 6.025 p = [.014]). They were also more likely to endorse moderate or above scores on the PHQ-9 (58.4%) than non-hazardous users (43.9%) (X^2([1], N = 894) = 7.629 p = [.006]). Similarly, individuals who endorsed clinically hazardous alcohol use were significantly more likely to endorse moderate or greater scores on the GAD-7 (56.9%) than non-hazardous users (37.7%) (X^2([1], N = 894) = 10.267 p = [.001), and more likely to endorse moderate or above scores on the PHQ-9 (59.7%) than non-hazardous users (44.3%) (X^2([1], N = 894) = 6.364 p = [.012]).

A post-hoc analysis was conducted to explore mTBI history in this group of individuals with comorbid hazardous cannabis or alcohol use and moderate or above scores on the PHQ9 and GAD-7. Individuals with comorbid hazardous alcohol use and moderate or greater GAD-7 scores, were more likely to report a positive mTBI history (41.5%), than those without these comorbid issues (21.5%) (X^2([1], N = 894) = 9.019 p = [.003]). Similarly, those with comorbid hazardous alcohol and moderate or greater PHQ-9 scores, were also more likely to report a positive mTBI history (41.9%), compared to those without these comorbid issues (21.4%) (X^2([1], N = 894) = 9.880 p = [.002]). In contrast, individuals with comorbid hazardous cannabis use and moderate or greater GAD-7 scores, were not more likely to report an mTBI history; however, those with comorbid hazardous cannabis use and moderate or greater PHQ-9 scores, were more likely to report a positive mTBI history (33.9%), compared to those without these issues (21.6%) (X^2([1], N = 894) = 4.833 p = [.028]). However, it is notable that the sample of participants with these comorbid issues was small and these results need to be interpreted with caution.

To investigate whether the number of past mTBIs (i.e., one, two, or three or more), was associated with the severity of substance use within users, we ran separate regression models for cannabis users only (n = 233) and alcohol users only (n = 481). Prior history of two (b = .194, t(229) = 3.01, p = .003) or three or more mTBIs (b = .162, t(229) = 2.52, p = .013), but not one (b = .093, t(229) = 1.43, p = .154), was associated with increased cannabis use in users compared to users without any mTBIs (R^2 = .062, F(3,229) = 5.07, p = .002). Experiencing three or more (b = .208, t(477) = 4.61, p < .001) mTBIs was associated with increased alcohol use, compared to users without mTBI (R^2 = .044, F(3,477) = 7.37, p <.001). As an exploratory analysis, associations between the number of substances used in the past year and mTBI history were examined in a linear regression, (R^2 = .036, F(3,890) = 11.13, p < .001) which showed that sustaining two (b = .067, t(890) = 2.02, p = .044) or three or more mTBIs (b = .180, t(890) = 5.44, p < .001), compared to no mTBI was associated with an increase in the *number* of different types of substances used.

Associations between mTBI, mental health, sex, and substance use outcomes

MTBI history (none versus any), sex, GAD-7 total scores, PHQ-9 total scores, and the interaction of mTBI with sex, GAD-7, and PHQ-9 were included in two binary logistic regressions to examine potential associations with increased likelihood of cannabis or alcohol use versus non-use (see Table 8). When examining the presence or absence of cannabis use, (χ2(7) = 22.72, p = .002) there was a significant association with anxiety where individuals with higher anxiety scores were more likely to endorse cannabis use (OR= 1.056, 95% CI [1.008, 1.107], p = .022). Additionally, an interaction term (i.e., mTBI history x anxiety) showed that higher anxiety scores were associated with greater likelihood of cannabis use for those without a previous mTBI compared to those with a mTBI (OR= .016, 95% CI [.799, .977], p = .016; see Figure 4). None of these variables showed a relationship with alcohol use (χ2(7) = 12.578, p = .083). Table 8 summarizes estimates of the unstandardized parameters, standard errors, along with the associated Wald statistics, p-values, odds ratios and 95% confidence intervals.

Table 8. Association between mTBI, mental health, and cannabis and alcohol use versus non-use for all participants (n = 894).

Predictors	B(SE)	Wald	*p*-value	*OR*	*95%CI OR*	R^2
	Model 1: Cannabis use versus non-use					.025
mTBI history	.326(.437)	0.556	.456	1.385	0.588, 3.260	
Sex	-.064(.207)	0.096	.757	0.938	0.625, 1.408	
Depression symptoms	.006(.022)	0.068	.794	1.006	0.963, 1.051	
Anxiety symptoms	.055(.024)	5.266	**.022***	1.056	1.008, 1.107	

mTBI history x sex	.013(.441)	0.001	.977	1.013	0.427, 2.406	
mTBI history x depression symptoms	.086(.045)	3.663	.056	1.090	0.998, 1.191	
mTBI history x anxiety symptoms	-.124(.051)	5.820	**.016***	0.883	0.799, 0.977	
Constant	-1.560(.206)	57.480	<.001	0.210		
Observations	**894**					
	Model 2: Alcohol use versus non-use					.014
mTBI history	.595(.387)	2.365	.124	1.814	0.849, 3.873	
Sex	.036(.176)	0.041	.840	1.036	0.734, 1.463	
Depression symptoms	.023(.020)	1.275	.259	1.023	0.983, 1.064	
Anxiety symptoms	.016(.021)	0.587	.444	1.016	0.975, 1.060	
mTBI history x sex	-.011(.396)	0.001	.978	0.989	0.455, 2.150	
mTBI history x depression symptoms	-.007(.040)	0.031	.861	0.993	0.919, 1.073	
mTBI history x anxiety symptoms	-.028(.045)	0.385	.535	0.973	0.891, 1.061	
Constant	-.278(.171)	2.637	.104	0.758		
Observations	**894**					

Note. *p < .05. **p < .01. ***p < .001

Abbreviations: CI= confidence interval, mTBI = mild traumatic brain injury, OR = odds ratio.

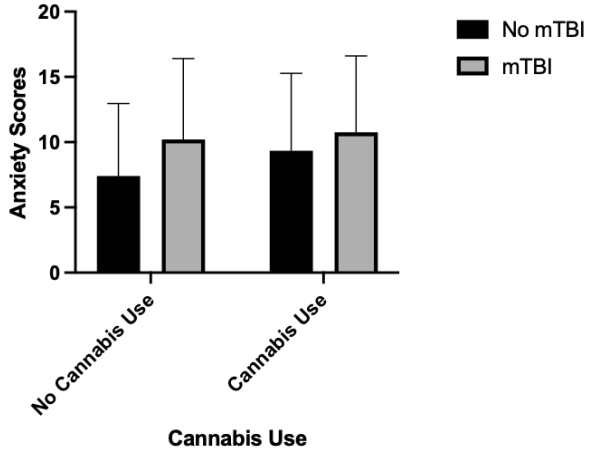


Figure 4. Mean anxiety symptoms in cannabis users and non-users by mTBI history.

To investigate whether mTBI history, sex, depression, and anxiety scores are associated with severity of use among users, the same variables were used to look at the association with CUDIT-R total scores in cannabis users. See Table 9 for estimates of the unstandardized parameters, along with the associated *t* statistics, *p*-values and 95% confidence intervals. The model had a R^2 of .098, $F(7,225) = 3.486$, $p = .001$. Among cannabis users, there was a significant association of mTBI (b = .438, t(225) = 2.69, $p = .008$) and depression scores (b = 301, t(225) = 2.80, $p = .006$) on CUDIT-R total scores, such that individuals who had sustained a prior mTBI endorsed

more severe cannabis use, and those with higher depression scores endorsed more severe cannabis use, keeping all other predictors constant. We then examined the associations of these factors with AUDIT scores among alcohol users. The AUDIT model had a R^2 of .050, $F(7,473)$ = 3.584, $p < .001$. There was a significant interaction between mTBI history and depression scores (b = .328, t(473) = 2.05, $p = .041$) score such that increased symptoms of depression were associated with more problematic alcohol use for those with a history of mTBI compared to those without.

Table 9. Association between mTBI, mental health, and sex variables and total cannabis and alcohol use in users.

Predictors	Unstandardized estimate	95 % CI	*t*-statistic	*p*-value
Model 1: Cannabis use in users				
(Intercept)	5.702	3.647,7.757	5.468	<.001
mTBI history	5.754	1.534, 9.975	2.687	**.008****
Sex	-1.398	-3.380, 0.583	-1.391	.166
Depression symptoms	0.286	0.085, 0.486	2.803	**.006****
Anxiety symptoms	-0.038	-0.233, 0.157	-0.383	.702
mTBI history x sex	0.298	-3.679, 4.274	0.148	.883
mTBI history x depression symptoms	-0.349	-0.816, 0.118	-1.474	.142
mTBI history x anxiety symptoms	0.062	-0.460, 0.585	0.235	.815
Observations		**233**		
Model 2: Alcohol use in users				
(Intercept)	3.332	2.491, 4.173	7.784	<.001
mTBI history	0.180	-1.584, 1.944	0.201	.841
Sex	0.177	-0.666, 1.019	0.412	.680
Depression symptoms	0.040	-0.054, 0.134	0.833	.405
Anxiety symptoms	0.025	-0.071, 0.122	0.516	.606
mTBI history x sex	-1.712	-3.444, 0.020	-1.943	.053
mTBI history x depression symptoms	0.187	0.008, 0.367	2.052	**.041***
mTBI history x anxiety symptoms	-0.059	-0.259, 0.140	-0.585	.559
Observations	**481**			

Note. *$p < .05$. **$p < .01$. ***$p < .001$

Abbreviations: CI= confidence interval, mTBI = mild traumatic brain injury.

Associations between mTBI, mental health, and substance use outcomes by sex

There were no significant differences in the proportions of males and females who used cannabis (X^2([1], N = 894) = .487, p = [.485]) or alcohol (X^2([1], N = 894) = .877, p = [.349])), in overall CUDIT-R or AUDIT scores (t(892) = -.094, p = .925; t(892) = .893, p = .372), or whether they endorsed

a history of mTBI (X^2([1], N = 894) = .862, p = [.353]). However, females had significantly higher symptoms of depression and anxiety than males (t(892) = 7.428, p = .004; t(892) = 8.309, p = <.001; See Table 10).

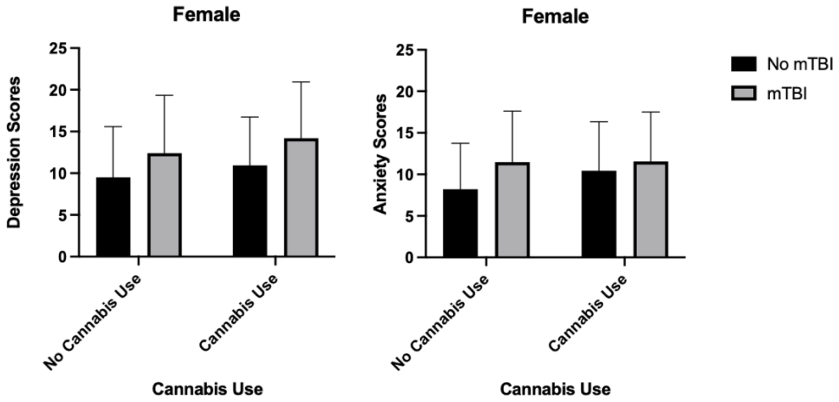
Additionally, current depression and anxiety symptom scores were significantly higher in females who endorsed a history of mTBI (M = 12.93, SD = 6.91; M = 11.50, SD = 6.07) compared to those who did not (M = 9.87, SD = 6.04; M = 8.78, SD = 5.70; t(650) = -5.276, p = .001; t(650) = -5.057, p = <.001). Current depression and anxiety symptom scores did not differ for males with a history of mTBI (M = 8.37, SD = 5.77; M = 6.92, SD = 4.68), versus those without (M = 6.83, SD = 5.37; M = 5.60, SD = 5.04); t(240) = -1.763, p = .079; t(240) = -1.658, p = .099).

Table 10. *Substance use, mTBI, and mental health demographics by sex*

	Female	Male	*p*-value
Cannabis use N(%)	174 (26.7%)	59 (24.4%)	.485
CUDIT-R total M(SD)	2.06 (4.49)	2.10 (4.71)	.925
Alcohol use N(%)	357 (54.8%)	124 (51.2%)	.349
AUDIT total M(SD)	2.36 (3.37)	2.14 (3.16)	.372
mTBI history N(%)	151 (23.2%)	49 (20.2%)	.353
PHQ9 total M(SD)	10.57 (6.38)	7.14 (5.48)	**.004****
GAD7 total M(SD)	9.41 (5.89)	5.87 (4.99)	<**.001*****

Note. *p < .05. **p < .01. ***p < .001

Abbreviations: AUDIT = Alcohol Use Disorder Identification Test, CUDIT-R = Cannabis Use Disorder Identification Test-Revised, GAD7 = Generalized anxiety disorder-7 item, mTBI = mild traumatic brain injury, PHQ9 = Patient Health Questionnaire-9 item.



