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Review Article

# Mechanisms underlying vulnerabilities after repeat mild traumatic brain injuries

T. Greco, L. Ferguson, C. Giza, M.L. Prins*

*UCLA Department of Neurosurgery, 300 Stein Plaza, Los Angeles, CA 90095, United States*

ABSTRACT

Traumatic brain injury (TBI) has drawn national attention for its high incidence and mechanistic complexity. The majority of TBI cases are "mild" in nature including concussions and mild TBI (mTBI). Concussions are a distinct form of mTBI where diagnosis is difficult, quantification of the incidence is challenging and there is greater risk for subsequent injuries. While concussions occur in the general population, it has become a hallmark injury consistently observed among adolescent and young adult athletes and the risks for repeat TBI (rTBI) is significant. Clinical and experimental evidence shows that the magnitude and duration of deficits is dependent on the number and the interval between injuries. Several studies suggest that metabolic vulnerabilities after injury may contribute to the window for cerebral vulnerability from rTBI. In addition to metabolism, this review addresses how age, sex and hormones also play an important role in the response to repeat concussions. Understanding how these factors collectively contribute to concussion and rTBI recovery is critically important in establishing age/sex appropriate return to play guidelines, injury prevention, therapeutic interventions and mitigation of long-term consequences of rTBI.

## 1. Epidemiology of repeat traumatic brain injury

Data from the National Federation of State High School Association and NCAA report 7,980,886 high school athletes, 497,600 collegiate athletes and 18,000 professional athletes within the United States between 2016 and 2017. This population is the most practical to monitor and collect epidemiological data about concussions and repeat concussions. It is estimated that 7% of high school athletes have concussions and 13.2% of these are at risk for repeat concussion (Schallmo et al., 2017). Among collegiate athletes 4% report concussions (Marshall et al., 2015) and 9% of those, report repeat concussions (Wasserman et al., 2016). The percentage of athletes with > 1 concussion obtained from studies that have examined middle school, high school and collegiate athletes from multiple sports are shown in Table 1 (Moser et al., 2005), (Collins et al., 2002), (Field et al., 2003), (Castile et al., 2012), (Yang et al., 2017), (Slobounov et al., 2007), (Langburt et al., 2001), (Collins et al., 1999), (Guskiewicz et al., 2003). Overall, the percentages range from 5.6–36%. More recent studies directly compare rates of new versus repeat concussion in high school athletes to show the rate of new concussions ranged between 22.2 and 35.3 per 100,000 athletic exposures (AE) (Yang et al., 2017), (Castile et al., 2012). The rates for rTBI ranged from 3.1 to 4.5 per 100,000AE. While boys have an overall higher average concussion rate than girls, when the rates are compared between similar sports, girls have 2× the concussion rate as boys and higher percentage of repeat concussions (12.4% versus boys 9%) (Yang et al., 2017). Among professional athletes the data is sports specific. In the NFL, 14.7% of the 1472 players were injured (Clark et al., 2017) with 2% at risk for repeat TBI (Casson et al., 2011).

In the general population, it is more difficult to determine accurate information regarding concussion incidence. Several studies have shown that estimates derived from a single entity (emergency room visits-ER) may only capture a small portion of regional concussions. A recent study examined the incidence of concussions across multiple health care entities (primary care, specialty care, emergency room, urgent care, inpatient) to determine a better estimate for pediatric concussions (Arbogast et al., 2016). Only 11.9% of patients went to the ER for concussion care, suggesting that epidemiological studies that estimate concussion rates based solely on this source will seriously underestimate the rates. The majority of 5-17yo patients (75%) were seen by their primary care doctors. The current annual estimate for concussions among children up to 18 years of age is 1.1–1.9 million based on multiple health care settings (Bryan et al., 2016), (Marar et al., 2012). This type of analysis is critically important and studies examining all age groups and sex are needed for more accurate epidemiological estimates of concussions, mTBI and rTBI.

## 2. Increased risk for vulnerability after repeat tbi

A unique concern to mTBI or concussive injuries is that individuals can acutely resume activities that expose them to potential additional concussions. This potential exposure leads to the question, "is there a

* Corresponding author.
*E-mail address:* mprins@mednet.ucla.edu (M.L. Prins).