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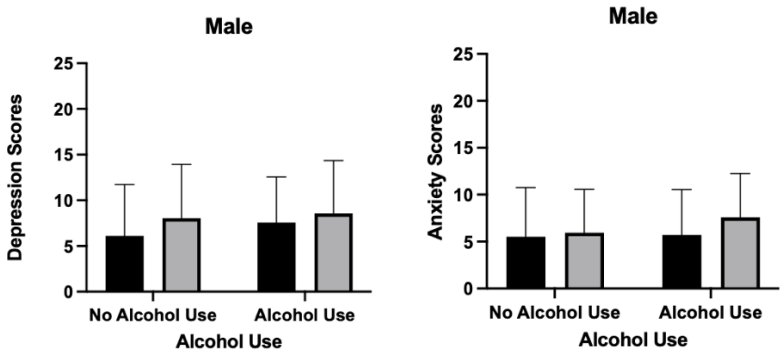

C *D*

Figure 5. Mean depression (a) and anxiety (b) symptoms in female cannabis users and non-users by mTBI history and mean depression (a) and anxiety (b) symptoms in male alcohol users and non-users by mTBI history.

In four binary logistic regressions, mTBI history (none versus any), depression and anxiety scores, and the interaction of mTBI with depression and anxiety scores were used to examine substance use or non-use for females and males, separately. When examining the presence or absence of cannabis use in females ($\chi2(5) = 21.14$, $p < .001$), there was a significant association with anxiety where those with higher anxiety scores were more likely to endorse cannabis use (OR= 1.088, 95% CI [1.032, 1.148], p =.022). Additionally interaction terms showed that, higher depression scores in females were associated with greater likelihood of cannabis use if they also had a history mTBI (OR=1.126, 95% CI [1.017, 1.246], p = .022; see Figure 5A), whereas higher anxiety scores in females were associated with greater likelihood of cannabis use for those without a mTBI compared to those with a mTBI (OR= .843, 95% CI [0.753, 0.945], p = .003; see Figure 5B). When examining the presence or absence of cannabis use in males only ($\chi2(5) = 8.28$, p = .141), increased depression scores were associated with greater likelihood of cannabis use (OR= 1.112, 95% CI [1.007, 1.228], p =.036).

When examining the presence or absence of alcohol use in females ($\chi2(5) = 10.71$, p = .057) there were no significant associations between any of the predictors and likelihood of alcohol use. However, for males ($\chi2(5) = 10.82$, p = .055), increased depression scores were associated with greater likelihood of alcohol use (OR= 1.121, 95% CI [1.026, 1.224], p = .012). Additionally, interaction terms showed that, males with higher depression scores were less likely to use alcohol if they had a history of mTBI (OR= .832, 95% CI [0.694, 0.997], p = .046; see Figure 5C), whereas

higher anxiety scores in males were associated with greater likelihood of alcohol use if they also had a history of mTBI (OR= 1.258, 95% CI [1.010, 1.568], p = .041; See Figure 5D). Table 11 summarizes estimates of the unstandardized parameters, standard errors, along with the associated Wald statistics, p-values, odds ratios and 95% confidence intervals for all of the above models. Additional sub analyses examining whether these variables are associated with the severity of use within female and male users, are included for interest in in the Appendices (see Appendix A).

Table 11. Association between mTBI, mental health, and cannabis and alcohol use verses non-use by sex.

Predictors	B(SE)	Wald	*p*-value	*OR*	*95%CI OR*	R^2
Model 1: Cannabis use versus non-use in females						.032
mTBI history	.464(.461)	1.016	.313	1.591	0.645, 3.925	
Depression symptoms	-.021(0.26)	0.681	.409	0.979	0.931, 1.030	
Anxiety symptoms	.085(.027)	9.600	**.002****	1.088	1.032, 1.148	
mTBI history x depression symptoms	.118(.052)	5.258	**.022***	1.126	1.017, 1.246	
mTBI history x anxiety symptoms	-.170(.058)	8.575	**.003****	0.843	0.753, 0.945	
Constant	-1.628(.216)	56.944	<.001	0.196		
Observations	**652**					
Model 2: Cannabis use versus non-use in males						.034
mTBI history	-.020(.710)	0.001	.978	0.981	0.244, 3.946	
Depression symptoms	.106(.051)	4.378	**.036***	1.112	1.007, 1.228	
Anxiety symptoms	-.057(.056)	1.046	.306	0.944	0.846, 1.054	
mTBI history x depression symptoms	-.033(.098)	0.113	.737	0.968	0.799, 1.172	
mTBI history x anxiety symptoms	.069(.119)	0.342	.559	1.072	0.850, 1.352	
Constant	-1.635(.295)	30.614	<.001	0.195		
Observations	**242**					
Model 3: Alcohol use versus non-use in females						.016
mTBI history	.692(.415)	2.776	.096	1.997	0.885, 4.507	
Depression symptoms	-.003(.023)	0.017	.897	0.997	0.953, 1.043	
Anxiety symptoms	.045(.025)	3.390	.066	1.046	0.997, 1.098	
mTBI history x depression symptoms	.038(.045)	0.731	.393	1.039	0.952, 1.134	
mTBI history x anxiety symptoms	-.088(.050)	3.074	.080	0.916	0.831, 1.010	
Constant	-.241(.178)	1.839	.175	0.786		
Observations	**652**					
Model 4: Alcohol use versus non-use in males						.044
mTBI history	.314(.597)	0.276	.599	1.369	0.425, 4.407	
Depression symptoms	.114(.045)	6.363	**.012***	1.121	1.026, 1.224	
Anxiety symptoms	-.086(.048)	3.177	.075	0.918	0.836, 1.009	
mTBI history x depression symptoms	-.184(.092)	3.990	**.046***	0.832	0.694, 0.997	
mTBI history x anxiety symptoms	.230(.112)	4.191	**.041***	1.258	1.010, 1.568	
Constant	-.330(.240)	1.903	.168	0.719		

Observations	**242**

Note. $*p < .05$. $**p < .01$. $***p < .001$

Abbreviations: CI= confidence interval, mTBI = mild traumatic brain injury, OR = odds ratio.

5.6 Discussion

This study aimed to examine the relationship between mTBI history and substance use, as well as to understand the contribution of mental health to this relationship and sex related differences in these associations. Similar to prior research, we found an association between mTBI history and substance use in the past 6-months to one year. (Olsen & Corrigan, 2022). Risk-taking behaviour such as problematic substance use is common following mTBI (Lawrence et al., 2020; McKinlay et al., 2014; Merkel et al., 2017) and may be related to underlying neuropathology following head injury (Merkel et al., 2017). Our study suggests that the number of past injuries was an important factor to consider when examining problematic use of these substances. It may be that while sustaining one injury is associated with current substance use in general, more severe use is associated with individuals who sustained multiple injuries. Specifically, sustaining one injury was not significantly associated with more severe current substance use in our study, however, sustaining two or more prior mTBIs was associated with more severe cannabis use and sustaining three or more previous injuries was associated with more severe alcohol use among users. These findings show that while there may be an association between mTBI and potentially hazardous substance use, this relationship may be mediated by the number of prior injuries. Similarly, sustaining multiple injuries was associated with a *greater number of substances* being used over the course of the past year. These findings are similar to other studies showing that a history of multiple head injuries is associated with increased odds of marijuana and prescription drug use and misuse among university students (Kort-Butler, 2017) and young adults who have experienced brain injury are more likely to engage in hazardous use of alcohol, marijuana, and illicit drugs (Rosenthal et al., 2023). It is notable that in our study, there was overall low endorsement of substance use in our sample, as measured by the CUDIT-R and AUDIT, and the associations observed were not necessarily with clinically significant levels of substance use. Nevertheless, we found that individuals with hazardous cannabis or alcohol use were more likely to have a history of mTBI and endorse current (i.e., within the last two weeks) moderate to severe mood and anxiety scores. When looking specifically at individuals with comorbid hazardous substance use and elevated mental health scores, we found that hazardous alcohol users with comorbid mood or anxiety scores were more likely to have a history of mTBI. However, hazardous cannabis users with

comorbid elevated mood scores (but not elevated anxiety scores) were more likely to have a history of mTBI.

The relationship between increased risk of mental health problems following mTBI has been shown consistently in the literature (Chrisman & Richardson, 2014; Delmonico et al., 2021; Scholten et al., 2016), with a recent meta-analysis of civilians and service members suggesting that these groups are more than three times as likely to experience depression following an mTBI (Hellewell et al., 2020). Furthermore, sustaining multiple mTBIs may place individuals at an even greater risk of experiencing depression (Strain et al., 2013). The relationship between mTBI and depression is complex and likely affects substance use behaviours, while substance use also likely impacts mental health (Esmaeelzadeh et al., 2018; Rosenthal et al., 2023). Recent research suggests that mTBI exposure has both direct and indirect effects on substance use via depression (Newman et al., 2020). Similarly, our study showed that both endorsement of a previous mTBI and higher current depression scores were independently associated with more problematic cannabis use in cannabis users. Additionally, when examining problematic use in alcohol users, there was a small but significant interaction where increased depression scores in individuals with a past mTBI were associated with more problematic alcohol use.

The relationship between mTBI and anxiety has been less studied, but other recent findings show that college athlete alumni who have a history of mTBI endorse greater long-term anxiety symptoms (Meehan et al., 2016) and one study examining adults following mTBI suggested that in the first few months following an mTBI, anxiety may be more prevalent than depression symptoms (Barker-Collo et al., 2018). In fact, another recent study following adults who experienced mTBI shows that over 30% of individuals met the criteria for one or more anxiety disorders within a year of sustaining an mTBI and those with pre-injury anxiety were even more susceptible (Lamontagne et al., 2022). Although individuals in our sample who had experienced an mTBI within the past six months showed statistically significant differences in total depression and anxiety scores, there was no significant difference in the proportion of individuals endorsing mild or greater symptoms (see Appendix B). Therefore, these differences are unlikely to reflect a clinically meaningful distinction between groups.

While anxiety and the use of alcohol and cannabis have been suggested to be associated via the self-medication model and the substance-induced model (Vorspan et al., 2015), additional endorsement of a previous mTBI may affect these models and may do so differently for these disorders. Consistent with this literature, current anxiety symptoms in our sample were associated

with an increased likelihood of cannabis use and current anxiety symptoms interacted with mTBI history such that females with a history of mTBI tended to have significantly higher anxiety scores than those with no mTBI history. Males showed the same pattern, despite not reaching significance. However, in individuals without a history of mTBI, higher anxiety scores were associated with greater likelihood of cannabis use. This aligns with other research showing associations between cannabis use and anxiety (Crippa et al., 2009). However, it also suggests a more nuanced relationship: anxiety is associated with cannabis use in individuals without an mTBI history, whereas in those with a history of mTBI, both anxiety and the injury itself may be linked to cannabis use.

A large proportion of young adults use substances, and this population is prone to risky substance use. However, trends in substance use are complex, with variations in the popularity of different substances over time (Compton et al., 2021; Crummy et al., 2020; Konefal et al., 2022; Zuckermann et al., 2019) . One of the objectives of this study was to investigate sex related differences in the associations between mTBI history, substance use, and mental health. The gender gap in the proportion of individuals with substance use disorders is narrowing (Keyes et al., 2008) and women may be particularly at risk of experiencing higher rates of psychiatric disorders co-occurring with substance use disorders, which further complicates treatment (Conway et al., 2006). Several studies have shown that women who use cannabis tend to report higher anxiety symptoms during treatment and withdrawal from use than men (Cuttler et al., 2016; Foster et al., 2016). While research shows that depression strongly co-occurs with cannabis use, results investigating sex differences in depression among cannabis users are more mixed (Calakos et al., 2017). In our sample, females had significantly greater current mental health symptoms compared to males, and interactions between mental health and mTBI on cannabis use were observed exclusively in females. More specifically, in females, cannabis use was associated with both a prior mTBI history and higher current depression symptoms, while higher current anxiety symptoms appeared to be associated with cannabis use in those without an injury history. In contrast, higher current depression symptoms in males were associated with cannabis use. No associations between anxiety and cannabis use were observed in males in our sample. Our findings suggest that there may be differential relationships between mental health symptoms and cannabis use between sexes.