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**Table 1**
Incidence of repeat concussions among young athletes.

| Age group | Population | % athletes with > 1 Concussions | Reference |
|---|---|---|---|
| Middle/High School (13–19yo) | Athletes | 20.2 | Moser et al., 2005 |
| High School | Athletes | 31.8 | Collins et al., 2002 |
| High School | Athletes | 7.7 | Field et al., 2003 |
| High School | Athletes | 13.2 | Castile et al., 2012 |
| High School | Athletes | 11.3 | Yang et al., 2017 |
| College | Athletes | 36 | Field et al., 2003 |
| College | Athletes | 5.6 | Slobounov et al., 2007 |
| High School | Football Players | 34.9 | Langburt et al., 2001 |
| College | Football Players | 30 | Collins et al., 1999 |
| College | Football Players | 6.5 | Guskiewicz et al., 2003 |

greater risk for injury after concussion?" In a 2003 study (Guskiewicz et al., 2003) 2905 college football players were baseline tested and provided self-reporting concussion history. Those players that reported having 3 or more concussions were 3 times more likely to sustain another concussion than those with no concussion history. While this study was based on self-reporting, the suggestion that a history of concussions could contribute to the risk of more concussions is of concern. This finding was further supported by a European study of male soccer players (Nordström et al., 2014) where those with concussions showed greater risk for subsequent head injuries in the first year compared to those with other bodily injuries. It has been postulated that the increased risk for concussions among athletes may be related to their risk-taking behaviors and not to the concussions themselves (Burman et al., 2016). Among the 15-35yo athletes studied in Sweden, athletes that sustained concussions were more likely to sustain injuries before and after the concussion compared to non-concussion groups. Since the frequency of injuries was the same before and after the concussions, the researchers concluded that the more aggressive playing styles contributed to their increased risk. Playing style and injury frequency before and after a concussion are important variables to consider along with age. Several studies have demonstrated age related differences in risk of subsequence concussions. College students from 26 universities and military schools provided self-reporting information regarding the age at first concussion and concussion history (Schmidt et al., 2018). Those athletes that sustained their first concussion during childhood had greater risk of future concussions than those that sustained their first injury during adolescence. The risk of subsequent concussion decreased 16% with each year of age at first concussion. In contrast, Annegers et al., (Annegers et al., 1980) who analyzed the general population in Olmsted County, Minnesota, reported that the incidence of second concussion was 2 times greater among children < 14 years old and 3 times greater among those 15–24 years old. Collectively these findings emphasize the need for future studies to examine play behaviors, before and after injury frequencies, age and sex when determining how a concussion can alter future risk of concussions.

Clinical and experimental studies both demonstrate that symptom recovery following multiple head injuries is prolonged, with greater symptom severity and early-onset of memory impairment reflecting the cumulative effects of repeat injuries. In athletes, the majority of subsequent concussions occur within 7–10 days of the prior injury, correlating to a "window of vulnerability" (McCrea et al., 2009). A study of 3000 NCAA football players found that those individuals suffering from 3 or more concussions were 3 times more likely to suffer an additional concussion, with risk correlating to number of concussions sustained (Guskiewicz et al., 2003). A retrospective study of high school and college athletes who return to play within this window, and while still experiencing symptoms, were shown a to be twice as likely to suffer subsequent concussions (McCrea et al., 2009). The cumulative nature of rTBI has also been observed in younger athletes. In adolescents (11–22 years old), those who suffered a 2nd injury within 1 year of the first had symptoms lasting twice as long (Eisenberg et al., 2013). However, when a 2nd injury occurred after 1 year, symptom duration was similar to those with a single injury, supporting concept for a "window of vulnerability" after a single TBI (Eisenberg et al., 2013). Results from both human and animal studies illustrate a vulnerability time period during which there is increased risk for subsequent injuries and increased symptom severity with slower recovery of neurological function.

Individuals with multiple concussions have also shown slower mental processing speeds, requiring an additional 7 days to perform at the level of their single injury counterparts (Gronwall and Wrightson, 1975) and increased recovery time relating to the number of concussions sustained (Guskiewicz et al., 2003). A retrospective study of middle and high school athletes measured balance, cognition, and school performance and found that athletes suffering from multiple concussions had higher symptom severity, particularly relating to cognitive function. Those with multiple concussions showed greater impairment in sustained attention and executive functioning (Wall et al., 2006). Length of recovery from multiple concussions was negatively correlated with age (Terwilliger et al., 2015). Children 13 years or older have taken longer to become symptom free than those younger than 13 (Eisenberg et al., 2013). This may be due to the delayed development of the frontal lobe, making it more vulnerable to disruption. Studies are lacking in regards to incidence of repeat injury in elementary-aged individuals, even though this age range may be more vulnerable to recurring injury and symptom severity due to the developmental changes occurring in the brain during this time period. While rTBI does not lead to morphological changes, it can induce structural changes including cortical thinning and enlargement of ventricles (Goddeyne et al., 2015). White matter axonal damage, and β-amyloid plaque formation, has shown to increase following multiple mild brain injuries as well (Prins et al., 2013), (Prins et al., 2010), (Grant et al., 2017) and has been linked to cognitive deficits including executive function and motor speed (Wozniak et al., 2007) and neurodegenerative disease (Grant et al., 2017). Astrocytic accumulation and impairment in a novel object recognition task were also exacerbated following multiple injuries (Prins et al., 2013).