Furthermore, in our male sample, we observed that current mental health scores and mTBI history were associated with alcohol use. Alcohol use and risky use have become more normative

particularly among university students (Karam et al., 2007), with about half our sample partaking in alcohol within the past year. The co-occurrence of anxiety and alcohol use (Smith & Randall, 2012) and depression and alcohol use (Boden & Fergusson, 2011; Mchugh & Weiss, 2019), and increased susceptibility to depression following mTBI have been well established (Rapoport et al., 2003; Stein et al., 2019). Likewise, in our sample, both depression and anxiety scores were higher, though not significantly, in males with mTBI compared to males without mTBI. However, higher anxiety scores, in addition to a history of mTBI were associated with greater alcohol use in males. None of these predictors were associated with alcohol use in females in our sample. This suggests that other factors may contribute to alcohol use in females, whereas alcohol use in males might be related to their mental health and history of mTBI.

Our findings have several potential clinical implications. While the number of females engaging in hazardous substance use is rising, they may be less likely to seek treatment (Greenfield et al., 2007) and may receive less specialized treatment than males (Edlund et al., 2012), despite experiencing more severe acute and long-term consequences (McHugh et al., 2018), including impairments across functional domains (Sherman et al., 2017; Wu et al., 2010). Our findings suggest that females with higher anxiety scores are more likely to engage in cannabis use. While neither higher depression scores nor a history of mTBI alone are associated with cannabis use, females with both factors are more likely to use cannabis. While mental health and mTBI may be associated with substance use, more research is needed to determine causality and temporal relationships. This, combined with research showing increased suicidal ideation following mTBI (Campbell-Sills et al., 2021; Fisher et al., 2016) emphasizes the need for specialized and transdiagnostic care (Greenfield et al., 2007), particularly for substance use disorders, where females tend to have higher rates of treatment success (McHugh et al., 2018). We also observed differential associations with substance use in males, where greater depressive scores were associated with higher likelihood of substance use. Thus, targeting depression symptoms in intervention efforts for young males may be more effective.

Limitations

There are several limitations to this study. First, we cannot assume temporal causality with any of these relationships. Although, we examined “past” mTBI by using self-report history of injury and “current” substance use (i.e., defined as within 6 month-1 year by the CUDIT and AUDIT), we cannot control for the possibility of lifetime substance use that preceded any injuries. As such, these findings should be interpreted as reflecting associations between these factors rather than

causal relationships. Similarly, while we examined current mental health symptoms, we did not account for past mental health history. Future prospective longitudinal studies should carefully address these limitations to fully elucidate the directional relationships between these factors. Second, the identification of mTBI history was based on a self-report questionnaire. Details about childhood injuries were not validated by medical records or a collateral source. Although a definition of mTBI was provided to participants, it is possible that this measure also captured more significant injuries. However, we attempted to address this by examining the characteristics of the reported injuries (see Analysis section) and found no differences in outcome measures for those who may have exhibited more significant signs or symptoms (e.g., LOC and PTA) following their injuries. Our mTBI variable was also limited, as individuals indicated whether they had sustained five or more injuries rather than specifying the exact number of mTBIs, which restricted our ability to conduct analyses requiring continuous data.

Similarly, our study relied on self-reported substance use habits, which may be subject to reporting bias. Our ability to analyze relationships between polysubstance use and mTBI history was constrained by the categorical nature of the substance use data, as it did not provide detailed information on the specific number of substances used within each category or the frequency and quantity of use. Furthermore, our results may not be generalizable to a non-university sample of young adults, as our study did not include this population. Therefore, these findings are particularly relevant to Canadian university students.

Conclusion

In conclusion, this study aimed to better understand the associations between mTBI and mental health on substance use among young adults and to explore how these factors may be associated differently in males and females. We found that while mTBI and mental health were not significantly associated with alcohol use patterns in females, mTBI history and either depression or anxiety symptoms were associated with cannabis use in females. In contrast, depression symptoms and mTBI history were correlated with alcohol and cannabis use in males. Our findings suggest that males and females may use substances for different reasons. Females may be more likely to use cannabis as a coping mechanism for anxiety, whereas depression may predispose males to alcohol or cannabis use in general. Additionally, individuals with mTBI tend to report more mental health problems. By recognizing these different factors in males and females, our findings support the need for more individualized treatment approaches for young adults.

Chapter 6: An Exploratory Study of Associations Among Substance Use, Mental Health Symptoms, mTBI History, and Resting-State Functional Connectivity (rsFC) Across Key Cortical and Subcortical Networks in Varsity Athletes

6.1 Publication status and author contributions

The following chapter has been drafted as a manuscript. The contents have been reviewed by the following authors: Wison, A., Stevens, D., Gicas, K., and Wojtowicz, M., also contributed to this work through the development of project ideas, data collection and management, psychometric expertise, and methodological discussions.

Alyssia Wilson, the first author, developed the conceptual rationale for the study, collected, analyzed and interpreted the data. She was also the primary contributing author to the manuscript, producing the initial draft and completing all major revisions.

6.2 Abstract

Objectives. Varsity athletes are a unique population who are at greater risk of sustaining a mild traumatic brain injury (mTBI) and are possibly at greater risk of hazardous substance use and mental health problems. We aimed to identify neural network changes associated with these variables in a varsity athlete population.

Methods. 69 varsity athletes self-reported their mTBI history, substance use, and psychological measures. Group independent component analysis (ICA) was used to identify networks of interest including the default mode network (DMN), frontoparietal network (FPN), salience network (SN), and subcortical networks including the striatum (ST) and medial temporal lobe (MTL).

Results. No significant differences in functional connectivity were identified across neural networks based on mTBI history or substance use. The only notable finding was a positive association between anxiety symptoms and altered DMN connectivity among athletes with a history of mTBI.

Conclusions. These results suggest that varsity athletes may constitute a relatively healthy population, with limited measurable effects of history of mTBI or substance use on large-scale brain network function.

6.3 Introduction

Recent research into substance use among athletes indicates that, although this group generally uses substances at lower rates than non-athletes, binge drinking rates are notably higher in this group and cannabis use is becoming more common (McDuff et al., 2019). Among varsity athletes, 37% reported risky alcohol use behaviours and 39% reported using cannabis, both significantly higher rates compared to non-athletes (Substance Abuse and Mental Health Services Administration, 2018; Shulenberg et al., 2017). Athletes may also be at greater risk for co-occurring mental health challenges as they have been shown to have a stronger dose–response relationship between poor mental health and problematic substance use compared to non-athletes (Lipkens & Qeadan, 2025). In addition, it is well documented that this population sustains mTBI at a significantly higher frequency than non-athlete counterparts (Langlois et al., 2006) which is concerning given the known association between mTBI and increased risk for substance use and related disorders.

Regular use of cannabis and misuse of alcohol have been related to structural changes and altered patterns of brain activity (Battistella et al., 2014; Harper, 1998; Nader & Sanchez, 2018; Shokri-Kojori et al., 2017). Similarly, mTBI has been shown to alter grey and white matter in the brain as well as affect multiple resting-state networks (Narayana, 2017; Stevens et al., 2012; Zhou et al., 2013). Resting-state fMRI studies of substance use and addiction have highlighted the anterior cingulate cortex (ACC), a central node of the salience network (SN), as playing a key role in modulating the dynamic interplay between the default mode network (DMN) and the frontoparietal network (FPN), involved in any goal-directed cognitive process, whether externally or internally focussed. (Sutherland et al., 2012). Substance use disorders have been associated with hypoconnectivity across the limbic system, SN, and FPN, as well as complex patterns of both hypo- and hyperconnectivity within the DMN (Taebi et al., 2022).

Disruptions in brain function observed in substance use are believed to reflect impairments in key cognitive processes, including inhibitory control and reward processing, which may contribute to the persistence of substance use behaviors (Taebi et al., 2022). Disruptions in frontal brain regions, common to both substance use and mTBI, may impair the ability to anticipate negative outcomes in unpredictable or risky situations (Shaw, 2002), and contribute to emotional dysregulation (Van Der Horn et al., 2016). In particular, dysfunction within cortico-striatal circuits has been linked to substance use due to their role in motivation, reward-based learning, and emotional processing (Koob & Volkow, 2010; Kravitz et al., 2015). Other subcortical structures,

such as the hippocampus, also contribute to the maintenance of substance use by reinforcing maladaptive learning patterns (Kutlu & Gould, 2016).

Substance use is closely associated with poor mental health outcomes, including higher rates of depression and anxiety (Degenhardt et al., 2016; Gobbi et al., 2019; Grant et al., 2004b; Hines et al., 2020; Mchugh & Weiss, 2019; Moore et al., 2007). These psychiatric conditions are increasingly understood as disorders of neural network dysfunction, where altered connectivity across brain networks –rather than isolated structures— contributes to symptomatology (Li et al., 2018). In particular, disruptions to DMN are commonly implicated in depressive disorders and across various forms of anxiety, including panic disorder, social anxiety disorder, and generalized anxiety disorder (Andrews-Hanna et al., 2014; Brakowski et al., 2017; Northoff, 2020). Both addiction and mental health disorders are associated with dysfunction of subcortical reward networks, with previous studies having implicated involvement of the striatum (ST) in substance use disorders and the and medial temporal lobe (MTL), including dysfunction of the amygdala and hippocampus across both substance use and mental health concerns (Campbell & MacQueen, 2004; Gabbay et al., 2013; Taebi et al., 2022).

The previous chapter of this dissertation highlighted the complex interplay between substance use, mTBI, and mental health. Specifically, individuals with higher anxiety scores were more likely to use cannabis. In contrast, problematic cannabis use was more strongly associated with both a history of mTBI and elevated depression scores. Among individuals who consumed alcohol, problematic use was most closely linked to higher depression scores in combination with a history of mTBI. These nuanced patterns underscore the multifaceted nature of these interactions. Given this complexity, evaluating the rsFC of key brain regions in varsity athletes may provide critical insights into how substance use and mTBI contribute to dysregulation within large-scale neural networks. The present study examined associations between substance use, mTBI, mental health symptoms, and rsFC across major cortical and subcortical networks. Specifically, we focused on networks implicated in internal and external information processing, the DMN, FPN, and SN (particularly the ACC) as well as subcortical circuits involved in reward processing, including the ST and MTL. We hypothesized that higher levels of substance use and a history of mTBI would be associated with dysregulated rsFC within the DMN, FPN, SN, ST, and MTL. Furthermore, we expected that mental health symptoms within this population would be specifically linked to altered connectivity in the DMN and MTL.

6.4 Method

Participants

Data were collected from varsity athletes from York University, Toronto. Participants were eligible if they: (i) were rostered to play on a university team for the current season, and (ii) met the requirements for safe MRI scanning. A total of 74 athletes were recruited, of whom 69 completed demographic and imaging data, and 62 completed demographic, clinical, and imaging data (seven participants were missing CUDIT-R data) (see imaging data flow chart, Figure 6). When possible, 69 participants were included in analyses, but when CUDIT-R was used as a variable, only the 62 athletes who completed the CUDIT-R were included.

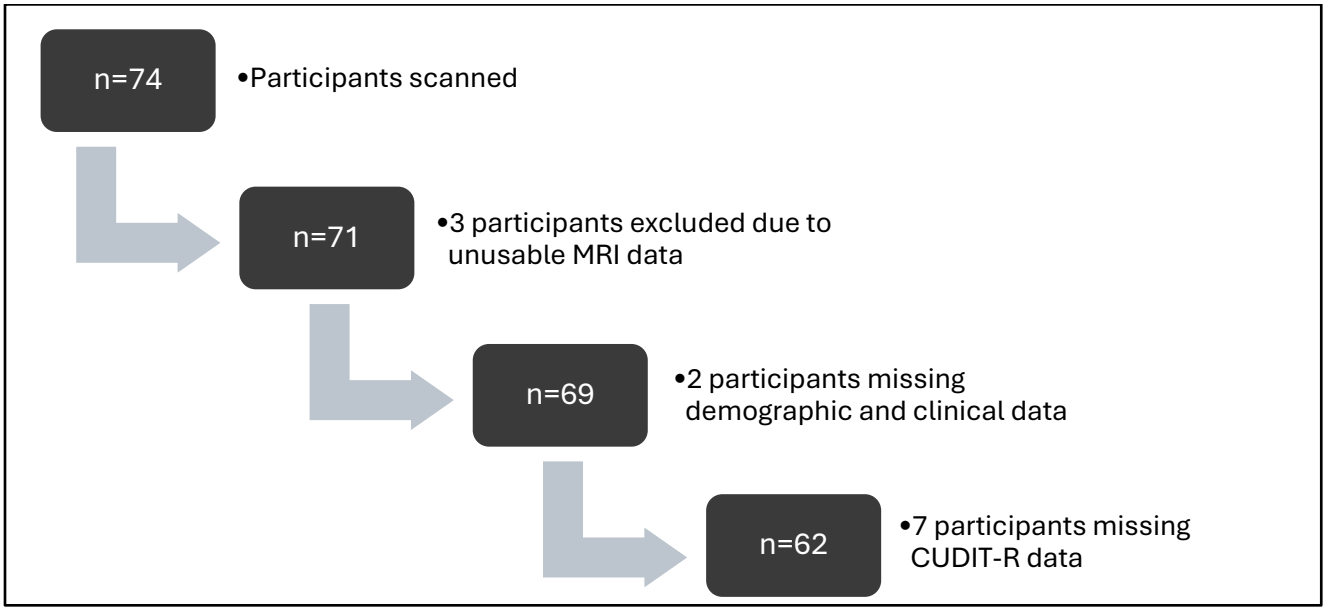

Figure 6. Participant data flow chart for athlete group ICA study

Procedure

This study was approved by the Human Participants Review Sub-Committee of York University's Ethics Review Board. Participants provided written informed consent to complete the imaging and behavioral components of the study. Participants completed one MRI session where structural and functional images were collected. Participants also completed questionnaires and were compensated $50 for their time.

Measures

Clinical and demographic data were collected using the same questionnaires used in Chapter 5, *Differential of associations of mental health, mild traumatic brain injury and substance use between males and female university students*. Please see the methods section of chapter 5 for summary of the Alcohol Use Disorder Identification Test (AUDIT), Cannabis Use Disorder Identification Test-Revised (CUDIT-R), Substance Use History, Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), mTBI history, and clinical history (including history of attention deficit hyperactivity disorder (ADHD), learning disorders, anxiety, and depression).

The Depression, Anxiety, and Stress Scale - 21 Item (DASS-21)

The DASS-21 (Lovibond & Lovibond, 1995) is a self-report tool consisting of three scales of 7 items each, used to measure emotional states of depression, anxiety, and stress. The item rating scale is as follows; 0- did not apply to me at all, 1- applied to me to some degree, or some of the time, 2- applied to me to a considerable degree or a good part of time, 3- applied to me very much or most of the time. On the depression scale, clinical cut-offs are identified as total scores of 0-9 indicate normal, 10-13 indicate mild, 14-20 indicate moderate, 21-27 indicate severe and 28 or above indicates extremely severe. On the anxiety scale, clinical cut-offs are identified as 0-7 indicate normal, 8-9 indicate mild, 10-14 indicate moderate, 15-19 indicate severe and 20 or above indicates extremely severe. On the stress scale, clinical cut-offs are identified as 0-14 indicate normal, 15-18 indicate mild, 19-25 indicate moderate, 26-33 indicate severe and 34 or above indicates extremely severe.

MRI acquisition

MRI data were acquired using a Siemens PrismaFit MRI scanner (Siemens, Erlangen, Germany). Whole brain, high-resolution, T1-weighted anatomical scans were collected using an ascending multi-slice 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) sequence (FOV = 256 mm, 1.0 x 1.0 x 1.0 mm voxels, TR = 2300 ms, TE =2.62 ms). To study brain function, a whole brain multi-echo planar imaging (EPI) sequence (T2*-weighted) was used to acquire functional data in 240 volumes (52 slices, FOV = 240 mm, 80 x 80 matrix, 3.0 x 3.0 x 3.0 mm3 voxels, TR = 961 ms, echo times [TEs] = 12.40 ms, 30.15 ms, 47.9 ms, flip angle = 50°). During fMRI scanning, patients lay still with their eyes closed.

Functional imaging preprocessing

Multi-echo rs-fMRI data preprocessing was performed using Analysis of Functional Neuroimages (AFNI) software package (R. W. Cox & Hyde, 1997). Data were converted from Dicom to NifTI (to_nifti.sh) and images were visually inspected. The AFNI_tedana.sh script was used to preprocess data where functional data underwent despiking, slice timing correction, registration of the functional and anatomical images, motion correction, and masking in AFNI. Tedana was then used for multi-echo denoising, followed by regression of head motion parameters to remove any residual head motion-related artifacts. Images, head motion estimates, and ICA components were visually verified for quality assurance. Freesurfer Recon-all (fs_recon-all.sh) was used to perform parcellation of the T1-weighted anatomical images and segmentation was verified visually by examining pial and white matter surface outlines and cortical parcellation. Functional and anatomical images were then coregistered (bbregister) using Freesurfer.

Further analyses of fMRI data were performed using CONN (Whitfield-Gabrieli & Nieto-castanon, 2012) (RRID:SCR_009550) release 22.v2407 (A. Nieto-Castanon & Whitfield-Gabrieli, 2022) and SPM (Penny et al., 2011) (RRID:SCR_007037) release 12.7219. Functional and anatomical data were preprocessed using a modular preprocessing pipeline (Nieto-Castanon, 2020) including indirect segmentation and MNI-space normalization, and smoothing. Functional and anatomical data were coregistered and normalized into standard MNI space, segmented into grey matter, white matter, and CSF tissue classes, and resampled to 2 mm isotropic voxels following an indirect normalization procedure (Calhoun et al., 2017) using SPM unified segmentation and normalization algorithm (Ashburner, 2007; Ashburner & Friston, 2005) with the default IXI-549 tissue probability map template. Last, functional data were smoothed using spatial convolution with a Gaussian kernel of 8 mm full width half maximum.

Independent Component Analysis

Group-level independent component analyses (group-ICA; Calhoun et al., 2001) were performed to estimate 40 temporally coherent networks from the fMRI data combined across all subjects. The BOLD signal from every timepoint and voxel in the brain was concatenated across subjects and conditions along the temporal dimension. A singular value decomposition of the z-score normalized BOLD signal (subject-level SVD) with 64 components separately for each subject was used as a subject-specific dimensionality reduction step. The dimensionality of the concatenated data was further reduced using a singular value decomposition (group-level SVD) with 40 components, and a fast-ICA fixed-point algorithm (Hyvärinen, 1999) with hyperbolic tangent (G1) contrast function was used to identify spatially independent group-level networks

from the resulting components. Last, GICA3 back-projection (Erhardt et al., 2011) was used to compute ICA maps associated with these same networks separately for each individual subject.

Spatial match-to-template correlations between each group-level spatial map and the CONN toolbox pre-defined networks based on Harvard-Oxford and Automated Anatomical Labeling atlases were used to identify resting-state networks. Highly correlated components were visually verified and selected by the experimenter. Specific networks were chosen based on involvement in clinical symptoms associated with mTBI, substance use, and mental health. Networks of interest including the DMN (anterior and posterior), FPN (right and left), striatum (ST), medial temporal, and the anterior cingulate cortex were used in second-level analyses (See Figure 7).

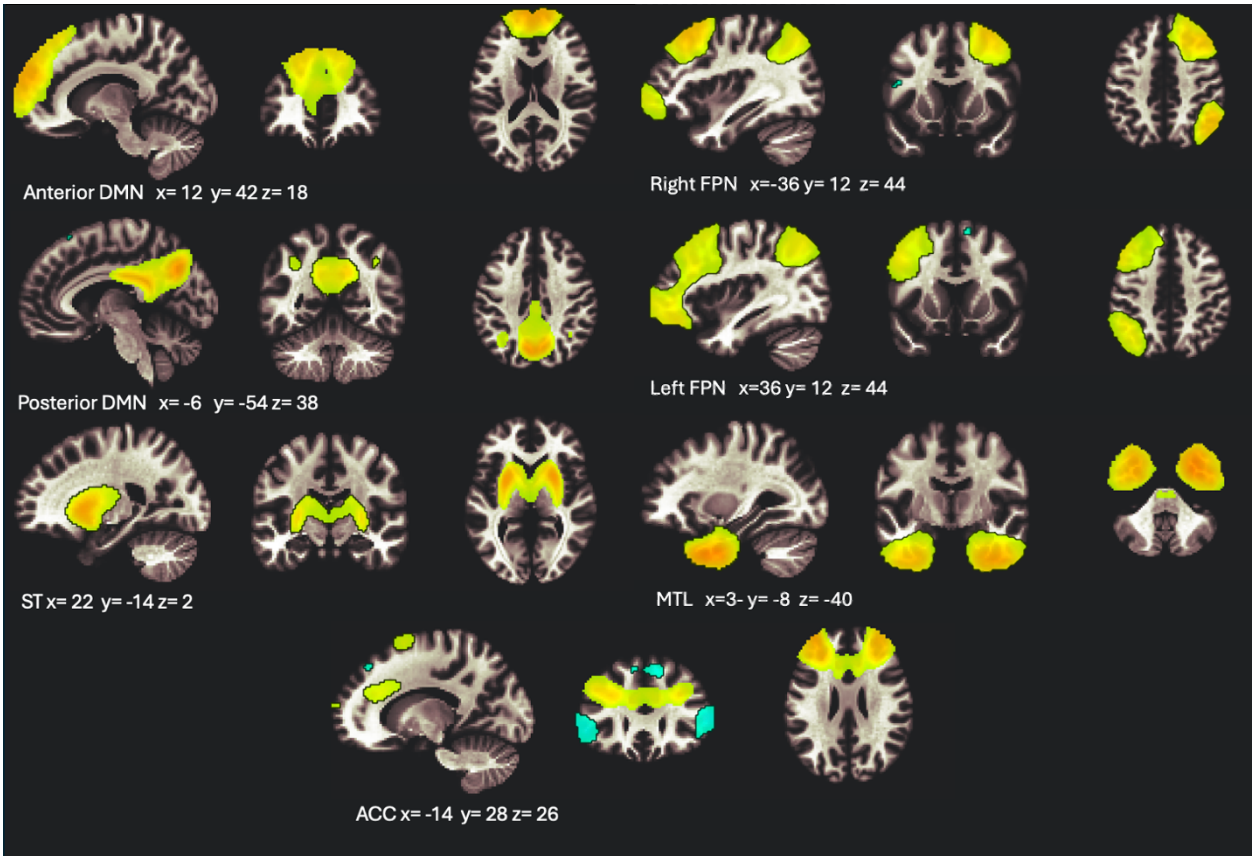

Figure 7. ICA components.

Abbreviations: ACC, anterior cingulate cortex; DMN, default mode network; FPN, frontoparietal network; MLT, medial temporal lobe; ST, striatum.

Data analysis

Clinical variables

Variables were examined for normality and univariate outliers; given violations of normality across total AUDIT, CUDIT-R, PHQ-9, and GAD-7 scores, non-parametric tests were used when comparing group means. Mann-Whitney U tests were run to compare total scores on clinical measures between individuals with and without a history of mTBI. Chi square analyses were performed to compare the number of alcohol and cannabis users and endorsement of hazardous use of each substance in each group, as well as the number of individuals meeting cut off criteria for mild or higher symptom endorsement on the PHQ-9, GAD-7, and DASS-21 subscales. Two-tailed alpha values of less than .05 were considered statistically significant.

fMRI analysis

Our primary objective was to investigate the effects of mTBI and substance use in each of the identified networks. Between-subjects contrasts were run comparing mTBI and no mTBI groups, substance users and non-substance users (for alcohol and cannabis individually), hazardous users and non-hazardous users (for alcohol and cannabis individually). Regression analyses were run using number of previous mTBIs, AUDIT scores, and CUDIT-R scores. Interaction analyses were run to investigate total AUDIT and CUDIT-R scores between mTBI and no mTBI groups, as well as hazardous use or non-hazardous use between mTBI and no mTBI groups.

Additional exploratory analyses were run to investigate mTBI and mental health variables in networks of clinical interest including the DMN (anterior and posterior) and ACC networks. Between-subjects contrasts were run comparing mild or above scores to normal scores on the GAD-7 and PHQ-9. Regression analyses were run using total GAD-7 and PHQ-9 scores. Interaction analyses were run to investigate total GAD-7 and PHQ-9 scores between mTBI and no mTBI groups, as well as individuals with mild or above compared to normal GAD-7 and PHQ-9 scores between mTBI and no mTBI groups. RsFC was examined using parametric statistics (gaussian random field theory) with the cluster threshold set to a False Discovery Rate (FDR) of $p < 0.05$, and an uncorrected voxel threshold of $p < 0.001$.