The incidence of rTBI among males and females is related to type of sport, equipment used, and rules of play (Finnoff et al., 2011). Those few studies that have analyzed rTBI in both sexes report no significant differences in incidence of repeat injuries, but do report differences in symptom severity (Colvin et al., 2009). Analysis of sex differences is often complicated by what comparisons are made. Female athletes with concussions should be compared to female controls, not to male controls. Studies have shown that female athletes have greater baseline symptoms than males (Brown et al., 2015). It may be that females inherently perform a given task differently than males, so their results following injury look dramatically different from their counterparts. The mechanism for sex differences is widely speculative. Some have indicated that females suffer greater concussions from surface hits versus males who suffer concussions through body contact (Dick,

2009). This may relate to physical differences between genders in body size, weight, and musculature strength (Mansell et al., 2005), (Tierney et al., 2005). Some have speculated that psychological differences may influence concussion rates in males and females; the importance of mental health and honest reporting of injury has shown to differ between males and females (Dick, 2009). Future studies need to be more diligent in planning and in running analyses to ensure males and females are compared in an equivalent and appropriate manner.

## 3. Mechanisms for cerebral vulnerability

Concussion management has evolved and athletes are advised by physicians to wait until they are symptom-free prior to returning to activity. While the return to play guidelines have set a standard for safety, the compliance among adolescent and young adult athletes is about 40% (Yard and Comstock, 2009). The increased risk for subsequent concussions has led to researchers addressing the vulnerability of the brain after concussion. What remains unclear is the mechanism (s) behind the vulnerability and are there physiological markers that reflect the window of vulnerability and a "safer" time for returning to play?

### 3.1. Cerebral glucose metabolism after concussion

Concussive injuries increase the *metabolic* vulnerability of the brain. It has already been demonstrated that following even a mTBI that there is an increase in glucose uptake due to changes in excitatory amino acid release, combined with a dissociation of cerebral metabolism, resulting in metabolic crisis (Giza and Hovda, 2014). This initial neuronal membrane disruption causes a release of neurotransmitters (glutamate) and an influx of excitatory amino acids (sodium and calcium) and efflux of potassium. This disruption of the ionic equilibrium requires activation of cellular pumps to push ions back across their membrane gradients (Katayama et al., 1990). These pumps are energy dependent and consequently there is an immediate increase in glucose uptake. This acute phase lasts 6 h in experimental TBI models and is followed by a period of glucose metabolic depression Fig. 1A. Could the duration of glucose metabolic depression reflect the window of vulnerability?

### 3.2. Metabolic vulnerability after concussions

Experimental studies have shown a post-injury period of metabolic derangement, during which there is increased vulnerability to further injury in *adult animal models*. In adult rodents, repeated mild weight drop injuries were induced with different time intervals (1,2,3,4,5 days) to examine their effects on mitochondrial function and oxidative damage at 48, 120 and 168 h post last injury (Vagnozzi et al., 2007), (Tavazzi et al., 2005). Brain extracts were used to measure concentrations of metabolites and reactive oxygen/nitric oxide species. Animals with concussions at 1,2,3,4d interval showed changes in ATP with the greatest decrease in ATP (adenosine triphosphate, 47%), acetyl CoA (acetyl coenzyme A, 25%), NAA (*N*-acetylaspartate, 60%), and NAD +/NADH ratio (nicotinamide adenine dinucleotide,30%) at 3d intervals and greatest increase in ADP (adenosine diphosphate, 63%). These markers all remained altered at 120 and 168 h timepoints. Animals with concussions at 1,2,3 and 4d interval showed increase in MDA (malondialdehyde) and nitrite relative to shams, reflecting the increase in oxygen reactive species and nitrosative stress. Injuries given at 5d intervals produced mitochondrial, reactive species and nitrosative stress markers that were not statistically different than controls. Another study examining the effects of repeat lateral fluid percussion injury (FPI) in adult male rats at 1,5, or 15d intervals and assessed for motor function, histology and glucose uptake (Selwyn et al., 2016). It is important to note that while a single injury did not produce pathology, delivery of a second injury at 24 h did produce a lesion, indicating that this injury may not be as mild as the concussive injuries observed in athletes. Lesions are not a common finding even in repeat concussions. Injuries at 24 h interval produced the greatest motor deficits, greatest lesion size and increased microglial and astrocytic activation relative to sham and single injury. The glucose metabolic changes were not typical in that many structures failed to show the characteristic metabolic depression and instead showed increase glucose uptake. Fluid percussion injuries are not typically used for repeat injuries due to the scarring of tissue that develops at the craniotomy, making each subsequent fluid