5.5 Results

Demographic and clinical characteristics

Demographic and clinical information is shown in Table 12 and 13. This comprised 69 individuals, of which only 62 completed the CUDIT-R. Of the 69 athletes, 42% (n = 29) reported female sex at birth and athletes were between the ages of 17 and 25 years (M= 20 years 5 months, SD= 2 years 1 month). At the time of the study, the athletes were engaged in one of the following

sports: basketball (n = 11, 15%), field hockey (n = 3, 4%), football (n = 11, 15%), hockey (n = 20, 29%), rugby (n = 6, 9%), soccer (n = 13, 19%), and volleyball (n = 5, 7%). Approximately 40% (n = 25) used cannabis is the past six months, and 81.2% (n = 56) used alcohol in the past year and 57% (n = 39) of athletes had a history of at least one mTBI. With respect to mental health, only 21.7% (n = 15) of individuals endorsed mild or higher symptoms on the GAD-7 and 21.7% (n = 15) endorsed mild or higher symptoms on the PHQ-9, with significantly fewer endorsing moderate of higher symptoms; 4.3% (n = 3) on the GAD-7, and 4.3% (n = 3) on the PHQ-9). Co-occurring substance use and mental health was minimally observed in our sample; 1.4% (n = 1) endorsement each for either hazardous cannabis or alcohol use occurring with moderate of higher GAD-7 or PHQ-9 scores.

Table 12. Demographic information of the university athlete sample in study 4.

Variable	
Age in years M(SD)	20.43 (2.11)
Range	17-25
Gender n (%)	
Female	28 (40.6)
Male	38 (55.1)
Non-binary	1 (1.4)
Transgender	1 (1.4)
Prefer to self-describe or not disclose	1 (1.4)
Female sex at birth n (%)	29 (42.0)
Race n (%)	
Asian	6 (8.7)
White	43 (62.3)
Middle Eastern	3 (4.3)
Black or African American	12 (17.4)
South Asian	1 (1.4)
Mixed Ethnicity	2 (2.9)
Hispanic, Latino, or Latina	1 (1.4)
American Indian or Alaska Native	0
Native Hawaiian or Pacific Islander	0
"European"	1 (1.4)

Education in years M (SD)	2.51 (1.31)
Range	1-6
ADHD n (%)	5 (7.2)
Learning disorder n (%)	11 (15.9)

Note. Overall sample includes n=69

Abbreviations: ADHD, Attention deficit/hyperactivity disorder

Table 13. Clinical characteristics of the university athlete sample in study 4.

Variable	
Cannabis use past six months n (%)	25 (40.3)
CUDIT-R total M(SD)	2.67 (4.33)
Range	0-19
Hazardous cannabis use (over 8) n (%)	10 (16.4)
Alcohol use past year n (%)	56 (81.2)
AUDIT total M(SD)	4.86 (4.67)
Range	0-20
Hazardous alcohol use (over 8) n (%)	16 (23.2)
PHQ-9 total M(SD)	2.83 (3.49)
Range	0-14
PHQ-9 mild or above n (%)	15 (21.7)
PHQ-9 moderate or above n (%)	3 (4.3)
GAD-7 total M(SD)	2.58 (3.60)
Range	0-20
GAD-7 mild or above n (%)	15 (21.7)
GAD-7 moderate or above n (%)	3 (4.3)
Hazardous cannabis use and PHQ-9 moderate or above n (%)	1 (1.4)
Hazardous cannabis use and GAD-7 moderate or above n (%)	1 (1.4)
Hazardous alcohol use and PHQ-9 moderate or above n (%)	1 (1.4)
Hazardous alcohol use and GAD-7 moderate or above n (%)	1 (1.4)
DASS-21 total M(SD)	8.20 (10.09)
Range	0-46
DASS-21 depression total M(SD)	2.23 (3.62)

Range		0-16
DASS-21 depression mild or above n (%)		6 (8.7)
DASS-21 depression moderate or above n (%)		2 (2.9)
DASS-21 anxiety total		2.43 (3.7)
Range		0-18
DASS-21 anxiety mild or above n (%)		8 (11.6)
DASS-21 anxiety moderate or above n (%)		5 (7.2)
DASS-21 stress total		3.54 (4.77)
Range		0-26
DASS-21 stress mild or above n (%)		2 (2.9)
DASS-21 stress moderate or above n (%)		1 (1.4)
Previous diagnosis of anxiety n (%)		11 (15.9)
Previous diagnosis of depression n (%)		5 (7.2)
Number of mTBIs endorsed across the lifetime n (%)		
	0	30 (43.5)
	1	15 (21.7)
	2	11 (15.9)
	3	8 (11.6)
	4	2 (2.9)
	5 or more	3 (4.3)
Hazardous cannabis use and mTBI endorsement (%)		6 (9.8)
Hazardous cannabis use and mTBI endorsement (%)		11 (15.9)

Note. Overall sample includes n=69, CUDIT-R includes n=62

Abbreviations: AUDIT, Alcohol Use Disorder Identification Test; CUDIT-R, Cannabis Use Disorder Identification Test-Revised; DASS-21, The Depression, Anxiety, and Stress Scale- 21; GAD-7, Generalized Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9.

Group differences between mTBI and no mTBI

Athletes with mTBI had significantly higher PHQ-9, GAD-7, AUDIT, and DASS-21 subscale scores compared to athletes without a history of mTBI (ps < .05; See Table 14). This group also had a higher number of athletes who used alcohol in the last year and who endorsed mild or above scores on the PHQ-9, GAD-7, and the DASS-21 depression scales. There were no significant

differences in number of cannabis users, total CUDIT-R scores, number of hazardous users (alcohol or cannabis), and number of individuals endorsing mild or higher scores on the DASS-21 anxiety and stress scales between athletes with or without a history of mTBI (ps > .05; See Table 14).

Table 14. Comparison of athletes with and without a history of mTBI using Mann-Whitney U tests in study 4.

Variable	No mTBIs	Any mTBIs	df	Mann-Whitney U	X^2	p	Z
PHQ9 total M, (SD)	1.57 (2.91)	3.79 (3.62)	67	833.5		**.002**	3.091
PHQ9 mild or above n (%)	2 (6.7%)	13 (33%)	1		7.09	**.008**	
GAD7 total M (SD)	1.53 (3.71)	3.38 (3.35)	67	1602.5		**.003**	2.973
GAD7 mild or above n (%)	2 (6.7%)	13 (33.3%)	1		7.09	**.008**	
Alcohol use in past year n (%)	21 (70.0%)	35 (89.7%)	1		4.323	**.038**	
AUDIT total M (SD)	3.53 (4.60)	5.87 (4.51)	67	1594.5		**.005**	2.796
Hazardous alcohol use (over 8) n (%)	5 (16.7%)	11 (28.2%)	1		1.267	.260	
Cannabis use in past six months n (%)	10 (35.7%)	15 (44.1%)	1		.451	.502	
CUDIT-R total M(SD)	2.41 (4.06)	2.88 (4.58)	59	498.0		.520	.643
Hazardous cannabis use (over 8) n (%)	4 (14.8%)	6 (17.6%)	1		.088	.767	
DASS depression total M (SD)	.93(1.72)	3.23 (4.34)	67	1543.5		**.016**	2.398
DASS depression scale mild or above	0 (0.0)	6 (15.4)	1		5.055	**.025**	
DASS anxiety total M (SD)	1.80 (3.80)	2.92 (3.61)	67	1518.0		**.046**	1.995
DASS anxiety scale mild or above	2 (6.7)	6 (15.4)	1		1.257	.262	
DASS stress total M (SD)	2.13 (4.84)	4.62 (4.48)	67	1591.0		**.004**	2.851
DASS stress scale mild or above	1 (3.3)	1 (2.6)	1		.036	.850	

Note. While the Mann Whitney U tests were used, means are presented for comparison.

ICA results

Results from the ICA analyses are summarized in Table 15 and shown in Figure 8. No differences were observed across networks in between-subject contrasts, regressions, or

interactions for mTBI and substance use variables. As such, we continued to explore the data by including follow-up analyses to investigate rsFC differences associated with mental health and mTBI. No differences were found in between-subject contrasts comparing mild or above scores on the GAD-7 or PHQ-9 and there were no main effects of total GAD-7 or PHQ-9 scores. Group-by-group interactions between mild or above compared to normal GAD-7 and PHQ-9 scores within mTBI and no mTBI groups were also non-significant within networks. However, there was a significant interaction between GAD-7 total scores and mTBI history within the anterior DMN (see Table 15, Figure 8). Post hoc analyses demonstrated that GAD-7 scores were positively correlated with functional connectivity between the DMN and both clusters in the left caudate (p = .066) and right paracingulate gyrus (p = .040) in individuals with a history of mTBI. In contrast, GAD-7 scores were negatively correlated with functional connectivity between the DMN and clusters in the left caudate (p = .002) and right paracingulate gyrus (p = .010) in individuals without a history of mTBI (see Figure 9).

Table 15. ICA results

Network	Primary region	Cluster size	MNI coordinates			T value	Mass p-FDR
			x	y	z		
Interaction between GAD-7 scores and mTBI group							
Anterior DMN	Left Caudate	2619	-18	12	10	3.46	<0.001
	Right Paracingulate Gyrus	820	06	36	34	3.45	0.029

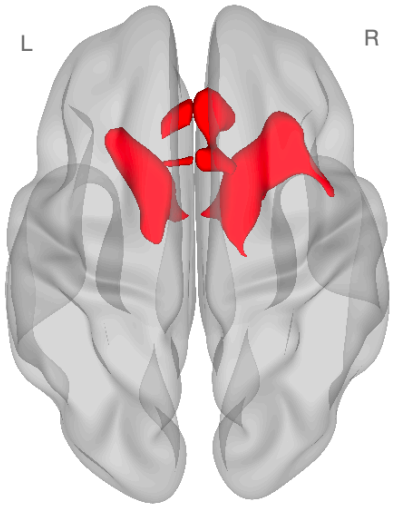

Figure 8. Clusters showing a significant interaction between GAD-7 total scores and mTBI history within the anterior DMN.

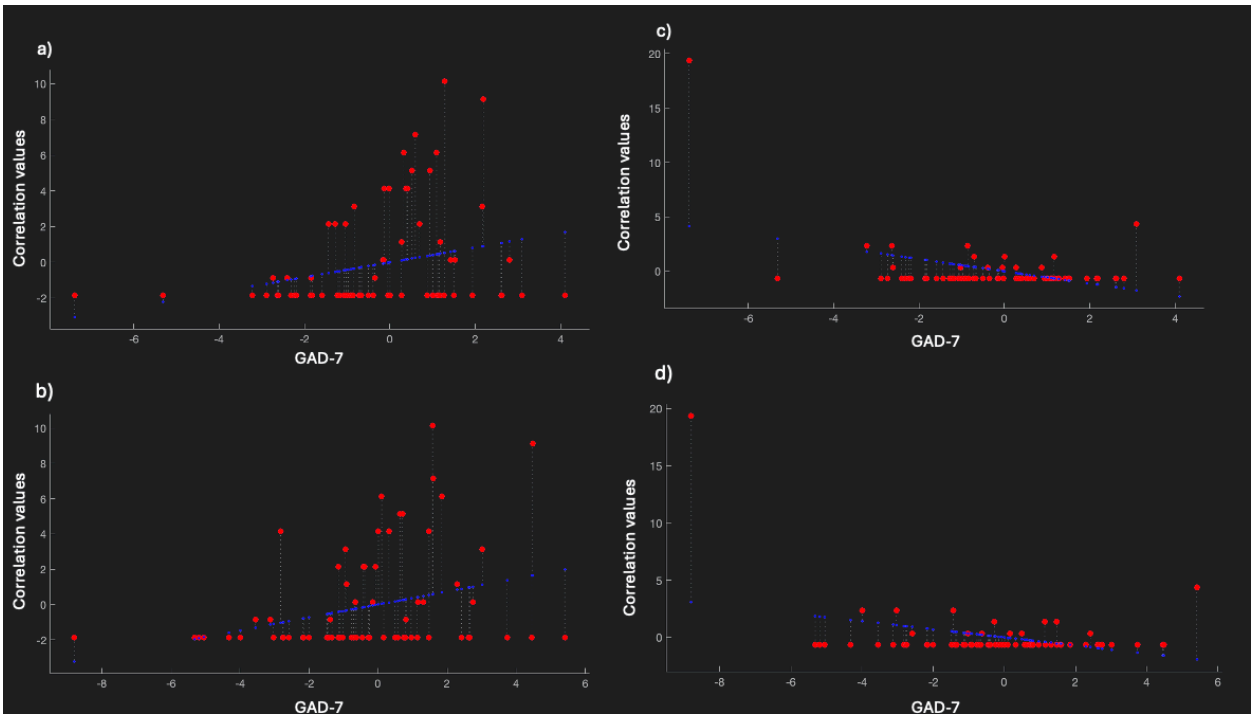

Figure 9. Correlation between GAD-7 scores and functional connectivity between anterior DMN and the left caudate for athletes with (a) and without (b) a history of mTBI and the right paracingulate gyrus for athletes with (c) and without (d) a history of mTBI.
Note: red dots= observed values; blue dots= fitted values.