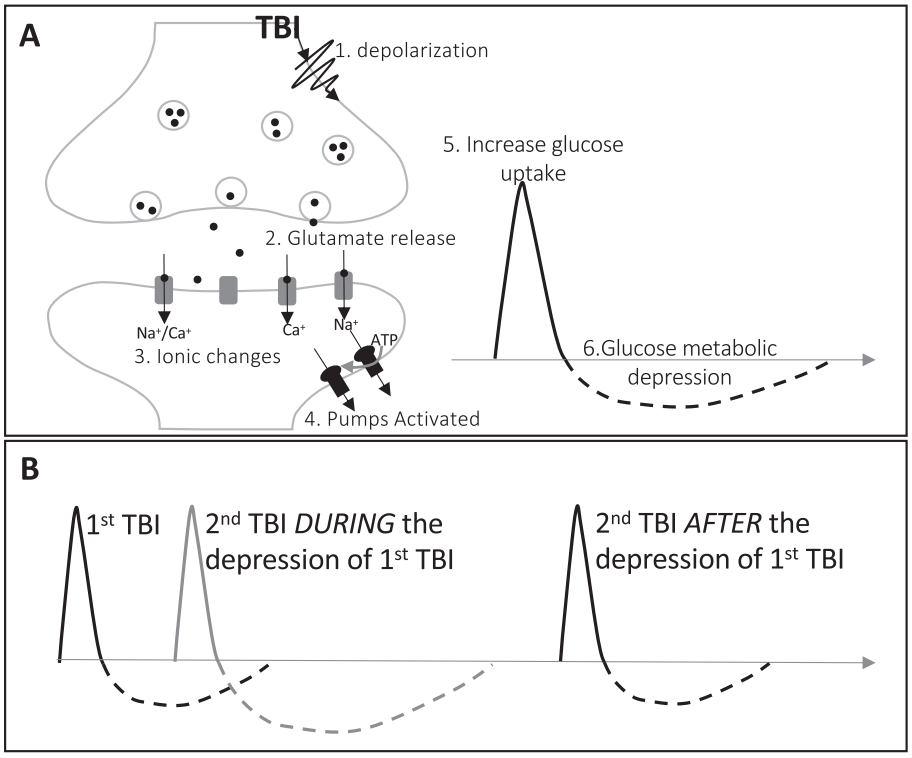


**Fig. 1.** The metabolic cascade after single and repeat concussions. (A) Upon impact, neuronal membranes are mechanically disrupted causing the indiscriminate release of neurotransmitters (glutamate) and neuronal depolarization. The activation of the post synaptic receptors causes an influx of excitatory amino acids (sodium and calcium) and efflux of potassium. The disruption of ionic equilibrium triggers activation of energy dependent pumps, thereby increasing energy demands of the cell and increases brain glucose uptake. The brain then enters a prolonged period of glucose metabolic depression, which may be a reflection of the brain's vulnerable state. (B) Illustration of the concept of metabolic vulnerability and how the interval between injuries can influence recovery.

pulse increasingly difficult to deliver. These studies provide evidence that the adult brain remains metabolically vulnerable after a mild injury.

Experimental studies have also shown a post-injury period of metabolic derangement, during which there is increased vulnerability to further injury in *the adolescent brain*. In an experimental model of male adolescent concussion, which produces no gross pathology and transient measurable behavioral deficits, a single injury produces significant cortical and hippocampal glucose metabolic depression that recovers within 3d (Prins et al., 2013). In this study, *adolescent male rats* were given 2 injuries at 24 h interval or 3 days based on the recovery profile of cerebral glucose metabolism (CMRg) Fig. 1B. When a second mTBI was introduced during the first injury CMRg depression (24 h) it resulted in prolonged CMRg dysfunction and behavioral impairments. But if the second mTBI was introduced *after* the CMRg depression of the first injury, the metabolism and behavior were not exacerbated. Collectively, these studies show that the cellular disruption in glucose metabolism and mitochondrial function significantly contribute to the vulnerable state of the brain even after a mild or concussive injury. Recovery of these processes are essential for safe return to activity. Development of a non-invasive surrogate metabolic indicators is essential for establishing practical clinical translation.

### 3.3. Sex as a vulnerability after concussion

In the past, male athletes were considered the vulnerable population to repeat concussive injuries. However, participation of women in sports has increased steadily since implementation of Title IX in 1972. The number of women in sports has increased between 2000 and 2017 from 2.7 to 3.4 million in high school (National Federation of State High School Associations) and from 157,740 to 217,584 in college (NCAA). The increase in sports participation is also associated with increases in the number of concussions and repeat concussions among females athletes. There are very few experimental studies addressing rTBI in females, but Wright et al. (Wright et al., 2017) has examined the issue of sex differences in responses to rTBI. Postnatal day 30 male and female rats were given sham, single or 3 rTBI (at 3d intervals) and assess for motor, anxiety, memory, depression and structural changes during the subsequent 12 days post injury. Both male and female adolescent rats showed motor deficits and anxiety, only male rats with rTBI had short term memory impairments. In contrast, only female rats with rTBI had increased depressive behaviors. The postmortem MRI showed females with greater prefrontal cortical atrophy and males with greater corpus callosum disruption. This finding is important as it suggests (Schallmo et al., 2017) that sex can be a vulnerability after rTBI involving different mechanisms and (Marshall et al., 2015) that there will be important sex differences after repeat concussions necessitating studies that use appropriate sex time course, outcome measures and controls for future studies and development of therapeutic options.

### 3.4. Behavioral vulnerabilities

In addition to sex differences after rTBI there are also age response differences. Adolescent and adult mice that were given 7 rTBI at 1d intervals revealed greater motor impairments, impulsivity and spatial memory impairments among adolescent mice (Mannix et al., 2017). These deficits persisted for 3 months. Both age groups showed decreased hippocampal expression of NMDA (*N*-methyl D aspartate) receptor subtype 2B. This finding is consistent with outcome comparisons between high school and collegiate athletes, where age contributes to vulnerabilities after rTBI.

### 3.5. Cerebral vulnerabilities for long term consequences

The dynamic early changes after rTBI reveal targets for reducing vulnerabilities that contribute to poor outcome. But one issue that does not fall into this category is the potential for long-term degenerative diseases. Since the highly publicized autopsy studies of football players with evidence of tau depositions, there has been a growing need for studies to address whether concussions, repeat concussions, or hits are sufficient to increase the brain's vulnerability to long term neurodegenerative processes. Epidemiological studies have reported increased risk for neurodegenerative diseases and Alzheimer's or Parkinson's disease following moderate or severe TBI (Gilbert et al., 2014), but fewer have addressed mTBI. Among the previous reviews of retrospective studies, 2 studies reported significant association between mTBI and risk of dementia (Graves et al., 1990), (Gardner and Yaffe, 2015). It is important to note that these studies were limited by small sample sizes. More recently the risk for dementia was studied in 160,000 mTBI trauma patients (> 55 year olds) compared to limb fractured patients. The authors report that mTBI increases the risk for dementia 22–26% within 5–7 years for ONLY those patients 65 years or older at the time of mTBI (Gardner et al., 2014). This study examined the consequences of a single mTBI, but what about rTBI? The data is unclear. There is a study of deceased retired NFL players that suggests a 3 fold increase in deaths by neurodegenerative diseases compared to the normal population (Lehman et al., 2012), but another study showed no increased risk (Savica et al., 2012). Like-wise the risk for CTE (chronic traumatic encephalopathy) is unknown in both the athletic and general population. Few experimental studies have addressed long-term effects following injury early in life. A study of rTBI in adolescent male and female transgenic APP/PS1 rats showed that 4 concussive injuries at 24 h intervals during adolescence increased hippocampal amyloid plaque loads in both plaque number and sizes in both sexes (Grant et al., 2017). However, among animals where the injuries were given at 72 h intervals (based on recovery of glucose metabolic profiles), the plaque loads were no different than the normal aged population. This study would suggest that it is not the total quantity of life time concussions, but the interval between the injuries can may contribute to potential risks. More research is needed to determine mechanisms that contribute to ongoing pathology.