5.6 Discussion

Psychological outcomes following mTBI has been a growing area of concern. This study provides an examination of resting-state neural network connectivity associated with substance use patterns in athletes with and without a history of mTBI. This study utilized a sample of both male and female athletes across contact and non-contact sports to increase generalizability across athletes. Among this group of individuals with relatively low mental health concerns and rates of substance use were higher compared to other university samples; however, there were minimal clinically significant differences in substance use and mental health symptoms between athletes with and without a history of mTBI. Additionally, our study found that neither the use nor hazardous use of alcohol or cannabis was associated with differences in connectivity across the cortical or subcortical networks of interest, regardless of mTBI history. However, the one notable effect observed was an interaction between anxiety and mTBI history, whereby increased connectivity between the DMN and striatal regions was associated with anxiety scores in athletes with a history of mTBI, compared to those without a history of mTBI.

Within our small sample of varsity athletes, 57% reported a history of mTBI, and substance use was relatively common—40% reported cannabis use and 81% reported alcohol use, with 16% and 23% endorsing hazardous use of cannabis and alcohol, respectively. These findings are in line with proportions of college students using alcohol and cannabis (Shulenberg et al., 2017) and with research demonstrating increasing normative cannabis use (McDuff et al., 2019). Substance use patterns were generally similar between athletes with and without a history of mTBI. Those with a history of mTBI were slightly more likely to use alcohol but were equally likely to use cannabis or report hazardous cannabis use, compared to those without an mTBI history. In terms of mental health, while athletes with a history of mTBI reported higher symptoms of depression, anxiety, and stress, only 4% of the overall sample endorsed moderate or higher levels of depression and 4% endorsed moderate or higher levels of anxiety (i.e., PHQ-9 and GAD-7). It is important to note that the moderate range is typically used as the clinical threshold for identifying individuals at risk for depression and/or anxiety disorders. Additionally, very few athletes had co-occurring hazardous substance use with possible clinical levels of depression or anxiety. Overall, our sample demonstrates a relatively psychologically healthy group of individuals with minimal levels of clinically significant mental health concerns. The existing literature shows variability regarding whether varsity athletes are at greater risk for mental health disorders. However, data from the U.S. National College Health Assessment (NCHA), confirm lower reporting of most mental health

symptoms among athletes (Edwards et al., 2022). Similarly, more recent findings have shown that varsity athletes are less likely to endorse mental health problems than their peers (Edwards & Froehle, 2023). Research suggests that while individuals are more susceptible to mental health concerns in the acute phase following an mTBI, these symptoms tend to diminish over time, particularly among athletes (Rice et al., 2018). It is possible that long-term outcomes following mTBI are less clinically significant, as athletes recover from their injury and may demonstrate a degree of psychological resilience.

Given the relatively small size and overall healthy nature of our sample, it is not surprising that no significant differences in functional connectivity were observed across the identified neural networks in relation to alcohol or cannabis use, whether general or hazardous, regardless of mTBI history. Similar studies involving athlete populations have also reported no significant resting-state or task-based functional connectivity differences between recovered athletes with a history of mTBI and those without (Churchill et al., 2017; Kontos et al., 2012; Terry et al., 2012). Churchill et al. (2017) suggested that this lack of observable differences may stem from the heterogenous nature of long-term functional changes following mTBI. However, their study did identify associations between cumulative injury effects and connectivity within the visual attention network and cerebellum –networks, which were beyond the scope of the present study.

Although it remains unclear whether cannabis may serve as a protective factor for athletes at risk of mTBI, several neurobiological models have been proposed, including anti-inflammatory effects and modulation of neurotransmitter reuptake (Belardo et al., 2019; Pazos et al., 2012). A recent review found that cannabis use most consistently affects rsFC between frontal-frontal, fronto-striatal and fronto-temporal regions (Thomson et al., 2022). However, it is possible that our sample population possess certain protective factors. For instance, substance use among athletes may be approached with greater caution, as they are often highly motivated to protect their physical health and athletic performance. Additionally, many athletes are subject to regular drug testing and strict organizational policies, which may deter risky substance use. The potential impact on team dynamics, scholarships, or future athletic opportunities may also lead athletes to be more cautious in their decisions around substance use. Additionally, our sample demonstrated limited co-occurrence of substance use and mental health concerns, a pattern that may differ from the general population.

Regarding mental health, our study identified increased functional connectivity between the anterior DMN and striatal regions related to anxiety symptoms in athletes with a history of mTBI

which approached statistical significance. In contrast, athletes without a history of mTBI showed a statistically significant decrease in connectivity between these regions. While anxiety is most commonly associated with regions such as the amygdala, hippocampus, and ventromedial prefrontal cortex, there is growing evidence for the involvement of the striatum, given its role in key behavioral processes related to anxiety, including attentional control, conditioning and prediction error processing, and motivational regulation (Lago et al., 2017). Although the clinical implications of this finding should be interpreted with caution, increased engagement of striatal and limbic regions within a self-referential network such as the DMN may suggest potential difficulties in emotional regulation among this subgroup. Specifically, heightened activity in these areas has been associated with increased emotional reactivity and rumination (Cooney et al., 2010), which can interfere with the ability to manage mood and stress effectively. This pattern of neural activation may indicate a vulnerability to mood disturbances or challenges in shifting attention away from internally focused, emotionally charged thoughts.

Several limitations should be considered when interpreting the findings of this study. First, the relatively small sample size may have limited the statistical power to detect subtle or network-level differences in brain connectivity related to clinical variables. Second, while it is encouraging that the sample was overall psychologically healthy, the limited number of participants endorsing clinically significant levels of depression, anxiety, or hazardous substance use presents challenges in identifying meaningful group differences. This study relied on self-reported data for substance use and mental health symptoms, and mTBI history rather chart reviews, which introduces the possibility of biased or inaccurate reporting, particularly for variables like past concussions or hazardous substance use, which may be under- or over-reported due to recall bias or social desirability. These limitations highlight the need for future studies with larger, more clinically diverse samples and validated clinical assessments to further explore the complex relationships between mTBI, substance use, mental health, and neural network connectivity.

In conclusion, this study aimed to explore the associations between mTBI, substance use, and underlying neural network connectivity in a sample of varsity athletes. Findings revealed limited clinically meaningful differences in substance use and mental health outcomes between athletes with and without a history of mTBI, with a low overall prevalence of clinically significant symptoms across the sample. Furthermore, no significant differences in functional connectivity were observed across key neural networks in relation to mTBI history or substance use. The one notable neural finding was an association between anxiety symptoms and altered connectivity

within the DMN among athletes with a history of mTBI. Taken together, these findings suggest that varsity athletes may represent a relatively healthy population, with minimal observable impact of mTBI or substance use on large-scale brain network functioning. Future research with larger and more clinically diverse samples is warranted to further clarify these relationships.

Chapter 7: Discussion

7.1 Overview of studies

In this dissertation, we sought to further clarify the associations between substance use, mental health, and mTBI using both clinical measures and functional neuroimaging. rsFC of key neural hubs involved in self-monitoring and emotional regulation was first examined in a sample of 31 substance-using and non-using female varsity athletes. We then analyzed clinical data from 416 male and female varsity athletes to better understand the relationships between mTBI, mental health, and substance use habits in a relatively healthy population. To expand on these findings, we conducted a study with a larger and more diverse sample of 894 university students, allowing for more nuanced and granular analyses of these variables. In this sample, we examined how mTBI and mental health symptoms were associated with alcohol and cannabis use, both overall and separately by sex. Finally, we adopted a resting-state network approach to explore potential underlying differences in connectivity across key neural networks related to substance use and mental health in a sample of 69 varsity athletes with and without a history of mTBI.

7.2 Summary of results

Study 1 (Chapter 3) found that in female athletes, substance use was linked to higher self-reported depression and altered rsFC in regions tied to self-monitoring and emotional regulation. Depression symptoms were higher in substance users than non-users, particularly among cannabis users, while anxiety and mTBI history did not differ across groups. rsFC differences were observed in the OFC and bilateral hippocampus: users showed decreased connectivity between the left OFC and occipital fusiform gyrus, and increased connectivity between hippocampal seeds and the right cerebellum. No rsFC differences were found between alcohol and cannabis users. Within cannabis users, higher depression was associated with reduced rsFC between the left hippocampus and posterior cingulate cortex. These findings suggest altered limbic connectivity in cannabis-using athletes, potentially contributing to risky substance use.

Study 2 (Chapter 4) found that university athletes with a history of mTBI were more likely to engage in single or polysubstance use, and those with anxiety were more likely to engage in polysubstance use. Alcohol users more often reported anxiety and mTBI history than non-users. Polysubstance users showed higher depression and were more likely to report anxiety and mTBI than both non-users and alcohol-only users. mTBI history significantly predicted alcohol and

polysubstance use, supporting its role as a risk factor. Anxiety also predicted polysubstance use. A small, non-significant association with male sex was observed.

Study 3 (Chapter 5) examined associations between mTBI history, mental health, and hazardous substance use in a larger, non-athlete sample. Alcohol users were more likely to report a history of mTBI than non-users, though this pattern did not hold for cannabis use. However, hazardous use of either substance was linked to mTBI history and moderate or greater symptoms of anxiety and depression. Higher anxiety scores were associated with cannabis use, especially in those without mTBI. Among cannabis users, both mTBI history and higher depression scores predicted greater severity of use. For alcohol users, depression was linked to more problematic use only in those with mTBI.

No sex differences were found in substance use rates, severity, or mTBI history. However, females reported higher depression and anxiety symptoms than males, particularly if they had a history of mTBI. This pattern was not observed in males. Sex-specific analyses revealed that in females, anxiety was linked to cannabis use, and depression was associated with cannabis use only in those with mTBI. Anxiety predicted cannabis use more strongly in those without mTBI. In males, depression predicted cannabis use, but anxiety and mTBI did not. For alcohol use, no significant predictors emerged in females. In males, depression was associated with alcohol use, but those with both depression and mTBI were less likely to drink. Anxiety predicted alcohol use in males with a history of mTBI.

Finally, Study 4 (Chapter 9) examined resting-state networks linked to clinical factors in varsity athletes. Athletes in our sample generally exhibited greater levels of hazardous use and lower levels of mental health concerns compared to our undergraduate student sample in Study 3. However, athletes with a history of mTBI reported significantly higher depression, anxiety, stress, alcohol, and cannabis use compared to those without an mTBI history. They also had a higher proportion of alcohol users and individuals endorsing mild or greater depression and anxiety symptoms. No significant differences in cannabis use or hazardous substance use were found. Notably, our study revealed that neither alcohol nor cannabis use, nor hazardous use, was associated with changes in connectivity across cortical or subcortical networks. However, increased connectivity between the DMN and striatum was observed in athletes with a history of mTBI, correlating with higher anxiety scores compared to those without mTBI.

7.3 General discussion

Relationship between substance use, mental health, and mTBI.

Indisputably, substance abuse and poor mental health are highly co-occurring conditions (Degenhardt et al., 2016; Gobbi et al., 2019; Grant et al., 2004b; Hines et al., 2020; Mchugh & Weiss, 2019; Moore et al., 2007). These issues share both environmental and genetic risk factors, which significantly increase the likelihood of experiencing both conditions concurrently (Khantzian, 1997; Sadock et al., 2016). As a result, the association between substance use and mental health problems has been long recognized (Brook et al., 1998; Rachbeiscl et al., 1999) and is very likely bi-directional in nature, with each condition potentially exacerbating the other (Khantzian, 1997; Sadock et al., 2016; Vorspan et al., 2015).