## 4. Repeat tbi and age and sex

Although men are more than twice as likely to sustain a TBI, women comprise a significant portion of the TBI population who continue to suffer long-term effects. The incidence of TBI among females continues to grow as participation in sports and the military increases, with a peak in injury incidence occurring during adolescence. Despite this, health related consequences directed towards only females have not yet been fully studied within the US {Dick, 2009 #67}. There is a distinct lack of studies observing the consequence of mTBI and rTBI on recovery in females, let alone adolescent females, and what pre- and post-injury factors could increase vulnerability or worsen recovery. While comparisons between the sexes may show significant differences, they do not define or address 3 important variables that influence recovery and outcome: (Schallmo et al., 2017) *Pre-injury factors*, such as circulating levels of reproductive hormones underlie differences in blood flow, cerebral metabolism and structural organization within the brain. How each of these interacts with outcome variables is currently unknown. (Marshall et al., 2015) *Post-TBI hormonal dysfunction*: Hypopituitarism following TBI is a well-recognized phenomenon but not studied after mTBI. Disruption of hormonal regulation will play a significant role in recovery of cognitive, emotional, physical and social domains following injury and can interrupt developmental processes. (Wasserman et al., 2016) *End-points of recovery*: Differences in the importance of specific long-term psychosocial outcomes between sexes is significant. Socialization and gender role expectations play a significant role in recovery. Natural differences between the sexes also influence perception of recovery.

### 4.1. Clinical symptoms

Despite conflicting evidence it is generally believed that females experience more severe and longer symptoms of concussion compared to males, but this generalization ignores which symptoms should be examined and importance of controls. While there are sex-differences in post-concussion symptomology, it is important to examine the data carefully. In self-reported symptoms females report more severe symptoms including headaches, concentration, irritability, fatigue and dizziness (Broshek et al., 2005), but comparison to pre-injury baseline is critically important especially in women as higher symptom reporting has been shown at baseline (Brown et al., 2015). In contrast, males have been reported to have higher incidence of depressive symptoms (Covassin et al., 2006). The majority of self-reported symptom studies show similar time course of resolution between the sexes. While self-reporting symptoms may not provide clear evidence of sex differences, analyzing symptomatology and recovery independently using computerized neurocognitive testing may be useful. This approach reveals that males and females can experience significantly different symptoms and testing outcomes. Normally the male and female brain show differential brain activation patterns when doing visuospatial or memory tasks (Weiss et al., 2003). But despite this, no post-concussive differences were seen in reaction time, verbal memory or processing speed (Covassin et al., 2006). This was in contrast to a 2009 study (Colvin et al., 2009), that showed females had worse reaction time and memory compared to males and that females with 2–3 concussions performed better in in visual memory, motor processing speed, and reaction time than males with the same number of injuries (Covassin et al., 2010). Confounds similar to incidence may be responsible for differences observed in these studies. Collectively, these data strongly suggest different symptomology between sexes with adult females experiencing more mood, cognition, psychosocial, sleep, and headache related impairments than males. Identifying key clusters of symptoms that differ between males and females could significantly aid in diagnosis, treatment and potential incidence of post-concussive syndrome.

### 4.2. Experimental studies

Research has yet to be done to identify unique risk factors that may influence recovery and outcome in females that have experienced a sports concussion. Some of the lack of clarity stems from issues related to timing and outcome measures that are not sex specific. The overall experimental TBI work suggests that female hormones may be neuroprotective against morbidity and mortality following TBI (Johann and Beyer, 2013; Shahrokhi et al., 2012), which is in contrast to clinical studies showing that females experience greater mortality and prolonged symptom recovery (mood, cognition, psychosocial, sleep, headaches, etc.) (Bazarian et al., 2010), {Kraus et al., 2000wc}. Differences may be in part due to the timing and use of outcome measures. In both clinical and animal studies, outcomes have been compared to tasks that are affected in males and at time points based on male recovery profiles. When care is taken to compare either recovery profiles over time, it is found in outcomes measures, that females exhibit different temporal profiles and injury peaks may be seen at different times (Maghool et al., 2013), (Hall et al., 2005), (Wagner et al., 2002) which is reflective of clinical symptomatology following concussion.