While our findings continue to suggest a relationship between substance use and mental health, the strength of this association appears to be more nuanced. Notably, this research was conducted within generally healthy populations of young adults rather than clinical samples with diagnosed mental health conditions or substance use disorders. This context likely contributes to the subtler manifestations of comorbidity observed. In Study 1, among female athletes, substance use was associated with higher depression scores; however, these scores remained within the normal range and do not show strong clinical significance, and no significant association was observed with anxiety symptoms. In Study 2, among male and female athletes, those endorsing combined substance use again demonstrated significantly higher depression scores relative to non-users, though still within the non-clinical range. Interestingly, this group reported experiencing anxiety at three times the rate of non-users, though this was not corroborated by clinical anxiety measures. Despite the high prevalence of substance use and hazardous consumption reported among athletes in Study 4, there was minimal endorsement of elevated mental health symptoms in this group. This may point to underreporting, normalization of distress, or the presence of protective factors unique to this subpopulation.

In contrast, within the broader undergraduate sample, hazardous alcohol or cannabis use was associated with both statistically and clinically meaningful increases in anxiety and depression, with a greater proportion of individuals meeting thresholds for moderate to severe symptoms. However, mental health symptoms alone were not strong predictors of substance use in this population. Rather, the interaction between mental health symptoms and a history of mTBI emerged as a more robust predictor of substance use patterns, suggesting a compounding effect.

Over the past several decades, a substantial body of literature has examined substance use within undergraduate populations. Historically, college attendance was considered a protective factor against the development of substance use disorders; however, over the last several decades, substance use within college populations has become increasingly more problematic (Ham & Hope, 2003). Substance use, particularly cannabis use, has increasingly become normative among college students, particularly in recent decades alongside legalization of cannabis (Hasin & Walsh, 2021). Recent trends further underscore this shift. For example, between 2020 and 2021, the Monitoring the Future study found a rise in the prevalence of marijuana vaping, a decline in daily alcohol use, and a simultaneous increase in binge drinking (Patrick et al., 2022). Notably, the prevalence of marijuana use reached its highest levels since 1988, and high-intensity drinking (defined as consuming 10 or more drinks in a row) remained at historically elevated levels not seen since (Patrick et al., 2022).

This increase in normative substance use may reflect a broader shift in the motivations behind use, suggesting that substance use may no longer be as strongly linked to coping with poor mental health but is instead increasingly driven by social or recreational factors. This shift may partially account for the weaker associations observed between substance use and mental health concerns among athletes in our studies. However, the relationship between substance use and mental health remains evident within the general population, where coping-related use may still be more prominent. In line with this, correlation with underlying functional connectivity is somewhat weaker in our data. In female athletes we noted some differences between substance users and non-users in self-monitoring and emotional regulation brain regions, but in a larger sample, there were no differences across substance users and non-users, or mental health when examined on their own.

More prominently demonstrated in our research is the association between substance use and a history of mTBI, aligning with prior studies that have identified increased vulnerability to substance use following mTBI (Alcock et al., 2018; Baiden et al., 2022; Kort-Butler, 2017; Veliz et al., 2021). Across studies, mTBI was both associated with and predictive of higher endorsement of alcohol use and combined substance use. Notably, in Study 4, this association was more specific to alcohol use than cannabis use. A dose-dependent relationship was also observed where individuals with a history of two or more mTBIs reported greater cannabis use, while those with three or more mTBIs reported greater alcohol use. Furthermore, a more nuanced interaction emerged wherein the combination of mTBI and elevated mental health symptoms was linked to a

higher likelihood of substance use and greater consumption among users. Despite these behavioral associations, mTBI history alone was not associated with significant differences in rsFC networks among athletes, suggesting that neural alterations may be more subtle or require the presence of additional factors, such as psychological distress, to manifest at the network level.

It is well-established clinically that mental health conditions, particularly depression, are more common following brain injuries, both mild and severe (Busch & Alpern, 1998; Pavlovic et al., 2019). These conditions also share overlapping neuropathological mechanisms even when they occur independently and are associated with the disruption of brain function and connectivity, particularly within the DMN, limbic system, and frontal circuitry (Pan et al., 2018; Shaw, 2002; Van Der Horn et al., 2016). Both mTBI and mental health conditions such as depression contribute to neuroinflammation, leading to neurotoxicity and altered synaptic function, as well as glutamate dysregulation, which results in neuronal injury and impaired emotional regulation (Beurel et al., 2020; Corps et al., 2015; Guerriero et al., 2015; Paul & Skolnick, 2003). Furthermore, mitochondrial dysfunction observed in both conditions contributes to symptoms like brain fog and fatigue (Allen et al., 2018; Lifshitz et al., 2004).

This overlap in neuropathology may help explain the notably high rates of depression following mTBI, with evidence showing that individuals who experience mTBI are at a threefold increased risk for developing depression, an elevated risk that can persist for decades ((Hellewell et al., 2020). While most studies in this dissertation focused on the associations between substance use with mental health and mTBI, rather than the associations between mental health and mTBI, Study 4 revealed that athletes with a history of mTBI not only reported higher depression scores but also higher anxiety scores compared to those without such a history. Additionally, although no other psychological factors were significantly associated with altered rsFC, anxiety scores in individuals with mTBI history were linked to changes in anterior DMN connectivity, suggesting functional consequences related to impaired emotional regulation and increased susceptibility to anxiety and mood disturbances.

Resilience in athlete populations.

Observationally, we noted psychological differences between our athletes and general student populations. As expected, rates of mTBI were higher among university athletes compared to general university students. In general, athletes reported fewer mental health problems but higher levels of hazardous substance use. However, they also reported lower levels of co-occurring mental health and substance use issues.

As pointed out by Grasdalsmoen et al. (2022), historically mental health may have been overlooked in elite athletes due to both our idealization of athletes (Doherty et al., 2016), as well as a lower tendency to seek out support among athletes, leading to assumptions about lower prevalence of mental health conditions in this group (Steinfeldt & Steinfeldt, 2012). From the outset of our research, we hypothesized that, despite the history of mental health not being assumed to be relevant to athletes, university athletes might be experiencing higher rates of mental health concerns compared to their non-athlete peers. This assumption was based on the unique challenges faced by athletes, including increased performance pressures, risk of sports-related injuries, overtraining, and interpersonal conflicts with coaches or teammates. These factors are compounded by the academic demands experienced by all university students, as suggested by Wolanin et al. (2015). Additionally, researchers have begun to suspect that athletes may be struggling more than previously assumed and some studies have indicated that elite and university athletes often do experience mental health problems at rates similar to, or even exceeding, those of their peers (Cox et al., 2017; Gouttebarge et al., 2019; Rice et al., 2016; Schaal et al., 2011).

However, while there is a rationale of why athletes may be at higher risk for mental health concerns, our observational comparisons between samples did not support this (note that no direct statistical comparisons were made). In fact, student athletes (Study 4) tended to report fewer mental health issues than a general undergraduate student population including non-athletes and athletes alike (Study 3). For instance, 45% of students in the general population endorsed moderate or higher levels of depression, whereas only 4.3% of athletes reported depression at similar levels. A similar pattern was observed with anxiety where 39% of general students reported moderate or higher levels of anxiety, compared to just 4.3% of athletes. When examining self-reported history of mental health conditions, the difference was less pronounced. Specifically, 12% of students reported a prior diagnosis of anxiety compared to 7% of athletes, while 19% of students versus 16% of athletes reported a previous diagnosis of depression. While athletes in Study 1 had a small sample and Study 2 had limited clinical data, endorsement of

depression and anxiety were also low in both university athlete samples (Study 1 PHQ-9 M= 3.32, GAD-7 M= 2.78; Study 2 PHQ-9 M = 2.49).

The literature has not been consistent regarding athletes' risk for experiencing mental health concerns. While systematic reviews suggest slightly higher rates of mental health issues among athletes, findings are inconsistent and they also emphasize the lack of control data and inconsistent operationalization of mental health (Gouttebarge et al., 2019; Reardon & Factor, 2010), both of which are important limitations that also apply to the interpretation of our findings. Despite these challenges, recent studies have begun to highlight potential protective factors associated with elite-level sport participation. Grasdalsmoen et al. (2022), for example, reported generally better mental health among elite athletes, including lower rates of depression and anxiety, less loneliness, and greater life satisfaction. Several factors may contribute to the conflicting findings across studies. One possibility is that, as societal awareness of mental health in sport has grown, stigma has decreased, and mental health discussions have become more normalized. As a result, more resources are now available and accessible to athletes. In fact, sports psychology and the inclusion of team psychologists have become integral components of modern athletic programs (Mehta, 2022; Zakrajsek et al., 2016), possibly contributing to improved mental health outcomes among players. Grasdalsmoen et al. (2022) also identified two additional protective factors: increased hours of exercise and participation in team rather than individual sports. These findings highlight the importance of aerobic exercise, which has been strongly implicated as a protective factor (Gordon et al., 2018; Kvam et al., 2016), as well as the mental health benefits derived from the social aspects of sport participation (Leonard & Bonnie, 1990).

While observational comparisons between our athlete and student samples suggest possibly better overall mental health among athletes, this observation reversed when examining substance use. A greater proportion of athletes reported using substances and engaging in risky patterns of use, particularly with cannabis and alcohol, compared to their non-athlete peers. Specifically, across Studies 3 and 4, 40% of athletes reported cannabis use, compared to 26% of students, with 16% versus 11% endorsing hazardous use. Similarly, 81% of athletes reported alcohol use compared to 53% of students, and 23% of athletes reported hazardous alcohol use compared to only 8% of students. Despite these elevated rates, athletes were less likely to endorse co-occurring hazardous substance use alongside moderate mental health conditions, likely due to the overall lower levels of mental health symptom endorsement in this group. Higher rates of substance use among athletes are well-documented and not unexpected. Despite being the focus

of targeted intervention and education efforts, university athletes tend to use substances at higher rates than their non-athlete counterparts (Nelson & Wechsler, 2001). They are particularly more likely to engage in risky substance use behaviors, such as frequent heavy alcohol consumption (Ford, 2007), and face a heightened risk of using other substances like cannabis (Hilderbrand, 2011). While a recent review indicates that overall alcohol and cannabis use among elite athletes is generally lower than among non-athletes, rates of binge drinking are notably higher among athletes, particularly those in power and collision sports. Moreover, cannabis has recently emerged as the second most commonly used substance among this population (McDuff et al., 2019). Factors such as team bonding, prevailing social norms around substance use, and the pressures associated with athletic performance have been proposed as contributing to this elevated use (Ford, 2007).

While participation in sport may offer some protective benefits for mental health, it may also contribute to increased engagement in risky substance use. When interpreting our findings, it is crucial to consider potential confounding factors, including the possibility of underreporting mental health concerns among athletes. Although confidentiality was emphasized to the athlete participants, the data collection during baseline testing may have led to perceptions of reduced anonymity. This perception has been associated with underreporting among athletes, as demonstrated in recent meta-analyses showing higher reporting rates under conditions of anonymity compared to non-anonymity (Harenberg et al., 2022). Additionally, data from non-athlete students were collected from first-year university students enrolled in an undergraduate psychology course, a population that may be particularly vulnerable due to the transitional stressors of beginning university, which are often associated with heightened symptoms of anxiety and depression. Furthermore, the academic context of a psychology course may prompt greater reflection on mental health, and the use of an online questionnaire may enhance the perceived anonymity and reduce stigma, thereby encouraging more accurate or increased reporting of mental health symptoms. These differences among our samples may contribute to a heightened difference in symptom reporting, particularly where it concerns mental health.

Sex differences related to mTBI, substance use, and mental health

Similar to existing research, our findings on sex differences varied across studies. Data from the studies in this dissertation suggest that sex differences in substance use may be present

within the general university student population. However, these differences appear to be less pronounced among athletes. This is noteworthy given athletes' increased exposure to mTBI, which we hypothesize is associated with substance use, particularly among females, who may experience more severe symptoms following injury. Among athletes, sex was not a significant predictor of substance use overall; however, when patterns of use were examined separately by sex in a university student sample, distinct differences emerged between males and females.

It is particularly important to examine the correlations between mTBI, substance use, and mental health factors through a sex-informed lens, as emerging evidence suggests that women may be at greater risk of sustaining mTBIs (Covassin et al., 2003; Gessel et al., 2007) and experiencing more severe outcomes post-injury (Covassin et al., 2007; Covassin & Elbin, 2011; Preiss-Farzanegan et al., 2017; Zuckerman et al., 2014). Additionally, at baseline, sex differences in substance use and mental health are well-documented. While males are more likely to engage in and escalate substance use behaviours (Skidmore et al., 2016; Choi et al., 2018), females are more likely to experience depression and anxiety (Piccinelli & Wilkinson, 2000).

Though the gender gap in substance use disorders is narrowing (Keyes et al., 2008), women remain at risk for co-occurring psychiatric and substance use disorders, further complicating treatment and recovery (Conway et al., 2006). This aligns with findings from Study 3, where female students reported significantly higher levels of depression and anxiety compared to males, and where these symptoms were further elevated among females with a history of mTBI. These sex-specific patterns were not observed in males, suggesting a heightened psychological vulnerability in females' post-injury.

Furthermore, consistent with Newman et al. (2020), associations between concussion history, substance use, and mental health may be stronger in females. Specifically in Study 3, anxiety was associated with cannabis use in females, while depression was associated with cannabis use only in those with an mTBI history. In contrast, among males, depression was associated with cannabis use regardless of mTBI history, while anxiety was associated with alcohol use only in males with a history of mTBI. These nuances in sex-related differences suggest there may be different pathways underlying mTBI, substance use, and mental health.

Despite these noted differences, sex was not a predictor of increased substance use at any level of our models investigating use in athletes in Study 2. However, a non-significant trend suggested higher rates of combined substance use in male athletes. This may reflect a normalization of substance use within the athlete culture, potentially masking sex differences

observable in boarded university samples which was demonstrated in Study 3. It is also important to note that had males and females been examined separately, differences in patterns of use may have emerged; however, these analyses were limited by small sample sizes.

Importantly, even under conservative Bonferroni correction, findings included from Study 3 in Appendix A demonstrate that mTBI remained a significant predictor of total cannabis use scores (CUDIT-R) in female students, supporting the hypothesis that psychological outcomes post-mTBI may be more pronounced in women. These findings underscore the importance of considering sex-specific mechanisms when assessing the long-term impacts of mTBI and related behavioural health outcomes and highlight the need for tailored interventions in female populations.

Overall, several key themes related to sex differences emerge from these findings. First, substance use and mental health are closely interrelated; however, the expression of these relationships appears to be both context- and population-dependent. These differences may be masked within the athlete population due to cultural norms or sample characteristics. Additionally, consistent with existing literature, our studies suggest that females may be especially vulnerable to the psychological impacts following mTBI. This highlights the importance of providing tailored mental health support and psychoeducation following injury.

This concern is further compounded by evidence that, while the number of females engaging in hazardous substance use is rising, they may be less likely to seek treatment (Greenfield et al., 2007) and often receive less specialized care compared to males (Edlund et al., 2012). Future research must consider the implications of analyzing these factors without separating by sex. Failing to do so may obscure meaningful differences, particularly in smaller or more specialized populations, where nuanced sex-specific patterns are more likely to emerge.

7.4 Clinical implications

Consistent with existing literature, our research demonstrates a correlation between substance use, mTBI, and mental health. While athletes may possess certain protective factors against mental health conditions, possibly due to growing recognition and support for athlete well-being, our findings suggest they remain at heightened risk for hazardous substance use behaviors. These results underscore the complexity of these relationships, which appear to be nuanced and likely vary by population and sex.

Our findings emphasize the importance of screening and early intervention for substance use, depression, and anxiety among young adults. While both substance use and mental health

warrant attention across the student population, clinicians should be particularly attuned to signs of substance use in athletes and to mental health concerns in the broader student body. The integration of sports psychologists and expanded access to psychotherapy should continue to be normalized within athletic programs, building on the broader societal movement to destigmatize mental health care. Mental health literacy and substance use education would do well to be incorporated into the team wellness program. Importantly, our study identified significant associations between mTBI and both substance use and mental health outcomes, placing athletes, particularly those involved in contact sports, at elevated risk. Following a diagnosed concussion or suspected mTBI, athletes would benefit from both psychoeducation and ongoing monitoring, particularly within the first year post-injury, to monitor for emerging symptoms and provide timely support. Polysubstance use in particular should serve as a "red-flag", warranting assessment for underlying mental health concerns. This population should be prioritized for access to comprehensive mental health resources.

Given the intersection of neurological, psychiatric, and behavioral factors, athletes may be especially well-served by an interdisciplinary and integrated care approach. This could include collaboration among athletic trainers, team medical staff, neuropsychologists, and psychologists with expertise in addiction and trauma, ensuring that the complex needs of these individuals are adequately addressed within both clinical and athletic environments.

Our data reveal clear sex differences in substance use patterns and associated risk factors. Broadly, research has shown that hazardous substance use among females is increasing (Greenfield et al., 2007), yet women often receive less specialized treatment than men despite experiencing more severe acute and long-term consequences (Edlund et al., 2012; McHugh et al., 2018). In our findings, females with higher anxiety scores were more likely to engage in cannabis use. Notably, while neither elevated depression scores nor a history of mTBI alone were significantly associated with cannabis use, females with both factors were more likely to use cannabis, highlighting the importance of considering intersecting risk factors.

These findings underscore the need for specialized, transdiagnostic care approaches for women, particularly in the treatment of substance use disorders, where females have been shown to respond more favorably to treatment (Greenfield et al., 2007; McHugh et al., 2018). Among males in our sample, substance use was more strongly associated with elevated depression scores, suggesting that interventions targeting depressive symptoms may be particularly effective for reducing substance use in males.

Special attention should also be given to female athletes. While much of the existing sports-related substance use research has focused on males, our data indicate that cannabis use among female athletes is associated not only with increased depression but also with altered functional connectivity in brain regions involved in emotional regulation. This further supports the call for tailored prevention and treatment strategies that account for sex-specific patterns and neurobiological correlates of substance use.

7.5 Limitations and future directions

Several limitations were noted across the studies in this project. One of the primary challenges lies in the measurement of head injury. There is a general lack of public understanding regarding brain injury, its mechanisms, and varying levels of severity. As a result, even when psychoeducation is provided, it remains difficult to determine whether self-reported history of mTBI is accurate. Self-reporting across the lifespan is particularly vulnerable to recall errors. While chart reviews may offer more objective information, not all mTBIs or concussions are formally reported or treated, and documentation by staff or personnel may be inconsistent or inaccurate. Future collection of mTBI history could possibly be done via interview with a professional in mTBI to facilitate more nuanced querying of possible injuries rather than questionnaire self-report.

In addition to limitations in self-reported mTBI history, self-report data on substance use and mental health are also subject to potential bias. This is especially relevant in athlete populations, where some of the substance use data were collected as part of larger baseline testing conducted in team settings. In contrast, university students completed mental health questionnaires anonymously online. The differing contexts in which data were collected may have influenced participants' willingness to report sensitive information. Among athletes, there may be a perception that their responses could impact their standing with the team, potentially leading to underreporting of symptoms or behaviors.

A very significant statistical limitation across our studies is the inability to identify clear temporal relationships between the onset of brain injuries and the onset of mental health symptoms or substance use over time. Across all studies, we were only able to comment on associations rather than make any conclusions about causation. This limitation stems from challenges in collecting general histories of symptoms and injuries in a way that accurately captures the timing and sequence of events.

More nuanced clinical interviews focused on the onset and progression of symptoms may provide greater clarity into the directionality of these relationships. This is particularly important in cases where individuals have experienced multiple mTBIs throughout their lives, along with recurring episodes of mental health symptoms and varying points of treatment or recovery. Without a detailed understanding of when these events occurred, it becomes difficult to determine whether mental health symptoms or substance use followed injury, or possibly predated or contributed to it. Future studies would benefit from more comprehensive, timeline-based data to better understand how these complex factors interact over time.

One unique benefit of studying athletes is the potential to track longitudinal data. Since athletes are part of the university system and are monitored over time as part of their involvement with a team, it may be possible to invest in this cohort by conducting clinical interviews to obtain a comprehensive history of their symptoms. This would allow for a more nuanced approach in tracking how their symptoms evolve over time. However, several constraints, such as time, funding, and the need for collaboration, present significant barriers to conducting longitudinal studies of this nature.

One question that this study was unable to address, due to the limited sample size in most of the studies, pertains to how these factors present among minority individuals. This is a clinically significant area of research, as studies have shown a notable prevalence of mental health conditions among student-athletes who are visible minorities or who identify as part of the LGBTQIA+ community (Kaishian & Kaishian, 2022). This underscores the importance of not only understanding why these subgroups of athletes may be at increased risk but also highlights the need for sports psychology to play a critical role in supporting the mental health of players who may be particularly vulnerable.

7.6 Conclusions

In summary, across four studies, important links were found between substance use, mental health, and brain connectivity in both athletes and non-athletes. Findings consistently showed that mTBI, anxiety, and depression are associated with increased substance use, with distinct sex-specific patterns. Female participants showed stronger associations between cannabis use, mood symptoms, and mTBI, while males showed broader links between depression and substance use. Athletes with mTBI reported worse mental health outcomes overall.

Neuroimaging results revealed altered brain connectivity, particularly in regions related to emotion regulation and self-monitoring, highlighting the neurobiological impact of these combined factors.

Further research into the temporal relationships between these variables is needed to better understand the directionality and causality between mTBI, substance use, and mental health factors, not only among males and females, but also among individuals from minority groups.

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Appendices

Appendix A: Association between mTBI, mental health, and sex variables and total cannabis and alcohol use in users by sex

Predictors	Unstandardized estimate	95 % CI	*t*-statistic	*p*-value
Model 1: Cannabis use in female users				
(Intercept)	3.636	1.534, 5.738	3.415	<.001
mTBI history	7.608	3.326, 11.891	3.507	**<.001*** **
Depression symptoms	0.304	0.089, 0.519	2.791	**.006** **
Anxiety symptoms	0.007	-0.204, 0.218	0.063	.950
mTBI history x depression symptoms	-0.493	-1.026, 0.039	-1.830	.069
mTBI history x anxiety symptoms	0.095	-0.495, 0.685	0.319	.750
Observations	**174**			
Model 2: Cannabis use in male users				
(Intercept)	7.667	3.901, 11.433	4.084	<.001
mTBI history	1.016	-6.765, 8.796	0.262	.794
Depression symptoms	0.180	-0.352, 0.711	0.678	.501
Anxiety symptoms	-0.211	-0.703, 0.280	-0.863	.392
mTBI history x depression symptoms	0.078	-0.934, 1.090	0.154	.878
mTBI history x anxiety symptoms	0.171	-1.010, 1.351	0.290	.773
Observations	**59**			
Model 3: Alcohol use in female users				
(Intercept)	3.241	2.365, 4.116	7.280	<.001
mTBI history	-1.525	-3.435, 0.385	-1.570	.117
Depression symptoms	0.041	-0.065, 0.146	0.761	.447
Anxiety symptoms	0.053	-0.055, 0.161	0.961	.337
mTBI history x depression symptoms	0.175	-0.028, 0.379	1.692	.091
mTBI history x anxiety symptoms	-0.051	-0.273, 0.172	-0.446	.656
Observations	**357**			
Model 3: Alcohol use in male users				
(Intercept)	3.945	2.715, 5.175	6.349	<.001
mTBI history	0.443	-2.272, 3.159	0.323	0.747
Depression symptoms	0.048	-0.166, 0.261	0.440	0.660
Anxiety symptoms	-0.092	-0.314, 0.129	-0.824	0.411
mTBI history x depression symptoms	0.235	-0.154, 0.624	1.195	0.234
mTBI history x anxiety symptoms	-0.120	-0.577, 0.338	-0.517	0.606
Observations	**124**			

Note. *$p < .05$. **$p < .01$. ***$p < .001$

Abbreviations: CI= confidence interval, mTBI = mild traumatic brain injury.

Appendix B. Comparison of individuals with a reported mTBI within the past six months to the rest of the sample.

Variable	mTBI less than 6 months (n = 27)	No mTBI within the past 6 months (n = 867)	df	t	p	Cohen's d	X^2
PHQ9 total M (SD)	12.63 (6.75)	9.56 (6.30)	892	-2.49	.006	-.487	
PHQ9 mild or above n (%)	23 (85.2%)	664 (76.6%)	1		.297		1.088
GAD7 total M (SD)	11.33 (5.76)	8.36 (5.86)	892	-2.60	.010	-.508	
GAD7 mild or above n (%)	22	597	1		.162		1.959
AUDIT-C total M (SD)	3.07 (3.51)	2.27 (3.30)	892	-1.24	.217	-.242	
Hazardous alcohol use (over 8) n (%)	3 (11.1%)	69 (8.0%)	1		.553		.351
CUDIT-R total M(SD)	2.22 (5.26)	2.07 (4.53)	892	-.175	.861	-.034	
Hazardous cannabis use (over 8) n (%)	4 (14.8%)	97 (11.2%)	1		.558		.344

Note-caution should be used while interpreting due to small proportions of individuals in some cells.