Another source that contributes to the lack of clarity in sex differences after is related to the selection of outcome measures. Sex differences in performance of several behavioral tasks may differ, influencing reporting of outcome measures. For example, there are well-reported age and sex related differences in novel object task performance and anxiety measures (Mychasiuk et al., 2015; Cyrenne and Brown, 2011; Petraglia et al., 2014). By not using a task that best represents those domains (such as mood or social behavior), we may be either under- or overestimating injury effects. Lastly, a commonly observed issue is comparison of data. Studies often compare female results directly to male making results seem like females recover faster than males. But when the female data are normalized to the appropriate female shams there are either no differences or females show worse outcomes (Kupina et al., 2003), (OConnor et al., 2003cr), (Wagner et al., 2002wm). In the few experimental studies that compare male to female “concussive” closed head injury, sex differences in outcome measures are revealed. Weight-drop injury in adolescent rats, show significant decreased long-term potentiation (LTP) in the CA1 and dentate gyrus (DG) of male rats, while LTP was decreased up to 28 days in the DG of female rats. This shows that a mild injury can result in persistent impairment of synaptic plasticity in female rats (White et al., 2017). Sex differences are also seen in social interaction tasks. Adolescent rats given weight drop injury showed immediate severe social deficits and injured animals were less likely to interact with peer animals. However, when house with uninjured animals, injured males were able to learn adaptive behaviors and became more social with their house mates, but females did not further ostracize them and emphasizing the role of social dynamics during recovery of injury (Mychasiuk et al., 2014). This same group also observed that mTBI resulted in sustained hypoactivity in female animals throughout adulthood, while males exhibited hyperactivity and greater impulsivity that were representative of ADHD-like behaviors (Mychasiuk et al., 2015). Interestingly the Mychasiuk group also showed differences in outcomes that were both injury-type and sex-dependent. Late adolescent animals were given either a weight-drop or lateral impact injury. The lateral impact appears to more affect emotional domains while weight-drop affected learning/memory and there was no injury-type difference with motor function. Males performed worse on the open-field test compared to females that performed worse on the elevated-plus maze, both being measures of anxiety-like behaviors. Females also showed less exploratory behavior on the novel object task while males failed the task independent of injury, females with a lateral injury performed better than males (Mychasiuk et al., 2016). This study may represent some of the heterogeneity observed of injury symptomatology due to different sport played and suggest location and/or mechanics of impact may influence symptoms experienced (Meaney et al., 2011 #692). Differences in addictive behaviors have also been noted after mTBI. In a murine model of mTBI, juveniles or adults and self-administration of alcohol was assessed during adulthood. Only the females injured as juveniles showed increased self-administration of alcohol (Weil et al., 2016).

There remains a significant lack of literature addressing sex differences in concussions and repeat concussions. The literature suggests that sex may not determine number or severity of symptoms, but rather males and females respond differently in both time course and groups of symptoms experienced. This makes it even more important that concussion and repeat concussion studies specifically address how the female brain responds to injury.

## 5. Concussion & pituitary dysfunction in athletes

It is common for athletes who have suffered a sports concussions to complain of neurobehavioral symptoms that affect quality of life, including memory and concentration deficits, impaired judgment, problem solving, depression, anxiety, fatigue, malaise and loss of libido (Bigler, 2008; Englander et al., 2010). These symptoms show significant overlap with those reported by patients with hypopituitarism and may be due to endocrinologic deficits rather than the TBI itself (Bavisetty et al., 2008). Growth hormones and gonadotropins are the more commonly affected hormones after TBI (Schneider et al., 2011) and are due to the unique anatomical vulnerability of the pituitary gland to brain movement. Disruption of the pituitary gland and hormones during adolescent developmental can have permanent structural and negative consequences on function and behavior as adults. This is of significant importance as the highest rates of concussion occur during this age group (Gilchrist et al., 2009). Beyond development, hormones are involved several biological activities within the brain that include, but are

not limited to neuronal plasticity, neurogenesis, synaptogenesis, neuronal survival, angiogenesis and myelination and act as neuroprotective and neurotrophic factors.

It is well established that TBI of moderate to severe severities can cause hypopituitarism, but it is currently unknown how a single concussion or repeat concussions may be a risk factor for developing pituitary dysfunction. There is a paucity of data regarding frequency of hypopituitarism due to sports-related brain injury and an even greater lack of data in female athletes although hormonal dysfunctional is routinely common in females following moderate and severe TBI (Wagner et al., 2002 #16) (Snook et al., 2017 #693) (Dimopoulou et al., 2004 #360). In adults, there is growing evidence that there is a cumulative effect between rTBI and hypopituitarism. In a clinical study, growth hormone (GH) status and IGF1 levels were compared between 11 competing or retired male amateur boxers and a control group. GH deficiency was found in 45% of the boxers and IGF1 levels were significantly lower in boxers (Kelestimur et al., 2004). Among kickboxers 22.7% had GH deficiencies with significant decreases in IGF1 (Tanriverdi et al., 2007). Retired boxers had a higher rate of pituitary dysfunction (47%) compared to active boxers (18%). Among football players, pituitary and metabolic function studied revealed that 28% of players were GH deficient. Players with hormone deficiencies had significantly lower quality of life and poor metabolic function and decreased erectile function (Kelly et al., 2014). These studies suggest TBI-induced hormonal deficiencies have consequences following repeat head injuries in adult athletes.

In younger athletes, the consequences of rTBI are less clear. Among four male intercollegiate athletes serum prolactin levels were significantly reduced at 2 and 7 days, recovering to normal by the second week. The recovery of PRL tracked with recovery of symptoms and return to play in all four athletes (La Fountaine et al., 2016). The link between rTBI and hypopituitarism has only been addressed in one case. In this case, a 14-year old soccer player experienced four concussions within four months after which the player showed stunted growth, decreased athletic ability and poor energy levels. Testing showed the patient had GH, ACTH and TSH deficiencies (Ives et al., 2007). These findings suggest that rTBI has a cumulative effect on pituitary dysfunction. While most patients presenting with hypopituitarism have spontaneous resolution within 3–6 months, a significant subset (> 20%) continue to have chronic symptomatology and/or develop new pituitary deficiencies over time (Schneider et al., 2011) and may play a significant role in the 20–30% of athletes that suffer from post-concussion syndrome.

As more attention is being paid to TBI-induced hypopituitarism, there is increasing interest in understanding the mechanisms behind how mild TBI and repeat concussive injuries can results in hypopituitarism, long-term consequences of hypopituitarism and how hormonal supplementation may affect brain recovery and behavioral outcome. Hypopituitarism remains an under-recognized area as there are few basic research publications dealing with the aforementioned questions. More recent research has focused solely on the effects of more significant TBI on pituitary function. Kasturi and Stein performed a bilateral frontal controlled cortical impact (CCI) in adult rats and found increased pituitary inflammation, two-months following injury and significant decreases in both pituitary tissue and serum GH (Kasturi and Stein, 2009). The increased inflammation may represent a secondary injury mechanism in addition to any mechanical shearing. The pituitary is located within the sella turcica in the base of the skull and any inflammation and/or edema as a result of TBI may result in ischemic injury leading to necrosis of the anterior portions of the pituitary gland. A 2010 study looked at the local paracrine response of IGF-1 to CCI injury showing IGF-1 upregulation in pericontustional areas for up to 48 h and was followed by changes in the IGF-1 receptor, total AKT and pAKT. The authors concluded this might be an early mechanism where by IGF-1 signaling is induced in response to injury in an attempt to stimulate endogenous recovery and/or repair (Madathil et al., 2010).

Far fewer studies have addressed hormonal consequences of concussive and repeat concussive injuries. Greco et al utilized an adolescent rat repeat concussive injury model to observe effects of GH deficiency on puberty in rats (Greco et al., 2013). Animals were given sham, one or four mild TBI (4TBI) injuries, with a 24 h interval based on changes of cerebral metabolism following mild repeat TBI. The authors found that GH and IGF-1 were significantly reduced in 4TBI compared to sham and single injury animals at one-week post-injury until one month. 4TBI animals were also significantly smaller in both length and weight. Evans Blue dye extravasation was used as a marker of vascular permeability and they found that with increasing injuries, permeability of the pituitary gland increased (Greco et al., 2013). Subsequent study used the same adolescent repeat concussion model to examine organization vs. activation effects of hormones after rTBI. Testosterone was significantly reduced 24 h to one month after injury, normalized by two months and was correlated to a delay in pubertal onset. Erectile function and reproductive behaviors and reproductive organ growth were significant impaired at 1 and 2-months following injury. The authors concluded that the impact of undiagnosed hypopituitarism following RTBI in adolescence has significance not only for growth and puberty, but also for brain development and neurobehavioral function as adults (Greco et al., 2015).

## 6. Summary

The effects of repeat mTBI or concussion are complex and affected by many factors. Epidemiology of rTBI is complicated by differences in injury identification, injury reporting and access to medical care at different levels. Potential risks for clinical rTBI may be based on but not limited to biology, type of activity/sport, sex, behavior (style of play or activity), comorbidities and premature return to risky activity. Response to injury and rTBI may also be affected by these factors. Preclinical models allow some separation between biological risks for rTBI and behavioral/performance factors, which can be hard to distinguish in clinical studies. Behavior/performance factors include aggressive or impulsive activity, incoordination, impaired reaction times and slowed thinking. Some of these are related to underlying physiological dysfunction and may improve with time after injury and some of these may be distinct to an individual. Nonetheless, experimental studies have also confirmed the importance of biological factors in both the risk and recovery from rTBI, including metabolic alternations, age- and sex-differences, hormones, axonal structure and synaptic function/plasticity. Understanding these differences and translating them to the clinical realm will have important implications for prevention, improving recovery and mitigating long-term consequences of rTBI.

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